The effects of air pollution on perinatal outcomes in North West England

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy (PhD) in the Faculty of Medical and Human Sciences.

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List of abbreviations

AM	Arithmetic mean
AOR	Adjusted odds ratio
AQG	Air quality guidelines
ARR	Adjusted relative risk
AURN	Automatic urban and rural network
BMI	Body mass index
BS	Black Smoke
CO	Carbon monoxide
COMEAP	Committee on the medical effects of air pollution
DEFRA	Department of food and rural affairs
DWTD	Distance weighted traffic density
EU	European Union
GA	Gestational age
GIS	Geographic information systems
GM	Geometric mean
GSD	Geometric standard deviation
IDW	Inverse distance weighting
IMD	Index of multiple deprivation
IQR	Interquartile range
LBW	Low birth weight
LMP	Last menstrual period
LSOA	Lower layer super output area
LUR	Land use regression
MAF	Monthly adjustment factor
MP	Manchester Piccadilly
MS	Manchester South

NAEI	National atmospheric emissions inventory
NSTAT	Nearest stationary monitor
NO	Nitric oxide
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
NWPSU	North West perinatal survey unit
O_2	Oxygen
O_3	Ozone
OK	Ordinary Kriging
OR	Odds ratio
PCM	Pollution climate mapping
PE	Personal exposure
PM	Particulate matter
$PM_{2.5}$	Particulate matter ≤2.5 μg/m³
PM_{10}	Particulate matter ≤10 μg/m³
PPB	Parts per billion
PPM	Parts per million
PTB	Preterm birth
SES	Socio-economic status
SGA	Small for gestational age
SO_2	Sulphur dioxide
SPTB	Spontaneous preterm birth
S-T model	Spatio-temporal model
TSP	Total suspended particles
UFP	Ultrafine particle
μg/m³	Micrograms per metre cubed
VOC	Volatile organic compounds
WHO	World health organization

The University of Manchester

Abstract of thesis submitted by Kimberly Jane Hannam

For the degree of Doctor of Philosophy

The effects of air pollution on adverse perinatal outcomes in North West England

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Over the past decade there has been a substantial increase in evidence suggesting an increased risk of adverse pregnancy outcomes from ambient air pollution exposure. However, there is yet to be enough convincing evidence to confirm a causal link between specific air pollutants and adverse pregnancy outcomes.

The objective of this project was to address the paucity of evidence from the UK on the risk from air pollution in pregnancy. The research aim was to investigate the effects of ambient air pollution on adverse pregnancy outcomes using retrospective birth outcome data from the 'North West Perinatal Survey Unit' (NWPSU) during the period 2004 to 2008.

In addition, primarily to determine the most appropriate exposure estimation method, a prospective comparison study (n=85) was performed to compare personal measurements of nitrogen oxides (NO_x) and specifically nitrogen dioxide (NO_2) with commonly used exposure estimation techniques. This study informed two further studies which quantified the effects from air pollution in pregnancy using a large retrospective cohort from the NWPSU. The first, investigated the effects of maternal residential proximity to major roads on low birthweight (LBW), small for gestational age (SGA) and preterm birth (PTB). The second, investigated the effects of NO_x, NO_2, carbon monoxide (CO) and particulate matter ($PM_{2.5}$ and PM_{10}) based on estimates from a novel spatio-temporal air pollution model and stationary monitor sites on SGA, PTB and mean birth weight change.

Linear and logistic regression models were used to quantify the risk of adverse pregnancy outcomes from living in close proximity to a major road and to specific ambient pollutants. Odds ratio (OR) associations and mean birth weight change were calculated for each of the pollutants with exposure averaged over the entire pregnancy and for specific pregnancy periods to establish critical windows of exposure. Models were adjusted for maternal age, ethnicity, parity, socio-economic status, birth season, body mass index and smoking.

No statistically significant associations were found between living <200m from a major road and adverse pregnancy outcomes. Based on the spatio-temporal modelled air pollution estimates, an increased risk of SGA was found in later pregnancy with NO_2 (OR=1.14, 95%CI= 1.00-1.30), CO (OR=1.21, 1.02-1.42), $PM_{2.5}$ (OR=1.10, 1.00-1.21) and PM_{10} (OR=1.12, 1.00-1.25).

This study provides additional evidence that women exposed to high air pollution concentrations in pregnancy are at an increased risk of an SGA birth, but not for PTB. However, there was no evidence of an effect on SGA for exposures below the current legal air quality limits.

Declaration

No portion of the work referred to in the thesis has been submitted in the support of an application for another degree or qualification of this or any other university or other Institute of learning.

Copyright Statement

Presentations relating to this thesis

- Institute of Human Development Research Showcase (Manchester): 2013 **[Poster presentation]** "The effects of air pollution on adverse perinatal outcomes in NW England"
- Festival of Public Health (Manchester): 2013 **[Poster presentation]** "The effects of air pollution on adverse perinatal outcomes in NW England"
- Maternal and Fetal Health, Works in Progress meeting: 2010, 2011, 2012, 2013 **[Oral presentations]**
- Lane lecture series (Manchester): 2013 **[Oral presentation]** "Maternal residential proximity to major roads and adverse perinatal outcomes"
- Centre for Biostatistics seminar series (Manchester): 2013 **[Oral presentation]** "Air pollution and adverse perinatal outcomes"
- ISEE: International Society of Environmental Epidemiology (South Carolina, USA): 2012 **[Oral presentation]** ''Evaluating Air Pollution Exposure Measurement Techniques in Pregnancy: A Validation Study in North West England'
- ISEE: International Society of Environmental Epidemiology (South Carolina, USA): 2012 **[Poster presentation]** ''Evaluating Air Pollution Exposure Measurement Techniques in Pregnancy: A Validation Study in North West England'
- ISEE: International Society of Environmental Epidemiology (South Carolina, USA): 2012 **[Poster presentation]** 'The association between air pollution and adverse Perinatal outcomes in North West England.'
- Festival of Public Health UK (Manchester): 2012 **[Poster presentation]** ''Evaluating Air Pollution Exposure Measurement Techniques in Pregnancy: A Validation Study in North West England'

- Cranfield Outdoor air pollution meeting (Cranfield): 2012 **[Oral presentation]** ‘'Evaluating Air Pollution Exposure Measurement Techniques in Pregnancy: A Validation Study in North West England'

- London Occupational and Environmental Epidemiology meeting (London): 2012 **[Poster presentation]** ‘'Evaluating Air Pollution Exposure Measurement Techniques in Pregnancy: A Validation Study in North West England'

- Maternal and Child health seminar series (Manchester): 2011 **[Oral presentation]** ‘Air pollution and perinatal outcome’

Publications relating to this thesis

- Kimberly Hannam, Roseanne McNamee, Frank de Vocht, Philip Baker, Colin Sibley, Raymond Agius. 2013 ‘A comparison of population air pollution exposure estimation techniques with personal exposure estimates in a pregnant cohort’. (Published) *Environmental Sciences: Processes and Impacts,* DOI:10.1039/C3EM00112A

- Kimberly Hannam, Roseanne McNamee, Philip Baker, Colin Sibley, Raymond Agius. 2013. ‘Residential proximity to major roads and adverse perinatal outcomes in North West England’. (In press) *Journal of Occupational and Environmental Medicine.*

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"Clean air is a basic requirement for life"

(WHO, 2010)[1]

Chapter 1: Introduction

1.1 Chapter introduction

Chapter 1 is the introduction to the thesis. At the beginning of the introduction the structure of this thesis is described with a schematic diagram summarising the overall thesis structure.

The introduction then goes on to provide a background on air pollution, air pollution estimation techniques and adverse perinatal outcomes. Subsequently, it presents evidence from the existing literature of the associations between air pollution and adverse perinatal outcomes.

The introduction thereafter provides an overview of biological plausible hypotheses and the main methodological challenges in investigating the relationship between air pollution and adverse perinatal outcomes.

Finally, the aims and objectives for the thesis are outlined.

1.1.1 Structure of the thesis

This thesis is structured in an 'alternative thesis format'. This format means that the majority of the main body of results in this thesis are written up as individual chapters suitable for submission to peer reviewed journals. At the time of submission, one paper has been published, one is in press and two have been submitted and are under review. The decision was made to implement this structure because the work fitted naturally into separate chapters within their own right, each requiring distinct discussions of the results and limitations. One chapter within the main body of the thesis (Chapter 4) has been included as an additional short chapter and not as a paper intended for submission; this was because the work done for this chapter was a small exploratory study nested

within the study presented in Chapter 3. The final output of this thesis is four separate papers for publication, three of which are presented as main chapters within the body of the thesis; the fourth is a review paper and is included in the introduction to this thesis. The four papers are titled:

(1) The effect of gaseous pollutants on preterm birth: A critical review of the literature. (Chapter 1.6.1) **[Under review]**

(2) A comparison of population air pollution exposure estimation techniques with personal exposure estimates in a pregnant cohort. (Chapter 3) **[Published]**

(3) Maternal residential proximity to major roads in North West England and adverse pregnancy outcomes. (Chapter 5) **[Accepted: In press]**

(4) Air pollution exposure increases risk of small for gestational age in a large UK birth cohort: use of a novel spatio-temporal modelling technique. (Chapter 6) **[Under review]**

The schematic below (Figure 1) summarises the thesis structure.

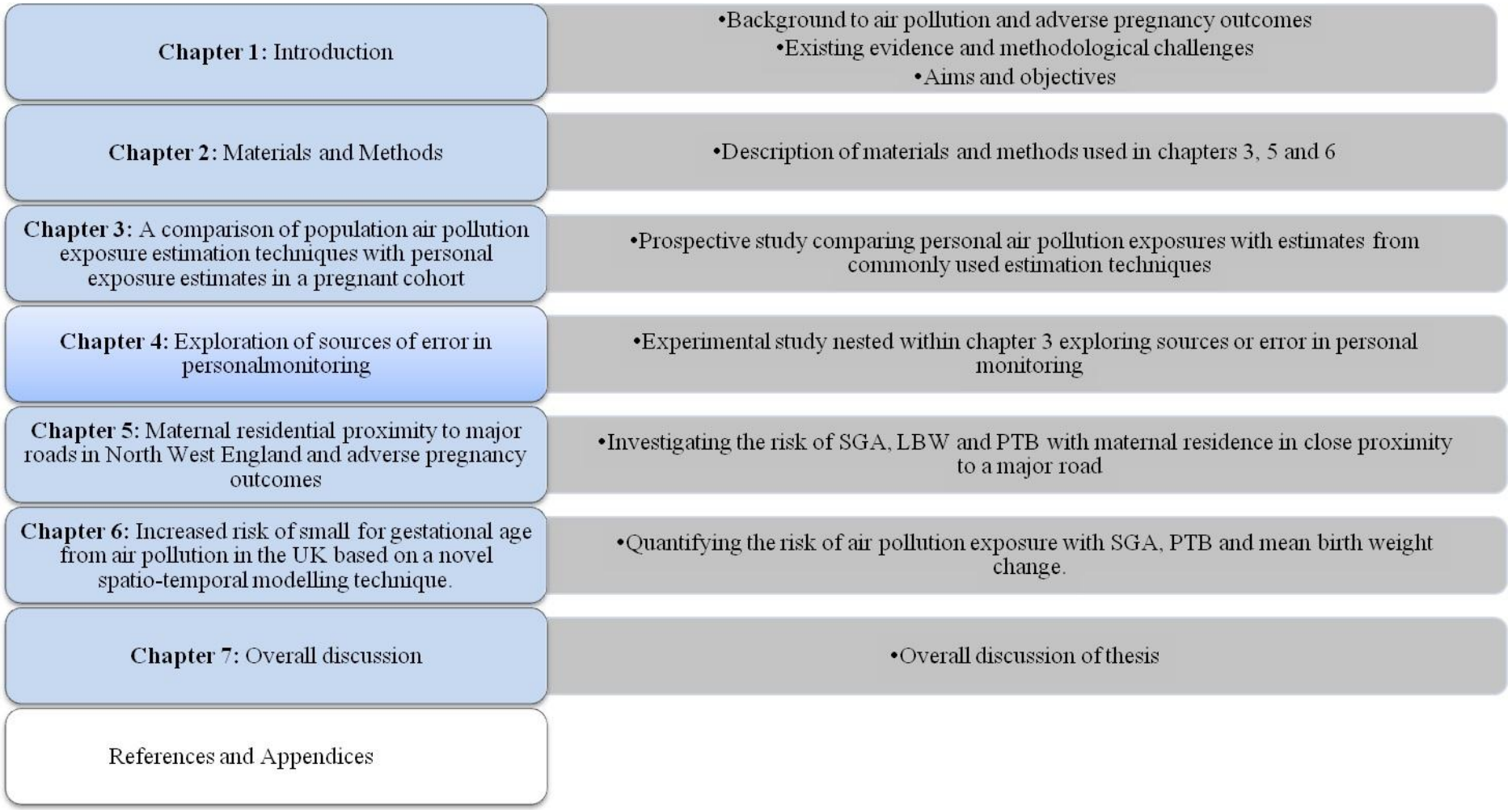


Figure 1: Schematic of the thesis structure

1.2 Air pollution

Air pollution in the United Kingdom (UK) has been an area of concern for many centuries. The earliest recorded legislation to control poor air quality was in 1273 when the use of coal was prohibited in London due to concerns over the effects on health [2]. In 1863, new legislation was introduced that set about controlling emissions in the air known as 'The Alkali Acts' and encouraged manufacturers to achieve the lowest possible levels of emissions and which was for the first time enforced by independent inspectors [3]. The series of acts were centred on concerns about the effects of air pollution on the land and subsequent effects on agriculture, rather than concern for the health of the population. The early legislation was specific to certain industries and it was not until the London smog occurred in 1952 that the effect air pollution was having on human health was truly recognized. The London smog was the worst documented pollution episode in UK history. During the 5th-9th December, a period of cold, windless conditions combined with a peak in coal usage, resulted in London being covered in a thick smog [4]. Medical records indicated that the smog resulted in the premature death of around 4,000 people and made 100,000 ill [5]. In response to the London smog, the government issued its first 'Clean Air Act' in 1956. The act set in place a number of emission control measures, mainly to decrease the amount of domestic and industrial coal being used as this was thought to be the main culprit of the episode [6]. By 1961, the UK established the world's first co-ordinated national air pollution monitoring network. Air pollution monitoring has since played an imperative role for research and legislative purposes for air quality in the UK [7].

Presently, management of air quality is largely driven by European Union (EU) legislation. The 2008 ambient air quality directive replaced almost all previous EU air

quality legislation setting legally binding limits for the major pollutants that impact upon health [8]. This directive was made law in the UK in June 2010 [9]. Table 1 summarises the limit values for the specified averaging period of main pollutants in this legislation.

The World Health Organization (WHO) designed air quality guidelines (AQG) based on the evidence of the health effects from ambient air pollution. The guidelines were first produced at a European level in 1987 and updated in 1997. In 2005 they were further developed to apply worldwide. [10]. These guidelines were not standards or legally binding criteria and although generally very similar to the 2010 UK legislation, when they differ, the WHO guideline limits are set lower than the current legislation.

Air quality monitoring and dissemination of air quality data in the UK is predominantly managed by the Department for Environment and Rural Affairs (DEFRA). Since 1987, DEFRA have maintained data sources to obtain monitored air pollution data, produced reports and annual statistical releases. The pollutants measured by DEFRA and the concentration bandings used to categorize exposure risk to the public are reviewed by an external committee of air quality experts known as COMEAP (Committee on the Medical Effects of Air Pollutants). COMEAP is an expert committee which provides advice on matters concerning the health effects of air pollutants. The findings and advice from the 2011 COMEAP report led to recent changes being made by DEFRA [11]. Changes had not occurred since 1992, two decades that has seen substantial changes to European and UK legislation on air quality as well as extensive broadening in scientific understanding of the health effects from air pollution. The suite of pollutants which are now reported on with bandings set in place include: nitrogen dioxide, ozone, and particulate matter (as PM_{10} and as $PM_{2.5}$). Carbon monoxide has been recommended for

removal and is no longer a pollutant that will be reported on because outdoor levels have fallen substantially since the index was last revised [12] (Table 2). The recommendations were based on evidence of current pollutant concentrations and evidence on the effects of air pollution on human health effects.

Table 1: Air quality standards regulations in the UK implemented in 2010 [9]

Pollutant	Averaging period	Limit value
PM_{10}	24-hour mean	50 µg/m^3, not to be exceeded more than 35 times a calendar year
	Calendar year	40 µg/m^3
$PM_{2.5}$	Calendar year	25 µg/m^3
SO_2	1-hour mean	350 µg/m^3 not to be exceeded more than 24 times a calendar year
	24-hour mean	125 µg/m^3 not to be exceeded more than 3 times a calendar year
O_3	Max eight hour daily mean	120 µg/m^3 not to be exceeded more than 25 days per calendar year
NO_2	1-hour mean	200 µg/m^3 not to be exceeded more than 18 times a calendar year
	Calendar year	40 µg/m^3
CO	Max eight hour daily mean	10 mg/m^3

Table 2: Summary of the most recent (2011) recommendations for air pollutant reporting by DEFRA in the UK from COMEAP [11]

Pollutant	Averaging period	Unit	Low	Moderate	High	Very High
PM_{10}	24-hour mean	µg/m^3	0–50	51–75	76–100	≥101
$PM_{2.5}$	24-hour mean	µg/m^3	0–35	36–53	54–70	≥71
SO_2	15-minute mean	µg/m^3	0–265	266–531	532–1063	≥1064
O_3	Running 8-hour mean	µg/m^3	0–80	81–160	161–240	≥241
NO_2	1-hour mean	µg/m^3	0–200	201–400	401–600	≥601
CO	*Recommend removal*					

Section 1.3 describes the composition, sources and patterns of the key pollutants identified by COMEAP and the pollutants that have been linked to adverse health effects: particulate matter, nitrogen oxides, carbon monoxide, sulphur dioxide and ozone. In this thesis, air pollution concentrations are generally described in $\mu g/m^3$ (micrograms of gaseous pollutant per cubic meter of ambient air) rather than parts per million (ppm) or parts per billion (ppb)[13] [1].

1.3 Pollutant composition, sources, patterns and thresholds

1.3.1 Particulate matter

Ambient particulate matter (PM) is made up of a range of particles with different size and composition. It is notoriously difficult to locate the specific natural or man-made source [14] [15]. Generally PM is described based on the aerodynamic diameter of the particle; this relates to the diameter of a sphere with unit density that has aerodynamic behaviour which is identical to the particle described, thus, particles can have the same aerodynamic diameter but be different dimensions and shapes [16]. The aerodynamic diameter of airborne PM ranges from several nanometres (the size of a virus) to around 100 micrometres (the diameter of a human hair) [17].

As demonstrated in Figure 2, PM is generally classified into four categories: UFP (ultrafine particles with a diameter less than or equal to 0.1µm), $PM_{2.5}$ (fine particles less than or equal to 2.5 µm aerodynamic diameter), PM $_{2.5 - 10}$ (coarse particles with a diameter between 2.5 and 10µm) and PM_{10} (supercoarse particles less than or equal to 10 µm aerodynamic diameter).

[1] The general conversion equation between $\mu g/m^3$ and ppb is:

$\mu g/m^3$ = (ppb)*(12.187)*(molecular weight of gaseous pollutant) / (273.15+ °C)

Total suspended particles (TSP) and black smoke (BS) have also been used as a measure of PM [18 19]. BS is rarely used as a surrogate measurement of PM nowadays, largely due to the crude measurement technique where only elemental carbon content is reflected to calculate the concentration rather than the mass of particles [14 20]. The inlet of the monitoring device was not designed to be size selective and has been shown to collect an approximate size fraction between $PM_{2.5}$ and PM_{10}. Black smoke monitoring now only takes place at five monitoring sites in the UK and has been replaced by the specific monitoring of black carbon [21].

TSP is an all-inclusive term incorporating all sizes of ambient PM in the air. TSP is rarely used in epidemiological studies due to the fact that the measurement also includes particles that are too large to enter the human respiratory system [19]. As demonstrated in Figure 3, the deposition of particles within the human system is dependent on the aerodynamic diameter. PM_{10} is often referred to as having a 'thoracic particle fraction', meaning that the particles are of a size that during respiration the PM can reach the thoracic region. $PM_{2.5}$ is known to have a 'respirable particle function', meaning the particles are capable of penetrating the alveolar region of the lung [19]. $PM_{2.5}$ has been identified as having the largest role in terms of health effects due to the deeper penetration, increased toxicity due to composition of sulphates, nitrates, acids and metals, longer suspension times and easier penetration into indoor environments [22]. Ultrafine particles which also have the ability to penetrate deep in the human circulation have been identified as potentially having health effects which are independent of fine particles; for example, there is evidence that ultrafine particles have a greater inflammatory effect than larger particles [23].

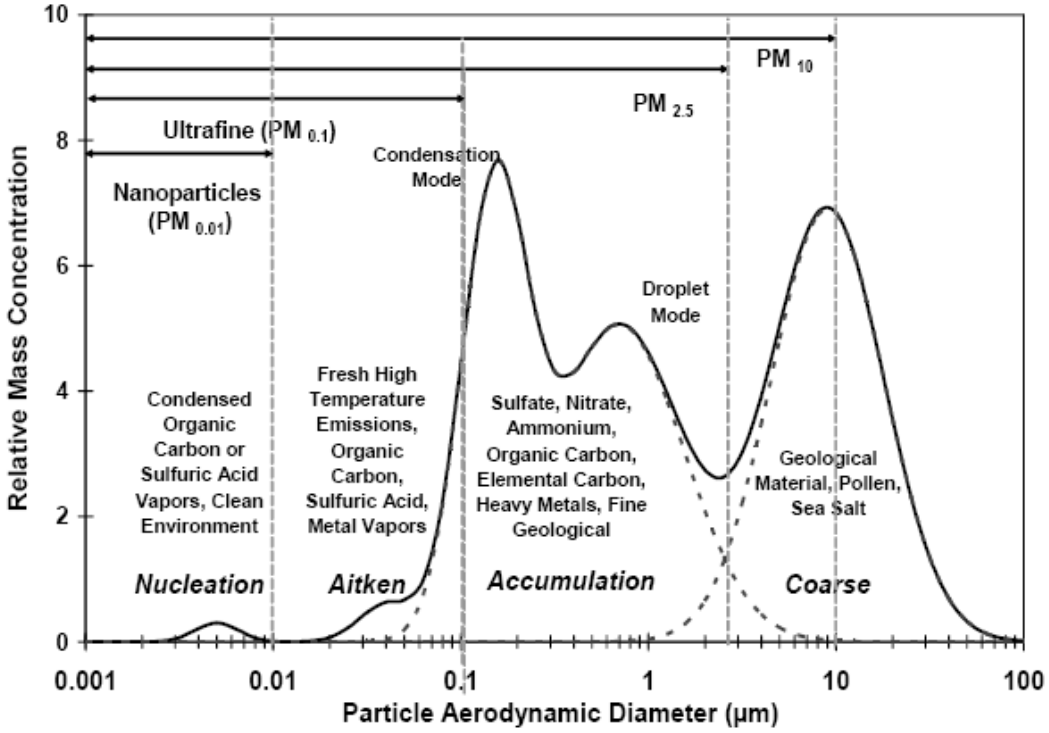


Figure 2: Interrelationship between size distributions of ambient particulate matter [24].

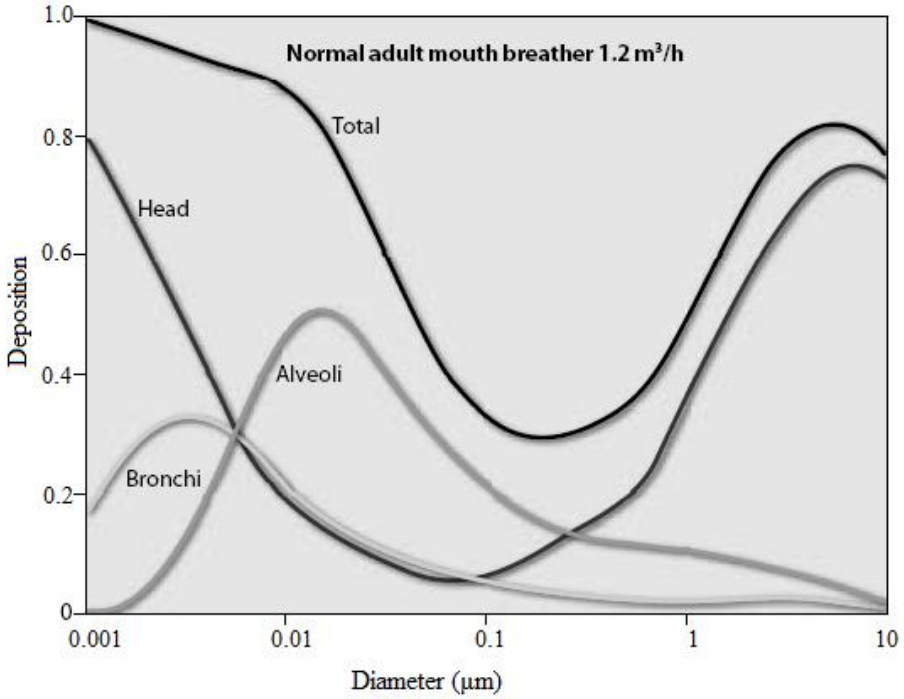


Figure 3: Relationship between aerodynamic diameter of particles and pulmonary deposition [25]

The primary components of PM are sodium chloride, elemental carbon, trace metals and mineral components. The secondary components are sulphate, nitrate and water. Organic carbon is a primary and secondary component to PM [17].

PM can be generated directly from a source (known as a primary pollutant) or generated subsequently as a result of physico-chemical reactions in the atmosphere (secondary pollutant). Primary particles come from stationary and mobile sources. The main mobile sources are from road transport emissions, the breakdown of vehicle tyres and road dust. The main stationary sources of PM include the burning of fuels for industrial, commercial and domestic purposes (primarily forming fine particles) [11]. Emissions can also be produced from construction sites or more natural sources such as sea spray and wind blown sand (primarily forming coarse particles). Secondary PM is generated from chemical reactions with the gases NH_3 SO_2 and NO_x (primarily forming ultrafine particles) [17 22].

In general in the UK, PM_{10} emissions decreased steadily throughout the 1990s. The main reason for this decline was due to the reductions in coal usage in domestic heating, energy production and industrial combustion [17]. Concentrations subsequently levelled off between 2000 and 2005, followed by a decrease during 2006-2008, after which a rise in levels occurred in 2010 and 2011. The recent increase in PM_{10} emissions is thought to be largely as a result of the cold weather during 2010 and resulting increased domestic heating. Long term time patterns of $PM_{2.5}$ cannot be observed due to the previous lack of routine monitoring [15].

No threshold has yet been identified for PM below which no damage to health is observed [17]. Thus, the guidelines were developed in an attempt to achieve the lowest possible concentrations that is achievable within the capabilities of public health

authorities. The 2010 UK air quality legislation for PM_{10} is set at an annual mean of 40µg/m³ and a 24-hour mean of 50µg/m³. The $PM_{2.5}$ annual mean was set at 25µg/m³[15]. The WHO guidelines recommend a PM_{10} annual mean of 20µg/m³ with the same 24-hour mean and the annual mean of $PM_{2.5}$ at 10µg/m³. The rationale for the WHO guideline values are based on key epidemiological studies which have reported on $PM_{2.5}$ concentrations. A large emphasis was placed on the evidence from the 'American Cancer Society' cohort study [26] and the 'Harvard Six Cities Study' [27]. The evidence suggested that health effects from $PM_{2.5}$ were likely to already occur at concentrations as low 11-15µg/m³; although it cannot be ruled out that adverse health effects can occur below this level [10].

1.3.2 Gaseous pollutants

1.3.2.1 Nitrogen oxides: nitric oxide and nitrogen dioxide.

Nitrogen oxides (NO_x) contribute to the formation of the toxic compound nitrogen dioxide (NO_2), act as a precursor of ozone (O_3) formation and also contribute to fine PM.

The principal components of NO_x include NO_2 and NO (nitric oxide). NO_x also consists of less prominent oxides of nitrogen: nitrous oxide (N_2O), nitrosylazide (N_4O), dinitrogen trioxide (N_2O_3), nitrate radical (NO_3), dinitrogen tetroxide (N_2O_4), dinitrogen pentoxide (N_2O_5) and trinitramide ($N(NO_2)_3$) [19]. Most of NO_x is released as NO, typically in the urban environment; in the troposphere, NO undergoes a photochemical reaction with O_3 (which has been formed by atomic oxygen combining to molecular oxygen) to form NO_2 and Oxygen (O_2). Ultraviolet radiation in the atmosphere (at <420nm wavelength) results in NO_2 decomposing back to NO and atomic oxygen (O) [19]

[28]. The changing concentrations between NO_2, NO and O_3 over time is demonstrated in Figure 4 [29]. These processes result in a photochemical equilibrium between NO, NO_2 and O_3 demonstrated in Figure 5.

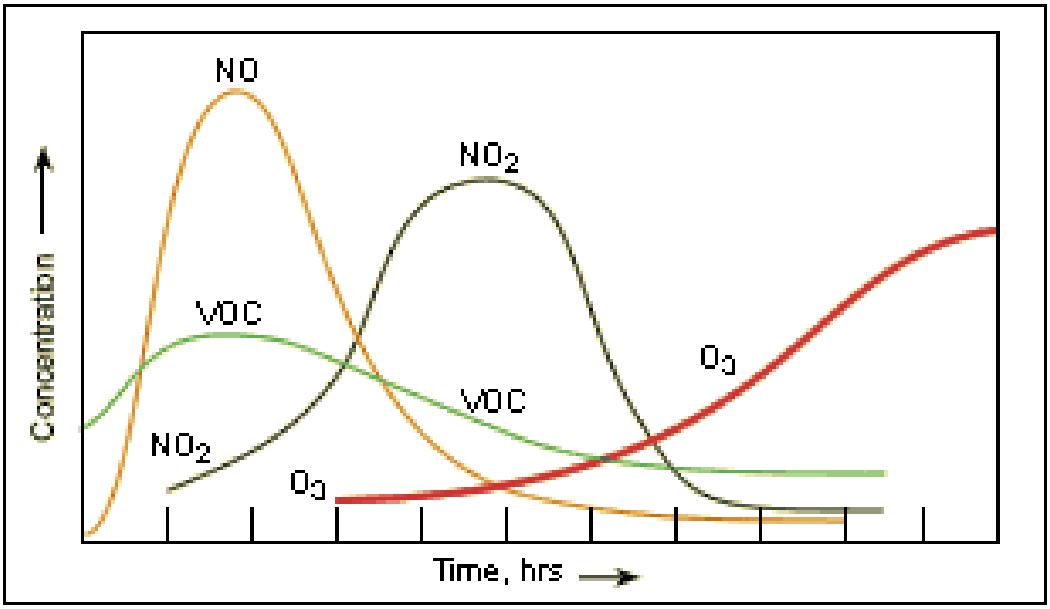
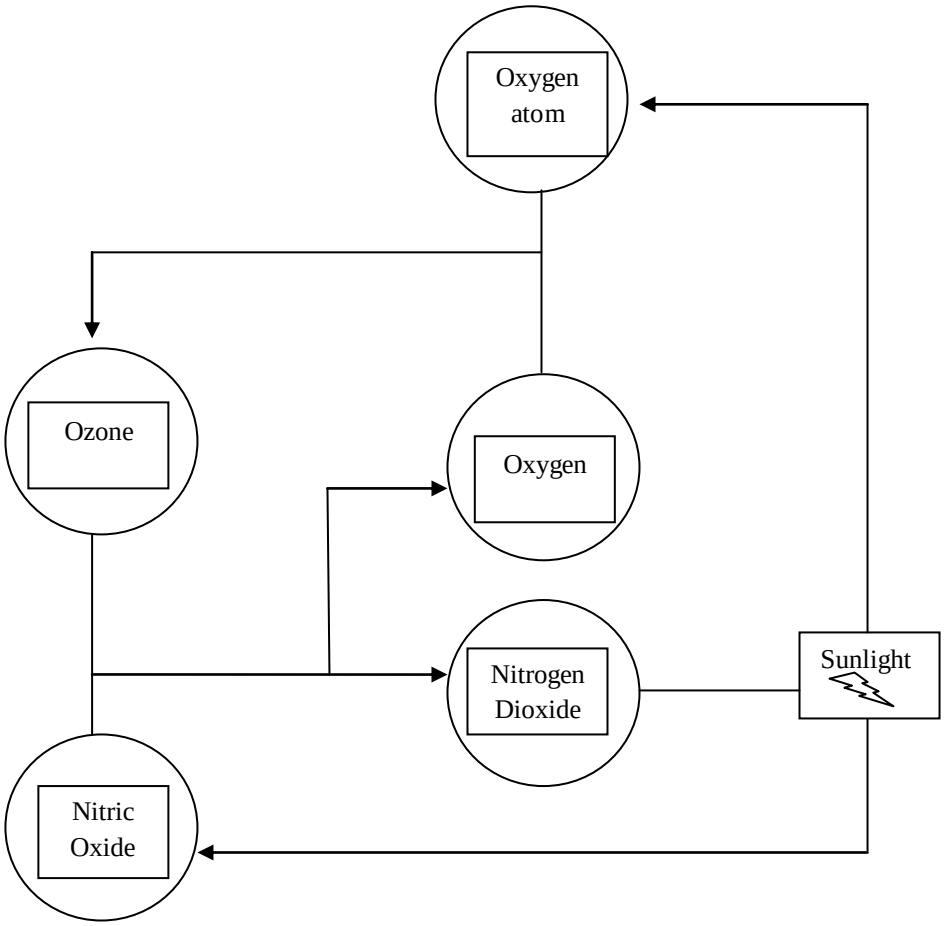


Figure 4: Graph from the United States environmental protection authority demonstrating the pollutant concentration profiles of NO, NO_2, VOCs and O_3. due to photochemical reactions [29]



$$NO_2 + uv\ (\lambda \leq 430nm) \longrightarrow O + NO$$

$$O + O_2 \longrightarrow O_3$$

$$O_3 + NO \longrightarrow NO_2 + O_2$$

Figure 5: A graphical representation of the photochemical reactions which result in an equilibrium of NO_2, NO and O_3.

NO_x is formed naturally in the atmosphere (e.g. due to the bacterial activity in soil) and anthropogenic emissions occur as a result of high-temperature combustion occurring in fossil fuel-fired power stations and industrial combustion. The largest contributor to NO_x is traffic, with the highest levels in UK cities found at the kerbside often exceeding 40µg/m³. Peak hourly concentrations at most urban sites exceed 100µg/m³ [15].

There has been a significant drop in NO_x emissions, particularly from the 1990s. This has largely been attributed to improved engine design of motor vehicles and the fitting of the 3-way catalyst converter [30]. Decreased emissions from power stations have also been shown to be important in this drop of emissions. Annual mean concentrations of NO_x emissions from burning fossil fuels are mainly released as primary NO and from certain sources, such as diesel vehicles, are released as primary NO_2. Secondary NO_2 is formed by the chemical reaction outlined above between NO and O_3. In areas where O_3 concentrations are scarce, such as close to busy roads, secondary NO_2 concentrations are reduced [30].

The 2010 legislation and the WHO guidelines both state an annual mean limit for NO_2 at 40µg/m³ and 1-hour mean of 200µg/m³ [9 10]. These limits have been set specifically for NO_2 because it is a good marker for complex combustion-generated pollution mixtures. The rationale for the short term guideline limit is based on animal and human experimental studies that have indicated that when short term concentrations exceed 200µg/m³, NO_2 can induce significant health effects [10]. Although there is a wealth of scientific evidence demonstrating the correlation between NO_2 and adverse health effects, it is unclear to what extent this can be directly attributable to NO_2 itself or instead to other strongly correlated pollutants. The WHO have outlined that the limit set in place should remain unchanged until more sufficient scientific evidence becomes

available, as the current limit value allows for the fact that effects from chronic NO_2 exposure at low levels could be toxic [10].

The European space agency (ESA) has produced high resolution global atmospheric maps of NO_2 from the world's largest satellite for environmental monitoring, using an instrument which records the spectrum of light shining through the atmosphere known as a Scanning Imaging Absorption Spectrometer for Atmospheric Cartography (SCIAMACHY). The World and European maps produced in 2003-2004 from the ESA below clearly highlight the higher concentrations in Europe, East coast America and China (Figure 6).

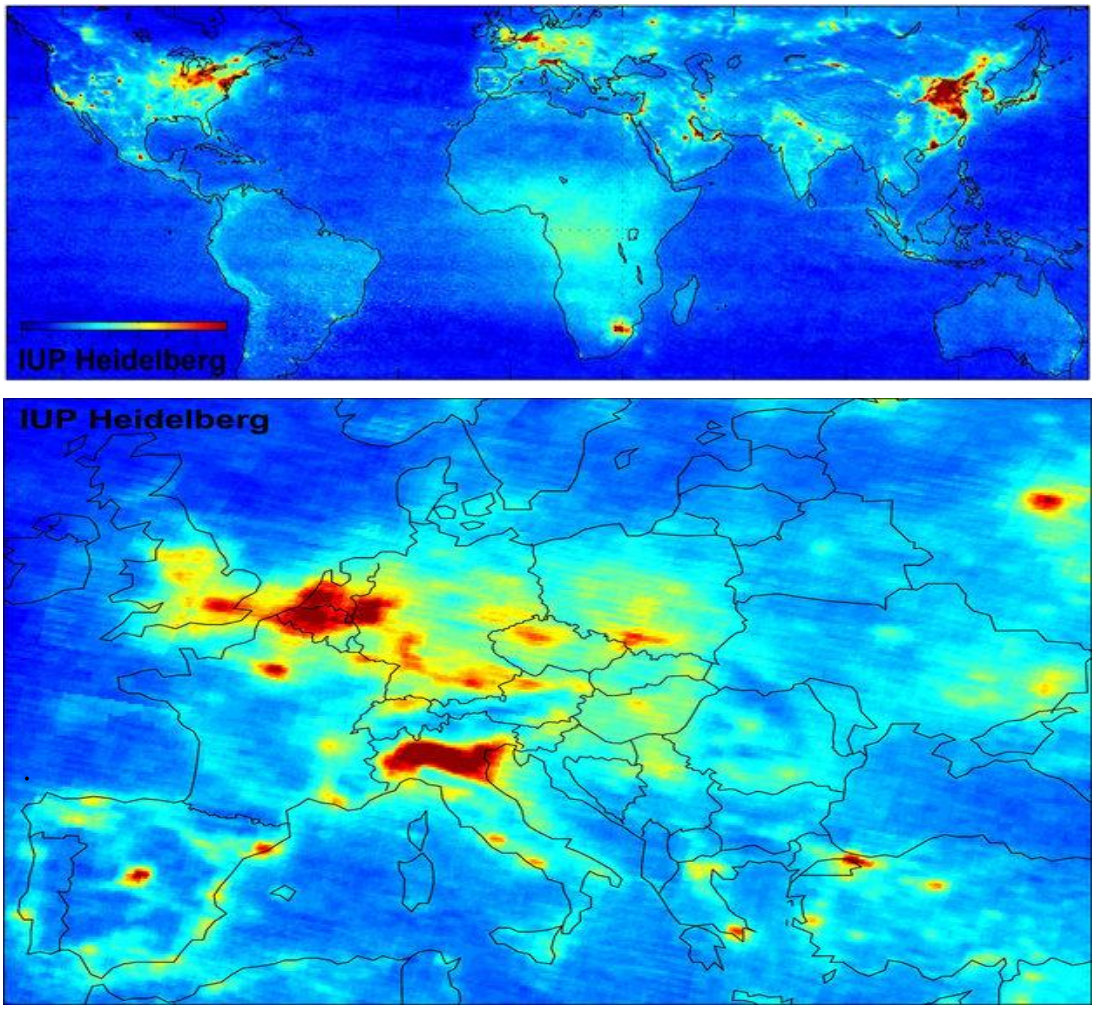


Figure 6: Global and European mean tropospheric NO_2 vertical column density (in 1015mol/cm^2) 2003-2004 [31]

1.3.2.2 Carbon monoxide

Carbon monoxide (CO) is a colourless and odourless gas that is emitted from the incomplete combustion of carbon-containing fuels, formed when there is not enough oxygen present to produce carbon dioxide (CO_2). Annual global emissions have estimated that 60% of CO emissions are from human activities and about 40% from natural processes [32]. The main source of CO is from traffic emissions, mainly from vehicles using petrol. Other sources of CO include incomplete combustion of other fuels, such as wood coal and propane. Exposure to high levels of CO is more likely to occur indoors as a result of poorly maintained and ventilated cooking or heating appliances as well as environmental tobacco smoke [15].

The UK legislation set in place for ambient CO concentrations are 10mg/m³ for 8-hours and 30mg/m³ for 1-hour mean [15]. The 2005 WHO guidelines did not assess the scientific evidence for CO and thus did not set any recommendations for limits.

1.3.2.3 Sulphur dioxide

Sulphur dioxide (SO_2) is a colourless, non-flammable gas. It is produced from the burning of fossil fuels which contain sulphur, which in the past was predominantly from coal. The main sources of SO_2 are domestic heating, motor vehicles and power generation [11]. SO_2 is a pollutant that has become less prevalent in western societies over the past few decades. SO_2 concentrations have dropped dramatically in the last forty years by over 90%, largely due to a decrease in the use of high sulphur coal and the increase in gas usage [15]. Another reason for this decline could be due to regulations in

place at power stations and industrial plants where SO_2 is trapped before it reaches the atmosphere [15].

The 2010 legislation sets the limits for SO_2 at 350µg/m³ for a 1-hour mean and 125µg/m³ for a 24-hour mean. The WHO guidelines are a 10-minute mean of 500µg/m³ and a 24-hour mean of 20µg/m³. An annual guidance was not deemed necessary, since compliance with the 24-hour level will assure low annual average levels of SO_2 [10]. The WHO guidelines based the short term average on a 10-minute mean of 500µg/m³ because studies which have investigated controlled exposure to SO_2 in asthmatics found that individuals experienced symptoms after 10-minutes of exposure above this level [10]. The WHO concluded that that there was considerable uncertainty as to whether observed correlations to long term SO_2 exposure was directly related to SO_2 concentrations or if it acts as a surrogate for another pollutant (likely to be ultrafine particles). As a result of the substantial uncertainty and epidemiological evidence from studies which have demonstrated very low thresholds of effect (one major study presenting associations with daily mortality at a 24-hour mean concentration as low as 5µg/m³ [33]), the WHO have set a very precautionary 24-hour guideline of 20µg/m³ [10].

1.3.2.4 Ozone

Ozone (O_3) is a secondary pollutant that is formed from primary pollutants NO_x and volatile organic compounds catalysed by sunlight [15]. Once O_3 is formed it can travel extensive distances and remain at high concentrations far away from the sources of the original pollutants it was formed from [11]. O_3 is a pollutant that generally demonstrates higher concentrations in rural areas compared to urban areas; in 2011, the mean annual 8-hr running mean was in the range of 40-60 µg/m³ at urban sites and 65-78 µg/m³ at

rural sites [15]. The increased concentrations in rural areas are largely due to peak O_3 concentrations occurring downwind of the original source and in areas where there are low NO concentrations which breakdown O_3 (Figure 5).

The O_3 guidelines are based on a running 8-hr average as this is the time period that is thought to most closely represent exposures likely to be harmful to human health [11].The guideline was recommended by the WHO for an 8-hour mean in 2000 was 120µg/m³. However, by the next WHO review in 2006, substantial amounts of new epidemiological evidence revealed associations between health effects and O_3 levels at concentrations lower than the previous guideline value, and as a result, the limit value was reduced to 100µg/m³ [10 11].

1.4 Air pollution exposure estimation

Exposure assessment has been described as "the science involved in characterizing the pathways, time course and magnitude of an individual's contact with the material under study" [34]. The assessment of exposure is often identified as one of the major challenges in observational epidemiological studies [34-36]. Appropriate exposure assessment is paramount in epidemiological studies assessing the risks posed by air pollution; without accurate exposure estimates, reliable and valid inferences of associations with health effects cannot be made [36 37]. Large well powered studies are required to investigate the relationship between air pollution and health effects because of the moderate effect sizes [38]. To achieve an adequate sample size, most studies implement a retrospective cohort study design [39 40]. When a large retrospective cohort is used, the actual exposure of an individual during the time period of interest is unknown unlike in a prospective study where personal measurements can, at least in theory, be done. Exposure therefore will have to be assessed retrospectively using an estimation technique. An air pollution exposure estimation technique is required in order to assign a 'best estimate' of each pollutant under study at a given time period and to ensure the correct ranking of exposure estimates in individuals. The ultimate aim of an exposure estimation technique is to maximize the accuracy of how close the estimate is to an individual's "real" personal exposure in order to minimize measurement error.

Estimating exposure can be done in a variety of ways, varying in accuracy and complexity. Estimation techniques such as interpolation, dispersion modelling and proxy measurements are commonly used in epidemiological studies and are discussed later in this chapter. More data intensive and complex exposure estimation techniques do not necessarily equate to a more accurate method [41]. It is important to have an

appreciation of the range of methods available and the advantages and disadvantages that come with implementing each in a specific study context. Often, a balance must be struck between the accuracy of the exposure measurement and the required sample size. For example, personal monitoring will likely be a more accurate estimate of 'true' exposure than other interpolation techniques; however, the practical issues pertaining to individual monitoring generally result in a restricted sample size; this limitation does not exist with more indirect methods such as interpolation methods. Although there is limited literature on validating and comparing air pollution exposure assessment methods, there is a generally acknowledged hierarchy (Figure 7) [37 42]. The triangle in Figure 7 crudely demonstrates the level of precision each of the categories of air pollution exposure estimation techniques have in relation to 'true' individual exposures; the highest level of precision is deemed to be personal measurements and the lowest is questionnaire data recorded from individuals about their perceived exposure. In recognition of the importance the exposure estimation technique has in epidemiological studies investigating the health effects of air pollution and the limited literature available for researchers to help inform this decision, Chapter 3 focuses specifically on comparing commonly used estimation techniques in epidemiological studies with personal exposure measurements.

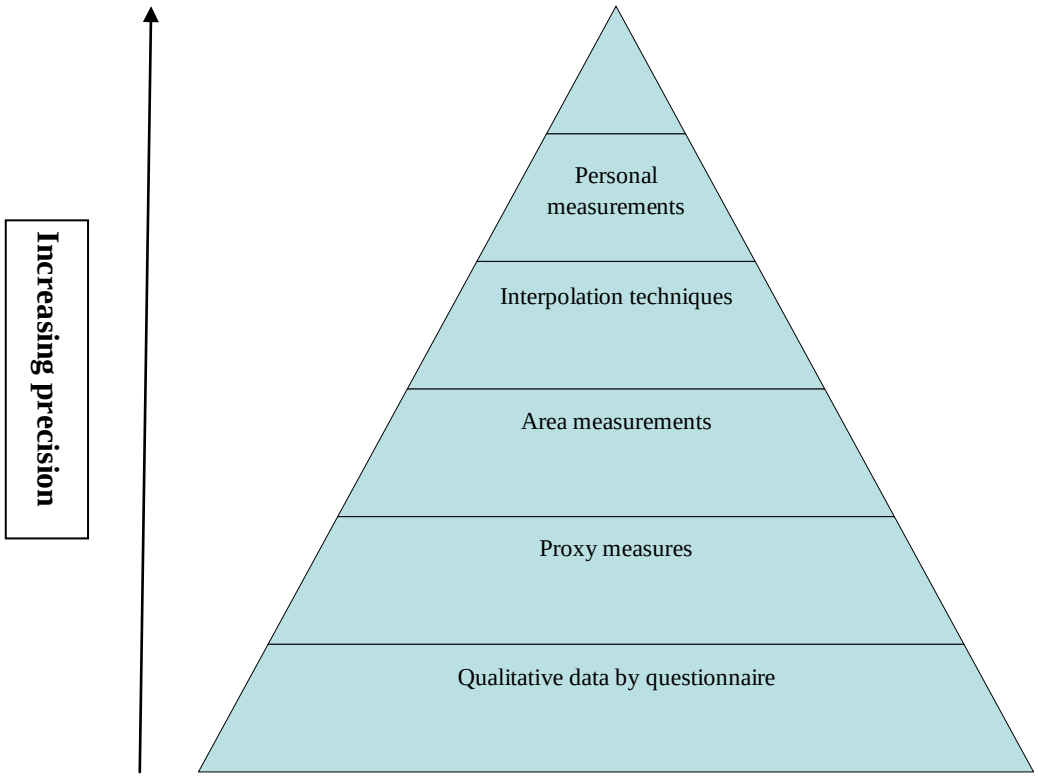


Figure 7: Hierarchy of exposure estimation techniques (adapted from Monn, 2001)[42]

Outdoor air pollution exposure estimation techniques may be classified as either direct personal measurements or indirect methods; the main categories of the latter include, but are not limited to: proximity based, statistical interpolation, dispersion modelling, traffic based proxy measurements, micro-environmental models and land use regression models. These will now be discussed in turn, starting with the most direct exposure estimation methods working through to the least.

1.4.1 Personal monitoring

Personal monitors are thought of as the 'gold standard' exposure assessment technique [43], providing the optimal spatio-temporal resolution. The personal monitor enables a measurement to be obtained which captures the substance of interest within an individual's breathing zone. They are more commonly used in validation or comparison studies of other estimation methods because of their cumbersome nature (i.e. they have to be worn by study participants for prolonged periods of time for example) [37 44 45], but have also been used in small epidemiological studies investigating health effects from air pollution [46 47]. Personal monitors benefit from their simplicity of use. Those that measure gaseous pollutants are mostly compact in size and can rely on simple gaseous diffusion rather than active sampling which makes use of a sampling pump and hence do not require an electrical supply. An example of a passive personal air pollution monitor, which is also used in the thesis, is demonstrated by the Ogawa sampler in Figure 8. The Ogawa personal sampler can simultaneously measure two gaseous pollutants using coated collection pads with specific absorbents relating to the pollutants measured, each pad held in place at either end of the tube between two round pieces of gauze and secured with a diffuser end cap with 2mm holes (described in more detail in Chapter 2.2.5 and Chapter 3.3.2). Personal monitors used to measure PM tend to be less compact and require a larger and more cumbersome active pump sampling device making their use in large population studies difficult [48 49].

The main benefit of personal monitoring over other indirect estimation techniques is that generally exposures estimated by indirect methods are based on one location only, which is usually the home environment (although *post hoc* combination of multiple locations is possible if combined with a secondary source on location of individuals).

Studies that have explored the relationship between personal measurements and indoor measurements have often found higher concentrations measured from personal monitors [42]. This may in part be due to the fact that monitors are rarely placed directly on sources and thus measure more 'background' concentrations, while humans move between background and source concentrations. It has also been suggested that this could be as a result of a "personal cloud" effect [49 50]. The "personal cloud" of air pollution has been found to be created largely due to human activity, primarily from resuspended coarse particulate matter [50].

The main limitation is that the personal monitors are costly and impractical to implement in a large cohort. If a study is able to implement personal monitors, often they can only be used for relatively short periods of time (for both analytical reasons and practical concerns). The protocol for one of the most commonly used passive personal air samplers and the sampler used in Chapter 3 (the Ogawa sampler) advises an exposure time of between 24 hours and 30 days (for low concentrations) [51]. This length of measurement may not necessarily be representative of the whole period which is under study, for example as in the case of this thesis, the nine months of pregnancy.

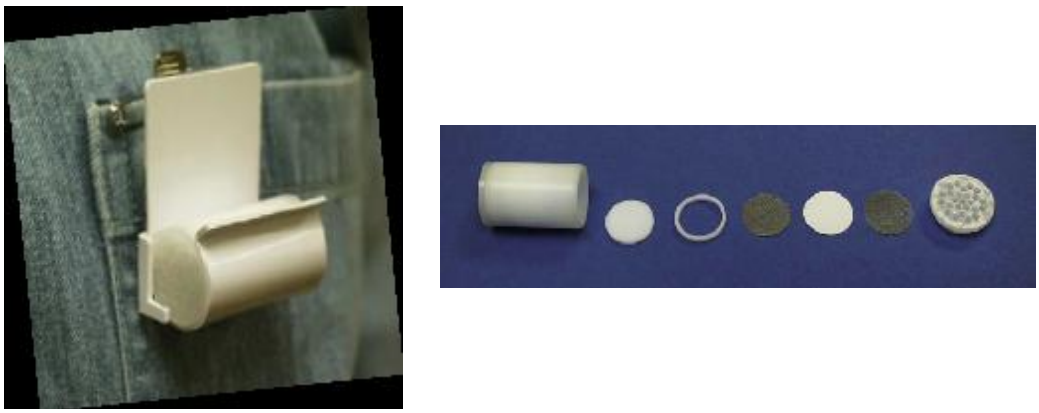


Figure 8: An Ogawa personal air sampler ***[51]***

There could be potential for error in personal monitoring resulting from differences in the handling of the monitors; for example, differences in the container they are kept in, the length of time between exposure and analysis, how they are handled by researchers/participants or where they are located in the breathing zone [51]. Personal monitors provide a single mean reading for the whole exposure period and thus cannot capture and identify the peaks and troughs of air pollution that an individual may experience. There is also a strong possibility of external factors such as meteorological interference and it is not possible to elucidate source allocation information [52] [53]. However, these are not distinctly different from drawbacks of stationary monitors; hence the general view is that if properly implemented, personal sampling is superior to indirect methods.

1.4.2 Micro-environmental models

Micro-environmental models provide an indirect method which can incorporate indoor and outdoor exposures. The term 'microenvironments' refers to the different locations in which an individual resides, within which, a homogenous pollutant concentration is assumed [42]. Studies have shown that people from industrialized countries spend around 80% of their time indoors [54] and this is likely to be higher for women during pregnancy, particularly in the later stages [55]. Most of the indirect exposure estimation techniques described have two main limitations: (1) Only outdoor concentrations can be estimated and (2) Pollution estimates are generally assigned to individuals based on their recorded place of residence only. The micro-environmental model has the benefit of estimating exposures in the indoor and outdoor environment and not being limited to exposure estimates at the residence location only. The model can take account of time-activity patterns as well as spatio-temporal variations in pollution between the separate micro-

environments. Although this has been found to perform well as a pollution estimation technique [45], micro-environmental models are rarely used in epidemiological studies [56] [57].

1.4.3 Proximity based measurements

Proximity based measurements utilize individual data on location (usually postal code) to obtain a pollutant concentration from the nearest stationary fixed site monitor. This technique is thought of as a more traditional method used more regularly before increasingly complex interpolation techniques had been developed; however, in the past decade they have still been utilised in epidemiological studies [58] [59]. Stationary monitors were first set up as an automatic monitoring network in the UK in 1987 to assess compliance with the new European Commission directive limits on air quality. By 1998, all the monitors that had been set in place in the urban and rural networks were combined to form the Automatic Urban and Rural Network (AURN) which now consists of 127 sites across the UK [7]. The main stationary air monitors in NW England are mapped in Figure 9. The main objectives of the AURN are to: check that air quality standards are met, inform the public about air quality, provide information for air quality reviews, identify long-term trends in air pollution concentrations and assess the effectiveness of intervention strategies [7].

The stationary monitor site types are often described based on their location:

- Urban (U): Areas of built up streets with buildings of at least two floors. Measured air quality is usually deemed representative of <10 km².
- Suburban (S): Mostly a built up area but with non-urbanised areas as well. Measured air quality is usually deemed representative of >10 km².

- Rural (R): Monitoring sites targeted at the protection of the ecosystem. Sites are located >5km away from built up areas. Measured air quality is usually deemed representative of around 1000 km².

- Traffic station (T): Monitor that measures air pollution levels largely from nearby traffic emissions. Sites are deemed representative of street segments of at least 100m.

- Industrial station (I): Monitor located to capture pollution predominantly from industrial areas. Measured air quality is usually deemed representative of an area at least 250m x 250m.

- Background (B): Monitor located in an area that captures integrated emissions and is not influenced predominantly by a single source. Generally, these sites are deemed representative of several km².

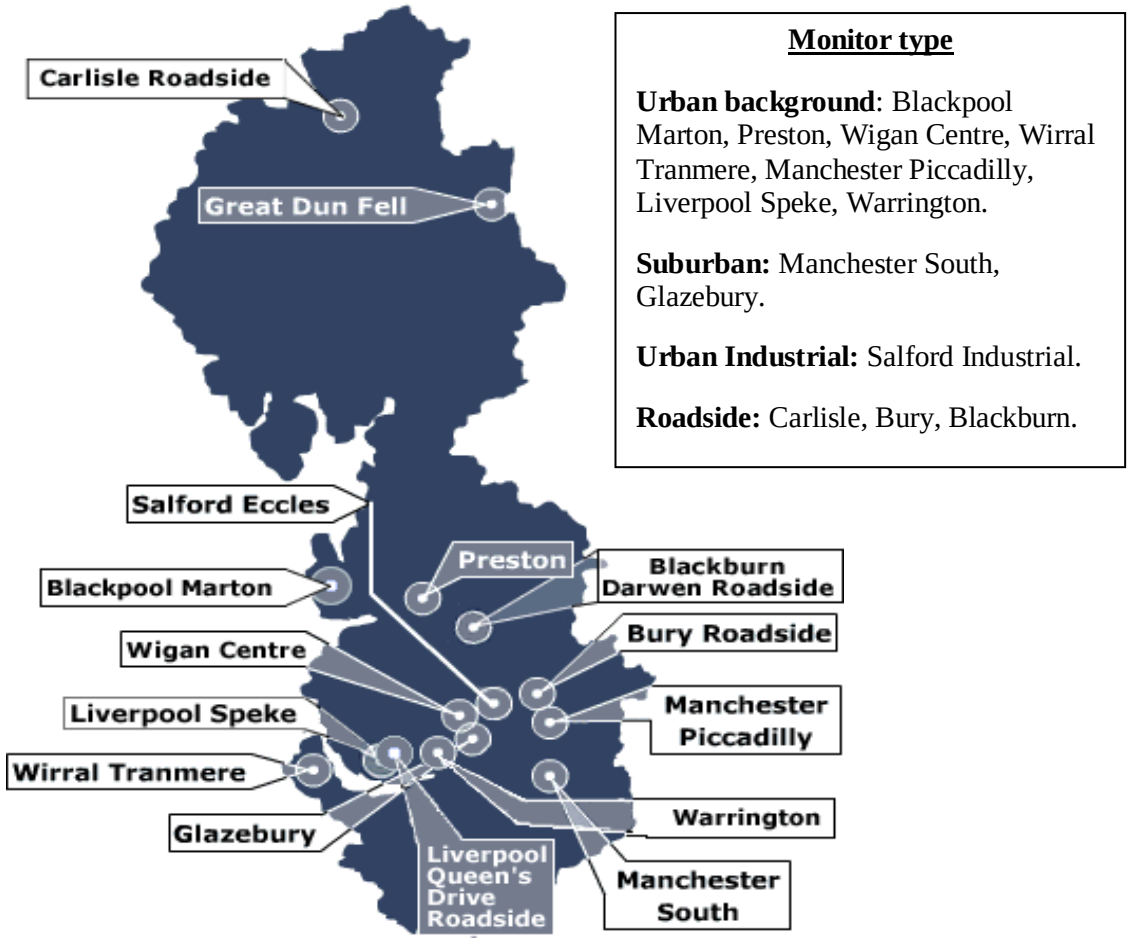


Figure 9: Map of the stationary monitors with publicly available data in North West England [7].

The main advantage of proximity based measurements is the relative simplicity compared to many other estimation techniques in terms of data collection/ extraction and implementation. For the nearest stationary monitor technique, easting (X) and northing (Y) co-ordinates of the postcode locations are mapped and linked to the nearest monitor site where the pollution concentration data can be extracted from. Often studies employ distance restrictions to determine the nearest stationary monitor within a certain radius, assuming that exposure within the radius is comparable to that at the

participants' location, and only those subjects that fall within the specified area are included in the analysis. Buffer zones of around 10km are commonly used [60 61]. Figure 10 presents an example map of 5 and 10km buffer zones being used around stationary monitor sites in NW England.

The nearest stationary monitor technique benefits from strong temporal resolution (24 hour mean) and validated concentration data by the Department for Environment, Food and Rural Affairs (DEFRA) and the Atomic energy authority (AEA) for a range of pollutants (including NO_x, NO, NO_2, SO_2, PM_{10}, $PM_{2.5}$, CO and O_3). The main disadvantage of the nearest stationary monitor technique is the lack of spatial resolution; the technique is unable to capture spatial heterogeneity for individual pollutants. There are a limited number of monitors and a disproportionately higher number in urban compared to rural areas, largely as a result of stationary monitors being set up in high exposure areas for air quality data purposes. This technique works under the assumption that everyone residing within close proximity to a particular stationary monitor is similarly exposed; it is well known that air pollution does not disperse in such a homogeneous manner, thus potentially introducing substantial exposure measurement error. Pollution decay from sources such as roads will differ depending on the pollutant in question and the meteorological conditions. A study from Canada investigating pollution decay from roadways found that NO and NO_x concentrations decreased faster (by 44% and 19% respectively) than NO_2 (3%) between 10-30m from the kerb side of a major road. The patterns of $PM_{2.5}$ were less consistent, with concentrations 39% higher 10m from the kerb side compared to 30m, but concentrations 60m from the kerb side were 22% higher than at 30m. These results suggest that NO and NO_x may provide a better marker for traffic related air pollution in close proximity to roads in comparison

with $PM_{2.5}$ and NO_2 [62]. PM_{10} has been found to have an increased spatial and temporal variation in comparison to $PM_{2.5}$, which has led to suggestions that PM_{10} concentrations largely originate from local traffic and $PM_{2.5}$ concentrations are largely of regionally and long-range transported origin [63].

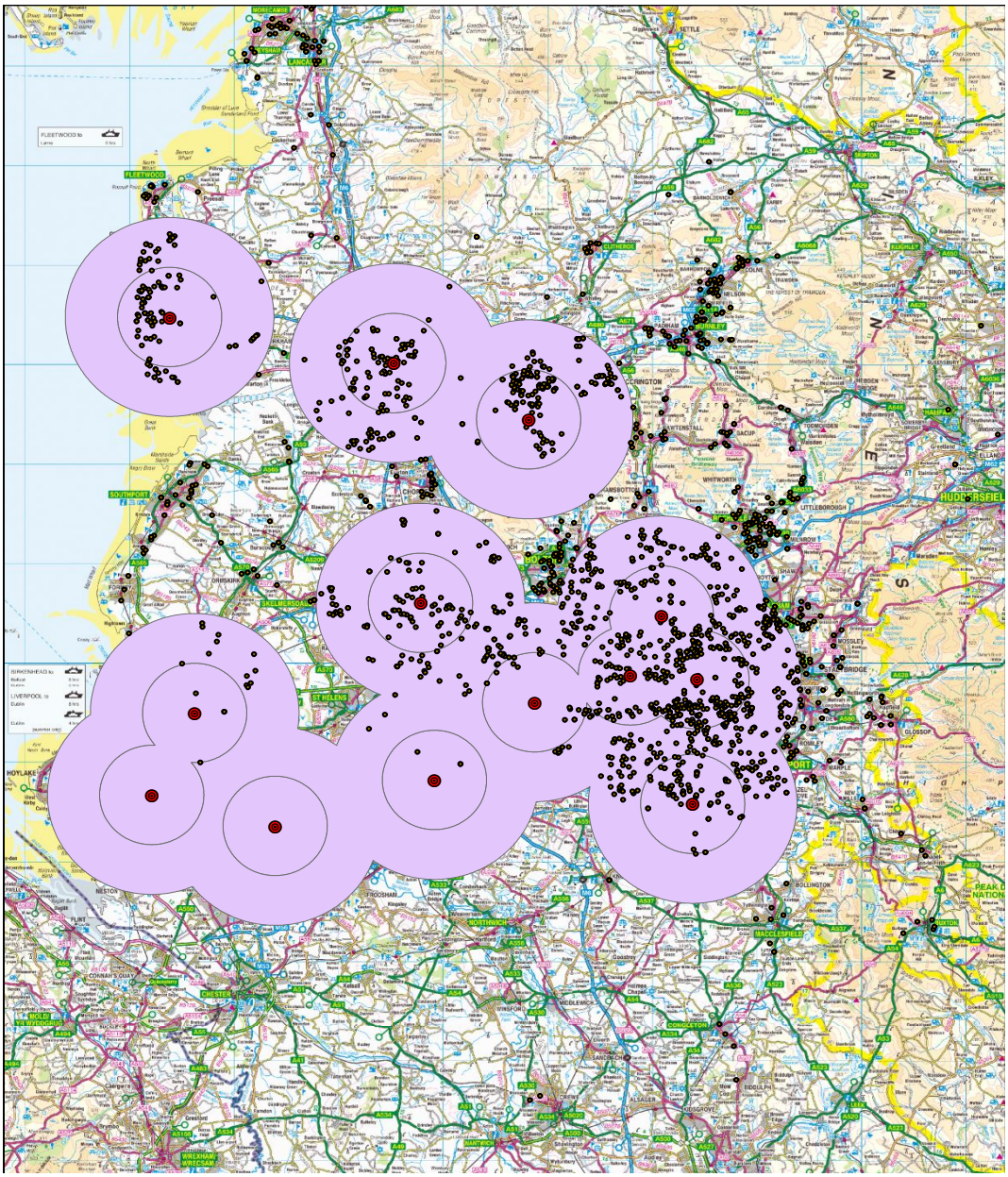


Figure 10: Example GIS map of a proximity based analyses using buffer zones around stationary monitors and postcode points.

1.4.4 Source based proxy measurements

Source based proxy measurements use nearest distance between a specific location (normally an individual's place of residence) and a point source (i.e. industrial complex etc.) or line source (i.e. roadway) as a proxy measure of air pollution. Figure 11 presents an example map of the major road networks in the UK along with residential points; the distance between the residential location and the nearest road can be calculated using the geographic software ArcGIS. Major road networks have a significant contribution to intra-urban distribution of air pollution (particularly the traffic related pollutants: CO, NO, NO_2, UFPs and larger PM) [64]. Air pollution concentrations surrounding major roadways are spatially and temporally heterogeneous; this is aptly demonstrated in the air pollution decay literature where an exponential decay from the road as a source has been identified [65 66].

The proximity to major road technique is a relatively new and infrequently used method compared to other estimation techniques. Studies using this technique in relation to pregnancy outcomes have only been published in the past decade [67-69]. In a validation study of long-term personal exposure to traffic related pollution, this technique was identified as a good way to predict air pollution exposure in epidemiological studies [70].

An advantage of the proximity to major road technique is that it provides a logical proxy for a mixture of traffic related air pollution. Complex interactions between the multitude of traffic related pollutants are likely to occur and the proxy technique provides an opportunity at a basic level to incorporate this. However, this can also be interpreted as a limitation due to the fact that individual pollutant effects cannot be investigated.

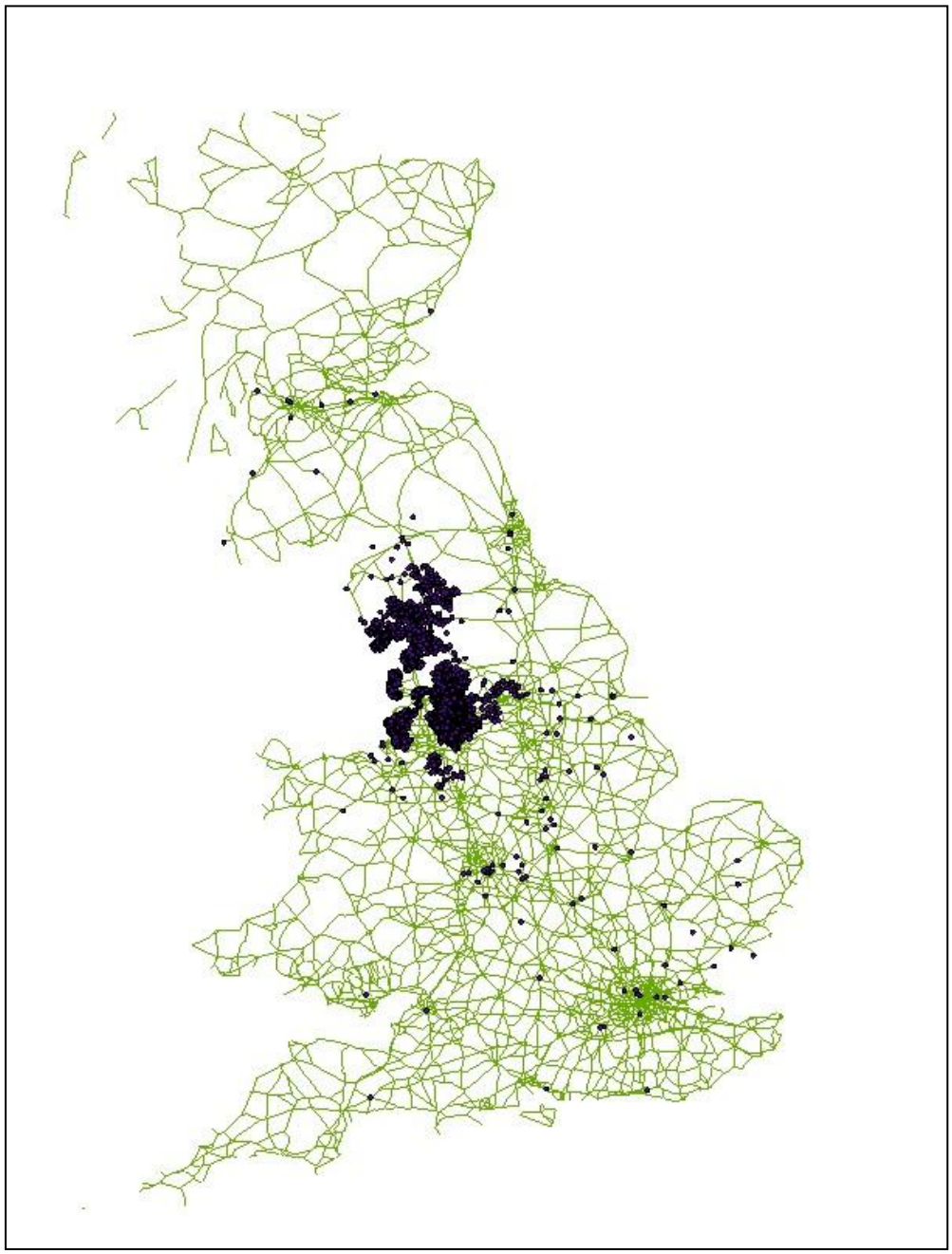


Figure 11: Example GIS map of UK road networks being linked to postcode points

1.4.5 Statistical interpolation techniques

Statistical interpolation techniques enable pollutant concentration estimates to be made in areas other than the area in which monitoring occurs. These techniques are based on the concept that points closer to each other have more similarities in pollutant concentrations than those further apart. The two main groups of interpolation techniques are deterministic and stochastic. Deterministic techniques create interpolated surfaces using measured points, generally based on the extent of similarity between nearby points. Stochastic techniques use information about the spatial structure of the measured data to predict the value at unsampled locations [71].

The most commonly used interpolation technique is the stochastic technique known as 'kriging' [41]. It provides an estimate at an unobserved location based on the weighted average of adjacent observed sites within a given area. The method incorporates the statistical properties of the measured points to quantify the spatial autocorrelation between points to determine estimated concentrations. A major advantage of this technique is its ability to calculate standard errors with each predicted value to quantify the degree of uncertainty at unmeasured sites [41]. ordinary kriging (OK) is the most basic and commonly used kriging technique; however, this technique does come with the disadvantage that is assumes spatially homogenous variation which could lead to estimation errors [41].

Inverse distance weighting (IDW) is a deterministic interpolation approach which is also commonly used for air pollution estimation. This technique works under the assumption that the similarities between neighbouring points are proportional to the distance between them. This technique does not, as the kriging technique does, take into

account spatial autocorrelation of points and also cannot produce error estimates for the predicted areas [71].

1.4.6 Air quality modelling techniques

Air quality modelling is an imperative part of evaluating air pollution concentrations to inform policy decisions relating to health effects, climate change and environmental damage. Modelling techniques enable the spatial and temporal variation of air pollution to be captured in a way that does not require the expensive implementation of a dense network of monitors. Pollution models have been developed by air quality government departments as a means of replacing stationary monitors whilst still complying with EU directives. There are a number of challenges in developing these models: they need to be suitable for a range of pollutants, incorporate hotspot areas (e.g. roads) and generate output for a country area at a spatial resolution of a few km² [72].

First, general modelling techniques that are regularly used in epidemiological studies of air pollution in relation to health effects are described. Following this is a description of a specific modelling technique which has been developed and made publicly available for research purposes by DEFRA and AEA Technology.

1.4.6.1 Dispersion modelling

Dispersion modelling uses mathematical functions to estimate pollutant concentrations based on the source, topography and meteorological conditions [73]. Data on emissions are usually obtained from locally managed stationary monitor sites. Emissions data are classified into two categories: stationary sources, such as pollution from the home and industries and second, mobile sources mostly from traffic emissions [41]. The dispersion model computes the pollution levels for the area and time period under study based on

the pollution, meteorological and emission data available. Air dispersion models are most commonly used for regulation purposes. However, validation of dispersion models have demonstrated that they perform well in explaining pollution concentrations at validation sites and can be a useful estimation technique in epidemiological studies [73 74].

A number of different dispersion models have been developed and applied to epidemiological studies investigating the effects of air pollution on health effects [75-78].

The main advantage of the dispersion modelling approach is the ability to incorporate spatial and temporal variation in air pollution estimation. The topography and meteorological conditions that account for a substantial amount of the intra-urban variability of air pollution can be taken account of in a dispersion model, thus making dispersion models an attractive option for the analysis of ambient air pollution in terms of health effects. The disadvantages, however, are that they are very data intensive and require a high level of Geographic Information Systems (GIS) expertise. There is also the potential for uncertainty in the estimates if assumptions about dispersion are incorrect, for example, due to unexpected air turbulence [41].

1.4.6.2 Land use regression modelling

Land use regression modelling (LUR) is a relatively new technique that has been developed in an attempt to increase the fine spatial resolution of exposure estimates by capturing the small-scale variations of air pollution using site-specific variables (e.g. proximity to roadways and area land use). The small scale urban air pollution variations are now well documented and it has been suggested that in some locations, the within-city spatial contrasts may be as large as the between-city contrast [79]. The first application of an LUR model in an epidemiological context was in the SAVIAH (Small

Area Variations in Air quality and Health) study [80]. Since 1997, LUR models have been developed in urban areas throughout the world [81 82] and have begun to incorporate increasingly sophisticated temporal adjustments [83-85].

LUR models use measured pollutant concentrations from a sampling campaign at multiple sites in a given area. A multivariate linear regression analysis is performed; the measured values from the sampling campaign are used as the dependent variable, while the independent variables are geographical variables such as land use (e.g. agricultural, industrial or residential), traffic and topography. Pollution concentrations can then be predicted for any location within the study area using parameter estimates derived from the model [41 86]. The main advantage of using LUR models in epidemiological studies is the ability to estimate exposures for large populations. Once the model has been developed for an area it can be applied to any number of locations within it, with no further costs incurred for greater sample sizes. The disadvantages of LUR models are that they are very data intensive and once developed the same model cannot be used for another study area. The models are data driven i.e. the predictor variables and buffers are determined by the data from the specific area under study, thus it is difficult to externally validate individual models. Limitations concerning spatial variation in areas away from major highways and poor correlations with measured data have also been raised in the literature [37 41]. The performance of the LUR model is largely dependent on the ability of the initial sampling campaign to adequately capture the local air pollution patterns [87].

1.4.6.3 Hybrid models

With the development of GIS technology, hybrid techniques have been developed which involve a combination of techniques in an attempt to more accurately capture spatial and temporal variation of air pollution across large areas and time periods [41]. Hybrid models are not commonly implemented in epidemiological studies, largely due to the complexities involved in combining techniques. However, recently hybrid techniques have been shown to be an effective tool in improving exposure data in epidemiological studies. For example, a recent study [88] demonstrated the benefits of using an existing dataset from a dispersion model in combination with an LUR technique data to complement each other in providing retrospective air pollution estimates.

1.4.6.4 DEFRA modelling techniques

Specific modelling techniques have been developed in the UK by DEFRA and the devolved administrations to meet some of the demands that have been made by recent EU regulations on air quality in the UK [89]. Six main models have been developed and independently reviewed by an expert panel [72], these include:

- ***The pollution Climate Mapping model* (PCM)**: A model designed to estimate exposures to report on pollution concentrations to comply with the UK's EU Directive (2008/50/EC). A model has been developed for each of the pollutants NO_x, NO_2, PM_{10}, $PM_{2.5}$, SO_2, CO, benzene and ozone, the model provides 1x1km grids of background concentrations with around 9000 road side values.

- *The community Multi-scale Air Quality Modelling System* (CMAQ): A model used to calculate daily air quality forecasts. The model outputs are 50x50km resolution over Europe, with 10x10km for the UK.
- *The Fine Resolution Atmospheric Multi-pollutant Exchange (FRAME)*: A statistical trajectory model which calculates annual averages of SO_x, NO_x and NH_x wet and dry deposition at a 5x5km resolution. FRAME is also used as a means of rapid calculation of emissions in the case of urgent policy concerns.
- *The European Monitoring and Evaluation Program Unified Model for the UK* (EMEP4UK): This model uses a UK grid of 5x5km and provides assessments of critical load exceedences.
- *Ozone Source Receptor Model* (OSRM): This model produces hourly concentrations of O_3, NO, and NO_2 on a 10x10km UK grid. The purpose of this model is to provide information on changes to precursor emissions to any proposed policies relating to O_3.
- *The UK integrated assessment model* (UKIAM): Imperial College London have developed the UKIAM model with funding support from DEFRA. The model uses information on projected UK emissions of NO_2, NO_x, NH_3, CO_2, N_2O, CH_4, PM_{10} and $PM_{2.5}$ to explore cost effective strategies to reduce emissions in the UK to ensure compliance with EU air quality regulations.

The **PCM model** developed by DEFRA was utilised as the basis for the primary exposure estimation technique in this thesis (Chapter 6) because it was the most appropriate model which included ambient background concentration estimates of the pollutants of interest in terms of potential health effects at a fine spatial resolution. It

was used in combination with temporal adjustments from nearest stationary monitors (as described in Chapter 2 and 6).

PCM model output is publicly available and provides annual estimates for the whole of the UK at a fine resolution for the pollutants that have been linked to adverse health outcomes (NO_x, NO_2, PM_{10} , $PM_{2.5}$, SO_2, CO) [90]. An example of the type of map the PCM model data can produce in the software used for the geospatial analysis in this thesis- ArcGIS- is demonstrated in Figure 12. The basis of this model is the 1x1 km 'background' concentration calculations. These are derived based on regional background levels using measured data with nearby area sources modeled using a dispersion kernel approach and concentrations from large point sources included in the model. An empirical approach is used for roadside concentrations at a distance of 4m from the roadside [91]. Finer temporal resolution than the annual mean concentrations that are provided by the model can be obtained by temporally adjustments using stationary monitor measured data [92].

One of the advantages of the PCM model is that it has been developed in a modular form so it is capable of adapting and incorporating new techniques as they develop to improve the model. It is also capable of providing future emission projections which can aid in better predicting how well future regulations will be met [72].

The main weakness of this technique is that the model output estimates are only as good as the emission estimates. Although true for most models, this is particularly pertinent for the PCM model as roadside concentrations are calculated based on the empirical relationship between measured levels and emission estimates at the specific road. Modeled PM_{10} concentrations for example, could be underestimated as resuspended material is not included in the inventories which the measurements are calibrated by [72].

An independent review of air quality modelling in DEFRA published in 2011 by the 'Air Quality Modelling Review Steering Group' found that this model performed well in independent intercomparison tests and concluded that it was "suitable for further development and use by DEFRA" [72]. It has also been recommended for use in future epidemiological studies [92].

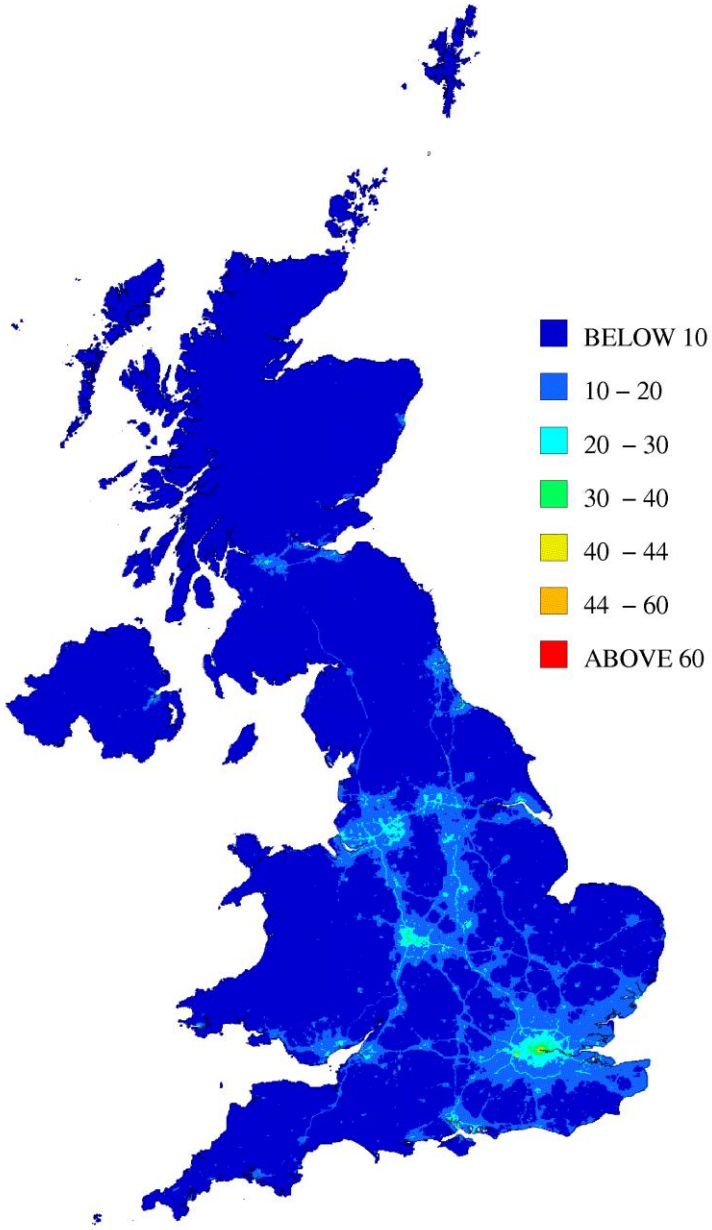


Figure 12: Example GIS map by DEFRA using the PCM model to map UK annual mean background NO_2 concentrations in 2010 (µg/m³) [93].

1.5 Adverse perinatal outcomes

This chapter introduces the definitions, aetiology and epidemiology of the adverse perinatal outcomes low birth weight, small for gestational age, intrauterine growth restriction, preterm birth and perinatal mortality.

Adverse perinatal outcomes have significant implications for families, the infant and the health care system. There is a substantial economic burden in terms of immediate NHS costs for additional neonatal care and long-term costs for the often inevitably more complex health care requirements [94 95].

An adverse perinatal outcome can include an infant who is born too small (low birth weight, small for gestational age or growth restricted) or too early (preterm). In the most serious of cases, the infant may not survive (perinatal mortality). Perinatal outcomes are important markers of future health. The link between abnormal growth *in utero* and subsequent long term health risks is well known as 'The Barker Hypothesis'. The theory, developed primarily by D.J. Barker in 1997 [96], proposed that low birth weight caused by intrauterine malnutrition predisposes individuals to long term health problems such as diabetes, stroke and coronary heart disease. In recent years, Barker's hypothesis has been demonstrated by other researchers showing increased cardiovascular risk in adulthood in relation to problematic birth outcomes, with links also found to diabetes and hypertension [97]. Follow up studies of individuals who experienced an adverse perinatal outcome have also demonstrated links with slower cognitive development and behavioural problems in childhood [98 99].

As shown in Figure 13 (adapted from Miranda et al 2009 [100]), an adverse perinatal outcome is a result of the fetus' inability to thrive based on the complex relationship

between social, genetic and environmental factors. Each of these domains will contribute to a varying degree in individuals. The space within the triangle represents the area in which the mother-child pair can prosper; this area is larger for women with fewer social and environmental stressors and more protective host factors and vice versa. Over the past decade there has been increasing recognition of the impact that environmental factors, such as air pollution, could have during pregnancy and on the resultant outcomes [101].

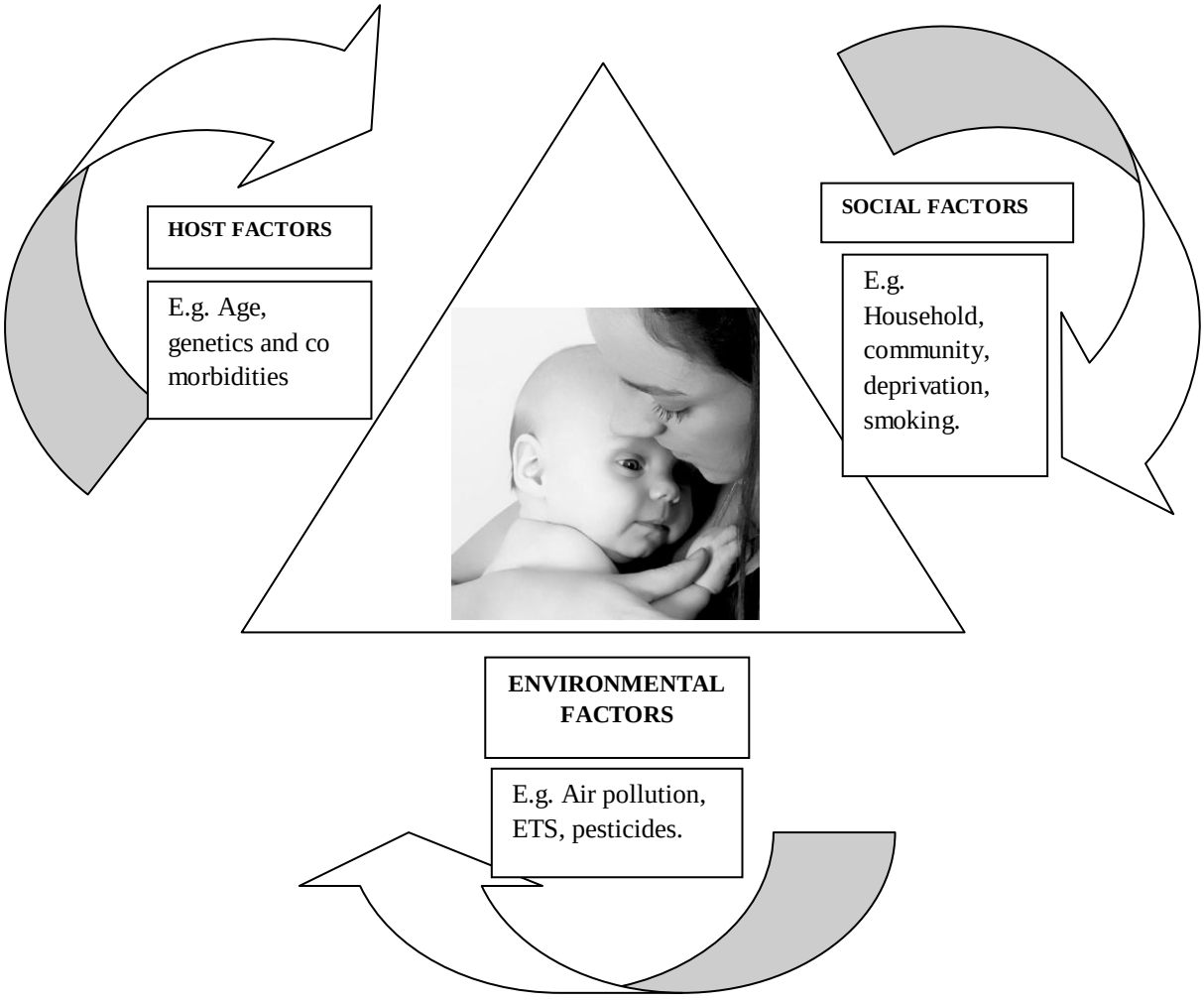


Figure 13: Forces shaping pregnancy outcomes, adapted from Miranda et al. [100].

This section outlines the definitions, aetiologies and epidemiology of each of the main adverse perinatal outcomes investigated in this thesis: Low birth weight, small for gestational age, intrauterine growth restriction, preterm birth and perinatal mortality. Perinatal mortality is discussed in this section due it being the most severe of the adverse perinatal outcomes, however, it is not included as an outcome in this thesis due to the lack of reliable data available. Congenital anomalies/malformations are not described here nor are included in any analyses in this thesis. This is due to the complex and numerous possible anomalies that could be investigated individually (and thus requiring detailed extensive data sources), the paucity of existing studies in this area and the studies which do exist have limited suggestion of an association with air pollution [102].

1.5.1 Low birth weight

The World Health Organisation (WHO) give the definition for low birth weight (LBW) as '1000-2499g' and very low birth weight (VLBW) as '999g or less' [103]. The LBW cut off of 2500g is based on epidemiological evidence that a baby born below this weight is 20 times more likely to die at birth [103].

LBW is either due to a preterm delivery or restricted intrauterine growth. A number of factors relating to the fetus, the mother and the environment can affect the length of gestation and fetal growth, consequently influencing birth weight. In terms of the fetus: first born infants are normally lighter than subsequent infants, twins weigh less than singletons and at a corresponding gestational age males weigh more than females [103]. In terms of the mother, the birth weight of her infant is strongly determined by her own body composition and diet during pregnancy [104 105]. Mothers who are younger, shorter and those who live at altitude or in more deprived socio-economic areas all tend to have

smaller babies [103] [106]. Working, particularly in standing jobs in the later stages of pregnancy, can also have a detrimental effect decreasing birth weight [107], as well as stress during pregnancy [108]. Lifestyle factors such as alcohol consumption, tobacco smoking and drug abuse have been found to have important implications for fetal development and subsequent outcomes [109] [110] . Maternal infections during pregnancy such as malaria, HIV or syphilis can also increase the risk of LBW [111].

LBW is rarely used to dictate a care pathway for a neonate in clinical practice within developed countries due to the crudeness of the measure. In developing countries where an accurate measure of gestational age (GA) is not always possible, it is often the only way to identify growth restricted or preterm infants requiring additional care in the neonatal period [103]. However, LBW is still a commonly used outcome measure in perinatal epidemiology studies [112] [113], although the measure is often used in conjunction with the outcome small for gestational age [78] [114]. In spite of the limitations due to the absolute cut off points, the validity and precision of the measure still makes it a logical option (this issue is described in more detail in Chapter 1.8.3). Birth weight is a very well recorded and a relatively consistent measure in the UK and in most developed countries. In developing countries, birth weight as a measure is less reliable; around 60% of births are not recorded (most of these occurring outside of hospital) and if the baby is weighed at delivery the weight is not always performed correctly, or recorded and reported accurately [103].

Worldwide, 20 million infants (15.5%) are born with LBW. In developing countries the proportion is more than double (16.5%) that in developed countries (7%). The highest percentage of LBW is in South-Central Asia (27%), although the percentage in most countries is somewhere between 10% and 20%. Of all the regions of the world, Europe

has the lowest average at 6%. It is difficult to develop a clear picture of incidence trends of LBW due to the limited comparable data between countries. However, the WHO have attempted to synthesise the information and found very little change in LBW incidence since 1990 [103].

1.5.2 Small for gestational age

LBW was historically always used as a proxy measure for the health status of a new born baby. However, once better data on GA was collected, it was recognised that around half of babies born LBW were not premature and that these term LBW babies still had excess risk of mortality [115]. These findings initiated the introduction of the term 'small for gestational age' (SGA).

Most epidemiological studies use the outcome definition of SGA as an indication of fetal growth rather than LBW. This is due to concerns that LBW may not be a sufficient indicator; GA at delivery is the most important determinant of birth weight and without accounting for GA it is unknown if the infant is premature and actually the right size for its GA or if it is pathologically growth restricted. The term SGA refers to a fetus that has not achieved an estimated weight threshold at a given GA[116]. The commonly used threshold for SGA is the 10^{th} centile of the population under study [60 117], however, other thresholds are also used to identify varying severity of SGA (e.g. 3^{rd}, 5^{th} centiles or 2.0 standard deviations below the population average) [116]. There are inherent variations between populations and for female and male babies, thus a definition of SGA which incorporates the population and sex into the calculation of the threshold enables the neonates' weight to be set in an appropriate context. SGA fetuses include those that have failed to achieve their growth potential (IUGR) as well as those who are

constitutionally small. The lower the centile cut off for defining SGA, the higher the likelihood of fetal growth restriction [116].

More recently, there have been concerns that SGA centiles based on birth weight in terms of only GA and fetal gender from a specific population may not be adequately differentiating between the growth restricted infants and the infants who are small because of other external factors e.g. ethnicity or maternal height and weight. Customised centiles have been developed so that maternal factors which are likely to influence the size of the infant- irrespective of a pathological reason- can be adjusted for [116]

A recent large scale international prospective pregnancy study which classified SGA infants using customised birth weight centiles identified a number of independent risk factors for SGA [116]: low maternal birth weight, low fruit intake pre-pregnancy, cigarette smoking, increasing maternal age, daily vigorous exercise, being a tertiary student (still attending university), head and abdominal circumference less that the 10th centile and increasing uterine artery Doppler indices at the 20-week scan.

1.5.3 Intrauterine growth restriction

Intrauterine growth restriction (IUGR) is an obstetric term used to describe a fetus that has failed to reach its genetically determined growth potential. The definition is often used interchangeably with the definition for SGA (weight below the 10th centile for their GA), frequently used by epidemiologists to quantify the condition more simplistically when ultrasound scan data are unavailable [116]. The problem in doing so is that although a fetus may be SGA because of IUGR, the fetus could be constitutionally small (e.g. appropriately small due to their ethnic background) rather than pathologically small.

The same is true that a new born may be growth restricted or preterm without being defined as LBW. Around 50-70% of SGA fetuses are constitutionally small, with appropriate weight for maternal size and ethnicity [116]. IUGR increases the risk of mortality and morbidity beyond what is predicted by their gestation [116]. This distinction is best made through the use of multiple growth scans during pregnancy using population-specific weight and GA percentile charts which take account of parental anthropometrics, often referred to as customised growth charts [116].

The causes of IUGR are similar to those of SGA and LBW and can be grouped into aetiologies relating to the fetus, the mother and environmental factors. In terms of the fetus: fetal malformations, chromosomal abnormalities, intrauterine infection (e.g. toxoplasmosis and cytomegalovirus), placenta praevia and chronic placental insufficiency [116] [118]. Maternal factors include: extremes of maternal age, artificial reproductive therapy, short pregnancy interval, multiple pregnancy, diabetes, renal disease, hypertension (previously diagnosed or pregnancy induced), pre-eclampsia, thrombophilias and maternal uterine malformations. In addition, environmental and social factors similar to most adverse perinatal outcomes: poor nutrition, smoking, alcohol consumption, drug use, residing at high altitude and low socioeconomic status [116] [118].

There is still no effective treatment for the condition of IUGR, however, better surveillance techniques during pregnancy have helped in the challenging decision process obstetricians face in managing the condition in terms of timing and mode of delivery to optimise the fetal outcome [116].

1.5.4 Preterm birth

Preterm birth (PTB) is defined as 'less than 37 completed weeks of gestation or fewer than 259 days since the first day of a woman's last menstrual period'. This is sub-categorised as extremely preterm (<28 weeks), very preterm (<32 weeks) and moderate to late preterm (32 to <37 weeks) [119]. PTB rates are increasing in almost all countries and prematurity is the leading cause of newborn death with over one million children dying each year due to complications associated with PTB [119]. The urgent need for research into underlying mechanisms of PTB has been stressed to achieve the WHO target of reducing PTB rates by 5% by 2015 [120].

Of those that are born preterm and survive, many will face short and long term health implications. In the short term, PTB has been shown to be a risk factor for at least 50% of neonatal deaths [120] and PTB has been linked to visual and hearing problems as well as learning disabilities [121]. In the long term, evidence has shown that those born preterm are at an increased risk of conditions such as type 2 diabetes and cardiovascular disease [122].

The WHO estimates global rates of PTB at 11.1% (around 15 million) annually. Although the highest rates occur in low-income (11.3%) compared to the high-income (9.3%) countries, the difference is relatively small making this a global health problem [119]. In almost all countries, an increase in PTB rates has been reported between 1990 and 2010 [119]. This increase should not necessarily be interpreted negatively only, since this is to a large extent due to obstetric intervention in an attempt to reduce the risk of more serious perinatal or maternal morbidities or mortality [123].

PTB is a syndrome with a multi factorial aetiology which can be spontaneous (occurring naturally) or iatrogenic (provider-initiated through induction or elective Caesarean section). The main risk factors for spontaneous PTB are: young and old maternal age, short pregnancy spacing, multiple pregnancies, infection (urinary tract infections, malaria, HIV, Syphilis, bacterial vaginosis), underlying maternal chronic medical conditions (diabetes, hypertension, anaemia, asthma, thyroid disease), nutrition (under nutrition, obesity, micronutrient deficiencies), lifestyle (e.g. smoking, alcohol consumption and excess physical activity), maternal psychological health (e.g. depression) and genetic factors (e.g. family history of cervical incompetence) [119]. The risk factors for different severities of PTB have been found to be similar [124]. A European case control study found differences in the risk factors of SGA and non SGA preterm births; stronger associations with SGA preterm births were found for social factors including high maternal age, smoking and low/high maternal BMI, while other factors were found to have similar effects regardless of birth weight: obstetric history, maternal education and marital status [125].

1.5.5 Perinatal mortality

Mortality surrounding pregnancy and infancy can be categorised in a number of ways: perinatal mortality, stillbirth, neonatal death, infant mortality, and post-neonatal mortality. The definition given for perinatal mortality by the WHO is ‘death in the first week of life including fetal death (Stillbirth).’ Neonatal death is defined as ‘death occurring during the first four weeks after birth’. Infant mortality is ‘death occurring in the first year of life’ and post neonatal mortality is the number of ‘deaths between 28 days and 1 year of life’ [126]. The trends in neonatal and infant deaths in developed countries demonstrate that rates are falling despite the increase in multiple births as a

result of advances in fertility treatments. The trends from developing countries are very unclear due to vital registration systems rarely recording and reporting early mortality data such as stillbirths [126]. Figure 14 presents the gradual decline in the rates of neonatal, infant and post-neonatal death rates in England and Wales between 2000 and 2011. There has been little change in the stillbirth rate [127].

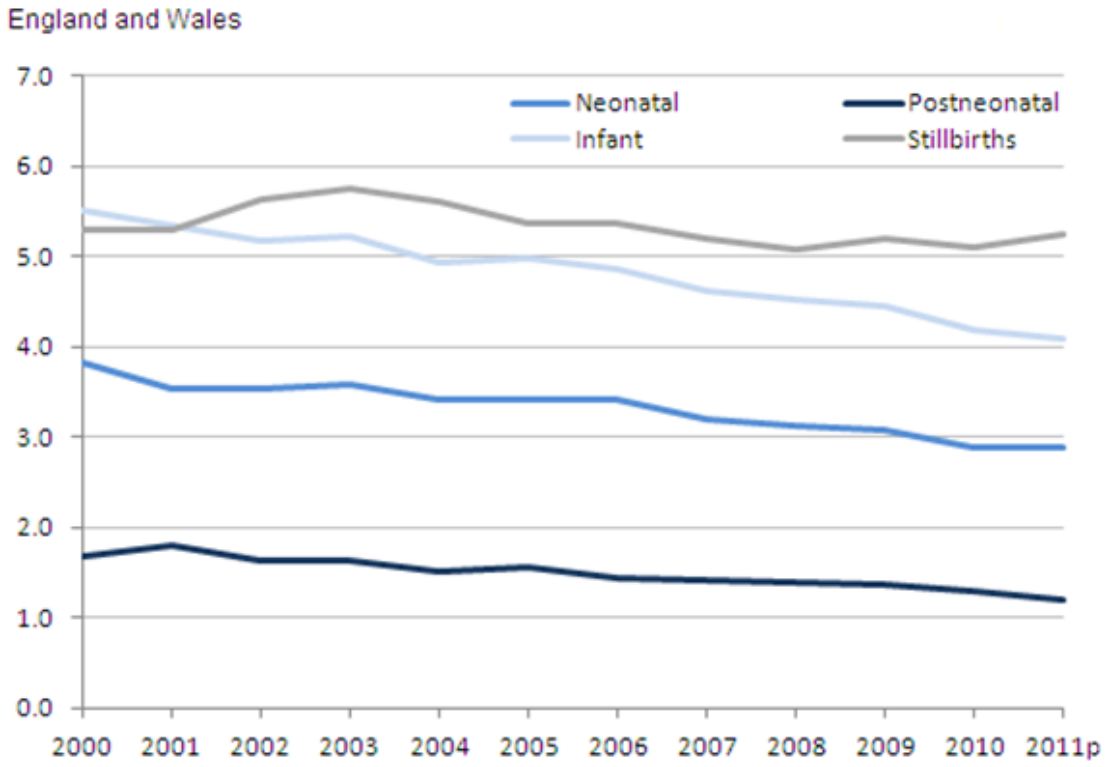


Figure 14: Stillbirths, neonatal, postneonatal and infant deaths, 2000-2011 ***[127]***

Note: Stillbirth deaths per 1,000 live births and stillbirths. Neonatal, postneonatal and infant deaths per 1,000 live births.

Mortality at this early stage can be as a result of inadequate care during pregnancy, inappropriate management of complications, poor maternal health, limitations in access to health care and poor newborn care [127]. Data collected by the Office for National Statistics (ONS) from 2011 (presented in Figure 15) show rates of perinatal mortality in

babies with mothers born in Africa (11.8/1000), the Middle East and Asia (4.7/1000) and the Americas and the Caribbean (8.0/1000) as higher than in the UK (7.1/1000 births). The UK rates of stillbirths, perinatal and infant mortality are all higher than the EU average.

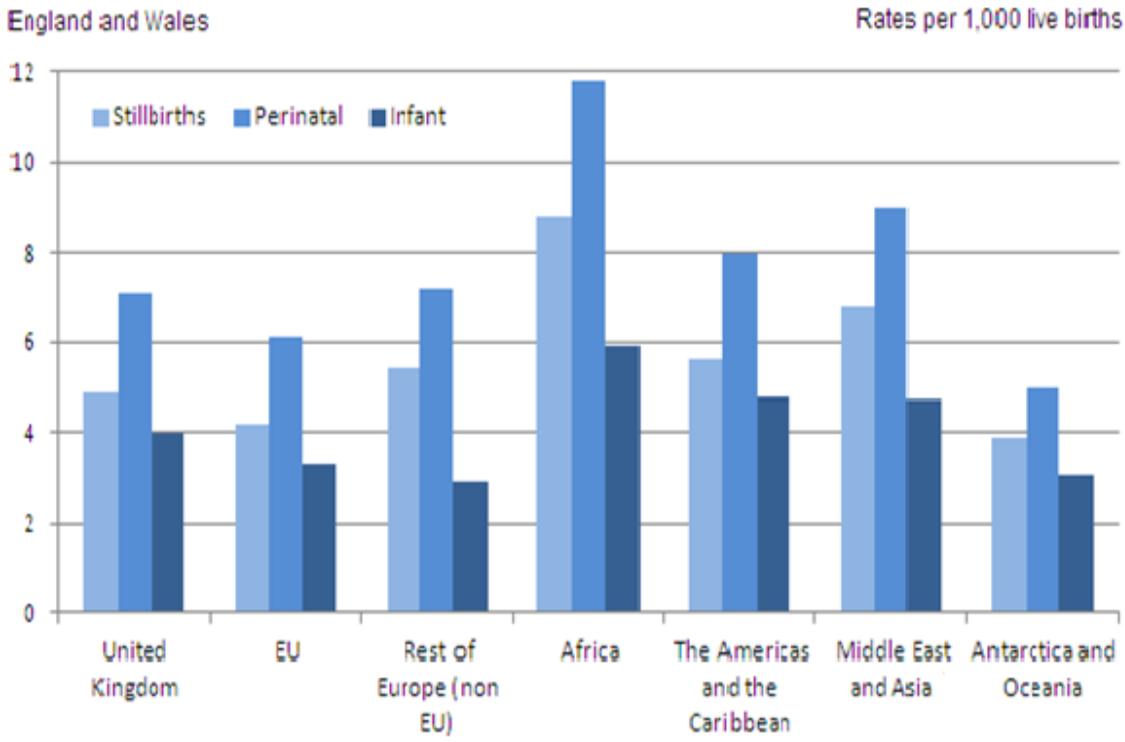


Figure 15: Stillbirths and infant deaths by mother's region of birth, 2011 [127]

Multiple pregnancies have long been identified as a strong risk factor for perinatal mortality; this can largely be explained by the lower birth weight distribution in twins, however, it has also been found that twin infants of normal birth weights have around a three times increased mortality risk than singletons [128]. Mortality rates in boys have also been reported as higher than for girls even after adjustment for gestational age and body size [129]. The main challenge of investigating mortality as a pregnancy outcome in epidemiological studies based on hospital audit data, even in developed countries, is the quality of the data. If the information is based solely on events recorded during the

initial hospital period immediately after birth- as most birth audit records in the UK are- then there maybe underreporting of perinatal and neonatal mortality because some deaths may occur post discharge from the maternity unit and consequently will not be recorded.

The next chapter (1.6) presents an overview of the literature relating to air pollution effects on preterm birth and fetal growth. In addition, the published literature reviews on the effects of air pollution on adverse perinatal outcomes and the methodological considerations for future research are outlined.

This chapter (1.6.1) is the submitted paper (at the time of thesis submission):

Kimberly Hannam, Roseanne McNamee, Raymond Agius, Philip Baker, Colin Sibley. 2013 'The effect of gaseous pollutants on preterm birth: A critical review of the literature' ***Paediatric and perinatal epidemiology***

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1.6 Evidence of air pollution effects on adverse perinatal outcomes

1.6.1 The effect of gaseous pollutants on preterm birth: A critical review of the literature.

1.6.1.1 Abstract

Background: Recent evidence suggests that there may be an association between ambient gaseous air pollutants and preterm birth (PTB). The heterogeneous nature of studies in this area makes synthesizing the evidence particularly challenging.

Objective: To investigate the association between gaseous air pollution and PTB by critically appraising the literature using a specifically designed quality assessment tool (QAT).

Methods: Worldwide observational studies up to January 2012 were identified using electronic databases. Risk of study bias was quantified using a specifically designed QAT assessing: selection bias, information bias (exposure and outcome), confounding, exposure assessment, missing data, statistical power and conflict of interest.

Results: A total of 24 studies met the eligibility criteria. A positive association with at least one gaseous pollutant was found in 18 of the studies- 10 of which were categorized as moderate risk of bias. The strongest evidence of an association with PTB was with nitrogen dioxide (NO_2) and traffic related pollutants (measured using the proxy of distance to major road).

Conclusions: There is some evidence of an association between gaseous air pollution, especially NO_2 and risk of PTB. A multidisciplinary approach should be taken to further knowledge on the biological mechanism and critical window of exposure in pregnancy.

1.6.1.2 Introduction

Effects of air pollution on health, particularly respiratory and cardiovascular morbidity in the young and old, have remained a consistently lively research area since the London Smog more than 50 years ago [4]. Worldwide, air pollution improvements have been observed, largely due to the help of strategic policy interventions; however, concerns remain over existing pollution levels in many areas [130 131]. In the last decade, a new research interest has emerged, namely the effects on pregnancy outcomes.

Pregnancy is a particularly vulnerable time for both mother and fetus to come into contact with toxic exposures. The strongest evidence for this is demonstrated in the extensive literature concerning smoking effects in pregnancy [132]. In addition to the physiological stress of pregnancy for the mother, other factors have been identified which could increase her susceptibility to air pollution exposure, namely, an increased alveolar ventilation rate due to the increased oxygen demands of the fetus and the decreasing oxygen binding capability of the mother [133]. Compounding this is a recently acknowledged unfortunate spatial coincidence, namely that women of an age most likely to reproduce (20-34yrs), as well as young children (1-9yrs) and babies (<1yr) tend to reside in the most polluted areas of the UK [134]. Further to this, those in the lowest socio-economic stratum - a demographic group known to be at increased risk of adverse birth outcomes- are also most likely to live where air pollution is at its highest [100 135].

Neonates born at less than 37 weeks gestation are defined as 'Preterm births' (PTB). This can be further subdivided according to gestational age: 'Extreme prematurity' at less than 28weeks (~5% of PTB), 'Severe prematurity' 28-31weeks (~15%), 'Moderate prematurity' 32-33weeks (~20%) and 'Near term' 34-36 weeks (~60-70%). Preterm

births are the leading cause of perinatal morbidity and mortality in developed countries [136]. The international PTB rate in industrialized countries now stands at 7-10% and an upward trend is reported in the US where the rate is at 9-12% [137]. The WHO has estimated that of all births worldwide in 2005, 9.6% (12.9 million) were born preterm [138]. 75% of neonatal complications are associated with PTB; including developmental delay, growth reduction, cerebral palsy and a range of respiratory and cardiovascular problems such as chronic lung disease, respiratory distress syndrome and patent ductus arteriosus [139]. Several causes of preterm birth have been identified: cervical incompetence, antepartum haemorrhage, intrauterine growth restriction, pregnancy associated hypertension, preterm rupture of membranes, multiple pregnancy and spontaneous preterm labour [140].

A number of reviews studying the effects of air pollution and perinatal outcome have been published between 2004 and 2010, many of which have included a limited review of the evidence on preterm birth [101 141-145]. The conclusions drawn from these reviews have been contradictory: several state that current evidence on air pollution effects on PTB are inconclusive, due to insufficient evidence or inconsistent study design and results [141 143], while other reviews have found evidence to infer effects on PTB as a result of air pollution, particularly sulphur dioxide and particulate matter [101 142]. Two recent reviews have focused solely on the pollutant group of particulate matter in relation to fetal health and perinatal outcome [141 144]. These reviews concluded that there was not convincing evidence of an association with PTB, LBW and SGA and if excess risks do exist, they are small. Particulate matter- particularly fine particulates- is the pollutant that has attracted most attention in recent literature. However, recent studies are still suggesting effects on adverse pregnancy outcomes from gaseous pollutants [117 137 146]. Gaseous pollutants, including nitrogen oxides (NO_x), nitrogen dioxide (NO_2),

sulphur dioxide (SO_2), carbon monoxide (CO) and ozone (O_3) remain at levels thought to be potentially harmful to human health [130].

The main objective of this review was to critically appraise the literature on gaseous pollutants and preterm birth with the use of a specifically developed quality assessment tool.

1.6.1.3 Methods

The review considered published observational studies worldwide up to January 2012 investigating the link between NO_x, NO_2, CO, O_3, SO_2 and proximity to major roads- as a proxy measure of traffic related pollutants- with PTB. Studies were only included if they were written in English and the full text was available. Conference abstracts were not included.

Search terms

Relevant literature was identified through searching Web of Knowledge, EMBASE and Pubmed. Search terms included "air pollution" OR "gaseous air pollution" OR "Carbon Monoxide" OR "CO" OR "Sulphur Dioxide" OR "SO_2" OR "Nitrogen Oxides" OR "NO_x" OR "Nitrogen Dioxide" OR "NO_2" OR "Ozone" OR "O_3" AND "Preterm delivery" OR "PTD" OR "Preterm birth" OR "PTB" OR "Premature".

Study quality assessment tool

A 'Quality assessment tool' (QAT) was designed specifically for this review so as to focus on quality issues most relevant to this type of research (see Table 3). Consensus statements have been published elsewhere for authors of reviews to aid a thorough assessment of research quality, including for randomized control trials (CONSORT) [147],

meta-analyses of observational studies (MOOSE) [148] and observational epidemiological studies (STROBE) [149]. However, the provision of a simple set of quality assessment items in epidemiology is difficult because of the number of possible designs (e.g. cohort, case-control, time-series) and often non-comparable measures of effect. Furthermore, unlike in meta-analyses of healthcare intervention studies where the intervention is well defined and easily measured, the intervention in observational studies is an 'exposure' which may not be easy to measure.

The QAT used in this review was developed specifically for studies investigating gaseous air pollution and PTB. The tool was initially based on a QAT by Shah et al. [101], designed to assess quality for all studies investigating the effects of air pollution on birth outcomes. That tool was further developed and improved to meet the specific objectives of this review by incorporating recommendations in the literature on optimal design of QATs, inclusion of aspects of quality believed by the authors to be most important in epidemiological studies and more detail on key aspects such as confounding (Table 3.1).

Recommendations that have recently been made for designing QATs include having a small number of key domains, being specific to the topic area and use of a simple checklist rather than a scale [150]. These were taken into account in the development process. The tool was then piloted by three of the authors. Feedback on the applicability and appropriateness of each category in practice led to further development. The final tool used incorporates aspects of quality that were believed to be most important in epidemiology studies investigating air pollution specifically in relation to PTB: selection bias, information bias (in exposure and outcome), confounding, exposure assessment, missing data, statistical analysis, statistical power and conflict of interests.

As confounding is a key issue in observational studies, a list of the most important potential confounders was agreed based on research into known risk factors for PTB [136]. The final list of high priority confounders included only PTB risk factors which have evidence to suggest a likely association with air pollution (Table 4). These are: maternal age, smoking, social class, ethnicity and birth year and month/season. Low priority confounders included: access to prenatal care, stress, parity and previous PTB. Factors thought to be risk factors, but not confounders included: diet, alcohol consumption, fetal sex, marital status and genetic factors.

Each of the studies was assessed using the QAT (Table 3) and were given a score based on their level of bias in each category: 'none' (0), 'Low' (1), 'Moderate' (2), 'High' (3). The results were then averaged and rounded to provide an overall category for the level of bias. The results are presented in Table 5.

Table 3: Quality assessment tool for study critique.

Quality assessment tool	None	Low	Moderate	High
1. Selection bias *Error due to systematic differences in characteristics between those who are selected for study and those who are not* [151]	-Sample selected is representative of the population. - If case-control selection used: Rationale is explained.	- A selected group studied (e.g. based on place of residence, ethnicity etc.) with clear eligibility criteria.	-Sample selection ambiguous, but sample may be representative. Eligibility criteria not explained. -Rationale for case-control selection not explained.	- Sample selection ambiguous and sample selection unlikely to be representative.
2.1 Information Bias-Exposure (Observational bias) *A flaw in measuring exposure that results in differential quality of information between compared groups* [151]	-Exposure assessed in an identical way, for all births, including PTB.		- Minor differences in exposure assessment methods between outcome groups.	- Substantial differences in measuring exposure between outcome groups.
2.2 Information Bias-Outcome *A flaw in measuring outcome that results in differential quality of information between exposure groups* [151]		-Assessment from birth certificate data or hospital based records. - Gestational age data consistently obtained from LMP.	-Gestational age data obtained from *both* LMP and scan data. -Gestational age data obtained *only* from scans.	-Preterm birth rates estimated from overall population data. - Assessment of GA from administrative database e.g. national register.
3.Confounding *The distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome* [151]	-Controlled for all confounders specified in the 'high' and 'low' priority confounder list (see Table 4).	-Controlled for confounders specified on the 'high' priority confounder list.		- Not all confounders on 'high' priority list controlled for.

4. Exposure Assessment	- Assessment method is based on personal sampling with extra individual information e.g. activity/GPS data, work location etc. -Mobility during pregnancy accounted for if appropriate.	-Assessment of exposure through interpolation techniques using national air quality databases e.g. LUR/DWTD or dispersion models *with* a temporal adjustment. - Proximity measurements to roads used as a proxy for personal exposure. -Pollution estimates assigned to individuals using temporally accurate stationary monitor data- case location within 10km of monitor.	-Pollution estimates assigned to subjects from nearest stationary monitor data (no distance limits set in place).	-County level air pollution estimates used.
5. Missing data	- No missing data from selected sample.	-Small amounts of missing data with explanation that satisfies that it is missing at random.	- Large quantities of missing data reported. -No explanation as to why the data is missing.	-Substantial missing data unlikely to be at random and consequently likely to exert a bias.
6. Statistical analysis	-Analyses and statistics appropriate to study type.			-Inappropriate analyses used.
7. Statistical power.	- Sample size calculation performed and implies adequate power.	-Sample size calculation not performed; all available eligible patients studied.	-Sample size calculated, but adequate sample size not used without adequate explanation.	-Sample size calculations not performed and small sample size included for analysis.
8. Conflict of interest	-Declaration of no conflict of interest. - Funding source stated is impartial as far as reviewer can tell.	- Declaration of no conflict of interest. -Funding source stated is unlikely to be impartial to the study question.	-A declaration of a conflict of interest is made. -No declaration stated.	-A conflict of interest has been declared. -Funding source stated is unlikely to be impartial to the study question.

Table 4: Confounding factors relating to section 3 in the quality assessment tool

High priority Confounders	**Low priority confounders**
Maternal age	Access to prenatal care
Smoking	Maternal Stress
Social Class	Parity
Ethnicity	Previous PTB
Birth year and month/ Season	

Table 5: Summary of quality assessment results

Study author and date	Selection bias	Information bias- Exposure.	Information bias- Outcome	Confounding	Exposure assessment	Missing data	Statistical Analysis	Statistical Power	Conflict of interest	Overall
1. Rudra et. al 2011	Low	None	High	Low	Low	Low	None	High	None	**Low**
2. Zhao et al. 2011	None	None	Low	High	High	Low	None	Low	None	**Low**
3. Yorifuji et al. 2011	Low	None	Low	High	Low	Low	None	Low	Moderate	**Moderate**
4. Malmqvist et al. 2011	None	None	Moderate	Low	Low	Low	None	Low	None	**Low**
5. Llop et al. 2010	Low	None	Moderate	Low	Low	High	None	High	None	**Low**
6. Gehring et al. 2010	Low	None	Moderate	High	Low	Low	None	High	Moderate	**Moderate**
7. Van den Hooven et al. 2009	None	None	Moderate	Low	Low	Low	None	High	None	**Low**
8. Wu et al. 2009	Low	None	Moderate	High	Low	Moderate	None	Low	None	**Moderate**
9. Darrow et al. 2009	Low	None	Low	High	Low	Low	None	Low	Moderate	**Moderate**
10. Brauer et al. 2008	None	None	High	Low	Low	Low	None	Low	None	**Low**
11. Gènerèux et al. 2008	None	None	High	High	Low	Low	None	Low	None	**Low**

Study author and date	Selection bias	Information bias- Exposure	Information bias- Outcome	Confounding	Exposure assessment	Missing data	Statistical Analysis	Statistical Power	Conflict of interest	Overall
12. Lee et al. 2007	None	None	Low	High	High	Low	None	Low	Moderate	**Moderate**
13. Ritz et al. 2007	Low	None	High	High	Moderate	Moderate	None	Low	None	**Moderate**
14. Huynh et al. 2006	None	None	High	High	Low	Moderate	None	Low	Moderate	**Moderate**
15. Leem et al. 2006	None	None	Moderate	High	Low	Low	None	Low	None	**Low**
16. Hansen et al. 2006	None	None	Low	High	High	Moderate	None	Low	Moderate	**Moderate**
17. Wilhelm & Ritz. 2005	Low	None	High	High	Low	Low	None	Low	None	**Moderate**
18. Sagiv et al. 2005	None	None	Low	High	Moderate	Low	None	Low	None	**Low**
19. Yang et al. 2003	Low	None	High	Low	Low	Low	None	High	Moderate	**Low**
20. Wilhelm & Ritz 2003	None	None	High	High	Low	Low	None	Low	Moderate	**Low**
21. Liu et al. 2003	None	None	Moderate	High	Moderate	Moderate	None	Low	High	**Moderate**
22. Maroziene et al. 2002	None	None	High	Low	Moderate	High	Low	High	None	**High**
23. Bobak, 2000	None	None	Low	High	Moderate	Moderate	None	Low	Moderate	**Moderate**
24. Ritz et al. 2000	Low	None	High	Low	Low	Low	None	Low	Moderate	**Moderate**

1.6.1.4 Results

The main findings and results from the 24 studies investigating gaseous air pollution and PTB are presented in tables 6 to 10. The study characteristics of the studies categorized as 'high quality' are detailed in Appendix 1 (Table A1).

Table 6: Results of studies investigating nitrogen oxides, nitric oxide and nitrogen dioxide (NO_x, NO, NO_2)

Author & Year	Time of exposure	Analysis comparison	Results OR/RR (95% CI)
Zhao *et al.* 2011 [137]	Entire pregnancy	Increase of 100µg/m³ in NO_2	ARR= 1.0542 (1.0080~1.1003)
Malmqvist *et al.* 2011 [152]	Entire pregnancy	NO_x exposure categories:	
		9.0-14.1 µg/m³	AOR=0.89 (0.81-0.97)
		14.2-22.6 µg/m³	AOR=0.87 (0.80-0.96)
		>22.7 µg/m³	AOR=0.85 (0.77-0.94)
Llop *et al.* 2010 [146]	Entire pregnancy	NO_2 >46.2 µg/m³	AOR=1.29 (1.13-1.46)
	1st trimester		AOR=0.96 (0.88-1.05)
	2nd trimester		AOR= 1.11 (1.03-1.21)
	3rd trimester		AOR= 1.10 (1.00-1.21)
Gehring *et al.* 2010[83]	Entire pregnancy	NO_2: IQR: 11.2 µg/m³	AOR=1.08 (0.80-1.47)
	1st trimester	IQR:14.4 µg/m³	AOR= 0.97 (0.73-1.27)
	Last month before birth	IQR: 13.7 µg/m³	AOR= 1.08 (0.86-1.36)
Wu *et al.* 2009 [75]	Entire pregnancy	5.65ppb increase of NO_x:	
		PTB	AOR=1.06 (1.03-1.09)
		Moderate PTB	AOR= 1.13 (1.09-1.18)
		Very PTB	AOR= 1.25 (1.17-1.33)
Darrow *et al.* 2009 [40]	1st month	Continuous NO_2	ARR=0.99 (0.98-1.01)
	6 weeks preceding birth		ARR= 1.00 (0.98-1.02)
	1 week preceding birth		ARR= 1.00 (0.98-1.01)
Brauer *et al.* 2008 [60]	Entire pregnancy (<30 weeks)	10µg/m³ increase of NO	
		IDW	AOR= 1.26 (1.08-1.47)
		LUR	AOR= 1.05 (0.94-1.18)
Brauer *et al.* 2008 [60]	Entire pregnancy (<30 weeks)	10µg/m³ increase of NO_2	

Author & Year	Time of exposure	Analysis comparison	Results OR/RR (95% CI)
		IDW LUR	AOR= 1.12 (0.89-1.40) AOR= 1.08 (0.91-1.29).
Ritz *et al.* 2007 [153]	1st trimester	>3.54pphm of NO_2	AOR=1.09 (1.00-1.19)
Leem *et al.* 2006 [154]	1st trimester 3rd trimester	NO_2 29.68-43.11 µg/m³ NO_2 29.68-43.11 µg/m³	ARR=1.13 (0.99-1.27) ARR=1.06 (0.93-1.20)
Hansen *et al.* 2006 [39]	1st trimester Last 90 days before birth	NO_2: IQR: 5.2ppb IQR: 4.5ppb	AOR=0.93 (0.78-1.12). AOR=1.03 (0.86-1.23).
Liu *et al.* 2003 [155]	1st month Last month	10 ppb increase in NO_2	AOR=1.01 (0.94-1.07)) AOR=0.94 (0.85-1.04)
Maroziene *et al.* 2002 [156]	1st trimester 2nd trimester 3rd trimester	NO_2 per 10 µg/m³ increase	AOR=1.67 (1.28-2.18) AOR=1.13 (0.90-1.40) AOR=1.19 (0.96-1.47)
Bobak, 2000 [157]	1st trimester 2nd trimester 3rd trimester	NO_x per 50 µg/mg³ increase	AOR=1.10 (1.00-1.21) AOR=1.08 (0.98-1.19) AOR=1.11 (1.00-1.23).
Ritz *et al.* 2000 [158]	1st month 6 weeks preceding birth		Results reported to be inconsistent and adjusted effects not presented

ARR= Adjusted relative risk; AOR= Adjusted odds ratio; IQR= Interquartile range; ppm= parts per million; ppb= Parts per billion; pphm= Parts per hundred million.

Table 7: Results of studies investigating carbon monoxide (CO)

Author & Year	Time of exposure	Analysis comparison	Results OR/RR (95% CI)
Rudra *et al*. 2011 [159]	Last 3 months of pregnancy	0.03-0.57 ppm	AOR=1.00
		0.58-0.79 ppm	AOR=0.99 (0.72-1.37)
		0.80-1.04 ppm	AOR=1.08 (0.77-1.53)
		1.05-3.77 ppm	AOR=0.88 (0.59-1.31)
		Per 0.1 ppm increase	AOR=0.97(0.93-1.01)
Darrow *et al.* 2009 [40]	1st month	Continuous	ARR=1.01 (0.99-1.04)
	6 weeks preceeding birth		ARR= 0.97 (0.94-1.01)
	1 week preceeding birth		ARR= 1.00 (0.98-1.02)
Brauer *et al.* 2008 [60]	Entire pregnancy (<30 weeks)	100 µg/m³ increase	AOR= 1.16 (1.01-1.33)
Ritz *et al.* 2007 [153]	1st trimester	>1.25 ppm vs. ≤0.58 ppm	AOR=1.25 (1.12-1.38)
	Last 6weeks		AOR=1.03 (0.93-1.14)
Huynh *et al.* 2006 [160]	Entire pregnancy (<36 weeks)	>0.96 ppm	AOR=1.02 (0.94-1.09)
	1st month of gestation	0.82-1.07 ppm	AOR=1.04 (0.97-1.11)
		>1.07 ppm	AOR=1.05 (0.96-1.14)
	Last two weeks of gestation	0.76-1.09 ppm	AOR=1.04 (0.97-1.12)
		>1.09 ppm	AOR=0.99 (0.91-1.08)
Leem *et al.* 2006 [154]	1st trimester	0.64-0.77 mg/m^3	ARR=0.92 (0.81-1.05).
	3rd trimester	0.64-0.77	ARR=1.07 (0.95-1.21).
Wilhelm & Ritz. 2005 [161]	Entire pregnancy	per 1ppm: <1 mile from monitor	ARR=1.21 (0.85-1.74)
		<2 mile	ARR=0.91 (0.76-1.10).
		<4 mile	ARR=1.01 (0.92-1.11)
Liu *et al.* 2003 [155]	1st month	1.0 ppm increase	AOR=0.95 (0.89-1.01)
	Last month		AOR=1.08 (1.01-1.15)
Ritz *et al.* 2000 [158]	1st month	3 ppm increase	ARR=1.05 (0.97-1.12)
	6 weeks preceeding birth		ARR=1.03 (0.96-1.11).

ARR= Adjusted relative risk; AOR= Adjusted odds ratio; ppm= Parts per million

Table 8: Results of studies investigating sulphur dioxide (SO_2)

Author & Year	Time of exposure	Analysis comparison	Results OR/RR (95% CI)
Zhao *et al.* 2011 [137]	Entire pregnancy	Increase of 100µg/m³	ARR=1.0388 (1.0096~1.3608)
Darrow *et al.* 2009 [40]	1st month 6 weeks preceding birth 1 week preceding birth	Continuous	ARR=0.97 (0.96-0.99) ARR= 0.99 (0.97-1.01) ARR= 0.99 (0.98-1.01)
Brauer *et al.* 2008 [60]	Entire pregnancy (<30 weeks)	1µg/m3 increase	AOR= 1.02 (0.96-1.09)
Leem *et al.* 2006 [154]	1st trimester 3rd trimester	17.62-22.74 µg/m³ 17.62-22.74 µg/m³	ARR=1.13 (0.99-1.28). ARR=0.87 (0.76-1.01).
Sagiv *et al.* 2005[162]	6 weeks preceding birth	per 15ppb increase	RR=1.06 (0.99-1.14).
Liu *et al.* 2003 [155]	1st month Last month	Per 5ppb increase	AOR=0.95 (0.88-1.03) AOR=1.09 (1.01-1.19)
Bobak, 2000 [157]	1st trimester 2nd trimester 3rd trimester	per 50 µg/mg³ increase	AOR=1.27 (1.16-1.39) AOR=1.25 (1.14-1.38) AOR=1.24 (1.13-1.36)

ARR= Adjusted relative risk; AOR= Adjusted odds ratio; ppb= Parts per billion.

Table 9: Results of studies investigating ozone (O_3)

Author & Year	Time of exposure	Analysis comparison	Results OR/RR (95% CI)
Darrow *et al.* 2009 [40]	1st month 6 weeks preceding birth 1 week preceding birth	Continuous	ARR=0.94 (0.83-1.05) ARR= 1.06 (0.91-1.24) ARR= 1.00 (0.94-1.08)
Lee *et al.* 2007 [163]		Effect of exposure on day of birth on daily PTB per 1000.	AOR=1.00 (1.00-1.01)
Ritz *et al.* 2007 [153]	1st trimester	>3.54pphm vs. ≤2.17pphm	AOR=0.93 (0.82-1.06)
Hansen *et al.* 2006 [39]	1st trimester Last 90 days before birth	IQR: 7.1 ppb 7.0 ppb	AOR=1.26 (1.10-1.45) AOR=1.06 (0.89-1.26)
Liu *et al.* 2003 [155]	1st month Last month	10ppb increase	AOR=0.98 (0.89-1.03) AOR=0.93 (0.86-1.00)
Ritz *et al.* 2000 [158]	1st month 6 weeks preceding birth		Results inconsistent and adjusted effects not presented

ARR= Adjusted relative risk; AOR= Adjusted odds ratio; IQR= Interquartile range; ppm= parts per million; ppb= Parts per billion; pphm= Parts per hundred million.

Table 10: Results of studies investigating proximity to major road/ traffic density

Author & Year	Time of exposure	Analysis comparison	Results OR/RR (95% CI)
Yorifuji *et al.* 2011 [164]	Residence at time of birth.	<200m vs. ≥200m: < 37 weeks <32 weeks <28 weeks	 AOR=1.5 (1.2-1.8) AOR=1.6 (1.1-2.4) AOR=1.8 (1.0-3.2)
Malmqvist *et al.* 2011 [152]	Residence at time of birth.	Traffic density (cars/min): <2 2 to 5 6 to 10 >10	 OR=1.01 (0.94-1.10) OR= 0.97 (0.88-1.06) OR=0.94(0.82-1.07) OR=0.88 (0.76-1.02)
Van den Hooven *et al.* 2009 [68]	Residence at time of birth.	DWTD: Highest vs. lowest quartile Prox to mjr road: 0-50m vs >200m	 OR= 1.18 (0.87-1.59) OR= 1.15 (0.84, 1.58)
Genereux *et al.* 2008 [165]	Residence at time of birth.	<200m vs. ≥200m	OR= 1.14 (1.02-1.27)
Yang *et al.* 2003 [166]	Residence at time of birth.	<500m vs >500m	AOR= 1.30 (1.03-1.65)
Wilhelm & Ritz 2003 [67]	Residence at time of birth.	DWTD: Highest quartile vs lowest quartile	AOR=1.08 (1.01-1.15)

ARR= Adjusted relative risk; AOR= Adjusted odds ratio; DWTD=Distance weighted traffic density.

Within the 24 studies included for review, NO_x were investigated in three studies, NO in one, NO_2 in 11, CO in nine, SO_2 in seven, O_3 in six and the traffic related pollution proxy of distance to major roads or distance weighted traffic density (DWTD) was investigated in six of the studies. The majority of the included studies used a cohort design (n=18), four were time-series and two case-control studies. Information on how gestational age was calculated was not included in 11 of the 24 studies, six reported to using only the 'last menstrual period' (LMP) technique to calculate GA and seven studies used both LMP and scan data to determine GA.

A positive association between PTB and at least one of the gaseous pollutants was found in 18 of the 24 studies. From the 24 studies, 11 were categorized as having a 'low' risk of bias (denoting a higher quality), 12 in the 'moderate' category and one as 'high' risk. Of the 11 low risk studies, eight had at least one positive association and three found no associations. Of the moderate risk studies, nine reported positive associations and three found no associations and the only high risk study reported a positive association.

Nitrogen oxides, nitric oxide and nitrogen dioxide (NO_x, NO, NO_2)

Three studies investigated NO_x [75 152 157]. The most recent 2011 study by Malmqvist et al. showed a statistically significant negative association (Highest quartile vs. lowest quartile adjusted OR=0.85; 95%CI=0.77-0.94). The study from Wu et al. presented positive associations between NO_x and an increased risk of PTB, particularly in very PTB cases (OR=1.25; 95%CI=1.17-1.33). The third study by Bobak (2000) found significant associations with NO_x and PTB risk in the 1st and 3rd trimester. The study to find negative associations [152] was categorized as having a low risk of bias and the two studies to report positive associations [75 157] were both categorized as having a moderate risk of bias.

The one study that explored NO effects [60] was classified as being of high quality (low risk of bias) and found mostly no associations with PTB, apart from slightly elevated ORs at <30weeks (OR= 1.26; 95% CI=1.08-1.47).

NO_2 was the most commonly investigated pollutant with 11 included studies [39 40 60 117 137 146 153-156 158]. NO_2 was also the pollutant with the most number of studies suggesting an association with increased risk to PTB. Of the 11 studies investigating NO_2, eight

demonstrated associations with increased PTB risk [39 60 117 137 146 153 154 156]. All of the low risk studies found positive associations [60 137 146 154], although in two studies these were not statistically significant [60 154]

Sulphur dioxide (SO_2)

Of the seven studies that explored the pollutant SO_2, four were categorized as high quality ('low' bias) [60 137 154 162] and three as moderate [40 155 157]. Of the four low risk studies, three found results suggestive of a positive association, but not significant [60 154 162] and one study found a significant association with SO_2 [137]. The only other study to find a significant positive association was the study by Liu et al. (2003), which was classified as a moderate risk of bias. This study found that associations were only present with pollution exposure in the last month before birth (OR=1.09; 95%CI= 1.01-1.19). The strongest associations were found in the study by Bobak (2000), which was classified as moderate quality, with increased risks of 20-30% per 50µg/mg³ increase in all three trimesters.

Ozone (O_3)

All six studies that investigated O_3 were classified as moderate risk. Four found no associations [40 153 155 163], one found an association with pollution exposure in the 1st trimester (OR=1.26; 95%CI=1.10-1.45) [39] and the study by Ritz et al. (2000) reported inconsistent results.

Carbon monoxide (CO)

Of the nine studies that investigated CO and risk of PTB, three studies were classified as low risk of bias. Of the low risk studies, one found a significant association [60] and two found very little evidence of an association between CO and PTB risk [154 159].

Of the six studies classified as moderate risk, four found results that were at least suggestive of positive associations [153 155 158 161] and of these, two found statistically significant associations [153 155].

Proximity to major road/ traffic density

The method of 'proximity to major road' as a proxy for traffic related air pollutants was used in six studies [67 68 152 164-166]. The exposure assessment in these studies was performed either by calculating the linear distance from the nearest major road or using DWTD (distance weighted traffic density) - a measure that takes into account residential proximity and traffic level of surrounding road ways.

Five of the six studies were classified as having low risk of bias. Of the five low risk studies, three found significant positive associations [67 165 166], one study with a particularly small sample size found suggestive associations [68] and one found no association [152]. The one study to be classified as having a moderate risk of bias reported the strongest associations in three categories of PTB (<37 weeks AOR=1.5, 95%CI=1.2-1.8; <32 weeks AOR=1.6 95%CI=1.1-2.4; <28 weeks AOR=1.8 95%CI= 1.0-3.2) [164].

Of the studies to find positive associations, two dichotomized distance to major road at ≤200m and >200m [164 165] finding adjusted odds ratios of 1.14 (95%CI=1.02-1.27) [165]

and 1.5 (95%CI=1.2-1.8) [164] for women living ≤200m. The study by Yang et al. [166] found adjusted odds ratios of 1.30 (95%CI=1.03-1.65) with women living <500m from a major road. The fourth study to find an association used the DWTD technique finding elevated relative risks of 1.08 (95%CI=1.01-1.15) for women in the highest traffic density quintile [67].

1.6.1.5 Discussion

Synthesizing the results of studies investigating gaseous air pollution effects on PTB is challenging due to the heterogeneity of analyses performed and exposure assessment methods used. This review provides a broad critique of the literature in this area and the conclusions that come out of the studies under review.

Of the studies included in this review, 18 of the 24 found some evidence of an association between gaseous air pollution and risk of PTB. The strongest evidence of an association with increased PTB risk in terms of the number of published studies, the proportion of studies to demonstrate positive associations and the level of bias was with proximity to major roads and nitrogen dioxide. Of the low risk studies investigating proximity to major road, three of five found statistically significant associations with increased PTB risk and one found suggestive associations. The strongest adjusted odds ratio was 1.30 (95%CI=1.03-1.65) comparing women living at less than 500m from a major road with those living more than 500m. Of the low risk studies investigating NO_2, all four studies found some evidence of an association. The strongest association was presented in the study by Llop et al. (2010), where for concentrations above 46.2µg/m³ over the entire pregnancy, there was a 29% (95%CI=1.13-1.46) increased risk of PTB.

One study that stands out as presenting results markedly different from the other studies is Malmqvist et al. (2011), which found small protective effects of NO_x on PTB risk. However, these results did not hold when the same cohort were analysed in relation to traffic density, where no associations were found in either direction. This study was classified as low risk overall and scored a 'none' or a 'low' risk in all categories except the 'Information bias: Outcome' category.

It must be emphasised that the results observed from studies using distance to major road or DWTD are based on a proxy measure rather than a direct measure of pollution levels. These measures using road traffic will likely be picking up joint effects of a range of gaseous pollutants as well as particulate matter exposures. Consequently, comparing these results with the studies using alternative more direct exposure measurement techniques is difficult. This is a technique, however, that has been encouraged as a measure of exposure in epidemiological studies investigating health effects of air pollution [70]

The studies critiqued in this review were from contrasting geographic areas. The strongest evidence of an association was from California, where four of the six studies reviewed demonstrated positive associations [75 153 158 161]. Studies from Washington [159], Pennsylvania [162] and Atlanta [40] were also reviewed and little evidence of an association was found. Three studies were from Canada, where two of the studies found positive associations [155 165] and one found mostly no associations [60]. Evidence of an association was found in studies from China [137], Japan [164], Korea [154], Taiwan [166] and Australia [39]. The area where the evidence of an association between gaseous air pollution and PTB was most mixed was in Europe. Studies from Sweden [152], London [163] and the Netherlands [68] found no associations, while positive associations were observed in

studies from Spain [146] and Czechoslovakia [157] and possible associations from the Netherlands [83] and Lithuania [156].

Six of the studies were classified as having inadequate statistical power; of these studies, two found positive associations [146 166], two presented weak associations [83 156] and two of the studies found no associations [68 159]. The weakly powered studies with results finding no significant associations should be interpreted with caution due to the possibility of false negative results which could be masking any true effects.

The specific nature of this review can be regarded as a strength of this study. Focusing on one adverse pregnancy outcome and one group of pollutants allows the review to focus attention and critique individual studies. Interpreting effects should be done cautiously when extracting results from single pollutants, as it is likely too simplistic to assume that each pollutant acts independently on the maternal and fetal systems when strong correlations between pollutants are well documented [15 167] This review has not broken down the results to further sub categories of PTB (extreme, severe etc.), which may well be of interest for future work. This was not included because many of the included studies did not present this data and for those that did, it was felt that the validity of the results was compromised due to lack of statistical power. This review may also be weakened by the effect of publication bias as only published data has been included. This could result in our conclusions overestimating the effects of an association between air pollution and PTB.

1.6.1.6 Conclusions and future work

A recurring theme in reviews investigating links between adverse pregnancy outcomes and air pollution exposure is the problem of synthesizing the evidence to draw

meaningful conclusions when so many differences exist between the studies. International collaborations (such as ICAPPO- International collaboration on air pollution and pregnancy outcomes [168]) are attempting to standardize analyses across datasets from around the world in recognition of this problem. This may provide a valuable tool in facilitating the use of evidence in this area to be translated into policy, with the ultimate aim to diminish harmful effects on the fetus.

With increasing numbers of detailed longitudinal birth cohort databases becoming available, the focus area for misclassification in epidemiological studies is in the exposure assessment. Greater temporal and spatial resolution in exposure models will continue to be the aim in this area to provide the best exposure estimate that is practical to implement on a large scale. Work on this from international groups such as ESCAPE [169] are aiding in pushing forward European wide homogenous air pollution exposure modelling in studies investigating health effects across large areas. It remains important that location specific studies continue to be carried out to facilitate appropriate policy decisions and local air quality management strategies, as populations and air pollution exposure issues will vary between areas, across and within countries.

This is an active area of research that has important implications in terms of public health policy, informing the public and local air quality management strategies and importantly, making a contribution to the evidence on the environmental contribution to adverse pregnancy outcomes. An expansion of experimental and toxicological work is required to compliment the observational studies by creating a better understanding of the physiological effects of air pollution and how they may exert an effect. However, it

is important that large scale epidemiological studies continue so as to provide fundamental evidence on population thresholds and area specific effects.

Ultimately, research in this area is multidisciplinary and requires the cohesion of expertise from core disciplines to uncover reliable and valid answers; the epidemiologist, environmental scientist, exposure assessor, statistician and toxicologist all have key roles to play.

This review demonstrates a suggestive, but not yet convincing, association of gaseous air pollution increasing the risk of preterm birth. The studies included in this review present the strongest evidence of an effect coming from traffic generated pollutants, particularly nitrogen dioxide. Further investigation into the effects of gaseous pollutants on adverse perinatal outcomes is certainly warranted.

1.6.2 Fetal growth

A large number of studies have been published across the world, mostly in the last decade, on the effects of air pollution on fetal growth. Studies have investigated fetal growth as an outcome measure in terms of LBW, SGA, IUGR and birth weight as a continuous measure. As with the studies investigating the effects of PTB, the studies are very heterogeneous in terms of their study design, exposure and outcome assessment and analysis techniques which make firm conclusions of effect sizes on fetal growth difficult to establish.

The evidence for an increased risk of restricted fetal growth from air pollution exposure appears to be strongest for the pollutants CO [60 155 170], NO_2 [60 155 171], PM_{10} [170 172] and $PM_{2.5}$ [160 171 173]. Pooled estimates calculated in a recent meta-analysis estimated the reduction in birthweight from an increase of 1ppm exposure to CO as -11.4g (95%CI= -29.7, 6.9), a 20ppb NO_2 increase as -28.1g (95%CI=-44.8, -11.5), 20µg/m³ increase of PM_{10} as -16.8g (95% CI= 20.2, -13.3) and a 10µg/m³ increase of $PM_{2.5}$ as -23.4g (95% CI= -45.5, -1.4) [174].

The critical window for pollution exposure effects on fetal growth varies greatly between studies [174]. The strongest evidence appears to be from estimates that are calculated for the entire pregnancy, however, there is increasing evidence from studies that present effect sizes by trimesters of the strongest effect on fetal growth occurring during the later stages of pregnancy in the second and third trimesters [78 171 175]

Nine studies investigating the effects of fetal growth from air pollution exposure have been specifically selected and their results presented in tables 11 to 15 and the study

characteristics detailed in Appendix 1 (Table A2). These studies have been selected based on three qualitative criteria (1) to represent the broad range of study designs that have been undertaken to investigate the associations between fetal growth and air pollution (2) the studies which are deemed to be of the highest quality in this area of research (primarily based on the exposure assessment methodology) and (3) studies which represent results from a range of countries throughout the world.

Table 11: Results of selected studies investigating fetal growth in relation to particulate matter (PM_{10} and $PM_{2.5}$)

Author & Year	Outcome	Time of exposure	Analysis comparison	Results AOR/birth weight change (95% CI)
Kloog *et al.* 2012 [175]	LBW/BW	Entire pregnancy	10 µg/m³ increase in $PM_{2.5}$	1.00 (0.96-1.04) / Change (g)= -13.80 (-21.10, -6.05)*
		30 days prior to birth	10 µg/m³ increase in $PM_{2.5}$	0.99 (0.94-1.03) / Change (g)=-8.80 (-10.32, -4.44)*
		90 days prior to birth	10 µg/m³ increase in $PM_{2.5}$	1.06 (1.01-1.13)*/ Change (g)= -9.20 (-15.00, -3.30)*
Gehring *et al.* 2012 [83]	Term BW	Entire pregnancy	10 µg/m³ increase in $PM_{2.5}$	Change (g)= 6.5 (-44.1, 57.2)
		Tri 1	10 µg/m³ increase in $PM_{2.5}$	Change (g)= 14.0 (-14.7, 42.6)
		Last month before birth	10 µg/m³ increase in $PM_{2.5}$	Change (g)= -12.1 (-31.2, 7.0)
Van den Hooven *et al.* 2012 [78]	LBW	Entire pregnancy	4th quartile PM_{10} (>32.9) vs 1st (<27.8)	0.91 (0.60-1.40)
	SGA	Entire pregnancy	4th quartile PM_{10} (>32.9) vs 1st (<27.8)	1.23 (0.89-1.70)
Madsen *et al.* 2010 [114]	LBW/ Term BW	Entire pregnancy	*Dispersion model:*	
			4th quartile PM_{10} (>16.2) vs 1st (<10.7)	0.7 (0.5-0.9)* / Change (g) = 15.9 (0.0, 31.9)*
			4th quartile $PM_{2.5}$ (>14.1) vs 1st (<9.7)	0.7 (0.5-1.0)* / Change (g) = 13.6 (-2.4, 29.5)
			Monitoring station: 4th quartile PM_{10} (>28.9) vs 1st (<22.3)	1.0 (0.7-1.3) / Change (g) = -6.1 (-21.6, 9.4)
			4th quartile $PM_{2.5}$ (>13.3) vs 1st (<11.9)	0.9 (0.6-1.2) / Change (g) = 4.5 (-10.9, 19.9)
	Term SGA	Entire pregnancy	*Dispersion model:* 4th quartile PM_{10} (>16.2) vs 1st (<10.7)	0.9 (0.8-1.0)
			4th quartile $PM_{2.5}$ (>14.1) vs 1st (<9.7)	0.9 (0.8-1.0)
			Monitoring station: 4th quartile PM_{10} (>28.9) vs 1st (<22.3)	1.1 (0.9-1.2)

Author & Year	Outcome	Time of exposure	Analysis comparison	Results AOR/birth weight change (95% CI)
			4th quartile $PM_{2.5}$ (>13.3) vs 1st (<11.9)	1.0 (0.9-1.1)
Bell *et al.* 2007 [171]	BW	Entire pregnancy Entire pregnancy	Per IQR increase in PM_{10} Per IQR increase in $PM_{2.5}$	1.027 (0.991-1.064) / Change (g) = -8.2 (-11.1, -5.3)* 1.054 (1.022-1.087) / Change (g) = -14.7 (-17.1, 12.3)

*BW= birth weight (as a continuous variable); AOR= Adjusted odds ratio; IQR= Interquartile range; *= p<0.05*

Table 12: Results of selected studies investigating fetal growth in relation to nitrogen oxides, nitric oxide and nitrogen dioxide (NO_x, NO, NO_2)

Author & Year	Outcome	Time of exposure	Analysis comparison	Results Adjusted OR (95% CI)
Pereira *et al*. 2012 [176]	SGA IUGR	Entire pregnancy Tri 1 Tri 2 Tri 3 Entire pregnancy Tri 1 Tri 2 Tri 3	IQR increase in NO_2 IQR increase in NO_2	1.02 (0.93-1.12) 1.04 (0.88-1.24) 1.17 (0.98-1.39) 1.00 (0.83-1.19) 1.08 (0.98-1.20) 1.12 (0.92-1.36) 1.31 (1.07-1.60)* 1.08 (0.98-1.20
Gehring *et al.* 2012 [83]	Term BW	Entire pregnancy Tri 1 Last month before birth	10 µg/m³ increase in NO_2 exposure 10 µg/m³ increase in NO_2 exposure 10 µg/m³ increase in NO_2 exposure	Change (g)= 5.0 (-12.6, 22.6) Change (g)= 12.2 (-1.7, 26.0) Change (g)= -5.5 (-24.4, 13.4)
Van den Hooven *et al.* 2012 [78]	LBW SGA	Entire pregnancy Entire pregnancy	4th quartile NO_2 (>42.2) vs 1st (<37.2) 4th quartile NO_2 (>42.2) vs 1st (<37.2)	0.95 (0.58-1.55) 1.35 (0.94-1.94)
Malmqvist *et al.* 2011 [152]	LBW	Entire pregnancy	4th quartile NOx (>22.7) vs 1st (2.5-8.9)	0.93 (0.82-1.06)

Author & Year	Outcome	Time of exposure	Analysis comparison	Results Adjusted OR (95% CI)
	SGA	Entire pregnancy	4th quartile NOx (>22.7) vs 1st (2.5-8.9)	1.07 (0.99-1.15)
Madsen *et al.* 2010 [177]	Term BW	Entire pregnancy	*Dispersion model:* 4th quartile NO_2 (>38.0) vs 1st (<20.3) *Monitoring station:* 4th quartile NO_2 (>39.7) vs 1st (<32.5)	1.0 (0.8-1.1) / Change (g) = 1.8 (-13.7, 17.2) 1.0 (0.9-1.2)/ Change (g) = -4.9 (-20.4, 10.5)
	Term SGA	Entire pregnancy	*Dispersion model:* 4th quartile NO_2 (>38.0) vs 1st (<20.3) *Monitoring station:* 4th quartile NO_2 (>39.7) vs 1st (<32.5)	 1.0 (0.8-1.1) 1.0 (0.9-1.2)
Aguilera *et al*. 2009 [178]	BW	Entire pregnancy Tri 1 Tri 2 Tri 3	Change in BW per IQR increase	Change (g) = 8.8 (-238,41.5) Change (g) = 3.3 (-33.2,39.7) Change (g) = 3.7 (-31.1,38.4) Change (g) = 16.8 (-18.8,52.4)
Brauer *et al.* 2008 [60]	LBW at term SGA	Entire pregnancy (<30 weeks)	10µg/m³ increase of NO IDW LUR IDW LUR	 1.03 (0.96-1.10) 1.01 (0.96-1.07) 1.05 (1.03-1.08)* 1.02 (1.00-1.04)*
Brauer *et al.* 2008 [60]	LBW at term SGA	Entire pregnancy (<30 weeks)	10µg/m³ increase of NO_2 IDW LUR IDW LUR	 1.11 (1.01-1.23)* 0.97 (0.89-1.05) 1.14 (1.09-1.18)* 0.99 (0.96-1.02)
Bell *et al.* 2007 [171]	BW	Entire pregnancy	Per IQR increase in NO_2	1.027 (1.002, 1.051)* / Change (g) =-8.9 (-10.8,-7.0)*

*BW= birth weight (as a continuous variable); AOR= Adjusted odds ratio; IQR= Interquartile range; *= p<0.05*

Table 13: Results of selected studies investigating fetal growth in relation to carbon monoxide (CO)

Author & Year	Outcome	Time of exposure	Analysis comparison	Results Adjusted OR (95% CI)
Brauer *et al.* 2008[60]	LBW at term	Entire pregnancy (<30 weeks)	100µg/m³ increase in CO	1.02 (0.96-1.09)
	SGA	Entire pregnancy (<30 weeks)	100µg/m³ increase in CO	1.06 (1.03-1.08)*
Bell *et al.* 2007 [171]	BW	Entire pregnancy	Per IQR increase in CO	1.028 (0.983, 1.074) / change (g) = -16.2 (-19.7, -12.6)*

*BW= birth weight (as a continuous variable);AOR= Adjusted odds ratio; IQR= Interquartile range; *= p<0.05*

Table 14: Results of selected studies investigating fetal growth in relation to sulphur dioxide (SO_2)

Author & Year	Outcome	Time of exposure	Analysis comparison	Results Adjusted OR (95% CI)
Brauer *et al.* 2008 [60]	LBW at term	Entire pregnancy (<30 weeks)	1µg/m³ increase in SO_2	0.99 (0.97-1.02)
	SGA	Entire pregnancy (<30 weeks)	1µg/m³ increase in SO_2	1.01 (1.00-1.02)*
Bell *et al.* 2007 [171]	BW	Entire pregnancy	Per IQR increase in SO_2	1.003 (0.961, 1.046) / Change (g) = -0.9 (-4.4, -2.6)*

*BW= birth weight (as a continuous variable);AOR= Adjusted odds ratio; IQR= Interquartile range; *= p<0.05*

Table 15: Results of selected studies investigating fetal growth in relation to road proximity/traffic density.

Author & Year	Outcome	Time of exposure	Analysis comparison	Results Adjusted OR (95% CI)
Malmqvist *et al.* 2011 [152]	LBW	Entire pregnancy	Traffic density >10 cars/min vs. no road	1.00 (0.83-1.06)
	SGA	Entire pregnancy	Traffic density >10 cars/min vs. no road	1.04 (0.93-1.15)
Brauer *et al.* 2008[60]	Term LBW	Entire pregnancy (<30 weeks)	<50 highway	1.22 (0.81-1.87)
	SGA	Entire pregnancy (<30 weeks)	<50 highway	1.26 (1.07-1.49)*

Most studies in this field of research use a retrospective cohort design, primarily to ensure a large enough cohort for adequate statistical power to detect relatively small effect sizes [152 176]. Prospective studies, although generally limited by their sample size, can provide useful insights into this area of research and this is an approach that has been adopted by a number of recent studies investigating fetal growth effects from air pollution [78 117 178]. The prospective studies have two main advantages over retrospective studies: (1) the type and detail of covariate information can generally be dictated during the study design process, which reduces the risk of residual confounding and (2) more detailed outcome assessment can be performed at specified time points during the pregnancy. A particularly good example of a high quality prospective study which has utilised these advantages is a recent study from the Netherlands [78]. This study prospectively evaluated the effects of air pollution using a dispersion model on fetal growth characteristics from 7,772 subjects using ultrasound measurements in each trimester. The detailed information on fetal growth parameters in combination with a comprehensive adjustment for confounders (including maternal and paternal anthropometrics) enabled effects from air pollution on fetal growth during specific pregnancy periods to be examined. The study concluded that NO_2 and PM_{10} were associated with impaired fetal growth, particularly during the second and third trimester [68]. The prospective study by Aguilera et al. (2009) demonstrates the ability for prospective study designs to incorporate individual time activity patterns into analyses [178]. However, as demonstrated in the results tables above (Tables 11-15), the three high quality prospective studies selected here all demonstrate the limitations of small sample sizes with the large confidence intervals and almost all effect estimates including the null [78 117 178].

The studies which were selected predominantly on their quality in terms of exposure assessment technique presented the effect estimates using more than one method, and at least one of the methods used was deemed to have particularly strong spatial and temporal resolution [60 152 175]. Studies which present effect estimate results based on more than one technique enable more transparency of the influence that the exposure assessment method is having on the effect estimates.

A recent particularly strong study in terms of exposure assessment is from Massachusetts where two exposure estimation techniques were used for the analysis [175]. The first, a novel prediction model using satellite data to produce daily estimates at a 10km² resolution and the second method, a more traditional approach of cumulative traffic density. Based on the satellite data estimates, this study reported a significant increased risk of LBW during the whole pregnancy period per 10µg/m³ increase of $PM_{2.5}$ (OR=1.06; 95%CI= 1.01-1.13) and a significant reduction in birth weight, particularly during the last trimester (-9.20g 95%CI= -15.00, -3.30). Another study with a particularly high quality exposure assessment element was from Canada in 2008 [60]. The study investigated traffic related pollutants effects on SGA and LBW using nearest and inverse distance weighting of study area monitors, temporally adjusted land use regression (LUR) models and proximity to major roads. The results of the study were small significant associations reported with SGA and LBW to NO, NO_2, $PM_{2.5}$ and black smoke from the LUR and monitoring estimates. Maternal residence within 50m of a highway increased the risk of SGA by 26% (95%CI= 1.07-1.49) and LBW by 11% (95%CI= 1.01-1.23). These results provide strong evidence of a modest effect on fetal growth from traffic related air pollution, even at low ambient air pollution concentrations.

To summarise, the results from the nine selected high quality studies investigating the effects of air pollution on fetal growth present very mixed results. Two of the studies investigating particulate matter presented small statistically significant reductions in birth weight [171 175]. Three of the studies investigating the effects of NO and NO_2 found significantly increased risks of a dichotomized fetal growth outcome measure [60 171 176]. Both of the two studies from the nine which investigated the effects of CO found significantly increased risks [60 171], as they did with SO_2 exposure, but to a lesser extent. No effects were found with LBW and SGA for those exposed to a traffic density of >10cars/min [152], however, another study demonstrated a 26% significantly increased risk for SGA at <50m from a highway [60].

1.6.3 Literature reviews

Fourteen review papers have been published in the field of air pollution and adverse pregnancy outcomes from 2004 to 2013 (Table in Appendix 1: Table A3). They have included a review of the studies investigating the outcomes LBW, PTB, SGA, IUGR, stillbirth and congenital abnormalities.

As Chapter 1.6.1 highlighted, reviewing studies in this area is particularly challenging due to the vast heterogeneity across studies in terms of their design, outcome definitions and analysis techniques. As a result of these challenges, earlier reviews largely based conclusions on qualitative observations from a small selection of included studies (many based on less than 15 [102 142 179] and consequently some concluded there to be insufficient evidence to draw conclusions [143 144]). The earlier review studies all introduce and discuss to some extent the common methodological issues in the area, however, few developed an approach to tackle the issues directly within the studies

under review [142] [144]. Earlier reviews highlight the future research need for the identification of critical windows of exposure and biological plausible mechanisms of effect; however, they do not incorporate these areas within the review (e.g. hypothesising a critical window of exposure based on included study results).

In recent years, review studies have become increasingly sophisticated in their approach to synthesising the evidence. Two recent reviews have performed additional meta-analyses to calculate pooled estimates of effect and funnel plot analyses as a means of assessing publication bias [174] [180]. These meta-analyses both found effects from $PM_{2.5}$ based on the entire pregnancy on LBW in the region of OR 1.05-1.09 per 10µg/m³. Sapkota et al. also investigated PTB effects of $PM_{2.5}$ and calculated a combined odds ratio of 1.15 (95%CI= 1.14-1.16). The meta-analysis investigating effects on LBW which included sixty two studies found statistically significant associations with CO (OR= 1.07; 95%CI= 1.02-1.12), NO_2 (OR= 1.05; 95%CI= 1.00-1.09) and SO_2 (OR=1.03; 95%CI= 1.02-1.05) [174].

Another recent high quality review by Shah et al (2012) systematically investigated the effects of a range of air pollutants on LBW, PTB and SGA from forty one studies using a specifically designed quality assessment tool (the basis of the QAT presented in Chapter 1.6.1). This review also concluded that $PM_{2.5}$ exposure was associated with LBW, PTB and SGA and that PM_{10} was associated only with SGA births. Exposure to SO_2 was also found to be associated with PTB and the evidence for NO_x, NO_2, O_3 and CO was inconclusive.

A 2010 literature review of the effects from particulate matter on LBW and PTB concluded that of the evidence reviewed (30 studies), there was not convincing evidence of an association with the risk of particulate matter on PTB, LBW/VLBW and SGA.

An important development in synthesising and reviewing evidence in this area has been made by 'The International Collaboration on Air Pollution and Pregnancy Outcomes' (ICAPPO) [181]. The main objective was to develop and conduct analyses using a standardized methodology across multiple research centres and countries to 'provide comparable results for research synthesis' [168]. Initial results are now being published and have found significant heterogeneity in estimated effects between locations despite the use of a common tool. There were statistically significant associations found between LBW and PM_{10} from 6 of the 13 centres involved. However, the most recent analyses have highlighted the need for more complex protocols to better synthesis the results [181].

Reviews on the outcomes of fetal death and congenital abnormalities in relation to air pollution, were also included in the summary table, although they are not outcomes further explored in this thesis. The review investigating fetal death found inconsistent associations, with the most consistent evidence coming from studies investigating post-neonatal mortality and air pollution exposure [144]. A systematic review and meta-analysis of ten studies investigating ambient air pollution and risk of congenital anomalies found some evidence of an effect on congenital cardiac anomaly risk [102].

1.6.4 Methodological considerations in future research

Many of the recommendations for future research from the early reviews have, to some extent, come to being in current work already. For example, a call for studies to present their results by specific time periods in pregnancy to better establish critical windows of exposure is now fairly common practice in published studies [142]. However, there is still a long way to go to establish firm conclusions on the associations between air pollutants and adverse perinatal outcomes. The directions for future work based on the recommendations from the literature can be divided into four main areas:

(1) Exposure assessment: The exposure assessment technique provides the backbone to making valid associations of the effects of air pollution on adverse perinatal outcomes. Studies comparing exposure assessment techniques are imperative to assess the performance of currently used techniques and the continued development of optimizing the spatial and temporal resolution of future techniques.

(2) Outcome assessment: Further work is required in ensuring reliable outcome assessment methods. Further studies using ultrasound measurements throughout pregnancy to get a detailed understanding of the effects on fetal growth trajectory will add an additional level of understanding to the biological mechanisms of effect from air pollution at critical windows of exposure [182]. If retrospective datasets are being used, the outcome assessment method should be stated.

(3) Confounding: A better understanding of confounders and residual confounding within studies is an important area of future work [182]. Recommendations of studies to adjust appropriately in their analyses for true confounders and to understand the extent to which they adequately capture what is intended to be adjusted for. A

particular focus here should be on the measurement and adjustment of socioeconomic status. If a study lacks the availability of information on particular confounders, this should be highlighted as a limitation of the study.

(4) Biological plausibility: One of the strongest and most consistent recommendations to come out of the literature to date is the need for a better understanding of the biological mechanisms by which air pollution may be exerting an effect on pregnancy [101 174]. Almost all of the reviews to date have highlighted the importance of clarifying the plausible biologic mechanisms of air pollution effects on the fetus. Ideally epidemiologic studies should be based on a biological hypothesis. Unexpected findings may generate new hypotheses which in turn need to take into account potentially previously overlooked biological mechanisms which might underlie them.

The next chapter outlines biologically plausible mechanisms of how air pollution may result in an adverse perinatal outcome.

1.7 Biological plausibility

The multifaceted nature of air pollution exposure in a dynamic human population creates a substantial challenge in understanding the mechanisms by which an effect may occur. Complexities exist due to the multiplicity of pollutants impacting via different mechanistic pathways; the effects of these will undoubtedly vary between individuals due to unique susceptibilities and temporality of assault. Characteristics such as genetics will clearly have an influence on susceptibilities, as well as other factors including age [183], socio-economic status [184], medication usage [185] and pre-existing cardiovascular and respiratory conditions.

The possible biological mechanisms by which air pollutants may be acting in pregnancy to influence fetal growth and prematurity may be in relation to factors relating to the mother, placenta or directly on the fetus (as demonstrated in Figure 16 [186])

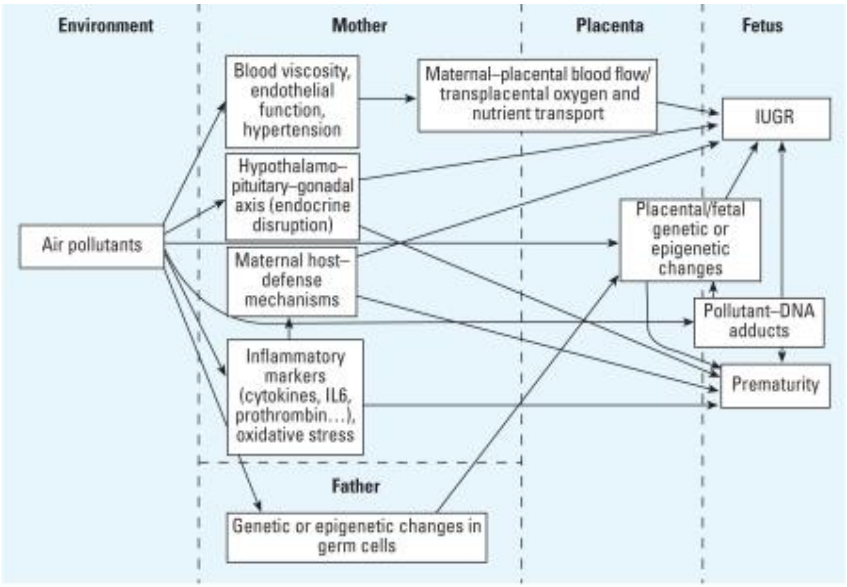

Figure 16: Plausible biological mechanisms by which air pollutants could influence fetal growth and prematurity, identified and created by 'The International Workshop on Air Pollution and Human Reproduction' in 2007 [186].

Epigenetic modification has been suggested as a possible influence on the risk of adverse perinatal outcomes and could have an influence on individual responses to pollutant exposure [187]. Epigenetics is the study of changes in phenotype or gene expression caused by mechanisms other than changes in the under-lying DNA sequence [188]. Epigenetics is particularly important during fetal development when the epigenome is more susceptible to environmental insults. Three areas of epigenetic modifications that could affect gene expression patterns have been identified that could alter the intrauterine environment and potentially increase the risk of adverse pregnancy outcomes: DNA methylation, post-translational histone modifications and non-coding RNA-mediated signalling pathways [187] [188]. Epigenetic changes may be induced by various pregnancy risk factors such as social factors e.g. smoking and poor nutrition and physiological factors e.g. infection and endocrine dysfunctions. It is thought that environmental effects- such as air pollution- can disturb placental epigenetics, alter placental development and function and subsequently result in a suboptimal birth outcome, which can have lifelong health implications [188] [189].

An important yet difficult point to establish is whether, and to what extent, pollutants may have a cumulative effect and if a critical window of exposure exists in pregnancy. The proportion of pollutants to reach the fetus from the mother is very difficult to quantify, so to is the exact effect of pollutants coming into contact with a vulnerable and biologically immature immune system of the fetus. Different mechanisms of action are thought to be in play at different pregnancy time points, and both acute and chronic effects need to be considered [155]. Some pollutants are thought to have direct toxic effects on the fetus, while others may be involved in a cascade of events that ultimately

leads to an effect on the fetus. Five broad biologically plausible mechanisms for air pollution to impact upon perinatal outcomes have been suggested: oxidative stress, inflammation, coagulation, endothelial function, and hemodynamic responses [133].

A well known risk factor for adverse perinatal outcomes is intrauterine infection. Infection is now thought to account for 25-45% of preterm births [136]. Air pollution might increase maternal susceptibility to infection [162]. Subtle immune system changes can alter the vaginal flora, and thus result in proinflammatory cytokines stimulating the release of prostaglandins, matrix-degrading enzymes and other inflammatory mediators; ultimately this leads to stimulated uterine contractility and preterm premature rupture of membranes (PPROM) [190].

Air pollution may interfere with placental development by affecting vital nutrient and oxygen delivery to the fetus. Tobacco smoke has been confirmed to increase the risk of PTB and restricting growth *in utero* [132]. CO is a major constituent of tobacco smoke and is particularly harmful to the fetus due to its rapid absorption time across the placenta; this results in a shift of the oxygen dissociation curve to the left and causes a decrease in oxygen availability to the fetus. It must be noted, however, that although there is convincing evidence to support this hypothesis, experimental studies investigating CO within tobacco smoke provide an exaggerated example due to levels being considerably higher and containing different particle compositions and size than in ambient air [191].

Oxidative stress is described as a potentially harmful process which occurs due to excess free radicals and a decrease in antioxidant defences [192]. Some gaseous pollutants which are abundant in ambient air e.g. NO_2 are free radicals or, like O_3, have the ability to drive free radicals. A further plausible hypothesis is that antioxidant

defences play an important role in regulating an individual's response to air pollution [192]. This hypothesis, coupled with evidence of maternal active and passive smoking significantly affecting neonatal antioxidant status, suggests that oxidative stress in the fetus may have a significant role to play in compromising gestational age and fetal growth [193], particularly in the early stages of pregnancy [194]. Although hypoxic stress is a favoured hypothesis, it is important to note that there is evidence from animal models to show remarkable adaptive processes to prevent PTB in the presence of chronic hypoxic stress. Following fetal hypoxia in sheep, the fetal adrenal appeared less responsive, thus preventing premature elevations in cortisol, a hormone which is key to the initiation of labour in this species [195].

One of the responses to oxidative stress is the influx of inflammatory cells. Along with infection, inflammation is the only pathological process with a solid causal link to PTB [196]. Studies have made associations with the biological mechanism of inflammation in human subjects with urban gaseous air pollution [197]. A Swedish study investigating the associations of long and short term air pollution exposure with markers of inflammation and coagulation found consistent associations with the pro-inflammatory cytokine Interleukin-6 to both NO_2 and SO_2 emissions in a sample of 1536 adults [198]. Most studies, however, have focused on the link between particulates and inflammation in relation to cardiovascular and respiratory effects in older human subjects [199]. It is thought that the relative balance between pro and anti-inflammatory cytokines may determine the timing of delivery onset [200]. In term spontaneous labour, a sudden influx of pro-inflammatory cytokines (IL-1β, IL-6, TNFα and IL-8) occurs. A decreased production of specific anti-inflammatory cytokines has been found to increase the risk of spontaneous PTB [200]. Placental inflammation has also been linked

to a predisposition to gestational hypertensive disorders which can indirectly result in restricted growth or a PTB [201 202].

It has also been hypothesized that oxidative stress may lead to DNA damage [133], causing disruption to DNA transcription resulting in an increased number of DNA adducts. No direct associations between increased DNA adducts and adverse pregnancy outcomes have been demonstrated, however, there is evidence of an increase in DNA adducts in areas with elevated ambient gaseous air pollution [203 204] and links to fetal growth [205].

The effect of gaseous pollutants on adverse perinatal outcomes may also be related to hematologic factors. Alterations in blood viscosity and coagulability have been associated with ambient air pollution [198 206]. It is plausible to hypothesize that the increased tendency towards hypercoagulability in the presence of increased ambient air pollution levels (particularly with NO_2 [206]) may impair uteroplacental and umbilical blood flow. This depletion of an adequate blood supply may result in the fetus not receiving sufficient oxygenation and nutrients and consequently restricting growth, or due to the suboptimal environment this may result in a PTB.

Due to the increased stress of pregnancy on the maternal cardiovascular system, hypertensive disorders are particularly common [202]. Of these, pre-eclampsia increases the risk of iatrogenic PTB because delivery is the only cure for the condition [207]. Air pollution exposure in adults has been shown to cause arterial vasoconstriction and alter autonomic balance. This is thought to occur due to a reflex increase in sympathetic nervous system activity [208 209]. A recent novel prospective cohort study which investigated exposure to PM_{10} and NO_2, in 7006 women, and took account of

temporal and spatial variations in the exposure model, concluded that air pollution might affect cardiovascular health in pregnancy [201]. The strongest evidence for alterations in blood pressure linked to air pollution concern particulate matter [210 211], however, evidence is gradually emerging on the influence of O_3 [212], NO_2 [201 213] and SO_2 [214].

Experimental studies provide the opportunity to give clarity and increased accuracy of the biological effects which pollutants may be having systemically and on target organs. Epidemiological studies provide the context and the impact of a cause-effect relationship on a large scale population. A noted gap exists in interpreting the results from the laboratory and the results from observational human studies [215]. For toxicological and epidemiological work to complement each other and for knowledge to progress in an area already being propelled by substantial and specific longitudinal datasets worldwide, future work will be required to bridge this gap.

1.8 Methodological challenges

This chapter address the key methodological challenges faced by studies investigating the effects of air pollution on adverse perinatal outcomes: exposure assessment, mobility, outcome assessment, critical exposure windows, confounding and co-pollutant interactions.

1.8.1 Exposure assessment

Heterogeneity in air pollution exposure estimation techniques is one of the biggest challenges in synthesizing the evidence of air pollution effects on adverse birth outcomes. A range of techniques are now available for estimating exposure in a cohort ranging in their ability to capture spatial and temporal variation (most of these techniques have been outlined in Chapter 1.4). Studies using different techniques, and even varying levels of temporal adjustments within the techniques, make generalising results very difficult. Recent work has been done in an attempt to harmonise exposure estimation across large areas by applying one homogenous technique [86 169], however, in most studies, the exposure estimation technique decision is specific to the individual study taking account of the geographic area, which health outcome is under study and data availability. More recently, studies have started to present their effect estimate results of the associations between air pollution and pregnancy outcomes based on several different exposure estimation techniques [60 77]. This not only makes the results more comparable with other studies, but importantly adds a level of robustness and reliability to the findings due to the transparency of how the effect estimates may be impacted by different exposure estimation techniques.

1.8.2 Mobility

Many studies based on registry data (to ensure a large sample size and reliability of birth outcome data) make the often unavoidable assumption that the location of maternal residence at time of birth was the primary location of the mother throughout pregnancy. Precise time-activity logs of accurate location are rarely practical. Occasionally retrospective datasets used for studies of this nature have a record of residential mobility during the pregnancy and if so, can be used when assigning exposure estimates [114]. It has been highlighted that caution should be exercised in assuming that residence within pregnancy remains constant. In a 2008 cohort study, it was found that 35% of the population moved during pregnancy [60]. However, a recent study which specifically investigated mobility during pregnancy and the potential for pollution exposure misclassification concluded that there was a low mobility rate (13%) and those that did move, did so over relatively small distances (average 10.4 miles) [216]. A study specifically in the North of England reported an estimated mobility rate of 9% [217].

1.8.3 Outcome assessment

Traditionally, gestation was estimated using the date of the mothers last menstrual period (LMP), with the assumption that pregnancy lasts 280 days from LMP to delivery[218]. Gestational age (GA) estimates based on scan estimates have now long been regarded as a more accurate technique[219 220] and are more commonly used than other techniques such as LMP in perinatal epidemiological studies. Ultrasound scan measurements to determine GA are generally undertaken before 15 weeks gestation and use the measurements of the crown to rump length (top of head to bottom of buttocks), bi-parietal diameter (transverse diameter of head), head circumference and femur length

measurement [221]. Problems associated with using LMP estimates over scan estimates have been suggested. The most significant problem is the recall from women of the exact date of the first day of their last period. Reliability of LMP recall seems to depend on the population under study and the time point. It is estimated that around 20% of women presenting to antenatal clinics have incorrectly recalled their LMP [222 223]. Several indicators are associated with unknown LMP. There is a U-shaped relationship between unknown LMP and age of the mother. A link between unknown LMP with increasing parity, illiteracy and women of a low professional status has also been made [224]. Higher levels of inaccurate LMP recall have been reported for non-white populations [225 226]. A more recent study from Washington DC that compared recalled date of LMP with prospectively recorded dates found that women were fairly good at recalling their LMP date, but when they were inaccurate, they tended to overestimate the time since their LMP [227]. A study published in 2000, was one of the few studies that has focused specifically on associations between adverse pregnancy outcome and unreliable last menstruation [222 223]. The study found that unreliable LMP was associated with increased risk of death, PTB and LBW, however, it is likely that these results are affected by confounding from the effects of socioeconomic status.

In most recent epidemiological studies that have investigated the effect of an exposure on the risk of PTB, scan measurements have been used with the reasoning that it is the most accurate measurement of GA. However, there is a potential bias that comes with using ultrasound in studies of this nature. If, for example, the effect of air pollution exposure on the risk of PTB is mediated through fetal growth in early pregnancy, then GA will be underestimated in those affected. This will result in an overestimation of PTB risk in the exposed when GA is measured by ultrasound. This point was

demonstrated in a study assessing GA measurements and the potential for bias by examining women who smoked- a well known risk factor to affect fetal growth. Risk estimates for PTB were found to be more extreme using biparietal diameter (BPD) scan measurements to estimate GA as opposed to estimates using LMP [228].

The date of conception is rarely known and ultimately GA is a 'best estimate'. Use of combined LMP and scan data comes with its own advantages and disadvantages and where possible in research, both measurements should be recorded and compared for discrepancies. Arguably, using scan data is more precise than LMP due to the reliance that LMP data has to place on maternal recall, regular menstrual cycles and particular socio-demographic factors. However, it is important to be aware of the bias that can occur in studies comparing exposed and unexposed groups, even when using what is widely believed to be a 'gold standard' measurement.

1.8.4 Critical exposure window

The nine months of pregnancy are a constantly changing time for the fetus. It is often postulated that there is a critical time period of exposure when the fetus is particularly susceptible to pollution exposure [229]. Identification of critical windows of exposure helps to identify potential biological mechanisms and a focus on these windows leads to better precision in exposure estimates and effects [38]. However, identifying these critical periods is particularly challenging and three main points have been raised as to the cause of this challenge: (1) different pollutants may act at different pregnancy time points, (2) the measured/estimated pollutants may be proxy markers of other pollutant(s) and (3) pollutant mixtures differ across location and time [186].

Most studies investigating exposure links to adverse perinatal outcomes have defined exposure windows either by trimesters [146] or pre and post conception months [40] and/or for the entire pregnancy period [75 117]. The evidence of a critical window of exposure in previous studies investigating the effects of air pollution on adverse perinatal outcomes is mixed which prevent any firm conclusions.

Most previous studies that specifically investigated the end of pregnancy in relation to gaseous pollutants and PTB have found no associations, particularly with NO_2 [39 40 155] and CO [40 158 160]. A recent study which developed a new spatio-temporal model to specifically identify susceptible windows of exposure in PTB concluded that focus should be on exposures in the first two trimesters of pregnancy [230]. Studies investigating particulate matter have also been inconsistent in trimester-specific results, but the strongest evidence is of an effect in the first trimester [39 153 157].

The evidence is also mixed for critical windows of exposure in terms of fetal growth. However, a number of studies have identified both early [194 231] and late [78 176] stages of pregnancy to be of most relevance. The first trimester is thought to be of particular susceptibility due to being the time for placental attachment and development occurring and the end of pregnancy because fetal growth is at its peak [38].

Little toxicological evidence exists to suggest whether effects might be due to short or long term exposure and if cumulative exposure should be considered. It may also be plausible to consider the lag effects of pollution exposure in the pre-conception period. Experimental studies have identified ambient air pollution, particularly NO_2, as having an impact on both female reproductive health [232] and male sperm quality [233]. Pre-conception exposure may also affect hormonal dysregulation or germ cell toxicity [234].

Results demonstrating exposure effects separately by trimesters or by months will aid in clarifying the uncertainty over the critical exposure period. It has been recommended that studies should explore shorter periods of susceptibility such as gestational months [38], however, this is reliant on accurate GA recording. Moreover, when it is possible to do so, it would be advantageous to study periods where effects may be amplified due to episodes of exceptionally high pollution levels, for example during the London smog in 1952 [4 6], the Meuse Valley fog of 1930 [235] and after the World Trade Centre attacks [236]. Further toxicological studies will be important in aiding knowledge on susceptibility windows.

1.8.5 Confounding

Confounding is "the distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome" [237]. The assessment of potential confounding in observational studies is of upmost importance, as are efforts to reduce it through appropriate study design and/or analysis. As there are complex relationships between environmental and social factors, the latter needs to be considered; also it is important to distinguish the true confounders from mediators of an exposure-outcome relationship.

There are two types of confounding factors which might affect the validity of studies on specific air pollutant associations with adverse pregnancy outcomes. First: environmental factors such as season, temperature and co-pollutants and second: maternal characteristics such as age, race, socioeconomic status, education and smoking. Many large scale epidemiology studies are based on historical, routinely collected data and so only limited covariate information may be available, thus affecting

the ability to assess confounding. An important aspect when considering confounders in the context of pregnancy and air pollution is deciphering where the confounding exists. We know that factors such as low socio-economic status and membership of an ethnic minority convey an increased risk of PTB and LBW [238]. If these groups of people are more likely to live within more polluted areas, then effects of these factors and pollution will be entangled, unless appropriate adjustments are made. For example, a study addressing air pollution disparities found that Hispanic, African-American and Asian/Pacific islander mothers experienced an increased mean pollution level compared to white mothers and were twice as likely to live in more polluted countries after adjusting for other maternal risk factors [239]. Black women have reported PTB rates in the region of 16-18% compared with 5-9% for white women [136] and may also be more likely to live in higher polluted areas [240]. Therefore, there may be a double jeopardy effect for certain populations in relation to PTB.

Meteorological factors have received very little attention as potential confounders. Only very recently have studies begun to adjust for factors such as seasonality, temperature, humidity and barometric pressure in the analysis. Seasonal variations in meteorological factors such as temperature have been found to correlate strongly with gaseous pollution levels and so the effects of temperature for example, could be mistakenly attributed to pollution. There is also evidence that meteorological factors have been associated independently with adverse perinatal outcomes across the world [40 163 241 242]. In the past two decades, seasonal patterns in reproductive outcomes have been reported across the world. Published studies from America [243 244], Northern Ireland [245], Scotland[246], England [247 248], Vietnam[249], Spain [250] and Japan [241] have all reported a seasonal pattern in birth numbers and adverse outcomes. The variation in patterns across the world has been

attributed to a number of different factors depending on the population. Environmental factors such as photoperiod and temperature are common explanations [251] for variations in pregnancy outcomes.

Deciphering if an association with a single pollutant represents its own effects or is acting as a surrogate marker for other pollutants is an important issue, and particularly pertinent when trying to study the effects of gaseous pollutants independently of particulate matter. Particulate matter and NO_2 for example, have been found to correlate quite strongly with one another, mainly as a result of them both being generated by combustion processes [252].

Residual confounding can occur in epidemiological studies where distortions of results remain even after confounders are controlled for in the design or analysis of a study. This can occur for three main reasons (1) data was not collected for certain confounders so could not be adjusted for (2) a confounder was not adjusted for adequately e.g. groups were not classified correctly and (3) errors occurred in the classification of confounding variables. It is well known that non-differential measurement error in an exposure generally leads to bias towards the null, however, less well known is it's effects on residual confounding; it has been suggested that residual confounding may be a cause of large exposure-outcome effect estimates [253]. Measurement error in certain variables is often unavoidable in large scale epidemiological studies, thus, residual confounding should be an important consideration when interpreting results.

1.8.6 Co-pollutant interactions

Little is known as to whether individual pollutants are interacting in a synergistic (effect of combination is greater than sum of individual effects) or antagonistic (effect of

combination is less than the sum of individual effects) way in the body or neither of these; that is, is the effect of one pollutant modified by the presence of another. A study characterizing air pollution and weather variables in the context of health effects models suggested the need for caution in including particulate matter and gaseous pollutants in health effects models simultaneously, to avoid biased effect estimates of individual pollutants [252]. Most studies have not adjusted for other pollutants [68 146 164]; although this could place limitations on identifying pollutant specific effects, it is likely that effect estimates will be erratic with large standard error if highly correlated pollutants are adjusted for. This is a methodological area that requires further work into more complex correlated exposure modelling, which has begun to be addressed in the field of exposure science [254].

1.9 Aims and objectives of the thesis

1.9.1 Overall aim

The primary and overarching aim of this thesis is to quantify the effects of air pollution on the adverse perinatal outcomes preterm birth, low birth weight and small for gestational age in North West England.

1.9.2 Specific objectives

The specific objectives of this thesis in order to fulfil the primary aim are:

1. To evaluate commonly used air pollution exposure estimation techniques used in previous large scale epidemiological studies to inform a decision on the estimation technique/s to be employed to fulfil the primary aim;
2. To investigate if living in close proximity to a major road in North West England increases the risk of an adverse perinatal outcome;
3. To estimate the risk of exposure to individual pollutants based on air pollution estimates identified by specific objective (1), on adverse perinatal outcomes;
4. To determine the critical windows of exposure from air pollution, if any, during pregnancy.

Chapter 2: Materials and Methods

2.1 Chapter Introduction

This Chapter includes a description of the materials and methods for the three main papers in the thesis which are presented in Chapters 3, 5 and 6. This Chapter is split into **five** main sections.

The **first** section describes the methods for the prospective study of a comparison between pollution estimation techniques with personal exposures in a pregnant cohort presented in Chapter 3 in more detail; covering the design of the study, the materials used and the analysis techniques.

The **second** section describes the study population from the 'North West Perinatal Survey Unit' (NWPSU) which is utilised as a retrospective cohort in Chapters 5 and 6. The second section goes on to define the outcome measures which are used consistently from this point on in the thesis. The confounders' selection procedure and categorization for the later chapters are also explained.

The **third** and **fourth** sections outline the exposure assessment methodology involved in the studies presented in Chapters 5 and 6. The **third** section describes the methodology for the proxy air pollution measure of 'proximity to major road' in relation to the NWPSU population. The **fourth** section describes the two exposure assessment methods used to quantify air pollution exposure in the NWPSU; this includes the fundamental development of the background modelled concentrations from DEFRA, how the model was temporally adjusted, a summary of the stationary monitors selected for the air pollution data extraction and how missing pollution data was handled.

The **fifth** section of this Chapter comprises the statistical methods used in Chapters 5 and 6.

2.2 Methods for Chapter 3

2.2.1 Study design

The study described in Chapter 3 is: 'A prospective comparison study of air pollution estimation techniques with personal exposures in a pregnant cohort'. The study was based on two study areas which included two antenatal clinics within hospital sites in Manchester and Blackpool. Participants were recruited between October 2010 and July 2011. Women were eligible for inclusion into the study if they were booked at either St Mary's hospital in Manchester or Victoria hospital in Blackpool and were less than 20 weeks gestation when approached. The exclusion criteria were women who were planning to move away from the study area (NW England) in less than 1 year, current smokers and women without a fluent grasp of the English language. Once recruited into the study, the consent procedure was fully explained and if the participant agreed, the consent form was signed along with a witness if possible (consent form included in Appendix 3). Participants were asked to complete three aspects of the study at two different time points in their pregnancy. Two questionnaires were delivered to participants; the first in person with the participant between 4-20 weeks gestation and the second delivered over the phone three months later (between 24-36 weeks gestation). Participants were also instructed to wear a personal air pollution sampler for 48-hours before the 24th week of pregnancy. At the corresponding time to the 48-hour personal monitoring period, a time-activity (TA) log was completed indicating the microenvironment location of the participant at half hourly time periods. The personal sampler, questionnaire and TA log are explained in more detail later in the Chapter.

The study procedure is outlined in the flow diagram below in Figure 17:

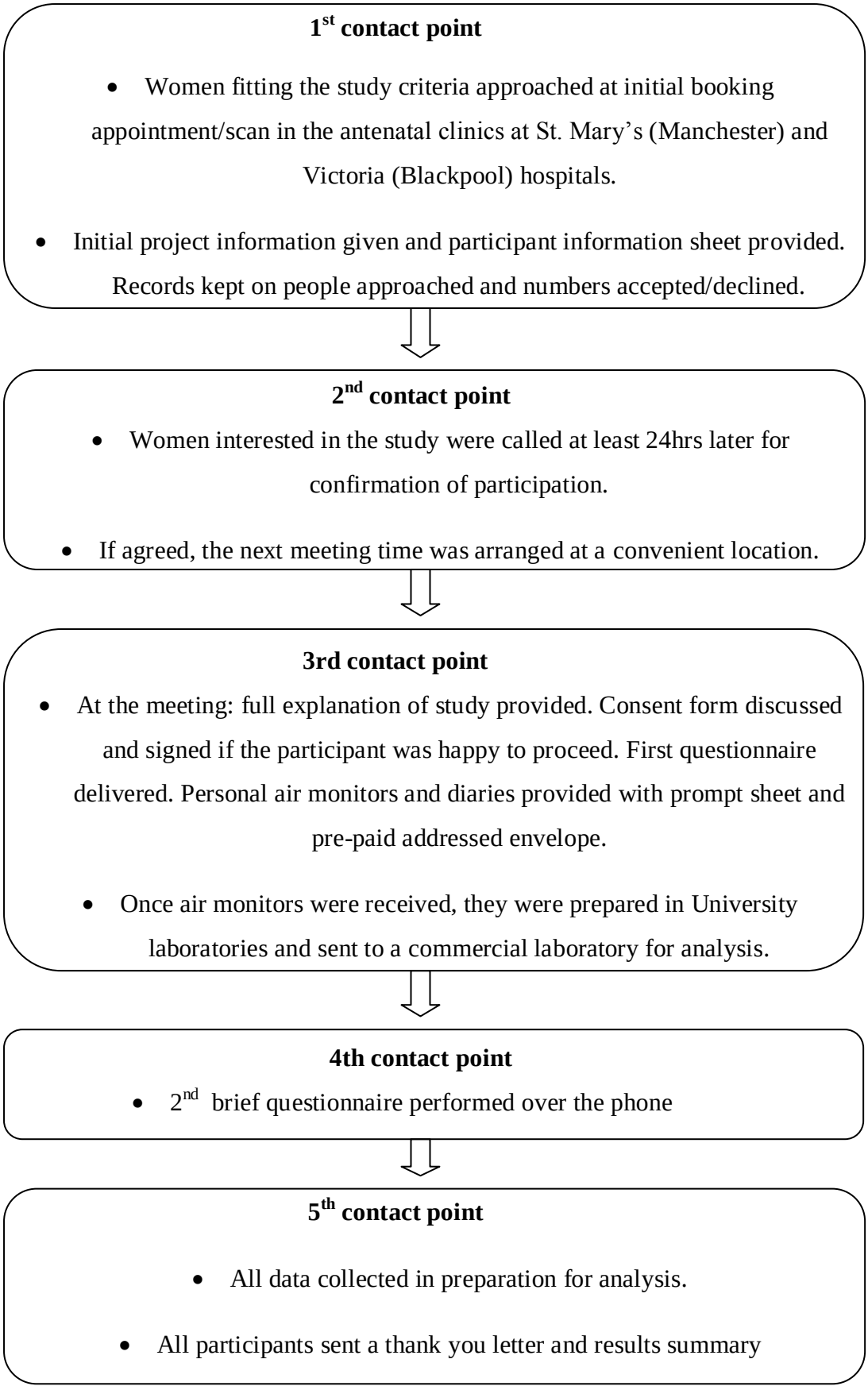

Figure 17: Flow diagram of study procedure described in Chapter 3.

2.2.2 Ethics

A fundamental part of planning any medical research study is the ethical considerations to ensure the rights, dignity and well-being of the participants involved. The prospective exposure comparison study involved the recruitment and follow up of subjects during their pregnancy. Personal identifiable information was collected and stored from the participants during and for a short period after data collection was completed. A number of ethical considerations were discussed and relevant safeguards put in place before the start of the study. The main ethical considerations for this study were: that the study entailed no adverse risks to their health and well being, to ensure that participants were fully aware of why the research was being carried out, what exactly would be required of them if they participated (to ensure informed consent could be provided), clarity that participation was entirely voluntary, that their decision to participate would not affect the care they received at any point and that all data collected would be handled confidentially in line with the Data Protection Act (1998).

The official ethics process for prospective research studies taking place between a University and NHS trust was adhered to for this study. The study protocol and additional documents were reviewed and approved by the University of Manchester ethics committee. The protocol, IRAS (Integrated Research Application System) form and relevant documents were then submitted to the Greater Manchester Regional ethics committee for approval. This involved a meeting with the committee to answer any outstanding questions relating to the project and to discuss any required amendments of study documents to ensure that all ethical issues had been addressed appropriately. Once Regional ethics approval was confirmed, written permission was sought from both trusts of the hospital sites involved in the project: St.Mary's hospital, Manchester and

Victoria hospital, Blackpool. The NHS approval was through the R&D (research and development) system. The R&D process is for the site specific NHS hospitals to ensure that there are adequate and realistic arrangements and resources set in place for the study to be successful. Once the study began, no further issues relating to ethics arose.

2.2.3 Data management

Data confidentiality was one of the most important ethical issues for this project. Each participant was issued with a unique study identifier which was used in electronic records to protect their anonymity. The key linking names and study identifiers was held by the principal investigator only and stored in a locked filing cabinet inside a key card protected office. The electronic data were kept in a password secured folder with no identifiers for the participants. A hard copy of any data was kept in a securely locked filling cabinet and will be destroyed within six months of the overall projects completion. No identifiable personal details were used when writing up the research for private or public viewing. It was agreed with the ethics committee that with the safe guards set in place that there was a very low risk of a participant being identified from the anonymous data held.

2.2.4 Recruitment

Women were recruited into the study almost solely based on approach in the waiting room of the antenatal clinics in Manchester (St. Mary's) and Blackpool (Victoria). Posters and flyers were also generated and ethically approved for the study (Appendix 3). A link was made with both antenatal teams who were fully aware of the study process to ensure recruitment did not interrupt the normal running of the clinic and potential participants could be identified by other members of staff if appropriate.

Before recruitment began, time was spent shadowing an experienced research midwife and appropriate training courses were attended (including 'Good Clinical Practice' and 'lone worker' training).

Recruitment into the study was primarily performed by the principal investigator of the project in both study locations. Due to the challenge of two study locations and one researcher performing the recruitment and follow-up of all participants, the decision was made to liaise with Blackpool and Fylde hospital trust research team to ensure the successful completion of the project and maintain recruitment figures. The project was accepted onto the UK Clinical Research Network (UKCRN) portfolio database at the beginning of the project in 2010; this portfolio is set up to monitor and support high quality research projects within NHS hospital trusts and enables the provision of some research staff support to aid projects. As a result, a research midwife from Blackpool antenatal clinic agreed to assist on the project for 3hrs/week during the final 4 months of the study. To ensure consistency in how participants were recruited and the information provided at the main meeting point with participants, several occasions of 'shadowing' one another took place. An important point that was agreed upon with the research midwife was the response to women who had concerns during the recruitment phase relating to the harm that air pollution may cause to their baby after raising the main aim of the project. It was agreed that to allay concerns we would always reassure the women that we spoke to that although there was some evidence to suggest high levels of air pollution may have some effects in pregnancy, we do not know exactly what the risks are and this is why we are carrying out the study. There was also an email address and phone number available to them if the participants remained concerned.

2.2.5 Personal monitoring

Personal air pollution measurements were undertaken using the Ogawa personal sampler for the prospective exposure estimation comparison study (Chapter 3). The Ogawa sampler was chosen for a number of reasons: (1) It had been used previously in a number of human exposure studies around the world [255 256] (2) It is a cost effective technique to measure two closely related pollutants simultaneously which was desirable for this study [257] (3) It is small and unobtrusive for the user and (4) Sampling begins as soon as it is removed from an air tight bag and does not require any additional action by the individual undertaking the sampling [51].

The pollutants measured in this study were NO_x and NO_2. This decision was based on previous literature of the health effects from air pollution where NO_2 had been identified as one of the pollutants most likely to be associated with respiratory [258] and cardiovascular [259] conditions, as well as adverse pregnancy outcomes [60]. NO_2 can also have a higher spatial variation that other traffic-related air pollutants (for example particulate matter) [10]. Other oxides of Nitrogen, such as NO [60], might also have a role to play in health effects, thus NO_x was measured simultaneously with NO_2.

The inclusion of particulate matter (PM) measurements was considered for this study, however, the PM measurement devices were more expensive and cumbersome. An active PM sampling monitor (Sidepak Personal Aerosol Monitor AM510) was piloted before making a final decision on the exposure assessment technique. The piloting was performed with two pregnant volunteers for a 48hr period and feedback obtained. The feedback was negative in terms of the imposing nature of the monitoring when carrying out normal activities. It was decided that it would not be feasible for this study because

of study costs, over burdening participants and potentially altering the behaviour of participants.

The Ogawa sampler is a badge with two end chambers which allows simultaneous monitoring of NO_x and NO_2. Pre-coated collection filters are placed between two circular gauzes which are coated with specific absorbents. The filters and gauze are secured by a diffuser end cap with 2mm diameter holes. For the measurement of NO_x and NO_2, the NO_2 filter is coated in triethanolamine (TEA) and the NO_x filter is coated with TEA and an oxidizing agent (2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide) which converts NO to NO_2 [51 257]. TEA is quite toxic; however, this posed no risk to the participants due to the small quantity used in each sampler. The Ogawa monitors can operate at temperatures ranging from -10 to 40°C and at relative humidity ranging from 50 to 80%.

The participants were provided with written and verbal instructions of how to carry out the sampling procedure. Each sampler number was linked to the participant's unique anonymous ID number. The participants were instructed to carry out the sampling for a full 48hours. This time period has been used by previous studies [37 45 260], chosen so as not to over-burden the participants and minimize the chance of sampler losses, whilst still capturing a 'normal' representative exposure. To initiate the 48hr personal sampling period, the Ogawa sampler was removed from an air tight bag and attached to the upper chest area, as near to the breathing zone as was comfortable. During the night, participants were instructed to place the personal sampler by their bed. The samplers were returned in the air tight bag after the completed 48hour sampling period and returned by post in pre paid padded envelopes. This was explained verbally in the meeting with a demonstration and written instructions were provided (included in

Appendix 3). The coated filters were then extracted from each sampler in laboratory conditions, placed into individual vials with the labelled unique ID number and sampler number and sent to a commercial laboratory for analysis.

2.2.6 Questionnaire data & Time-activity logs

Two questionnaires were delivered to participants during the study. At the main meeting point with the participant (<22 weeks gestation), a comprehensive questionnaire was delivered face to face (questionnaire 1) and three months after this point, a second less substantial follow up questionnaire collecting any details which had changed from questionnaire 1 was delivered over the phone (questionnaire 2). This thesis presents only results based on data collected from questionnaire 1. This decision was made for two main reasons: (1) It was felt in hind-sight that the additional data collected in late pregnancy did not help to answer the research questions intended for the study described in Chapter 3 (2) The main purpose of the additional questionnaire was to ascertain changes in activity patterns in pregnancy, however, questionnaire 2 relied on participant recall of activity patters rather than a real time log and may not have been robust enough on which to base firm conclusions.

The main early pregnancy questionnaire broadly collected data on four main areas (the full questionnaire can be found in Appendix 3):

1. Personal information (Current/previous/work addresses, age, parity, ethnicity and health status).
2. Education and Employment
3. Home environment details (area of residence, use of heating/ air conditioning)

4. Lifestyle (cooking behaviour, transport usage, smoking/environmental tobacco smoke exposure, time spent outdoors and perceptions of air pollution exposure.)

The time-activity (TA) log was based on previous studies investigating TA patterns [45] [261] and adapted to fit with the study aims as well as ensuring that there was no unnecessary burden on participants (full version of the TA log can be found in Appendix 3). The TA log requested information at half hourly intervals for the corresponding 48hour period of personal monitoring. The participant used tick boxes to state whether they were in a rural or urban environment and what microenvironment they were in (outdoor/indoor/travel).

The questionnaires and TA log were developed and improved upon in a four stage process to ensure they were suitable for use with study participants.

1. The questionnaires and TA log were initially drafted based on the information required to answer the original research questions of this study.
2. Input was then sought from academics from a range of disciplines (environmental health, biostatistics, obstetrics and maternal and fetal health).
3. The questionnaire was piloted by 40 women in the Manchester antenatal clinic and asked to report back on the understanding and ease of answering the questions.
4. Finally, all participant documents were presented and reviewed by a user involvement group in St. Mary's hospital, Manchester (July, 2010). The group included lay members of the public who had recently had experience of the antenatal department, clinicians and other researchers in the area.

On the basis of the above, the final versions included in Appendix 3 were adopted.

2.2.7 Statistical analyses

The primary aim of this prospective study was to quantify the correlation and agreement between personal exposures and air pollution estimation techniques commonly used in large scale epidemiological studies. To describe the study population and the personal air pollution exposure data, descriptive statistics were used. To assess the correlations, Spearman rank correlation coefficients were calculated between the personal exposures (PE) and the exposure estimation techniques. The decision was made to present the rank correlations because the priority was to identify an estimation technique that could appropriately rank exposures correctly i.e. the estimation techniques picking up the high concentrations that matched to the high PE measurements and the low with the low. Agreement was quantified using the absolute difference (AD) and the mean ratio between the PE and the estimation techniques investigated.

As women from two study locations were included in this study, differences in the correlation coefficients between the locations were of interest. A test of difference based on a Fisher transformation was used to obtain a two-tailed p-value [262]. The calculated p value allowed us to determine if the correlation coefficients were statistically significantly different from one another ($p<0.05$).

All statistical analysis for this study was performed using SPSS (version 16) or STATA (version 9.2/12).

2.3 Study population methods for Chapter 5 & 6

2.3.1 The North West Perinatal Survey Unit database

The North West Perinatal Survey unit (NWPSU) based in St. Mary's hospital, Manchester collected audit data spanning nearly two decades of birth outcomes in North West (NW) England. This pre-collected dataset was used as the outcome assessment data source in the main analyses of this thesis (Chapter 5 & 6).

The initial objective of setting up the NWPSU database in 1990 was to 'establish a comprehensive database that could be used for both clinical and administrative staff for audit purposes.' [263]. It has since been utilized for research purposes [264]. A standardized birth register was introduced to the maternity units in NW England to collect the information for the database using a systematic approach. It was the midwife's responsibility in each participating hospital to manually complete maternal and neonatal information prior to discharge from their care. This data was then input into a computerized database.

Over the years, the quality and quantity of data collected improved. From 2004 onwards there was a substantial increase in the number of maternity units involved in data collection and the type of information recorded became more detailed. Twenty one out of the twenty nine maternity units in the NW region were contributing data to the NWPSU by 2004 and information on around 55,000 births per year were recorded.

Listed below are the variables data was collected on for each maternal and neonatal pair at the time of delivery from 2004 to 2008:

Table 16: Variables collected in the NWPSU dataset

Maternal information	Birth outcome information
Hospital name	Date of delivery
Postcode	Type of delivery
Region	Delivery number
Ethnicity	Livebirth / stillbirth
Mothers DOB	Type of death
Maternal age	Multiple birth
Maternal height	Gestational age by last missed period
Maternal weight	Gestational age by scan
BMI at booking	Apgar scores
Parity	Birth Weight
Agreed estimated date of delivery	Mother/baby skin to skin contact at birth
Smoking at time of delivery	Gender

A limitation of many large databases, particularly when collecting data from multiple sites is the quality of the data. The NWPSU database was designed and managed for audit purposes and not directly for research. As a result, data cleaning work was required to address four main areas of data quality concerns before the dataset was ready for use: Missing and implausible values, duplicate entries and heterogeneity of variable names across years.

In response to the concern of implausible values within the dataset, rules were made and implemented through a combination of evidence from the literature and expert obstetric advice. The main rules set to eliminate implausible values were:

1. Birth weight outside of 400-5500grams was deemed implausible and set to missing.

2. Live births with a GA <24 weeks and >44 weeks was deemed implausible and set to missing.

3. Birth weight >1500g at a GA of <28 weeks was deemed implausible and set to missing.

4. Birth weight >2800g at a GA of <32 weeks was deemed implausible and set to missing.

5. Maternal age outside of 13-60 years was deemed implausible and set to missing.

6. Maternal height outside of 1.4-1.9 meters was deemed implausible and set to missing.

7. Maternal weight outside of 40-150 kilograms was deemed implausible and set to missing.

2.3.2 Definitions of outcome measures

The adverse pregnancy outcomes investigated in this thesis (in Chapters 5 and 6) are low birth weight (LBW), small for gestational age (SGA), preterm birth (PTB) and spontaneous preterm birth (SPTB). As explained in Chapter 1.5, the outcomes were defined as:

1. **LBW:** Birth weight <2500g [265]

2. **SGA:** <10th percentile of birth weight for gestational age and sex within the NWPSU population [116]

3. **PTB**: <37 weeks completed gestation [119]

4. **SPTB**: <37 weeks completed gestation excluding elective deliveries [119].

For gestational age measurements (GA) for the outcomes SGA, PTB and SPTB, last menstrual period (LMP) data from the NWPSU dataset was used wherever available and GA from scan data was when LMP data was missing, or when discrepancy exceeded seven days.

2.3.3 Confounders

Confounders were decided on *a priori*, based on previous literature and biological plausibility. To aid in the decision process of selecting the appropriate variables as confounders in the analyses investigating the effects of air pollution on adverse perinatal outcomes, an exploratory causal diagram based on the outcome PTB was proposed. Figure 18 presents possible pathways between PTB and factors thought to be involved in the relationship between air pollution and PTB. A coding system has been used to highlight which variables are believed to be confounders (a factor which influences both the exposure and outcome resulting in a distortion of the apparent effect [237]) and which are risk factors or mediators (occur on the causal pathway from an independent to a dependent variable [237]) for the outcome. The straight arrows represent the direction of a likely association and the broken arrows denote a possible/tenuous direction of an association. Due to the complexities of the relationships, the causal diagram is not an exhaustive description of all possible relationships, but more to serve as a guide for the main analyses in this thesis.

This *a priori* exploration of potential confounders led to the decision that for all the analyses investigating the association between air pollution and adverse perinatal outcomes, the following variables should be adjusted for: maternal age, birth season, ethnicity, body mass index (BMI), socio-economic status (SES), smoking and parity.

Parity and BMI are indicated as risk factors and not confounders in the diagram, however, it was decided that they should be adjusted for in the analyses due to the complex relationships with SES and because they are strong risk factors for the adverse pregnancy outcomes investigated. The evidence for the confounders in terms of their relationship with both air pollution and adverse perinatal outcomes is described later in Chapter 5.

All of the confounders were treated as categorical variables:

- **Maternal age**: <20, 20-24, 25-29, 30-34, 35-39 and 40+ years
- **Birth season**: Winter (December-February), Spring (March-May), Summer (June-August) and Autumn (September-November)
- **Ethnicity:** white / non-white
- **Parity:** 1st order birth (nulliparous) / higher order birth (multiparous)
- **Body Mass Index:** Underweight (<18.5), normal (18.5-24.9), overweight (25-29.9) and obese (>30)
- **Socio-economic status (SES)**: Quintiles of deprivation based on English National Standards of 'Index of Multiple Deprivation' scores [266]
- **Smoking:** Smoker / Non-smoker at time of delivery

The covariate data were all included in the NWPSU dataset apart from a measure of SES. This was calculated using the maternal postcode at the time of delivery to extract an 'Index of Multiple Deprivation' (IMD) score using the *geoconvert* software [267]. The measure was first made available in 2004, updated in 2007 and the most recent update was in 2010 [266]. For the analyses in this thesis, the 2007 version was used as this was

the most up to date version that corresponded to the time period under investigation (2004-2008). The score is a 'lower super output area' (LSOA) measure of deprivation comprising of seven indices of deprivation with a specific domain weighting: income (22.5%), employment (22.5%), health and disability (13.5%), education (13.5%), living environment (9.3%), crime (9.3%) and barriers to housing and services (9.3%) [266]. Super output areas were designed in 2004 to improve the reporting of small area statistics. There are 32, 544 LSOAs in England, within each one the population range is 1,000-3,000 people and the household range is 400-1,200 [268]. The IMD score is currently regarded of as one of the most comprehensive methods to quantify socio-economic status at a relatively fine spatial level if a direct method is not available [269].

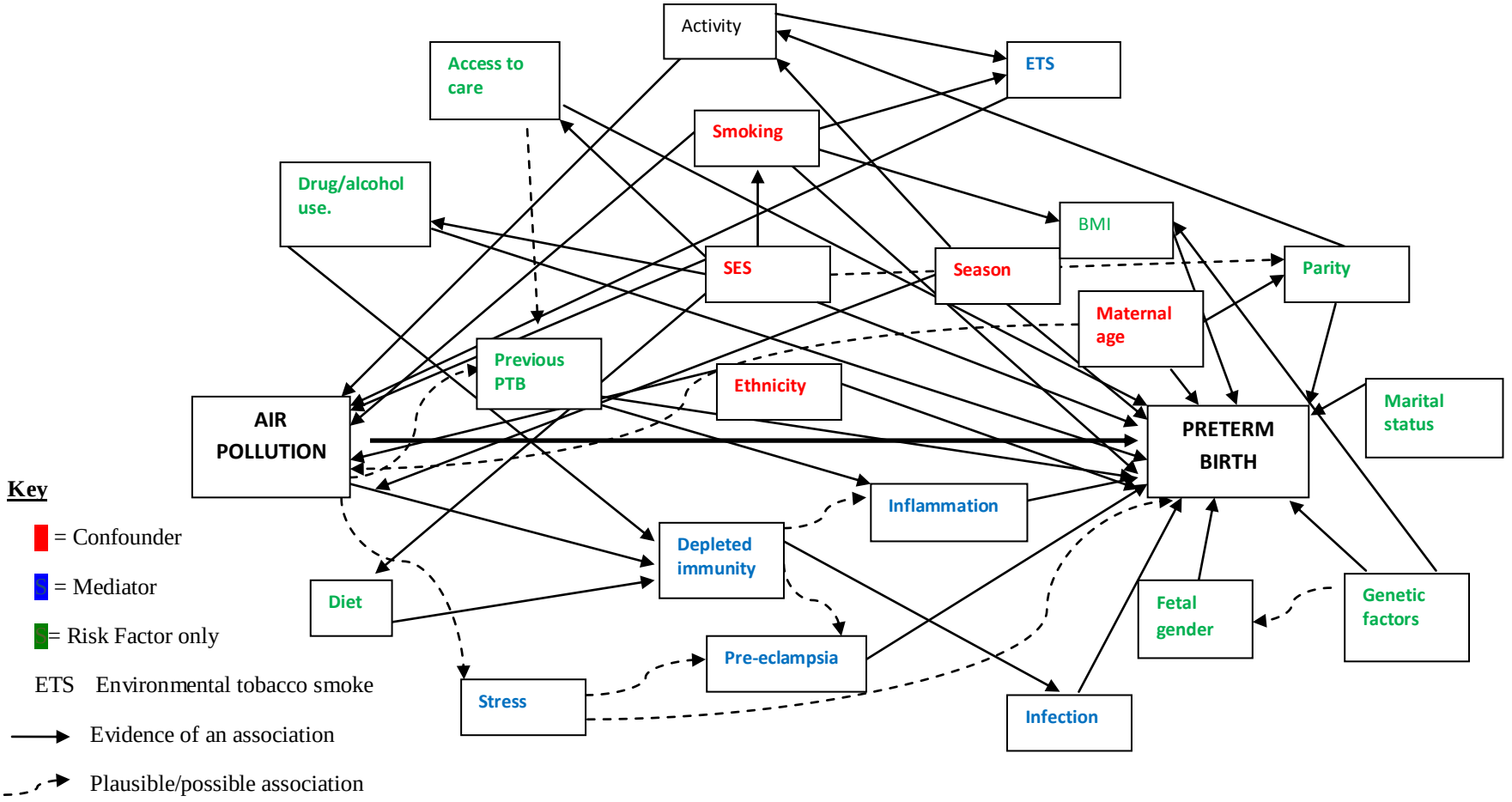

Figure 18: Factors associated with air pollution and/or preterm birth.

2.4 Exposure assessment methods for Chapter 5

Chapter 5 is the study entitled 'Maternal residential proximity to major roads in North West England and adverse pregnancy outcomes'. The pregnancy outcome data for this study was derived from the NWPSU dataset as described above and the exposure assessment was based on proximity to major roadways in the NW England study population which is described below.

2.4.1 Road network data

The UK major road networks were obtained from the freely available Department for Transport website [270]. A major road is defined as all motorways and 'A' roads [271]. The road network data was downloaded and mapped using *ArcGIS* software. The NWPSU postcodes were mapped as an additional layer to the road network data layer and the 'join to nearest' GIS function was used to calculated the nearest linear distance from the postcode points to the major road.

The continuous distance variable was dichotomized to those living <200m and ≥200m from a major road. Major roads only were used in this analysis as a means of restricting the proxy measure of air pollution to high exposure only. The cut-off point of 200m was used to categorize the 'low' and 'high' exposure groups. This decision was primarily based on the air pollution distance decay literature that demonstrates the exponential decay in pollution concentrations from a roadway until a plateau at around 300m where concentrations largely return to background levels [66]. Another important consideration was to be consistent with previous epidemiological studies which have investigated the effects of air pollution using the proxy method of distance to roadway and effects on

perinatal outcomes to enable comparability between results [68 165]. A sensitivity analysis was also performed to investigate associations at additional closer proximities.

2.5 Exposure assessment methods for Chapter 6

Chapter 6 is the study entitled: 'Air pollution exposure increases risk of small for gestational age in a large UK birth cohort: use of a novel spatio-temporal modelling technique'. This study, as with Chapter 5, uses the birth outcome data from the NWPSU dataset described above. The exposure assessment for this study includes two separate methods: (1) Estimates concentrations based on a temporal adjustment to background modelled air pollution concentrations from a model previously developed by DEFRA and (2) A nearest stationary monitor technique.

2.5.1 Background modelled air pollution concentrations

Annual mean background modelled air pollution data for NO_x, NO_2, PM_{10} and $PM_{2.5}$ were obtained from the publicly available DEFRA website (CO was unavailable during the time period of our study) [90]. Concentrations were modelled at a fine spatial resolution of 1km² using the 'pollution climate model' (PCM). The full methodology and validation has been described in detail in a number of reports by DEFRA and AEA technology [89 91 272]. The model has been externally validated by an air quality expert panel which concluded that the model performed well in independent comparison tests [72]. The PCM has been developed in a modular form with pollution specific methodologies. The background concentrations of NO_x and NO_2 extracted for use in this study were calculated by summing concentrations from the following layers [272]:

- Large point sources: modelled using an air dispersion model (ADMS) and emissions estimates from the National Atmospheric Emissions Inventory (NAEI).
- Small point sources: modelled using the small points model and emissions estimates from the NAEI.
- Distant sources: characterised by the rural background concentration.
- Area sources: modelled using a dispersion kernel technique and emissions estimates from the NAEI.

NO_2 was additionally calibrated using an oxidant-partitioning model which describes the inter-relationships between NO, NO_2 and O_3 [272 273].

For PM_{10} and $PM_{2.5}$, the background maps were calculated using the following layers [272]:

- Secondary inorganic aerosol: derived from measurements of SO_4^{2-}, NO_3^- and NH_4^+ at rural sites.
- Secondary organic aerosol: semi-volatile organic compounds formed by the oxidation of non-methane volatile organic compounds.
- Large point sources of primary particles: modelled using ADMS and emissions estimates from the NAEI.
- Small point sources of primary particles: modelled using emissions estimates from the NAEI.
- Regional primary particles: from results from the TRACK model (Trajectory model with Atmospheric Chemical Kinetics) and emissions estimates from the NAEI.

- Area sources of primary particles: modelled using a dispersion kernel and emissions estimates from the NAEI.
- Iron and Calcium rich dusts: Measured from a combination of actual measurements and a dispersion kernel technique.
- Sea salt: derived by interpolation and scaling of measurements of chloride at rural sites.

2.5.2 Stationary monitor air pollution data

Monthly and annual mean concentrations from 2004-2008 of NO_2, NO_x, CO, $PM_{2.5}$ and PM_{10} were extracted from the publicly available online data source from DEFRA [274]. Data was obtained from eight stationary monitors including: Manchester Piccadilly, Manchester South, Blackpool Marton, Preston, Salford, Wigan, Wirral Tranmere and Liverpool Speke. The stationary monitor sites at Bury, Blackburn Darwen and Carlisle were excluded because they were roadside monitors set up specifically to capture roadside pollutants and would be unlikely to provide representative concentrations of a wider area. The monitoring site at Warrington was excluded due to pollutant data not being captured before 2008 and the site at Glazebury was excluded because it was a rural background site and measured a limited suite of pollutants. The stationary air monitor locations in North West England are presented in the map below (Figure 19), with the included monitors for this study labelled.

For each of the eight sites, monthly adjustment factors (MAFs) were calculated where data were available for each of the sixty months between January 2004 and December 2008 by dividing the monthly mean by the annual mean.

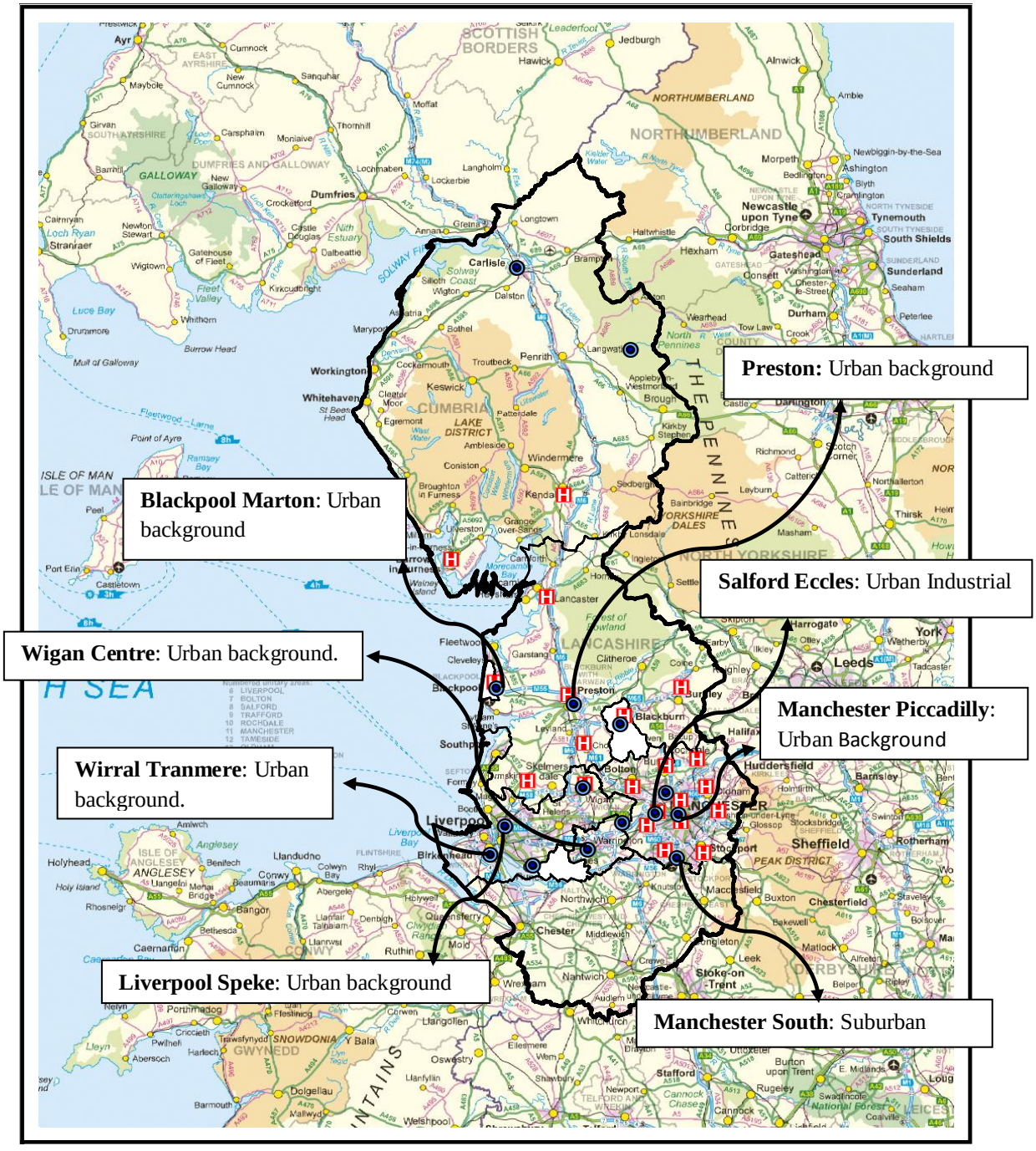

Figure 19: Map of the included stationary monitor sites in NW England

2.5.3 Temporal adjustment of background modelled air pollution concentrations

The extracted annual mean modelled concentration data was temporally adjusted by month for the sixty months spanning January 2004 to December 2008. The nearest stationary monitor of the eight included sites was calculated for each centroid point of each 1km² grid using the 'join to nearest' function in ArcGIS. This identified the monitoring site from which the MAF should be taken from to adjust each grid.

2.5.4 Missing data

Missing air pollution stationary monitor data was quite common (as detailed below). The missing data can occur due to a fault with the monitor, data not inputted or a monitoring station may have stopped measuring a specific pollutant during the study period.

Missing monthly or annual mean pollution values from the stationary monitors in the studies described in this thesis would have resulted in missing exposure estimates for some births in the main analysis and ultimately a loss of statistical power. Of the monthly mean data, 33% of CO data was missing, 10% NO_2 and NO_x, 25% PM_{10} and 93% of $PM_{2.5}$ data. Data on $PM_{2.5}$ was only collected at the Manchester Piccadilly monitoring site.

The decision was made to generate an imputation strategy to reduce the amount of missing pollution estimates from the eight stationary monitors used in the nearest stationary monitor technique and for the temporal adjustment to the PCM model.

The imputation method used a simple hierarchal approach so as to include all possible scenarios of missing data imputation required and a preferred order by which to impute the data.

A two stage approach was taken which included both a *'quantitative'* and a *'qualitative'* method for choosing the most appropriate replacement site from which to impute the MAFs from. The quantitative method was the preferred method and the qualitative method was the second choice method if the quantitative method was not possible.

The quantitative method was performed by substituting the MAFs from a replacement monitor for the corresponding time period by calculating the standard deviations (SD) of the difference between each stationary monitor pair using only the months with complete data. The monitor pair with the smallest SD was then selected. This was done separately for PM_{10} (Table 17) and NO_2 (Table 18) under the premise that it is likely these pollutants would behave in a different temporal and spatial way to each other due to source and composition differences (as described in Chapter 1.3). The NO_2 results can be applied to the NO_x data and the PM_{10} to the $PM_{2.5}$ data.

The qualitative method involved selecting the nearest (geographic proximity) same 'type' of stationary monitor as the replacement monitor to impute from (e.g. urban background with nearest urban background etc.), as demonstrated in Table 19.

A record was kept for each MAF in the main dataset as to whether it was based on an imputation or original data. Sensitivity analyses including and excluding the imputed data were performed on the main analyses investigating the associations between air pollution and adverse pregnancy outcome in Chapter 6.

Table 17: Quantitative technique: Stationary monitor replacement decision based on standard deviation values between sites using 24 months of complete data for PM_{10}

Site name	Replacement site	Standard deviation
Manchester Piccadilly	Wigan	0.095
Manchester South	*Data unavailable*	
Blackpool	Preston	0.143
Preston	Wigan	0.085
Salford	Wigan	0.075
Wigan	Salford	0.075
Wirral Tranmere	Preston	0.135
Liverpool	Manchester Piccadilly	0.117

Table 18: Quantitative technique: Stationary monitor replacement decision based on standard deviation values between sites using 36 months of complete data for NO_2.

Site name	Replacement site	Standard deviation
Manchester Piccadilly	Preston	0.179
Manchester South	Salford	0.216
Blackpool	Wirral Tranmere	0.183
Preston	Wirral Tranmere	0.149
Salford	Wigan	0.161
Wigan	Wirral Tranmere	0.159
Wirral Tranmere	Liverpool	0.144
Liverpool	Wirral Tranmere	0.144

Table 19: Qualitative technique: *A priori* suggestion of monitor replacement decision.

Site name	Replacement stie
Blackpool	Preston
Preston	Blackpool
Manchester Piccadilly	Salford
Manchester South	Average Salford and Manchester Piccadilly
Wigan	Average Preston and Salford
Liverpool	Wirral
Wirral	Liverpool
Salford	Manchester Piccadilly

Hierarchal imputation method:

1. If >75% daily data within the month is missing, month was set to 'missing'.

2. Monthly adjustment factors calculated for each site for each month for each pollutant where possible using: *monthly mean/annual mean.*

3. Impute the missing MAFs:

    a. Use the MAFs from the replacement site indicated by the 'quantitative' method (Table 17 and 18). If these data are missing:

    b. Impute the MAFs using the site indicated by the 'qualitative' method in Table 19. If these data were also missing:

    c. Impute with the NW average from the complete stations for that month.

4. For PM_{10} data in Manchester South where no data existed for the quantitative method to be used, impute an average of the MAFs from Salford and Manchester Piccadilly.

5. For $PM_{2.5}$ data which has only been collected in Manchester Piccadilly: For 2004-2007, impute performed using PM_{10} MAFs for each individual site and month and calibrated by multiplying the value from $PM_{2.5}$ /PM_{10} MAF from Manchester Piccadilly. For 2008, the average calibration factor of 2004-2007 was used.

2.5.5 Merging exposure and outcome data

The complete exposure dataset was merged with the NWPSU outcome dataset, matching each month of the pregnancy time period for each subject to the corresponding monthly estimates based on the nearest stationary monitor and temporally adjusted PCM estimates.

Exposure estimates were assigned to each participant for the three months pre-conception and each month of pregnancy up to the date of delivery. Date of conception was calculated based on the gestational age subtracted from the date of delivery.

The easting and northing coordinates of maternal residence at the time of birth were matched to the nearest centroid point of the 1km² PCM grids using the *'distmatch'* command in STATA.

2.6 Statistical analyses

All statistical analyses were performed using SPSS (v.16) or STATA (v.9.2/12).

Descriptive statistics were used to present the results on the study population and air pollution estimates in the studies described in Chapters 5 and 6.

In Chapter 5, logistic regression models were used to determine if living in close proximity to a major road (<200m) increased the risk of an adverse perinatal outcome. The pregnancy outcomes under investigation (LBW, SGA, PTB and SPTB) were each treated as dichotomous variables, for example, all births defined as LBW (<2500g) were coded as '1' and all other births were coded as '0'. The covariates adjusted for in the analysis were: Maternal age, ethnicity, IMD, birth season and parity. Further

adjustments of BMI and smoking were made separately due to the substantial missing data on these variables. These variables are described above in section 2.3.3.

In Chapter 6, logistic regression models were used in the analysis to quantify the risk of air pollution on the dichotomous adverse pregnancy outcomes SGA and PTB. Linear regression analyses were used for the continuous measure of birth weight to determine change in birth weight in grams. Air pollution concentrations based on spatio-temporal modelled estimates and nearest stationary monitor estimates were categorized into quartiles for each technique and pollutant, based on the distribution of the values for the average of the whole pregnancy period. The lowest air pollution quartiles were used as the reference categories.

Adjustments were made in the regression models for maternal age, ethnicity, birth season, parity, IMD, BMI and smoking. Tests for trends were performed for each pollutant by including the pollution estimates as continuous variables in the regression models.

To investigate potential critical windows of exposure, pollutant estimates were averaged across the whole pregnancy period as well as for four distinct pregnancy periods: three months pre-conception, 1st trimester, 2nd trimester and 3rd trimester up to birth. Regression analyses were performed for each of these time periods.

Stratification by fetal gender was also performed based on previous evidence suggestive of a differential effect of air pollution on gender [179 275].

A sensitivity analysis was performed using only the original non-imputed air pollution estimates to explore the difference in effect sizes between the two data groups.

This chapter (Chapter 3) is the published paper:

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3. A comparison of population air pollution exposure estimation techniques with personal exposure estimates in a pregnant cohort

3.1 Abstract

There is increasing evidence of the harmful effects for mother and fetus of maternal exposure to air pollutants. Most studies use large retrospective birth outcome datasets and make a best estimate of personal exposure (PE) during pregnancy periods. We compared estimates of personal NO_x and NO_2 exposure of pregnant women in the North West of England with exposure estimates derived using different modelling techniques. A cohort of 85 pregnant women was recruited from Manchester and Blackpool. Participants completed a time-activity log and questionnaire at 13-22 weeks gestation and were provided with personal Ogawa samplers to measure their NO_x/NO_2 exposure. PE was compared to monthly averages, nearest stationary monitor to participant's home, weighted average of closest monitor to home and work location, proximity to major road, as well as to background modelled concentrations (DEFRA), Inverse distance weighting (IDW), ordinary kriging (OK), and a Land use regression model with and without temporal adjustment. PE was most strongly correlated with monthly adjusted DEFRA (NO_2 r=0 .61, NO_x r=0.60), OK and IDW (NO_2 r=0.60; NO_x r=0.62) concentrations. Correlations were stronger in Blackpool than in Manchester. Where there is evidence for high temporal variability in exposure, methods of exposure estimation which focus solely on spatial methods should be adjusted temporally, with an improvement in estimation expected to be better with increased temporal variability.

3.2 Introduction.

Pregnancy is a particularly vulnerable time for both mother and fetus to be exposed to a harmful environment. In the last decade there has been increasing evidence indicating that maternal exposure to ambient air pollutants may be related to an increased risk of harmful effects on the growing fetus [67 276 277]. The adverse effects observed include low birth weight (LBW) [171], preterm birth (PTB) [40] and 'small for gestational age' (SGA) [60]. Factors associated with adverse effects on the fetus are important to identify because suboptimal birth outcomes have been associated not only with neonatal morbidity but also long term health risks, including increased cardiovascular disease, hypertension and diabetes [278 279].

Health effects of the environment in pregnancy cannot simply be extrapolated from studies in the general population. The fetus may be more susceptible to exposure because it has an immature immune system and a high cell proliferation rate [133 280] The mother may be more vulnerable to air pollution exposure because of increased ventilation rate due to the higher oxygen requirements of the fetus and a decreased oxygen binding capability [133]. Therefore, the unique susceptibilities of pregnant women and fetuses require specific studies investigating air pollution effects. However, the design of high quality epidemiological studies investigating the link between air pollution and birth outcomes is challenging. Biased results can arise from failure to account for confounding factors and from problems of measurement, notably exposure misclassification [38]. Most study designs [60 153 160] are retrospective using large routinely collected birth outcome datasets with recorded time of birth. However, this usually means that no directly measured exposure data prior to this event are available. As such,

a significant challenge for these types of studies is to apply valid, practical and accurate techniques to best estimate the mothers' 'personal exposure' (PE).

Exposure estimation techniques commonly used in air pollution epidemiology can be classified as either direct or indirect [281]. The latter group includes proximity-based measurements [39 60 282], statistical interpolation techniques [154], dispersion models [283], traffic based proxy measurements [60 67], land use regression analyses [82] and microenvironmental models [284]. These methods are indirect in the sense that they infer personal exposure from general environmental characteristics and/or measurements. Temporal adjustment of the interpolation based techniques has become increasingly common in large scale epidemiological studies of health effects that require precision in the temporality of exposure [84 285 286].

Use of personal monitors, a direct method, is widely considered as a more accurate method compared to indirect methods for estimating personal exposure [287]. Personal passive air samplers have become an increasingly popular technique for occupational exposure of gaseous air pollution measurement studies to quantify cumulative exposures over a given sampling time [288]. Their compact size, relative cost effectiveness, non reliance on electrical power and ease of use for individuals carrying out the sampling makes them an attractive choice. In many studies, personal monitors have been used as a 'gold standard' against which to compare other methods [37 45 260]. However, the major limitation of personal monitoring is that the 'snap shot' time period from which the measurement is taken may not be representative of the overall period of interest, in this case, the duration of pregnancy.

Even in prospective studies, problems with burden on participants, time and study resources often mean that personal monitoring is not a practical technique and most studies rely on indirect methods. Therefore there is a need to understand how estimates using the various indirect methods relate to personal exposure, whether this is different in pregnancy compared to studies in the "normal" population, or in children, and the extent to which the performance of techniques is the same across geographical areas. Past work has compared indirect air pollution spatial interpolation techniques with each other [289] and there is a growing body of literature focused on predicting personal exposure (PE) in pregnancy on the basis of social factors [290 291]. However, there is limited research comparing the many indirect exposure measurement techniques to PE, particularly within a pregnant cohort.

This study investigates commonly used exposure measurement techniques in air pollution exposure epidemiology studies, investigating specifically their agreement and correlation with direct estimates of PE in a pregnant cohort. The study focuses on populations in North West England so as to inform a larger retrospective epidemiological study of birth outcomes in this area, where specific individual data e.g. on housing characteristics such as heating and cooking appliances is unavailable

3.3 Materials and Methods

3.3.1 Recruitment and study outline

This study included two areas in the Northwest of England, Manchester and Blackpool, which provide contrasting air pollution levels, the former being a large inland city and the latter a much smaller seaside town. The mean NO_x level between 2004 and 2008 recorded in central Manchester was 64.79 µg/m³ (SD: 58.0), compared to 28.19 µg/m³

(SD: 27.82) in Blackpool [292]. For both locations, the health and deprivation status is generally below the England average [293]. Both have an average life expectancy of 74 and 79 years for males and females respectively, compared to the England average of 78 and 82 years (2007-2009). Similarly, the infant death rates of 6.00 for Blackpool and 6.85 for Manchester are also worse than the England average of 4.71 per 1,000 live births [293].

Pregnant women attending Manchester and Blackpool Hospital antenatal clinics were approached between October 2010 and July 2011 after their hospital dating scan appointment. Blackpool Victoria Hospital and Manchester St. Mary's Hospital were chosen so as to obtain a sample with expected high variability in exposures between areas. Participants were recruited in winter (October-December), mid-season (February-April) and summer (May-July) to enable investigation of seasonal differences in exposure levels and behaviours. Women were eligible for inclusion if they were <20 weeks gestation. Eligibility criteria further included a fluent grasp of the English language and no current cigarette smoking. Due to the multiple contact points between the principal investigator and participants, it was not feasible to have an interpreter to incorporate non-English speaking participants. Current smokers were excluded because it is already widely accepted that tobacco smoke is a strong determinant of personal NO_x and NO_2 exposure [290]. There was also a concern that the Ogawa personal samplers used in this study were sensitive to tobacco smoke and the mean readings would not represent personal exposure to air pollution correctly.

After approach in the antenatal clinic, basic contact details were obtained from those who expressed interest in being involved in the study and an information sheet was provided. Participants were given at least 48hrs to consider their decision before a

researcher initiated contact for confirmation of their participation status. For those who agreed to participate, a meeting was arranged before 22 weeks gestation. At the meeting the researcher (KH) or midwife (JB) explained the study in detail and the decision could be made by each woman to sign the consent form. If they agreed to participate, a questionnaire was delivered and the participant was provided with a personal air sampler, time-activity log, pre-paid padded envelope and instruction leaflet. The participants were instructed to post the monitor and log immediately after the measurement period.

Participants were each assigned an Index of Multiple Deprivation (IMD) score from their postcode using the geoconvert software [267]. The score comprises of seven indices of deprivation: income, employment, health and disability, education, living environment, crime and barriers to housing and services. The scores were then categorized into quintiles of deprivation based on English National Standards [266].

The study protocol was approved by the University of Manchester and the North West Ethics Committee (ref: 01290). Site specific R&D approval was obtained from Manchester St. Mary's Hospital and Blackpool Victoria Hospital.

3.3.2 Personal Monitoring

Personal nitrogen oxides (NO_x) and nitrogen dioxide (NO_2) measurements were obtained for a 48-hour period by each participant in early pregnancy (13-22 weeks gestation) using badge sized passive Ogawa personal air samplers [51] which they were instructed to wear in the breathing zone (73 measurements in total). Monitoring was carried out either in winter (n=23), midseason (n=36) or summer (n=14). The Ogawa samplers contain two chambers holding a coated NO_x and NO_2 collection pad at either

end [51]. Often the two chamber design is used for simultaneous measurements of NO_2 as an additional quality assurance measure, with the result being rejected if the variation of the two collection pads is less than 0.25 [284]. However, in this study we did not do this because the work aimed to analyze performance for both NO_2 and NO_x separately for each participant and there was concern that using two samplers per participant would result in an increased burden and consequently a higher risk of monitor loss. For the same 48-hr period, participants completed a time-activity (TA) log consisting of 30 minute interval tick boxes stating whether they were in an urban/rural environment, and were indoors (home/work/public building/other), outdoors (walking/biking/running) or travelling (car/bus/train/tram/other).

3.3.3 Quality Assurance

Each participant was assigned an anonymous ID to ensure participant confidentiality and blind analysis. Each sampler was also given a separate number (but with a key to link it to the ID) to ensure correct matching of the monitor to the participant

Personal monitoring was performed for 48hr periods only to encourage participation in the cohort of pregnant women and minimize sampler loss, yet still attempt to capture a representative reading of 'normal' personal exposure. Participants were instructed to post the personal sampler in a labelled air tight bag along with the activity log immediately after completion of monitoring. It was not feasible for the fieldworker to collect individual monitors immediately after exposure. There was also a concern that due to some participants requesting a hospital meeting point instead of a home visit, picking up the monitors directly may have resulted in a loss of participation.

Once the samples were received, they remained in the air tight bag and stored in a refrigerator at 4°C before filters were analysed for NO_x and NO_2 by a commercial laboratory. The laboratory analysed the samples using the recommended method by Ogawa [51], blank-correcting the results which were reported in units of µg. Final NO_x and NO_2 concentrations were calculated using the appropriate conversion coefficients outlined in the protocol, incorporating a relative humidity of 60%, ambient temperature of 12°C and water vapour pressure of 17.54mmHg. The manufacturer recommended that the shelf life of a loaded sampler before exposure in an airtight bag is 60 days and for an exposed sample 14-21 days. Due to the time between exposure and analysis being largely out of the researchers' control, a quality control measure was set in place at the beginning of the study to record the number of days between exposure and analysis for each monitor included in the study. This allowed us to identify the monitors sent back outside of the recommended time frame and specifically analyse this through stratification.

Participants were provided with full written and verbal instructions to carry out the monitoring, along with a number to call if there were any questions relating to the monitoring.

3.3.4 Exposure modelling methods

Ten exposure estimation techniques were selected for comparison with personal measurements (summarised in Table 20).

Participants' postal codes and the relevant stationary monitor locations were geocoded using *geoconvert* software [267]. Automatic stationary monitor data was obtained from the UK automatic urban and rural network (AURN) managed by DEFRA and Bureau

Veritas (DEFRA 2012). The monitors in this network use the Chemiluminescence technique to analyze the measurements, and daily NO_x and NO_2 concentrations from stationary monitors in Manchester and Blackpool were obtained for 146 days between October 2011 and July 2012 from the publicly available UK air quality website [292]. The stationary monitors in Manchester were urban background (Manchester Piccadilly), suburban (Manchester South) or urban industrial (Salford). In Blackpool, only one urban background monitor was available for all participants. Using the mapping and analysis software ArcGIS[294], the closest monitor to each postcode was identified and the relevant pollution measurements were assigned.

M1a. Monthly averages (NSTATmth)- Monthly average values relating to the month in which the 48hr sampling took place were obtained from the stationary monitor nearest to each participant's home location. These data were obtained from the publicly available UK air quality website [292].

M1b. Nearest stationary monitor (NSTATdys)- The *NSTATdys* technique differs from the *NSTATmth* technique in that it assigns exposure from the nearest stationary monitor from the corresponding 2 days in which the measurement took place, rather than a monthly average value.

M1c. Nearest stationary monitor to home and work location (NSTAThw)- This technique was designed to give a stronger spatial resolution than the *NSTATdys* technique by including more detail on each participant's location during the 48hr measurement period. The nearest stationary monitors to work and home locations were identified and, using the time-activity log, the time spent at the home and work location was used to weight the two stationary monitor results in the overall value.

M2. Distance to major road (DistMjRd)- Distance between residence and a major road is often used as a practical proxy for traffic related exposures [164]. A major road is defined as a road with traffic intensity of >5 000 motor vehicles an hour in 24hrs [295]. Road network data were downloaded from the EDINA website using master map ITN layers [296] Major roads data were spatially joined to the cohort's geocoded home addresses in ArcMap. The distance in metres was calculated to the nearest major road.

M3. Modelled background concentrations (DEFRA)– Modelled background concentration data from the Department for Environment, Food and Rural Affairs (DEFRA) and AEA technology for Manchester and Blackpool (1km x 1km) was obtained from the publicly available DEFRA website [90]. This method provides annual mean modelled concentrations of NO_2 and NO_x using a dispersion kernel approach by incorporating distant sources (characterised by rural background concentration), large and small point sources and local area sources calibrated using automatic measurement data [91]. A more detailed description of the model, including instructions on how to extract the modelled data, are available online [90].

M4. Inverse distance weighting (IDW)- IDW is a commonly used interpolation technique to predict a value for an unmeasured location as a function of the distance between observed stationary monitor [297]. The technique assumes a linear correlation with distance from a measurement point or between two adjacent measurement points. *DEFRA* annual modelled data was imported into ArcGIS and using the geostatistical analyst function in ArcMap, the IDW interpolation was applied. The geocoded postcode points were then joined to the IDW layer to obtain the IDW annual pollution estimates for each participant's home address.

M5. ordinary kriging (OK)- OK is a comparable interpolation technique to IDW. However, while kriging also bases weights on distance between measured points, it takes into account the spatial autocorrelation among measured points when calculating these [289]. The kriging technique creates variograms and covariance functions and then predicts the unknown values. OK is the most commonly used kriging technique and was therefore selected for this study. As with IDW, the DEFRA NO_2 and NO_x data were mapped in ArcMap for Manchester and Blackpool, the geostatistical analyst tool was used to model the data and the layer was joined to the geocoded postcode data to obtain the modelled annual pollution estimates for their home addresses.

M6. Land Use Regression (LUR)- LUR is a modelling technique increasingly being used in studies relating air pollution to health in an attempt to model a higher spatial resolution than for other techniques [295] It incorporates site-specific variables into a regression model to map pollution. The model used here [88] had only been developed for Central Manchester, so its application was limited to the Manchester cohort for NO_x. The predictor variables for NO_x in the LUR model were: (a) distance to a major road- using local road networks with major road defined as traffic intensity >5,000 motor vehicles per hour in/ 24hrs, (b) Road length of a central road network within a 1000m buffer radius, (c) length of all segments of the local road network within100m buffer multiplied by total traffic load of all roads within the buffer zone and (d) the Y coordinate. The model was applied to each participant to obtain an LUR estimate for home location.

In addition to the methods described above, methods M3, M4, M5 and M6 were also adjusted to provide two stronger temporal components: each value was multiplied by a monthly and, separately, by a daily adjustment factor. This was performed in SPSS after

the annual means had been extracted for each postcode point from ArcGIS. The monthly and daily adjustment factors were calculated from location specific stationary monitor data, as the monthly or the corresponding 48hr means divided by the relevant annual means. The temporally adjusted methods are referred to in the results by adding the prescript "Ma" to the abbreviated names.

Table 20: Look up table for the included exposure estimation techniques

Method name	Acronym	Temporality of exposure method
M1a. Monthly averages	*NSTATmth*	Month
M1b. Nearest stationary monitor	*NSTATdys*	Day
M1c. Nearest stationary monitor to home and work location	*NSTAThw*	Month
M2. Distance to major road	*DistMjRd*	None
M3. Modelled background concentrations	*DEFRA*	Annual
M3.1 Monthly adjusted Modelled background concentrations	*Ma DEFRA*	Month
M4. Inverse distance weighting	*IDW*	Annual
M4.1 Monthly adjusted Inverse distance weighting	*MA IDW*	Month
M 5. ordinary kriging	*OK*	Annual
M5.1 Monthly adjusted ordinary kriging	*Ma OK*	Month
M6. Land use regression modelling	*LUR*	Annual
M6.1 Monthly adjusted land use regression modelling	*Ma LUR*	Month

3.3.5 Statistical analysis

Descriptive statistics were used to summarize the study population and the air pollution data.

Spearman rank correlation coefficients were used to measure the ranked correlations between personal measurements and each of the estimation techniques. Correlations were also calculated separately for the subset of PE data analysed within 21 days. Agreement was assessed using absolute differences (AD) and the ratio of personal measurements and modelled values.

The Manchester and Blackpool correlation coefficients were compared using a Fisher transformation [262]. Two-tailed p-values were calculated to determine if the correlations were significantly different between locations using $p<0.05$ as indicating statistical significance. This analysis could not be carried out for the LUR technique due to an unavailable LUR model in Blackpool.

To assess the relative importance of spatial versus temporal variation, a random effect one way analysis of variance was conducted using the STATA command 'loneway', applied to monitor data for Manchester Piccadilly, Manchester South, and Blackpool Marton during 2011. This analysis estimates the fraction of total variation in exposure across time and space that is attributable to each factor.

All statistical analysis was performed using SPSS (version 16) or STATA92.

3.3.5.1 Sensitivity analyses

The quality assurance procedures required recording of the exact number of days between exposure and analysis of the monitors, thus enabling performance of a sensitivity analysis comparing results of the personal samplers analysed within the 21 day recommended limit and those analysed outside of these limits.

The Spearman rank correlation coefficients between the personal measurements and each of the exposure estimation techniques were performed separately for the two locations to observe any differences in correlations and a test of significance between the coefficients from Manchester and Blackpool was performed.

In addition, a subset of 16 participants who self-reported living with a smoker were also analysed separately from the remaining participants to observe any differences in PE levels and patterns in the different correlation coefficients.

3.4 Results

3.4.1 Study population

From the 327 pregnant women approached in antenatal clinics over a 10 month period, a total of 85 women were included in the study; 51 were recruited from Manchester St. Mary's Hospital and 34 from Blackpool Victoria Hospital. After the initial approach, 46% of women were excluded because they were: non-English speakers (8%), current smokers (13%) or declined to take part with no reason given (25%). From the women who expressed an interest at the initial approach, 49% of women did not continue to the researcher meeting point due to subsequent non-response (21%), deciding not to take part (17%), miscarriage (3%) or loss to follow-up after initially agreeing (8%). Returned

completed data (including time activity logs and personal air monitors) were received from 75 (81%) of included participants. At the laboratory phase 2 samplers were mislaid; this resulted in a total of 73 included personal sampler measurements for analysis. This is summarised in a flow chart in Appendix 4.

Basic data on 119 (of 242) declined/excluded women was also collected. Participant and non-participant groups were generally similar in their characteristics, although in the non-participant group about 60% of women were in the most deprived quintile in comparison to 47% of included participants. Reasons for declining participation in the study were recorded when appropriate; the predominant reasons were "too busy" or "not interested in research".

Participants' demographic data are summarized in Table 21 and participants' residential location is displayed in Figure 20. The study population had a mean age of 28.8 years and were predominately White British in both Manchester and Blackpool (77% and 97% respectively). Over half worked full time (55%) at the time of the study and 65% of participants were educated beyond college level (16-18yrs). Half of the participants were experiencing their first pregnancy (51%). 71% of participants belonged to the 2 most deprived quintiles of the population. Participant home locations were on average 5.2km from the nearest stationary monitor (range= 0.3-13km).

Table 21: Demographics of included participants

	Manchester (n=51)	Blackpool (n=34)
Age (years)	Mean: 28.8 SD 5.6 (17-41)	Mean: 28.9 SD 5.9 (16-38)
Ethnicity:		
White	39 (76%)	33(97%)
Non-white	12 (24%)	1 (3%)
Parity:		
Primiparous	32 (63%)	14 (41%)
Multiparous	19 (37%)	20 (56%)
Education level:		
Left school at 16	5 (10%)	7 (21%)
Higher education college	13 (25%)	14 (38%)
Vocational training post college	10 (20%)	3 (9%)
University (graduate)	15 (29%)	6 (18%)
University (postgraduate)	8 (16%)	4 (12%)
Employment:		
Unemployed/homemaker	13 (25%)	8 (24%)
Student	3 (6%)	2 (6%)
Work part time	6 (12%)	6 (18%)
Work full time	28 (55%)	18 (50%)
Self employed	1 (2%)	0
Index of Multiple Deprivation		
Quintile 1 (Most deprived)	26 (51%)	13 (38%)
2	15 (29%)	5 (15%)
3	6 (12%)	7 (21%)
4	4 (8%)	4 (12%)
5 (Least deprived)	0 (0%)	4 (12%)
Missing		1(3%)

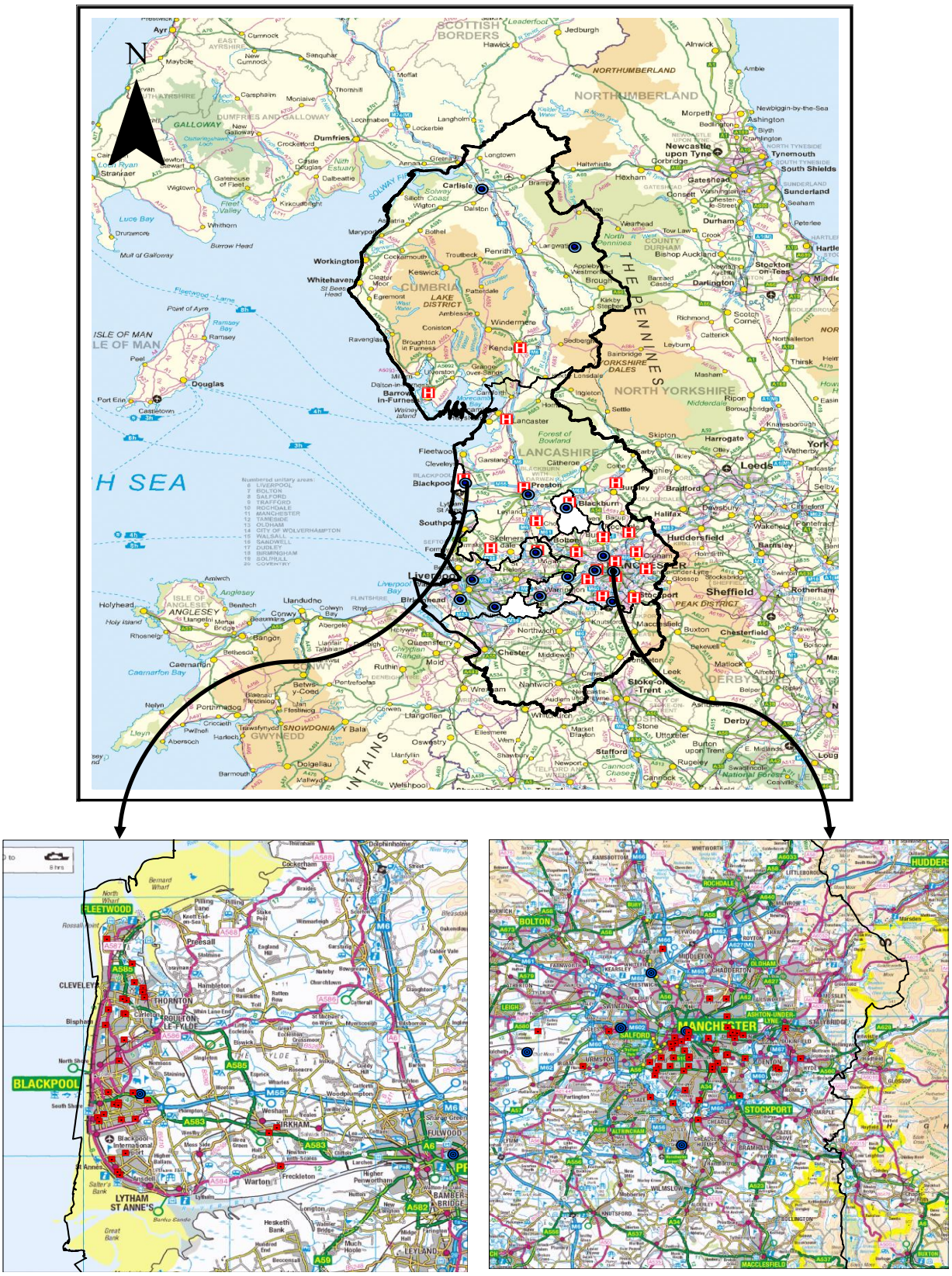

Figure 20: A map of the study locations, Blackpool (left) and Manchester (right) and participant residential points.

Personal measurements were carried out across three seasons: winter (n=23), midseason (n=36) and summer (n=14) as demonstrated in Figure 22 and 23. Participants spent on average 66% of their time at home, 13% in work, 6% travelling in a car/bus/train, 5% walking/biking/running and 5% in a public building (5% of time-activity data was missing). A total of 16 participants moved during or just before their pregnancy, 12 (75%) of these women moved <10 miles away from their original location. Data from the PE measurements are presented in Table 22 and graphically in Figure 21. The geometric mean (GM) levels of PE across the participants were 17.3 µg/m³ (GSD: 16.4) for NO_2 and 52.2 µg/m³ (GSD: 54.6) for NO_x. GMs were higher in Manchester (NO_2= 20.1µg/m³; NO_x = 60.9µg/m³) than in Blackpool (NO_2= 13.3µg/m³; NO_x = 40.1µg/m³). The median time between exposure and analysis of the personal monitors was 22 days.

Table 22: Descriptive statistics of Personal NO_2 and NO_x exposure in Manchester and Blackpool

	N	Arithmetic Mean[1]	Geometric Mean[1]	GSD[2]	25th Percentile	75th Percentile	Min	Max
Manchester								
Personal NO_2	46	22.0	20.1	18.2	11.8	27.6	6.1	82.7
Personal NO_x	46	70.3	60.9	54.6	36.1	98.4	15.9	244.5
Blackpool								
Personal NO_2	27	17.8	13.3	11.0	7.9	24.1	3.2	55.2
Personal NO_x	27	54.3	40.1	36.6	23.2	59.6	9.7	189.9
Overall								
Personal NO_2	73	22.0	17.3	16.4	10.3	27.6	3.2	82.7
Personal NO_x	73	70.3	52.2	54.6	25.2	82.0	9.7	244.5

[1]In µg/m³; [2] Geometric Standard Deviation

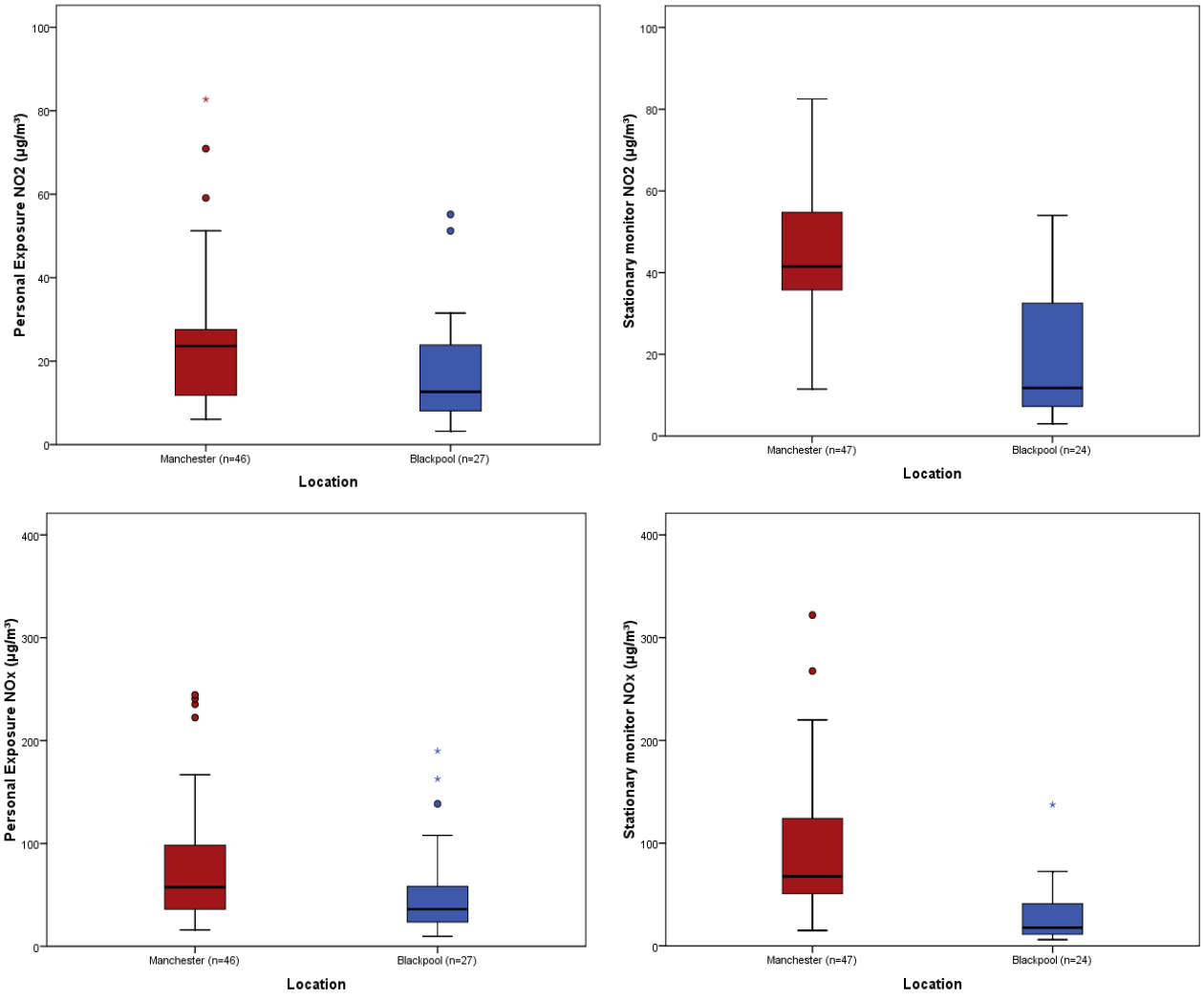

Figure 21: Boxplots summarizing the personal exposure and stationary monitor results of NO_2 and NO_x in Manchester and Blackpool.

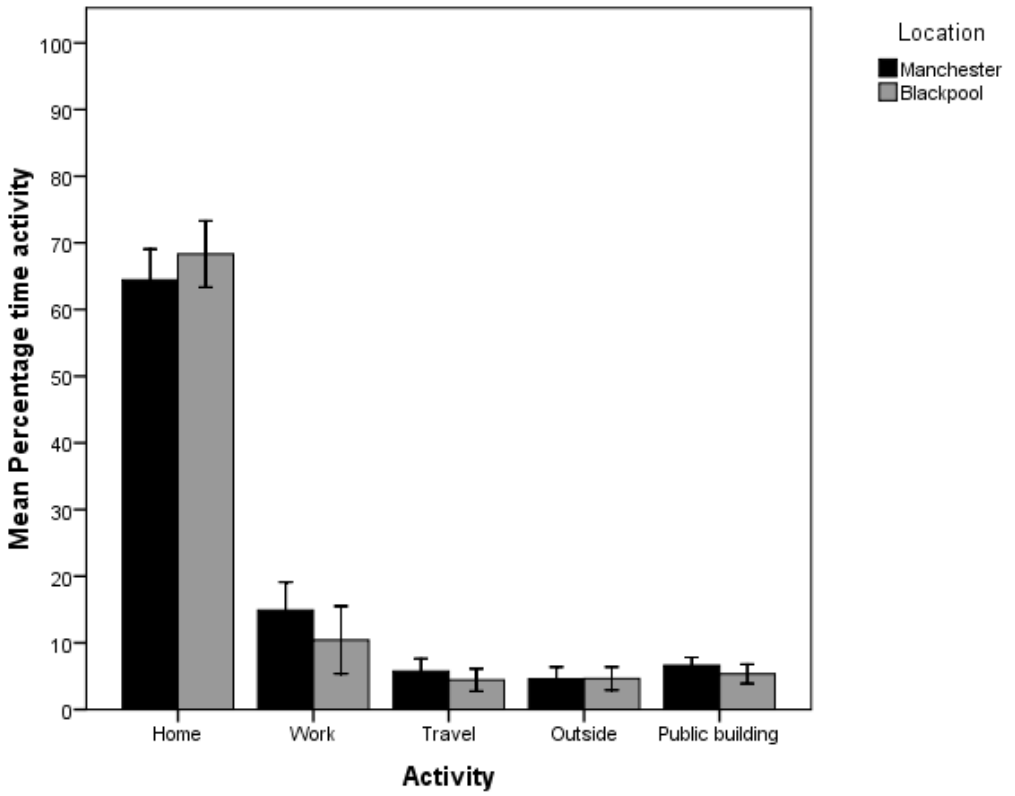

Figure 22: Time activity patterns of Manchester and Blackpool participants from 48hr time-activity log data (Error bars: 95% CI).

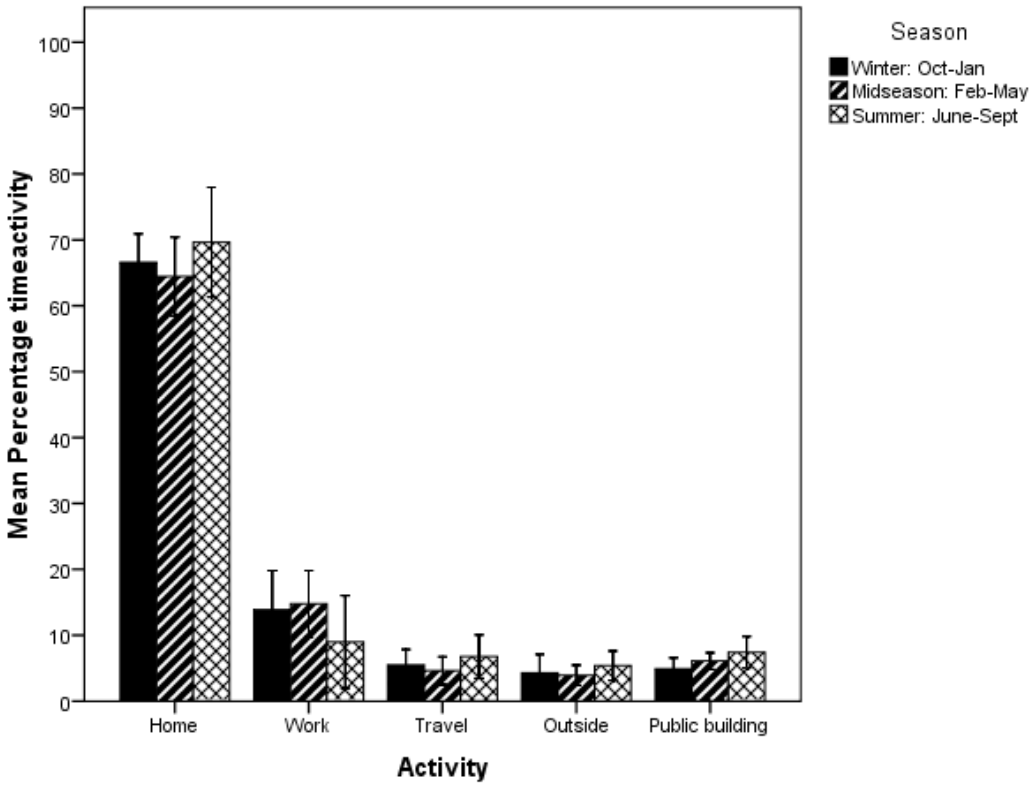

Figure 23: Time activity patterns from 48hr time-activity log data by season (Error bars: 95% CI).

Seasonal variation in Manchester and Blackpool was studied separately using the monthly average values (*NSTATmth*) for the study period. Figure 24 demonstrates the higher seasonal variation that occurred in Blackpool during 2011 compared to Manchester.

The overall variation in PE has two components: spatial and temporal variation. To measure the relative importance of these components, data from the stationary monitors in Manchester Piccadilly, Manchester South, Salford and Blackpool for 2011 were used. A similar fraction of variance due to location and time was found for both NO_2 (0.52 and 0.48 for location and time, respectively) and NO_x (0.45 and 0.55, respectively).

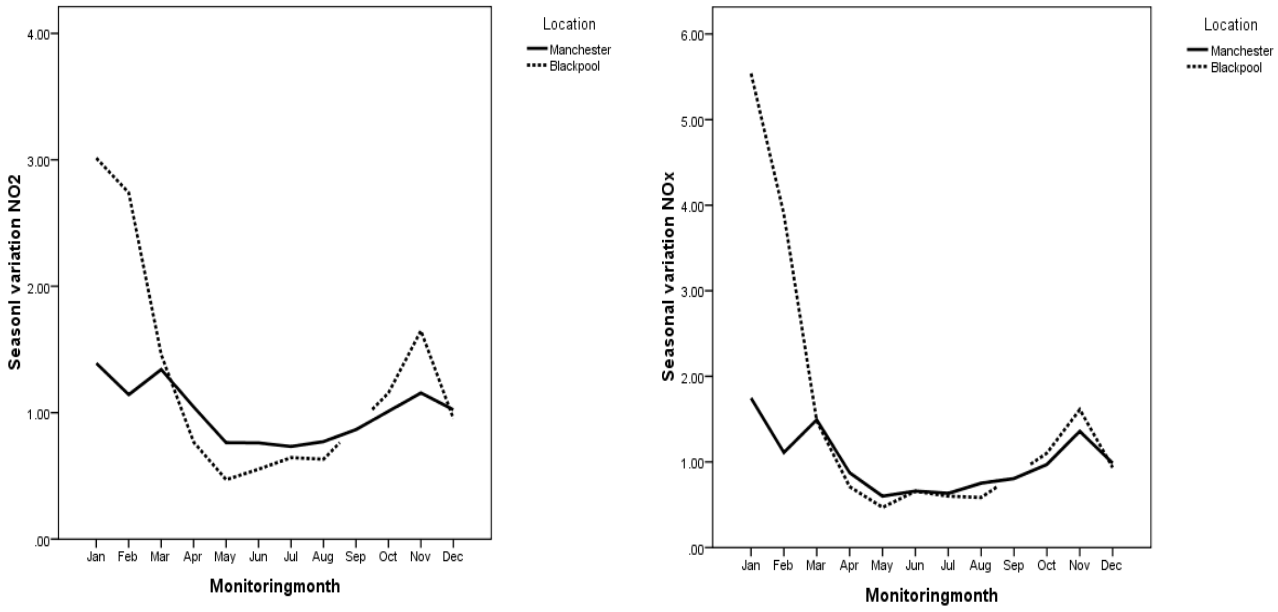

Figure 24: Seasonal variation of NO_2 and NO_x from stationary monitor data in Manchester (averaged between the two stationary monitors) and Blackpool during 2011 (µg/m³). **(Seasonal variation= month average/annual average).**

3.4.2 Correlation of exposure measurement techniques

The Spearman rank correlation coefficients for the personal exposure measurements and the exposure modelling techniques are presented in Table 24. Results from the samplers analysed within the recommended ≤21 days time frame are presented separately in the final column of Table 24.

The techniques with the overall strongest correlations with PE were *MaDEFRA (*NO_2 r=0 .61, NO_x r=0.60; p<0.01) (Figure 25), *MaOK* and *MaIDW* (NO_2 r=0 .60, NO_x r=0.62; p<0.01). The weakest correlations were found with the Manchester *LUR* NO_x model (r=0.06). However, the temporally adjusted LUR model correlated almost as well as the techniques with the strongest correlations (NO_x r=0.59; p<0.01).

The subset of samplers analyzed ≤21days from exposure demonstrated stronger correlations for all exposure estimation techniques. The strongest correlations with PE in this group were again with *MaOK (*NO_2 r=0 .77, NO_x r=0.71; p<0.01) and with similarly strong correlations, *MaDEFRA* (NO_2 r=0 .74, NO_x r=0.67; p<0.01) and *MaIDW* (NO_2 r=0 .74, NO_x r=0.69; p<0.01). The weakest correlations were obtained using the *LUR* model *(*NO_x r=0.11; p>0.05).

Correlations with PE were always stronger in Blackpool (range: r=0.07-0.86) than Manchester (range: r=0.06-0.53) (Table 24). For NO_2 and NO_x, correlations with PE NO_2 were significantly different between cities for *MaOK, MaDEFRA* and *MaIDW*. For NO_x, *MaOK* with PE was significantly stronger in Blackpool than Manchester. The strongest correlations were with the monthly adjusted estimation techniques, followed by the daily adjusted and the weakest were the unadjusted (annual average) techniques. Without temporal adjustments, the correlation coefficients for *DEFRA, IDW, OK* and

LUR were not significant (p>0.05). After monthly and daily adjustments, the correlations of all four interpolation techniques (*DEFRA, IDW, OK and LUR*) with PE became significant. The importance of the monthly adjustment is highlighted by the fact that a method based purely on the seasonal adjustment – *NSTATmth ((NO_2)r=0.58; (NO_x)r=0.57)* gives similar correlations to the monthly adjusted interpolation techniques *((NO_2)r~0.60; (NO_x)r ~0.62).* Participants lived an average of 412 metres (range: 17-1508 metres) from a major road. PE was weakly positively correlated with *DistMjRd* in NO_2 (*r=0.24*; p>0.05) and NO_x (*r=0.33*; p<0.05). Although this may indicate that those living farther away from a major road had a higher PE both in Manchester and Blackpool, in the subset of monitors analysed ≤21 days, conversely, negative correlations for NO_2 (*r=-0.30*; p=0.13) and NO_x (*r=-0.23*; p=0.18) were found.

PE correlations with *NSTATmth*, *NSTATdys* and *NSTAThw* were moderate for NO_2 (*r=0.58, r=0.49* and *r=0.55* respectively) and NO_x (*r=0.57, r=0.56* and *r=0.53*) (p<0.01). Incorporating work location stationary monitor estimates (*NSTAThw*) based on time-activity log data for the 46 employed participants did not strengthen the correlations. Correlations between PE and *NSTATdys* concentrations were stronger during the summer and mid-season months (NO_2 *r=0.61, r=0.36*) than in winter (NO_2 *r=0.05*).

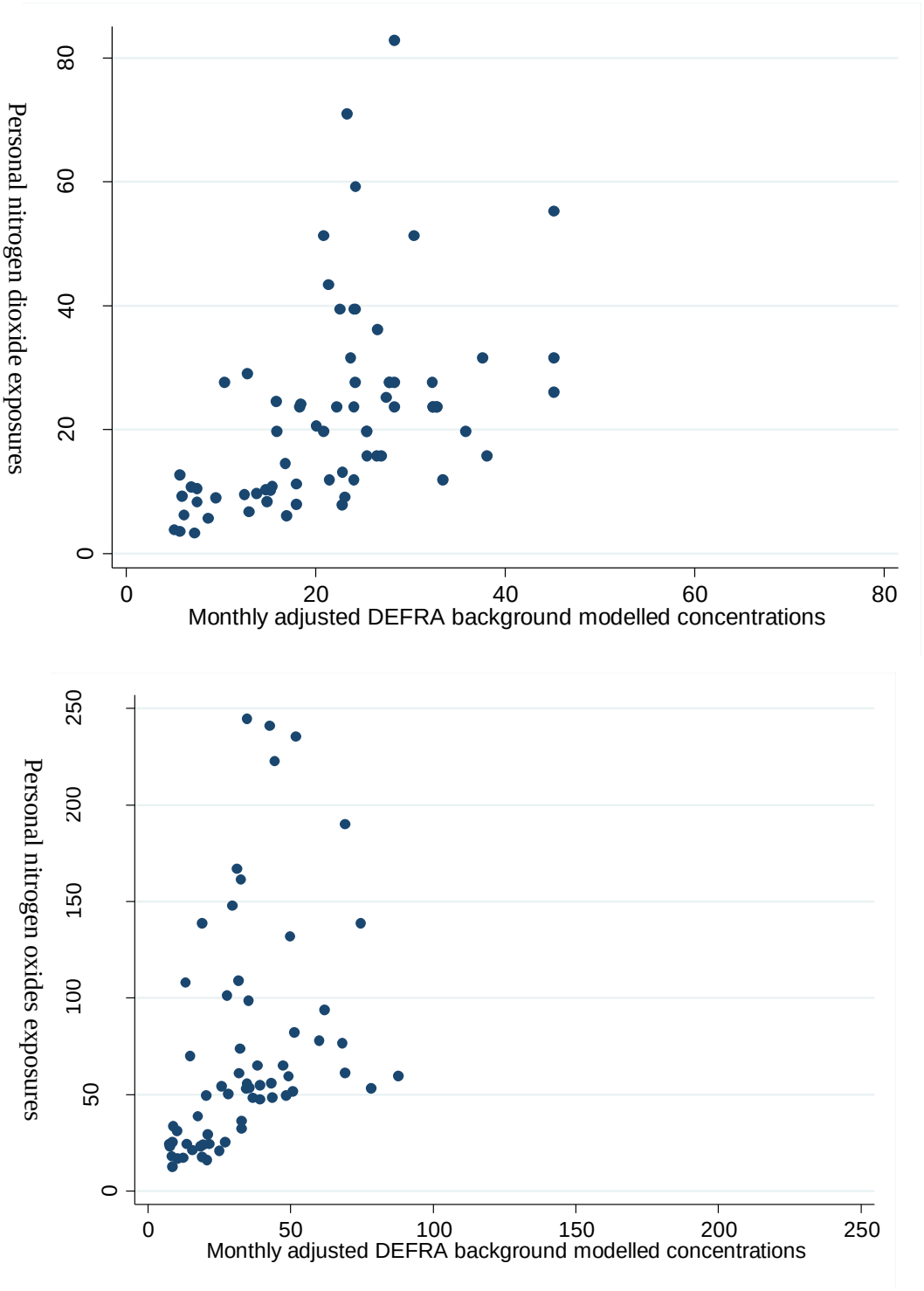

Figure 25: Scatter plot of NO_2 and NO_x personal exposures and monthly adjusted background modelled concentrations (PCM model).

3.4.3 Agreement of exposure measurement techniques

Absolute differences (AD) between PE and each estimate are shown in Table 23. For NO_2, the smallest AD was between PE and *MaDEFRA* technique (-0.48µg/m³) and for NO_x the smallest AD was with the *NSTATdys* method (0.93µg/m³). The largest AD for NO_2 were with the proximity based techniques (*NSTATdys*=-14.20 µg/m³, *NSTAThw*= -19.21µg/m³ and *NSTATmth=13.75* µg/m³), and for NO_x the spatial interpolation techniques had the larger average AD- the largest being *OK (*-42.99µg/m³). The LUR model agreement was strong for both the temporally unadjusted and adjusted estimates. For all proximity based methods excluding *NSTATmth* NO_x, the estimation values were higher than the PE values. For all spatial interpolation methods (*DEFRA, IDW, OK* and *LUR*), the PE values were all higher and NO_2 had consistently smaller AD compared to NO_x. The mean ratios ranged from 0.62 (*Ma DEFRA* NO_x) to 2.76 (*NSTAThw* NO_2). Smaller mean ratios were consistently found with NO_x compared to NO_2. The AD and mean ratios showed that there was a stronger agreement between PE and the modelling technique for NO_x compared to NO_2 when using the proximity based methods while the agreement was better for NO_2 when using the spatial interpolation techniques.

Table 23: Descriptive statistics, absolute differences and mean ratios of the exposure estimation techniques with personal exposure.

Estimation technique(µg/m³)	Pollutant	Obs	Arithmetic Mean	Geometric Mean	25th Percentile	75th Percentile	²AD	³Mean ratio
1. NSTATmth	NO_2	73	35.62	34.62	25.50	44.84	13.75	2.41
	NO_x	73	63.18	58.78	37.78	85.47	-7.00	1.34
1b.NSTATdys	NO_2	69	36.06	29.01	16.50	50.50	14.20	2.14
	NO_x	69	70.20	48.00	21.00	98.00	0.93	1.27
1c. NSTAThw	NO_2	23	39.40	34.18	23.25	48.75	19.21	2.76
	NO_x	23	79.23	57.17	32.00	82.5	2.27	1.45
2.¹DistMjRd		73	411.95	269.80	153.92	589.12	NA	NA
3.DEFRA	NO_2	72	17.75	16.93	12.85	21.1	-4.00	1.27
	NO_x	64	27.14	25.23	18.13	32.6	-43.39	0.64
3.1. Ma	NO_2	71	21.19	18.85	14.87	27.81	-0.48	1.25
DEFRA	NO_x	63	34.09	28.38	27.81	44.46	-38.14	0.62
4.IDW	NO_2	68	18.26	17.37	12.42	21.77	-3.28	1.27
	NO_x	66	26.96	25.00	16.67	33.12	-42.93	0.65
4.1.Ma	NO_2	65	21.40	19.27	15.89	27.15	-0.71	1.22
IDW	NO_x	67	33.55	28.02	19.89	44.86	-37.7	0.63
5. OK	NO_2	67	18.09	17.09	11.29	21.67	-3.67	1.27
	NO_x	69	26.66	24.79	15.99	32.86	-42.99	0.64
5.1. Ma	NO_2	66	21.19	18.85	15.63	27.48	-1.19	1.21
OK	NO_x	68	34.09	28.38	19.89	44.86	-36.84	0.63
6. LUR	NO_x	46	75.84	63.61	46.381	65.77	-3.09	1.48
6.1. MA LUR	NO_x	46	76.38	58.13	30.03	91.32	-2.00	1.21

¹DistMjRd: Distance to major road in Metres (M). ²AD: Absolute differences (Exposure estimation technique-PE) (ug/m³)

³Mean: mean difference ratios from arithmetic mean (Exposure estimation technique/Personal measurements) (ug/m³)

Table 24: Spearman rank correlation coefficients in measured concentrations between exposure estimation techniques and personal measurements

		All participants	Manchester	Blackpool	p diff	≤21	Days only
Estimation technique(µg/m³)	*Pollutant*	[1]*r (p)*	*r (p)*	*r (p)*	[2]*P*	*N*	*r(p)*
1a. NSTATmth	NO_2	0.58(0.00)	0.53(0.00)	0.76(0.00)	0.11	36	0.72 (0.00)
	NO_x	0.57(0.00)	0.51(0.00)	0.74(0.00)	0.13	36	0.69 (0.00)
1b. NSTATdys	NO_2	0.49(0.00)	0.30(0.04)	0.67(0.00)	0.06	35	0.61 (0.00)
	NO_x	0.56(0.00)	0.42(0.00)	0.68(0.00)	0.16	35	0.61 (0.00)
1c. NSTAThw	NO_2	0.55 (0.00)	0.23 (0.21)	0.48 (0.06)	0.40	10	0.62 (0.06)
	NO_x	0.53 (0.00)	0.42 (0.02)	0.56 (0.03)	0.25	10	0.54 (0.11)
2.DistMjRd	NO_2	0.13(0.26)	0.24(0.11)	0.26(0.20)	0.94	36	-0.30 (0.07)
	NO_x	0.15(0.21)	0.33(0.03)	0.17(0.39)	0.50	36	-0.23 (0.18)
3.DEFRA	NO_2	0.23(0.05)	0.04(0.78)	0.30(0.13)	0.16	35	0.41 (0.01)
	NO_x	0.19(0.13)	0.00(0.98)	0.14(0.54)	0.62	33	0.22 (0.21)
3.1. Ma DEFRA	NO_2	0.61(0.00)	0.43(0.00)	0.78(0.00)	0.02	34	0.74 (0.01)
	NO_x	0.60(0.00)	0.48(0.00)	0.76(0.00)	0.10	32	0.67 (0.00)
4. IDW	NO_2	0.14(0.26)	0.09(0.56)	0.15(0.52)	0.78	33	0.35 (0.05)
	NO_x	0.20(0.10)	0.09(0.54)	0.01(0.96)	0.76	35	0.25 (0.14)
4.1. Ma IDW	NO_2	0.60(0.00)	0.41(0.56)	0.78(0.00)	0.01	32	0.74 (0.00)
	NO_x	0.62(0.00)	0.47(0.00)	0.77(0.00)	0.07	34	0.69 (0.00)
5.Kriging	NO_2	0.18(0.14)	0.15(0.34)	0.11(0.62)	0.88	34	0.42 (0.01)
	NO_x	0.23(0.06)	0.02(0.90)	0.07(0.75)	0.85	35	0.28 (0.10)
5.1. Ma Kriging	NO_2	0.60(0.00)	0.38(0.01)	0.86(0.00)	0.00	33	0.77 (0.00)
	NO_x	0.62(0.00)	0.49(0.00)	0.79(0.00)	0.05	34	0.71 (0.00)
6. LUR	NO_x	0.06 (0.67)	0.06(0.67)			21	0.11 (0.64)
6.1. Ma LUR	NO_x	0.59 (0.00)	0.59(0.00)			21	0.48 (0.28)

[1]Spearman rank correlation coefficient [2] P value from the comparison of spearman rank correlation coefficients between Manchester and Blackpool.

3.5 Interpretation

This study describes the performance of ten exposure measurement techniques commonly used in epidemiological air pollution exposure studies relative to 48-hr personal NO_2 and NO_x exposure measured in pregnant participants from North West England. The results focus on ranked correlations because for epidemiology studies, the correct exposure ranking of individuals is particularly important. The agreement between the estimation techniques and PE was also included in determining the performance of the techniques included.

The results demonstrated that monthly adjusted exposure interpolation techniques (*MaDEFRA*, *MaOK* and *MaIDW*) correlated strongest with personal NO_2 and NO_x measurements compared to all the techniques included in this study. This was consistent with previous recommendations from studies in the general population, i.e. that kriging seems to provide the most unbiased estimates of personal exposure [298]. The most recently developed technique, the land use regression model, demonstrated reasonably good correlation with PE in the temporally adjusted model, but not the unadjusted model and strong agreement in both models. The daily temporally adjusted estimates, although performing better than the unadjusted annual estimates, were not as good as the monthly adjusted concentrations.

A number of personal exposure studies have been published [299-301] and more recently there has been a focus on PE in subpopulations such as woman in pregnancy [44 291]. However, only one other limited validation study specifically in this population comparing different modelling techniques has been published to date. Comparable to this study, Nethery et al. investigated various exposure measurement techniques in

pregnancy in Canada [37]. They compared personal measurements during pregnancy to ambient stationary monitors and estimates from an LUR model, and examined spatial and temporal variability by monitoring the participants one to three times. They found weak correlations between overall PE measurements (n=127) and stationary NO_2 monitors (*r=0.05*), as well as with the LUR model (*r=0.18*) and LUR model combining work and home locations (*r=0.28*). These correlations were weaker than those found in our study. They also found that incorporating work home locations improved the ability to predict PE, which was not evident in our results. Our study builds on this work and provides an investigation of a broader range of techniques.

Studies that have used a non-pregnant cohort to investigate PE correlations with nearest stationary monitor estimates have found results more similar to those in this study. Kousa et al. [300] reported a correlation coefficient of *0.37* in a study including sites from Switzerland, Finland and the Czech Republic. A study also conducted in the same geographical area (Manchester) as in this study, but in children aged 12-13 years reported a correlation of *0.44* [45], broadly comparable to results from this study of *r=0.57* (and in Manchester specifically *r=0.30*).

Our results have corroborated the importance of taking into account temporality in using air pollution estimation techniques [37] [285]. The techniques that incorporated temporal variability (*NSTATmth, NSTATdys* and *NSTAThw*) performed better than the unadjusted spatial interpolation techniques (*DEFRA, IDW, OK and LUR*). However, once the spatial interpolation techniques were adjusted (by month or by day), they correlated and agreed better with PE, demonstrating the importance of temporality in air pollution exposure estimation. Interestingly, monthly adjustments provided a stronger correlation with 48 hour PE than daily adjustments in all the interpolation technique

(Appendix 2, Tables A4 & A5). This seemingly counter-intuitive result could be as a result of imprecise estimates from the personal samplers. Another plausible explanation lies in the role played by measurement error in daily stationary monitor estimates, specifically the error in using these as estimates of individual exposure. In general, averaging over a long period will reduce the impact of random measurement error while increasing error due to temporal variation when trying to estimating 48 hour exposure. If the degree of random measurement error is greater than the degree of heterogeneity in true exposure across a month, we might expect the monthly average to have less error overall.

An important question is the degree to which these results can be generalised to studies where the objective is to estimate exposure during a pregnancy trimester or in the whole of pregnancy. Additional measurements at different time points in pregnancy might have helped to elucidate this important question and this ideally should be incorporated into future personal exposure studies in pregnancy. Further to this, future studies could better explore exposure profiles with multi-day continuous samplers in order to capture peak pollutant episodes. Time-activity patterns are likely to change during the pregnancy period which could affect the relationship between PE and exposure estimates, and an increase of one hour per day spent in the home for each trimester of pregnancy [55]. As noted, the participants were encouraged to capture a 'normal' 48 hours; preferably work days (54.8% of the women monitored on a workday and 45.2% on a non-workday). Although 48 hours was chosen as a trade off between a long enough to capture "normal exposure" and a short enough period to encourage participation in this cohort of pregnant women, it is unknown how representative this period is for longer periods such as three or nine months.

It is well known that season plays an important role in air pollution levels [44 302]. The correlations between PE and nearest stationary monitor estimates were found to be stronger during the mid–season and summer months compared to winter. This has been argued to be because of increased time spent outdoors in the summer months and applies also during pregnancy [261]. However, in our study there is little evidence of difference in time spent outdoors, with an average of 4.3% of time spent outside in the winter months, and 5.4% in summer months.

All the exposure modelling techniques (apart for the *LUR* model that was only used for the Manchester cohort) were better correlated with PE in Blackpool than in Manchester. These differences between Manchester and Blackpool reached statistical significance for the *MaOK*, *IDW* and *DEFRA* techniques for NO_2 and *MaOK* for NO_x. The percentage time spent inside/outside/travelling was almost identical between the groups, (4.6% and 4.7% outside in Manchester and Blackpool, respectively). However, our analyses of stationary monitor data shows a greater temporal variation across the year of 2011 in Blackpool compared to Manchester (Figure 24), which could possibly explain the better correlations found in Blackpool than in Manchester. We expect the greater temporal variation to increase correlations due to the bigger range in data causing smaller variation due to sampling error to be less important.

A limitation which hinders most exposure validation studies including this one is the relatively limited sample size. Previous personal exposure studies have included a similar number of participants as this study [44], with a common sample size of around 100 participants [303 304]. Recruiting women in pregnancy can be particularly demanding and research may be viewed with scepticism and concerns over the burden of participation. A particular challenge was the exclusion criteria of smokers in Blackpool,

a maternity unit that has a maternal smoking rate of 33% [293], but nonetheless the demographics of the participants from both Manchester and Blackpool show a similar distribution in age, ethnicity, education, parity and IMD level.

Differences were observed between results including all monitors in the study and the subset of monitors which were analyzed within the suggested time period (≤21 days). Those monitors that were posted back late and consequently analyzed >21 days post exposure had significantly higher exposure estimates than those analyzed within the recommended time frame (mean difference: NO_2= 11µg/m³; NO_x= 39µg/m³; $p<0.01$). The results were comparable, although correlations between personal measurements and the exposure estimation techniques were stronger for the group analyzed within the 21 day time period than the samplers analyzed later. It did further have an effect when PE was compared to the 'distance to major road' model, indicating time between exposure and analysis of Ogawa personal samplers should be considered in future study designs.

Housing characteristics and TA logs were not incorporated further in this study because the primary aim was to investigate the relationship between the exposure estimation techniques and PE that are applicable to a large-scale epidemiological study where individual characteristics are unavailable. Past studies have shown that indoor exposure generally correlated better with PE than outdoor exposure [300 304]. Regardless, many studies to date have focussed on ambient exposure in relation to health effects alone [143] and have not, or only to a very limited extent, considered indoor exposure, and hence this approach was also taken for this comparison study.

Environmental tobacco smoke (ETS) can affect PE levels in the indoor environment [304]. In this study, 16 participants lived with smokers- of which, only 3 reported that they

smoked inside. We found no major differences in PE levels and there was no pattern in the correlation coefficients, which was likely due to the small numbers of women who lived with a smoker and very few were likely to have been exposed to any ETS.

One of the strengths of this study was the variability in exposure between the two locations under study. It has provided the opportunity to examine if certain exposure modelling techniques perform differently in different geographic areas and to begin to explore the reasons behind this. A further strength of this study was the extensive range of commonly used modelling techniques investigated specifically for a pregnancy cohort. By comparing the techniques with and without seasonal adjustment, the importance of spatial and temporal resolution could be examined independently.

3.6 Conclusions

In conclusion, future epidemiological studies requiring air pollution estimates to link with health outcomes need to consider their estimation technique on an individual study basis, taking into account the health outcome under study, data availability and geographic location. The results of this study, although based only on a 48 hour snap-shot period during pregnancy, help to inform some important issues in air pollution estimation techniques. Where there is evidence for high temporal variability in exposure, methods which focus solely on spatial methods (e.g. kriging and Inverse distance weighting) will likely benefit from a temporal adjustment. Nearest stationary monitor techniques may also provide a practical technique for a large scale pregnancy cohort. In this study in a pregnancy cohort, the monthly adjusted DEFRA background modelled concentrations, Inverse distance weighting and ordinary kriging were the strongest techniques second relative to measure personal exposure in this population.

Studies using personal air samplers should pay close attention to the recommended time between exposure and analysis as this may have substantial effects on results.

Acknowledgements

We would like to thank all the women who kindly participated in the study and to the antenatal staff at St. Mary's, Manchester and Blackpool Victoria antenatal clinic. Particular thanks are due to Jane Brooks (research midwife at Blackpool Victoria Women's health Unit) for recruitment support and data collection. Suzanne Thomas (research midwife at Central Manchester Foundation Trust) is also thanked for her guidance in the setting up of the study.

4. Exploration of sources of error in personal air pollution monitoring

4.1 Introduction

The study described in Chapter 3 was designed to compare the correlation and agreement between personal air pollution exposures and commonly used air pollution exposure estimation techniques. This was carried out under the assumption that the Ogawa personal air samplers were a 'gold standard' technique representative of personal exposure. Within the study in Chapter 3, a number of potential sources of error with the Ogawa samplers were identified. To better understand the influence of these factors, an experimental study described in this chapter was carried out.

Good quality epidemiological studies investigating the effects of air pollution on health effects require reliable and valid air pollution estimates assigned to individuals. Active air sampling from stationary monitoring sites have been the preferred method used to monitor air pollution concentrations, enabling large volumes of air to be sampled within relatively short time periods and able to detect low pollutant concentrations [257]. However, this sampling method is not practical to implement in studies attempting to capture personal air pollution exposure.

As demonstrated in the previous chapter (Chapter 3), a number of different air pollution exposure estimation techniques have been developed, validated and implemented in epidemiology studies [37 41]. These exposure estimation techniques are often designed with the premise that they will best reflect the personal exposure (PE) of the individuals within the study. Measuring PE using personal air pollution samplers is believed to be the best practical method of estimating actual air pollution exposure [281] and has been used in a number of studies as a standard against which to compare other estimation

techniques [37 45]. However, if personal samplers are handled differently from one another or incorrectly by individuals within a cohort, researchers or analysts they may not accurately reflect PE.

Personal air pollution samplers have been developing since the early 1970's and have now evolved to become relatively small transportable monitors for everyday use [305]. The personal samplers have the ability to provide a measurement of an individual's exposure to the desired pollutant in every microenvironment that the individual inhabits for the sampling period.

The commercially produced 'Ogawa passive air sampler' is a commonly used personal sampler which has been in use for over 25 years [37 45 51]. The Ogawa sampler was the chosen device for the exposure estimation technique comparison study described in Chapter 3 and has been described in more detail in the introduction section (Chapter 1.4.1) and the main methods section (Chapter 2.2.5).

The literature to date that has explored the reliability and validity of the Ogawa personal air monitors and the potential sources of error when using them generally present similar findings. However, this literature is limited and is mostly focused on the pollutant Ozone [306 307]. A number of studies have found generally good agreement between stationary active monitors and the Ogawa passive samplers [52 53 288]. This association is thought to be, to some extent, dependent on the site location of the continuous monitor [307]. A study from the University of Minnesota reported a relatively low correlation coefficient of $r=0.48$ between NO_x measured by passive samplers and continuous monitors [52]. The study found that although overall mean values were very close between the two methods, the individual daily means were very variable. Another

similar study which focused on validating SO_2 and NO_2 passive sampler measurements in Australia found better agreement, with both pollutants producing correlation coefficients of around $r=0.85$ [53]. These two studies differ, however, not just from taking place in different countries, but also in their equipment and timescale. The Minnesota study was carried out using a stationary continuous tunable diode laser measurement, whilst the Australian study used the more common stationary Chemiluminescence continuous monitor as used in this study. A study from Texas that investigated the comparison between Ogawa air samplers and continuous monitors for Volatile Organic Compounds (VOCs) and NO_2 found that although the Ogawa samplers demonstrated a high level of precision and reproducibility, the results suggested an over prediction of exposure measurements compared to the stationary Chemiluminescence monitors [288]. The limited evidence that has broadly investigated compatibility of Ogawa passive samplers with active continuous monitors goes some way to help inform a user of the Ogawa samplers' reliability and validity. However, to more specifically examine potential sources of error nested in individual studies using the Ogawa samplers, specifically designed studies are required.

This small additional experimental study was designed and implemented to explore potential sources of error in the Ogawa personal samplers which were utilised by the participants in the exposure comparison study described previously in Chapter 3. The objective of this study was to explore the measurement differences between Ogawa and stationary monitors and the effect of differences in the treatment of samplers post-analysis, specifically, the time between exposure and analysis and usage of air tight containers.

4.2 Materials and methods

4.2.1 Study outline

Data collection took place during the months of June and November 2011. In total, 32 Ogawa personal samplers were positioned on the outside of stationary monitors in Manchester, NW England with the permission and assistance from Manchester City Council. Half of the samplers (n=16) were placed on an urban background monitor at the Manchester Piccadilly site and half (n=16) were on a suburban monitor at the Manchester South site (Table 25).

The group was split into two separate seasons, one group exposed during June (n=16) ('summer' season) and the other in November (n=16) ('winter' season). For each season, eight Ogawa samplers were put out at Manchester Piccadilly and eight at Manchester South on the same day and collected 48hours later (<4 hours between monitors put out at the urban site compared to the suburban site). The samplers were positioned directly next to the inlet of the Chemiluminescence analyzer at the top of the stationary monitor with a protective cover to shield the sampler from the rain.

Table 25: Outline of the study design of the treatment of each sampler placed at Manchester Piccadilly (MP) (n=16) and Manchester South (MS) (n=16).

Summer season	***Not in sealed bag***	***In sealed bag***
Posted immediately after exposure.	MP1 & MP2 MS1 & MS2	MP3 & MP4 MS3 & MS4
Posted 21 days after exposure.	MP5 & MP6 MS5 & MS6	MP7 & MP8 MS7 & MS8

Winter Season	***Not in sealed bag***	***In sealed bag***
Posted immediately after exposure.	MP9 & MP10 MS9 & MS10	MP11 & MP12 MS11 & MS12
Posted 21 days after exposure.	MP13 & MP14 MS13 & MS14	MP15 & MP16 MS15 & MS16

4.2.2 Stationary monitors

Two stationary monitor locations were used for this study as demonstrated in Figure 26: Manchester Piccadilly and Manchester South.

Manchester Piccadilly is an urban background monitoring station within self contained air conditioned housing in the west-end of central Manchester. The area surrounding the monitor is generally open with commercial properties. Manchester South is a suburban background monitoring station situated on the edge of a sports field and directly under the approach for Manchester airport (approx 1.1km from the end of the runway).

Measured NO_x and NO_2 concentrations from the two sites were extracted from the air quality statistics DEFRA website once verified [274]. The mean of the two days in which the 48hr sampling took place was calculated.

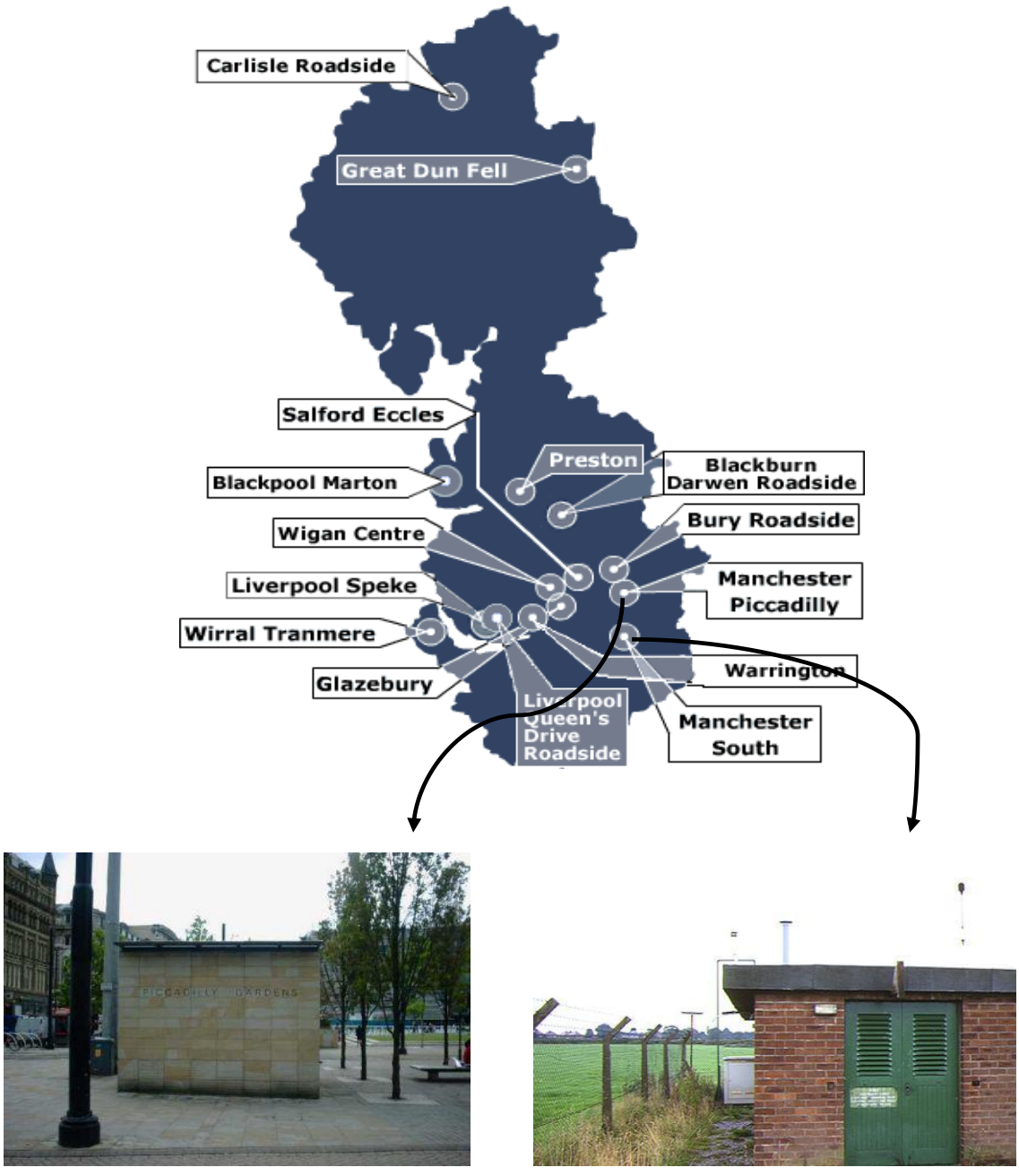

Figure 26: Map of the stationary monitor locations in NW England with photos of Manchester Piccadilly and Manchester South monitoring sites used in this study [7]

4.2.3 Personal samplers

Ogawa sampler measurements of NO_x and NO_2 were obtained for the two 48-hour periods under study at each stationary monitor site. Each sampler was assigned an ID number as indicated in the study design in Table 25. Once the samples were collected, they were stored at 4°C before being sent at the appropriate time point to a commercial laboratory for analysis.

Three main sources of potential error when using the personal samplers were of interest within the exposure estimation comparison study (Chapter 3): 1. Difference in measurement between stationary monitors and personal Ogawa samplers due to the different measurement techniques (and if season or stationary monitor location affects this). 2. Treatment of the personal samplers post exposure (whether the samplers were returned post exposure in a sealed plastic bag or not) and 3. The length of time between exposure and analysis of the personal samplers.

Potential source of error 1: different measurement techniques

Two of the three stationary monitors used in the exposure estimation technique comparison study (Chapter 3) were used for this exploration study. Manchester Piccadilly and Manchester South monitoring stations were selected as two monitors set in different locations: urban and suburban. The stationary monitors use a different technique to measure air pollution exposure compared to the Ogawa personal monitors which could result in differences in results irrespective of how close the Ogawa sampler is to the stationary monitor. The stationary monitors use a Chemiluminescence

technique to measure NO/NO_2 concentrations [7] and the Ogawa passive samplers use coated collection pads designed to react with the specific gases intended to be measured [51] (described in Chapters 1.4.1 and 2.2.5). The study was repeated at two time points in the year to further explore the effect of season on the relationship between the Ogawa and stationary monitor measurements.

Potential source of error 2: time between exposure and analysis

The Ogawa sampling protocol recommends that unexposed Ogawa filters sealed in their original glass vial should be kept frozen for no more than 12 months and refrigerated for 90 days. Once the sampler has been loaded, it can be kept refrigerated in a bag within the airtight container for 60 days. Once the filter has been exposed for monitoring, the loaded sampler should be refrigerated in its bag and air tight container for no more than 21 days before analysis [51].

For studies implementing personal monitoring by lay participants, the practicalities of handling the monitors is likely to vary between participants. Chapter 3 identifies this as an important potential source of error, with around half of the samplers (n=38) in the study being analyzed at >21days post exposure.

Potential source of error 3: non-sealed bag during transport

It is recommended that once the sampler has been loaded and is awaiting the monitoring period *and* between exposure and analysis, the samplers should always be kept in a

sealed plastic bag to prevent exposure to air outside of the desired monitoring period [51]. This difference in the handling of the samplers by lay participants was another potential source of error identified in the study in Chapter 3.

4.3 Statistical analysis

Descriptive statistics were used to summarize the pollutant concentrations from the personal and stationary air pollution monitors.

The data was log-transformed due to it being non- normally distributed and independent T-tests were used to compare the sample means using the log-transformed data. For the purposes of data presentation in this chapter, original (non log-transformed) data are presented in the tables.

Spearman rank correlation coefficients were used to measure the ranked correlations between the personal measurements and the stationary monitor measurements in the different conditions.

Absolute differences and mean ratios were used to assess agreement between the concentrations. Absolute differences were calculated by subtracting the Ogawa personal monitor measurements from the stationary monitor measurements and mean ratios were calculated by personal Ogawa monitor measurements divided by stationary monitor measurements.

Mean difference percentages were calculated for each of the four possible scenarios (sent immediately vs. sent after 21 days and posted in a bag vs. posted not in a bag) under the assumption that the 'true' difference between the Ogawa sampler and the stationary performance is the 'posted immediately and posted in bag' scenario.

4.4 Results

The descriptive results of the Ogawa and stationary monitor measurements are presented in Table 26, the agreement between the Ogawa and stationary monitor measurements in Table 27 and the spearman rank correlation coefficients in Table 28; each stratified by season, station site, time between exposure and analysis of the Ogawa samplers and by the treatment of the samplers in terms of if they were kept in a sealed bag or not. The mean difference percentages for each of the four scenarios are presented in Table 29.

On average, the stationary monitor measurements for NO_2 (mean=37.21µg/m³) and NO_x (mean=76.68 µg/m³) were significantly higher than the Ogawa measurements for NO_2 (mean=18.30µg/m³) (t=-4.58; $p<0.01$) and NO_x (mean=41.50 µg/m³) (t=-2.41; $p<0.05$). There were moderate to good overall correlations between the measurement devices (NO_2 *r=.72*; NO_x *r=.71*). The agreement overall was stronger with NO_2 (AD=18.97µg/m³) than NO_x (AD=35.18 µg/m³).

Both the stationary monitor and Ogawa sampler mean estimates were significantly higher in the winter season compared with summer for NO_2 and NO_x ($p<0.01$). Larger differences were observed between the Ogawa and stationary monitors in the winter group for both NO_2 (AD=29.28µg/m³) and NO_x (AD=65.15µg/m³) than the summer group (NO_2 AD=8.54 µg/m³ and NO_x AD=5.21 µg/m³). The correlations between the Ogawa and the stationary monitors were stronger for NO_2 in the summer, but stronger for NO_x in the winter.

Both the stationary monitor and Ogawa sampler mean estimates measured significantly higher concentrations at the Manchester Piccadilly station site compared to Manchester

South ($p<0.01$). The spearman rank correlation coefficients between the Ogawa and stationary monitor measurements were slightly stronger at Manchester South for NO_2 (*r=.71*) and stronger at Manchester Piccadilly for NO_x *(r=.81)*. For both NO_2 and NO_x, the agreement was better in Manchester South.

Ogawa measurements were on average higher when handled not in a sealed bag compared to a sealed bag, however, the results were not statistically different for NO_2 ($t=1.04$; $p=0.31$) or NO_x ($t=0.54$; $p=0.59$). Stronger correlations were observed between the Ogawa samplers and the stationary monitor measurements when the Ogawa samplers were in a sealed bag (NO_2 *r=.82*; $p<0.01$) compared to an open bag (NO_2 *r=.65*; $p<0.01$). The agreement between the Ogawa and stationary monitor measurements were stronger in the open bag compared to the sealed bag. The smallest mean difference percentage was for the scenario of the Ogawa samplers sent immediately but not in a sealed bag (NO_2= -0.5% and NO_x= 2.4%), suggesting bag use has a negligible impact upon the result if analysed within the recommended time frame between exposure and analysis.

Ogawa measurements were statistically significantly higher when posted and analysed 21 days later compared to immediately post exposure for NO_2 ($t=-2.74$; $p<0.05$) and NO_x ($t=-2.18$; $p<0.05$). The rank correlation coefficients were similar between the Ogawa samplers sent immediately and those that were sent after 21 days. However, the NO_x correlations were slightly stronger in those posted immediately (*r=.81*; $p<0.01$) than those posted later (*r=.70*; $p<0.01$). There was stronger agreement in the samplers sent later than those sent immediately in terms of the absolute differences and the mean ratios. The mean difference percentages demonstrated that samplers analysed more than

21 days post exposure had a substantial impact on measurement error, particularly if the samplers were not handled in a sealed bag (NO2= 67.9% and NOx=59.8%).

Table 26: Mean pollutant concentrations recorded by the Ogawa personal samplers and the stationary monitors (µg/m³).

	Ogawa NO_2 mean (SD)	**Stationary NO_2 mean (SD)**	**Ogawa NO_x mean (SD)**	**Stationary NO_x mean (SD)**
Total N=32	**18.30 (13.11)**	**37.21 (17.90)**	**41.50 (26.68)**	**76.68 (55.47)**
Season				
Summer (n=16)	13.13 (6.87)	21.67 (11.10)	28.89 (16.02)	34.11 (21.22)
Winter (n=16)	23.47 (15.89)	52.75 (4.91)	54.10 (29.59)	119.25 (45.18)
Station				
Man Pic (n=16)	24.40 (14.67)	44.96 (12.95)	58.60 (27.03)	108.83 (55.95)
Man South (n=16)	12.20 (7.81)	29.46 (19.15)	24.39 (10.78)	44.53 (31.99)
Bag				
Open (n=16)	21.24 (16.69)	37.21 (18.20)	46.37 (32.18)	76.68 (55.38)
Sealed (n=16)	15.36 (7.66)	37.21 (18.20)	36.63 (19.62)	76.68 (55.38)
Posted				
Immediately (n=16)	21.24 (16.69)	37.21 (18.20)	33.23 (22.21)	76.68 (55.38)
21 days later (n=16)	15.36 (7.66)	37.21 (18.20)	49.77 (28.85)	76.68 (55.38)

Table 27: Absolute differences and mean ratios between NO_2 and NO_x Ogawa personal monitors and stationary monitors, stratified by season, station site, bag and postage time (µg/m³).

	[1]NO_2 AD Mean (SD)	[1]NO_x AD Mean (SD)	[2]NO_2 Mean Ratio	[2] NO_x Mean Ratio
Total **N=32**	**18.91 (15.28)**	**35.18 (37.03)**	**0.54 (0.27)**	**0.75 (0.58)**
Season				
Winter (n=16)	29.28 (14.38)	65.15 (25.36)	0.64 (0.42)	1.06 (0.69)
Summer (n=16)	8.54 (6.82)	5.21 (16.59)	0.44 (0.27)	0.44 (0.12)
Station				
Man Piccadilly (n=16)	20.56 (15.04)	50.22 (39.57)	0.55 (0.25)	0.60 (0.23)
Man South (n=16)	17.26 (15.83)	20.14 (28.04)	0.53 (0.30)	0.90 (0.77)
Bag				
Open (n=16)	16.00 (16.97)	30.31 (36.39)	0.62 (0.33)	0.83 (0.71)
Sealed (n=16)	21.86 (13.27)	40.05 (38.20)	0.46 (0.17)	0.66 (0.42)
Posted				
Immediately(n=16)	24.14 (13.92)	43.45 (35.26)	0.38 (0.11)	0.51 (0.17)
21 days later (n=16)	13.68 (15.18)	26.91 (38.02)	0.69 (0.30)	0.99 (0.74)

[1]AD= Stationary-Ogawa [2]Mean ratio= Ogawa/Stationary

Table 28: Spearman rank correlation coefficients between NO_2 and NO_x Ogawa samplers and stationary monitors.

	NO_2	NO_x
All monitors **N=32**	**.72**	**.71**
Season		
Summer (n=16)	.87	.65
Winter (n=16)	.61	.71
Station		
Man Pic (n=16)	.60	.81
Man South (n=16)	.71	.52
Bag		
Open (n=16)	.65	.61
Sealed (n=16)	.82	.82
Posted		
Immediately (n=16)	.81	.81
21 days later(n=16)	.61	.70

Table 29: Mean difference percentage error due to sampling mishandling

	Not in sealed bag	***In sealed bag***
Posted immediately after exposure.	NO_2= -0.5% NO_x= 2.4%	NO_2=0% NO_x=0%
Posted 21 days after exposure.	NO_2= 67.9% NO_x=59.8%	NO_2=18.5% NO_x=17.8%

4.5 Discussion

This small experimental study has provided information on the effects of potential sources of error that can occur when using Ogawa samplers in personal monitoring studies. Due to these potential sources of error being so specific to this study, it is not possible to directly compare results with other studies.

The results of this study found stationary monitor results of NO_2 and NO_x to be higher than the Ogawa samplers when positioned at the same location. The increased concentrations measured by the stationary monitors compared to the Ogawa samplers are likely to be due to the differences in measurement techniques. The stationary monitors use continuous active Chemiluminescence analyzers and the Ogawa samplers use a passive diffusion technique. The Ogawa samplers rely on a passive diffusion technique using pre-coated filters with pollutant specific absorbents as explained in Chapter 2.2.5. The stationary monitors actively measure gaseous pollution concentrations using a Chemiluminescence technique which uses fluorescence resulting from a chemical reaction between NO and O_3. The passive samplers have a lower equivalent sampling rate than active monitors, thus generally requiring longer sampling times [257].

This study found increased concentrations from the Ogawa samplers which were analysed >21 days after exposure (as was also found in the exposure comparison study in Chapter 3). In this study, correlations between the Ogawa samplers and the stationary monitor concentrations did not differ much between the group that were sent for analysis immediately compared to those analysed later. Agreement was stronger in those analysed later due to the longer reaction time resulting in higher concentrations and thus agreeing better with the higher stationary monitor measurements.

Increased concentrations were recorded from the Ogawa samplers left out of a sealed bag post exposure. This may be due to the continued sampling of ambient air in other microenvironments for longer than the 48hr sampling period when the sampler is not returned to an air tight bag. Correlations were stronger in those kept in a sealed bag, however, agreement was stronger in those not in a sealed bag. This could again be due to the increased concentrations when not in a sealed bag due to the continued monitoring, thus stronger agreement with the higher stationary monitor measured concentrations.

There was a negligible mean difference percentage error for the samplers that were posted for analysis immediately, but not in a sealed bag. In the worst case scenario in this experimental study of the Ogawa sampler handling i.e. analysed later than 21 days and not kept in a sealed bag, the mean difference percentage error was 68% for NO_2 and 60% for NO_x.

4.6 Conclusion

This experimental study found that the rank correlations between Ogawa and stationary air pollution measurement devices are reasonably good, especially when the samplers are handled as per the study protocol recommendations (Ogawa sampler to remain in air tight bag and analysed at <21 days post exposure). The agreement between the concentrations measured by the two devices was not very strong, suggesting the systematic differences between the active and passive measurement devices have an impact on concentrations measured. This study emphasises the importance of Ogawa samplers being analysed as soon after exposure as possible to minimise measurement error.

This study demonstrated the importance of taking into consideration external factors which could bias results in personal monitoring studies. In particular, personal monitoring studies which involve lay participants where external sources of error are often inevitable, preventative strategies need to be considered *a priori* or stratified analysis of results should be performed post data collection.

The next two chapters in this thesis seek to quantify the effects of air pollution on adverse perinatal outcomes in NW England. Chapter 5 quantifies effects using a proxy technique of air pollution exposure of distance to major roads and Chapter 6 uses two techniques to estimate effects from individual pollutants and establishes a critical window of exposure during pregnancy.

This chapter (Chapter 5) is the accepted and in press paper (at the time of thesis submission):

Kimberly Hannam, Roseanne McNamee, Philip Baker, Colin Sibley, Raymond Agius. 2013. 'Residential proximity to major roads and adverse perinatal outcomes in North West England' *Journal of Occupational and Environmental Medicine.*

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5. Maternal residential proximity to major roads in North West England and adverse pregnancy outcomes

5.1 Abstract

Recent evidence suggests that traffic related air pollution can affect fetal growth and prematurity.

Major road networks in North West England were linked to the maternal residence of 190,909 births (2004-2008).

Distance between residence and nearest major road was calculated and dichotomized at 200m. Logistic regression analyses were performed to investigate the association between distance to major road with small for gestational age (SGA), low birthweight (LBW) and preterm birth (PTB). Analyses were adjusted for maternal age, ethnicity, socio-economic status, parity, birth season and body mass index.

No significant associations were observed in the adjusted analyses between PTB (OR=1.04; 95%CI=0.98-1.11), LBW (OR=0.99; 95%CI=0.93-1.05) and SGA (OR=1.00; 95%CI=0.95-1.06) and living <200m from a major road.

These results, from a study with high statistical power, suggest that living <200m from a major road *per se* does not pose any great risk of an adverse perinatal outcome. However, this may be limited to this geographic location. Further work is needed to quantify individual pollutant effects in pregnancy.

5.2 Introduction

Links between air pollution and ill health in adult and child populations are well documented, particularly for cardiovascular and respiratory conditions [308] [309]. More recently, associations have been shown between maternal exposure to air pollution and adverse pregnancy outcomes [142] [143] [282]. Evidence of an increased risk of low birthweight [171], small for gestational age [60], preterm birth [40] and perinatal mortality [310] have been reported in epidemiological and toxicological studies. Oxidative stress, inflammation and changes in blood viscosity, endothelial function and hemodynamic responses have been suggested as plausible mechanistic pathways by which air pollution may act to restrict growth in utero or create a suboptimal environment which results in a premature delivery [133].

Road traffic emissions in the UK are the largest contributor to ambient air pollution[15]. In 2011, the overall motor vehicle traffic volume in the UK was 303.8 billion vehicle miles, a 0.2% increase from 2010 and ten times higher than in 1949 (28.9 billion vehicle miles) [70]. Pollutants emitted from motor vehicles occur as a result of the combustion process and include metals and polycyclic aromatic hydrocarbons which are largely absorbed to carbon monoxide (CO), nitric oxide (NO), nitrogen dioxide (NO_2), ultra-fine particles and larger particulate matter (PM) [161].

Most epidemiological studies investigating associations between air pollution and adverse perinatal outcomes use large retrospective birth outcome datasets and assign pollution values using an exposure assessment technique based on the residential information at the time of birth [60] [153]. Studies that use air pollution stationary monitors often rely on pollution data recorded a long way from the maternal residence and lack

the spatial resolution required to capture reliable pollution estimates. Stationary monitors are generally set up with the intention to capture urban background levels, suburban or roadside concentrations for local air quality data purposes, which may well result in exposure misclassification of individuals by attenuating or amplifying estimates. More recently, land use regression models have been implemented as an exposure estimation technique that predicts pollution concentrations based on surrounding land use and traffic characteristics thought to have a stronger spatial and temporal resolution [81 286]. However, these models are very data intensive and have been found to have limitations with spatial variation in areas away from major highways and poor correlations with measured data [41].

Road traffic networks and traffic density significantly affect the spatial and temporal distribution of air pollution, thus making it a logical proxy method. Using proximity to major road as a proxy for traffic pollutants provides a more practical method for investigating the effects of traffic pollutants on pregnant women and is a technique that has shown to be a good measure of air pollution exposure for use in epidemiological studies [70]. The technique has many of the limitations that exist in other commonly used exposure estimation techniques, such as only being able to assess exposure at the home location, thus not taking into account time-activity patterns in other locations e.g. at work or commuting and it does not take into account the indoor pollution levels. However, a reasonable correlation has been demonstrated between indoor/outdoor air pollution [304 311] and a number of studies have shown that pregnant women spend the majority of their time at the home location (around 60-90%) [261].

Even with the recognition of traffic sources generating the majority of the pollutants that have been linked to increasing the risk of adverse health outcomes, as well as

plausible biological hypotheses presented of the effect on adverse birth outcomes, relatively few studies have used proximity to major road as a method for estimating exposure in links to a pregnant cohort. This is the first published study to use this method in a British pregnancy cohort.

Studies that have investigated residential close proximity to major roads and distance weighted traffic density (DWTD) in relation to preterm birth, low birthweight and small for gestational age have been worldwide. Studies have been published from America [60 67 69 135], Taiwan [166], Japan [164] Australia [312] and Europe [68 165]. The two European studies had sample sizes of 7, 288 [68] and 99,178 [165], both smaller than the sample size for this study. Of the studies that have found positive associations, effect sizes have typically been around 10-30% [60 67 166].

The aim of this study was to investigate whether maternal residential proximity to major roadways is associated with low birthweight, small for gestational age, preterm birth and spontaneous preterm birth in North West England between 2004 and 2008.

5.3 Methods

5.3.1 Birth outcome data

The North West Perinatal Survey unit (NWPSU) based in Manchester collected information on hospital births that took place within North West England between 1990 and 2009. NW England has a total area of 5,469sq miles and a population of 7,052,000 (2011) [313]. It has a contrasting mix of rural and urban landscape. Greater Manchester (population density: 2,629,400) is the largest urban area with the highest pollution

levels in NW England with 1.083 million motor vehicles [130]. The principal road link in the region is the M6 motorway which carries almost 12, 000 vehicles a day [314].

For this study, only the births recorded by the NWPSU between 2004 and 2008 were included as several key variables did not feature in the data collection before this time point. Between 2004 and 2008, 274,563 births were recorded. Each birth contains maternal and perinatal data collected at the time of delivery from 21 out of the then 29 maternity units in NW England. Data was input by the responsible midwife and was then coded by the NWPSU admin team. Data was collected on: hospital site, ethnicity, postcode, region, mothers' date of birth, body mass index (BMI) at booking, parity, date of delivery, gestational age from last menstrual period and from scan data, birthweight, multiple birth, live birth/stillbirth and smoking. Home births were not included in the NWPSU; (the percentage of home births in the North West of England between 2004-2008 was around 2% [315]).

The data was cleaned by removing all deemed implausible entries (birthweight <400g and >5500g n=336 and gestational age <24weeks and >44 weeks n=274). Within the NWPSU database there were 1,235 missing birthweight entries and 12,833 missing gestational age entries.

We investigated four adverse pregnancy outcomes: preterm birth (PTB), spontaneous preterm birth (SPTB), small for gestational age (SGA) and low birthweight (LBW). LBW was defined as births <2500g, SGA was defined as <10th percentile of birthweight for gestational age and sex in the NWPSU population. PTB was defined as <37 weeks completed gestation and SPTB as <37 weeks completed gestation excluding elective deliveries (n=1,456). For gestational age (GA) measurements, last missed period (LMP) data was used wherever possible and GA from scan data when LMP data was missing,

or when discrepancy exceeded seven days. This decision was made in an attempt to reduce the risk of bias that may arise in scan estimates if fetal growth is influenced by traffic related pollutants in early pregnancy, resulting in the scan underestimating GA and thus overestimating PTB risk [228].

5.3.2 Road proximity data

The Geographical software package *ArcGIS* was used to map the geocoded postcodes from the NWPSU birth outcome dataset and the UK major road networks [270]. A 'major road' includes all motorways and 'A' class roads [271]. The road length of major roads in NW England recorded in 2011 was 2,882 miles [271]. The postcodes and the road network layers were joined using the 'join to nearest' function to determine the nearest linear distance in metres from each residential location to a major road.

All singleton live births (N=265,613) were extracted for geocoding to obtain the individual X Y coordinates. The postcode data was completely missing for 4.5% of cases (n=12,072) and 23.6% (n=62,632) could not be geocoded and linked due to an incomplete or incorrect postcode entry. The non-geocodable cases appeared to be missing at random across the years and hospitals. This left 190,909 live singleton births for which location could be established and linked to the major road network.

Most pollutants thought to be harmful to health return to background levels by 300 metres from a major road [41 66 69]. Pollution decay studies have also found a negative linear relationship up to 200 metres from a major roadway [316]. One study reported that the fraction of maximum particle concentration when wind is blowing from the road to a sampling point drops from 1.0 to around 0.3 at 200m from the major road [65]. Based on this literature and on previous epidemiological studies investigating proximity to major

roads and adverse pregnancy outcomes [69 164] we decided to dichotomize our exposure indicator as <200m and ≥200m. We hypothesised that women living <200m from a major road would have an increased risk of an adverse perinatal outcome, specifically PTB, SPTB, SGA and LBW. In addition, a sensitivity analysis was performed at proximity cut off points below 200m (at 5, 10, 25, 50 and 100m).

5.3.3 Covariate data

Potential confounders were determined *a priori,* based on previous evidence. These comprised: maternal age, ethnicity, socioeconomic status (measured using the index of multiple deprivation score), birth season, parity, body mass index (BMI) and smoking.

Maternal age was categorized as <20, 20-24, 25-29, 30-34, 35-39 and 40+ years. There is evidence that women of childbearing age and young children (<1yr) are more likely to live in more polluted areas [134], moreover the relationship between maternal age and adverse birth outcomes has been shown to be a 'U' shaped curve, where young/old mothers have an increased risk of adverse birth outcomes [136 317].

Ethnicity was dichotomized into white and non-white rather than sub-categorized into more detailed ethnic groups. This was due to a large majority of this population being white (79%). The other ethnicities included in the NWPSU database were: Black African (2%), Black Caribbean (1%), Black other (1%), Indian (3%), Pakistani (8%), Bangladeshi (2%), Chinese (1%) and other (3%). Disparities of air pollution exposure on certain sub groups have been reported in the literature and termed 'environmental injustice' [134]. Black populations in particular have been shown to be exposed to a disproportionate level of air pollution compared to other ethnicities [240]. Black Afro-Caribbean women have an increased risk of PTB compared to other ethnicities [190] and it

is has long been recognised that compared to white populations, other ethnic groups (particularly black and Asian) have an increased rate of LBW [318].

The 'Index of multiple deprivation' (IMD) was used as a measure of socio-economic status (SES). The score comprises of seven indices of deprivation: income, employment, health and disability, education, living environment, crime and barriers to housing and services. IMD scores were assigned to each participant using postcodes with the Geoconvert software [267]. The scores were then categorized into quintiles of deprivation based on English National Standards [266]. Evidence exists that in most countries lower SES individuals are more likely to live in areas of increased urban air pollution [100]. There is also clear evidence indicating that lower social classes have an increased risk of adverse perinatal outcomes [136 319].

Birth season was categorized as: Winter (December-February), Spring (March-May), Summer (June-August) and Autumn (September-November). A well known strong seasonal variation in air pollution levels exists and there is evidence of seasonal patterns in adverse birth outcomes [63]. It is not clear if the observed seasonal birth patterns are independent associations or surrogates for other factors such as temperature or infection patterns. PTB rates have been shown to peak in winter and summer with extremes in temperature [248]. The evidence in terms of fetal growth is less consistent, however, a recent review analysing the evidence on the seasonality of low birthweight suggests that a pattern may exist between those countries in a middle latitude area (40°-55°) and a different pattern in high/low latitude countries (>40°->55° north or south). Chodick et al. (2009) suggest that the large annual temperature ranges in middle latitude climates may cause low birthweights in the summer and in the high and low latitude regions,

differences in sunlight exposure between seasons may contribute to low birthweights apparent in the winter [242].

Parity was included as a dichotomous variable, a first birth or a higher order birth. Evidence suggests a higher risk of adverse pregnancy outcomes for first births and grand parity (≥5 births) [320]. Parity and SES have a complex relationship [321] and due to the evidence of the relationship between SES and air pollution [100 134], it was decided that parity should be treated as a confounder.

BMI was categorized using the standard cut off points set by the World Health Organisation and used consistently in studies of BMI [128]: Underweight (<18.5 kg/m²), normal (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²) and obese (≥30 kg/m²). There is strong evidence of an association between high and low BMI with an increased risk of adverse perinatal outcomes [127]. As with parity, there is a strong relationship with SES [126] and as such BMI was also included in the analysis.

Smoking data (recorded only in 2007 and 2008) was a dichotomous variable stating if the mother was smoking at the time of delivery or not. Smoking directly exposes an individual to an increased concentration of pollutants and smokers tend to live in more polluted areas, mostly due to the links with lower SES. It is well documented that smoking is a strong risk factor for PTB, SGA and LBW [132].

5.3.4 Statistical analysis

The associations between proximity to major road and adverse pregnancy outcomes were analysed using logistic regression models. Each of the pregnancy outcomes were treated as dichotomous variables (e.g. Low birthweight/not low birthweight). All

models adjusted for maternal age, maternal ethnicity, index of multiple deprivation, birth season and parity. Due to BMI data not being recorded during 2004 and smoking data not recorded between 2004 and 2006, further adjustments for these variables were made separately.

The main outcome of interest in terms of the effects of air pollution on a premature delivery is spontaneous PTB, so as to reduce the risk of iatrogenic preterm deliveries biasing the results. All logistic regression analyses were therefore performed with and without the elective preterm deliveries to present the effect estimates of all PTB and SPTB.

If we assume a background rate for PTB of 6% and a relative risk of 1.067, with a population of 130,000 of which 35% are exposed (<200m), the study power will be 85%.

5.4 Results

Table 30 compares the demographic data for the 190,909 included births from the NWPSU database for those living <200m and ≥200m from a major road. A total of 34% of the women lived less than 200m from a major road and 66% lived at least 200m away. There was a 19.74% maternal smoking rate at the time of delivery; this was higher than the England and Wales average of 17% [322]. There was a very small difference (1.1%) in the percentage of women who smoked. A higher percentage of non-white mothers resided <200m from a major road (23.9%) than ≥200m (18.7%). There was a positive relationship between deprivation and proximity to a major road; 44.5% of those living <200m from a major road were in the most deprived group compared to 41.5% living ≥200m.

Table 31 presents the total number of births from each birth outcome investigated. A total of 12,752 (6.7%) of births were classified as LBW and 16, 283 (8.6%) classified as SGA within the NWPSU population. The LBW prevalence in this population is lower than the estimate made by the World Health Organization of LBW prevalence worldwide (17%) and in industrialised countries (7%) [265]. For the analysis of PTB, 11,702 (6.4%) deliveries were preterm and 10,668 (5.8% were spontaneous PTB. This is consistent with rates from other resource rich countries, estimated at 5-10%, but lower than the worldwide estimation of 9.6% [138] and US rates of nearly 13% [136].

Table 30: Numbers (% of column total) of NWPSU births by distance to a major road.

	<200m	≥200m	Total
Total	**65, 043 (34.1%)**	**125, 866 (65.9%)**	**190, 909 (100%)**
Smoking			
Smoker at time of delivery	4, 795 (19.0%)	9, 680 (20.1%)	14, 475 (19.7%)
Index of Multiple Deprivation			
1 (Most deprived)	28, 940 (44.5%)	52, 264 (41.5%)	81, 204 (42.5%)
2	14, 756 (22.7%)	24, 929 (19.8%)	39, 685 (20.8%)
3	9, 340 (14.4%)	19, 514 (15.5%)	28, 854 (15.1%)
4	8, 044 (12.4%)	17, 994 (14.3%)	26, 854 (15.1%)
5 (Least deprived)	3, 961 (6.1%)	11, 156 (8.9%)	15, 117 (7.9%)
Ethnicity			
White	43, 265 (76.1%)	88, 799 (81.3%)	132, 064 (79.5%)
Non-white	13, 602 (23.9%)	20, 481 (18.7%)	34, 083 (20.5%)
Parity			
1st order birth	21, 484 (34.6%)	41, 110 (34.1%)	62, 594 (34.3%)
Higher order birth	40, 592 (65.4%)	79, 391 (65.9%)	119, 983 (65.7%)
Maternal age			
<20	4, 492 (8.3%)	8, 834 (8.5%)	13, 326 (8.4%)
20-24	12, 550 (23.3%)	22, 974 (22.1%)	35, 524 (22.5%)
25-29	14, 800 (27.4%)	27, 573 (26.5%)	42, 373 (26.8%)
30-34	13, 536 (25.1%)	26, 895 (25.9%)	40, 431 (25.6%)
35-39	7, 168 (13.3%)	14, 644 (14.1%)	21, 812 (13.8%)
40+	1, 430 (2.7%)	3, 051 (2.9%)	4, 481 (2.8%)
BMI (kg/m²)			
Underweight (<18.5)	1, 506 (3.8%)	2, 459 (3.3%)	3, 965 (3.5%)
Normal (18.5-24.9)	19, 745 (50.1%)	37, 230 (49.8%)	56, 975 (49.5%)
Overweight (25-29.9)	11, 092 (28.1%)	21, 428 (28.7%)	32, 520 (28.5%)
Obese (≥30)	7, 077 (18.0%)	13, 646 (18.3%)	20, 723 (18.2%)
Birth Season			
Winter	15, 651 (24.1%)	30, 561 (24.3%)	46, 212 (24.2%)
Spring	16, 100 (24.8%)	31, 014 (24.6%)	47, 114 (24.7%)
Summer	16, 734 (25.7%)	32, 306 (25.7%)	49, 040 (25.7%)
Autumn	16, 558 (25.5%)	31, 985 (25.4%)	48, 543 (25.4%)

Table 31: Pregnancy outcomes by distance to major road (<200m and >200m)

	Total	<200m	≥200m
SPTB	10, 668 (5.8%)	3, 658 (5.9%)	7, 010 (5.8%)
PTB	11, 702 (6.4%)	4, 016 (6.5%)	7, 686 (6.4%)
Term	170, 893 (93.6%)	58, 179 (93.5%)	112, 714 (93.6%)
LBW	12, 752 (6.7%)	4, 493 (6.9%)	8, 259 (6.6%)
ABW	177, 344 (93.3%)	60, 275 (93.1%)	117, 069 (93.4%)
SGA	16, 283 (8.6%)	5, 761 (9.0%)	10, 522 (8.5%)
AGA	172, 162 (91.4%)	58, 400 (91.0%)	113, 762 (91.5%)

PTB, Preterm birth (<37 completed gestation weeks);SPTB, Spontaneous preterm birth (<37 completed gestation weeks excluding elective deliveries);Term (≥37 completed gestation weeks); ABW, Appropriate birth weight (≥2500g); LBW, low birth weight (<2500grams); SGA, Small for gestational age (weight for GA and sex <10th centile of population); AGA, Appropriate for gestational age (Birth weight for GA and sex ≥10th centile).

Table 32 presents the unadjusted odds ratios for PTB, LBW and SGA with each of the covariates. Maternal smoking and BMI in the 'underweight' category were the strongest risk factors for PTB, LBW and SGA. Deprivation status demonstrated a significant relationship with risk of all three adverse birth outcomes. Risk estimates decreased linearly with an increase in SES (less deprived). The non-white ethnicity group did not demonstrate any increased risks for PTB. However, there was a significantly increased risk of restricted growth in the non-white population compared to white; this was particularly evident for SGA (OR=1.97; 95%CI=1.90-2.03). Women who had experienced a previous pregnancy were at a significantly lower risk of having a LBW or SGA birth compared to first time mothers (SGA OR=0.74; 95%CI=0.72-0.76). The patterns with maternal age were similar for the PTB and LBW. A 'U' shaped relationship was evident, with higher risks occurring in the younger and older age

categories. For SGA, the risks were highest in the younger age categories and lower in the older categories. For all three birth outcomes under study, the '<20' maternal age category presented the highest risk. Season of birth was not a significant risk factor for any of the adverse birth outcomes.

Table 32: Odds ratios for adverse pregnancy outcomes by covariate level (unadjusted).

Covariates	PTB		LBW		SGA	
	OR	**CI (95%)**	**OR**	**CI (95%)**	**OR**	**CI (95%)**
Non-smoking	ref group		1.00		1.00	
Smoking	1.59	1.48-1.69	2.10	1.99-2.21	1.98	1.89-2.08
IMD quintiles						
1 (most deprived)	ref group		1.00		1.00	
2	0.88	0.84-0.93	0.75	0.71-0.79	0.72	0.69-0.75
3	0.79	0.75-0.84	0.62	0.59-0.66	0.57	0.54-0.60
4	0.73	0.68-0.77	0.56	0.53-0.60	0.52	0.49-0.55
5 (least deprived)	0.65	0.60-0.70	0.48	0.44-0.52	0.46	0.43-0.50
White	ref group		1.00		1.00	
Non-white	0.98	0.94-1.02	1.44	1.38-1.49	1.97	1.90-2.03
First birth	ref group		1.00		1.00	
Higher order birth	0.97	0.94-1.00	0.86	0.83-0.89	0.74	0.72-0.76
Maternal age						
<20	1.24	1.16-1.32	1.32	1.24-1.40	1.29	1.22-1.37
20-24	1.05	1.00-1.11	1.18	1.13-1.24	1.25	1.20-1.30
25-29	ref group		1.00		1.00	
30-34	1.02	0.98-1.08	0.96	0.92-1.01	0.83	0.80-0.87
35-39	1.18	1.11-1.25	1.01	0.95-1.06	0.78	0.74-0.83
40+	1.19	1.07-1.32	1.07	0.96-1.18	0.88	0.80-0.97
BMI						
Underweight	1.59	1.43-1.76	2.17	2.00-2.36	1.98	1.84-2.14
Normal	ref group		1.00		1.00	
Overweight	0.91	0.86-0.96	0.72	0.68-0.76	0.67	0.64-0.70
Obese	0.96	0.90-1.02	0.66	0.62-0.71	0.53	0.50-0.56
Birth season						
Winter	ref group		1.00		1.00	
Spring	0.99	0.94-1.03	0.99	0.94-1.03	0.99	0.96-1.03
Summer	1.01	0.97-1.06	0.99	0.95-1.03	0.99	0.95-1.03
Autumn	0.98	0.93-1.02	0.98	0.94-1.02	0.95	0.91-0.98

PTB, Preterm birth; LBW, low birth weight; SGA, Small for gestational age; OR, Odds ratio; CI(95%), 95% confidence interval; IMD, Index of multiple deprivation; BMI, Body Mass Index

Table 33 presents the unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals from the logistic regression analyses for PTB, SPTB, LBW and SGA, with <200m compared to ≥200m from a major road. Three adjusted analyses are presented due to the substantial missing data from the variables recording BMI (43.0% missing) and smoking (61.9% missing). Analysis 1 adjusts for all the confounders previously described not including BMI and smoking. Analysis 2 includes the BMI adjustment and analysis 3 includes both BMI and smoking adjustments. The unadjusted analyses of LBW and SGA with living <200m from a major road demonstrated a small significant association. Once adjusted for maternal age, ethnicity, SES, birth season and parity with and without BMI and smoking, there was no statistically significant association. The unadjusted and adjusted analyses of PTB and SPTB found no significant associations with living <200m from major road.

Table 33: Odds ratio associations between low birth weight, small for gestational age, preterm birth and spontaneous preterm birth and living <200m from a major road using all available births.

	PTB		SPTB		LBW		SGA	
	Total births	**OR (95%CI)**	**Total births**	**OR (95% CI)**	**Total births**	**OR (95%CI)**	**Total births**	**OR (95%CI)**
Unadjusted Analyses	182 595	1.01 (0.97-1.05)	182 595	1.01 (0.97-1.05)	190 096	1.06* (1.02-1.10)	188 445	1.07* (1.03-1.10)
Adjusted$_1$	127 880	1.01 (0.96-1.06)	127 880	1.00 (0.95-1.05)	131 964	1.01 (0.97-1.06)	131 053	1.02 (0.97-1.06)
Adjusted$_2$	81 178	1.04 (0.98-1.11)	81 178	1.02 (0.96-1.09)	83 097	0.99 (0.93-1.05)	82 602	1.00 (0.95-1.06)
Adjusted$_3$	35 005	1.06 (0.96-1.16)	35 005	1.04 (0.94-1.15)	35 692	1.03 (0.94-1.13)	35 488	1.06 (0.98-1.14)

**, Significant at the p<0.05 level*

$_1$Adjusted for Maternal age, ethnicity, SES (using Index of Multiple Deprivation), Birth season, Parity
$_2$Adjusted for Maternal age, ethnicity, SES (using Index of Multiple Deprivation), Birth season, Parity and BMI
$_3$Adjusted for Maternal age, ethnicity, SES (using Index of Multiple Deprivation), Birth season, Parity, BMI and Smoking

There was a small increase in the effect size after adjustment for smoking (analysis 3). It is not clear why the ORs should increase after adjustment for smoking since the proportion of smokers is very similar for both exposure groups. Further exploratory analyses (not presented here) of the differences between the group with smoking data and those without did not provide an explanation for this small increase and could be due to chance.

The sensitivity analysis demonstrates the general trend of a small increased risk of adverse perinatal outcomes at closer proximities than 200m to a major road (Table 34).

Table 35 presents the sensitivity analysis results of the associations between the adverse perinatal outcomes and proximity increments below 200 metres from a major road. These results generally demonstrate increased effect sizes at closer proximities to major roads. However, in the fully adjusted models, statistically significant results ($p<0.05$) were only found with PTB at 5 metres (OR=1.54; 95%CI=1.01-2.35) and with PTB and SPTB at 25 metres (OR= 1.26; 95%CI= 1.03-1.55 and OR=1.25; 95%CI= 1.00-1.56).

Table 34: Descriptives of pregnancy outcomes by proximity to major road increments

Distance from major road (Metres)	All births	PTB	SPTB	LBW	SGA
5	1, 582 (0.8%)	113 (7.5%)	98 (6.5%)	122 (7.7%)	143 (9.2%)
10	3, 260 (1.7%)	224 (7.2%)	199 (6.4%)	262 (8.1%)	313 (9.7%)
25	7, 983 (4.2%)	507 (6.7%)	464 (6.1%)	591 (7.4%)	721 (9.2%)
50	16, 361 (8.6%)	996 (6.4%)	910 (5.8%)	1, 120 (6.9%)	1, 439 (8.9%)
100	33, 758 (17.7%)	2, 023 (6.3%)	1, 845 (5.7%)	2, 298 (6.8%)	3, 021 (9.1%)
200	65, 043 (34.1%)	4, 016 (6.4%)	3, 658 (5.9%)	4, 493 (6.9%)	5, 761 (9.0%)

PTB, Preterm birth; SPTB, Spontaneous preterm birth; LBW, low birth weight; SGA, Small for gestational age

Table 35: Odds ratio associations between preterm birth, spontaneous preterm birth, low birth weight and small for gestational age and living 5, 10, 25, 50, 100 and 200 metres from a major road in NW England.

		PTB		SPTB		LBW		SGA	
Adjustments	**Distance cut off (Metres)**	**Total births**	**ORCI (95%)**	**Total births**	**OR (CI 95%)**	**Total births**	**OR (CI 95%)**	**Total births**	**OR (CI 95%)**
Unadjusted analyses	**5**	182 595	1.18 (0.97-1.43)	182 595	1.11 (0.91-1.37)	190 096	1.17 (0.97-1.41)	188 445	1.07 (0.90-1.27)
	10	182 595	1.13 (0.98-1.29)	182 595	1.10 (0.95-1.27)	190 096	1.23 (1.08-1.39)*	188 445	1.14 (1.02-1.29)*
	25	182 595	1.04 (0.95-1.14)	182 595	1.05 (0.95-1.15)	190 096	1.12 (1.03-1.22)*	188 445	1.07 (0.99-1.16)
	50	182 595	0.99 (0.93-1.06)	182 595	1.00 (0.92-1.02)	190 096	1.03 (0.97-1.10)	188 445	1.04 (0.98-1.10)
	100	182 959	0.97 (0.92-1.02)	182 595	0.97 (0.92-1.02)	190 096	1.03 (0.98-1.07)	188 445	1.07 (0.91-1.11)
	200	182 595	1.01 (0.97-1.05)	182 595	1.01 (0.97-1.05)	190 096	1.06 (1.02-1.10)*	188 445	1.07 (1.03-1.10)*
Adjusted$_1$	**5**	127 880	1.24 (0.99-1.56)	127 880	1.18 (0.92-1.50)	131 964	1.18 (0.94-1.48)	131 053	1.18 (0.96-1.44)
	10	127 880	1.15 (0.97-1.35)	127 880	1.12 (0.94-1.34)	131 964	1.22 (1.04-1.42)*	131 053	1.11 (0.97-1.28)
	25	127 880	1.08 (0.97-1.21)	127 880	1.08 (0.97-1.21)	131 964	1.10 (0.99-1.22)	131 053	1.04 (0.95-1.14)
	50	127 880	0.99 (0.91-1.07)	127 880	0.99 (0.91-1.08)	131 964	0.98 (0.91-1.06)	131 053	0.99 (0.93-1.06)
	100	127 880	0.97 (0.92-1.03)	127 880	0.96 (0.90-1.02)	131 964	0.99 (0.93-1.05)	131 053	1.01 (0.96-1.06)
	200	127 880	1.01 (0.96-1.06)	127 880	1.00 (0.95-1.05)	131 964	1.01 (0.93-1.05)	131 053	1.02 (0.97-1.06)
Adjusted$_3$	**5**	35 005	1.54 (1.01-2.35)*	35 005	1.35 (0.85-2.16)	35 692	1.05 (0.65-1.69)	35 488	0.81 (0.52-1.28)
	10	35 005	1.31 (0.96-1.79)	35 005	1.26 (0.90-1.77)	35 692	1.24 (0.90-1.69)	35 488	1.10 (0.84-1.46)
	25	35 005	1.26	35 005	1.25	35 692	1.16	35 488	1.18

		PTB		SPTB		LBW		SGA	
Adjustments	**Distance cut off (Metres)**	**Total births**	**ORCI (95%)**	**Total births**	**OR (CI 95%)**	**Total births**	**OR (CI 95%)**	**Total births**	**OR (CI 95%)**
			(1.03-1.55)*		(1.00-1.56)*		(0.94-1.24)		(0.99-1.41)
	50	35 005	1.13 (0.97-1.32)	35 005	1.15 (0.98-1.35)	35 692	1.07 (0.92-1.24)	35 488	1.04 (0.91-1.18)
	100	35 005	1.05 (0.93-1.18)	35 005	1.05 (0.93-1.19)	35 692	0.99 (0.88-1.11)	35 488	1.02 (0.92-1.12)
	200	35 005	1.06 (0.96-1.16)	35 005	1.04 (0.94-1.15)	35 692	1.03 (0.94-1.13)	35 488	1.06 (0.98-1.14)

**, Significant at the p<0.05 level*

[1]Adjusted for Maternal age, ethnicity, SES (using Index of Multiple Deprivation), Birth season, Parity

[3]Adjusted for Maternal age, ethnicity, SES (using Index of Multiple Deprivation), Birth season, Parity, BMI and Smoking

5.5 Discussion

This large retrospective cohort study investigated the association between proximity to major road as a proxy measure for traffic related air pollution and risk of LBW, SGA, PTB and SPTB. This study had a high level of power to detect a small effect, however, no statistically significant effect in the adjusted analyses was observed in any of the adverse pregnancy outcomes investigated with living <200m from a major road.

It is difficult to make direct comparisons with results from other studies due to the heterogeneity of definitions of proximity to road and outcomes investigated. However, the small and largely non-significant effect estimates found in this study were comparable to the results found in the two largest studies (n>400,000) that have previously investigated maternal residential proximity to major roads in relation to adverse pregnancy outcomes [69 135]. Significant associations have been reported for studies investigating close proximity to major roads and LBW [67 69 165]. Genereux et al (2008) reported the strongest significant effect estimate for LBW (OR=1.17; 95%CI: 1.04-1.33) comparing, as this study did, woman living <200m with those living ≥200m from a major road. Wilhelm and Ritz (2003) reported the same risk estimate using a DWTD method comparing the 40th-59th centile with <20th centile. Previous studies investigating SGA have largely found no significant associations with living in close proximity to a major road. One 2008 study reported significant associations of 26% increased odds of SGA [60], however, this was in relation to a closer proximity of <50m from a highway.

More convincing evidence from previous studies is of an association with PTB. A number of studies have found a small significant association [67 69 164-166]. Increased risks

for PTB when living near to a major road have been reported in previous studies ranging from 4-30%. Two studies found particularly strong associations with PTB of OR=1.50 (95%CI=1.20-1.80) [164] and OR=1.30 (95%CI= 1.03-1.65) [166]. However, these results should be interpreted with some caution as the studies were based on relatively small sample sizes of n=14,226 and n=6,251 respectively. Only the study by Yorifuji et al. (2011) which presented particularly strong PTB effects from living ≤200m from a major road also restricted their analysis to preterm premature rupture of membranes (PPROM) and stated that GA estimates were based on LMP and confirmed or corrected by ultrasound measurements. Although only 816 births were categorized as PPROM, adjusted odds ratios of 1.90 (95%CI= 1.30-2.80) were found with living ≤200m from a major road [164]. The other studies reporting positive associations with PTB risk did not state that they excluded elective PTB nor how GA was determined. This could have resulted in an artificial inflation of PTB risk due to iatrogenic deliveries.

There is limited published work on the mechanistic pathways by which traffic related pollutants may be exerting an effect on fetal growth and preterm deliveries. The mechanism of effect is likely a combination of pathways individual to the pollutant and temporality of gestation; some with a direct toxic effect on the fetus and others involved in a cascade of events. It is plausible to hypothesise that an effect may be exerted both pre and post conception. Pre-conception, experimental evidence exists on effects from air pollution on sperm quality [323], implantation failures and number of viable fetuses [324]. Post-conception, pollutants might affect implantation and invasion of the trophoblast layer into the endometrium of the placenta. Abnormal invasion followed by inadequate conversion of spiral arteries, restricting uterine blood supply, resulting in placental dysfunction and consequent fetal growth restriction has been well documented [325]. The

links between placental dysfunction and pre-eclampsia (for which delivery is the only treatment in severe conditions) may in turn result in an iatrogenic increase in PTB. Effects on haemodynamic responses from air pollution exposure have also been suggested as a plausible mechanism, indirectly through the links with pre-eclampsia and directly from the effects of the feto-placental circulation causing oxidative stress and culminating in restricted fetal growth [326]. Carbon monoxide is a gaseous pollutant of traffic origin which binds avidly to circulating maternal haemoglobin, and even more so to fetal haemoglobin. Any consequent diminution in the delivery of oxygen could adversely affect implantation and also directly reduce placental and fetal growth [191 327].

A strength of this study is the high statistical power resulting from the large sample size (n=130,000 for main results). Aside from two particularly large retrospective cohort studies with over 400,000 births [69 135], this study cohort is considerably larger than other studies with a similar methodology and objective [164 166 328]. The 85% power to detect a RR as small as 1.067 enables us to infer, with a high level of confidence, that if an effect from traffic related air pollution in pregnancy as large as this existed, this study would have been able to detect it.

For this study, the commonly used classification of SGA based on population centiles was used: <10th centile for GA and sex in the NWPSU population. Some concerns that population centiles may not be adequately differentiating between infants that are physiologically small as opposed to pathologically growth restricted has led to the further investigation and implementation of customised centiles. Customised centiles adjust for maternal factors such as ethnicity, parity, height and weight which may better represent the truly growth-restricted infants [329]. There is evidence that a greater

proportion of preterm births are likely to be classified as SGA when using customized centiles, compared to population based centiles [330].

The PTB analysis was split into two outcome groups, all PTB and spontaneous PTB (excluding elective deliveries). There are sound arguments for both splitting and grouping elective and spontaneous PTB when studying the aetiology [331]. The main argument for splitting is that spontaneous onset of labour is clinically quite distinctive from some situations that require intervention for an early delivery, such as fetal distress. The main counter argument in favour of grouping is that situations which result in the intervention for an iatrogenic birth such as pre-eclampsia, often share similar mechanisms that lead to a spontaneous PTB e.g. inflammation [331]. A common reason to group is often made based on the size of the study to maintain power. The large sample size of this study provides the opportunity for us to observe the results separately, potentially gaining validity.

The exposure assessment method implemented in this study was able to estimate air pollution over the pregnancy period (under the assumption that maternal residence remains largely constant). This method has many practical advantages; it is not as data intensive as most methods, can be easily replicated and has minimal cost implications. It enables comparable results across studies from different areas with easily interpretable results that have the potential to translate well to public health based policy decisions and town planning.

The relative simplicity of the exposure estimation technique has its limitations. Reducing exposure misclassification in epidemiological studies linking air pollution exposure to health outcomes is paramount in ensuring valid quantification of the effects.

In epidemiological studies of causation, the emphasis is on the correct ranking of exposure level to ensure correct 'high' and 'low' classification of exposure categories, even if the absolute level is unknown. The distance to major road method enables a clear distinction between the 'high' exposed (women residing at <200m from a major road) and 'low' exposed (≥200m). However, dichotomizing in this way could introduce a level of misclassification. Pollution decay occurs differently with each pollutant; this may result in different exposures and response at particular distances from the major road. Effects may differ depending on the pollution combination and whether that combination is acting antagonistically or synergistically. For example, it has been found that particulate matter levels are not elevated past 75m from a major roadway [332] and gaseous pollutants such as carbon monoxide have been found to be more influenced by traffic and effects from roadways have been seen up to 300m from a major roadway [316].

The decision to analyse these data with the proximity to major road dichotomised at 200m was decided upon *a priori* as previously explained. The additional sensitivity analysis which explored a range of cut offs at closer proximities than 200m found results which were suggestive of a negative linear relationship between risk of adverse perinatal outcomes and residential distance from a major road. However, despite the large sample size, few of the increased effect estimates at cut offs less than 200m were statistically significant.

Two factors which could influence exposure which were not taken into account in this study were traffic densities and meteorological factors. Wind direction and speed has a significant effect on pollution concentrations and dispersion [316]. It has been suggested that wind patterns may violate the assumption of isotropic dispersion (identical in all

directions) which is what this method is largely based upon [41]. The exponential decay curve from a roadway has been shown particularly in downwind conditions [65].

Residential mobility and individual time-activity patterns are limitations which hinder the accuracy of individual exposure estimates in almost all retrospective cohort studies investigating the effects of air pollution in pregnancy. Recorded mobility during pregnancy in US populations has been reported at 12% and 17% [216 333]. In the North of England specifically, a lower mobility estimate of 9% has been made [217]. Studies of mobility in pregnancy have shown that those that do move tend to move short distances which will likely decrease the chance of exposure misclassification. This method does not incorporate data on indoor pollution levels, exposure in transport or work location. However, studies have shown that women in pregnancy spend around 60-90% of their time in the home [261]. Without a prospective study to measure individual exposures in all microenvironments and a time-activity log or GPS system, it is not possible to incorporate this data in a large-scale study where estimates are required.

In this study, confounders were decided upon based on *a priori* decisions from existing evidence that a variable was associated with both air pollution and adverse birth outcomes and not just a mediator of an exposure-outcome relationship. The process of selecting confounders based on evidence rather than data availability reduces the risk bias from unmeasured confounding. However, one factor that was considered a confounder but for which data was unavailable was noise pollution. Limited work has been published on the association between noise pollution and adverse pregnancy outcomes, however, it has been shown to correlate strongly with air pollution and road traffic and recommendations have been made for future studies on air pollution associations with health outcomes to incorporate noise pollution [334].

There is a possibility of residual confounding from measurement error in the confounders that were adjusted for. It is not always entirely clear what direction of bias this residual confounding may have [253]. The smoking variable is a likely source of residual confounding. The recording of smoking information was performed as a yes/no at the time of delivery. This may well not adequately capture and adjust for all the women who smoked during pregnancy. This reporting bias could potentially amplify the effects of traffic related pollutants, attributing more of the risk to pollution that should be attributed to smoking. Another potential source of residual confounding may come from the measurement of SES. IMD scores were used to measure SES based on individual postcodes. The score is based on seven domains at a neighbourhood area level and may not entirely capture an individuals specific SES correctly. The IMD score is widely recognised as one of the more sophisticated and robust measures of SES, although with no 'gold standard' by which to compare the index, its performance cannot be easily quantified [269]. The predictive power of the IMD score has been shown to be weaker in rural areas and caution has been advised when using the index in these areas [335]. In this study, however, the majority of the maternal residences were in urban areas.

5.6 Conclusion

Maternal and perinatal data from the majority of hospital births that occurred in NW England during 2004-2008 has been used in combination with road network data to explore the associations between traffic related pollutants and adverse birth outcomes. Our results with narrow confidence intervals suggest that, if there is any effect at all from living <200m from a major road, it is unlikely to be very large. However, we

cannot rule out the possibility that specific pollutants may exert an effect and future work to quantify these separately is needed.

The sensitivity analysis performed in this study suggests that future studies should investigate associations between adverse perinatal outcomes and proximity to major roads at cut off points below 200m. In this population, the majority of residences were located more than 200m from a major roadway; however, our results suggest that there maybe increased risks for those that are living in closer proximity to major roads, particularly at less than 25m.

This is an important area of public health research; adverse pregnancy outcomes are associated with life long ill-health [336] and although effect sizes of air pollution appear small, at a population level this could have significant public health implications. The aetiology of LBW, SGA and PTB is complex with a multiplicity of interacting factors; the environmental influence of air pollution may be a piece of the puzzle that is more easily quantified and preventable than other factors and warrants further study. Future studies should take a multidisciplinary approach to further exploring the effects of air pollution in pregnancy. To better understand this relationship and compliment the interpretation of epidemiological studies, focus should be directed on a better understanding of the biological mechanisms by which traffic related air pollution may be exerting an effect on the maternal and fetal systems to restrict growth in utero. Specific local area studies are also required to quantify effects and aid appropriate air quality management strategies to drive forward with evidence-based decisions.

The next chapter in this thesis presents a study that quantifies individual effects from air pollution exposure on adverse perinatal outcomes in NW England and seeks to identify a critical window of exposure during pregnancy.

This chapter (Chapter 6) is the under review paper (at time of thesis submission):

Kimberly Hannam, Roseanne McNamee, Philip Baker, Colin Sibley, Raymond Agius. 2013. 'Air pollution exposure increases risk of small for gestational age in a large UK birth cohort: use of a novel spatio-temporal modelling technique'. *Paediatric and Perinatal Epidemiology*

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This paper was written by Kimberly Hannam, the author of thesis. The conception of the paper and data analysis was performed by Kimberly Hannam. The data for this study was collected by the midwifery and clerical staff affiliated with the North West Perinatal Survey Unit. All authors were involved in the general development of the paper, supervision and review of the write up.

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6. Air pollution exposure increases risk of small for gestational age in a large UK birth cohort: use of a novel spatio-temporal modelling technique.

6.1 Abstract

Previous work suggests an association between air pollution exposure and adverse pregnancy outcomes, even at relatively low concentrations. Conclusive findings have been hampered due to small sample sizes and exposure misclassification.

Our aim was to quantify the effect of air pollution having an adverse effect on preterm birth and fetal growth in a large UK cohort using a novel exposure estimation technique alongside a traditional stationary monitor approach.

All available postcodes from a NW England birth outcome dataset during 2004-2008 were geocoded (n=203,562 deliveries). Pollution estimates were linked to corresponding pregnancy periods using temporally adjusted background modelled concentrations and a nearest stationary monitor technique. Associations with preterm birth (PTB), small for gestational age (SGA) and birth weight were investigated using regression models adjusting for maternal age, ethnicity, parity, birth season, socio-economic status, body mass index and smoking.

Based on the novel spatio-temporal model, statistically significant associations were found between NO_2, CO, $PM_{2.5}$ and PM_{10} (OR=1.14; 95% CI= 1.01-1.29) and increased risk of SGA. No associations were found with PTB or reduction in birth weight. The critical window of exposure varied between the pollutants, but was generally in later pregnancy.

Our findings demonstrate an association between air pollution exposure and birth of a SGA infant, but not with PTB.

6.2 Introduction

Pregnancy outcome is determined by the ability of the fetus to thrive, which depends on a complex combination of genetic, social and environmental factors [100]. If, during pregnancy, a mother is exposed to increased environmental or social stressors, this could result in an increased risk of restricted growth of the fetus or a preterm delivery. These adverse perinatal outcomes are strong predictors for infant mortality and morbidity [119]. Moreover, strong epidemiological evidence has demonstrated the long term implications of a sub-optimal *in utero* environment with links to an increased risk for health conditions in later life, such as cardiovascular disease and type 2 diabetes [278] [336].

A range of environmental exposures during pregnancy have been investigated to better understand the contribution of environmental factors on the vulnerable fetus, including water contamination [337], electromagnetic fields [258] and pesticides [338]. A large body of work now exists from around the world investigating the effects of air pollution on pregnancy and the subsequent birth outcomes [174]. Numerous studies have found evidence to support the hypothesis that air pollution can increase the risks of a preterm birth [40] and impaired fetal growth [60], however, the results are not yet consistent enough to confirm a causal link with specific pollutants.

Limitations of previous studies mostly relate to exposure assessment methods which may not adequately capture spatial and temporal pollution variation, small sample sizes and appropriateness of confounder adjustments [38]. Most studies investigating the association between air pollution and adverse pregnancy outcomes use a retrospective cohort study design in order to be better able to achieve the necessary power to detect

relatively small effects. A retrospective design presents the challenge of assigning pollution estimates that best represent the spatial and temporal heterogeneity of multi-pollutant exposure during an individual's pregnancy; some exposure misclassification seems likely. A number of different exposure estimation techniques have been designed and implemented to address this challenge [41]. This heterogeneity of exposure assessment techniques that exists in the current literature makes it difficult to synthesise results. Different exposure estimation techniques may lead to different effect sizes. Few studies implemented more than one technique in parallel on the same population; such parallel investigation facilitates a comparison of the different estimates provided and the effect on risk estimates [23 60].

The objective of this study was to use a novel air pollution estimation technique with strong spatial and temporal resolution as well as stationary monitors to estimate the effects from pollutants known to cause adverse health effects on pregnancy outcomes in a large North West England cohort from 2004 to 2008.

6.3 Methods

6.3.1 Study design and cohort

A retrospective cohort study was conducted in the region of North West (NW) England on births that occurred between 1st January 2004 and 31st December 2008. NW England has a total area of 5,469 sq miles and a population of 7,052,000 (2011) [313]. Some of the major cities within NW England record some of the highest air pollution levels outside of London in the UK [15].

Maternal and perinatal data between 2004 and 2008 were obtained from the 'North West Perinatal Survey Unit' (NWPSU). The NWPSU was based in Manchester and during this time period collected maternal and perinatal data at the time of delivery from 21 of the 29 maternity units in NW England. Data included: hospital site, ethnicity, postcode, region, mothers' date of birth, body mass index (BMI) at booking, parity, date of delivery, gestational age calculated from last menstrual period (LMP) and from scan measurements, birth weight, multiple birth, live birth/stillbirth, type of delivery and smoking. Home births were not included in the NWPSU; the percentage of home births in the North West of England between 2004-2008 was around 2% [315].

All singleton live births recorded during 2004-2008 were extracted from the NWPSU (n=265,613) and the data were cleaned by removing all entries deemed to be implausible (birth weight <500g and >5500g n=336 and gestational age <24weeks and >44 weeks n=274). Birth weight entries were missing from 1,235 births and gestational age entries were missing from 12, 833. The total number of births included in each analysis varied depending on the outcome and exposure measure and the covariates adjusted for. Missing covariate data is presented in Table 37.

6.3.2 Pregnancy outcomes

Three outcome measures were investigated: birth weight as a continuous variable, small for gestational age (SGA) and preterm birth (PTB). SGA was defined as <10th percentile of birthweight for gestational age and sex in the NWPSU population [116]. PTB was defined as <37 weeks completed gestation [119]. Gestational age (GA) estimates were based on LMP data wherever possible, and GA from scan data when LMP data was missing, or when the discrepancy exceeded seven days. The GA estimates were made in

this way to reduce the risk of bias that may arise in scan estimates if fetal growth is influenced by air pollution in early pregnancy, resulting in the scan underestimating GA and thus overestimating PTB risk [228].

6.3.3 Covariate data

Potential confounders were determined primarily on *a priori* decisions based on previous evidence. Further exploration of data availability and the relationship between the considered covariates with the adverse pregnancy outcomes under study (Table 37) and air pollution estimates (Table 38) were used to make final decisions regarding confounders.

The following variables were considered as potential confounders: maternal age, ethnicity, socioeconomic status (measured using the index of multiple deprivation score), birth season, parity, BMI and smoking. All variables adjusted for in the analyses were treated as categorical variables.

Maternal age was categorized as <20, 20-24, 25-29, 30-34, 35-39 and 40+ years. In the NWPSU population, 79% were recorded as white British; therefore, ethnicity was dichotomized into white and non-white rather than sub-categorized into more detailed ethnic groups. The other ethnicities included in the NWPSU database were: Black African (2%), Black Caribbean (1%), Black other (1%), Indian (3%), Pakistani (8%), Bangladeshi (2%), Chinese (1%) and other (3%). Socio-economic status (SES) was quantified using scores from the 'Index of multiple deprivation' (IMD) for the maternal residence [266]. The score comprises of seven indices of deprivation weighted as follows: income (22.5%), employment (22.5%), health and disability (13.5%), education (13.5%), living environment (9.3%), crime (9.3%) and barriers to housing and services

(9.3%). These scores were calculated at a lower super output level (a housing range of 400-1,200) [268]. The scores were then categorized into quintiles of deprivation based on English National Standards [266]. Birth season was categorized as: Winter (December-February), Spring (March-May), Summer (June-August) and Autumn (September-November). Parity was included as a dichotomous variable: first birth or a higher order birth. BMI was categorised using the standard cut off points set by the World Health Organisation (WHO) [128]: Underweight (<18.5 kg/m²), normal (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²) and obese (≥30 kg/m²). BMI data was only available for 2006-2008. Maternal smoking data were recorded as a dichotomous variable stating if the mother was smoking at the time of delivery or not. Smoking data were only available for 2007 and 2008.

6.3.4 Exposure data

Air pollution exposure was estimated for each pregnancy using two different exposure methods for nitrogen oxides (NO_x), nitrogen dioxide (NO_2), particulate matter ($PM_{2.5}$ and PM_{10}) and carbon monoxide (CO). First, a more traditional method using nearest stationary monitors (NSTAT) and the second, a more sophisticated spatio-temporal air pollution model (S-T model) using annual mean background modelled concentration maps with a temporal adjustment from nearest stationary monitors.

Nearest stationary monitor

All available postcodes of maternal residence at the time of delivery from the NWPSU (n=203,562) along with eight available stationary monitors located within NW England were geocoded using the *geoconvert* software [267] and mapped in ArcGIS (Figure 27 and 28). Roadside stationary monitors were excluded because the estimates were not

deemed representative of the wider study area. Automatic stationary monitor data were obtained from the UK automatic urban and rural network (AURN) managed by the Department for Environment and Rural Affairs (DEFRA) and Bureau Veritas (DEFRA 2012). Each maternal residential location was linked to the nearest stationary monitor using the 'join to nearest' function in ArcGIS. Monthly mean pollution estimates from the relevant monitor and time period were matched to the relevant corresponding pregnancy periods.

Background modelled concentrations

'The pollution climate mapping' (PCM) model, developed and made publicly available by DEFRA [90] in the UK, was used as the basis of the second exposure assessment technique in this study. The PCM model calculates background annual concentrations at a resolution of 1km². The modelling process is described in detail elsewhere [272 339]. The 2008 annual concentration maps for NO_2, NO_x, PM_{10} and $PM_{2.5}$ in the North West region of England are presented in Figures 29-32.

The main points of the model development are the summing together of concentrations from several layers of data including: large and small point sources from the National Atmospheric Emissions Inventory (NAEI), distant sources characterised by rural background concentrations and areas sources from the NAEI modelled using a dispersion kernel technique [272]. Sources specific to the formation of particulate matter (PM) were included in the calculation of PM estimates including: secondary inorganic and organic aerosol, iron and calcium rich dusts, sea salt (from measurements of chloride at rural sites), area and regional sources of primary particles (from emission estimates from the NAEI).

The PCM model has demonstrated strong correlation and agreement with verification sites across the UK [272] and has recently been externally reviewed by the 'Air quality Modelling Review Steering Group' and found to perform well in independent comparison tests and deemed suitable for use [72]. The PCM model with an additional monthly temporal adjustment has been previously compared, along with other estimation techniques which can be implemented in large scale epidemiological studies, with personal exposures from a cohort in NW England and performed as one of the strongest exposure estimation techniques [338]. The model has been recommended for use in epidemiological studies investigating the health impacts from air pollution; as yet, however, it has only been implemented in one recent epidemiological study to the authors' knowledge [340]. The advantage of the PCM model over commonly used regression based methods is the incorporation of detailed data from emission inventories and meteorological data to model the dispersion of pollutants at a fine spatial level [92 339].

Temporal adjustment

The PCM modelled annual estimates were multiplied by monthly adjustment factors (MAFs) enabling investigation of pollution effects during specific pregnancy periods. The temporal adjustments were derived from stationary monitor data. Each centroid point from the PCM map was linked to the nearest stationary monitor. MAFs were calculated, for each monitoring site, where data was available, for each of the sixty months between January 2004 and December 2008 by dividing the monthly mean by the annual mean concentration of the pollutant concerned. The PCM annual mean concentrations were multiplied by the relevant MAF values. These temporally adjusted modelled estimates are referred to here as the spatio-temporal model (S-T model).

6.3.5 Data linkage

Each available maternal residence was spatially linked to the nearest PCM centroid point using the '*distmatch*' STATA command. Monthly exposure estimates from the S-T model and the nearest stationary monitor were assigned to each month of pregnancy and to the three months pre conception. Date of conception was calculated based on the recorded gestation subtracted from the date of delivery.

6.3.6 Missing data

During the study period, there was missing monthly mean concentration data to a varying extent among pollutants from the eight stationary monitor sites; this precluded temporal adjustment of PCM estimates and assignment of nearest stationary monitor estimates. For CO, there was 33% of data missing, 10% NO_2 and NO_x, 25% PM_{10} and 93% of $PM_{2.5}$ data. The $PM_{2.5}$ data was only collected at the Manchester Piccadilly site.

In order to maximise the number of pregnancies which could be included, data were imputed using a simple hierarchal imputation strategy. If >75% of data within each month was missing, the month was classed as 'missing'. Two methods were used to impute missing data, a preferred quantitative and a secondary qualitative option. The quantitative approach involved the substitution of MAFs for the corresponding time period of a different monitor; after calculation of the standard deviations (SD) of the difference between each monitor pair based on complete data, the monitor with the smallest SD was chosen. The secondary qualitative approach, used when data were not available for the quantitative approach, involved data being imputed from the nearest

and most similar monitor 'type' e.g. urban background monitors were matched to the nearest urban background monitor.

Sensitivity analyses were performed including only the original non-imputed data (Table 42).

6.3.7 Statistical analysis

Logistic regression analyses were used for the dichotomous outcome variables SGA and PTB. Linear regression analyses were used for the continuous outcome measure of birth weight. Odds ratios for SGA and PTB are presented as the fourth quartile of pollution exposure compared to the first quartile (quartile concentration cut offs are presented in Table 38). Odds ratios were calculated for the following pregnancy time periods: 3 months pre-conception, 1st trimester (week 1-13), 2nd trimester (week 14-27), 3rd trimester (week 28-to birth) and an average for the whole pregnancy period (conception to birth).

A test for trend was performed by including the exposure variables as continuous measures for SGA only, because this was the only outcome where an effect was observed.

Adjustments were made for maternal age, parity, ethnicity, birth season, IMD, BMI and smoking. Statistical significance was defined as $p<0.05$.

A further investigation of fetal gender as an effect modifier was performed by stratifying the results by female/male and calculating the odds ratios for the whole pregnancy period. To determine if pollution effects varied by gender, a term

representing the statistical interaction between pollution and gender was included in the logistic regression models and tested for statistical significance.

Figure 27: Map of North West England study location with NWPSU hospitals and stationary monitor sites

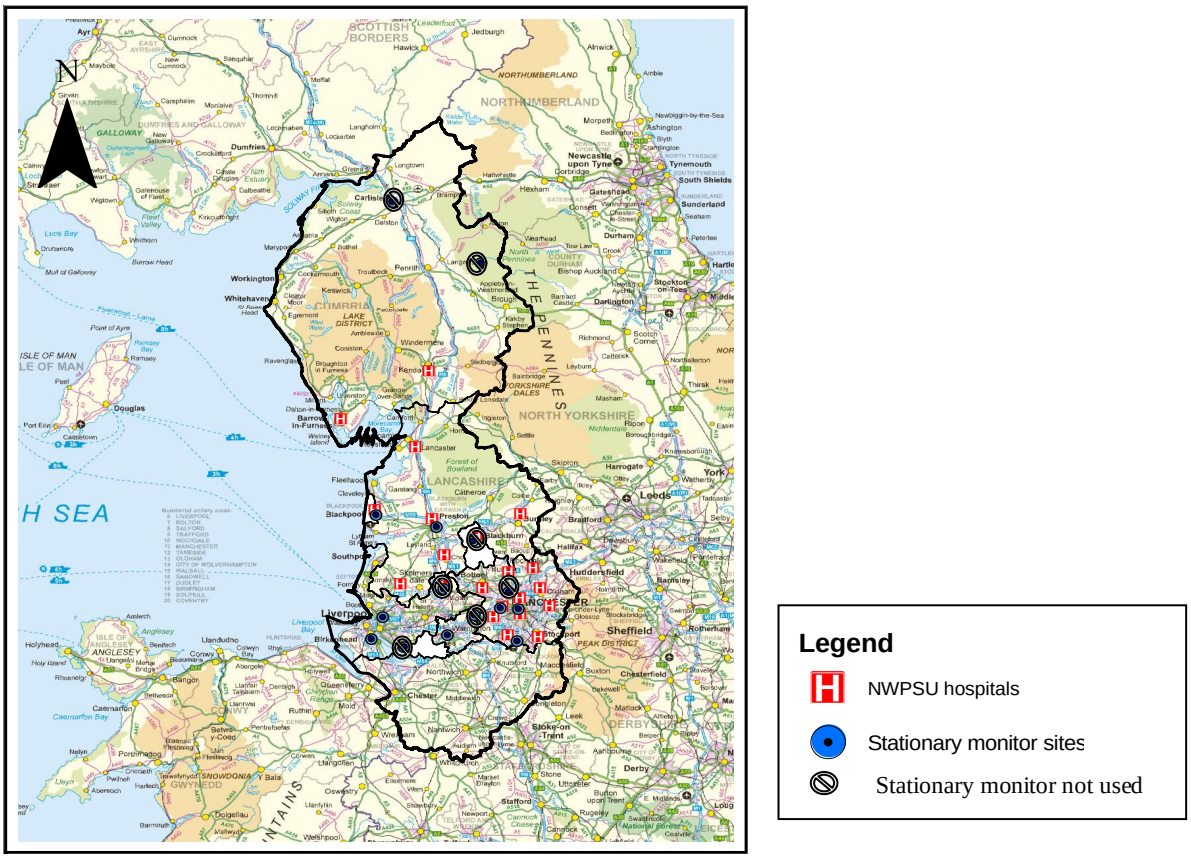


Figure 28: Map of study area with NWPSU maternal residential locations

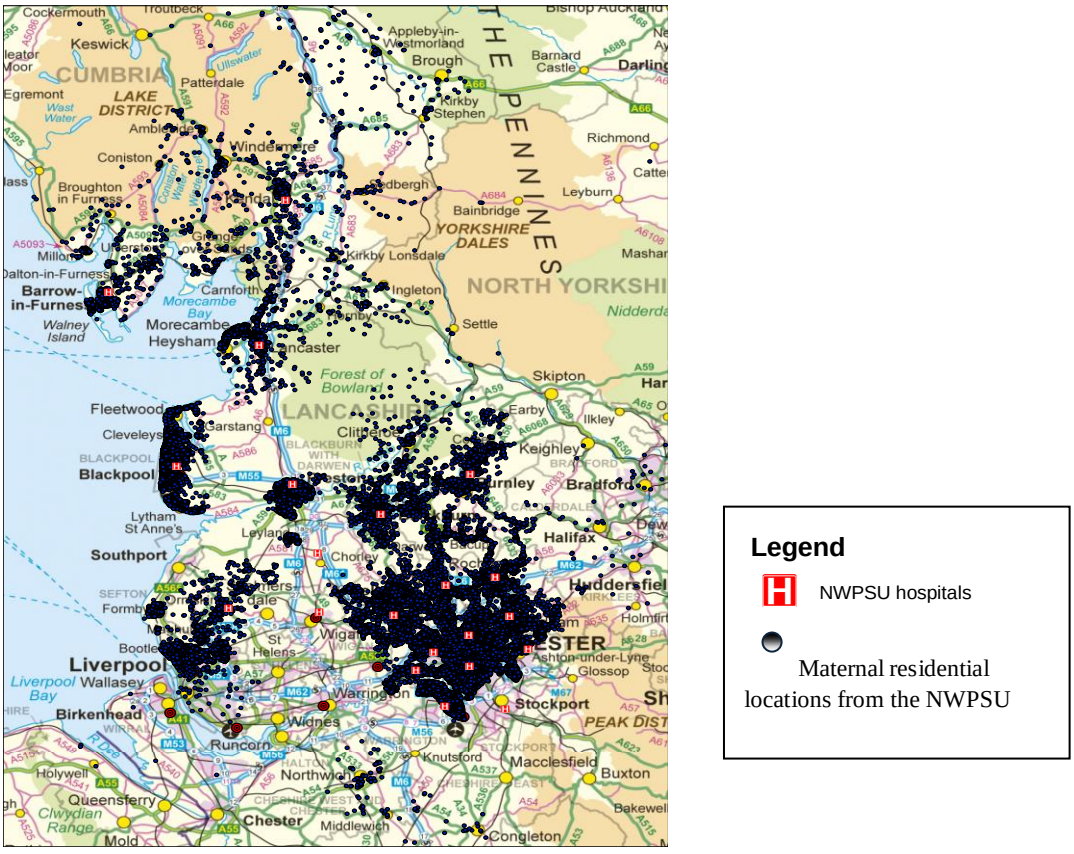


Figure 29: PCM modelled NO_2 concentrations (2008)

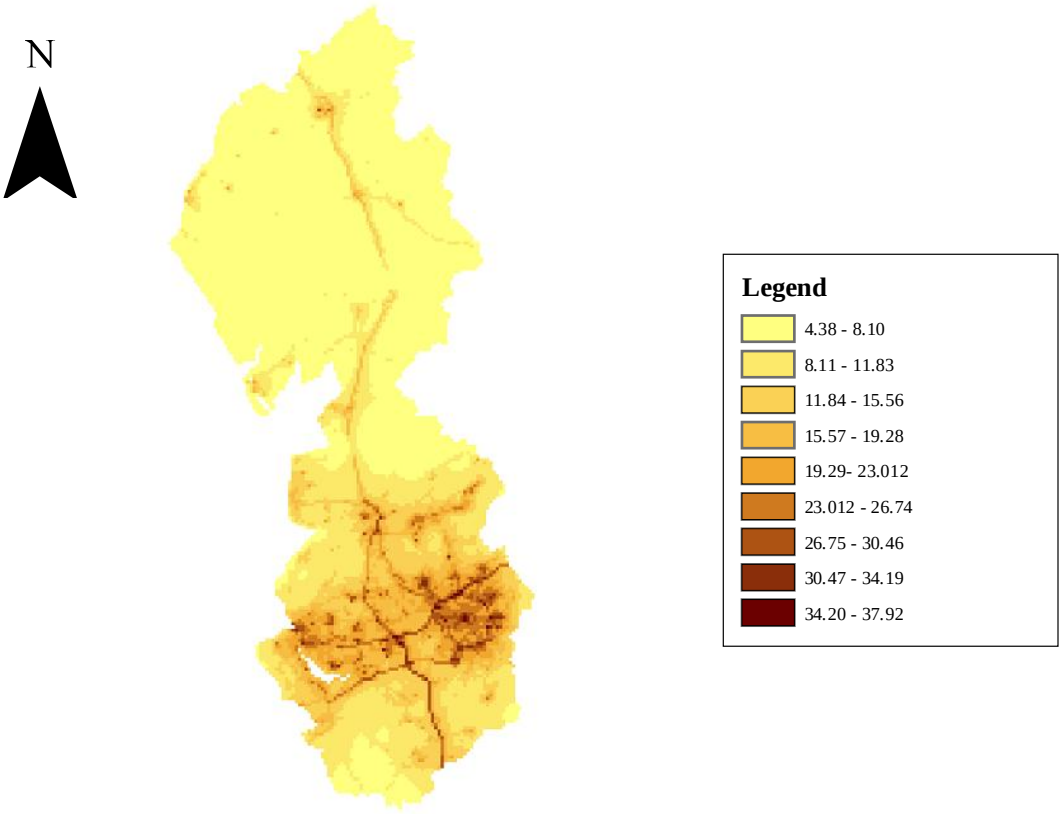


Figure 30: PCM modelled NO_x concentrations (2008)

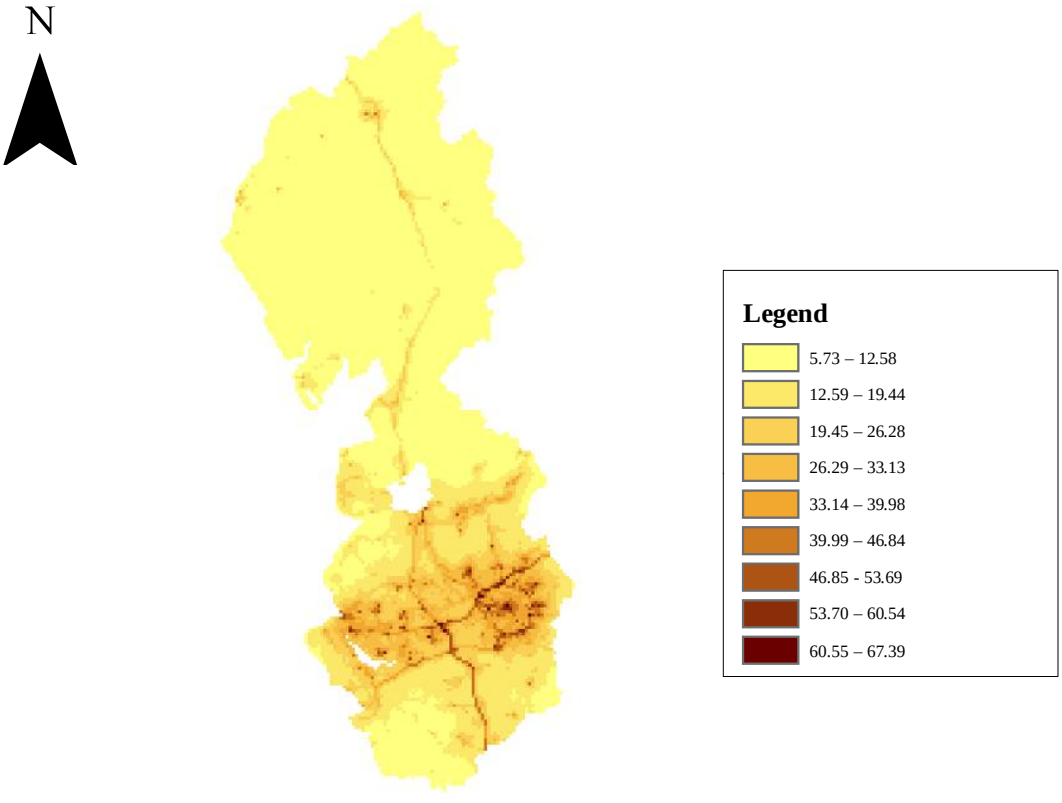


Figure 31: PCM modelled PM_{10} concentrations (2008)

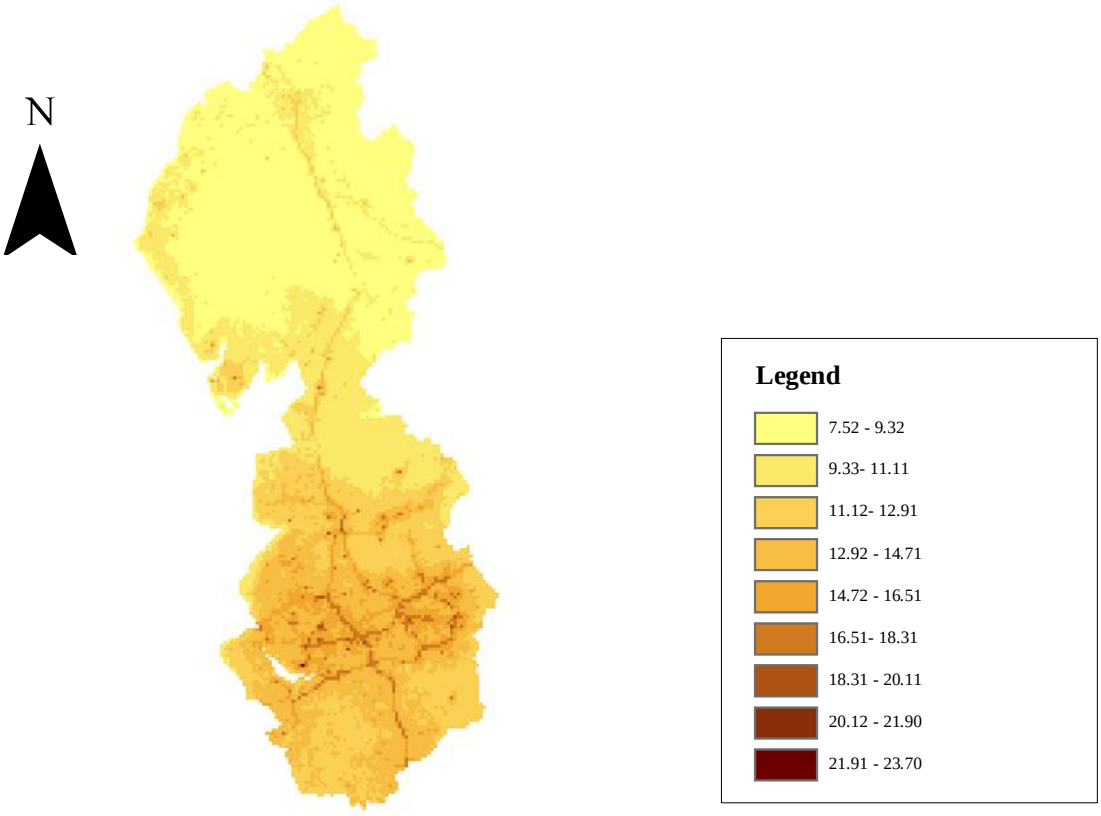
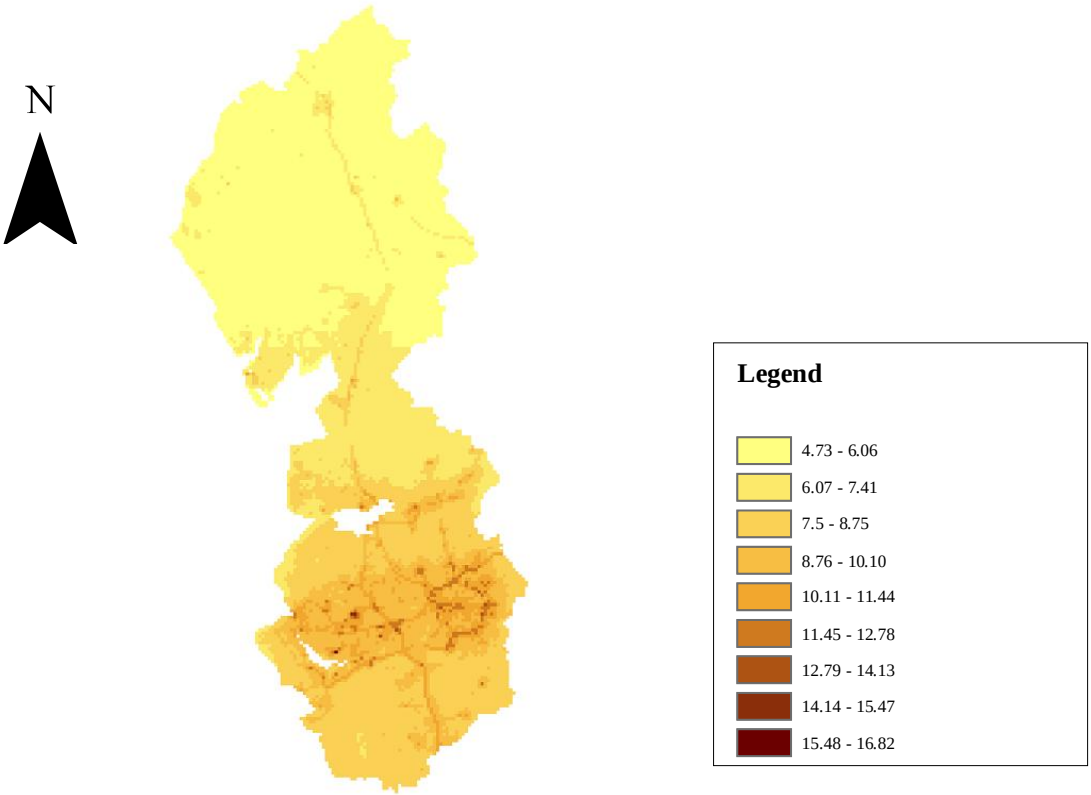


Figure 32: PCM modelled $PM_{2.5}$ concentrations (2008)



6.4 Results

The descriptive statistics of each pollutant by estimation technique and pregnancy period are presented in Table 36. Table 37 describes the covariates and their associations with the outcome measures PTB and SGA; the associations with birth weight change are also presented. The strongest association with SGA and reduction in birth weight was with maternal smoking (OR=2.23; 95%CI= 2.04-2.45 and reduction of -231g; CI= -246, -217). The equal strongest associations with PTB were with maternal smoking and being categorized as underweight based on BMI scores (OR=1.47; CI=1.20-1.80).

Table 38 demonstrates how each of the covariates relates to the exposure estimates. The table presents data based on first trimester NO_2 estimates from the S-T model by quartiles. Maternal smoking rates did not vary much between the pollution quartiles; 3% more smokers were in pollution quartile 4 compared to quartile 1. A higher percentage of younger mothers (<30) lived in more polluted areas and vice versa for older mothers (>30). The strongest associations were with socio-economic status and ethnicity. There was a clear pattern of more deprived women living in more polluted areas. In the lowest air pollution quartile, 25% women are in the most deprived IMD quintile compared to 64% in the highest pollution quartile. A higher percentage of non-white mothers lived in more polluted areas compared to white mothers. In the lowest air pollution quartile, there was 9% non-white and 91% of white mothers and in the highest air pollution quartile, 65% were white and 35% were non-white.

Table 39 presents the Pearson correlation coefficients and the descriptive statistics for the five pollutants and the two exposure estimation techniques investigated. The mean

pollutant concentrations were significantly higher based on the stationary monitor estimates compared to the S-T model. The strongest correlations were between NO_2 and NO_x (*r=0.96*) and with PM_{10} and $PM_{2.5}$ (*r=0.90*). Correlations between the two exposure techniques were stronger for PM than NO_x and NO_2.

Table 40 presents the adjusted associations between the adverse perinatal outcomes with air pollution exposure by quartiles from the entire pregnancy period based on spatio-temporal modelled estimates. Table 41 presents the unadjusted and fully adjusted effect estimates for PTB, SGA and mean birth weight change from both pollution estimation techniques based on exposure averaged for the entire pregnancy period. There were no significant positive associations between any of the air pollutants with PTB. Based on the S-T model, there was a significant increased risk of SGA with PM_{10} in the adjusted model (OR=1.14; CI= 1.01-1.29). CO estimates could only be made based on stationary monitor estimates and although not statistically significant in the fully adjusted model, the effect estimates for SGA were suggestive of an association (OR=1.32; CI=0.90-1.92). Generally, the effect estimates calculated from NSTAT estimates found lower effect sizes compared to the S-T model, especially for SGA and PM_{10}.

Table 42 presents the adjusted OR, mean birth weight change and the test for trend analysis between the air pollution estimates based on the S-T model and adverse pregnancy outcomes by specific pregnancy periods. Again, no associations were found with PTB. Significant associations were found with SGA in the third trimester for NO_2 (OR=1.14; CI= 1.00-1.30) and $PM_{2.5}$ (OR=1.10; CI= 1.00-1.21), with evidence of trend with exposure for $PM_{2.5}$. Although significant associations were also found in trimester 3 with PM_{10} (OR=1.12; CI= 1.00-1.25), the effect estimates were very similar across all

pregnancy periods. The strongest association was found with CO in the second trimester (OR= 1.21; CI= 1.02-1.42). The test for trend was significant for $PM_{2.5}$ in trimester 3 and particularly strong for CO in trimester 2 (OR=1.29, CI= 1.01-1.65) and trimester 3 (OR=1.32, CI= 1.03-1.69).

A sensitivity analysis including only the original non-imputed air pollution data performed for NO_2 and PM_{10} showed similar but stronger effect sizes (Table 43). The association between SGA and PM_{10} during the pre-conception period with the imputed data included was OR=1.10 (CI= 0.99-1.23), compared to the association excluding the imputed data which was stronger and statistically significant at OR=1.39 (CI= 1.15-1.69). With or without the imputed data, no associations were found with PTB.

Table 44 presents associations based on the S-T model estimates for the entire pregnancy stratified by gender. The data were suggestive of a differential effect of air pollution by gender with all the effect estimates higher in female infants compared to males, except for the association between CO and SGA, however, these differences were not statistically significant.

Table 36: Descriptive statistics of the pollutant concentration estimates by pregnancy period.

		Pre conception	**1st trimester**	**2nd trimester**	**3rd trimester**
Pollutant (µg/m³)	**Estimation technique**	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
NO2	*S-T model*	53.60 (18.88)	53.52 (18.98)	53.59 (18.90)	53.52 (18.98)
NO2	*NSTAT*	72.98 (25.63)	72.91 (25.58)	72.95 (25.55)	72.95 (25.59)
NO_x	*S-T model*	76.26 (34.26)	76.17 (34.38)	76.41 (34.23)	76.27 (34.32)
NO_x	*NSTAT*	125.69 (26.33)	125.48 (56.16)	125.52 (56.05)	125.59 (56.21)
PM10	*S-T model*	41.24 (8.73)	41.20 (8.72)	41.26 (8.72)	41.23 (8.74)
PM10	*NSTAT*	52.89 (9.49)	52.87 (9.51)	52.95 (9.51)	52.91 (9.51)
PM2.5	*S-T model*	22.27 (4.97)	22.26 (4.95)	22.31 (4.95)	22.27 (4.96)
PM2.5	*NSTAT*	40.46 (7.24)	40.48 (7.17)	40.45 (7.22)	40.53 (7.24)
CO (mg/m³)	*NSTAT*	0.62 (0.26)	0.62 (0.26)	0.62 (0.26)	0.62 (0.27)

Table 37: Associations between population characteristics and preterm birth, small for gestational age and birth weight.

		PTB			SGA			Birthweight		
	Missing data (%)	% PTB	[1]OR	CI (95%)	% SGA	[1]OR	CI (95%)	Mean	[1]Mean difference	CI (95%)
Total		**6.51**			**8.63**			**3328**		
Non-smoking	**61.8**	5.51	ref group		7.25	1.00		3381	0	
Smoking		8.51	1.47	1.32-1.64	13.43	2.23	2.04-2.45	19822	-231	-246; -217
IMD quintiles	**23.4**									
1 (most deprived)		7.22	ref group		10.97	1.00		3255	0	
2		6.42	0.81	0.72-0.92	8.17	0.90	0.82-0.99	3342	32	17; 46
3		5.80	0.80	0.69-0.93	6.53	0.79	0.70-0.90	3395	53	35; 70
4		5.35	0.78	0.67-0.92	6.05	0.81	0.70-0.92	3429	59	41; 78
5 (least deprived)		4.79	0.71	0.57-0.87	5.39	0.74	0.61-0.89	3453	87	63; 111
White	**14.3**	6.50	ref group		7.37	1.00		3368	0	
Non-white		6.36	0.94	0.84-1.05	13.52	2.33	2.14-2.54	3179	-214	-227; -201
First birth	**4.3**	6.60	ref group		10.20	1.00		3285	0	
Higher order birth		6.41	0.89	0.81-0.98	7.72	0.70	0.65-0.76	3353	69	57; 81
Maternal age	**16.8**									
<20		7.37	0.96	0.80-1.16	10.88	0.93	0.80-1.08	3241	9	-15; 32
20-24		6.34	0.95	0.83-1.07	10.58	1.08	0.98-1.19	3274	-2	-17; 13
25-29		6.03	ref group		8.63	1.00		3329	0	
30-34		6.17	1.06	0.94-1.20	7.28	0.99	0.89-1.10	3375	-2	-17; 13
35-39		7.03	1.30	1.14-1.50	6.89	1.08	0.95-1.22	3383	-14	-32; 3
40+		7.08	1.26	0.99-1.61	7.65	1.03	0.82-1.30	3364	-2	-34; 29
BMI	**43.0**									
Underweight		9.20	1.47	1.20-1.80	18.29	1.66	1.43-1.91	3038	-163	-192; -134
Normal		5.97	ref group		10.18	1.00		3276	0	
Overweight		5.46	1.00	0.90-1.11	7.03	0.70	0.64-0.76	3391	110	97; 122

		PTB			SGA			Birthweight		
	Missing data (%)	**% PTB**	**[1]OR**	**CI (95%)**	**% SGA**	**[1]OR**	**CI (95%)**	**Mean**	**[1]Mean difference**	**CI (95%)**
Obese		5.74	0.95	0.99-1.25	5.65	0.56	0.50-0.62	3476	186	171; 201
Birth season	**0**									
Winter		6.54	ref group		8.77	1.00		3320	0	
Spring		6.45	0.98	0.86-1.11	8.73	1.01	0.89-1.09	3326	11	7; 37
Summer		6.63	0.99	0.88-1.12	8.69	0.99	0.90-1.11	3333	22	13; 43
Autumn		6.40	0.95	0.83-1.07	8.33	1.00	0.08-0.11	3333	28	13; 43

[1] Effects for each covariates are adjusted for other covariates.

PTB, Preterm birth (<37 completed gestation weeks); SGA, Small for gestational age (weight for GA and sex <10th centile of population);

OR, Odds ratio; 95%CI, 95% confidence interval; IMD, Index of multiple deprivation; BMI, Body Mass Index

Table 38: Associations between spatio-temporal modelled NO_2 exposure (1st trimester) and covariates (column percentages).

	Quartile 1 *(8.07-42.9 µg/m³)* ***mean (SD)***	**Quartile 2** *(43.0-53.7 µg/m³)* ***mean (SD)***	**Quartile 3** *(53.8-63.6 µg/m³)* ***mean (SD)***	**Quartile 4** *(63.7-200.8 µg/m³)* ***mean (SD)***	**Total**
Maternal age	29.14 (6.2)	28 27 (6.2)	27.81 (6.1)	27.47 (6.0)	28.11 (6.1)
BMI	25.71 (5.5)	25.51 (5.5)	25.50 (5.5)	25.49 (5.5)	25.55 (5.5)
IMD scores	24.08 (17.5)	32.00 (19.2)	37.34 (19.1)	42.01 (18.6)	33.39 (19.7)
	Quartile 1 n (%)	**Quartile 2 n (%)**	**Quartile 3 n (%)**	**Quartile 4 n (%)**	**Total**
Smoking					
Smoking at time of delivery	2, 886 (18)	3, 250 (20)	3,034 (20)	2, 202 (21)	11, 372 (20)
Index of Multiple Deprivation					
1 (Most deprived)	8,103 (25)	11,939 (43)	13,785 (54)	17,721 (64)	51, 548 (45)
2	6,251 (19)	5,921 (21)	5,242 (21)	5,592 (20)	23,006 (20)
3	6,362 (20)	4,306 (15)	3,196 (13)	2,562 (9)	16,426 (15)
4	6,729 (21)	3,477 (12)	2,329 (9)	1,614 (6)	14,149 (12)
5 (Least deprived)	4,657 (15)	2,190 (8)	958 (4)	381 (1)	8,186 (7)
Ethnicity					
White	24,711 (91)	19,635 (80)	16,135 (73)	15, 814 (65)	76,295 (79)
Non-white	2,532 (9)	4,809 (20)	6,028 (27)	8,492 (35)	21,861 (21)
Parity					
1st order birth	10, 917 (35)	9, 943 (37)	8, 541 (34)	9, 250 (34)	38, 651 (35)
Higher order birth	20, 226 (65)	17, 293 (63)	16, 544 (66)	18, 140 (66)	72, 203 (65)
Maternal age					
<20	1,727 (7)	1,841 (8)	1,804 (8)	2,153 (9)	7,525 (8)
20-24	4,650 (19)	5, 040 (22)	5, 235 (24)	6, 085 (26)	21, 010 (23)
25-29	6,272 (25)	6, 063 (27)	6, 026 (28)	6, 853 (29)	25, 214 (27)
30-34	6,892 (28)	5, 666 (25)	5, 103 (24)	5, 401 (23)	23, 062 (25)
35-39	4,255 (17)	3, 204 (15)	2. 701 (13)	2, 762 (12)	12, 922 (14)
40+	979 (4)	689 (3)	531 (2)	569 (2)	2, 768 (3)
BMI (kg/m²)					
Underweight (<18.5)	517 (3)	690 (3)	708 (4)	754 (4)	2, 669 (3)
Normal (18.5-24.9)	9,893 (50)	10, 573 (50)	9, 603 (49)	9, 591 (50)	39, 660 (50)
Overweight (25-29.9)	5,694 (29)	6, 091 (28)	5,539 (29)	5, 466 (28)	22, 790 (29)
Obese (≥30)	3,686 (19)	3, 817 (18)	3,491 (18)	3, 567 (18)	14, 561 (18)
Birth Season					
Winter	7,226 (23)	6,580 (24)	7, 140 (25)	6,425 (25)	27, 760 (25)
Spring	7,211 (22)	6,627 (24)	6, 858 (24)	6,177 (24)	26, 751 (24)
Summer	8,733 (27)	7,033 (25)	6, 850 (24)	6,132 (24)	28, 301 (25)
Autumn	8,935 (28)	7,593 (27)	7, 482 (26)	6,776 (26)	30, 506 (27)
Gender ratio (M/F)	51.04 / 48.96	51.61 / 48.39	50.86 / 49.14	50.87 / 49.13	51.10 / 48.90

Table 39: Pearson correlation coefficients and descriptive statistics for the included air pollution metrics.

Pollutant		**NO_x**		**NO_2**		**PM_{10}**		**$PM_{2.5}$**		**CO**
	Exposure technique	*S-Tmodel*	*NSTAT*	*S-Tmodel*	*NSTAT*	*S-Tmodel*	*NSTAT*	*S-Tmodel*	*NSTAT*	*NSTAT*
NO_x	*S-Tmodel*	1.00								
	NSTAT	0.25	1.00							
NO_2	*S-Tmodel*	0.96	0.12	1.00						
	NSTAT	0.26	0.53	0.17	1.00					
PM_{10}	*S-Tmodel*	0.66	-0.17	0.73	0.02	1.00				
	NSTAT	-0.09	-0.12	0.02	-0.03	0.58	1.00			
$PM_{2.5}$	*S-Tmodel*	0.70	0.03	0.78	0.05	0.90	0.48	1.00		
	NSTAT	0.02	0.21	0.11	0.06	0.47	0.81	0.62	1.00	
CO	*NSTAT*	0.29	0.75	0.11	0.41	-0.11	-0.24	0.00	0.02	1.00
	[1]Descriptives									
	Mean	76.86	127.97	54.63	74.01	40.99	53.07	22.11	41.69	0.61
	SD	28.70	47.64	18.51	24.58	7.51	7.91	3.31	3.17	0.26
	Min	13.01	39.62	8.56	22.50	18.36	28.89	10.32	31.44	0.23
	Max	225.92	267.89	169.69	130.89	69.78	77.22	41.01	51.67	1.25
	Quartile 1	13.0 - 55.4	13.0 - 88.9	8.6 - 42.9	22.5 - 52.7	18.3 - 35.4	28.9 - 47.7	10.3 - 19.7	31.4 - 39.5	0.2 - 0.4
	Quartile 2	55.4 - 73.8	88.9 - 116.0	42.9 - 53.7	52.7 - 70.33	35.4 - 40.8	47.7 - 53.2	19.7 - 22.0	39.5 - 41.7	0.4 - 0.6
	Quartile 3	73.8 - 96.0	116.0 - 169.8	53.7 - 63.6	70.3 - 97.5	40.8 - 46.3	53.2 - 59.0	22.0 - 24.3	41.7 - 43.9	0.6 - 0.8
	Quartile 4	96.0 - 225.9	169.8 - 267.9	63.6 - 169.7	97.5 - 130.9	46.3 - 69.8	59.0 - 77.2	24.3 - 41.0	43.9 - 51.7	0.8 - 1.3

[1] Descriptive statistics concentrations in µg/m³. CO in mg/m³

Table 40: [1]Adjusted associations between preterm birth, small for gestational age and birth weight with air pollution exposure by quartiles from entire pregnancy period estimates based on the spatio-temporal model.

		PTB		SGA		Birth weight	
Air pollutant	**Quartile cut off points**	**No. of subjects**	**OR (95%CI)**	**No. of subjects**	**OR (95%CI)**	**No. of subjects**	**Change (95%CI)**
NO_2		11 133		28 926		11 094	
Q1	8.6 - 42.9		REF		REF		REF
Q2	42.9 - 53.7		0.89 (0.69-1.14)		0.91 (0.74-1.12)		21. (-9; 51)
Q3	53.7 - 63.6		1.00 (0.77-1.29)		0.92 (0.75-1.15)		10 (-22; 41)
Q4	63.6 - 169.7		1.10 (0.82-1.48)		1.00 (0.79-1.27)		-10 (-46; 27)
NO_x		24 439		24 246		24 298	
Q1	13.0 - 55.4		REF		REF		REF
Q2	55.4 - 73.8		1.04 (0.86-1.26)		0.98 (0.83-1.15)		0.5 (-22; 23)
Q3	73.8 - 96.0		1.04 (0.86-1.25)		0.95 (0.81-1.12)		16 (-6; 38)
Q4	96.0 - 225.9		1.07 (0.89-1.28)		1.06 (0.91-1.23)		1 (-9; 35)
$PM_{2·5}$		38 608		38 331		38 422	
Q1	10.3 - 19.7		REF		REF		REF
Q2	19.7 - 22.0		1.06 (0.93-1.21)		0.95 (0.85-1.06)		-7 (-23; 10)
Q3	22.0 - 24.3		0.96 (0.84-1.10)		0.98 (0.88-1.10)		12 (-4; 29)
Q4	24.3 - 41.0		0.98 (0.85-1.12)		1.04 (0.93-1.17)		5 (-11; 22)
PM_{10}		38 156		37 877		37 969	
Q1	18.3 - 35.4		REF		REF		REF
Q2	35.4 - 40.8		0.99 (0.89-1.11)		1.00 (0.91-1.10)		-3 (-16; 11)
Q3	40.8 - 46.3		0.94 (0.83-1.06)		1.09 (0.98-1.21)		8 (-7; 24)
Q4	46.3 - 69.8		1.05 (0.90-1.22)		1.14 (1.01-1.29)*		-12 (-32; 7)
CO		18 418		18 317		18 359	
Q1	0.2 - 0.4		REF		REF		REF
Q2	0.4 - 0.6		1.01 (0.87-1.19)		0.97 (0.84-1.11)		8 (-12; 27)
Q3	0.6 - 0.8		1.02 (0.88-1.19)		1.11 (0.98-1.26)		-9 (-28; 10)
Q4	0.8 - 1.3		0.65 (0.34-1.23)		1.32 (0.90-1.92)		17 (-47; 81)

*[1] Adjusted for: maternal age, ethnicity, parity, birth season, socio-economic status, body mass index and smoking. *P<0.05*

Table 41: Associations between preterm birth, small for gestational age and birth weight with air pollution exposure from entire pregnancy period estimates based on the spatio-temporal model and nearest stationary monitor approach (4th quartile compared to 1st).

		PTB			SGA				Birth weight		
Air pollution metric	**Adjustments**	**No. of subjects**	**OR**	**95% CI**	**No. of subjects**	**OR**	**95% CI**	**Test for trend** (per 1µg/m³ increase)	**No. of subjects**	**Mean change**	**95% CI**
S-T model											
NO_2	*Unadjusted*	46 882	1.14	1.03-1.27*	46 602	1.57	1.44-1.72*	1.01 (1.01-1.01)*	46 723	-104	(-119; -90)*
	Adjusted[1]	11 133	1.10	0.82-1.48	11 070	1.00	0.79-1.27	1.00 (0.99-1.01)	11 094	-10	(-46; 27)
NO_x	*Unadjusted*	57 770	1.03	0.93-1.14	55 971	1.45	1.33-1.57*	1.04 (1.00-1.01)*	57281	-81	(-95; 68)
	Adjusted[1]	24 439	1.07	0.89-1.28	24 246	1.06	0.91-1.23	1.00 (1.00-1.01)	24 298	13	(-9; 35)
$PM_{2.5}$	*Unadjusted*	81 058	1.00	0.92-1.09	79 714	1.29	1.04-1.20*	1.03 (1.02-1.04)*	80 478	-53	(-64; -42)*
	Adjusted[1]	38 608	0.98	0.85-1.12	37 591	1.04	0.93-1.17	1.01 (1.00-1.02)	38 422	5	(-11; 22)
PM_{10}	*Unadjusted*	81 141	1.07	0.99-1.16	156 590	1.41	1.34-1.48*	1.02 (1.02-1.02)*	157 988	-79	(-86; -70)*
	Adjusted[1]	19 087	0.90	0.74-1.11	37 862	1.14	1.01-1.29*	1.01 (1.00-1.01)*	37 969	-12.2	(-32; 7)
Monitoring stations											
NO_2	*Unadjusted*	111 096	0.97	0.91-1.04	110 320	1.25	1.17-1.32*	1.00 (1.00-1.00)	110638	-44	(-54; -35)*
	Adjusted[1]	31 822	0.90	0.79-1.04	31 597	0.99	0.88-1.11	1.00 (1.00-1.00)	31672	28	(11; 45)
NO_x	*Unadjusted*	99 941	1.00	0.93-1.07	99 199	1.20	1.13-1.27*	1.00 (1.00-1.00)	99 489	-40	(-50; -30)*
	Adjusted[1]	32 827	0.94	0.81-1.09	32 585	1.00	0.89-1.12	1.00 (1.00-1.00)	32670	21	(-3; 39)
$PM_{2.5}$	*Unadjusted*	56 786	1.02	0.94-1.11	56 786	1.02	0.94-1.11	1.01 (0.99-1.03)	11 460	7	(-23; 37)
	Adjusted[1]	5 761	0.44	0.23-0.85*	5 721	1.63	1.13-2.37*	1.04 (0.97-1.12)	1338	8	(-133; 148)
PM_{10}	*Unadjusted*	81 141	1.07	0.99-1.16	80 734	1.01	0.95-1.08	1.00 (1.00-1.00)	80 961	-8	(-19; 3)
	Adjusted[1]	19 087	0.90	0.74-1.11	18 972	1.06	0.90-1.25	1.00 (1.00-1.01)	19 019	28	(4; 53)
CO	*Unadjusted*	78 112	1.10	1.01-1.19*	77 728	1.27	1.19-1.36*	1.60 (1.45-1.75)*	77 945	-56	(-67; -44)*
	Adjusted[1]	18 418	0.65	0.34-1.23	18 317	1.32	0.90-1.92	1.34 (0.98-1.85)	18 359	17	(-47; 81)

*[1] Adjusted for: maternal age, ethnicity, parity, birth season, socio-economic status, body mass index and smoking. *P<0.05*

Table 42: [1]Adjusted associations between preterm birth, small for gestational age and birth weight with air pollution exposure by four pregnancy time periods.

		PTB			SGA				Birth weight		
[2]Air pollutant (µg/m³)		No. subjects	OR	95% CI	No. Subjects	OR	95% CI	[3]Test for trend (per 1µg/m³ increase)	No. subjects	Mean change	95% CI
NO_2	*Pre-conception*	36 123	0.93	0.81-1.07	28 926	1.10	0.96-1.26	1.00 (1.00-1.01)	29 000	1	-19; 21
	Trimester 1	29 181	1.08	0.92-1.27	28 980	1.05	0.92-1.20	1.00 (1.00-1.00)	29 045	-11	-31; 9
	Trimester 2	29 042	1.07	0.91-1.25	28 832	1.08	0.95-1.23	1.00 (1.00-1.01)	28 897	5	-15; 25
	Trimester 3	29 104	1.01	0.86-1.19	28 899	1.14	1.00-1.30*	1.00 (1.00-1.01)	28 974	-8	-28; 11
NO_x	*Pre-conception*	32 988	0.93	0.81-1.07	32 744	1.01	0.90-1.13	1.00 (1.00-1.00)	32 821	18	1; 35
	Trimester 1	32 839	1.04	0.91-1.19	32 593	0.96	0.86-1.07	1.00 (1.00-1.00)	32 667	15	-2; 32
	Trimester 2	33 019	1.08	0.94-1.24	32 774	1.05	0.93-1.18	1.00 (1.00-1.00)	32 855	7	-9; 24
	Trimester 3	32 749	1.00	0.87-1.15	32 504	1.03	0.92-1.16	1.00 (1.00-1.00)	32 579	26	9; 43
PM_{10}	*Pre-conception*	38 252	1.01	0.88-1.16	37 972	1.10	0.99-1.23	1.00 (1.00-1.01)	38 065	-1	-18; 16
	Trimester 1	38 237	1.06	0.92-1.21	37 901	1.13	1.02-1.26*	1.00 (1.00-1.01)	38 050	-2	-19; 15
	Trimester 2	38 243	0.95	0.83-1.09	37 902	1.11	0.99-1.24	1.01 (1.00-1.01)	38 056	-3	-20; 14
	Trimester 3	38 242	0.97	0.84-1.11	37 902	1.12	1.00-1.25*	1.00 (1.00-1.01)	38 055	-3	-20; 14
$PM_{2.5}$	*Pre-conception*	38 609	0.98	0.87-1.09	37 953	0.99	0.90-1.08	1.00 (0.99-1.01)	38 424	15	1; 28
	Trimester 1	38 615	1.00	0.90-1.12	38 337	0.98	0.89-1.07	1.00 (0.99-1.01)	38 429	4	-10; 18
	Trimester 2	38 610	0.98	0.92-1.05	38 333	1.05	0.96-1.15	1.00 (1.00-1.01)	38 424	-6	-20; 8
	Trimester 3	38 611	0.91	0.82-1.02	38 334	1.10	1.00-1.21*	1.01 (1.00-1.02)*	38 425	11	-3; 25
[3]CO	*Pre-conception*	23 225	1.06	0.85-1.31	23 098	1.02	0.85-1.21	1.15 (0.90-1.47)	23 144	11	-15; 38
	Trimester 1	23 224	0.94	0.75-1.18	23 089	0.92	0.77-1.10	1.03 (0.80-1.32)	23 141	12	-15; 38
	Trimester 2	23 265	0.92	0.74-1.15	23 128	1.21	1.02-1.42*	1.29 (1.01-1.65)*	23 181	-2	-29; 24
	Trimester 3	23 136	0.95	0.76-1.18	23 005	1.16	0.98-1.38	1.32 (1.03-1.69)*	23 053	12	-15; 38

*[1]Adjusted for: maternal age, ethnicity, parity, birth season, socio-economic status, body mass index and smoking [2] Air pollution exposure estimates based on the spatio-temporal model [3] Carbon monoxide (CO) estimates were made using the nearest stationary monitor technique and recorded in mg/m³; *P<0.05*

Table 43: Sensitivity analysis of the associations between preterm birth and small for gestational age with the pollutants NO_2 and PM_{10} using only non-imputed data.

Air pollution metric	Adjustments	Pregnancy time period	PTB			SGA		
			No. of subjects	OR	95% CI	No. of subjects	OR	95% CI
S-T model								
NO_2	*Unadjusted*	*Pre-conception*	82 052	1.07	0.99-1.16	81 435	1.46	1.36-1.56*
		1st tri	86 520	1.15	1.06-1.24*	85 911	1.52	1.42-1.62*
		2nd tri	86 841	1.15	1.07-1.24*	86 211	1.41	1.32-1.51*
		3rd tri	86 577	1.08	1.00-1.17*	85 940	1.54	1.44-1.65*
	Adjusted[1]	*Pre-conception*	24 820	0.95	0.80-1.13	24 624	1.12	0.97-1.30
		1st tri	25 687	1.07	0.90-1.27	25 515	1.07	0.93-1.23
		2nd tri	25 670	1.08	0.91-1.27	25 485	1.04	0.90-1.20
		3rd tri	25 537	0.99	0.83-1.18	25 361	1.16	1.01-1.33*
PM_{10}	*Unadjusted*	*Pre-conception*	66 623	1.04	0.95-1.15	66 285	1.52	1.15-1.69*
		1st tri	71 275	1.13	1.03-1.24*	70 908	1.41	0.89-1.28
		2nd tri	70 961	1.16	1.06 -1.28*	70 578	1.47	1.07-1.55*
		3rd tri	25 537	1.23	1.12-1.35*	70 762	1.58	1.11-1.60*
	Adjusted[1]	*Pre-conception*	14 189	0.98	0.79-1.21	14 100	1.39	1.15-1.69*
		1st tri	15 412	0.99	0.80-1.22	15 319	1.07	0.89-1.28
		2nd tri	15 286	0.94	0.76-1.17	15 193	1.29	1.07-1.55*
		3rd tri	15 294	1.10	0.88-1.37	15 198	1.33	1.11-1.60*
NSTAT								
NO_2	*Unadjusted*	*Pre-conception*	119 338	1.00	0.93-1.06	118 535	1.21	1.15-1.28*
		1st tri	120 266	0.99	0.93-1.05	119 444	1.21	1.15-1.28*
		2nd tri	120 383	1.03	0.97-1.10	119 543	1.22	1.16-1.29*
		3rd tri	120 240	0.97	0.91-1.04	119 416	1.26	1.19-1.33*
	Adjusted[1]	*Pre-conception*	32 963	1.01	0.88-1.15	32 731	1.02	0.91-1.14
		1st tri	33 171	0.97	0.85-1.11	32 939	0.97	0.86-1.08
		2nd tri	33 217	1.00	0.88-1.15	32 972	0.94	0.84-1.05
		3rd tri	33 076	0.92	0.80-1.05	32 844	0.99	0.89-1.11

Air pollution metric	Adjustments	Pregnancy time period	PTB			SGA		
			No. of subjects	OR	95% CI	No. of subjects	OR	95% CI
PM_{10}	*Unadjusted*	*Pre-conception*	60 924	1.08	0.98-1.18	60 612	1.21	1.11-1.31*
		1st tri	62 997	1.10	1.00-1.21*	62 688	1.23	1.13-1.33*
		2nd tri	62 547	1.13	1.03-1.25*	62 221	1.30	1.19-1.41*
		3rd tri	62 611	1.13	1.02-1.25*	62 292	1.33	1.23-1.45*
	Adjusted[1]	*Pre-conception*	13 574	1.05	0.86-1.30	13 941	1.16	0.96-1.38
		1st tri	14 175	1.05	0.85-1.30	14 095	1.09	0.92-1.29
		2nd tri	14 049	0.97	0.78-1.20	13 961	1.21	1.02-1.43*
		3rd tri	14 041	0.98	0.80-1.21	13 957	1.25	1.05-1.49*

[1] *Adjusted for: maternal age, ethnicity, parity, birth season, socio-economic status, body mass index and smoking. *P<0.05*

Table 44: Associations between air pollution[1] and preterm birth/ small for gestational age stratified by gender (4th quartile compared to 1st).

		PTB			SGA		
[1]Air pollutant (µg/m³)	**Gender**	**No. of subjects**	**OR**	**95% CI**	**No. of subjects**	**OR**	**95% CI**
NO_2	*Female*	5 447	1.25	0.80-1.96	5 433	1.07	0.77-1.18
	Male	5 684	0.99	0.67-1.47	5 637	0.95	0.67-1.35
NO_x	*Female*	11 840	1.11	0.84-1.46	11 788	1.17	0.95-1.45
	Male	12 596	1.03	0.80-1.32	12 458	0.94	0.75-1.23
$PM_{2.5}$	*Female*	18 756	1.02	0.83-1.25	18 687	1.12	0.96-1.30
	Male	19 847	0.94	0.78-1.13	19 644	0.97	0.82-1.14
PM_{10}	*Female*	18 537	1.17	0.93-1.46	18 468	1.20	1.02-1.43*
	Male	19 614	0.96	0.77-1.18	19 409	1.08	0.96-1.30
[2]CO	*Female*	8 930	0.94	0.26-1.60	8 906	1.26	0.75-2.12
	Male	9 487	0.65	0.26-1.61	9 411	1.37	0.78-2.39

[1] Air pollution exposure estimates based on the spatio-temporal model.

[2] Carbon Monoxide (CO) estimates were made using the nearest stationary monitor technique and recorded in mg/m³

**P<0.05*

6.5 Discussion

Summary of findings

This large retrospective cohort study investigated the effects of air pollution based on a traditional stationary monitor approach and a novel high spatial (1km²) and temporal (monthly) resolution exposure estimation technique with adverse pregnancy outcomes in NW England.

The results of this study found no significant associations between any air pollutants and PTB. There were statistically significant associations between NO_2, CO, PM_{10} and $PM_{2.5}$ and increased risk of SGA. The critical window of exposure of this association differed between pollutants. For the pollutants NO_2 and $PM_{2.5}$, this was in the third trimester. There was no strong evidence of a particular critical window of exposure for PM_{10}. CO was the only pollutant to exert the strongest effects during the second trimester. The associations were stronger in females compared to males.

Effect estimates based on NSTAT monitoring sites which has poor spatial resolution were weaker than the effect estimates based on the S-T pollution model.

In relation to other studies

The results from this study are consistent with much of the published evidence to date. Many previous studies have found no effects on PTB of NO_2 [39 40], CO [40 159] or PM [83]. A recent comprehensive meta-analysis [174] found that the majority of studies reported an increased risk of LBW/reduction in birth weight in relation to the same pollutants that were found to have an effect on SGA in this study: CO, NO_2, PM_{10} and $PM_{2.5}$.

Stronger effect sizes were found for PTB and SGA from air pollution exposure in females compared to males (aside from CO and SGA). However, this was not significant in the fully adjusted models. An increased risk to fetal growth in females associated with air pollution had also been reported by a review investigating gender effects in this relationship [179] and by other recent studies [60 152].

Significant effects of air pollution exposure with SGA were generally in the later pregnancy stages. Most studies present results based on an average across the whole pregnancy period. However, more recently studies present results by trimesters or months of pregnancy [117 176]. Previous studies have reported mixed results on the critical windows of exposure; based on recent evidence in this field of research our later gestation findings seem plausible. A recent prospective study investigating the effects of air pollution on fetal growth assessed by ultrasound measurement throughout pregnancy concluded that maternal exposure is inversely associated with fetal growth and weight at birth in the second and third trimesters [78]. It is of interest to compare findings for which might have similar mechanistic pathways, in terms of critical windows of exposure for reduced fetal growth effects. A prospective study investigating maternal smoking habits and fetal growth using ultrasound measurements at 11 and 20 weeks gestation found that maternal smoking is also associated with reduced fetal measurements in the second and third trimesters [341]. Recent work investigating critical pregnancy time windows to air pollution exposure through cord serum antibody response measurements found elevated Immunoglobulin E (IgE) levels in relation to $PM_{2.5}$ exposure in later gestation (a peak in month 6) [342].

Biological plausibility

The extent to which pollutants have a direct toxic effect on the fetus or are involved in a cascade of events consequently affecting fetal growth is yet to be established. It may be that air pollution reduces umbilical blood flow preventing adequate placental transfer of oxygen and other low molecular weight, lipophilic molecules. Increased air pollution exposure has been associated with alterations in blood viscosity and coagulability [198], which will likely affect umbilical blood flow and consequently fetal growth. Oxidative stress occurs due to excess free radicals (for example, NO_2) and a decrease in antioxidant defences [192]. Oxidative stress can have direct effects on placental function [343]. Furthermore, a response to oxidative stress in some cells is the influx of inflammatory cells. Studies have found associations between air pollution exposure and markers of inflammation (particularly with the pro-inflammatory cytokine Interleukin-6) [197 198]. Placental inflammation has been linked to a predisposition to gestational hypertensive disorders [201 202]. Therefore a link between air pollution, oxidative stress, and placental inflammation is also worth considering in relation to our observations here regarding SGA. A number of studies have reported associations between pre-eclampsia and air pollution exposure [75 343], even at low concentrations [344]. In severe pre-eclampsia cases, intrauterine growth restriction will occur in 10-25% of neonates [344] and is associated with small for gestational age infants [1].

Strengths and weaknesses

The main strengths of this study are the large sample size, the comprehensive adjustment for confounding factors and the exposure assessment technique which takes into account both fine spatial and temporal variation of air pollution. However, although

this spatial and temporal accuracy will help to reduce exposure misclassification, as with most large scale epidemiological studies, it remains the case that estimates are based on the maternal residence at the time of delivery. Individual mobility and time-activity data was not available for the cohort, therefore, we could not account for exposures that the subjects inevitably had when they were not at their residence (e.g. in work or commuting) or if they moved during pregnancy. Modelled estimates and stationary monitors were based on outdoor ambient concentrations and not inside the home where most of the time is spent [55]. However, strong correlations in air pollution levels between indoor and outdoor environments have been shown, particularly with particulate matter ($r=.73$) [311].

The possibility of residual confounding cannot be ruled out in this study. Although the confounders were decided *a priori* based on previous evidence, there were variables which would have been included if the data had been available, for example, noise pollution during pregnancy. There was also a risk of residual confounding from the included covariates, particularly for the variables maternal smoking and socio-economic status. Maternal smoking data was collected based on subject recall at the time of delivery with a yes/no response. This variable is unlikely to adequately capture all the women who smoked during their pregnancy. The IMD score provided a comprehensive measure of socio-economic status and is currently one of the strongest estimation techniques of socio-economic status at a population level in the UK [269]. However, the score was calculated based on data at a lower super output area level (LSOA) and not at an individual level. A LSOA includes a range of 1,000-3,000 people and 400-1,200 households [268].

Guidelines from the WHO on air pollution thresholds based on epidemiological evidence of health effects published in 2005 and the most recent UK air quality legislation enforced in 2010 set annual concentration limits for NO_2 and PM_{10} at 40µg/m³ and 25µg/m³ for $PM_{2.5}$. Our data showed no evidence of effect on SGA for exposure below these limits. Therefore, these limits appear to be appropriate for protecting pregnant women from risks of adverse perinatal outcomes. However, during the study period of 2004-2008, a significant number of women were exposed to concentrations above the recommended (and now legal in the UK) concentrations. Of the NWPSU women which could be assigned pollution estimates for their whole pregnancy, 80% were exposed to mean concentrations of NO_2 above 40 µg/m³, 54% were exposed to concentrations above 40 µg/m³ of PM_{10} and 19% above the 25µg/m³ $PM_{2.5}$ limit.

6.6 Conclusions

Based on a strong exposure estimation technique, this study suggests that exposure to NO_2, PM_{10}, $PM_{2.5}$ and CO in later pregnancy can increase the risk of having an SGA outcome, particularly in female babies. The air quality standards currently set in place in the UK do seem appropriate for protecting maternal and fetal health, however, these limits in some areas of the UK are not being adhered to. Long term improvements in ambient air pollution up to 2008 have been identified in the UK, particularly with particulate matter, but this has since remained stable [345]. Up to date country specific epidemiological studies investigating the health effects of air pollution are important to ascertain if limits set in place are a) appropriate in protecting population health, including susceptible sub-populations and b) if these standards are being met.

A better understanding of the pathophysiology of the effects of air pollution in pregnancy is required. Studies incorporating toxicological and epidemiological evidence will provide the strongest insight into the pathways of effect. A study working to do this is currently underway in Mexico City, collecting air pollution estimates along with an extensive range of toxicological samples during each month of pregnancy to investigate the inflammatory effects of air pollution in 800 women [259]. Future studies collecting only epidemiological data (and not biological samples) will aid this area of understanding by presenting effect estimates by specific exposure windows of pregnancy, for example by trimesters.

7. Overall discussion

The overall discussion of this thesis provides a general summary, the broad strengths and limitations of the thesis, potential directions for future research, public health implications and a final conclusion.

7.1 Summary

The work described in this thesis aimed to quantify the effects of air pollution on adverse perinatal outcomes, and used data from North West England to investigate this. To achieve this, specific objectives originally laid out in the introduction of this thesis were investigated:

1. To evaluate commonly used air pollution exposure estimation techniques used in previous large scale epidemiological studies to inform a decision on the estimation technique/s to be employed to fulfil the primary aim.
2. To investigate if living in close proximity to a major road in North West England increases the risk of an adverse perinatal outcome.
3. To estimate the risk of exposure to individual pollutants based on air pollution estimates identified by specific objective (1), on adverse perinatal outcomes.
4. To determine the critical windows of exposure from air pollution, if any, during pregnancy.

The first of the specific objectives is described in Chapter 3. The study concluded that interpolation techniques, including the DEFRA PCM model, coupled with a monthly temporal adjustment correlated best with personal measurements from the cohort. Correlations with the traditional stationary monitor approach were also reasonable. The

study found, in line with most previous studies, that pregnant women spend most of their time in the home (66%). One of the key findings from the study described in Chapter 3 was the importance of incorporating temporal adjustments, specifically at a monthly resolution into annual estimates based on spatial techniques, which corroborates with previous literature [37]. Women spent the majority of their time in the home location which is also in line with previous studies, however, most found a higher percentage of time was spent in the home compared to this North West England cohort [57 261].

As an addition to Chapter 3, an exploration of potential sources of error in personal monitoring was performed for additional insight into the effect of differences in the handling of the monitors by lay participants (Chapter 4). This study found that the active sampling method used by stationary air pollution monitors measure consistently higher concentrations compared to the passive diffusion technique in the Ogawa passive samplers. This was also evident in Chapters 3 and 6 where the results demonstrated that the active stationary monitoring methods generally produce higher estimates than other exposure estimation techniques; this finding could suggest that stationary monitor results used for estimating exposures in large scale retrospective studies are overestimating individual exposures. In this controlled experimental study, measured concentrations did differ with different handling of the personal samplers; higher concentrations were measured from the samplers analysed later and not kept in a sealed bag. The results from Chapter 3 and Chapter 4 demonstrated that ranked correlations between Ogawa samplers and other air pollution exposure estimation techniques were stronger when Ogawa samplers were analysed within the protocol recommended time frame (<21 days). These chapters highlight the importance of consistency in handling

personal samplers. Although longer time periods between the exposure and analysis of the Ogawa samplers did introduce some error, the stratified results presented in Chapter 3 demonstrate that this did not have any substantial impact on the overall conclusions of the exposure estimation technique comparison study.

Chapter 5 fulfilled the second specific objective. This chapter investigated the effect of living in close proximity to a major road (<200 metres) on the adverse pregnancy outcomes PTB, SPTB, LBW and SGA. The proximity to major road technique was the weakest performing technique in terms of correlation with personal NO_2 and NO_x exposure from the exposure comparison study in Chapter 3. However, proximity to a road involves exposure to a mixture of numerous pollutants from traffic, including exposures that were not measured in Chapter 3 and so may still be a relevant measure. The mixture of traffic related pollutants differs during different temporal periods and across locations [65 66]. The decision to implement this exposure technique was based on the fact that it is a logical proxy for exposure to all air pollutants; road traffic emissions are the largest contributor to ambient air pollution [15], thus road networks and traffic density will strongly affect the spatial and temporal patterns of air pollution. This study found no significant associations between maternal residential proximity to major roads of <200m and adverse perinatal outcomes. An additional sensitivity analysis found increased risks of adverse perinatal outcomes at closer proximities to a major road, particularly for residences at <25m. For this study, the *a priori* objective decision was to use 200m as a cut off based on evidence from the pollution distance decay literature and to be consistent with previous literature investigating this research question. However, results from this study suggest that future work in this area should focus on closer proximities to roadways. The findings from this study demonstrating no increased risk

at <200m is largely consistent with the results from two previous studies which included particularly large sample sizes and high statistical power [69] [135]. However, there have been published studies presenting some evidence of a statistically significant association between close proximity to a major roadway or highway with PTB [164], LBW [165] and SGA [60]. These findings may differ to our study because countries such as Japan[164] and Canada[60] are likely to have more substantial roadways with a higher volume of traffic than in England. The differences in findings could in part also be due to publication bias, with positive findings more likely to be published.

The third specific objective was successfully achieved in Chapter 6. This study addressed previously acknowledged methodological issues through improved exposure estimation, a large sample size and appropriate adjustment for confounders in a geographical area where the association between air pollution and pregnancy outcomes has not been previously quantified. This chapter investigated the effects on SGA, PTB and mean birth weight change from individual pollutant effects of NO_2, NO_x, CO, $PM_{2.5}$ and PM_{10} estimated from a fine resolution spatio-temporal (S-T) model and stationary monitors. The S-T model based on the DEFRA PCM model was decided upon as the primary exposure estimation technique for two main reasons: (1) it performed as one of the strongest techniques in the exposure comparison study in Chapter 3 and (2) the method involved the integration of a fine resolution (1km²) spatial technique developed by DEFRA in a multiple module process and validated externally with the optimal temporal adjustment (monthly) identified in Chapter 3.

Statistically significant associations were observed between NO_2, CO, $PM_{2.5}$ and PM_{10} with SGA in the fully adjusted logistic regression models using the S-T model estimates. The associations were generally stronger in females compared to male

newborns. No significant associations in the fully adjusted models were observed between any of the pollutants and the outcomes PTB and mean reduction in birth weight. These results substantiate much of the existing literature on the effects of air pollution and adverse pregnancy outcomes to date, particularly with the evidence on effects from particulate matter. This is evident from the most recent published review of the literature in this area which included a comprehensive meta-analysis [174]. The meta-analysis found a pooled small increased risk of LBW (PM_{10} OR= 1.10, $PM_{2.5}$ OR=1.05) from the included studies to the same pollutants identified in this thesis to be associated with a small increased risk of SGA (PM_{10} OR= 1.14, $PM_{2.5}$ OR=1.04). The meta-analysis found mixed results for PTB, as was found in the critical review of the literature of the effects of gaseous pollutants on PTB in Chapter 1.6.1 of this thesis.

The study described in Chapter 6 included effect estimates when exposure was estimated from nearest stationary monitors. This was included as a means of comparing results between a modern technique with a fine (1km²) spatial resolution (the S-T model) and a traditional technique with a poor spatial resolution (nearest stationary monitor from 8 monitors situated throughout NW England). The pollution estimates made from nearest stationary monitors only were on average higher than those made from the S-T model. There was a decreased strength of an association with the adverse pregnancy outcomes investigated based on estimates from stationary monitors compared to the S-T model. This is consistent with the well known epidemiological concept that random error in exposure measurements generally biases an effect measure toward the null [346]. It has been suggested that researchers should be more cautious in concluding there to be no causal association from a negative study if measurement error is thought to exist in a study [346]. Under the most likely assumption that the S-T model

will have less measurement error than the nearest stationary monitor approach, the results of this study suggest that some previous studies implementing techniques with a poor resolution for estimating exposure could be attenuating effect sizes.

The final specific objective was to determine the critical window of exposure to air pollution. The study described in Chapter 6 utilised the temporal adjustment by month in the S-T model to produce risk estimates averaged over each trimester and 6 weeks pre-conception. The critical window of exposure was generally in the later stages of pregnancy. This was particularly evident between CO and SGA in trimester two and three. Statistically significant associations were also found in trimester 3 between NO_2, $PM_{2.5}$ and PM_{10} and SGA.

The existing evidence on the critical window of exposure to air pollution in pregnancy is mixed, however, the results from Chapter 6 demonstrating the strongest effects in later pregnancy is consistent with the biological mechanisms proposed earlier in this thesis. Evidence from a range of fields was explored in Chapter 1.7 to establish plausible mechanisms. These mechanisms broadly included: oxidative stress, inflammation, coagulation, and alterations in hemodynamic responses. During the later stages of pregnancy the fetal growth curve becomes steeper; it has been argued that fetal growth velocity reaches a peak at around 35 weeks gestation [347]. The mechanisms identified from the existing literature will all result in impaired maternal-fetal blood flow and a reduction in transplacental oxygen and nutrient transport, thus it is plausible that these will have the strongest effect during this late stage of pregnancy. As stressed previously, uncovering the mechanisms behind this association will require a multidisciplinary approach in the future. The biological mechanisms are likely to be a

complex combination of mechanisms that are dependent on individual maternal and fetal susceptibilities.

7.2 Strengths and Limitations of the thesis

7.2.1 Limitations

The specific limitations of each individual study included in this thesis are described in the individual discussion sections at the end of each chapter. However, there are some general limitations of this thesis that apply to most or all of the main chapters.

There is substantial missing data within the NWPSU dataset in certain variables. The variables that had the most amount of missing data were maternal smoking (61% missing) and BMI (43% missing). This was largely due to the fact that data was not requested from the midwives on maternal smoking until 2007 and BMI until 2006. A balance had to be struck in the main analyses in Chapters 5 and 6 which quantified the risk from air pollution, to maximise statistical power whilst still adequately adjusting for confounders. The analyses were initially performed with a number of different adjustments in sensitivity analyses evaluating the different compromises between adequate confounder adjustments and statistical power. In terms of the main results in Chapters 5 and 6, the analyses limited to the core confounders (maternal age, ethnicity, parity, birth season and IMD) and the analyses with the core plus BMI and smoking adjustments, made no significant impact on the overall findings. Aside from the larger confidence intervals due to the decreased sample size and minor fluctuations in the ORs, the results were consistent between the fully adjusted analyses and the analyses adjusted only for the core confounders. For the main analysis in Chapter 6, the same statistically

significant findings occurred in the core confounder adjustment models as in the fully adjusted models, thus only the unadjusted and fully adjusted model results were presented. The consistency in these results could be due to the fact that although BMI and smoking are strong risk factors for adverse pregnancy outcomes, they are not strongly related to air pollution exposure in this cohort and thus are not confounding the relationship in the way that was anticipated *a priori*. The lack of relationship between BMI and smoking with air pollution exposure is demonstrated in Table 30 in Chapter 5 and in Table 38 in Chapter 6.

Another important limitation was the potential measurement error resulting from the absence of data on mobility and indoor air pollution. The exposure estimation techniques in this thesis were entirely based on the postcode provided in the NWPSU dataset. These postcodes were recorded at the time of delivery and may not necessarily be accurate for the whole pregnancy period because women may have moved during pregnancy, thus introducing the possibility of exposure misclassification. Mobility during pregnancy has been previously reported at around 9% in the North of England [217] and in the prospective study carried out in Chapter 3, the mobility rate was around 19%. However, most research into mobility during pregnancy indicates that the majority of women who move do not move far from their original residence [217 333], suggesting measurement error is likely smaller than would be initially expected from mobility rates alone.

Exposure to these pollutants from indoor sources was not included in this study due to practical limitations, which is also a potential source of exposure misclassification. As demonstrated from the time-activity log data in Chapter 3 and from previous literature [57 261], people spend the majority (~60-90%) of the time in the home environment,

particularly during pregnancy. Exposures to indoor sources such as solid fuel and more commonly to gas heating and cooking appliances within the home could significantly influence pollution exposure [348]. However, on a population level, this is likely to be non-differential and furthermore, indoor air pollution levels have been demonstrated to correlate strongly with outdoor pollution levels [311]

Due to the lack of individual level data in the NWPSU, no adjustment could be performed for exposure to environmental tobacco smoke (ETS). The occupational status of the mother would have a substantial implication on the extent of exposure to ETS, particularly on those recorded before the summer of 2007 when smoking was not prohibited in public indoor areas. The smoking ban was not incorporated into the analyses in this thesis even though the cohort spanned the period in which it was introduced. Although it is likely that before the smoking ban ETS would have resulted in substantially increased air pollution exposure in the indoor environment, it is reasonable to postulate that women during pregnancy would have been less likely to spend time in bars and restaurants compared to non-pregnant populations.

There are a number of limitations that apply specifically to the proxy air pollution estimation technique implemented in Chapter 5 of proximity to major roads. The technique does not incorporate traffic density and cannot differentiate between relatively quiet 'A' roads and major motorways which will inevitably have a substantial influence on traffic related air pollution exposure. The technique also does not incorporate areas where traffic may stagnate and accelerate, for example, at traffic lights, junctions or roundabouts. The technique only identifies the one nearest major roadway and does not incorporate the possibility that the maternal residence may have

more than one major roadway in close proximity, which again will likely substantially influence air pollution exposure.

7.2.2 Strengths

In order to fulfil the overall objective of this thesis, the most significant methodological challenge, that of an appropriate exposure estimation methodology, required further exploration. A particular strength of this thesis was the comparison of such an extensive range of commonly used exposure estimation techniques with personal measurements from the study area in order to make an informed decision for the main analyses. The comparison study not only assessed individual spatial methods, but also the varying levels of temporal adjustment, which facilitated the development of an exposure estimation technique for the main analysis capable of exploring critical windows of exposure during pregnancy.

A major strength of this thesis is the spatio-temporal modelled air pollution estimates implemented in Chapter 6. This is a novel technique based on the PCM model developed by DEFRA, which has only been used once previously in a published epidemiological study [340]. For this study, the annual modelled estimates were enhanced with specific temporal adjustments from local stationary monitors which enabled the further exploration of critical exposure windows during the pregnancy period (specific objective 4). The strong spatial and temporal resolution of this exposure estimation technique used to quantify the association decreased the extent of exposure misclassification in this study.

The NWPSU dataset included the majority of the births that occurred in NW England during 2004-2008 enabling a large sample size and high statistical power for the main

analyses in this thesis. To the author's knowledge, this is the largest UK cohort study investigating the effects of air pollution in pregnancy. A time-series ecologic study from London published in 2008 included 482,568 births, although this represented almost twice the sample size of the cohort used in this thesis, just one stationary monitor was used to estimate O_3 exposure in the population. No associations were found in this study [163]. Aside from a small number of particularly large studies [69 135 171], most previous studies included a sample size of <100 000 (see study summary tables in Appendix 1).

7.3 Directions for future research

The directions for future research in this field fall into three broad areas: exposure assessment, birth outcome data and biological mechanisms.

In terms of exposure assessment, the work in Chapter 3 of this thesis not only helped inform the main analyses in this thesis, but can also serve to inform choice of exposure estimation technique for future environmental epidemiology studies. The exposure comparison study included traditional and modern techniques, thus, the work can also be used as a tool to better inform a critique of exposure estimation techniques implemented in previous studies.

Work is currently underway in Europe by the ESCAPE project to develop more homogeneous approaches to exposure assessment enabling investigation into health effects (including birth outcomes) across larger geographical areas and to enable more comparable results [86 169].

Individuals, particularly women during pregnancy, are spending most of their time in the home environment, yet almost all of the exposure estimation techniques practical to

implement for a large cohort are based on outdoor air pollution estimates. Recently, some work has been done on the development of microenvironmental models to incorporate indoor exposures [45]. Future research in air pollution exposure assessment methodology will likely be directed towards the development of more precise, yet practical air pollution estimation techniques. The use of mobile phones to establish exact locations of individuals using GPS technology and phones equipped with air pollution detection sensors is a potential future technique which, if budget constraints allow, could be implemented in epidemiological studies. Providing individuals with personal pollution sensors to collect their own exposure data could result in altering behaviour towards air pollution. The notion of 'Citizen Science' which involves enlisting the public to collect large quantities of data whilst better informing individuals, commonly used in ecology studies [349], could be implemented as a practical technique for future air pollution studies.

In terms of future directions for birth outcome data, there has recently been a drive to amalgamate birth outcome datasets to increase sample sizes for enhanced statistical power e.g. the recent work to pool birth outcome data from across Europe by the projects ENRIECO and ICAPPO [168 177]. Future epidemiological studies investigating risk factors for adverse pregnancy outcomes will also be improved through better quality routinely collected data from maternity units which can be exploited for research purposes.

In terms of the future direction of research for establishing biological mechanisms of effect from air pollution exposure in pregnancy, cohesive work incorporating a range of disciplines such as epidemiology, genetics, exposure science, toxicology and physiology is required. Indeed, there is already some evidence of more multidisciplinary

projects developing to investigate the effects of air pollution on adverse perinatal outcomes [259].

Gene-environment interaction studies investigate the complex interaction between an individual's genetic makeup and environmental factors. Future gene-environment interaction studies may help to elucidate whether thresholds to air pollution exposure during pregnancy vary between individuals and why this occurs. Inter-individual variation in response to air pollution exposure could be due to genetic variations which make some sub-populations more susceptible to exposure. For example, hereditary polymorphisms (such as glutathione S-transferase) have been identified which modulate the levels of an oxidative stress biomarker in pregnancy, which is known to be associated with a poor pregnancy outcome [350]. Future research in this area is important to better inform air quality policy decisions to ensure that limits set in place are adequately protecting all susceptible sub populations.

In addition, with ever increasing capabilities of patient record storing and data linkage, a future research aim could be to investigate the long term effects of air pollution exposure during pregnancy using very large cohorts that could be followed up not just for birth outcomes but for other health effects later in life.

Further to follow up studies later in life, studies which follow up subsequent generations exploring epigenetic effects from air pollution will provide insight into the longer term effects of environmental exposures in utero [351]. Adequately powered studies into this may become more feasible in the UK with improvements in large birth outcome datasets with the ability for cross generational data linkage, as has been shown in other countries [108].

A future direction for research which would naturally follow from perinatal epidemiology studies investigating the effects of air pollution, as in this thesis, would be research into the economic and policy implications of findings demonstrating a health effect from ambient air pollution. This would involve incorporating epidemiological evidence of air pollution effects during pregnancy with the economic implications of implementing air pollution reduction strategies and the potential health care costs of adverse pregnancy outcomes.

7.4 Public health implications

This thesis found significantly increased risks of a SGA outcome at air pollution levels above those which have been set in place by current air quality standards. Based on estimates made from the temporally adjusted PCM model, a large proportion of the women included in this study were exposed to levels above the air quality standards.

Although the effect sizes from air pollution in this study were relatively small (~OR=1.14), the public health impact is potentially substantial because of the large number of people exposed to air pollution and the potential long term health implications of a poor pregnancy outcome. The current air quality guidelines and legislation seem to be appropriately set in terms of protecting fetal health, however, there may need to be stronger links to policy to ensure that the air quality guidelines are appropriately adhered to.

It is important to note that although this study found no statistically significant increased risks of adverse pregnancy outcomes with air pollution levels below the highest quartile compared to the lowest, this does not categorically mean that no risk may be posed below this level. This thesis does not further explore if the relationship between air

pollution and risk of SGA is an exposure-response relationship or if an absolute threshold exists. A test for linear trend in the main analysis of this thesis demonstrated a particularly strong positive relationship between SGA and CO; but this does not necessarily imply a linear exposure-response relationship. This requires further investigation however, because establishing the shape of an exposure-response relationship could have important implications for the future development of air quality regulations.

It is the responsibility of researchers and policy makers to ensure that research into the health effects of air pollution are available and understandable to the lay public. A more informed public on the impact of air pollution will likely result in an increase of social responsibility to help reduce emissions. It also can help to equip those who are particularly susceptible to air pollution effects with the information to take appropriate precautions. Work from the UK Air information resource website [345] and COMEAP [11] have already taken considerable steps to ensure that the dissemination of information to the public continues in the right direction.

In terms of the key messages for pregnant women and the health care professionals who care for them, this work demonstrates that for those living in city centre locations where air pollution is at its highest it is likely that there is a small increased risk of air pollution affecting fetal growth. However, other better established and well known risk factors which are more modifiable at an individual level, such as smoking, drug abuse and alcohol consumption during pregnancy carry a substantially higher risk to restricting fetal growth in utero.

It is important that applied health related research is translated to both patients and health care professionals. The key messages from this thesis can be communicated to health care professionals through publications in peer review journals, conference presentations and direct communication between researchers and health care professionals (in particular lecturers of future health care professionals). The messages are likely to be better communicated to patients through the use of the media using newspaper and magazine articles. Health care professionals should be equipped with the knowledge of environmental exposures on pregnancy outcomes in the event that a patient has concerns about this during their pregnancy.

7.5 Final Conclusion

This perinatal epidemiology thesis has provided a thorough investigation of the effects from air pollution on adverse perinatal outcomes in North West England.

The results from this thesis suggest that there is a relatively small, but statistically significant, increased risk from the ambient air pollutants NO_2, CO, $PM_{2.5}$ and PM_{10} on fetal growth in pregnancy. The critical window of exposure is most likely during the later stages of pregnancy.

It has been argued that one of the primary goals of Epidemiological research is to identify important determinants of disease or ill-health that can be modified to improve public health [352]. This thesis has added to the evidence base on the effects of air pollution in pregnancy, the results of which support the further reduction of a very modifiable environmental factor, namely air pollution, in order to improve public health for the future.

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Appendix 1

Table A1: Main findings from the highest quality epidemiologic studies investigating the association of air pollution effects on preterm birth (based on the quality assessment tool described in Chapter 1.6.1)

Author & **Year**	**Study date, design & population**	**Gaseous Pollutants studied**	**Definition of outcome measure**	**Exposure measurement technique**	**Confounder Adjustments**	**Authors conclusions**
Rudra et al. 2011 'Ambient Carbon Monoxide and Fine Particulate Matter in Relation to Preeclampsia and Preterm Delivery in Western Washington State.'	1996-2006 Prospective cohort study in Western Washington state. 3,509 births.	CO	PTB: <37 completed weeks gestation.	Predicted CO using regression models based on regional air pollutant monitoring data containing predictor terms for year, month, weather and land use characteristics.	Maternal age, parity, pre-pregnancy BMI, race/ethnicity, smoking history and season.	Little evidence to support the hypothesis that CO is associated with PTB among Western Washington state women.

Author & **Year**	**Study date, design & population**	**Gaseous Pollutants studied**	**Definition of outcome measure**	**Exposure measurement technique**	**Confounder Adjustments**	**Authors conclusions**
Zhao et al. 2011 'Effects of air pollution on neonatal prematurity in guangzhou of China: a time-series study.'	2007 Time-series study in Guangzhou of China. 142,312 births (9,083 preterm).	NO_2 SO_2	PTB: <37wks. GA computed by difference in date of LMP and date of birth.	Daily concentrations from 9 Fixed- site stations. Daily average temperature and humidity from 1 fixed site station. Generalized Additive model extended Poisson regression model used for analysis.	Seasonality, day of the week, calendar time, temperature, humidity.	Daily concentrations of NO_2 and SO_2 have positive correlations with PTB in Guangzhou, China.
Malmqvist et al. 2011 'Maternal Exposure to Air Pollution and Birth Outcomes.'	1999-2005 Retrospective cohort study in Scania, Sweden. 81,110 births.	NO_x Traffic related pollutants.	PTB: <37weeks (based on ICD-10 codes from the Swedish Medical Birth Registry)	Individual modelled concentrations for NO_x using dispersion modelling techniques. For proximity to major road, individuals were assigned the road with heaviest traffic density within 100m of residence.	Maternal age, smoking birth year, sex, parity and country of origin.	No statistically significant associations were found. NO_x was found to have a small protective effect on PTB risk.
Llop et al. 2010 'Preterm birth and exposure to air pollutants during pregnancy.'	2003-2005 cohort study in Valencia, Spain. 785 Pregnant women from INMA cohort	NO_2	PTB: <37 weeks gestation. GA estimated by difference between delivery date and	Ambient levels measured using 93 radial symmetry passive samplers during 4 sampling periods of 7days. Individual exposure assignments estimated as means and per	Sex, pre-pregnancy BMI, maternal age, parity, season of conception, working status, alcohol and caffeine consumption,	Results suggest maternal exposure to traffic-related air pollution is associated with PTB. Future suggestions:

Author & Year	Study date, design & population	Gaseous Pollutants studied	Definition of outcome measure	Exposure measurement technique	Confounder Adjustments	Authors conclusions
			LMP reported by women or early ultrasound of crown-rump length.	trimester using LUR techniques (data from Kriging, industrial & urban land cover, traffic information and topography).	smoking, educational level, country of origin, and zone of residence.	beneficial to carry out a prospective follow up study and to construct indicators for individual exposure to air pollution.
Van den Hooven et al. 2009 'Residential traffic exposure and pregnancy-related outcomes: a prospective birth cohort study.'	2002-2006 Generation R cohort in Rotterdam, the Netherlands. 7, 339 maternal cases.	Traffic related pollutants.	PTB: <37wks gestation. For participants enrolled early-mid pregnancy: GA calculated by ultrasound. For those enrolled in late pregnancy: LMP used.	DWTD within 150m radius around the home divided into quartiles. AND Distance to major road (m) categorized as: 0-50 50-100 100-150 150-200 >200	Maternal age, maternal education level, maternal ethnicity, BMI, parity, maternal smoking, maternal alcohol consumption and fetal sex.	Exposure to residential traffic did not increase associations with adverse pregnancy outcomes. However sample size was a major limitation to this study.
Brauer et al. 2008 'A cohort study of	1999-2002. Cohort study in	NO	PTB: <37wks gestation (GA as indicated by birth	Residential exposures estimated by month of pregnancy using nearest and	Sex, parity, month and year of birth. Maternal age, smoking. Income	Generally no associations with gaseous pollutants and PTB. However, risk of very

Author & Year	Study date, design & population	Gaseous Pollutants studied	Definition of outcome measure	Exposure measurement technique	Confounder Adjustments	Authors conclusions
traffic-related air pollution impacts on birth outcomes.'	Vancouver, Canada. 70,249 singleton births.	NO_2 CO SO_2	records). Subgroup analyses on GA <30, 30-34, 35-37wks.	IDW of area monitors. Temporally adjusted land use regression models and proximity to major roads.	& maternal education level obtained using census data based on residence (no individual data).	preterm birth (<30wks) presented elevated OR's for NO, NO_2, CO.
Genereux et al. 2008 'Neighbourhood socioeconomic status, maternal education and adverse birth outcomes among mothers living near highways.'	1997-2001 Retrospective cohort study in Montreal, Canada. 99 819 live singleton births.	Traffic related pollutants.	PTB: <37 completed weeks.	Postcodes were geocoded and distance to major road calculated. For analysis, distance was dichotomized to <200m and ≥200m.	Maternal age, country of birth, civil status, history of prior stillbirth, birth order, newborn sex and year of birth.	Living <200m from a major road is associated with increased risk of PTB, especially in mothers with a high SES.
Leem et al. 2006 'Exposures to air pollutants during pregnancy and preterm delivery.'	2001-2002 Cohort study in Incheon, Korea. 52,113 singleton births.	CO NO_2 SO_2 PM_{10}	PTB: <37wks. GA based on date of LMP and mother's estimate of date of conception. (from Korean National	Average daily conc. of ambient SO_2, NO_2, PM_{10} and CO collected from 26 monitoring stations. Data used for ordinary block Kriging.	Maternal age, parity, sex, season of birth, education level of both parents.	The study found a significant association with gaseous air pollutants and increased risk of PTB. Results suggest fetuses in early and late stages are

Author & Year	Study date, design & population	Gaseous Pollutants studied	Definition of outcome measure	Exposure measurement technique	Confounder Adjustments	Authors conclusions
			birth registry).			particularly susceptible.
Sagiv et al. 2005 'A time-series analysis of air pollution and preterm birth in Pennsylvania, 1997-2001.'	1997-2001 Time-series analysis in Pennsylvania. 187,997 live singleton births.	SO_2 PM_{10}	PTB: <36wks gestation. GA computed as no. of weeks between date of LMP and date of birth.	Stationary monitor data.	Gestations at risk, co-pollutants, temperature, dew point temperature and day of the week lag.	Evidence of a small increased risk of PTB with exposure to SO_2 and PM_{10}. Critical exposure window not ascertained.
Yang et al. 2003 'Evidence for increased risks of preterm delivery in a population residing near a freeway in Taiwan.'	1992-1997 Retrospective cohort study in Taiwan.6,251 first parity singleton live births.	Traffic related pollutants.	PTB: <37 completed weeks.	Proximity to freeway: <500m 500-1,500m	Maternal age, season, marital status, maternal education and infant gender.	The results support the hypothesis that traffic related air pollution could affect risk of PTB.
Wilhelm & Ritz 2003 'Local variations in CO and particulate air pollution and	1994-1996. Case control study in LA, California, 56, 965 cases and	Traffic related pollutants.	PTB: <37 weeks. GA obtained from birth certificates.	DWTD .	Maternal age, maternal race/ethnicity, maternal education, parity, interval since previous live birth,	Observed an approximate 10-20% increased risk of PTB born to women potentially exposed to high levels of traffic pollution. Risks were highest for

Author & Year	Study date, design & population	Gaseous Pollutants studied	Definition of outcome measure	Exposure measurement technique	Confounder Adjustments	Authors conclusions
adverse birth outcomes in Los Angeles County, California, USA.'	controls.				level of prenatal care, infant sex, previous PTB/LBW infant, birth season and year of birth.	women whose third trimester fell during fall/winter months.

Table A2: Main findings from the selected epidemiologic studies investigating the association of air pollution on fetal growth (LBW/SGA)

Author & Year	Study date, design & population	Pollutants studied	Definition of outcome measure.	Exposure measurement technique	Confounder Adjustments	Authors conclusions
Kloog et al. (2012) 'Using new satellite based exposure methods to study the association between pregnancy $pm_{2.5}$ exposure, premature birth and birth weight in Massachusetts'	Cohort study in Massachusetts (2000-2008).	$PM_{2.5}$	Continuous birth weight	Satellite based exposure method with a spatial resolution of 10x10km	Infant sex, maternal age, maternal race, mean income, maternal education level, prenatal care, gestational age, maternal smoking, percent of open space near mother's residence, average traffic density and mothers health.	Exposure to $PM_{2.5}$ during the last month of pregnancy contributes to risks for LBW and PTB in infants.

Author & **Year**	**Study date, design & population**	**Pollutants studied**	**Definition of outcome measure.**	**Exposure measurement technique**	**Confounder Adjustments**	**Authors conclusions**
Pereira et al. (2012) 'Locally derived traffic-related air pollution and fetal growth restriction: a retrospective cohort study.'	Retrospective cohort study in Perth, Australia (2000-2006) of 23 452 births.	NO_2	SGA: <10^{th} percentile for GA and sex of the Australian population. Fetal growth restriction: Proportion of optimal birth weight below the 10^{th} centile	Temporally adjusted LUR model.	Gestational diabetes, aboriginal status, presence of congenital anomalies, marital status, threatened PTD, UTI, PROM, pre-eclampsia, fertility treatments, haemorrhage, maternal smoking and ambient temperature.	Exposure to traffic- related air pollution (IQR increase) in mid-late pregnancy was associated with risk of SGA (OR=1.31; CI 1.07-1.60) and low proportion of optimal birth weight. Effects of SGA higher in women who moved house.
Van den Hooven et al. (2012) 'Air pollution exposure during pregnancy, ultrasound measures of fetal growth and adverse birth outcomes.'	Embedded within the 'Generation R' study, a population-based prospective cohort study in the Netherlands (2001-2005) of 7,772 births.	NO_2 PM_{10}	SGA: GA and sex adjusted birth weight less than 5^{th} percentile. LBW (<2500g). During each trimester, fetal head circumference,	Combination of dispersion modelling technique and continuous monitoring data (full residential history from participants).	Maternal age, education level, parity, folic acid use, ethnicity. Maternal smoking and alcohol use before and during pregnancy. Maternal and paternal anthropometrics and noise exposure.	Air pollution is inversely associated with fetal growth during the 2^{nd} and 3^{rd} trimester and with weight at birth. PM_{10} exposure was positively associated with PTB and SGA (OR=1.38; CI 1.00-1.90).

Author & Year	Study date, design & population	Pollutants studied	Definition of outcome measure.	Exposure measurement technique	Confounder Adjustments	Authors conclusions
			length and weight measurements by ultrasound.			
Malmqvist et al. (2011) 'Maternal exposure to air pollution and birth outcomes.'	Retrospective cohort study in Scania, Sweden. (1999-2005) 81,110 births.	NO_x Traffic related pollutants.	Birth weight as a continuous measure and LBW: <2500g.	Individual modelled concentrations for NO_x using dispersion modelling techniques. For proximity to major road- individuals were assigned the road with heaviest traffic density within 100m of residence.	Maternal age, smoking birth year, sex, parity and country of origin.	Small increased risk of SGA in the highest NO_x quartile, especially in girls (OR=1.12; CI=1.01-1.24). Also, an increased risk in mothers who moved in pregnancy. No effect on LBW.
Gehring et al. (2010) 'Traffic-related air pollution, preterm birth and term birth weight in the PIAMA birth cohort study.'	Prospective birth cohort study in The Netherlands (1996-1997) of 3853 singleton births.	NO_2 $PM_{2.5}$	Term (≥37 and <43 weeks GA) birth weight.	Temporally adjusted Land-use regression model.	Maternal education, ethnicity, gestational age, sex, parity, education, BMI, alcohol and work stress.	No association with term LBW and traffic related air pollution during pregnancy; however, the study had low statistical power.

Author & **Year**	**Study date, design & population**	**Pollutants studied**	**Definition of outcome measure.**	**Exposure measurement technique**	**Confounder Adjustments**	**Authors conclusions**
Madsen et al. (2010) 'Ambient air pollution exposure, residential mobility and term birth weight in Oslo, Norway.'	Population based cohort study from Norway (1999-2002) of 25, 229 singleton pregnancies.	NO_2 $PM_{2.5}$ PM_{10}	LBW at term: GA ≥37 weeks gestation and a birth weight of <2500g. SGA: birth weight below 10^{th} centile of study population, by gender and gestational week.	A dispersion model (per square km) and stationary monitoring stations.	Birth season, temperature, maternal education, maternal ethnicity, income (at a neighbourhood level).	No clear association between term LBW and traffic related pollution during pregnancy. Mobility patterns could introduce possible confounding when examining small-scale variations.
Brauer et al. (2008) 'A cohort study of traffic related air pollution impacts on birth outcomes'	Retrospective cohort study in Vancouver, Canada (1999-2002) of 70,249 singleton births.	NO NO_2 CO SO_2	SGA: < 10th percentile of the cohort, by sex and gestation. Term LBW < 2,500g.	Residential exposures estimated by month of pregnancy using nearest and IDW of area monitors. Temporally adjusted land use regression models and proximity to major roads.	Sex, parity, month and year of birth. Maternal age, smoking. Income & maternal education level obtained using census data based on residence (no individual data).	Associations identified between traffic related air pollution and birth outcomes to relatively low levels of ambient air pollution exposure. Particularly between NO, NO_2 and CO and SGA. No consistent patterns suggested exposure

Author & Year	Study date, design & population	Pollutants studied	Definition of outcome measure.	Exposure measurement technique	Confounder Adjustments	Authors conclusions
						windows of greater relevance
Aguilera et al. (2009) 'Association between GIS-Based Exposure to Urban Air Pollution during Pregnancy and Birth Weight in the INMA Sabadell Cohort'	Prospective cohort study in Barcelona, Spain (2004-2006) of 570 births.	NO_2 Aromatic Hydrocarbons.	LBW and SGA	Temporally adjusted land-use regression (LUR) models.	Health status, use of drugs, occupational data, environmental exposures, time–activity patterns, and a food-frequency questionnaire	Neither NO_2 nor BTEX exposure was significantly associated with birth weight in any of the exposure periods. Reductions in birth weight did exist in exposure to BTEX for women who spent <2hr/day outside Demonstrated that time-activity patterns can complement GIS-based models in exposure assessment.
Bell et al. (2007) 'Ambient air pollution and low birth weight in Connecticut and	Register based cohort study in Connecticut and Massachusetts (1999-2002) of 385, 504 births.	PM_{10}, $PM_{2.5}$, NO_2, CO and SO_2.	LBW (<2500g)	Average county-level concentration based on mothers' residence.	Mothers marital status, tobacco and alcohol use, education, mothers age and birth weight, race, temperature by trimester, child's sex,	Exposure to even low levels of air pollution may increase risk of LBW. LBW associated with exposure to PM_{10} in 3rd trimester, CO in 1st and 3rd

Author & **Year**	**Study date, design & population**	**Pollutants studied**	**Definition of outcome measure.**	**Exposure measurement technique**	**Confounder Adjustments**	**Authors conclusions**
Massachusetts'					mode of delivery, prenatal care, birth order, gestational length and year of birth.	trimester and 1st trimester for NO_2 and the 2nd and 3rd trimester for SO_2.

Table A3: A summary table of the review papers investigating the effects of air pollution on adverse perinatal outcomes (relating to Chapter 1.6.3).

Author & **Year**	**Review aims**	**Review methods**	**Authors conclusions and further research recommendations.**
Sapkota et al. (2012) 'Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis'	To perform a literature review and meta-analysis to quantify the association between maternal exposure to particulate matter ($PM_{2.5}$ and PM_{10}) and the risk of LBW and PTB.	Literature review identified 20 articles providing quantitative estimates of exposure and outcome that met the selection criteria.	Results from random-effect meta-analysis suggested a 9% (OR 1.09; 95%CI 0.90-1.32) increase in risk of LBW associated with a 10µg/m³ increase in $PM_{2.5}$ (combined odds ratios). An estimated 15% increase in risk of PTB for each 10-mg/m³ increase in $PM_{2.5}$ (combined OR, 1.15; CI, 1.14-1.16). The results suggest that maternal exposure to PM, particularly $PM_{2.5}$ may have adverse effect on birth outcomes. Additional mechanistic studies are required.

Author & **Year**	**Review aims**	**Review methods**	**Authors conclusions and further research recommendations.**
Stieb et al. (2012) 'Ambient air pollution birth weight and preterm birth: A systematic review and meta-analysis'	To perform a systematic review and meta-analysis of the literature investigating the effects of air pollution on LBW (including IUGR and SGA) and PTB (1980-2011).	Online databases and bibliographies searched. Data extracted and pooled estimates of effect were calculated and heterogeneity quantified. A meta-regression was conducted and publication bias examined. 62 studies met inclusion criteria.	Heterogeneity between studies varied widely between pollutants and outcomes. There is a large evidence base suggestive of associations between CO, NO_2, PM and adverse pregnancy outcomes. Variation in effects by exposure period and sources of heterogeneity between studies should be further explored.
Shah et al. (2012) 'Air pollution and birth outcomes: A systematic review'	To systematically review the association between air pollution and LBW, PTB and SGA births.	Electronic databases and bibliographies searched for English language studies reporting on birth outcomes. Included studies assessed for risks of bias using a specifically designed quality assessment tool including: selection, exposure assessment, confounder adjustment, analyses, outcomes assessment, and attrition. Unadjusted and adjusted estimates from included studies were extracted. 41 studies met eligibility criteria.	Exposure to SO_2 was associated with PTB. $PM_{2.5}$ exposure was associated with LBW. PTB and SGA births. Exposure to PM_{10} was associated with SGA births. The evidence for NO_x, NO_2, O_3 and CO was inconclusive. Future research directions include: developing improved methods to detect the duration and intensity of exposure, performing well-designed nested studies that ascertain complete outcomes, avoiding residual confounding and adjusting for residential mobility.

Author & **Year**	**Review aims**	**Review methods**	**Authors conclusions and further research recommendations.**
Parker et al. (2011) 'The international Collaboration on Air Pollution and Pregnancy Outcomes (ICAPPO): Initial Results.'	The ICAPPO was formed to review evidence on the effects of air pollution on pregnancy outcomes across geographically diverse research groups using a common protocol.	A protocol was developed to homogenously estimate ORs for the association of PM_{10} and term LBW from 14 research groups and 9 countries.	There was significant heterogeneity in estimated effects among locations despite the use of a common tool used for all. There were statistically significant associations with LBW from 6 of the 13 centres involved in this analysis. More complex protocols are required for future analyses to synthesis results.
Bonzini et al. (2010) 'Impact of ambient air pollution on birth outcomes: systematic review of the current evidences'	To systematically review available evidence to establish whether recent literature (from 2004) provides more conclusive evidence of a link between air pollutants and birth outcomes.	Electronic databases were searched and 18 original epidemiological studies published since 2004 were reviewed on maternal exposure to PM NO_2, CO and O_3 and PTB and LBW.	Large variability across studies. Evidence suggests PM (particularly $PM_{2.5}$) may adversely affect birthweight. Limited evidence of an association with PTB and of exposure in the 1st trimester.

Author & Year	Review aims	Review methods	Authors conclusions and further research recommendations.
Bosetti et al. (2010) ‘Ambient particulate matter and preterm birth or birth weight: a review of the literature’	To review the literature on maternal exposure to particulate matter and adverse pregnancy outcomes	MEDLINE search of the literature up to June 2009 on studies investigating TSP, PM_{10} or $PM_{2.5}$ on PTB, LBW or VLBW.	The epidemiologic studies reviewed do not provide convincing evidence of an association with the risk of PM on PTB and LBW/VLBW and SGA.
Vrijheid et al. (2011) ‘Ambient Air Pollution and Risk of Congenital Anomalies: A Systematic Review and Meta-analysis’	To systematically review epidemiologic studies on ambient air pollution and congenital anomalies. Meta-analyses were conducted for a number of pollutant-anomaly combinations.	From bibliographic searches, 10 original epidemiologic studies were extracted that examined associations between congenital anomaly risk and air pollution. Meta-analyses were conducted if at least four studies published risk estimates for the same pollutant and anomaly group.	There was some evidence for an effect of ambient air pollutants on congenital cardiac anomaly risk. Improvements in the areas of exposure assessment, outcome harmonization, assessment of other congenital anomalies, and mechanistic knowledge are needed to advance this field.

Author & Year	Review aims	Review methods	Authors conclusions and further research recommendations.
Stillerman et al. (2008) 'Environmental exposures and adverse pregnancy outcomes: A review of the science.'	A review of the literature was performed to better understand the science behind the links between environmental contaminants and adverse pregnancy outcomes.	Pubmed was searched using key word combinations for selected environmental exposures (including air pollution and pesticides) and the associations with pregnancy outcomes (1995-2006).	In terms of outdoor air pollution, an association with reduced term birth weight and preterm delivery was found.
Ghosh et al. (2007) 'Does the effect of air pollution on pregnancy outcomes differ by gender? A systematic review'	Systematically review evidence on the effects of air pollution on adverse pregnancy outcomes and assess the difference by gender in those studies that separate results in this way.	Systematic search using electronic databases and bibliographies based on the guidelines by the Cochrane review. Comprehensive criteria List: 11 articles fulfilled inclusion criteria.	The evidence was limited and inconclusive. Males were found to be at a higher risk of LBW in the presence of higher levels of air pollution. Further investigations are required into ascertaining interaction in high powered datasets across different populations.

Author & **Year**	**Review aims**	**Review methods**	**Authors conclusions and further research recommendations.**
Pope et al. (2007) 'Systematic Review and Meta-Analyses of Risk of Indoor Pollution for Low Birth Weight and Stillbirth'	To perform a systematic review and meta-analyses of the risk of indoor pollution on LBW and stillbirth.	Studies were identified by searching main bibliographic databases, symposium of experts at ISEE (2005) and contact with investigators. Random effects meta-analyses were conducted for each outcome. 6 relevant studies for LBW and 3 for stillbirth were identified and rated methodological quality.	Marked increases in risk of LBW and stillbirth associated with exposure to Indoor air pollution from solid fuel. Indoor air pollution is an important area of future research due to the high exposure levels, particularly in developing countries. These risks are likely to translate into substantial population attributable risk.
Sram et al. (2005) 'Ambient air pollution and pregnancy outcomes: A review of the literature'	This review examined the evidence of associations between air pollution and the following outcomes: ***a***) mortality of fetuses and infants, ***b***) LBW, ***c***) premature (preterm) births, ***d***) IUGR, and ***e***) birth defects.	All publications searched in electronic databases and bibliographies. Studies were assessed based on: random error, selection or measurement bias, and confounding. Biological plausibility was also discussed.	Evidence is suggestive of causality between air pollution and birth weight. Evidence is insufficient to infer causality but justifies further studies between air pollution and PTB/IUGR. Evidence base is so far insufficient to draw conclusions from air pollution and birth defects Future research should focus on confirming if effects on birth weight, prematurity and IUGR are genuine and causal, identifying the most vulnerable period, identifying the contribution of different pollutants and examining if impaired

Author & Year	Review aims	Review methods	Authors conclusions and further research recommendations.
			reproductive outcome have any long term health consequences.
Gilianaia et al. (2004) 'Does particulate air pollution contribute to infant death? A systematic review.'	A systematic review to assess the evidence of associations between particulate matter and infant death.	Databases searched using comprehensive list of search terms with 4 main inclusion criteria; non-accidental, an infant outcome, publication between 1966-2003, available through the British library or internet. Appraised by pairs of reviewers and information was extracted on study design, measurement methods for pollutants and outcomes, stats techniques, confounding factors and results. 15 studies met inclusion criteria.	Inconsistent conclusions between particulate air pollution and fetal death. The review suggests some evidence of an association between PM levels and different subgroups of infant mortality. More consistent with post neonatal mortality due to respiratory causes and SIDS. Further studies to explore overall and cause-specific infant mortality with individual information on key confounders. Exposure assessment to include details of level, size, and composition of PM. The use of physiologic measurements and biomarkers of exposure and effect will be beneficial.
Glinianaia et al. (2004) 'Particulate air pollution and Fetal health. A systematic review of the epidemiologic evidence.'	A systematic review of epidemiologic studies investigating the effects of air pollution on birth weight, prematurity and stillbirth.	Online databases searched to identify English studies (1996 and 2001). Inclusion criteria: original data reported on birth weight, gestational age at delivery, or non accidental stillbirth.	Current evidence advocates either a small adverse effect of particulate air pollution on fetal growth and duration of pregnancy or no effect. Future research should involve clarifying and quantifying the possible effects shown in this paper and constructing hypotheses on plausible biologic mechanisms.

Author & **Year**	**Review aims**	**Review methods**	**Authors conclusions and further research recommendations.**
Maisonet et al. (2004) 'A review of the literature of the effects of ambient air pollution on fetal growth.'	A literature review exploring the effects of air pollution on the outcomes LBW, PTB and IUGR	Articles identified in Medline, bibliographies of individual articles and reviews of scientific journals (1996-2001). Limited to English language, peer reviewed literature. Reports had to include the following pollutants: CO, SO_2, NO_x, PM and O_3. 12 studies were included for review.	Effects of air pollution were apparent on PTD and IUGR, but not for LBW. Most associations, if any, were small. Future research should include the use of biomarkers to clarify the mechanisms by which pollutants induce an effect and to determine a critical window of exposure. Also, collecting data on social and community factors that may affect the association.

Appendix 2

Table A4: Spearman rank correlation coefficients between all exposure estimation techniques for Nitrogen Dioxide (NO_2).

NO_2	PE	NSTAT mth	NSTAT dys	NSTAT hw	DistMjRd	DEFRA	Ma DEFRA	Da DEFRA	IDW	Ma IDW	Da IDW	Kriging	Ma Kriging	Da Kriging
PE	1	.58*	.49*	.51*	.13	.23	.61*	.48*	.14	.60*	.43*	.18	.60*	.46*
1a.NSTATmth	.58*	1	.43*	.46*	.13	-.08	.77*	.39*	-.12	.79*	.37*	-.08	.78*	.40*
1b.NSTATdys	.49*	.43**	1	.52*	-.02	.53*	.54*	.94*	.42*	.55*	.96*	.47*	.59*	.96*
1c.NSTAThw	.51*	.46*	.52*	1	.11	.21	.45*	.43	.24	.41	.44	.26	.34	.42
2.DistMjRd	.13	.13	-.02	.11	1	-.35*	.02	-.04	-.39*	-.13	-.07	-.32*	-.10	-.05
3.DEFRA	.23	-.08	.53*	.21	-.35*	1	.34*	.62*	.90*	.36*	.56*	.87*	.40*	.61*
3.1.MaDEFRA	.61*	.77*	.54*	.45*	.02	.34*	1	.59*	.25*	.96*	.55*	.28*	.94*	.57*
3.2.DaDEFRA	.48*	.39*	.94*	.43	-.04	.62*	.59*	1	.46*	.57*	.96*	.51*	.61*	.95*
4.IDW	.14	-.12	.42*	.24	-.39*	.90*	.25*	.46*	1	.34*	.55*	.96*	.34*	.54*
4.1.Ma IDW	.60*	.79*	.55*	.41	-.13	.36*	.96*	.57*	.34*	1	.56*	.33*	.98*	.57*
4.2.DaIDW	.43*	.37*	.96*	.96*	-.07	.60*	.55*	.96*	.55*	.56*	1	.58*	.58*	.99*
5.Kriging	.18	-.08	.47*	.26	-.32*	.87*	.28*	.51*	.96*	.33*	.58*	1	.40*	.61*
5.1.MaKriging	.60*	.78*	.59*	.34	-.10	.40*	.94*	.61*	.34*	.98*	.58*	.40*	1	.62*
5.2.DaKriging	.46*	.40*	.96*	.42	-.05	.61*	.57*	.95*	.54*	.57*	.99*	.61*	.62*	1

**P<0.05*

Table A5: Spearman rank correlation coefficients between all exposure estimation techniques for Nitrogen Oxides (NO_x).

NO_x	PE	NSTAT mth	NSTAT dys	NSTAT hw	DistMjRd	DEFRA	Ma DEFRA	Da DEFRA	IDW	Ma IDW	Da IDW	Kriging	Ma Kriging	Da Kriging	LUR	Ma LUR	Da LUR
PE	1	.57*	.56*	.59*	.15	.19	.60*	.55*	.20	.62*	.56*	.23	.62*	.56*	.06	.59*	.39*
1a.NSTATmth	.57*	1	.44*	.50*	.08	.02	.84*	.44*	-.02	.83*	.49*	-.05	.86*	.48*	.08	.54*	.43*
1b.NSTATdys	.56*	.44*	1	.48*	-.03	.57*	.56*	.98*	.53*	.62*	.90*	.54*	.59*	.98*	.28	.54*	.85*
1c.NSTAThw	.59*	.50*	.48*	1	.08	.35	.36	.46*	.35	.37	.43*	.34	.35	.46*	-.23	.47	.29
2.DistMjRd	.15	.08	-.03	.08	1	-.34*	-.07	-.04	-.39*	-.05	-.04	-.30*	-.05	-.02	-.19	.04	.13
3.DEFRA	.19	.02	.57*	.35	-.34*	1	.36*	.61*	.93*	.40*	.59*	.97*	.32*	.59*	.56*	.43*	.36*
3.1.MaDEFRA	.60*	.84*	.56*	.36	-.07	.36*	1	.57*	.35*	.99*	.59*	.31*	.99*	.56*	.24	.64*	.49*
3.2.DaDEFRA	.55*	.44*	.98*	.46*	-.04	.62*	.57*	1	.59*	.60*	.99*	.61*	.56*	.99*	.38*	.56*	.87*
4.IDW	.20	-.02	.53*	.35	-.39*	.93*	.35*	.59*	1	.35*	.59*	.94*	.30*	.56*	.51*	.32*	.30*
4.1.MaIDW	.62*	.83*	.62*	.37	-.05	.40*	.99*	.60*	.35*	1	.62*	.33*	.99*	.61*	.20	.61*	.51*
4.2.DaIDW	.56*	.49*	.98*	.43*	-.04	.59*	.59*	.99*	.59*	.62*	1	.58*	.61*	.99*	.33*	.54*	.86*
5.Kriging	.23	-.05	.54*	.34	-.30*	.97*	.31*	.61*	.94*	.33*	.58*	1	.26*	.58*	.60*	.40*	.36*
5.1.MaKriging	.62*	.86*	.59*	.35	-.05	.32*	.99*	.56*	.30*	.99*	.61*	.27*	1	.57*	.21	.63*	.49*
5.2.DaKriging	.56*	.48*	.98*	.46*	-.03	.59*	.56*	.99*	.56*	.61*	.99*	.58*	.57*	1	.30*	.54*	.85*
6.LUR	.06	.08	.28	-.23	-.19	.56*	.25	.38*	.51*	.21	.33*	.60*	.21	.30*	1	.61*	.66*
6.1.Ma LUR	.59*	.54*	.54*	.47	.04	.43*	.64*	.56*	.32*	.62*	.54*	.40*	.63*	.54*	.61*	1	.78*
6.2.DaLUR	.39*	.43*	.85*	.29	.13	.36*	.49*	.87*	.30*	.51*	.86*	.36*	.49*	.85*	.66*	.78*	1

**P<0.05*

Appendix 3 (study documents relating to Chapter 3)

University Hospital of South Manchester NHS Foundation Trust

Blackpool Teaching Hospitals NHS Foundation Trust

Evaluating air pollution measurement techniques in pregnancy

(Version 4, 12/8/2010)

Participant information leaflet

Introduction

You are being invited to take part in a research study investigating the personal exposure of air pollution in pregnant women living in the North West of England.

Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take some time to read the following information carefully and ask any of the researchers/midwives involved in the study if anything is unclear.

Your participation in this study is **entirely voluntary,** if you do not wish to take part in the study you will in no way be affected in the standard of care you receive.

What is this research study all about?

Air pollution is something that affects us all in some way and is of particular concern in and around large cities. It is important that we have the best information on the levels of air pollution we are exposed to and what effect it has on us.

This project is specifically interested in the **personal air pollution exposure** of pregnant women and how **activity patterns** day to day affect this. The study will collect this information from two hospitals in the North West; One in Manchester and the other in Blackpool from around 100 different women.

Tommy's [Let's talk baby]

MRC Medical Research Council

Why am I being asked to take part?

You are being asked to take part because you are less than 20 weeks pregnant and live near St. Mary's or Blackpool hospital.

Do I have to take part?

No. It is entirely your choice. If you agree to join the study you will be given this information sheet to keep and be asked to sign a consent form. You are free to change your mind at any point during the study without giving a reason. If you decide not to take part or to withdraw during the study this will not affect the care you receive now or in the future.

What will happen to me if I decide to take part?

Three things will be asked of you at two different points (3 months apart) in your pregnancy:

1. Two brief **questionnaires**. Basic questions about yourself, the buildings you spend time in and transport that you use. One will be done in early pregnancy (between 4-20 weeks gestation), and the next, 3 months later (between 24-36 weeks gestation) over the phone.
2. Wearing a personal **air monitor** (the size of a badge) for a full 48 hours before your 24th week of pregnancy.
3. Filling out an easy to use **time-activity log** (recording where you are spending your time) for the same 48 hours as wearing the monitor.

First action point: Once agreeing to take part in the study, a meeting will be arranged at your convenience by phone/post/email. This meeting will take place before 20 weeks of pregnancy and can either be at your home, next hospital appointment, research facility or a location more convenient to you. You will meet with the principle researcher (Kim) who will explain exactly what you need to do and answer any questions or concerns you may have. At this meeting, you will decide if you want to sign the consent form. A questionnaire will be administered and you will be provided with the personal air monitor and time-activity diary. This meeting is expected to take up to one hour.

Second action point: The personal air monitor and time-activity log given to you at the 1st meeting will then be used by yourself for 48 hours. Once this is completed, the monitor and log will need to be sent back to the researcher in a pre-paid stamped addressed envelope (provided at 1st meeting).

Third action point: You will be phoned in the last few months of your pregnancy by the same researcher to answer a very brief questionnaire.

All data collected will be kept strictly confidential.

What are the benefits of taking part?

There is no direct benefit in taking part.

What happens to the information we collect?

A unique study identifier (a number to protect your identity) will be used and your name will be removed from records. Your address will need to be used to place your location on a map and will be linked to your information by a separate code. Once your address has been used in this way, the information will be safely destroyed.

All information we collect about you will be handled with complete confidence by the research team in line with the Data Protection Act 1998.

Are there any risks to myself or my baby taking part in the study?

The study does not involve any intervention or action that should change your daily routine, the study is just concerned with observing and monitoring. The air monitor should in no way pose a risk to you or your baby.

What happens if any harm does occur?

In the event that something goes wrong and you are harmed during the research you may have grounds for a legal action for compensation against The University of Manchester and Central Manchester NHS but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

The university of Manchester has cover for no fault compensation for bodily injury, mental injury or death where the injury resulted from a trial or procedure you received as part of the trial. This would be subject to policy terms and conditions.

Any payment would be without legal commitment (Please ask if you wish more information on this).

What happens if there is a problem at any point?

If at any point you are concerned about any aspect of the study, you can speak with the researcher (Kim) at any time or any of the research supervisors (contact details below), who will do their best to answer any questions.

If they are unable to resolve your concerns or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 2757583 or 0161 2758093 or by email to research-governance@manchester.ac.uk.

What will happen to the results of this study?

The study results will be written up as part of a PhD thesis. The study results may also be published in professional journals and presented at conferences.

Please contact Kimberly.hannam@postrad.manchester.ac.uk for a copy of the results.

Who is organizing and funding the research?

The research study is being undertaken as part of a doctoral study through the Maternal and Fetal Research department at the University of Manchester. The research is closely monitored by experienced clinical and academic supervisors.

The project is funded jointly by the Medical Research Council and the charity Tommy's.

The hospital and other clinicians do not receive any payment if you take part in this project.

Who has reviewed this study?

The university ethics board, as well as the regional ethics committee and local NHS site specific research and development offices have reviewed the study.

Thank you for taking the time to read this information

Contact for further information:

Principle investigator: Kim Hannam

Maternal and Fetal research centre, Floor 5, St. Mary's hospital, Hethersage Road, Manchester M13 9WL.

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Recruitment poster

Could you help with research during your pregnancy?

What is this specific research about?

We are investigating pregnant women's exposure to air pollutants.

Can I help?

Yes!

As long as you are under 20 weeks pregnant & a non-smoker.

Will it take up much time?

No.

- Just one meeting with the researcher Kim for ~20min at whatever location is convenient to you.

- Wearing a personal air monitor and completing a time-activity log for 48hrs in your own time.

- A 10 minute over the phone questionnaire 3 months later.

If you think you might be able to help or want to know more about the study, we would love to hear from you!

Contact: Kim on **07909265077** or email Kimberly.hannam@postgrad.manchester.ac.uk

Personal exposure to air pollution during pregnancy in North West England

Participants consent form

Patient ID:

Chief investigator: Kim Hannam ***Lead supervisor: Roseanne McNamee***

Please read the consent form and initial box indicating your consent for each point.

1. I have read the information sheet for the above named study (version 4) and have had the opportunity to ask questions. ☐
2. I understand that participation in this study is voluntary and I am free to withdraw at any time, without giving a reason. ☐
3. I consent to take part in the above named study which will involve completing a short questionnaire. ☐
4. I consent to take part in the above named study which will involve wearing a personal air monitor for a full 48 hours during the pregnancy as well as a completing a personal activity log. ☐
5. I consent to the researcher collecting data relating to my pregnancy and pregnancy outcome. ☐
6. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

Signed (participant)……..Date……..

Print Name (participant) ……

Signed (researcher)……Date……..

Print name (researcher)…….

Signed (Witness, if available)……Date……..

Questionnaire (1)

Study ID number: **Date:**

Section 1

General Background

1. Are you or have you been involved in any other medical/ health related research in the last 3 years?

Yes

……

……

No

2. What is your current address?

……

……

Postcode: __ __ __ __ __ __ __

3. Have you moved residence in the past 6 months?

No

Yes (if so, what were the first 3 digits of your previous address?)

__ __ __

4. If you work, what is your work address?

……

……

Postcode: __ __ __ __ __ __ __

5. How old are you?

……

6. When is your baby due?

……

7. Do you have any current health problems?

No

Yes (Please state)

……

……

<u>Section 2:</u>

Education and employment

8. What is the highest educational level you have reached?

Left/finished school before 16
Left school at 16
Higher Education College (16-19)
Vocational training post college
University (graduate)
University (post graduate)
Currently in full time/part time education

9. What is the employment status of the baby's father?

Unemployed
Work full time
Work part time
Have previously worked part time (please state how long ago)
……
Have previously worked full time (please state how long ago)
……
Employed but long term sickness/disability
Not employed due to sickness
Student
Homemaker
Self employed

10. What is your employment status?

Unemployed *(Go to section 4)*
Work full time *(Go to section 3)*
Work part time *(Go to section 3)*
Have previously worked part time - please state how long ago. *(Go to section 4)*

Years…… Months……..

Have previously worked full time - please state how long ago *(Go to section 4)*

Years……. Months…….

Employed but long term sickness/disability *(Go to section 4)*
Not employed due to sickness *(Go to section 4*)
Student *(Go to section 4)*
Homemaker *(Go to section 4)*
Self employed *(Go to section 3)*
Maternity leave *(Go to section 4)*

Section 3

11. What is your job title?

……

11. How many hours do you work in a normal week?

……

12. Please give a short description of the tasks involved in your work.

……

……

……

Section 4

Your Home.

13. How would you describe the buildings around your home?

Derelict land or waste dump
Crop fields
Other open land (e.g. countryside or grazing)
Usual city parks
Other (please specify)

14. How would you best describe the traffic outside your home?

Busy main road
Moderate traffic
Quiet residential
Hardly any traffic

15. How is your home heated?

Central heating radiators (Gas and electric)
Storage heaters
Gas fires
Electric fires
Solid fuel including coal
Portable gas or paraffin heaters

16. Does your current house have double glazed windows (more than half the windows in the house)?

Yes

No

Section 5
Lifestyle

17. How frequently do you cook with the following fuels in a normal week?

	Never	1x per wk	2x per week	3x per week	4x per week	5x per week	More than 5x per week
Gas							
Electric							
Dual gas and electric							
Solid fuel							
Paraffin							
Microwave							

18. On a usual day, which of these modes of transport would you use and for how long?

	Hours	Minutes
Foot		
Car		
Bus		
Train/Tram		
Bike		

19. How long do you *think* you normally spend outside (not including travelling in a vehicle) in a day?

Weekday: Hours……. Minutes……..
Weekend: Hours…….. Minutes…….

20. Has this changed since becoming pregnant?

Yes
No

21. Does anyone in your house smoke?

Yes
No

22. Have you made any conscious effort to avoid areas you believe to have bad air pollution since becoming pregnant?

A lot
Sometimes
Not sure
Rarely
Never

Thank you for taking the time to complete this questionnaire

Time activity log prompt sheet

- **For every half hour of your day:**

1. First- decide *and* tick whether you are in a rural or urban area.

2. Second- look along the row and choose 1 or 2 columns which best describes where you spent your time in that 30 minutes. (See example below)

TIME	Area		Travel				Outdoor			Indoor			
	Urban (in town/city)	Rural (large, more isolated areas)	Car	Bus	Train/ tram	Other	Walking	Biking	Running	Home	Work	Public building	Other
7.00am	✓						✓						

Don't forget!

- Do not tick more than two boxes for each 'travel, outdoor or indoor' 30 minute row.

- Do write any details that you feel might be relevant to your activity on the back of the log.

- Do not leave a time blank.

- Do ask the researcher if you have any problems or concerns (e-mail: Kimberly.hannam@postgrad.manchester.ac.uk or call (during office hours 9am-6pm): 07909265077

For every half hour FIRST mark either Urban area or rural and SECONDLY mark your activity

Time-activity log

Study ID number:

Date started:

TIME	Area		Travel				Outdoor			Indoor			
	Urban (in town/city)	Rural (large, more isolated areas)	Car	Bus	Train/ tram	Other	Walking	Biking	Running	Home	Work	Public building	Other
7.00am													
7.30													
8.00													
8.30													
9.00													
9.30													
10.00													
10.30													

Instructions for the personal air monitors

1. The monitor will be given to you in a sealed, clear bag by the researcher.

2. ONLY take the monitor out of the bag once you are ready to start the 48 hour monitoring. Once the monitor is exposed to air, it will begin monitoring.

3. When you are sure you are ready to start, take the monitor out of the bag and pin it to your clothes on the upper part of your chest (as near to your head as is comfortable and practical).

4. The monitor should stay attached to whatever item of clothing you are wearing during the day time of the monitoring period.

5. During the night or when in the bath/shower, leave the monitor by your bed.

6. Do not expose the monitor to excessive steam (if you are washing up with hot water please remove the monitor.

Frequently asked questions

1. **What do I do when I go to bed?**

   We still want to know about the air you breathe when you are sleeping. Simply leave the monitor next to your bed (i.e. on your bed side table) for the night. Just make sure you reattach it in the morning!

2. **What about when I am having a shower?**

   The monitors will not work properly if they are exposed to intense levels of steam. When you are having a shower or bath, please leave the monitors outside of the bathroom. Remember to record this in your time-activity log.

3. **The clip on my monitor has broken, what shall I do?**

   If the clip on your monitor breaks, attempt to reattach the spare clip that will be provided in the bag. If you are unable to mend it with the clip provided or do not feel confident that it will stay on your clothing, please ring the contact number for the principle researcher for further advice (07909265077).

4. ***I am playing sport, should I keep the monitor on?***

   If you are playing a vigorous sport, remove the monitor and attempt to leave it in a similar area to where you are playing. If the sport is non-contact and passive, the monitor should not pose any added problems and should remain attached to your sportswear.

5. **I have lost/ broken my monitor, what shall I do?**

   We ask that you try your best to look after the monitors as they are very important for our research, however, if an accident does happen please call the researcher as soon as possible (number: 07909265077) who will attempt to solve the problem as soon as possible.

Appendix 4: Flow chart of participation from study in Chapter 3.