Identifying and defining “At Risk” groups to better target air quality information:

Evidence assessment for diabetes, obesity, subtypes of asthma and life-stage - July 2023

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Executive Summary

This report presents the findings of a rapid review assessing the evidence regarding the susceptibility of specific subpopulations to short-term exposure to ambient air pollution (NO_2, PM_{10}, $PM_{2.5}$, O_3 and SO_2), aimed at providing guidance for the Air Quality Information System (AQIS) review of the Daily Air Quality Index (DAQI).

A review of the literature was conducted to identify the epidemiological and experimental evidence bases for increased susceptibility of individuals with metabolic disorders, specific subtypes of asthma and older/younger people (as well as a short commentary on pregnant women). These subgroups were assessed either because they have been discussed in the literature but are not mentioned in the current DAQI (metabolic disorders or asthma subtypes) or to strengthen the current evidence (life-stage).

The rapid review of the evidence did not allow for definitive categorisation of a group being "at-risk". However, some of the reviewed evidence does suggest increased susceptibility.

Diabetic individuals show signs of heightened susceptibility to particulate matter (PM)-related health effects. The limited evidence from panel and animal studies indicates that exposure to particulate air pollution can cause heart rhythm disorders and have thrombotic effects in diabetics, which aligns with the epidemiological observations of an increase in hospital admissions for cardiac arrhythmia, cardiovascular diseases and myocardial infarctions. Caution is advised in defining diabetics as an "at-risk" group and further research is recommended, given that the evidence for PM-related health effects was suggestive (but not conclusive) and was also less clear for gaseous pollutants.

For individuals who are obese or overweight, the evidence suggests increased susceptibility to respiratory health effects related to ozone (O_3) exposure. This is based on human panel and controlled exposure studies that report greater lung function decline and animal studies showing heightened pulmonary resistance, inflammation and airway hyperresponsiveness in response to O_3 exposure. Contributing factors may include obesity-related mechanical factors and/or mediation via inflammatory adipokines and the gut microbiome. The potential increased susceptibility amongst this subgroup of the population is particularly significant considering the high prevalence of obesity and projected increases in ambient O_3 concentrations due to climate change.

While there is ample evidence supporting an increased susceptibility to the short-term health effects of air pollution amongst the asthmatic population as a whole, this report concludes that the evidence base is currently too limited and heterogenous to determine whether specific subtypes of asthma are more susceptible than others.

The present review indicates that older and younger populations are more susceptible compared to young/middle-aged adults. Older individuals may be more vulnerable to air pollution-related mortality and asthma hospitalisations associated with PM and O_3 exposure, although geographic heterogeneity in studies is limited. The experimental evidence is suggestive that older individuals may be more susceptible to gaseous and particulate air

pollution exposure. An increased risk of asthma and respiratory disease hospital admission in children is indicated from the reviewed epidemiological evidence.

The conclusions reached in this review do not call for modifications to be made to the groups presently acknowledged as being “at-risk” in the health advice and recommended actions of the DAQI. While evidence is not robust enough to categorise diabetics as highly sensitive to air pollution, it is notable that cardiovascular diseases, which enhance susceptibility to air pollution, are prevalent among diabetics. Asthmatics should remain classified as a susceptible group, but clarifications regarding differential susceptibility among asthma subtypes await future research. Obese and overweight individuals may be more susceptible, especially to the health effects of O_3, but this requires further investigation. The elderly and children should still be considered at-risk groups.

It is critical to understand that the absence of evidence confirming the susceptibility of a particular group does not necessarily imply that they are devoid of risk. For instance, within the framework of the current DAQI, individuals with diabetes who also have cardiovascular disease (a cohort that predominantly comprises older individuals) remain considered at risk, regardless of the underlying characteristic for increased susceptibility. In the same vein, it remains prudent to treat the overall asthmatic population as sensitive to air pollution, since the present evidence is insufficient to dictate more nuanced recommendations for distinct subtypes within the broader asthmatic demographic.

In defining a group as susceptible to air pollution, a rigorous evidence base is essential. Epidemiological studies should clearly define and estimate effects of exposure on both the susceptible group and a reference group, quantify the differences, and test for statistical significance. Multiple consistent studies reporting higher effect estimates for one or more health outcomes with statistical significance are necessary. In addition, corroborating evidence from panel or controlled human exposure studies and relevant animal studies that provide plausibility of increased susceptibility is crucial. The current report emphasises that absence of evidence for increased susceptibility does not rule out risk. It is important to be cautious when defining “at-risk” groups, acknowledging the potential health implications of designating a population as being at increased risk versus not at increased risk.

Here we focused on the impacts of short-term exposure to air pollution in relation to the DAQI. It is essential to also consider spatial variations in pollutants such as nitrogen dioxide, as these discrepancies can contribute to environmental inequalities and interact with factors such as poverty and healthcare access. Air quality indices reflecting long-term pollution levels can effectively communicate these issues to the public when used alongside temporal indices.

Knowledge gaps remain in identifying subpopulations at higher risk from short-term ambient air pollution exposure. Future research should encompass larger epidemiological studies and more harmonised controlled human exposure and animal studies to evaluate less common factors such as diabetes, obesity and specific asthma subtypes. There is a pressing need to investigate under-studied pollutant-outcome pairs and to examine the health effects of non-criteria pollutants such as ultrafine particles. Asthma subtypes need better definition, and maternal health requires further investigation regarding air pollution’s impact. The research should also include studies that concurrently evaluate short- and long-term pollution

exposure effects. Additionally, intervention studies should focus on the efficacy of air quality communication among both the public and vulnerable groups. Comprehensive systematic reviews should be undertaken to provide more extensive insights into identifying “at-risk” subpopulations.

Chapter 1 – Introduction

1.1 Background

The Department for Environment, Food and Rural Affairs (Defra) and the UK Health Security Agency (UKHSA; formerly Public Health England) have launched the Air Quality Information System (AQIS) review which will be guided by evidence from air quality and health studies as well as other disciplines. As part of this exercise, the Environmental Research Group (ERG) at Imperial College London were commissioned to provide an expert rapid review of studies that have attempted to identify subgroups of the general population that are more likely to have higher risks of experiencing a health outcome associated with their short-term exposure to air pollution. The aim is to propose a set of actionable recommendations for enhancing the current AQIS, including the Daily Air Quality Index (DAQI). The DAQI informs the public regarding levels of air pollution and provides recommended actions and health advice for the general population and individuals who may experience more noticeable symptoms (i.e., those "at-risk"). The at-risk population groups included in the current DAQI are adults and children with lung or heart problems, older people and children.

Defra are seeking to identify the existence of and strength of evidence that may provide a medical rationale for revising the groups that are defined as at-risk, due to their individual characteristics. This is of particular importance for communicating air quality information/alerts and associated health advice to the general public. Clarification of individual susceptibility might also be useful to understand mechanisms leading to the clinical health effects.

Although it is acknowledged that certain subpopulations exhibit an enhanced response to air pollution owing to personal and/or community-level characteristics, much remains to be learned about the specific characteristics that cause some people to be especially sensitive, the interplay between the various characteristics and different types of air pollution and the physiological response.

Although the terms susceptibility and vulnerability are often interchangeably used, distinct definitions appear in the literature. Hooper and Kaufman (2017) define vulnerability as referring to external factors (e.g., socioeconomic position, nutritional status, personal behaviours) that confer increased risk for an adverse outcome and susceptibility to intrinsic characteristics (e.g., underlying disease, age, genetic background, sex, race, epigenetic changes, ethnicity) that increase risk. Some of these characteristics are dynamic over a person's lifetime.

This report does not investigate whether there is evidence for involvement of every possible risk factor as it was a time-limited project. Rather, it focusses either on susceptible groups that have already been discussed in the literature but are not mentioned in the advice accompanying the current DAQI or on refining advice on current groups. This report does not cover whether those with cardiovascular disease are a vulnerable group as this group is already identified in the advice linked with the DAQI.

More details on the potential susceptible groups we chose to investigate are given in the paragraphs below.

Asthma is a common respiratory condition in the UK with a prevalence of 12% in 2012[1]. It is also a complex, multifactorial health endpoint, as it is a combination of multiple phenotypes or endotypes (Kuruvilla et al. 2019). Exposure to various air pollutants, including gases and particles, has been associated with increased risks of asthma incidence (Gehring et al. 2015) and prevalence (Fuertes et al. 2020), as well as asthma exacerbations and hospital admissions (Orellano et al. 2017). There is substantive evidence on the links between short-term exposure to air pollution and asthma as an umbrella term which are considered likely to be causal (US EPA 2016, 2017, 2019, 2020). The proposed biological mechanisms for these links include oxidative stress, inflammation and immunological responses (Chatkin et al. 2021). However, little is known as to whether exposure to air pollution has differential effects on certain asthma phenotypes or endotypes. While it is highly likely that exposure to air pollution is associated with asthma outcomes among all recognised asthma subtypes (Chatkin et al. 2021), we proposed to review the evidence from the epidemiological and experimental literature that may or may not support this and quantify potential differential health impacts in asthma patients of different subtypes. Indeed, there is always the possibility that for diseases displaying complex heterogeneity, the size of the effect of air pollution on a worsening of the condition (in this case, an exacerbation of asthma) is underestimated due to dilution by endotypes/phenotypes that are less affected by poor air quality.

Type 2 diabetes and obesity both represent a widespread public health burden, globally (Xie et al. 2022) and in the UK (Darbà et al. 2015). The number of people with diabetes in the UK is approximately 5 million, worldwide the number is estimated to be 415 million[2]. A health survey for England in 2021 estimated that 25.9% of adults in England are obese and a further 37.9% are overweight but not obese[3]. Evidence continues to build for associations between long-term exposure to ambient air pollutants (especially for particulate matter) and increased risks of developing diabetes (Yang et al. 2020). Studies have also found air pollution to be positively associated with body weight (Lin et al. 2022; Jerrett et al. 2014). These findings are supported by results from experimental research, demonstrating that mice on a high fat diet and exposed to ambient $PM_{2.5}$ develop greater visceral fat and insulin resistance than animals on the same diet but breathing filtered air (Sun et al. 2009). People with diabetes or obesity may also be especially responsive to air pollution owing to underlying metabolic characteristics that increase susceptibility to both cardiovascular and respiratory disease.

Life-stage is another important risk factor for multiple health outcomes and is also a well-established confounder that needs to be adjusted for in studies that quantify the relationship between air pollution and health using individual data (e.g., panel or cohort studies). However, it is less common, especially in epidemiological time-series studies in which age and other non-time varying individual characteristics are not potential confounders, to stratify their analysis by age and provide age-specific exposure-response associations. These studies usually use aggregated data at city level, and for certain outcomes, the exposure-response

[1] https://statistics.blf.org.uk/asthma
[2] https://www.diabetes.co.uk/diabetes-prevalence.html
[3] https://researchbriefings.files.parliament.uk/documents/SN03336/SN03336.pdf

associations may be driven by stronger relationships in specific age groups, such as the elderly or children. Original studies and meta-analyses exist that quantify effect modification of exposure-response associations by age and provide evidence for particular groups that may be regarded more at-risk compared to others or the general population. For example, it has been shown that children and older adults (>65 years of age) are more vulnerable to the effects of particulate matter and nitrogen dioxide on asthma hospitalisations (Evangelopoulos et al. 2022). These groups are already considered as at-risk subpopulations in the current DAQI. Identifying or strengthening the evidence for potentially increased vulnerability with regards to air pollution exposure in specific groups based on their life-stage is crucial both for policy makers, the vulnerable populations and the general public. In addition, these subpopulations form a large percentage of the total population and even small increases in the risks related with air pollution exposure can result in high health and economic impacts.

Whether pregnant women are a sensitive group was also covered in this project, but only as a short commentary. This focused on potential effects on the mothers rather than their developing baby, as the latter is covered in the forthcoming COMEAP report on air pollution and adverse birth outcomes[4].

We conducted a rapid review of studies investigating the health effects of short-term exposure to criteria air pollutants, i.e., particulate matter ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), ground-level ozone (O_3) and sulphur dioxide (SO_2), and the potentially differential health impacts for the subpopulations identified above (i.e. people with different asthma subtypes, diabetics, obese people, individuals of different ages). Investigating the associations between air pollution and specific health outcomes almost automatically implies the existence of a vulnerable group, e.g., asthma admissions occurring in asthmatics (Orellano et al. 2017). On the other hand, assessing whether the effects of air pollution on standard health endpoints, e.g., all-cause mortality, are more pronounced for specific subpopulations, such as diabetics or the elderly, compared to the general population, also indicates susceptibility. Therefore, we reviewed the scientific literature to identify experimental and epidemiological studies that either looked at specific health outcomes that imply susceptibility or examined potential effect modification by subgroups for more broad health endpoints.

As part of our rapid review, we also searched for comprehensive documents that have already critically reviewed and synthesised the evidence base with respect to susceptible groups, thus we examined the relevant US Environmental Protection Agency Integrated Science Assessments (https://www.epa.gov/isa).

Our report is structured as follows:

- In Chapter 2 – Methods, we present the search strategies applied to identify the relevant studies included in our review.
- In Chapter 3 – Evidence from the US Environmental Protection Agency Integrated Science Assessments, we discuss the summary of evidence from the US Environmental Protection Agency Integrated Science Assessments (EPA ISAs) for the causality of the

[4] https://www.gov.uk/government/groups/committee-on-the-medical-effects-of-air-pollutants-comeap#minutes

health effects on subpopulations associated with short-term exposure and to PM, NO_2 and O_3.

- In Chapters 4 to 6, we report our findings on the identification of the health effects of short-term exposure to air pollution on specific subpopulations, defined by diabetes/metabolic syndrome/obesity, asthma and life-stage status respectively.
- In Chapter 7 – Discussion, we discuss these findings, provide research recommendations and conclusions.

Chapter 2 – Methods

2.1 Search strategy

We reviewed two large electronic databases, *PubMed* and *Web of Science*, to retrieve peer-reviewed, published, experimental and epidemiological studies that provided evidence on a differential impact of air pollution on the subgroups defined above. A detailed literature search protocol was prepared in November 2022 and shared with Defra (Appendix 1). We summarise briefly the search strategy followed below.

2.1.1 Search strings

In order to simplify our searches and collect relevant studies for each research question, we conducted separate searches for each subpopulation under investigation. All of the search strings were built using three main components, i.e., one for air pollution, one for study type and one for the subgroups under investigation. Our rapid review included both experimental and epidemiological studies. For the former, separate searches were performed for short-term animal exposure studies and controlled human exposure studies, while for the latter, we searched for studies on short-term exposure to ambient levels of $PM_{2.5}$, PM_{10}, NO_2, O_3 and SO_2, such as time-series, case-crossover and panel studies. The review of experimental evidence also included data generated from studies employing traffic-related air pollutants because controlled human exposure and animal studies commonly employ these exposures which of course dominate in urban environments where most people live, work and commute. There was no restriction on the type of health outcomes that were assessed, as the main aim was to investigate whether there are potentially differential risks for people from specific subgroups (e.g., diabetics, people with obesity, asthmatics with a specific subtype or people of a specific age group) compared with groups not-at-risk (e.g., non-diabetics or normal weight people) or the general population.

2.1.2 Data extraction and synthesis

This rapid review followed standard approaches for reviewing the scientific literature but not necessarily all aspects of formal systematic review guidelines. For example, there were insufficient resources for duplicate screening – instead researchers discussed with the wider team specific studies that seemed unclear in some way. The panel studies identified for metabolic disorders in particular were screened by at least two of the authors (JF, DW, DE). Screening included title, abstract and full-text assessment. We collected various study characteristics and main findings in bespoke data extraction forms including authors, year and journal of publication, study design, location, period, pollutant(s) studied, methods of exposure assessment, number of participants/animals, health outcome(s) (or for experimental studies: endpoints such as organ function, cellular changes, molecular alterations) under investigation, effect estimates and covariate adjustment. Time restraints ruled out formal methods of appraising for quality and bias, but expert commentary and limitations in the identified studies are provided and discussed. EndNote and Microsoft Excel were used to maintain and record the papers and the information extracted from them.

Analysis of effect modification of the pollutant-exposure relationship in epidemiological studies provides evidence for differential effects of short-term exposure to air pollution in

potentially susceptible sub-groups compared with the general population or those not regarded as susceptible (e.g., diabetics and non-diabetics). For clarification, effect modification refers to the alteration of the effect of an exposure on an outcome by the presence of another variable. This implies that the association between the exposure and the outcome differs across levels of a third variable, termed the effect modifier (in this case the presence of diabetes, subtype of asthma, obesity etc.). For instance, the effect of air pollution on respiratory endpoints may differ across age groups, with younger or elderly individuals being more susceptible. It also needs to be distinguished whether any differences seen are just random chance variations or a statistically robust real difference. Effect modification studies are crucial for the identification of vulnerable subpopulations and for tailoring interventions. Therefore, the present review aimed at identifying studies in which potentially susceptible subpopulations were identified and the modification of effect of the exposure to air pollution was estimated.

Chapter 3 – Evidence from the US Environmental Protection Agency Integrated Science Assessments

3.1 Background

The US EPA ISAs form the scientific foundation for the review of the US National Ambient Air Quality Standards. They are considered particularly comprehensive reviews of epidemiological evidence and the toxicological and mechanistic literature for the years included in each ISA.

In characterising the causal nature between exposure to an ambient air pollutant and health effects, the ISAs also evaluate whether there are populations and life-stages potentially at increased risk of a pollutant-related health effect (owing to a greater magnitude of effect or exposure), with specific emphasis on studies that compare responses to a reference population (EPA 2020, 2019, 2017, 2016). This consideration of at-risk populations places greatest emphasis on patterns or trends across different types of studies (including both short-term and long-term exposures), drawing upon the following evidence:

- Epidemiologic studies that conducted stratified analyses to compare populations or life-stages exposed to similar air pollutant concentrations within the same study design.
- Epidemiologic studies that examine a specific population or life-stage, to provide supporting evidence for the pattern of associations observed in studies that formally examine effect measure modification.
- Controlled human exposure studies conducted in specific populations (e.g., people with mild asthma).
- Animal toxicological studies using animal models of disease.
- Information on the dosimetry within the body.
- Consideration of information on differential exposure within a population or life-stage.

Table 1 summarises the overall confidence in the current ISAs that individual factors potentially result in increased risk for PM- ($PM_{2.5}$, $PM_{10-2.5}$, UFPs; EPA, 2019), NO_2- (EPA, 2016) and O_3-related health effects (EPA, 2020). Factors evaluated that are not relevant to the current report appear in grey text. With relevance to the factors evaluated in this report the ISAs concluded that:

- There was adequate evidence that children are at increased risk of PM-, NO_2- and O_3-related health effects.
- There was inadequate evidence that older adults are at increased risk of PM-related health effects and adequate evidence that this life-stage is at increased risk of NO_2- and O_3-related health effects.
- There was inadequate evidence that people with pre-existing diabetes are at increased risk of PM-, NO_2- and O_3-related health effects.
- There was suggestive evidence that populations that are overweight/obese are at increased risk of PM- and O_3-related health effects but inadequate evidence for NO_2.

The ISAs note that although risk of an air-pollutant-related health effect is evaluated for each factor individually, it is likely that portions of the population are at increased risk of a health effect owing to a combination of co-occurring factors, but that information on such interactions remains limited. It is also noted that differential effects of air pollutants may arise depending on disease type, severity, management, but that few studies include this level of detail.

Table 1 - Summary of evidence for populations at increased risk to the health effects of ambient air pollutants from the US Environmental Protection Agency Integrated Science Assessments.

Factor evaluated		Conclusions from 2019 PM ISA	Conclusions from 2016 NO_2 ISA	Conclusions from 2020 O_3 ISA	Conclusions from 2017 SO_2 ISA
Life-stage	Children	Adequate evidence	Adequate evidence	Adequate evidence	Suggestive evidence
	Older adults	Inadequate evidence	Adequate evidence	Adequate evidence	Suggestive evidence
Pre-existing disease	Pre-existing respiratory disease Pre-existing asthma Pre-existing COPD Pre-existing CVD Pre-existing diabetes Obesity	Suggestive evidence Not evaluated Not evaluated Suggestive evidence Inadequate evidence Suggestive evidence	Not evaluated Adequate evidence Inadequate evidence Inadequate evidence Inadequate evidence Inadequate evidence	- Adequate evidence Inadequate evidence Inadequate evidence Inadequate evidence Suggestive evidence	Not evaluated Adequate evidence Not evaluated Not evaluated Not evaluated Not evaluated
Sex	Males[a]	Inadequate evidence	Suggestive that females are at increased risk	Suggestive evidence (males in some studies; females in others)	Inadequate evidence
Race		Adequate evidence (Non-white populations)	Inadequate evidence	Inadequate evidence	Not evaluated
Genetic factors	Individuals with genetic variant	Suggestive evidence	Inadequate evidence	Adequate evidence	Inadequate evidence
SES	Low SES	Suggestive evidence	Suggestive evidence	Suggestive evidence	Inadequate evidence
Residential location		Inadequate evidence (near-road or urban residence	Inadequate evidence (urban residence)	-	Not evaluated
Proximity to roadways		Not evaluated	Inadequate evidence	-	Not evaluated
Outdoor workers		Not evaluated	Not evaluated	Adequate evidence	Not evaluated
Behavioural	Current smoking Diet	Suggestive evidence Inadequate evidence (individuals with reduced fruit/veg intake, alcohol	Inadequate evidence Suggestive evidence (low antioxidant intake)	Inadequate evidence Adequate evidence (individuals with reduced Vit E & C intake)	Inadequate evidence for behavioural factors as a whole

		consumption or elevated cholesterol)			
	Physical activity	Not evaluated	Inadequate evidence	-	

Evaluation of the evidence (from short- and long-term exposures) includes (1) epidemiologic studies that conducted stratified analyses; (2) evidence from animal toxicological studies using animal models of disease and epidemiologic or controlled human exposure studies conducted in specific populations (e.g., lung function growth in children, people with mild asthma); (3) information on the dosimetry of PM within the body; (4) consideration of information on differential exposure to PM within a population or life-stage;
[a]For PM ISA, Males selected as a potential at-risk group due to shorter lifespan.

3.2 Evidence from experimental studies

The following text and Table 2 draw out the evidence cited in the current ISAs that stems from (a) *controlled human exposure studies* and (b) *animal toxicological studies* on relevant populations (i.e., *children, older adults, diabetes and obesity*) at increased risk of PM-, NO_2- and O_3-related health effects following *short-term exposures*.

Children:

- No experimental studies cited for PM, O_3 or SO_2.
- One toxicological study that does not indicate greater NO_2-related lung injury, inflammation, or lung host defense among juvenile compared to mature rodents (Azoulay-Dupuis et al. 1983).

Older adults:

- No experimental studies quoted for SO_2.
- For PM, controlled human exposure and animal studies provide evidence for the occurrence of effects (particularly cardiovascular ones) among this life-stage, but by restricting analyses to older animals/subjects (e.g., Hemmingsen et al. 2015, Nadziejko et al. 2004), they are unable to determine whether this life-stage is at increased risk.
- For NO_2, examination of older adults in controlled human exposure studies is limited to healthy adults showing statistically non-significant decrements in lung function following NO_2 exposure (Gong et al. 2008, Morrow et al. 1992).
- For O_3, acknowledgment is given to prior work (e.g., Hazucha et al. 2003 and reports (U.S. EPA 2006, 1996a)) concluding that O_3-induced decrements in lung function decline with increasing age, but may still be present in older adults, 50-60 years of age. A more recent controlled human exposure study (restricted to subjects 59.9 ± 4.5 years old) conducted at a lower ozone delivery rate more representative of that likely to occur in ambient air, was also cited showing that small lung function decrements, airway inflammation and epithelial injury may occur in older healthy adults (Arjomandi et al. 2018).

Populations with diabetes:

- No experimental studies cited for PM, NO_2 or O_3.
- Populations with diabetes not evaluated for SO_2.

Obese populations or populations with metabolic syndrome:

- No experimental studies cited for PM or NO_2.
- For O_3, controlled human exposure studies demonstrate that ozone-induced decrements in lung function increase with increasing BMI (Bennett et al. 2007, Bennett et al. 2016, McDonnell et al. 2010, McDonnell et al. 2013), but that neither airway responsiveness nor pulmonary inflammation differed between normal-weight and obese women (Bennett et al., 2016). Multiple toxicological studies report that compared to lean mice, obese mice exhibit enhanced airway responsiveness and pulmonary inflammation in response to ozone exposures. These studies will be described in detail in 4.5.3 Ozone exposures.
- Obese populations not evaluated for SO_2.

Table 2 - Evidence from experimental studies for populations at increased risk of short-term exposure from the US EPA ISAs

At-risk factor		2019 PM ISA Effects of short-term $PM_{2.5}$ exposures	2016 NO_2 ISA Effects of short-term NO_2 exposures	2020 O_3 ISA Effects of short-term O_3 exposures	2017 SO_2 ISA Effects of short-term SO_2 exposures
Life-stage	Children		ANIMAL In healthy rats, lung injury, inflammation, host defense no greater in juvenile v. mature		
	Older adults	ANIMAL & CHE Evidence for occurrence of effects (particularly CV); lack of comparator groups to evaluate whether this life-stage is at increased risk versus younger adults	CHE Statistically non-significant decrements in lung function; lack of comparator groups to evaluate whether this life-stage is at increased risk versus younger adults	CHE Decrements in lung function decrease with increasing age but small lung function decrements, airway inflammation and epithelial injury may still occur in older adults	
Pre-existing disease	Diabetes				
	Obesity			ANIMAL Increased airway responsiveness, airway inflammation and lung injury in mouse models of obesity versus lean controls CHE Decrements in lung function (but not airway responsiveness or inflammation) increase with increasing BMI	

Abbreviations. BMI: body mass index; CHE: controlled human exposure; CV: cardiovascular

3.3 Evidence from epidemiologic studies

The following text and Table 3 outline the *epidemiologic evidence* for at-risk populations (i.e., *children, older adults, diabetics, those with pre-existing diabetes, obese populations or those with metabolic syndrome and those with pre-existing asthma*) at greater risk to the health effects of *short-term* exposure to NO_2, PM and ozone. It should be noted that the US EPA ISA for NO_2 was last updated in 2016 and therefore may not fully represent the current epidemiologic evidence base which is discussed in greater detail in Sections 4.2 Epidemiological evidence on diabetics from time-series and case-crossover analyses, 5.2 Susceptibility to the health effects of air pollution amongst different asthma subtypes and 6.2 Epidemiological studies assessing certain age groups as potentially more susceptible to the effects of air pollution.

Children:

- Strong evidence for an increased risk of O_3-related health effects in children. More recent multi-city studies have provided further evidence to support associations between O_3 exposure and hospital admissions/emergency room visits (HA/ERV) for asthmatic children, particularly for those aged between 5 and 18 years old. Larger associations also reported for HA/ERV visits for respiratory diseases in children than for adults.
- Exposure to $PM_{2.5}$ also related to an increased risk of associated health effects in children, including impaired lung function growth and asthma development.
- Epidemiologic evidence (supported by broad heterogeneity in study location) provides strong evidence for a relationship between increased short-term NO_2 exposure and larger increases in HA/ERV for asthma in children compared to adults, with the majority of evidence comparing children aged 0 – 14 years to older children/adults aged 15 – 64 (increasing short-term NO_2 exposure associated with a 1.8 – 3.4% increased risk of HA for asthma in the younger age group).
- Suggestive but inconsistent evidence for an increased risk of SO_2-related health effects in children.

Older adults:

- Consistent evidence for an association between short-term exposure to O_3 and mortality in older adults. The majority of relevant studies relate short-term O_3 exposure to mortality in older adults, however there is adequate epidemiologic evidence for older adults to be at greater risk for O_3-related health effects in general.
- Inadequate evidence for increased susceptibility to $PM_{2.5}$-associated health effects in older adults, with current studies finding similar associations between younger and older adults.
- Epidemiologic evidence is strong for an increased risk of NO_2-related health effects in adults aged 65 years and older in comparison to those younger. Short-term exposure to NO_2 in older adults generally shown to increase the risk of asthma exacerbations at a magnitude one to three times higher than that observed in younger adults and children.
- As for children, the epidemiological evidence is inconsistent when assessing the susceptibility of older adults to SO_2-related health effects in comparison to younger age groups. Some evidence suggests that individuals aged 75 years and older may be

at greater risk of mortality and asthma-related hospital admissions than those younger, however, the results from the limited number of studies remain inconsistent.

Populations with pre-existing diabetes:

- Current evidence is inadequate to conclude that the presence of diabetes increases the risk of O_3-related health effects.
- Inadequate evidence for short-term (and long-term) exposure from epidemiologic studies for increased risk of $PM_{2.5}$-associated health effects for individuals with pre-existing diabetes, despite recent stratified analyses (further outlined in Section 4.2 Epidemiological evidence on diabetics from time-series and case-crossover analyses).
- Evidence of effect modification of NO_2-related health effects by diabetes not consistent for any health outcome (mortality, ischaemic heart disease, myocardial infarction and subclinical endpoints such as heart rate variability among others assessed).
- Evidence base lacking in studies on SO_2-related health effects.

Obese populations or populations with metabolic syndrome:

- Suggestive evidence for increased risk of respiratory health effects associated with O_3 exposure in obese populations.
- Inadequate evidence for increased risk to PM-associated health effects in studies stratifying analyses by obese and non-obese populations.
- As for PM, inadequate evidence and inconsistent findings for NO_2-related health effects, with studies assessing subclinical cardiovascular effects finding no increased risk in obese study samples.
- No reporting on SO_2-related health effects in obese populations or those with metabolic syndrome.

Table 3 - Evidence from epidemiological studies for populations at increased risk of short-term exposure from the US EPA ISAs.

At-risk factor		2019 PM ISA Effects of short-term $PM_{2.5}$ exposures	2016 NO_2 ISA Effects of short-term NO_2 exposures	2020 O_3 ISA Effects of short-term O_3 exposures	2017 SO_2 ISA Effects of short-term SO_2 exposures
Life-stage	Children	Exposure to $PM_{2.5}$ related to an increased risk of associated health effects in children, including impaired lung function growth and asthma development.	Strong evidence for increased risk of hospital admissions in asthmatic children in relation to NO_2 exposure.	Strong evidence for an increased risk of O_3-related health effects in children, strengthened by recent multi-city studies, included increased risk of hospital admissions for asthmatic children and for respiratory diseases.	Suggestive evidence for increased risk of respiratory disease health endpoints in children but results are inconsistent. Biological plausibility not backed up by recent epidemiological evidence.
	Older adults	Inadequate evidence for increased susceptibility to $PM_{2.5}$-associated health effects in older adults in comparison to younger age groups.	Epidemiological evidence is strong for an increased risk of NO_2-related health effects in adults aged 65 years and older in comparison to those younger. Evidence shows an increased risk of asthma exacerbations in older populations when compared to children.	Consistent evidence for an association between short-term exposure to O_3 and mortality in older adults, as well as adequate epidemiologic evidence for older adults to be at greater risk for O_3-related health effects in general.	Inconsistent recent epidemiological evidence for increased risk of respiratory disease outcomes despite evidence in previous ISA. Limited number of mortality studies have provided inconsistent results.
Pre-existing disease	Diabetes	Inadequate evidence for increased risk despite recent studies stratifying by diabetic subgroups to assess effect modification.	Evidence of effect modification of NO_2-related health effects by diabetes not consistent for any health outcome.	Current evidence is inadequate to conclude that the presence of diabetes increases the risk of O_3-related health effects.	
	Obesity	Inadequate evidence for increased risk to PM-related health outcomes.	Inadequate evidence for increased risk to NO_2-related health outcomes.	Suggestive evidence for increased risk of respiratory health effects associated with O_3 exposure in obese populations.	

Chapter 4 – Metabolic disorders

4.1 Introduction

This chapter considers a group of potential susceptible sub-groups. Metabolic disorders, and more specifically, metabolic syndrome is a medical term for a group of diseases/characteristics (diabetes, hypertension (high blood pressure) and obesity) which often occur in the same patients. This is why they are included together in this chapter. Diabetes, metabolic syndrome (MetS) and obesity increase susceptibility to cardiovascular disease (CVD) (Kannel and McGee, 1979, Mottillo et al., 2010, Powell-Wiley et al., 2021). All three conditions are associated with underlying inflammation (Dandona et al., 2004, Dandona et al., 2005, Shore, 2008) and oxidative stress (Maritim et al., 2003, Esposito et al., 2006, McMurray et al., 2016) as well as impaired endothelial function (De Vriese et al., 2000, Palomo et al., 2006, Engin, 2017), increased atherosclerosis (Beckman et al., 2002, Hulthe et al., 2000, McGill et al., 2002), pro-thrombotic tendencies (Sambola et al., 2003, Sakkinen et al., 2000, Rahmani et al., 2020) and autonomic dysfunction (Schroeder et al., 2005, Fraley et al., 2005, Ma et al., 2017).

Weight gain is associated with a decline in lung function in both patients with asthma (Marcon et al 2009) and in the general population (Pistelli et al 2008). Obesity is also a risk factor for asthma (Beuther et al., 2006). Epidemiologic data indicate that obesity increases the prevalence and incidence of asthma. Obesity also appears to worsen asthma control and some, but not all, studies indicate that it can increase the severity of the disease (Lavoie et al., 2006, Taylor et al., 2008). Obese mice exhibit innate airway hyperresponsiveness and augmented responses to certain asthma triggers, further supporting a relationship between obesity and asthma (Shore, 2007).

Against this background, this section of the report evaluates the epidemiological and experimental literature to assess whether people with metabolic stressors such as diabetes, obesity or MetS may be more susceptible to detrimental health effects induced by short-term exposure to ambient air pollutants. The different potential susceptible sub-groups (diabetes, metabolic syndrome and obesity) are then considered within each section but not every group is considered in every section. For example, section 4.2 only considers diabetics because routine health statistics do not provide information on metabolic syndrome or obesity.

4.2 Epidemiological evidence on diabetics from time-series and case-crossover analyses

The present review identified studies assessing the relationship of specific health outcomes with ambient air pollution concentrations as modified by the comorbidity of diabetes as a potentially vulnerable subgroup. The pollutants investigated were NO_2, PM_{10}, $PM_{2.5}$, SO_2 and ozone. The majority of identified studies were conducted in North American populations, alongside a number of publications from East Asia, whilst the bulk of the relatively smaller number of European studies were undertaken in Italy. The studies ranged in date from 2000

to 2022 and included analyses on populations with data reaching back as far as 1988, with several multi-city studies identified. A total of 309 studies were returned via search of the literature in both the PubMed and Web of Science databases (Appendix 1) and 24 were included in review. Studies were placed into one or more of the following categories: all-cause mortality, cause-specific mortality and hospital admissions. Across all studies, the inclusion of a diabetic subpopulation as a comparator group varied in terms of reporting an effect modification in comparison to the total sample population (including diabetics) or to non-diabetics only. The International Classification of Diseases (ICD) coding used for the definition of diabetics was generally consistent across studies (ICD-10 code: E10-E14), but there were exceptions. Discussion and dissemination of the overall findings from the literature across the three outcome categories is provided here.

4.2.1 All-cause mortality

A total of eight studies investigated the potential for increased risk of all-cause mortality for diabetics in relation to exposure to ambient concentrations of the aforementioned pollutants, ranging in publication from 2004 to 2016, seven of which implemented a case-crossover study design (Bateson and Schwartz, 2004; Zeka et al., 2006; Forastiere et al., 2008; Staffogia et al., 2010; Chiusolo et al., 2011; Zanobetti et al., 2014; Alessandrini et al., 2016) and one a time series study (Goldberg et al., 2013). All studies were conducted in the USA, Canada or Italy, identifying a lack of geographic heterogeneity in such investigations. One study was excluded (Forastiere et al., 2006) as it investigated a sub-sample of the population assessed in Forastiere et al. (2008). Zeka et al. (2006) was the only identified study to compare associations between a diabetic sub-sample with non-diabetics. All other investigations compared diabetic individuals to a larger sample (most often the total sample population) which included both diabetics and non-diabetics.

No statistically significant difference in association between any gaseous pollutant and all-cause mortality was reported for diabetics in comparison to the total sample.

- Both Chiusolo et al. (2011) and Goldberg et al. (2013) found no modified effect of diabetes in the association between NO_2 and all-cause mortality in large sample populations drawn from Italy (a multi-city study) and Montreal, Canada, respectively.
- The results of both analyses suggest an increase in mortality risk in diabetics, but the nominal level of statistical significance was not reached.
- Goldberg et al. (2013) also found no statistically significant modification of the effect of ozone, although the direction of association was suggestive of a protective effect.
- In contrast, Stafoggia et al. (2010) found a marked increase in risk for all-cause out of hospital deaths related to ozone exposure in diabetics in comparison to the total sample across 10 Italian cities for the years 2001- 2005, although the results were not statistically significant. No evidence of effect modification was found for total deaths.
- Modification of the effects of SO_2 and CO were also investigated by Goldberg et al. (2013), although no statistically significant differences between the comparator groups were reported.

In terms of particulate matter, two studies reported statistically significant modification of associations between $PM_{2.5}$ concentrations and all-cause mortality for diabetics (Zanobetti et al., 2014; Alessandrini et al., 2016).

- In a multi-city sample of 6,982,678 deaths in US adults aged 65 years and older between the years 1999 and 2010, Zanobetti et al. (2014) found an increased risk in a diabetic subgroup (n = 955,547; percentage increase in risk [95% confidence interval]: 0.76 [0.39, 1.12]) per 10 μg/m^3 increase in $PM_{2.5}$, in comparison to the total sample (0.64 [0.42, 0.85]).
- A larger increase in effect was reported by Alessandrini et al. (2016) for a sample of Italian adults also aged 65 years and older (n = 228,619 deaths, 31,730 of which were diabetics). The study reported an increased percentage risk of 1.98% [0.54, 3.44] in the diabetic subpopulation, in comparison to 0.34% [-0.74, 1.44] for all those in the total sample not hospitalised in the five years prior to death (n = 56,539), per 10 μg/m^3 increase in $PM_{2.5}$.
- Additionally, of the four studies assessing PM_{10}, just Alessandrini et al. (2016) reported a marginally statistically significant difference in association for diabetics in the aforementioned sample population (2.43% [-0.39, 5.32] for diabetics compared to -0.18% [-1.28, 0.94] per 10 μg/m^3; p = 0.09).
- No significant modification of risk was observed in the results of Bateson and Schwartz (2004), Zeka et al. (2006) or Forastiere et al. (2008).

4.2.2 Cause-specific mortality

Three studies identified through searches of the literature implemented case-crossover designs in order to assess the modification of increased risk for cause-specific mortality in diabetics (Forastiere et al., 2005; Zeka et al., 2006; Qian et al., 2013). Each of the studies was undertaken in a different region and no statistically significant difference in increased risk was observed for any cause-specific mortality across all pollutants.

- Forastiere et al. (2005) investigated the association between out-of-hospital- coronary deaths and concentrations of NO_2, PM_{10}, SO_2 and ozone in diabetics (n = 318) compared to the total sample of 5,144 adults aged 35 years and older in Rome, Italy, finding no increase in risk.
- Zeka et al. (2006) observed a similar lack of statistically significant difference between diabetics and non-diabetics for respiratory, heart disease, myocardial infarction and stroke deaths across 20 US cities in relation to PM_{10} exposure. However, the was a general trend of higher percentage increases in risk of all outcomes except heart disease for diabetics compared to non-diabetics. The total number of deaths included in the study was 1,896,306 but the number of asthmatics was not reported.
- In an analysis of 66,366 stroke deaths in Shanghai, China, Qian et al. (2013) found no statistically significant difference in increased risk in diabetics (n = 5,933) in relation to PM_{10}, SO_2 or NO_2 exposure.

Table 4 - Epidemiological studies assessing the potential effect modification of diabetes on associations between air pollution exposure and mortality.

Pollutant	All-cause mortality	Cardiovascular mortality	Respiratory disease mortality
PM_{10}	**Alessandrini et al. (2016)** Bateson and Schwartz (2004) Zeka et al. (2006) Forastiere et al. (2008)	Forastiere et al. (2005) Zeka et al. (2006) Qian et al. (2013)	Zeka et al. (2006)
$PM_{2.5}$	**Zanobetti et al. (2014)** **Alessandrini et al. (2016)**		
NO_2	Chiusolo et al. (2011) Goldberg et al. (2013)	Forastiere et al. (2005) Qian et al. (2013)	
O_3	Staffogia et al. (2010) Goldberg et al. (2013)	Forastiere et al. (2005)	
SO_2	Goldberg et al. (2013)	Forastiere et al. (2005) Qian et al. (2013)	
CO	Goldberg et al. (2013)		

* In bold: statistically significant difference between sub-groups ($p<0.05$).

4.2.3 Hospital admissions

In total, 14 studies were identified assessing the interaction between air pollution exposure and diabetes in relation to cause-specific hospital admissions, the majority of which were conducted in North America and Asia. Most studies investigated multiple causes of hospital admission and analysed associations in more than one pollutant. Therefore, only the results of statistically significant differences observed in diabetic subgroups are reported here.

- Utilising Medicare data for 156,717 New England, USA, residents (aged 65 years and older), Qiu et al. (2020) assessed the effects of exposure to $PM_{2.5}$ and ozone on hospital admissions for acute myocardial infarction, congestive heart failure and ischemic stroke between the years 2000 and 2012, including analyses on the difference in associations between diabetics (n = 64,511) and non-diabetics. The investigation reported a statistically significant percent increase in hospital admission risk only for acute myocardial infarction per 10µg/m^3 increase in $PM_{2.5}$ in non-diabetics (2.93% [0.46, 5.39]), as well as a statistically significant further increased risk in diabetics (7.85% [2.59, 13.11]). No other statistically significant differences were observed across all outcomes and pollutants in the study.

- Zheng et al. (2018) assessed hospital admissions for cardiac arrhythmia in relation to particulate matter exposure in a multi-city study across China for the years 2014 to 2015 (n = 175,625 admissions in individuals aged 18 years and older across 26 cities). In non-diabetics (n = 155,678), an increment of 47.5μg/m^3 in $PM_{2.5}$ concentrations showed no significant association at lag day four (percentage increase: -0.24% [-0.79, 0.32]), however, a statistically significant difference was observed in diabetics (n = 19,947; 1.80% [0.28, 3.35]). Similarly, for PM_{10}, non-diabetics showed a marginally not statistically significant association at lag day four (0.37% [-0.29, 1.05]) but a significant difference was observed in diabetics (2.73% [0.89, 4.59]).
- A time-series analysis conducted in Beijing, China, for the years 2014 to 2020 (Liu et al. 2021) investigated the difference in percent change in the risk of hospital admission for respiratory diseases between non-diabetics (n = 1,274,771 admissions) and those with type-2 diabetes (T2D; ICD-10 code E12; n = 275,383) in relation to PM exposure. An increase of 57.6μg/m^3 in $PM_{2.5}$ was associated with an increase in admissions for respiratory diseases as a whole (1.92 [1.46, 2.39]) and a statistically significant increase was observed in those with T2D (2.16 [1.08, 3.25]) at lag day eight. No significant difference was observed for PM_{10} exposure, although an increase of 72μg/m^3 was associated with an increase in admissions for both groups at lag day eight. No difference was observed between groups for the associations of PM and selected cause-specific respiratory disease admissions.
- Zanobetti and Schwartz (2001) investigated whether diabetes modified the effect of PM_{10} on hospital admissions for heart and lung disease in persons with or without diabetes. The study conducted a time-series analysis using Medicare data (individuals aged 65 years and older) in Cook County, Illinois for the years 1988–1994. Percent increase in admissions for cardiovascular disease (CVD) were reported for both non-diabetics (0.94% [0.61, 1.28]) and diabetics (2.01% [1.40, 2.62]) per 10μg/m^3 increase in exposure, with the latter statistically significant in difference in comparison to the non-diabetics group. No statistically significant differences between groups were observed in admissions for pneumonia and chronic obstructive pulmonary disease (COPD) despite elevated admissions for both groups across both conditions.

As shown in Table 5, most studies did not find statistically significant differences in the air pollution-mortality associations in diabetics and non-diabetics or the general population. However, most papers reported that the risks of death in relation to air pollution were generally statistically significant for diabetics. The lack of significance for the interaction terms can be explained by either the lack of a real difference between the two groups or the low statistical power to detect it, since the number of diabetics was relatively low in these studies, compared to the general population.

Table 5 - Epidemiological studies assessing the potential effect modification of diabetes on associations between air pollution exposure and hospital admissions.

Pollutant	CVD	Ischemic heart disease	Myocardial infarction	Heart failure	Cardiac arrhythmia	Atrial fibrillation	Ischemic stroke	Respiratory diseases	Pneumonia	COPD
PM_{10}	Linn et al. (2000) **Zanobetti & Schwartz (2001)*** Colais et al. (2012)	Xu et al. (2021)	Tsai et al. (2012) Argacha et al. (2016) Li et al. (2019) Colais et al. (2012)	Lee et al. (2008) Colais et al. (2012)	**Zheng et al. (2018)*** Colais et al. (2012)	Yitshak Sade et al. (2015)		Liu et al. (2021)	Zanobetti & Schwartz (2001)	Zanobetti & Schwartz (2001)
$PM_{2.5}$		Xu et al. (2021)	**Qiu et al. (2020)*** Argacha et al. (2016) Li et al. (2019) Qorbani et al. (2012)	Qiu et al. (2020)	**Zheng et al. (2018)***		Qiu et al. (2020)	**Liu et al. (2021)***		
NO_2		Xu et al. (2021)	Tsai et al. (2012) D'Ippoliti et al. (2003)	Lee et al. (2008)		Yitshak Sade et al. (2015)				

			Argacha et al. (2016)							
O_3			Tsai et al. (2012) Qiu et al. (2020) Argacha et al. (2016)	Qiu et al. (2020) Lee et al. (2008)		Yitshak Sade et al. (2015)	Qiu et al. (2020)			
SO_2		Xu et al. (2021)	Tsai et al. (2012)	Lee et al. (2008)		Yitshak Sade et al. (2015)				
CO			Tsai et al. (2012) D'Ippoliti et al. (2003) Qorbani et al. (2012)	Lee et al. (2008)		Yitshak Sade et al. (2015)				

* In bold: statistically significant difference between sub-groups ($p<0.05$).

4.2.4 Diabetes mortality and morbidity

A recent systematic review by Yang et al. (2020a) investigated the relationship between air pollution and type-2 diabetes (T2D) and glucose-homeostasis markers. They reviewed epidemiological studies assessing health effects of both long- and short-term exposure to outdoor air pollution including diabetics as a vulnerable group and used the Newcastle-Ottawa scale in combination with the Cochrane risk of bias tool for quality assessment. They concluded that there is evidence for adverse effects on T2D related to exposure to outdoor air pollution, particularly PM, and that diabetics might be more vulnerable to air pollution exposure, however, these conclusions were not mainly based on the findings of the effects of short-term exposure on diabetes mortality. For this association, they identified 11 time-series and case-crossover studies, six of which showed statistically significant estimates for air pollutants such as $PM_{2.5}$, PM_{10}, NO_2, O_3 and SO_2. They reported increased risks of death from diabetes by 6-49% for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ but did not perform a meta-analysis due to heterogeneity in design and the limited number of studies. We conducted an update search to identify studies published after the cut-off date of the Yang et al. (2020) review, i.e., May 2019, and identified nine papers that looked at the associations between air pollution exposure and diabetes mortality.

- Li et al. (2019) conducted a monthly time-series analysis in Ningbo, China, but this study was excluded from our review as one of the quality assessment criteria for time-series studies was to incorporate daily data.
- In a case-crossover analysis of the US Medicare database for 2000-2012, Wei et al. (2019) reported increased risks of diabetes hospitalisation (0.21% [0.13, 0.28%]) per 1 $\mu g/m^3$ increase in $PM_{2.5}$.
- Gu et al. (2020) also observed statistically significant increases in the risk of endocrine, nutritional, and metabolic diseases hospitalisation (0.24% [0.15, 0.32%] and 0.12% [0.02, 023%]) per 10 µg/m3 increase in $PM_{2.5}$ and O_3. This was a multi-city, time-series analysis in China, with data from 252 cities from 2013-2017. Similar results were reported by Du et al. (2022) based on a time-series study in Chongqing, China in 2013-2019, in which increased risks of diabetes hospitalisation (1.57% [0.48-2.65%]) per 10 $\mu g/m^3$ increase in NO_2 were observed.
- Another two time-series studies from China found statistically significant associations between diabetes mortality and air pollution. Yang et al. (2020b) found increased risks (0.53% [0.27, 0.80]) per 10 $\mu g/m^3$ increase in PM_{10} in 16 cities from 2007-2013, while Wu et al. (2021) reported increased risks of 1.10% [0.45, 1.75], 1.02% [0.52, 1.51], 1.59% [0.65, 2.53] and 3.84% [1.48, 6.19] per 10 $\mu g/m^3$ increase in lag02 $PM_{2.5}$, PM_{10}, NO_2 and SO_2 (lag03 for the latter).
- Sui et al. (2021) did not find statistically significant estimates on the associations between diabetes mortality and $PM_{2.5}$ or O_3 in a time-series analysis in Hefei, China, in 2013-2018.
- A time-series study in 110 provinces in Italy from 2013-2015 showed no statistically significant associations between diabetes/metabolic mortality and $PM_{2.5}$, PM_{10} or NO_2 (Gariazzo et al. 2023).
- Another time-series analysis in Seoul, Korea from 2005 to 2009 investigated the association between short-term exposure to air pollution (PM_{10}, NO_2, SO_2, CO and ozone) and emergency department visits for diabetes coma (n = 3,532 cases) (Kim et al. 2018). Using distributed-lag non-linear models, they reported statistically

significant associations for 18.42 ppb (IQR) increase in NO_2 at single lag 1 (increased risk: 12.5% [3.9, 21.9]) and cumulative lags 0-1 (12% [2.8, 21.9]) and 0-3 (9.2% [0.5, 18.6]). The findings for the other pollutants were not statistically significant.

- Finally, Luo et al. (2023) conducted a case-crossover analysis in 20 regions in China, from 2013-2021, and reported increased risks of diabetes hospitalisation of 2.08% [0.88, 3.29], 1.71% [0.56, 2.87], 4.85% [3.29, 6.44], 2.44 [1.22, 3.67] associated with increases in PM_{10} (per 51 $\mu g/m^3$), $PM_{2.5}$ (per 29 $\mu g/m^3$), NO_2 (per 26 $\mu g/m^3$) and SO_2 (per 11 $\mu g/m^3$) respectively but not with O_3.

Interestingly, the associations between short-term exposure to outdoor air pollution and diabetes mortality are consistent over the years and suggest an exposure-response relationship. This does not automatically mean that diabetics are more susceptible to air pollution than other groups. In fact, the effect sizes seem quite similar to those for $PM_{2.5}$-related all-cause mortality (Zanobetti et al., 2014; Alessandrini et al., 2016). It is unclear whether these deaths occur via a diabetes-specific mechanism e.g., diabetic coma or are a result of cardiovascular complications. In theory, the latter should not be coded as diabetes mortality but as cardiovascular mortality with diabetes the underlying cause of death (Morell et al., 2019). But as the coefficient for air pollution and diabetes mortality is small, it is still possible that this relates to the known association of air pollution with cardiovascular mortality, represented another way via small inconsistencies in ICD coding. Cardiovascular mortality is common amongst diabetics, indeed more common than in those without diabetes (Rosenquist and Fox, 2018).

Summary of epidemiological studies assessing the interaction of diabetes in associations between all-cause mortality, cause-specific mortality, cause-specific hospital admissions and exposure to ambient air pollution

- Epidemiological studies investigating air pollution exposure and increased all-cause mortality in diabetics generally compared diabetics to the total sample population (including diabetics and non-diabetics), rather than comparing to a non-diabetic subgroup only.

- Evidence for the presence of diabetes increasing all-cause mortality risk associated with particulate matter (based on only two studies), but no such findings in studies with gaseous pollutants. Geographic heterogeneity in existing studies is limited.

- No evidence for increased risk in diabetics for cause-specific mortality.

- Diabetes mortality was found to be associated with short-term exposure to ambient air pollution levels, but unclear whether this indicates a unique susceptibility or is mediated via already established links with cardiovascular disease.

- Of all studies assessing cause-specific hospital admissions, limited statistically significant evidence precludes any conclusive inference on increased vulnerability in diabetics, with evidence of effect modification in only some studies only for myocardial infarction, respiratory diseases (as a whole) and cardiac arrythmia in relation to $PM_{2.5}$, as well as cardiac arrythmia and cardiovascular disease in relation to PM_{10}.

4.3 Epidemiological and semi-experimental evidence from panel studies

The literature searches conducted to identify controlled human exposure studies that have evaluated whether metabolic stressors increase susceptibility to air pollution-related health effects (Appendix 1) uncovered a number of relevant experimental/individual level epidemiological/panel type studies.

Findings from these studies, plus additional ones identified from hand searching reference lists of the primary search results, that examined the relationship between short-term exposure to air pollution and health effects in populations with diabetes and/or obesity (compared with responses among non-diabetic/non-obese subjects) are summarised below and in Table 6.

4.3.1 Populations with diabetes

Studies comparing effects in diabetics versus non-diabetics have focused on endpoints that may contribute to underlying pathophysiological changes associated with the link between elevated concentrations of air pollutants (PM_{10}, $PM_{2.5}$, ozone, NO_2, SO_2) and risk of cardiovascular disease:

- Biomarkers of inflammation, (Liao et al., 2005, Dubowsky et al., 2006, Dabass et al., 2016, Lee et al., 2018)
- Biomarkers of haemostasis (Lee et al., 2018, Dabass et al., 2016, Liao et al., 2005)
- Biomarkers of oxidative stress (Dabass et al., 2016, Li et al., 2016)
- Heart rhythm disorders (Hampel et al., 2012, Park et al., 2005, Dahlquist et al., 2020).

Inflammation

- Amongst 44 seniors (≥ 60 years of age) residing in St Louis, Misssouri, Dubowsky et al. found larger associations between $PM_{2.5}$, averaged over 1 to 7 days, and C-reactive protein (CRP) in people with diabetes (n=8) (Dubowsky et al., 2006). For example, an IQR increase in the 5-day mean $PM_{2.5}$ (6.1 µg/m^3) was associated with a 12% increase in CRP (95% CI, -25-67%) for all individuals and a 74% (95% CI, 18-158) increase for diabetics. Individuals with diabetes also demonstrated significantly larger associations between $PM_{2.5}$ and IL-6, but the condition did not significantly modify white blood cell (WBC) counts.
- In a cross-sectional analysis from a nationally representative US adult sample (NHANES; all ages but an oversampling of ≥ 60 years), Dabass et al. reported stronger associations between 2 day lag (out of multiple different lags examined) $PM_{2.5}$ and WBC counts (but not CRP) among diabetics (n≈1760) compared to non-diabetics (n ≈14380) (Dabass et al., 2016).
- A significantly higher association between exposure to air pollutants and inflammatory markers (WBC counts and serum CRP) among diabetes (n=248) versus non-diabetics (n=6161) in a hospital-based cohort study in Korea was limited to WBC-NO_2 (Lee et al 2018).
- Liao et al. did not however observe a greater association between any criteria pollutants and WBC counts or serum albumin among middle-aged people with diabetes (n=919 versus n=9289 non-diabetics) enrolled in the US Atherosclerosis Risk in Communities (ARIC) study cohort (Liao et al., 2005).

Oxidative stress

Two studies looked at the vulnerability in people with diabetes to oxidative stress effects of air pollution.

- In the Boston-based Framingham Heart Study (mean age 64.1 years), stronger positive associations of black carbon and sulphate (but not $PM_{2.5}$) with blood myeloperoxidase (but not urinary 8-epi-PGF2α) were observed among participants with diabetes (n=569) compared to those without (n=1466) (Li et al., 2016).
- Dabass et al. reported stronger associations between 2-day lag $PM_{2.5}$ and homocysteine among diabetics compared to non-diabetics (Dabass et al., 2016).

Haemostasis

- Liao et al. reported that PM_{10} was significantly associated with 3.93% higher vWF among diabetics but not non-diabetics (Liao et al., 2005), but no increased response with respect to fibrinogen and Factor VIII-C, in line with observations from others (Dabass et al., 2016, Lee et al., 2018).

Heart rhythm disturbances

Three studies have looked at the susceptibility of diabetics to heart rhythm disturbances following short-term exposure to increased concentrations of air pollution.

- Among a group of 75 and 76-year old in Stockholm undergoing ambulatory ECG monitoring, the association between increased concentrations of PM_{10} and ozone (not $PM_{2.5}$ or NO_2) and the risk of atrial fibrillation was significantly greater among participants with diabetes (n=24) versus those without the condition (n=193) (Dahlquist et al., 2020).
- In the Normative Aging Study (mean age 72.7 years), Park et al observed a larger (but not significant) reduction in heart rate variability (HRV) in relation to $PM_{2.5}$ among people with diabetes (n=72) compared with subjects without diabetes (n=425) (Park et al., 2005). Diabetes did not modify the effect of ozone on HRV. A sustained reduction in HRV in patients with diabetes has been associated with increased risk of mortality (Gerritsen et al 2001).
- Hampel et al. investigated the effects of ozone on heart rate and repolarization parameters in individuals (mean age 61.6 years) recruited from the KORA (Cooperative Health Research in the Region of Augsburg) follow up (Hampel et al., 2012). The population included subjects with diabetes or impaired glucose tolerance indicating an enhanced risk of diabetes (n=64) and healthy individuals with a potential genetic predisposition on detoxification pathways (n=46). Increases in heart T-wave flattening and T-wave complexity in association with increments in ozone were stronger (but not significantly so) in individuals with diabetes or prediabetes. A normal T-wave loop is long and narrow whilst an abnormal one is wider, usually represented by lower and flatter T-waves and has greater complexity. Flattened T-waves may represent ischemia or an electrolyte abnormality.

Summary of panel studies investigating increased susceptibility to air pollution-related health effects in populations with diabetes

- Studies comparing effects in diabetics versus non-diabetics have focused on biomarkers of inflammation, haemostasis and oxidative stress as well as heart rhythm disorders.

- Larger associations between exposure to air pollutants and increased inflammatory markers among diabetics have been reported, but not consistently so, for $PM_{2.5}$ and NO_2 and CRP, IL6 and WBC counts.

- Limited evidence was uncovered that people with diabetes have a greater vulnerability to oxidative stress effects of air pollution.

- One study reported a significant association between PM_{10} and the thrombotic marker vWF (but not fibrinogen or Factor VIII-C) among diabetics that was not observed in non-diabetics.

- Studies suggest that diabetics may be more susceptible to heart rhythm disorders following increased concentrations of PM and O_3.

Table 6 - Panel studies investigating the health effects of air pollution in diabetic versus non-diabetic subjects.

Study	**Comparison groups (n; definitions)**	**Age**	**Pollutant (conc; lags)**	**Endpoints**
Dahlquist et al 2020	Diabetic (24; no definition) Non-diabetic (193)	75/76-year-olds	PM_{10} (ambient 24-h mean: 10.8 µg/m^3) 12–24 h moving averages	Atrial Fibrillation*
Lee et al 2018	Diabetic (428; definition not reported) Not diabetic (6161)	90% <60	PM_{10} (day of blood draw mean: 46.7 µg/m^3) 1,2,3,4,6,8	Markers of systemic inflammation: CRP Ferritin Fibrinogen WBC counts
Liao et al 2005	Diabetic (919; defined as fasting (8 h) serum glucose ≥140mg/dl, Non-fasting glucose ≥200mg/dl, history of physician diagnosed diabetes, or use of an oral hypoglycemic agent or insulin Not diabetic (9289)10 SDNN Log10 HF Log10 LF Log10 LF:HF	54	PM_{10} (1 day prior to blood draw mean: 29.9)	CV (Haemostatic & inflammatory markers): Fibrinogen Factor VIII-C VWF* Albumin WBC counts * One SD increment of PM_{10} (12.8 mg/m3) was significantly (P<0.05) associated with 3.93% higher of vWF among diabetics
Dubowsky et al 2006	Diabetic (8; defined by report of a doctor diagnosis or use of diabetes medications) Non-diabetic (36)	≥ 60	$PM_{2.5}$ (1-d mean: ambient 6 µg/m^3) 1,2,3,4,5,6,7 d moving averages	CV (Markers of systemic inflammation): CRP* (with 4, 5 & 6-d mean) IL-6* (with 4, 5 & 6-d mean) WBC counts
Lee et al 2018	Diabetic (428; definition not reported)	90% <60	$PM_{2.5}$ (day of blood draw mean: 24.9 µg/m^3)	Markers of systemic inflammation:

	Not diabetic (6161)		1,2,3,4,6,8	CRP Ferritin Fibrinogen WBC counts
Li et al 2016	Diabetic (569; definition not reported) Not diabetic (1466)	Mean: 64.1	$PM_{2.5}$ (1-Day moving average: 9.86 $\mu g/m^3$) 1,2,3,5,7 moving averages	Markers of oxidative stress: Plasma myeloperoxidase Urine 8-epi-PGF_{2a}
Dabass et al 2016	Diabetic (1763 / 1759 / 1139 / 318 for each biomarker respectively; self-report of physician diagnosed) Not diabetic (14397 / 14377 / 10085 / 2143)	NHANES study. All ages, with oversampling of minorities and the elderly (African Americans, Mexican Americans and ≥ 60 years of age)	$PM_{2.5}$	Biomarkers of cardiovascular disease risk: CRP WBC count* - lag2 Homocysteine* - lag2 Fibrinogen
Dahlquist et al 2020	Diabetic (24; no definition) Non-diabetic (193)	75/76 year-olds	$PM_{2.5}$ (ambient 24-h mean: 4.3 $\mu g/m^3$) 12–24 h moving averages	Atrial Fibrillation
Park et al 2000	Diabetic (72; defined by a physician's diagnosis of type 2 diabetes and/or use of a diabetes medication [e.g., oral hypoglycemic drug, metformin, or Insulin]) Non-diabetic (425)	72.7	$PM_{2.5}$ (24 h moving avergae: 11.4 $\mu g/m^3$) 48 h moving average	CV (HRV): Log_{10} SDNN Log_{10} HF Log_{10} LF Log_{10} LF:HF
Dahlquist et al 2020	Diabetic (24; no definition) Non-diabetic (193)	75/76-year-olds	O_3 (ambient 24-h mean: 50.2 $\mu g/m^3$) 0–12 h moving averages	Atrial Fibrillation*
Hampel et al 2012	Diabetic (64; individuals with type 2 diabetes or impaired glucose tolerance (32 of each))	Mean 61.6, SD 11.7 years	O_3 (Concurrent and 1-4h delayed effects of 1h averages of ozone)	Heart rate T-wave amplitude

	Non-diabetic (46; healthy individuals with a potential genetic pre-disposition on the detoxification pathways)			T-wave complexity
Lee et al 2018	Diabetic (428; definition not reported) Not diabetic (6161)	90% <60	O_3 (day of blood draw mean: 30 ppb) 1,2,3,4,6,8	Markers of systemic inflammation: CRP Ferritin Fibrinogen WBC counts
Li et al 2016	Diabetic (569; definition not reported) Not diabetic (1466)	Mean: 64.1	O_3 (1-Day moving average 20 ppb) 1,2,3,5,7 moving averages	Markers of oxidative stress: Plasma myeloperoxidase Urine 8-epi-PGF_{2a}
Liao et al 2005	Diabetic (919; defined as fasting (8 h) serum glucose ≥140mg/dl, Non-fasting glucose ≥200mg/dl, history of physician diagnosed diabetes, or use of an oral hypoglycemic agent or insulin Not diabetic (9289)	54	O_3 (1 day prior to blood draw mean: 40 ppb)	CV (Haemostatic & inflammatory markers): Fibrinogen Factor VIII-C VWF Albumin WBC counts
Park et al 2000	Diabetic (72; defined by a physician's diagnosis of type 2 diabetes and/or use of a diabetes medication [e.g., oral hypoglycemic drug, metformin, or Insulin]) Non-diabetic (425)	72.7	O_3 (24 h moving average: 23 ppb 48 h moving average	CV (HRV): Log_{10} SDNN Log_{10} HF Log_{10} LF Log_{10} LF:HF
Lee et al 2018	Diabetic (428; definition not reported) Not diabetic (6161)	90% <60	NO_2 (day of blood draw mean: 35.8 ppb)	Markers of systemic inflammation:

			1,2,3,4,6,8	CRP Ferritin Fibrinogen WBC counts* (d1,2,3,4,6,8)
Li et al 2016	Diabetic (569; definition not reported) Not diabetic (1466)	Mean: 64.1	NOx (1-Day moving average: 40 pb) 1,2,3,5,7 moving averages	Markers of oxidative stress: Plasma myeloperoxidase Urine 8-epi-PGF_{2a}
Liao et al 2005	Diabetic (919; defined as fasting (8 h) serum glucose ≥140mg/dl, Non-fasting glucose ≥200mg/dl, history of physician diagnosed diabetes, or use of an oral hypoglycemic agent or insulin Not diabetic (9289)	54	NO_2 (1 day prior to blood draw mean: 20 ppb)	CV (Haemostatic & inflammatory markers): Fibrinogen Factor VIII-C VWF Albumin WBC counts
Lee et al 2018	Diabetic (428; definition not reported) Not diabetic (6161)	90% <60	SO_2 (day of blood draw mean: 5.3 ppb) 1,2,3,4,6,8	Markers of systemic inflammation: CRP Ferritin Fibrinogen WBC counts
Liao et al 2005	Diabetic (919; defined as fasting (8 h) serum glucose ≥140mg/dl, Non-fasting glucose ≥200mg/dl, history of physician diagnosed diabetes, or use of an oral hypoglycemic agent or insulin Not diabetic (9289)	54	SO_2 (1 day prior to blood draw mean: 5 ppb)	CV (Haemostatic & inflammatory markers): Fibrinogen Factor VIII-C VWF Albumin WBC counts

*Denotes statistically significant effect modification by diabetes

4.3.2 Obese populations

Several studies investigating differential susceptibility to short-term exposure to air pollution in obese versus non-obese subjects have examined

- Lung function (Alexeeff et al., 2007, Rice et al., 2013).
- Endpoints linked to an increased risk of cardiovascular disease:
    - Biomarkers of inflammation (Dabass et al., 2016, Dubowsky et al., 2006, Hu et al., 2021, Wang et al., 2022).
    - Biomarkers of haemostasis (Hu et al., 2021, Dabass et al., 2016, Ossoli et al., 2022)
    - Biomarkers of oxidative stress (Dabass et al., 2016, Li et al., 2016).
    - Blood pressure (Chung et al., 2015, Wang et al., 2022).
    - Heart rhythm disorders (Li et al., 2021, Dahlquist et al., 2020)
    - Metabolic health indicators (Wang et al., 2022, Hu et al., 2021).

Lung function

- In the Normative Aging Study (elderly men, most of whom were white with a mean age 68.8 years), obesity was reported to modify the acute effect of ozone on lung function (Alexeeff et al., 2007). For a 15 ppb increase in ozone, obese subjects (n=206) were estimated to have greater drops in FEV1 (-0.96%; 95% CI, -1.70 to -0.20 versus -0.96%; 95% CI, -1.70 to -0.20%) and FVC (-2.05%; 95% CI, -3.17 to -0.91 versus -1.18%; 95% CI, -1.88 to -0.48) than the non-obese (n=698).
- Obese individuals also had a significantly larger decrease in FEV_1 in association with previous-day ozone exposure than non-obese participants in the Framingham Heart Study (Rice et al., 2013). In the obese, a 10-ppb increase in ozone was associated with a lower 30.4-ml lower FEV_1 (95% CI, 247.0, 213.7) compared with a 12.4-ml lower FEV_1 (95% CI, 226.4, 1.7) in the non-obese.

Inflammation

- In the population of 44 seniors residing in St Louis, Dubowsky et al. found larger associations between $PM_{2.5}$ and CRP (but not IL-6 or WBC counts) in 14 individuals with obesity (Dubowsky et al., 2006). An interquartile increase in the 5-day mean $PM_{2.5}$ (6.1 µg/m^3) was associated with a 12% increase in CRP (95% CI, -25-67%) for all individuals and a 48% (95% CI, 5.3-109) increase for people with obesity.
- An increase in ambient $PM_{2.5}$ was not however associated with increased levels of CRP or WBC counts amongst obese NHAMES participants (n≈5400) compared to non-obese subjects (n≈10,700) (Dabass et al., 2016).
- A study in Beijing, has investigated effects of ambient ozone and $PM_{2.5}$ concentrations (at multiple different lags) on multiple proinflammatory biomarkers in a younger population (18-26 years) of obese (n=39-44) and normal weight (n=49-53) adults (Hu et al., 2021, Wang et al., 2022). Indicators that were negatively affected by ozone to a greater extent in obese people compared to normal weight people, were leptin (lag 05), eosinophil proportion (lag 07) and neutrophil proportion (lag 05) (Wang et al., 2022), while increases in MCP-1 (at lag 04) were associated with $PM_{2.5}$ in the obese group only (Hu et al., 2021).

Oxidative stress

No evidence has been found of differing associations between air pollutants and biomarkers of oxidative stress by obesity (Dabass et al., 2016, Li et al., 2016).

Haemostasis

- Ossoli et al. studied the modifying effect of BMI on the relationship between exposure to PM and HDL function in obese (n=42), overweight (n=26) and normal weight (n=23) subjects (mean age 52.1 years) in Milan (Ossoli et al., 2022). HDL function was assessed as promotion of nitric oxide release by endothelial cells (which progressively declined with the increase in BMI) and reduction in cholesterol in macrophages (which was independent of BMI). No association was found between HDL function and $PM_{2.5}$ or PM_{10} exposure, but a modifying effect of BMI was observed in that the positive association between PM_{10} exposure at day −1 and NO production found in subjects with a normal BMI was lost in participants with higher BMI. Similar results were obtained for the reduction in macrophage cholesterol.
- Studies investigating pro-coagulant effects of $PM_{2.5}$ have observed a significant effect modification of obesity on an association with sCD40L (Hu et al., 2021) but no increased response in obese subjects with respect to fibrinogen (Dabass et al., 2016).

Blood pressure and heart rhythm disturbances

- An analysis of associations between PM (particle number count (PNC), $PM_{2.5}$, BC) with systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) in 220 individuals (mean age 58.5 years) from the Boston-based CAFEH (Community Assessment of Freeway Exposure and Health) study observed that PNC in the preceding day were significantly associated with a higher DBP (Chung et al., 2015). The positive associations of DBP with PNC were more pronounced among obese (n=68) than non-obese individuals (n=122).
- The effect of $PM_{2.5}$ on heart rate and HRV in the obese and normal weight young adults in Beijing was examined using personal monitors and fixed monitoring sites and dividing the study period into waking and sleeping hours (Li et al., 2021). When the fixed monitoring measurement was used, no significant associations were found between HR and HRV and $PM_{2.5}$ exposure in both groups during the whole day. After dividing the study period into waking and sleeping hours, HR had a negative association with ambient $PM_{2.5}$ exposure during waking hours but not significantly more so in the obese group.
- Among the Stockholm residents, the association between increased concentrations of PM_{10} and ozone (not $PM_{2.5}$) and the risk of atrial fibrillation was significantly greater among overweight participants (BMI >25; n=128) compared to those with a BMI <25 (n=92) (Dahlquist et al., 2020).

Metabolic health

Studies of the younger Beijing population examined effects of ambient ozone and $PM_{2.5}$ concentrations (at multiple different lags) on multiple indicators of insulin resistance, glucose homeostasis and lipid metabolism (Hu et al., 2021, Wang et al., 2022). Indicators that were negatively affected by ozone to a greater extent in obese people compared to normal weight people were C-peptide (lag 07), high-density lipoprotein cholesterol (HDL-C), (lag 07), low-

density lipoprotein cholesterol (LDL-C) (lag 05), non-HDL-C (lag 05) and non-HDL-C/HDL-C (lag 03) (Wang et al 2022).

Summary of panel studies investigating increased susceptibility to air pollution-related health effects in obese populations

- Studies comparing effects in obese versus non-obese have focused on lung function, biomarkers of inflammation, haemostasis and oxidative stress, heart rhythm disorders and metabolic health indicators.
- Studies are consistent in findings of greater decreases in lung function in association with ozone exposure in obese compared to non-obese people.
- Limited evidence exists from the studies reviewed of larger associations between exposure to air pollutants and increased inflammatory markers among people with obesity.
- No evidence was uncovered suggesting that obese people have a greater vulnerability to oxidative stress effects of air pollution.
- The compensatory response, involving HDL's ability to induce NO production with exposure to PM_{10}, in subjects with a normal weight is progressively lost with increasing BMI.
- Increases in sCD40L (a marker of platelet activation) in association with $PM_{2.5}$ has been found in obese but not in normal weight adults.
- More pronounced associations between concentrations of PM_{10} and ozone and atrial fibrillation have been reported among overweight individuals.
- One study observed (at selected lags) stronger associations between ozone concentrations and markers of glucose homeostasis and lipid metabolism in obese compared to normal weight people.

Table 7 - Panel studies investigating the health effects of air pollution in obese versus non-obese subjects

Study	Comparison groups (n; definitions)	Age	Pollutant (conc; lags)	Outcome
Dahlquist et al 2020	Obese (128; BMI>25) Non-obese (98)	75/76-year-olds	PM_{10} (ambient 24-h mean: 10.8 µg/m^3) 12-24h moving averages	Atrial Fibrillation*
Ossoli et al 2020	Obese (42; BMI>30) Overweight (26; 25<BMI<30) Normal weight (23; BMI<25)	Mean age 52.1 years (SD = 9.6); 70% females	PM_{10}	Biological samples: NO production* HDL-mediated reduction in macrophage cholesterol mass*
Chung et al 2015	Obese (68; no definition) Non-obese (122)	Mean age 58 years (SD = 12); mainly middle aged, white, females, living near a major highway	$PM_{2.5}$	Diastolic blood pressure Systolic blood pressure Pulse pressure
Dabass et al 2016	Obese (5438 / 5431 / 3629 / 781 for each biomarker respectively; BMI>30) Not obese (10722 / 10705 / 7595 / 1680)	NHANES study. All ages, with oversampling of minorities and the elderly (African Americans, Mexican Americans and ≥ 60 years of age)	$PM_{2.5}$	Biomarkers of cardiovascular disease risk: CRP WBC count Homocysteine Fibrinogen
Dahlquist et al 2020	Obese (128; BMI>25) Non-obese (98)	75/76 year-olds	$PM_{2.5}$ (ambient 24-h mean: 4.3 µg/m^3)	Atrial Fibrillation

			12–24 h moving averages	
Dubowsky et al 2006	Obese (14; defined as BMI ≥ 30 kg/m^2) Non-obese (30)	≥ 60	$PM_{2.5}$ (1-d mean: 6 µg/m^3) 1,2,3,4,5,6,7 d	CV (Markers of systemic inflammation): CRP* (with 3 & 4-d mean) IL-6 WBC counts
Hu et al 2021	obese (>28kg/m^3; n = 44) vs normal weight (n = 53)	18 – 26	$PM_{2.5}$ 24-h means **Increment**: IQR increase (36.3µg/m^3) Lag 01 - 07	**Biomarker, exposure lag and p-value for interaction** **Proinflammatory markers:** WBC lag05 0.124 Leptin lag05 0.059 TNF-α lag05 0.388 MCP-1 lag04 0.043* MIP-1α lag05 0.144 IL-1β lag04 0.951 IL-6 lag05 0.089 IL-8 lag04 0.521 MPO lag04 0.335 Fractalkine lag06 0.967 PAI-1 lag05 0.657 **Insulin resistance:** FPG lag07 0.789 C peptide lag01 0.052 HOMA-IR lag06 0.511 **Platelet activation:** PLT lag06 0.502 MPV lag07 0.633 sCD40L lag07 0.048* sP-selectin lag02 0.120 PAgT lag07 0.947

Li et al 2021	obese (>28kg/m^3; n = 44) vs normal weight (n = 53)	18 – 26	$PM_{2.5}$ **Increment**: IQR increase (25.38µg/m^3)	**Biomarker, % change in normal-weight, % change in obese and p-value for interaction:** **Waking hours** SDNN (ms), 4.28 (-0.81, 9.62), 0.30 (-3.25, 3.98), 0.216 Total power (ms^2), 6.03 (-2.47, 15.26), 0.03 (-7.36, 7.80), 0.117 HF (ms^2), 2.55 (-8.50, 14.94), -18.11 (-23.14, -12.75), 0.018* LF (ms^2), 2.33 (-5.49, 10.79), 0.10 (-7.68, 8.54), 0.269 LF/HF, 8.94 (-0.23, 18.94), 20.67 (12.41, 29.54), 0.112 HR (bpm), -1.10 (-3.28, 1.14), 2.81 (0.95, 4.69), 0.010* **Sleeping hours** SDNN (ms), 5.24 (-9.44, 22.31), -1.12 (-17.45, 18.44), 0.243 Total power (ms^2), 17.30 (-11.76, 55.94), -28.79 (-42.20, -12.26), 0.176 HF (ms^2), 28.9 (5.85, 57.17), 78.32 (31.39, 142.01), 0.177 LF (ms^2), 12.72 (-21.09, 61.00), 11.78 (-23.71, 63.79), 0.368 LF/HF, -3.79 (-25.34, 23.98), -9.90 (-38.61, 32.24), 0.318 HR (bpm), 14.03 (8.38, 19.98), -7.89 (-12.19, -3.38), <0.001*
Li et al 2016	Obese (1077; definition not reported) Not obese (2309)	Mean: 64.1	$PM_{2.5}$ (1-Day moving average: 9.86 µg/m^3) 1,2,3,5,7 moving averages	Markers of oxidative stress: Plasma myeloperoxidase Urine 8-epi-PGF_{2a}
Ossoli et al 2020	Obese (42; BMI>30) Overweight (26; 25<BMI<30) Normal weight (23; BMI<25)	Mean age 52.1 years (SD = 9.6 years); mainly females (70%)	$PM_{2.5}$	Biological samples: NO production HDL-mediated reduction in macrophage cholesterol mass
Alexeeff et al 2007	Obese (206; defined as BMI ≥ 30 kg/m^2)	68.8 (mean)	O_3	Respiratory (AHR): FEV_1*

	Non-obese (698)		(48-h mean: 24.4 ± 11 ppb) 48-8	FVC For a 15-ppb increase O_3, obese had greater drops in FEV_1 & FVC. Interaction between O_3 & obesity was significant for FEV_1. Same exposure was associated with greater declines in FEV_1 & FC for those with AHR but only significant for FEV_1. Also evidence of interaction between obesity & AHR that modifies decrease in lung function from O_3 exposure.
Li et al 2016	Obese (1077; definition not reported) Not obese (2309)	Mean: 64.1	O_3 (1-Day moving average: 20 ppb) 1,2,3,5,7 moving averages	Markers of oxidative stress: Plasma myeloperoxidase Urine 8-epi-PGF_{2a}
Rice et al 2013	Obese (n not reported; defined as BMI > 30 kg/m^2) Non-obese (n not reported)	51.8	O_3 (day prior to spirometry mean: 28.7 ppb) Previous day	Respiratory: FEV_1* FVC *In obese participants, a 10-ppb increase in previous-day O_3 was associated with a 30.4-ml lower FEV_1 (95% CI, 247.0, 213.7) compared with a 12.4-ml lower FEV_1 (95% CI, 226.4, 1.7) in the non-obese ($P_{interaction}$ = 0.010)
Wang et al 2022	MHO (39; defined as BMI ≥ 28 kg/m^2 MH-NW (49; defined as BMI 18.5-24 kg/m^2	23.4 (mean)	O_3 (26.2 µg/m3 - daily adjusted based on environ. monitoring & time activity diary) 1,2,3,4,5,6,7 d	Metabolic Blood pressure indicators: • SBP • DBP • PP* (lag 04) Glucose homeostasis indicators • FPG • FINS • C-peptide* (lag07)

				• HOMA-R Lipid metabolism indicators: • TC • TG • HDL-C* (lag 07) • LDL-C* (lag 05) • Non-HDL-C • TC/HDL-C* • non-HDL-C/HDL-C* (lag 03) • LDL-C/HDL-C • TG/HDL-C* (lag 07) Inflammatory indicators • Leptin* (lag05) • Eosinophil counts • Eosinophil proportion* (lag 07) • Lymphocyte counts • Lymphocyte proportion • Monocyte counts • Monocyte proportion • Neutrophil counts • Neutrophil proportion* (lag05) • MCP-1 • MCP-1α • MPO • IL-1β • IL-6 • TNFα • SAA • IL-8 • MBC count

				• PLT • NLR • PLR • sCAM-1 • Fractalkine • PAI-1
Dahlquist et al 2020	Obese (128; BMI>25) Non-obese (98)	75/76 year-olds	O_3 (ambient 24-h mean: 50.2 µg/m^3) 0–12 h moving averages	Atrial Fibrillation*
Li et al 2016	Diabetic (569; definition not reported) Not diabetic (1466)	Mean: 64.1	NOx (1-Day moving average: 40 pb) 1,2,3,5,7 moving averages	Markers of oxidative stress: Plasma myeloperoxidase Urine 8-epi-PGF_{2a}

*Denotes statistically significant effect modification by obesity

AHR: airway hyperresponsiveness; BMI: body mass index; DBP: diastolic blood pressure; FINS: fasting insulin; FPG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; HF: high frequency power; HOMA-IR: homoeostasis model assessment of insulin resistance index; IL: interleukin; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-8: interleukin-8; LDL-C: low-density lipoprotein cholesterol; LF: low frequency power; LF/HF: ratio of low–high frequency power; MCP-1: monocyte chemotactic protein-1; MH-NW: metabolically health normal weight; MIP-1α: macrophage inflammatory protein-1α; MHO: metabolically healthy obese; MPO: myeloperoxidase; MPV: mean platelet volume; PAgT: platelet aggregation rate; PAI-1: plasminogen activator inhibitor-1; PLT: platelet; PP: pulse pressure; SAA: serum amyloid A; SBP: systolic blood pressure; sCD40L: soluble CD40 ligand; SDNN: standard deviation of all normal-to-normal intervals; TC: total cholesterol; TG: triglycerides; TNF-α: tumor necrosis factor-α; WBC: white blood cell count;

Green cells represent studies using the same study sample.

4.4 Controlled human exposure studies

4.4.1 Literature searches – overview of studies

The literature searches conducted through PubMed and Web of Science, plus supplementary methods, identified 12 publications. Detailed tabular summaries of the methodology can be found in Appendix 1. An abbreviated description of study-specific details methodology appears in Tables Table 8, Table 9 and Table 10.

- Six publications evaluated the effects of DE exposure.
- One publication evaluated the effects of $PM_{2.5}$ from a busy street.
- One publication evaluated the effects of ambient ultrafine (UFP; $PM_{0.1}$) concentrated ambient particles (UCAPs).
- Two publications evaluated the effects of elemental carbon UFPs.
- Two publications evaluated the effects of O_3.

Seven publications included participants with MetS, 3 included overweight/obese subjects and 2 included diabetics.

With the exception of a retrospective ozone re-analysis (Bennett et al., 2007), all studies utilised a crossover design in which each subject inhales both clean air and on a separate occasion, the air pollutant under investigation. Of the 11 studies, 6 included a healthy control group. The endpoints assessed pertained to oxidative stress, inflammation, cardiovascular outcomes and respiratory outcomes.

4.4.2 Diesel exhaust exposures

Studies evaluating the effects of DE reside from a research group at the University of Washington (Table 8). They have investigated endpoints pertaining to oxidative stress, inflammation and cardiovascular outcomes in subjects with MetS, fulfilling any three of the following five criteria:

- Waist circumference ≥102 cm in males and ≥ 88 cm in females.
- Triglycerides ≥ 150 mg/dL.
- High-density lipoprotein (HDL) cholesterol < 40 mg/dL in males and < 50 mg/dL in females.
- Systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥ 85 mmHg.
- Fasting glucose ≥ 100 mg/dL

Oxidative stress

Despite robust evidence from CHE studies supporting the presence of both systemic and pulmonary oxidative stress in healthy and asthmatic subjects following DE exposure at 300 $\mu g/m^3$ PM (DE300) (Pourazar et al., 2005, Pettit et al., 2012, Jiang et al., 2014), a study of subjects with MetS exposed to DE200 for 2 hours was unable to detect increased markers of oxidative stress or an antioxidant response (Allen et al., 2009). This may reflect adaptations within the MetS participants to the chronic oxidative challenge associated with their condition.

Cardiovascular disease-related endpoints

A number of pathophysiological mechanisms thought to underlie the association between air pollution exposure and cardiovascular disease has been explored in subjects with MetS exposed to DE, including an impairment of vascular function, thrombosis and cardiac dysfunction.

- A study of participants with and without MetS assessed effects of DE100 and DE200 exposure on vascular tone and mediators thereof (Peretz et al., 2008a). Following DE200, acute vasoconstriction was reported, along with increased plasma concentrations of endothelin-1. Both responses were greater in healthy participants. This may be artifactual owing to small numbers of healthy subjects with paired pre and post exposure data and/or the higher variability of their baseline brachial artery diameter (Bad) compared with MetS individuals. Alternatively, biological explanations include greater vessel plasticity amongst healthy participants and with that, a greater responsiveness to DE exposure.
- A study evaluating a propensity of thrombus formation in individuals with MetS (Carlsten et al., 2008) after exposure to DE100 or DE200 was unable to demonstrate a subclinical hyperprothrombotic state. This was also the case in an earlier study by the same group of workers in which healthy volunteers underwent identical exposures (Carlsten et al., 2007).
- In another study, healthy, but not MetS subjects demonstrated an increase in platelet count a day following DE200 exposure (Krishnan et al., 2013). It was postulated that since the MetS subjects were older, age-related inflammatory process and/or impaired bone marrow function might have blunted the response reported in the healthy subjects.
- A study involving healthy and MetS subjects found no consistent effect of DE100 or DE200 exposure on heart rate variability (Peretz et al., 2008b). Another study found that exposure to DE200 did not significantly affect DBP but did increase SBP by an average of 4.4 mmHg post-exposure (Cosselman et al., 2012). Metabolic syndrome did not modify this effect and no significant effect on heart rate was reported.

Table 8 - Diesel exhaust controlled human exposure studies.

Study	Population, n, sex, age (range or mean ±SD)	Exposure details (concentration, duration)	Endpoints examined
Allen et al 2009	Subjects with MetS n=4 female, n=6 male Age: 31-48 y	FA, 2h DE ($PM_{2.5}$ =200 µg/m^3), 2h	Urinary 8-isoPGF2α, 24 PE Urinary 8-OHdG, 24 PE Plasma AA, 24 PE
Peretz et al 2008a,b	Healthy Subjects n=3 male Age: 24-39 Subjects with MetS n=5 female, n=8 male Age: 31-48 y	FA, 2h DE ($PM_{2.5}$ =100 µg/m^3), 2h DE ($PM_{2.5}$ =200 µg/m^3), 2h	Bad FMD Blood ET-1 Blood catecholamines HRV
Carlsten et al 2008	Subjects with MetS n=6 female, n=10 male Age: 25-48 y	FA, 2h DE ($PM_{2.5}$ =100 µg/m^3), 2h DE ($PM_{2.5}$ =200 µg/m^3), 2h	Blood D-dimer Blood vWF Blood PAI-1
Krishnan et al 2013	Healthy Subjects Age: 28 y Subjects with MetS Age: 41 y	FA, 2h DE ($PM_{2.5}$ =200 µg/m^3), 2h	Blood platelets
Cosselman et al 2012	Healthy Subjects Age: 20-36 y Subjects with MetS Age: 32-48 y	FA, 2h DE ($PM_{2.5}$ =200 µg/m^3), 2h	DBP SBP HR

8-OHdG; 8-hydroxy-2'-deoxyguanosine; 8-isoPGF2α: 8-Iso-Prostaglandin F2α; Bad: brachial artery diameter; ET-1: endothelin-1; DE: diesel exhaust; FA: filtered air; FMD: endothelium-dependent flow-mediated dilation; HRV: heart rate variability; MetS: metabolic syndrome; PAI-1: plasminogen activator inhibitor-1; PE: post exposure; vWF: von Willebrand factor;

Summary of DE exposures in subjects with MetS

- Controlled human exposure studies involving participants with MetS provide no evidence of increased susceptibility to oxidative stress or cardiovascular endpoints following a 2-hour exposure to DE.
- It is possible that the chronic oxidative/inflammatory state experienced by individuals with MetS is sufficient to upregulate the expression of antioxidant enzymes and other protective mechanisms to an extent that overcomes any insult of the DE exposure.
- Such an explanation is not however supported by laboratory evidence that suggests subjects with MetS have depleted antioxidant capabilities (Ford et al 2003, Palmieri et al 2006).

4.4.3 Particle exposures

Controlled human particles exposure studies in subjects with metabolic disturbances have employed urban street air (Hemmingsen et al., 2015), ambient UCAPs (Devlin et al., 2014) and elemental carbon UFPs (Stewart et al., 2010, Vora et al., 2014) (Table 9).

All studies focused on cardiovascular responses. None included a healthy comparator group of subjects.

- Hemmingsen et al (2015) studied a group of overweight (body mass index > 25 kg/m^2) middle-aged and elderly subjects were underwent 5-hour exposure to particle-filtered or sham-filtered air from an urban street on vasomotor function and HRV (Hemmingsen et al., 2015). Sham-filtered urban street air was associated with decreased vasodilation and HRV, but this could not be explained by changes in inflammation or oxidative stress.
- In a MetS cohort exposed for 2 hours to ambient UCAPs, no signs of endothelial dysfunction or changes in blood pressure were observed whilst changes in cardiac repolarization and HRV were only observed in a subgroup of individuals carrying the null allele for GSTM1 (Devlin et al., 2014). Exposure was associated with a decrease in markers of fibrinolysis and an increase in inflammatory mediators. The same group of workers published an earlier study in which healthy young volunteers were exposed to similar concentrations of UCAPs using the same exposure system (Samet et al., 2009). The magnitude of changes in cardiac repolarization, HRV and proteins associated with fibrinolysis in both studies were comparable.
- The effects of a 2-hour exposure to UFPs, in this case freshly generated elemental carbon, have also been investigated in subjects with stable type 2 diabetes, but otherwise healthy (Stewart et al., 2010, Vora et al., 2014). Vascular effects comprised a transient activation of platelets and increased plasma von Willebrand factor immediately after exposure but no effects on plasma tissue factor, coagulation factors VII or IX, or D-dimer (Stewart et al., 2010). Effects on cardiac function constituted reduced HRV and an unexpected delayed (24-48 post exposure) increase in heart rate (Vora et al., 2014). There were no effects on parameters of cardiac repolarisation or cardiac rhythm. No significant relationships between any of the significant UFP exposure effects and BMI were found. In a study of healthy, younger, non-diabetic subjects, tested under similar conditions by the same group of researchers, no effects on heart rate, and generally non-significant effects on HRV and cardiac repolarization were reported (Zareba et al., 2009).

Table 9 - Controlled human exposure studies: PM.

Study	Population, n, sex, age (range or mean ±SD)	Exposure details (concentration, duration)	Endpoints examined
Hemmingsen et al 2015	Overweight Subjects (BMI > 25kg/m^2) N=35 female, n=25 males Age: 55-83 y	FA ($PM_{2.5}$: ~1800/cm^3; 3µg/m^3), 5h Urban street air (($PM_{2.5}$: ~23.000/cm^3; 24 µg/m^3), 5h	HRV Vasodilation CRP WBC counts Ascorbate/dehydroascorbate, nitric oxide-production cofactor tetrahydrobiopterin and the oxidation product dihydrobiopterin
Devlin et al 2014	Subjects with MetS	Ambient UCAPS (189,000 particles/cm^3; 98 µg/m^3), 2h	Bad BP HRV Blood plasminogen Blood thrombomodulin CRP Serum amyloid A
Stewart et al 2010, Vora et al 2014	Subjects with type 2 diabetes N= 13 obese (BMI > 30 kg/m^2), n=6 non obese N= female, n= male Age:	Elemental carbon UFP (~10^7 particles/cm^3), 2h	Platelets Plasma vWF Plasma TF Coagulation factors VII & IX D-dimer HRV HR

Bad: brachial artery diameter; ET-1: endothelin-1; FA: filtered air; FMD: endothelium-dependent flow-mediated dilation; HRV: heart rate variability; MetS: metabolic syndrome; PAI-1: plasminogen activator inhibitor-1; PE: post exposure; vWF: von Willebrand factor;

Summary of particle exposures in subjects with metabolic disturbances

- The small numbers of studies are very heterogeneous with respect to exposures (urban street $PM_{2.5}$, ambient UCAPs, carbonaceous UFPs) and the type of metabolic disturbances of the recruited participants (overweight, MetS, diabetics).
- Moreover, the absence of healthy control arms precludes the ability to determine whether the various subject characteristics confer increased susceptibility to the observed cardiovascular effects.
- Of note however, the 2 studies that made comparisons to healthy subjects studied under analogous conditions, were unable to conclude that people with MetS or diabetes are overall more responsive to UFPs than people without those risk factors.

4.4.4 Ozone exposures

Bennett et al (2007) assessed the effect of BMI of healthy subjects on respiratory responses to a 2-hour exposure to 420 ppb ozone by re-analysing their previous controlled exposure data (Bennett et al., 2007) (Table 10). Although the population studied was predominantly normal weight, the decrement in lung function was significantly correlated with BMI, with a slightly stronger correlation in women and no significant correlation in men. In women, greater ozone-induced decrements were seen in overweight (BMI > 25 kg/m^2) than in normal weight (BMI 18.5 to 25 kg/m^2) subjects for all spirometric variables studied (FEV_1, FVC, FEF_{25-75}, FEF_{25-75}/FVC). No measurements of systemic/airway inflammation or airway hyperresponsiveness were made.

Having found evidence of a variation in ozone effects based on variation in BMI, the researchers went on to investigate whether obesity affects ozone-induced changes in airway function, reactivity, and inflammation in women (Bennett et al., 2016) (Table 10). The decrease in FVC post a 2-hour exposure to 400 ppb ozone was significantly ($p<0.05$) greater in the obese group (12.5%) than in the normal weight women (8.0%). The FEV decrement also tended ($p=0.08$) to be greater in the obese African-Americans (15.7%) relative to other obese subjects (9.6%). There was also a tendency for greater ozone-induced FEV_1 decrements in obese women (15.9%) relative to the normal weight women (11.7%). The degree of hyperresponsiveness was similar for the two groups. Both BMI groups showed similar and significant ozone-induced increases in sputum neutrophils. There was also a significant increase in interleukin (IL)-6 in the normal weight group and a trend for an increase in the obese that was not statistically significant.

Both the above studies set the exercise level to achieve a similar minute ventilation and, by extension, ozone dose to the lungs (Bennett et al., 2007, Bennett et al., 2016).

The results of Bennett et al (2007, 2016) are in line with the ozone exposure-response model for lung function that predicts FEV_1 responses increase with increasing BMI (McDonnell et al., 2013). Data for this model includes FEV_1 responses of 741 individuals (104 females, 637 males; age 18-36 years) exposed one or more times to ozone and/or filtered air.

Table 10 - Controlled human exposure studies: O_3.

Study	Population, n, sex, age (range or mean ± SD)	Exposure details (concentration, duration)	Endpoints examined
Bennett et al 2007	Healthy adults N=75 female, n=122 male Age: 18-35 y	420 ppb, 2 h With intermittent exercise	FEV_1 FVC FEF_{25-75} FEF_{25-75}/FVC
Bennett et al 2016	N=19 healthy females (BMI <25Kg/m^2) Age: 24 ± 4 y N=19 obese females (30<BMI<40Kg/m^2) Age 28 ± 5 y	0 ppb, 2 h 400 ppb, 2 h With intermittent exercise	Airway responsiveness, 3 h PE FEV1, FVC, sGaw, before & PE Symptoms, immediately PE Sputum neutrophils, 3h PE IL-6

Bad: brachial artery diameter; ET-1: endothelin-1; FA: filtered air; FMD: endothelium-dependent flow-mediated dilation; HRV: heart rate variability; MetS: metabolic syndrome; PAI-1: plasminogen activator inhibitor-1; PE: post exposure; vWF: von Willebrand factor

Summary of ozone exposures in overweight/obese subjects

- Studies have found that a higher BMI or obesity per se, may be a modest risk factor for adverse lung function effects associated with ozone exposure. No obesity related difference in airway reactivity and inflammation has been observed.

4.5 Animal studies

4.5.1 Literature searches – overview of studies

The literature searches conducted through PubMed and Web of Science, plus supplementary methods, identified 35 publications (Appendix 1; Tables Table 11, Table 12, Table 13 and Table 14).

4.5.2 Particle exposures

4.5.2.a Particle exposures in animal models of obesity

The differential effects of $PM_{2.5}$ CAPS on the sympathetic nervous system (SNS), and more specifically, activation of one of its important sites, the paraventricular nucleus (PVN), in lean Brown Norway rats and spontaneously obese JCR/LAcp rats that are corpulent, have hyperlipidemia and are insulin resistant has been investigated (Balasubramanian et al., 2013).

- One-day exposure ($PM_{2.5}$: 519 µg/m^3) to Detroit CAP increased noradrenaline levels in the PVN of BN rats but this was not apparent after a 3-day exposure (average $PM_{2.5}$: 592 µg/m^3).
- A 4-day exposure to Grand Rapids CAP (average $PM_{2.5}$: 219 µg/m^3) increased noradrenaline levels in the PVN of JCR/LA rats.
- Increased noradrenaline suggests activation of the SNS. A possible interpretation of these findings is an adaptive response amongst lean rats, which was lost in obese animals, and in turn could contribute to a prolonged activation of the SNS. Differences however in exposure durations as well as the source, composition and mass concentrations of $PM_{2.5}$ limit the comparability and analysis of these findings.

Pardo et al. investigated whether early nutritional obesity synergistically interacts with an urban PM exposure (London PM_3; 10 µg i.t. every other day for 10 d) to alter gene expression of selected pathways (including Nrf2, antioxidant defense, inflammation and autophagy and apoptosis) in lung, liver, white and brown adipose tissues (Pardo et al., 2018).

- Lung tissue was markedly responsive to the dietary challenge and the liver was highly responsive to the PM exposure.
- The potential for an interaction in the gene responses to PM and dietary challenges was also seen.
- For example, the combined PM/HFD challenge influenced genes relating to MAP kinase (especially in the liver and adipose tissue), inflammation and oxidative stress (especially in the lungs) and autophagy in adipose tissues.

Respiratory effects of DEP (300 µg i.n. for 5 days; then 3 mg/m^3 in a closed chamber on days 6 and 8) have also been investigated in Otsuka-Long Evans Tokushima Fatty (OLETF) obese rats (used as a model of insulin resistance because of their natural manifestation of hyperglycemia and non-insulin-dependent diabetes mellitus) and compared to those in Long Evans Tokushima-Otsuka (LETO) non-obese rats (Moon et al., 2014). Airway resistance and inflammation were increased to a greater extent in the DEP-exposed OLETF group compared to the DEP-exposed LETO group.

4.5.2.b Particle exposures in animal models of diabetes/metabolic syndrome

$PM_{2.5}$ (~1 mg/kg i.t.), collected from a busy traffic area, increased markers of lung damage and inflammation and systemic inflammation to the same extent in STZ-diabetic and non-diabetic rats (Lei et al., 2005). There was also no difference between a decrease in plasma [nitrate + nitrate], however increases in 8-OHdG (15.6% v 4.0%; $p<0.01$) and ET-1 (40.3% v 2.6%; $p=0.08$) after PM exposure were more prominent in diabetic rats than in non-diabetic (ND) rats.

Carll et al. (2017) studied the influence of repeated exposures to traffic-derived primary and secondary organic aerosols (P + SOA; 5 h/day, 4 days/week over a 3 week period) from an urban highway tunnel on cardiovascular dysfunction in healthy rats (56.3 ± 1.2 μg/m^3) and in a rat model of MetS (20.4 ± 0.9 μg/m^3) characterized by hypertension, hypertriglyceridemia, hyperglycemia, and insulin resistance (Carll et al., 2017). Autonomic cardiovascular responses to P + SOA were pronounced among MetS rats compared to healthy rats despite recieving a lower exposure concentration.

Studies utilising DEP (0.4 mg/kg i.t.) have compared respiratory effects, coagulation events and pancreatic effects in a mouse model of streptozotocin-induced type 1 diabetes and non-diabetic mice (Nemmar et al., 2013a, Nemmar et al., 2013b, Nemmar et al., 2014).

- Diesel exhaust particles equally increased airway resistance and caused pulmonary infiltration of inflammatory cells in diabetic and non-diabetic mice (Nemmar et al., 2013a). However, the occurrence of oxidative stress and inflammation, the presence apoptotic cells in lung sections and the increase of total proteins and albumin in BALF were only seen in DEP-exposed diabetic mice.
- Systemic and coagulation events were aggravated in type 1 diabetes in mice. DEP caused leucocytosis and a significant increase in plasma CRP, 8-isoprostane, plasminogen activator inhibitor and von Willebrand factor in diabetic mice compared to non-diabetic mice. The number of platelets and the thrombotic occlusion time in pial arterioles assessed in vivo were also significantly decreased in diabetic mice, whilst the in vitro addition of DEP (0.25-1 μg/ml) to untreated mouse blood significantly and dose-dependently induced in vitro platelet aggregation, and these effects were exacerbated in blood of diabetic mice (Nemmar et al., 2013b).
- An effect of DEP on the pancreas was evaluated by measuring several histological and biochemical endpoints (Nemmar et al., 2014). In diabetic mice, DEPs resulted in a marked decrease in the size and number of islet cells with cellular vacuolation and increases in apoptotic islet cells. DEP also significantly increased pancreatic amylase activity and markers of oxidative stress (8-isoprostane, superoxide dismutase, reduced glutathione) in diabetic compared with non-diabetic mice. A marked cytoplasmic staining for inducible nitric oxide synthase (iNOS) in most pancreatic islets cells and some acini cells was only observed in diabetic mice.

Table 11 - Particle exposures in animal models of diabetes, metabolic syndrome and diabetes.

Study	Population	Exposure details	Endpoints examined
Balasubramanian et al 2013	Lean and obese rats Brown Norway [BN] or JCR/LAcp [spontaneous obesity, hyperlipidemic, insulin resistant] rats)	FA PM2.5 CAPs BN: Detroit, MI CAPs 519 µg/m^3 for 1 d or 592 µg/m^3 for 3 d JCR/LAcp : Grand Rapids, MI CAPs 219 µg/m^3 for 4 d	PVN: NE, DA, 5-HIAA, 24 h PE ME: CRH, 24 h PE
Pardo et al 2018	Lean and obese mice Mice fed a normal chow or high fat diet for 7 weeks	Vehicle control London PM_3 (10 µg i.t. every other day for 10 d)	Expression of 61 selected genes representing key response pathways in lung, liver, white and brown adipose tissues, 24 h PE
Moon et al 2014	Lean and obese rats Long Evans Tokushima-Otsuka (LETO; 100 g) non-obese and Otsuka-Long Evans Tokushima Fatty (OLETF, 120 g) obese rats	Saline DEP (300 µg i.n. for 5 d; 3 mg/m^3 in closed chamber for 1 h on d 6 to 8)	Airway responsiveness Lung histology BALF: Total & differential cell counts Lung: inflammatory cell infiltration, IL-4, IL-6 and TNF-α Lung RNA All immediately PE
Lei et al	Rats (Sprague Dawley: healthy & STZ-induced diabetic)	PBS $PM_{2.5}$ collected from a busy traffic area (~1 mg/kg i.t.)	BALF: LDH, total proteins, inflammatory cells - 24 PE Blood 8-OHdG, ET-1), [nitrate+nitrite], CRP, IL-6, TNF-α – 24 PE
Carll et al 2017	Rats (Sprague Dawley: fed a normal or high fructose diet)	FA, 5 h/day, 4 days/week over a 3 week period Traffic-derived primary and secondary organic aerosols (healthy: 56.3 ± 1.2 µg/m^3; MetS: 20.4 ± 0.9 µg/m^3) from an urban highway tunnel, 5 h/day, 4 days/week over a 3 week period	Throughout exposure: • Autonomic balance • Haemodynamics • Baroreflexes • Arrhythmia • Breathing parameters

Nemmar et al 2013a	Mice (TO; healthy and STZ-induced type 1 diabetic)	Saline DEP (0.4 mg/kg i.t.)	Airway reactivity, 24 h PE BALF total proteins, albumin, SOD, GSH, IL-6 TNF-α – 24 h PE Lung histopathology, 24 h PE
Nemmar et al 2013b	Mice (TO; healthy and STZ-induced type 1 diabetic)	Saline DEP (0.4 mg/kg i.t.)	Plasma leucocytes, CRP, 8-isoprostane, PAI-1, vWF, ALT, AST, platelets – 24 h PE Arterial blood gases, 24 h PE Thrombosis in vivo, 24 h PE Platelet aggregation in vitro, 24 h PE
Nemmar et al 2014	Mice (TO; healthy and STZ-induced type 1 diabetic)	Saline DEP (0.4 mg/kg i.t.)	Pancreatic histology amylase, lipase, 8-isoprostane, SOD, GSH, iNOS – 24 h PE

Summary of particle exposures in animal models of diabetes/MetS/obesity

- A small number of studies have, in the main, investigated the effects of traffic-related PM but are very heterogeneous with respect to exposure system (route, dose, duration), animal model (obese, MetS, diabetic) and endpoints studied.

- Studies in obese animals suggest that compared to healthy controls, PM could cause a prolonged activation of the SNS and enhance increases in airway resistance and inflammation. A study has also shown that urban PM may interact with obesogenic nutrition to regulate pathways including inflammation and oxidative stress in a tissue-specific manner.

- In a rat model of MetS, autonomic cardiovascular responses to traffic aerosols were pronounced compared to healthy rats.

- In a rat model of type 1 diabetes, increased respiratory and coagulation susceptibility and heightened injurious effects on the pancreas have been demonstrated compared to non-diabetic mice. These exacerbated effects could be attributed to an increase in local and/or systemic oxidative stress and/or inflammation.

4.5.3 Ozone exposures

4.5.3.a Ozone exposures in animal models of obesity

Acute exposures (2 ppm for 3 hours)

A large number of studies have originated from a group of researchers at the Harvard School of Public Health, led by Stephanie Shore, in acknowledgement that epidemiological data indicated that obesity is a risk factor for asthma and thus have focused on respiratory endpoints.

These studies have used the following obese mice with a pulmonary phenotype that includes innate airway hyperresponsiveness:

- ob/ob and db/db mice: obese because of a genetically deficiency in leptin (satiety hormone) or the leptin receptor.
- Cpe mice: obese because of a genetic deficiency in carboxypeptidase E (Cpe), an enzyme that regulates neuropeptides involved in eating behavior.
- Mice with diet-induced obesity (DIO).

Pulmonary mechanics and airway responsiveness have been measured 24 hours after the cessation of ozone exposure (2 ppm for 3 h) in ob/ob mice (Shore et al., 2003, Rivera-Sanchez et al., 2004), db/db mice (Lu et al., 2006), Cpe^{fat} mice (Johnston et al., 2006), mice fed a high

fat diet from the time of weaning (Johnston et al., 2008) and their lean age- and sex-matched C57BL/6J wild-type (WT) controls. Ozone exposure increased pulmonary resistance in obese mice, regardless of the cause of obesity, but had no effect on lean mice. Exposures led to more robust changes in airway responsiveness in obese than in lean mice.

The pulmonary inflammatory response to ozone over time as obesity develops has also been examined by exposing to ozone (2 ppm for 3h), 7-, 10-, and 14-wk-old Cpe^{fat} mice, whose body weight averaged 20, 50 and 75% more than their age-matched WT controls (Johnston et al., 2010, Johnston et al., 2006). Ozone-induced airway inflammation was greater in Cpe^{fat} than lean mice, regardless of age, indicating that even a 20% increase in body weight is sufficient to increase the inflammatory effects of ozone in mice.

Role of inhaled dose

The inhaled dose of ozone is the product of ozone concentration, exposure time and minute ventilation (Wiester et al., 1987). Among the studies described above, ozone concentration and exposure time were identical in obese and lean mice and although there was greater minute ventilation in db/db mice than WT mice during ozone exposure (Lu et al., 2006), this was not true in ob/ob mice or in Cpe^{fat} mice (Shore et al., 2003, Johnston et al., 2006, Lu et al., 2006).

Furthermore however, the small lung size of the ob/ob and db/db mice means that even if the inhaled dose of ozone were equivalent in obese and lean mice, the dose per gram of lung tissue would be higher in the ob/ob and db/db mice. The researchers were doubtful however that this accounted for the greater responses to ozone observed in obese mice, since similar increased responses were observed in Cpe^{fat} mice and in mice with DIO, both of which have lungs of normal mass.

Role of IL-33

IL-33 is released upon ozone exposure (Kumagai et al., 2016, Yang et al., 2016) and in mice, pulmonary administration of IL-33 causes AHR and increases in bronchoalveolar lavage fluid (BALF) neutrophils (Barlow et al., 2013, Mizutani et al., 2014). For these reasons, the role that IL-33 plays in obesity-related increases in the response to ozone has been examined (Mathews et al., 2017b, Kasahara and Shore, 2020).

- Both obese db/db mice and their lean WT controls were treated with an antibody blocking the IL-33 receptor, ST2, or an isotope antibody prior to ozone exposure (2 ppm for 3 h).
- As expected, ozone-induced increases in BAL IL-33 and neutrophils, pulmonary resistance and the magnitude of AHR were greater in db/db than in WT mice.
- In ozone-exposed db/db mice, anti-ST2 treatment reduced AHR, BAL neutrophils and pulmonary resistance towards levels observed in WT mice, however the treatment had no effect in WT mice.

IL-33-dependent increases in IL-13 appear to contribute to the changes in pulmonary mechanics and inflammatory cell recruitment observed in obese mice after ozone exposure since anti-IL-13 attenuates both effects (Williams et al., 2013). However, IL-33–driven factor(s) other than IL-13 appear responsible for ozone-induced AHR since this is not

attenuated by blocking IL-13 (Williams et al., 2013). Further studies suggest that these other factors may include CXCL1 and IL-6 (Lang et al., 2008, Johnston et al., 2005).

Role of TNF-α

Several strands of evidence suggest that TNF-α may also contribute to obesity-related increases in the respiratory response to ozone.

- Obesity is characterised by elevated circulating concentrations of TNF-α (Johnston et al., 2008).
- Obesity confers a greater risk for asthma in subjects with TNF-α polymorphisms that promote TNF-α expression, particularly amongst nonatopic asthmatics (Castro-Giner et al., 2009).
- Exogenous administration of TNF-α can induce AHR (Thomas et al., 1995), and TNF-α is known to contribute to ozone-induced AHR in lean mice (Shore et al., 2001).

Studies have used obese Cpe^{fat} mice deficient in TNF-α (Cpe^{fat}/TNF-$\alpha^{-/-}$) and compared their responses to ozone exposure to obese TNF-α–sufficient Cpe^{fat}, lean TNF-$\alpha^{-/-}$ or WT mice (Williams et al., 2015). Similar experiments were performed in Cpe^{fat} mice deficient in TNF-α receptor 2 (TNFR2; Cpe^{fat}/$TNFR^{-/-}$ mice) (Williams et al., 2013). Data indicate complex and differing roles for TNF-α in the ozone response of lean and obese mice.

- In obese mice, genetic deficiency in either TNF-α or TNF-α receptor 2 augments ozone-induced AHR, whereas TNF-α receptor 2 deficiency virtually abolishes ozone-induced AHR in lean mice.
- In contrast, both TNF-α and TNFR2 deficiency effectively abolished obesity-related differences in neutrophil recruitment but this was not the case in lean mice.

Role of IL-17 and the gastrin-releasing peptide receptor

Ozone and obesity both increase IL-17A in the lungs (Pichavant et al., 2008, Marijsse et al., 2014). Furthermore IL-17A contributes to the pathogenesis of comorbidities of obesity, such as glucose intolerance (Zúñiga et al., 2010) and the innate AHR observed in mice with DIO (Kim et al., 2014). For these reasons, a contribution from IL-17A in obesity-related increases in the pulmonary responses to acute ozone exposure has been explored (Mathews et al., 2018).

- Lean WT and obese db/db mice were treated with anti–IL-17A or isotype antibody 24 hours before air or ozone (2 ppm for 3h) exposure.
- Anti–IL-17A decreased ozone-induced AHR in obese but not in lean mice.
- A microarray analysis to identify genes altered both by ozone and anti–IL-17A in db/db mice identified the gene for gastrin-releasing peptide receptor (GRPR), and moreover, obesity augmented ozone-induced increases in BAL GRP, whilst treatment with anti-GRP neutralizing antibodies significantly reduced obesity-related increases in ozone-induced AHR. Taken together, these findings suggest that the GRPR is as an important contributor to obesity-amplified, ozone-induced lung injury downstream of IL-17.

Role of lung metabolites

Metabolomic profiling has also been performed on lung tissue from db/db and WT mice exposed to ozone (2 ppm for 3h) in an attempt to identify metabolic pathways that may contribute to the augmented AHR observed in obese animals (Mathews et al., 2017a). Both obesity and ozone exposure caused changes in the lung metabolome.

- Obesity caused changes in carbohydrates and lipids.
- Ozone exposure caused differential effects on lung lysolipids, induced an increased reliance upon branched chain fatty acids (BCAA) for energy production in lungs of lean mice and an increased reliance upon fatty acids for energy in obese mice, possibly as a result of greater ozone-induced increases in corticosterone in the obese mice.
- Evidence for increased pulmonary oxidative stress in obese mice after ozone exposure was increases in the redox-regulated gene, Gclc, and oxidised glutathione (GSSG).

Role of the microbiome

The metabolomic analysis discussed above also indicated a role for the microbiome in the effects of obesity on pulmonary responses to ozone - amongst the metabolites identified that require bacteria for their generation in mammals, each was affected by obesity, ozone or a combination of the two (Mathews et al., 2017a).

Further data from mice indicate that the gut microbe contributes to effects of obesity on airway responses triggered by ozone: the obesity-related difference in ozone-induced AHR in db/db mice is markedly attenuated by treatment with antibiotics (Tashiro et al., 2019).

Acute exposures (0.25, 0.5 or 1.0 ppm for 4h)

Kodavanti and co-workers have included James C. Russell (JCR) rats in a number of animal models (three healthy; five CVD-prone) that were exposed to ozone (0.25, 0.5 or 1.0 ppm for 4 h) and evaluated immediately or 20h post exposure. JCR rats have a susceptibility to develop obesity and atherosclerosis. Owing to leptin receptor mutation, they exhibit metabolic syndrome (e.g. increased body weight, elevated lipid levels and insulin resistance).

Endpoints examined included ventilatory responses, blood chemistry changes, pathology, pulmonary injury/inflammation, tissue and airway lining antioxidants and pulmonary global gene expression. Pertinent findings are outlined below:

- JCR rats were amongst those strains (together with spontaneously hypertensive stroke-prone [SHSP] and spontaneously hypertensive heart failure [SHHF]) with the highest plasma levels of malondialdehyde (a marker of systemic oxidative stress) (Kodavanti et al., 2015b).
- In a concentration-dependent manner, ozone exposure resulted in decreased minute ventilation across all strains except the SHHF. Effective dose estimates (ozone concentration in ppm x h of exposure x minute volume) demonstrated that the JCR rats received the lowest effective dose (10% less than Wistar Kyoto [WKY] rats). (Dye et al., 2015).

- JCR rats had a baseline indication of lung pathology (alveolar histiocytosis) but ozone exposure did not have a greater effect on the lung of this strain compared to the healthy and CVD prone rats (Ramot et al., 2015).
- Ozone exposure did not have any effect on heart pathology in any strain but JCR rats had greater coronary inflammation than the CVD strains (Ramot et al., 2015).
- Ozone-exposed JCR showed modest pulmonary injury (BALF proteins) compared to the healthy and CVD strains. Whilst a relatively large inflammatory (BALF neutrophils) response was observed, this was not exacerbated relative to the healthy or lean CVD strains (Kodavanti et al., 2015a).
- JCR rats had high basal levels of ascorbate and glutathione in BALF as well as high basal lung uric acid (Hatch et al., 2015). At 0 h post exposure to 1 ppm ozone, BALF ascorbate tended to decrease in healthy strains, but not in JCR rats.
- Lung gene expression data revealed that at baseline, JCR rats exhibited the largest difference in the number of genes among all strains when compared with WKY. JCR rats also had the fewest number of genes affected by ozone, including those genes responsive to oxidative stress (Ward and Kodavanti, 2015).

Role of adiponectin

Adiponectin is an energy-regulating hormone, secreted almost exclusively by adipocytes. Circulating adiponectin has anti-inflammatory properties (Yokota et al 2000) and is reduced in obesity, type 2 diabetes and insulin resistance (Weyer et al 2001). The hormone, which circulates in multimeric forms, can also has pro-inflammatory properties and it is believed that its pro- or anti-inflammatory effects may depend upon which adiponectin isoform is present (Haugen & Drevon 2007).

Mice lacking adiponectin (Adipo-/- mice) have increased neutrophilic influx into the lungs following sub-acute exposure to ozone (0.3 ppm for 24–72 h) and data suggests this is dependent upon IL-6, and its ability to induce serum amyloid A3 (SAA3), IL-17A and granulocyte colony-stimulating factor (G-CSF) release (Kasahara et al., 2012, Kasahara et al., 2014). It is possible therefore that in obese animals, loss of the anti-inflammatory effects of adiponectin contribute to increases in responses to ozone.

In contrast, Adipo-/- mice exposed to acute ozone (2 ppm for 3 h) had decreased neutrophilic inflammation and decreased induction of cytokines and chemokines compared to WT (Zhu et al., 2010), suggesting differing impacts of adiponectin deficiency on pulmonary responses to subacute versus acute ozone exposure.

Sub-acute exposures (0.3 ppm for 24-72 hours)

Since elevated ambient ozone concentrations tend to persist for days rather than hours, repeated exposures at lower concentrations have been studied, again using obese and lean WT mice. In WT mice, ozone exposure (0.3 ppm for 72h) caused pulmonary injury and neutrophilic inflammation, and these events were associated with reduced pulmonary compliance. In obese db/db and Cpe^{fat} mice however, ozone-induced neutrophil emigration into the lungs was reduced and no evidence of lung injury or reduction in compliance was observed (Shore et al., 2009). This reduction in ozone-induced neutrophil influx was shown to be the result of a reduction in IL-6 driven neutrophil recruitment in obese mice.

Table 12 - Ozone exposures in animal models of obesity.

Study	Population	Exposure details	Endpoints examined
Shore et al 2003	Mice (C57BL/6J) WT & ob/ob	0 ppm, 3 h 2 ppm, 3h	Pulmonary mechanics & responsiveness, 24 h PE BALF protein, eotaxin, MIP-2, KC, IL-6, neutrophils - 4h & 24 h PE
Rivera-Sanchez et al 2004	Mice (C57BL/6J) WT & ob/ob	0 ppm, 3 h 2 ppm, 3h	Pulmonary mechanics & responsiveness, 24 h PE
Lu et al 2006	Mice (C57BL/6J) WT & db/db	0 ppm, 3 h 2 ppm, 3h	Pulmonary mechanics & responsiveness, 24 h PE BALF eotaxin, IL-6, KC, MIP-2, protein, neutrophils, sTNFR1&2 - 4 h & 24 h PE Pulmonary gene expression, 4 h & 24 h PE
Johnston et al 2006	Mice (C57BL/6J) WT & Cpe^{fat}	0 ppm, 3 h 2 ppm, 3h	Pulmonary mechanics & responsiveness, 24 h PE BALF eotaxin, IL-6, KC, MIP-2, protein, neutrophils, sTNFR1&2 - 4 h & 24 h PE
Johnston et al 2008	Mice (C57BL/6J) fed a normal (lean) and high fat diet (DIO)	0 ppm, 3 h 2 ppm, 3h	BALF protein, eotaxin, IP-10, IL-6, KC, MIP-2, sTNFR1&2 - 4 h PE
Mathews et al 2017b	Mice (C57BL/6J) WT & db/db, WT & TCR gamma delta deficient mice on a HFD for 24 weeks	0 ppm, 3 h 2 ppm, 3h	Airway responsiveness, 24 h PE BALF total cells, cell differentials, cytokines, chemokines, 24 PE
Kasahara & Shore 2020	Mice (C57BL/6J) WT & $ST2^{-/-}$ fed a normal or HFD	0 ppm, 3 h 2 ppm, 3h	Airway responsiveness, 24 h PE BALF total cells and cell differentials, inflammatory mediators, 24 h PE Serum inflammatory mediators, 24 h PE Gut microcial community, 24 h PE
Williams et al 2013	Mice (C57BL/6J) WT) & $TNFR2^{-/-}$ & Cpe^{fat} & Cpe^{fat} $TNFR2^{-/-}$	0 ppm, 3 h 2 ppm, 3h	Pulmonary mechanics & responsiveness, 24 h PE BALF protein, total cells, cell differentials, cytokines, chemokines, hyaluronan – 24 h PE

Lang et al 2008	Mice (C57BL/6J) WT & ob/ob +/- anti-IL-6 antibody or isotope control	0 ppm, 3 h 2 ppm, 3h	BALF protein, total cells, cell differentials, IL-6, KC, MIP-2, sTNFR1, IP-10, LIX, CXCL5, MCP-1, LIF, eotaxin – 24 h PE Lung STAT expression
Johnston et al 2005	Mice (BALBc) WT & CXCR-2 deficient	0 ppm, 3 h 1 ppm, 3 h	Airway responsiveness, 3 h PE BALF total protein, total cells, cell differentials, KC, JE/MIP-2, IP-10, 3 or 24 h PE
Williams et al 2015	Mice (c57BL/6J) WT & $TNF\alpha^{-/-}$ & Cpe^{fat} & $Cpe^{fat}/TNF\alpha^{-/-}$	0 ppm, 3 h 2 ppm, 3 h	Airway responsiveness, 24 h PE BALF total protein, total cells, cell differentials, MCP-1, G-CSF, IL-13, hyaluronan, osteopontin, protein carbonyls or 24 h PE
Mathews et al 2018	Mice (C57BL/6J) WT & db/db, and CPE^{fat}/TNFR2 deficient mice, WT & TCR gamma delta-deficient mice; some mice on a HFD for 24 weeks	0 ppm, 3 h 2 ppm, 3h	Airway responsiveness, 24 h PE BALF total cells and cell differentials, IL-17A, IL-23, IL-33, CCL20, CXCL1, CXCL2, IL-6, G-CSF, GRP, lung tissue flow cytometry for IL-17A producing cells – 24 h PE
Matthews et al 2017a	Mice (C57BL/6J) WT & db/db	0 ppm, 3 h 2 ppm, 3h	Lung metabolome, 24 h PE
Zhu et al 2010	Mice (C57BL/6J) WT & $Adipo^{-/-}$ & T-$Cad^{-/-}$	0 ppm, 3 h 2 ppm, 3h	Airway responsiveness, 24 h PE BALF total cells and cell differentials, IL-6, KC, MCP-1, eotaxin, MIP-2 – 24 h PE
Kodavanti et al 2015b	WKY, WIS, SD, SH, SHSP, SHHF, FHH, JCR	-	Baseline clinical chemistries
Dye et al 2015	WKY, WIS, SD, SH, SHSP, SHHF, FHH, JCR	0, 0.25, 0.5, 1.0 ppm, 4 h	Ventilatory parameters
Ramot et al 2015	WKY, WIS, SD, SH, SHSP, SHHF, FHH, JCR	0, 0.25, 0.5, 1.0 ppm, 4 h	Lung histopathology
Kodavanti et al 2015a	WKY, WIS, SD, SH, SHSP, SHHF, FHH, JCR	0, 0.25, 0.5, 1.0 ppm, 4 h	BALF total cells, cell differentials, protein, albumin, LC, NAG 0 & 20 h PE Lung mRNA for HO-1, MIP-2, TNF-α, IL-6, IL10 0 & 20 h PE
Hatch et al 2015	WKY, WIS, SD, SH, SHSP, SHHF, FHH, JCR	0, 0.25, 0.5, 1.0 ppm, 4 h	BALF, lung & heart: total glutathione, AH2, UA & antioxidant enzymes 0 & 20 h PE

Ward & Kodavanti 2015	WKY, WIS, SD, SH, SHSP, SHHF, FHH, JCR	0, 0.25, 0.5, 1.0 ppm, 4 h	Lung gene expression profiling, immediately PE	
Shore et al 2009	Mice (C57BL/6J) WT & db/db & CPE^{fat} & IL-$6^{-/-}$	0 ppm, 72 h 0.3 ppm, 72 h	Pulmonary mechanics, 30 min PE BALF total protein, sTNFR1, IL-6, KC, MIP-2 – 30 min PE	

AH2: reduced ascorbate; BALF: bronchoalveolar lavage fluid; CCL20: chemokine ligand 20; CXCL: C-X-C motif chemokine ligand; FHH: Fawn Hooded hypertensive; G-CSF: granulocyte colony-stimulating factor; GRP: gastrin releasing peptide; HO-1: heme oxygenase-1; IL: interleukin; IP-10: interferon-inducible protein 10; JCR: James C Russell; KC: keratinocyte chemoattractant; LIF: leukemia inhibitor factor; LIX: lipopolysaccharide-inducible CXC chemokine; LC: MCP: monocyte chemoattractant protein; MIP-2: macrophage inflammatory protein; NAG: N-acetyl glucosaminidase; PE: post exposure; ppm: parts per million; SAA3: serum amyloid A3;SD: Sprague Dawley; SH: Spontaneously hypertensive, SHHF: Spontaneously hypertensive heart failure; SHSP: SH-stroke prone; sTNFR: soluble tumor necrosis factor receptor; TNF: tumor necrosis factor; UA: uric acid; WIS: Wistar; WKY: Wistar Kyoto; WT: wild type

Summary of ozone exposures in animal models of obesity

- Studies in genetically obese mouse models (ob/ob, db/db/ Cpe^{fat}, DIO) have shown that obesity enhances various respiratory responses to ozone (2 ppm, 3h), including lung mechanics, airway responsiveness, and airway inflammation.
    - The consistency of these findings in several mice models of obesity, characterised by different minute ventilations and lung sizes, may suggest that these parameters do not (wholly?) account for the greater responses to ozone observed in obese mice.
    - Data indicate that mediators of these events include (a) IL-33, possibly via IL-13, CXCL1 and IL-6, (b) IL-17A, via GRPR and (c) the gut microbiome.
    - TNF-α and adiponectin appears to have complex and differing roles in the ozone response of lean and obese mice.

- In contrast, neutrophil migration into the lungs of obese db/db and Cpe^{fat} mice following sub-acute ozone exposure (0.3 ppm for 72) was markedly attenuated compared to that in lean WT mice.

- Relative to a number of different rat models of CVD plus healthy strains exposed to (0.25, 0.5 or 1.0 ppm for 4 h), obese JCR rats exhibited minimal lung injury and inflammation (along with high basal levels of pulmonary ascorbate, glutathione and uric acid). JCR rats had greater ozone-induced coronary inflammation compared with the CVD strains.

4.5.3.b Ozone exposures in animal models of diabetes

Ozone (1.0 ppm; 6 hrs/day for 1 or 2 days)-induced pulmonary and vascular responses (Snow et al., 2021b) and metabolic effects (Snow et al., 2021a) have been examined in healthy Wistar and Wistar-derived Goto-Kakizaki (GK) rats - a non-obese model of type 2 diabetes.

- No strain-related differences were noted in pulmonary histopathological effects or BALF biomarkers of lung injury, except for an early and persistent protein leakage in GK relative to Wistar rats.
- Ex vivo aortic contractility to phenylephrine was lower in GK versus Wistar rats at baseline (~30%) and ozone exposure for 1 day led to a marked increase in PE-induced vasocontraction in Wistar rats but not GK rats. Ozone exposure increased e-NOS expression in GK but not Wistar rats.
- In GK but not Wistar rats, baseline hyperglycemia and glucose intolerance were exacerbated by ozone after one or 2 days of exposure, but not at the 18-hour recovery period.
- On day one, ozone exposure led to increases in blood triglyceride levels in GK but not Wistar rats, but not at the 18-hour recovery period.
- Gene expression changes in the liver indicated distinct responses to ozone in GK rats related to lipid and glucose metabolism and transport mechanisms.

Pulmonary responses following repetitive ozone exposures (0.5 ppm ozone, 4 h/d, for 13 consecutive weekdays) have been evaluated in normoglycemic and insulin-sensitive C57BL/6J mice, hyperglycemic, but mildly insulin-resistant and obesity prone, KK mice (a model of MetS) and hyperglycemic and markedly insulin-resistant KKAy mice (a model of type 2 diabetes) (Wagner et al., 2020, Zhong et al., 2016, Ying et al., 2016).

- Higher BAL fluid inflammatory cells were observed in all mice (KKAy > KK > C57BL/6), with a notable influx of neutrophils and eosinophils in KK and KKAy mice (Wagner et al., 2020).
- The lungs of C57BL/6J and KK mice had minimal histological changes without fibrosis, and the lungs KKAy mice contained marked epithelial hyperplasia in proximal alveolar ducts and adjacent alveoli with associated centriacinar fibrosis (Wagner et al., 2020).
- KK mice develop even greater insulin resistance following ozone exposure and this accompanied by enhanced inflammation and oxidative stress in visceral adipose tissue (Zhong et al., 2016).
- In KKAy mice, ozone markedly increased adipose tissue and systemic inflammation but increased insulin sensitivity, possibly as a consequence of weight loss and/or leptin sensitization (Ying et al., 2016).

Table 13 - Ozone exposures in animal models of diabetes.

Study	Population	Exposure details	Endpoints examined
Snow et al 2021b	Rats (Wistar & Wistar-derived Goto-Kakizaki)	0 ppm, 6h/d for 1 or 2 d 1.0 ppm, 6hd for 1 or 2 d	Blood platelets, thrombin/antithrombin, platelet aggregation – 2 h PE BALF protein, NAG, GGT – 2 h PE Lung histology, 2 h PE Serum TNF-α, IL6, IL1β, KC/GRO, IFN-γ – 2 h PE Aortic ring contractility, 2 h PE Aortic gene expression (eNOS, ET-1; tPA, TF) – 2 h PE
Snow et al 2021a	Rats (Wistar & Wistar-derived Goto-Kakizaki)	0 ppm, 6h/d for 1 or 2 d 1.0 ppm, 6hd for 1 or 2 d	GTT, immediately PE & 18 h post 2d exposure Serum/plasma HDL, triglyercide, lipase, AST, SGOT, LDL, ALT, SGPT, insulin, glucagon, leptin Liver & adipose tissue histopathology Liver RNA expression
Wagner et al 2020	Mice (C57BL/6 & KK & KKAy)	0.5 ppm ozone, 4 h/d, for 13 consecutive weekdays	ITT, 2 h PE BALF total cells, cell differentials, KC, IL-1β, IL-5, IL-6, IL13, IL-17A – 22 h PE Plasma insulin, leptin, adipoectin – 22 h PE Lung histopathology, 22 h PE Lung hydroxyproline, 22 h PE Lung mRNA expression (fibrosis associated genes), 22 h PE
Zhong et al 2016	Mice (KKAy)	0.5 ppm ozone, 4 h/d, for 13 consecutive weekdays	ITT, 2 h PE BALF total cells, cell differentials – 22 h PE Lung & adipose tissue histopathology – 22 h PE Plasma insulin, adiponectin, leptin – 22 h PE Systemic & adipose tissue inflammation – 22 h PE Liver lipid metabolism, 22 h PE Adipose tissue gene expression, 22 h PE
Ying et al 2016	Mice (KKAy)	0.5 ppm ozone, 4 h/d, for 13 consecutive weekdays	ITT, 2 h PE Plasma glucose, insulin, adiponectin, lepin, 22 h PE HOMA-IR, 22 h PE Systemic & adipose tissue inflammation, 22 h PE Liver, skeletal muscle, fat Akt phosphorylation, 22 h PE

ALT: alanine aminotransferase; AST: aspartate aminotransferase; eNOS: endothelial nitric oxide synthase; ET-1: endothelin-1; GGT: gamma-glutamyl transpeptidase; HDL: high-density lipoprotein; IFN: interferon; IL: interleukin; KC/GRO: keratinocyte chemoattractant human growth-regulated oncogene; LDL: Low-density lipoprotein NAG: N-acetylglucosaminidase; ppm: parts per million; SGOT: AST, glutamic-oxaloacetic transaminase; SGPT: ALT, glutamic-pyruvic transaminase; tPA: tissue plasminogen activator; TF: tissue factor; TNF-α: tumor necrosis factor-α

Summary of ozone exposures in animal models of diabetes

- Relative to normal rats, GK rats with non-obese type 2 diabetes demonstrate minimal or no pulmonary/vascular responses to ozone (1.0 ppm; 6 hrs/day for 1 or 2 days). Metabolic effects include exacerbation of glucose intolerance and increases in blood triglycerides in GK rats that was not observed at the 18-hour recovery period.

- Relative to normal mice, mouse models of diabetes demonstrate varying degrees of lung injury and inflammation following ozone exposure (0.5 ppm ozone, 4 h/d, for 13 consecutive weekdays). Metabolic effects include enhanced inflammation and oxidative stress in adipose tissue and strain dependent alterations in insulin resistance.

4.5.4 Pollutant mixtures

The effects of two simulated smog atmospheres (SA) with different compositions (high particulate matter [SA-PM]: ozone 0.09 ppm, NO_2 0.26 ppm, $PM_{2.5}$ 1140 µg/m^3; and high ozone [SA-ozone]: ozone 0.3 ppm; NO_2 0.60 ppm, $PM_{2.5}$ 100 ug/m^3) were compared in GK rats, (McGee Hargrove et al., 2018). Rats were exposed to filtered air, SA-PM or SA-ozone for 4h per day for 1 or 5 consecutive days.

- Effects on pulmonary function were limited to an increase in airflow limitation following SA-ozone after days 1 and 2 of exposure.
- Neither atmosphere affected markers of pulmonary inflammation or injury.
- Both SA-PM and SA-ozone decreased cholesterol levels immediately after a 4-hour exposure but these metabolic markers returned to baseline levels following 5 days of exposure to SA.
- No control rats were included in this study and the concentration used was lower than those (0.5 to 1.0 ppm) that induced hyperlipidemia, hyperglycemia, and glucose intolerance in normal rats No control rats were included in this study and the concentration used was lower than those (0.5 to 1.0 ppm) that induced hyperlipidemia, hyperglycemia, and glucose intolerance in normal rats (Bass et al., 2013, Vella et al., 2015),
- No control rats were included in this study and the concentration used was lower than those (0.5 to 1.0 ppm) that induced hyperlipidemia, hyperglycemia, and glucose intolerance in normal rats (Bass et al., 2013, Vella et al., 2015).

Table 14 - Pollutant mixture exposures in animal models of diabetes.

Study	Population	Exposure details	Endpoints examined
McGee Hargrove et al 2018	Rats (Goto-Kakizaki)	SA-PM (O_3: 87.3 ppb; NO_2: 262.2 ppb; $PM_{2.5}$ 1140.3 µg/m^3) SA-O_3 (O_3: 326.4 ppb; NO_2: 603.9 ppb; $PM_{2.5}$ 443.5 µg/m^3) 4h /d for 1 d SA-PM (O_3: 100.3 ppb; NO_2: 274.5 ppb; $PM_{2.5}$ 1107.9 µg/m^3) SA-O_3 (O_3: 369.7 ppb; NO_2: 639.9 ppb; $PM_{2.5}$ 308.7 µg/m^3) 4h /d for 5 consecutive days	Pulmonary function, 1, 2, 4 d PE BALF protein, LDH, GGT, NAG, protein, inflammatory cells - immediately PE Blood glucose, 1,2,4 d PE Glucose tolerance 1,2,4 d PE Insulin tolerance 3 d PE Serum cholesterol, HDL cholesterol, LDL cholesterol, trigylcerides - immediately PE BALF total cells, cell differentials, markers of lung injury, immediately PE Haematological parameters, immediately PE

BALF: GGT: HDL: LDH: LDL: NAG: PE: post exposure; ppb: parts per billion; SA: smog atmospheres

Summary of pollutant mixture exposures in animal models of diabetes

- Acute exposures to simulated smog atmospheres containing either high concentrations of PM (SA-PM) or ozone (SA-ozone) produced limited health effects in GK rats.
- Respiratory effects of SA-ozone tended to be greater than those of SA-PM.
- Lack of a control group of rats makes it difficult to judge whether effects observed were the result of the diabetic state.

4.6 Discussion: are subjects with metabolic disorders at increased risk from short-term exposure to air pollution?

4.6.1 Discussion of the epidemiological time-series and case-crossover studies

Some evidence exists for diabetic individuals having increased risks to health outcomes attributed to short-term exposure to air pollution. However, results are inconsistent, in most cases, between studies investigating a given pollutant, as well as those focusing on different pollutants. There are also a number of limitations in the current evidence base that must be addressed in future work.

Diabetics may be more susceptible to $PM_{2.5}$-related all-cause mortality, with consistent reporting across the two studies identified (Zanobetti et al. 2014, Alessandrini et al. 2016). However, such a limited evidence base (one study undertaken in North America and one in Europe) precludes any ability to conclusively attribute such effect modification to the presence of diabetes, whilst the evidence for PM_{10} is currently even less conclusive and the associations between cause-specific mortality and particulate matter have not been found to be modified in diabetic populations thus far. Mortality directly attributed to diabetes is associated with increased short-term exposure to ambient air pollution, however, further work is required to ascertain whether this is a unique susceptibility within diabetics, or the association is mediated by CVD. Limited evidence does suggest increased susceptibility in diabetics for cause-specific hospital admissions attributable to particulate matter exposure, but the relatively few statistically significant findings do not allow for conclusive inference in terms of increased vulnerability for a given outcome.

The evidence base is further limited for gaseous pollutants, with even less evidence suggesting increased susceptibility in diabetics for the aforementioned health endpoints in relation to NO_2, O_3 or SO_2.

In addition to the limited number of studies (both gaseous pollutants and particulate matter) assessing the potential for effect modification in diabetics, a number of other limitations in the current evidence should be highlighted. For instance, geographic heterogeneity of studies was extremely limited, with studies restricted to North America, Asia and Europe represented only by studies drawn from a large project based in Italy. Additionally, the majority of studies compared a diabetic sub-group to the entire sample population (including diabetics and non-diabetics), limiting the ability to accurately compare effect estimates. Some studies included many thousands of diabetics in their analysis (Alessandrini et al. 2016, Qiu et al. 2020), but most analyses had smaller sample sizes compared to standard time-series or case-crossover studies that do not assess effect modification. This results in lower statistical power to detect statistically significant associations, even if one really exists in the study population. Future work must be conducted on more diverse study populations and comparisons drawn between large diabetic and non-diabetic sub-samples. Such work has already been conducted for the effects of long-term exposure to air pollution on diabetics, with strong evidence for an effect of exposure to particles and diabetes incidence and prevalence, and exposure to NO_2 and prevalence (Yang et al. 2020).

Overall, suggestive evidence for effect modification by diabetes status can be drawn from the literature with regards to the effects of short-term ambient particulate air pollution exposure

on several health outcomes, but the evidence base is currently small, inconsistency in results is present and the current methodological limitations preclude any conclusive inference.

4.6.2 Discussion of the epidemiological and semi-experimental panel studies

The panel studies discussed in this section of the report appeared in the output of literature searches tailored to identify controlled human exposure studies or were identified from hand searching the reference lists thereof. It is acknowledged therefore that they may not represent an exhaustive set of such studies citing susceptibility to air pollution-related health effects in populations with diabetes/obesity compared to non-diabetics/non-obese subjects. The publications do however cover a broad timeframe (2000 to 2022) and whilst the majority stem from studies that were conducted in the US (n=8; including output from the NHANES, Normative Ageing Study and Framingham Heart Study), others originate from work conducted in Europe (n=3; German, Italy, Sweden) and Asia (n=4; China, South Korea).

Whilst most of the US and European study populations were elderly, the Chinese study subjects were younger adults. Studies stemming from the Normative Ageing Study (Alexeef et al 2007; Park et al 2005) drew upon a cohort consisting of all males and almost all whites whilst participants of the Framingham Heart Study were predominantly white individuals of European ancestry and middle-aged to older adults (Li et al 2016; Rice et al 2013). Such demographics will limit the degree to which the results can be extrapolated across age, gender and race.

Studies comparing inflammatory effects were inconsistent in their findings, with some identifying larger associations between exposure to air pollutants ($PM_{2.5}$ and NO_2) and increased CRP, IL-6 and WBC counts among diabetics (Dubowsky et al 2006; Dabass et al 2016); Lee et al 2018). One study reported a significant association between PM_{10} and the thrombotic marker vWF among diabetics that was not observed in non-diabetics (Liao et al 2005) and 3 studies reported greater effects of certain pollutants on heart rhythm disorders in the diabetic population. The latter constituted associations between PM_{10} and ozone and atrial fibrillation (Dahlquist et al 2020), $PM_{2.5}$ and reduced HRV (Park et al 2000) and ozone and abnormal repolarization parameters (Hampel et al 2012). Surprisingly, none of the studies addressed potential effects of air pollution on metabolic health indicators among diabetics versus non-diabetic subjects.

Two studies are consistent in findings of greater decreases in lung function in association with ozone exposure in obese compared to non-obese people (Alexeef et al 2007; Rice et al 2013), with Alexeef et al (2007) also providing evidence of an interaction between airway hyperresponsiveness and obesity that causes a greater than additive effect. Evidence of larger associations between exposure to air pollutants ($PM_{2.5}$ and ozone) and increased inflammatory markers among people with obesity is inconsistent and rather limited (Dubowsky et al 2006; Debass et al 2016; Hu et al 2021; Wang et al 2022). Studies focusing on cardiovascular endpoints have reported larger effects in obese populations with respect to PM and HDL dysfunction (Ossoli et al 2022), $PM_{2.5}$ and increased sCD40L (Hu et al 2021) and PM_{10} and ozone and atrial fibrillation (Dahlquist et al 2020). One study observed (at selected lags) stronger associations between ozone concentrations and markers of glucose

homeostasis and lipid metabolism in obese compared to normal weight people (Wang et al 2022).

4.6.3 Discussion of the CHE studies findings

Individuals deemed susceptible to adverse health effects attributed to air pollution are often excluded from CHE studies or, as is in the case of the studies reviewed above, their inclusion has been limited. The available evidence does however suggest that individuals with MetS do not exhibit increased oxidative stress or cardiovascular endpoints following exposure to DE. There is also consistent evidence across a small evidence base that a higher BMI or obesity per se, may be a modest risk factor for adverse lung function (but not systemic/pulmonary inflammation or airway hyperresponsiveness) effects associated with ozone exposure. The small number of studies investigating cardiovascular effects of particle exposures in subjects with metabolic disturbances, their heterogeneity and absence of a healthy control arms precludes the ability to determine whether the various subject characteristics confer increased susceptibility.

Limitations across studies include those inherent in human clinical studies, i.e., relatively limited number of study subjects and exposure concentrations (typically on the high end relative to real world exposures). In addition, and as mentioned above, out of an abundance of caution, those with significant medical comorbidities are often excluded from participating in CHE studies. Indeed, Allen et al. (2009), investigating an oxidative stress response to DE, noted that while participants met the criteria for metabolic syndrome, they had only mildly abnormal metabolic and physiologic characteristics, precluding the evaluation of more sensitive subjects. Stewart et al. (2010), investigating cardiovascular endpoints following ultrafine carbon particle exposures studied a relatively small number of persons with stable type 2 diabetes in a specific age range, without clini-cal cardiovascular disease and who were not on lipid-lowering statin drugs so findings may not be representative of individuals with type 2 diabetes in general.

4.6.4 Discussion of the animal studies

A small number of studies investigating particle exposures in animal models of diabetes/MetS/obesity have, in the main, investigated the effects of traffic-related PM but are very heterogeneous with respect to exposure system (route, dose, duration), animal model (obese, MetS, diabetic) and endpoints studied. They all however have reported increased responses in cardiovascular endpoints, be that prolonged activation of the SNS in obese animals, autonomic responses in a model of MetS or increased susceptibility to coagulation in a model of type 1 diabetes. A number of these studies have reported evidence that these exacerbated effects could be attributed to an increase in inflammation and oxidative stress.

For ozone exposures, there is consistent evidence across a large evidence base of increased susceptibility to pulmonary inflammation and airway hyperresponsiveness in obese mice following an acute (2h) exposure. The consistency of these findings in several mice models of obesity, characterised by different minute ventilations and lung sizes, may suggest that these latter parameters do not wholly account for the greater responses to ozone observed in obese mice. Data indicate that mediators of these events include IL-33, IL-17A and the gut

microbiome. Adiponectin and TNF-α appear to have complex and differing roles following acute versus sub-acute exposures and in the response of lean versus obese mice. In contrast, in rat models with genetic predisposition to obesity, ozone exposure did not result in increased lung protein leakage and inflammation relative to healthy rat strains (Kodavanti et al., 2015).

Similarly, relative to healthy animals, whilst the GK rat model of type 2 diabetes demonstrates minimal or no pulmonary/vascular responses to ozone, mouse models of diabetes demonstrate varying degrees of lung injury and inflammation following ozone exposure. Metabolic effects include a transient exacerbation of glucose intolerance and increases in blood triglycerides in GK rats and in mice, enhanced inflammation and oxidative stress in adipose tissue and strain dependent alterations in insulin resistance.

These results may highlight the complexity of interactions between metabolic status and lung injury and the importance of understanding physiological status and the model. For example, although GK rats have impaired insulin secretion leading to insulin resistance, hyperglycemia and glucose intolerance, similar to advanced forms of human type 2 diabetes, insulin resistance may develop via different mechanisms compared to diabetes in humans. In addition, the GK diabetic model is non-obese, which is often a major contributing factor to the pathogenesis of type 2 diabetes in humans.

4.6.5 Overall evidence for type 2 diabetes

The review of the literature base on potential susceptibility among populations with diabetes and animal models of diabetes to short-term health effects of air pollution exposure is summarised in (Table 15). Within the epidemiological data, a general trend exists for an increased risk in all-cause mortality (but not cause specific) and cause-specific hospital admissions (cardiovascular disease, myocardial infarction, cardiac arrythmia, respiratory diseases) among diabetics in association with particulate matter, but no findings of such for gaseous pollutants.

There is little coherence between epidemiological data and the panel and experimental studies owing to the small evidence base and a lack of comparable data. One could argue however, that findings from the panel and animal studies of a greater effects of PM on heart rhythm disorders among diabetes/models of metabolic syndrome is consistent with increased hospital admissions for cardiac arrythmia. A panel study has also found a greater effect of PM on and vWF (a marker of increased propensity to thrombosis), therefore supportive of increased hospital admissions for cardiovascular disease and myocardial infarction. Very little and/or inconsistent evidence was uncovered that people with diabetes have a greater vulnerability to the inflammatory or oxidative stress effects of air pollution, limiting any suppositions that can be made with respect to potential mechanisms underlying these cause-specific hospital admissions.

Mechanistic evidence underlying the epidemiological finding of an association between death due to diabetes and short-term exposure to ambient air pollution levels has not been identified.

The US EPA ISAs for PM concluded that there was inadequate evidence that individuals with pre-existing diabetes are at potentially increased risk of PM-related health effects (US EPA 2019). The conclusion reached in the present report generally reflects this sentiment, given that the evidence base for PM-related mortality is based on only two studies finding statistically significant increased susceptibility in diabetics (both of which were published prior to 31 March 2017 - the cutoff date for publications considered in the ISA), no evidence exists for cause-specific mortality and the limited evidence from hospital admissions studies precludes any conclusive inference despite some evidence for increased risk. No short-term experimental studies contributed to the US EPA findings, but from our findings, there was little evidence from heterogenous studies on cardiovascular endpoints (Table 15).

The conclusion in the US EPA ISAs for NO_2 and ozone that there was inadequate evidence that individuals with pre-existing diabetes are at potentially increased risk of PM-related health effects (US EPA 2016, 2020) are in line with the conclusions reached in the present report.

Table 15 - Type 2 diabetics - a population at increased risk from short-term exposure to air pollution? Overall evidence.

Study	Pollutant	Main findings
Epidemiological time-series & case-crossover	PM	General trend for increased risk of all-cause mortality & hospital admissions (CVD, MI, cardiac arrhythmia, resp. disease)
Epidemiological panel	$PM_{2.5}$ & NO_2	Inconsistent evidence of increased inflammation
	PM_{10}	Increased von Willebrand factor
	PM & ozone	Increased risk of heart rhythm disorders
Controlled human exposure	DEP	Evidence of no increased susceptibility - MetS subjects
	UFP	Evidence of no increased susceptibility – MetS subjects & diabetics
Animal	DEP	Increased lung & pancreatic injury; coagulation - rat model of T1D
	P + SOA	More pronounced autonomic CV responses
	Ozone	Greater susceptibility in mice v rats (respiratory & metabolic effects)

4.6.6 Overall evidence for obesity

The review of the literature base on potential susceptibility among obese subjects and mouse models of obesity to short-term health effects of air pollution exposure is summarised in Table 16. Coherence between the epidemiological panel studies and experimental data (CHE and animal studies) is limited to an augmented respiratory response to ozone. This is consistent with the US EPA ISA for ozone, which states 'there is suggestive evidence indicating that individuals with pre-existing obesity are at potentially increased risk of ozone-related health effects'. This statement was based on a number of studies reviewed in the current report, and as such, is based on an exaggerated pulmonary response to ozone.

Panel studies (consisting of predominantly white, middle- and older-aged men and women) have found a greater lung function decline in response to acute ozone exposure for subjects who are obese compared to the non-obese population (Alexeef et al 2007, Rice et al 2013). One of these studies also provided evidence of an interaction between airway hyperresponsiveness and obesity that causes a greater than additive effect (Alexeef et al 2007). We could not compare these results with findings from epidemiological studies investigating the effects of short-term exposure to air pollution on relatively large populations, i.e. time-series or case-crossover designs. This is because presence/absence of obesity or BMI measurements are not generally available in routinely collected administrative mortality or morbidity daily data. This information is usually recorded in cohort studies with individual data which however assess the effects of long- rather than short-term exposure to pollution.

Controlled human exposure studies also suggest that a higher BMI (Bennett et al 2007) and obesity (Bennett et al 2016) may be a modest risk factor for adverse lung function effects associated with ozone exposure, especially for women. These results are in line with the ozone exposure-response model for lung function that predicts FEV1 responses increase with increasing BMI (McDonnell et al., 2013). Data for this model includes FEV1 responses of 741 individuals (104 females, 637 males; age 18-36 years) exposed one or more times to ozone and/or filtered air. The finding of variations in air pollution effects based on variation in BMI rather than frank obesity (Bennett et al 2007), is supported by studies that have shown particle deposition (Bennett and Zeman 2004) and responsiveness (Alexis and Peden 2006) relationships with BMI, with few or no obese subjects in the analyses. The human studies are consistent with a wealth of animal data demonstrating increased susceptibility to ozone-associated pulmonary resistance and inflammation and airway hyperresponsiveness in obese mice compared to non-obese control mice and those effects do not depend on the mode of obesity.

Mechanisms that may contribute towards the greater decline in lung function after ozone exposure with increasing BMI include lower lung volumes in individuals with an increased BMI that in turn, influences ozone dose to lung tissue. Bennett et al (2007) did not however find a significant relationship between BMI and baseline FVC (i.e. an index of lung volume). Obese humans are also known to breathe with relatively smaller tidal volumes than normal weight individuals, resulting in reduced stretching of lung tissue that might play a role in the increased responsiveness to ozone with BMI. However, Bennett et al (2007) reported that in the subset of 127 (80M/47F) subjects with minute ventilation measurements, tidal volumes actually tended to increase with BMI, though not significantly. Breathing frequency may also

affect ozone dose to the lung by controlling the residence time of ozone within the airways. No relationship however was found by Bennett et al (2007) between BMI and breathing frequency.

Adipose tissue secretes inflammatory adipokines (e.g. hormones including leptin and adiponectin; cytokines including TNFα and IL-6) into the blood that may modulate inflammation throughout the body, including the lungs where they may affect airway function and responsiveness to ozone (Shore 2008). Indeed, a possible role for these adipokines, as well as the gut microbiome, has been demonstrated in the exaggerated pulmonary response to ozone seen in obese mice (Section 4.5.3.a). If adipocyte-derived factors play a role in the spirometric response observed in the CHE studies, then the fact that females have a considerably greater percent body fat for a given BMI than males may explain the observations of a more significant relationship among women (Bennett et al 2007).

The implication of these findings with ozone for heightened respiratory effects of pollutant particles among obese subjects is not certain, owing to a lack of comparable data (Table 16). As previously mentioned, we do know however that BMI is associated with a graded increase in the estimated total lung dose of deposited particles (Bennett & Zeman 2004), suggesting that increased weight may be associated with increased risk from inhalation of pollutant particles in ambient air. No studies were identified that compared respiratory effects of NO_2 in obese versus non-obese subjects or animal models. Data is also lacking however across panel, CHE and animal studies on increased cardiovascular or metabolic susceptibility to gaseous and particulate air pollution in obese subjects/animal models (Table 16).

Table 16 - Obese - a population at increased risk from short-term exposure to air pollution? Overall evidence.

Study	Pollutant	Main findings
Epidemiological (e.g., time-series & case-crossover)		No studies to report upon
Epidemiological panel	Ozone	Greater decrement in lung function; stronger associations with atrial fibrillation & markers of glucose homeostasis/lipid metabolism
	$PM_{2.5}$	Inconsistent evidence of increased inflammation; increased sCD40L
	PM_{10}	Stronger association with atrial fibrillation and HDL dysfunction
Controlled human exposure	Urban $PM_{2.5}$	Decreased vasodilation & HRV (overweight)
	Ozone	Increased decrement in lung function (overweight & obese)
Animal	DEP	Increased airway resistance & inflammation
	Urban PM_3	Altered gene expression relating to inflammation & OS; SNS activation
	Ozone	In mice increased airway resistance, responsiveness & inflammation

Chapter 5 – Asthma subtypes

5.1 Introduction

The pathogenesis of asthma exhibits marked and complex heterogeneity, with numerous and overlapping (a) phenotypes that define observable characteristics and (b) endotypes that define molecular mechanisms (Hekking and Bel 2014, Boonpiyathad et al 2019, Nadif and Savoure 2023).

This heterogeneity calls for the relevant sub-division of asthma to correctly characterise the disease in a given individual so that better and more precise strategies, be they selected treatments and/or avoidance measures, can be prescribed. The stratification of asthma into different types is however controversial and current definitions (e.g., by phenotype or endotype) are different to what they were a decade or so ago and future definitions will undoubtedly be different from those used today (Appendix 2 – Clinical perspective on asthma subtypes).

Some of the first asthma phenotypes to be defined included trigger-induced ones such as allergic asthma, non-allergic asthma (i.e., asthma that is or is not allergen driven), infectious asthma and aspirin-exacerbated asthma. Other approaches have adopted phenotypes associated with environmental exposures (e.g. occupational agents, cigarette smoke, cold dry air) or specific symptoms/ clinical characteristics (e.g. exacerbation prone, cough, obesity[5], age of onset) (Hekking and Bel 2014).

With respect to age of onset, asthma phenotypes in childhood and adulthood have been proposed:

- Phenotypes in childhood focus on the time of onset (early/preschool i.e. <6 years or late/school age), the frequency of the wheeze (transient or persistent), the triggers (episodic viral wheeze or multiple-trigger wheeze), the allergic expression of the disease and other comorbidities (Just et al., 2015, Just et al., 2017, Deliu et al., 2017).
- From childhood to adulthood, the number and heterogeneity of asthma phenotypes increase to include early or late onset (e.g. >65 years), triggers (e.g. environmental/occupational exposures, aspirin, exercise), an association with menstruation and an overlap with COPD later in adulthood. A recent systematic review of asthma phenotypes has been undertaken of 68 studies reporting adult asthma phenotypes derived by data driven methods. The review reported a lack of consistency in the choice of the statistical method and variables, and in the identified phenotypes. Overall, the most frequent phenotypes were related to allergy/atopy, gender and severe asthma.

Another strategy in the subdivision of asthma is based on biomarkers of airway inflammation found in bronchial biopsy specimens, sputum, peripheral blood or exhaled air. This approach

[5] Within the obese asthma subcategory, at least two different phenotypes have been described: one includes mostly female, non-atopic subjects with late-onset asthma; the other, subjects with atopic asthma, usually early-onset (Dixon et al 2011).

can be defined as endotyping the disease and is deemed to be the most promising because it attempts to identify molecular characteristics/underlying mechanisms that can be effectively targeted by implementing specific treatments and/or protective measures (Wenzel, 2012).

Table 17 summarizes the endotypes most commonly reported in the literature:

- The type 2 (T2) response (also called type-2 high [T2-high] on the basis of elevations in pathways downstream of type 2 cytokines or eosinophilic inflammation) with or without allergy.
- The non-type 2 (non-T2) response (also called T2-low or non-eosinophilic inflammation) that involves neutrophils or less inflammatory cells (Table 1).

Table 17 - Asthma endotypes based on Type 2-high and -low inflammation (taken from Nadif and Savoure 2023).

Inflammation	Endotype	Driven cell	Biomarkers	Characteristics
T2-high				
	Allergic	Eosinophils	IgE, FeNO IL-4, IL-5, IL-13 TSLP, IL25, IL-33 Periostin	Most common in childhood Early-onset severe asthma Impaired lung function Increased AHR Steroid responsiveness
	Non-allergic	Eosinophils	FeNO IL-4, IL-5, IL-13 TSLP, IL-25. IL-33 Periostin PGD2	Most common in adulthood Steroid insensitivity
T2-low		Neutrophils, Th17	IL-17	Often severe Steroid insensitivity
		None	MMP9 Oxidative stress?	Steroid insensitivity

FeNO: exhaled nitric oxide; IgE: immunoglobulin E; IL: interleukin; MMP9: Metalloproteinase 9; PGD2: prostaglandin D2; T2: Type 2; Th17: T helper 17; TSLP: thymic stromal lymphopoietin

Type 2 asthma comprises the interplay of several inflammatory pathways. Allergy-driven T2 asthma includes a large majority of children and about 50% of adults with asthma. Patients classified as having type 2 non-allergic eosinophilic asthma are most often adults with adult-onset disease.

Non-type 2 asthma is often associated with neutrophilic or paucigranulocytic inflammation, driven for example by IL-17, or it may be independent of a specific inflammatory process.

The existence of neutrophils and eosinophils observed in some asthmatics with severe asthma is called the mixed (type 2/type 1/type 17) endotype and adds further complexity in the identification of endotypes related to type 2 versus non-type 2 inflammation (Agache, 2019).

A problem with categorising patients this way is that the Th status changes with treatment so that with medication, an asthmatic can change from being T2 high to T2 low. A more useful stratification may therefore be one of the earlier and aforementioned subdivisions, namely allergic asthma versus non-allergic asthma as these are static characteristics (e.g. irrespective of treatment).

5.2 Susceptibility to the health effects of air pollution amongst different asthma subtypes

This section of the report evaluates the literature to determine whether there is evidence that certain subtypes of asthma may be more or less susceptible to the health effects of air pollution. For example, IL-17 is recognised as an important driver of asthma pathogenesis, particularly in severe, treatment resistant cases (Chesné et al. 2014). The recognition that ozone and obesity synergistically induce IL-17 (Mathews et al 2018) in the lung raises the question as to whether environmental exposures or medical conditions contribute to exacerbation prone endotypes and as such, whether obese patients with asthma and the IL-17 endotype may benefit particularly from weight loss and should be vigilant against exposure to elevated ambient concentrations of ozone.

The literature searches conducted through PubMed and Web of Science are tabulated in Appendix 1. As suspected, very little research has been conducted on this topic and for this reason the few studies identified and summarised below, are not limited to short-term exposure to ambient air pollutants but also include one study that examined the response to indoor PM amongst children with non-atopic versus atopic asthma (McCormack et al 2011) and well as studies of differential susceptibility to chronic exposure in allergic and non-allergic phenotypes of asthma (Pekince and Baccioglu 2022) and early versus late-onset disease (Wu et al 2016).

5.2.1 Human studies

Allergic and non-allergic asthma

Rosenquist et al. (2020) conducted a time-stratified case-crossover study assessing the effects of $PM_{2.5}$ and O_3 on asthma exacerbations in individuals with allergic (n = 8,821; defined as those with asthma and an allergy comorbidity diagnosed through ICD-9 or ICD-10 codes) and non-allergic (n = 14,498) asthma (both adults and children) in Nevada, USA. Asthma and allergy diagnoses were assigned through medical records at a specified health facility. A total of 49,832 acute exacerbation hospital visits were recorded between January 2011 and June 2017 at the health facility, with a relatively even split between the two subgroups. Three-day moving averages of $PM_{2.5}$ and O_3 were calculated from a fixed-site monitor. Associations were assessed using single- and multi-pollutant distributed lag non-linear models.

- Statistically significant differences were observed between asthma subgroups, with 3-day moving average $PM_{2.5}$ associated with hospital visits in those with allergic asthma (adjusted OR: 1.10 [1.07, 1.13]) higher than that for those without (1.05 [1.02, 1.09]).
- Further subgroup analyses reported allergic asthma admissions to be more strongly associated with $PM_{2.5}$ and O_3 exposure (in two-pollutant models) in comparison to non-allergic visits when stratified by sex, age, season and temperature.
- Further subgroup analyses reported allergic asthma admissions to be more strongly

associated with $PM_{2.5}$ and O_3 exposure (in two-pollutant models) in comparison to non-allergic visits when stratified by sex, age, season and temperature.

A prospective, case-control study in Kirikkale, Turkey examined the effects of air pollution in subjects with allergic and non-allergic phenotypes of asthma (Pekince and Baccioglu, 2022).

- Of the 57 subjects with well-controlled asthma under regular treatment, 22 had allergic and 35 had non-allergic phenotypes. An allergic asthma phenotype was defined as the presence of respiratory symptoms that were clinically relevant with the positive allergens (pollens, n = 6; house dust mites, n = 8; blatella, n = 3; and mix, n = 5) in allergy tests. Fifty-one healthy individuals were also included. The overall mean age was 43.39 years.
- Clinical parameters (respiratory symptoms, pulmonary function, hospital admissions, medication use), total antioxidant status, total oxidant status and thiol/disulphide levels were compared during the most (January - PM_{10} : 27 µg/m^3; SO_2 : 18 µg/m^3) and least (June - PM_{10} : 18 µg/m^3; SO_2 : 3 µg/m^3) air-polluted months of the year.
- The rate of antibiotic and short-term corticosteroid use, emergency admissions, and hospitalization due to asthma exacerbation were higher in the non-allergic asthma group than the allergic group in January compared to June.
- Pulmonary function increased in June compared to January in both asthma groups with a more significant difference in favour of the non-allergic group.
- A significant decrease in eosinophil counts, total antioxidant status and total oxidant status in June, compared to January, was only observed in the non-allergic group.
- Of note, 34% of the non-allergic asthma patients were obese, compared to none in the allergic group.
- One explanation given for why allergic asthma patients were less affected during the most polluted month of January was a lower amount of allergens in the environment in that period.

Noh et al. (2016) conducted a time-series analysis on the effect of short-term exposure to ambient air pollution (O_3, PM_{10}, CO, NO_2 and SO_2) on emergency department visits for asthma in Seoul, Korea from 2005 to 2009, and assessed effect modification by prior allergic disease (i.e., with no history of allergic disease, with any history of allergic disease, with a history of asthma, or with a history of atopic dermatitis or allergic rhinitis).

- The number of patients in the study was 27,146 and from the 33,751 total asthma attack cases in the study, 12,765 (37.8%) had no history of allergic disease or asthma, 16,661 (49.4%) had a history of asthma and 4,325 (12.8%) had a history of atopic dermatitis or allergic rhinitis.
- The largest risk for emergency room visit was observed for ozone among patients with a history of atopic dermatitis or allergic rhinitis, but the difference with other groups was not statistically significant.
- However, for PM_{10}, statistically significant differences were observed for lag 1 among participants with a previous history of atopic dermatitis or allergic rhinitis compared with participants without any history of allergic disease or with a history of asthma.
- In conclusion, a general trend for higher risk estimates among those with a history of allergic disease, including asthma, compared with those without any history was observed but statistical power was not enough to show statistically significant differences in most cases.

In a longitudinal study, McCormack et al. examined the response to in-home PM exposure amongst a predominantly African American cohort, based in East Baltimore, of pre-school age children with non-atopic and atopic asthma (McCormack et al., 2011).

- Children (n=41 non-atopic, mean age 3.9; n=92 atopic, mean age 4.6) were evaluated at baseline, 3, and 6 months. At each time interval, $PM_{2.5}$ and $PM_{2.5-10}$ was monitored for 3 consecutive days in the child's bedroom and health outcomes (rescue medication and symptoms during the previous 2 weeks) were assessed through a caregiver report. Atopy was defined as at least 1 positive skin test, defined as wheal size at least 2 mm greater than the negative control.
- The median indoor $PM_{2.5–10}$ concentrations were similar among children with non-atopic and atopic asthma, with concentrations of 13.4 $\mu g/m^3$ and 11.6 $\mu g/m^3$ respectively (p=0.52). The indoor $PM_{2.5}$ concentrations were higher in the homes of children with non-atopic asthma compared to those with atopic asthma, 35.7 $\mu g/m^3$ and 27.6 $\mu g/m^3$ respectively (p=0.04).
- Higher concentrations of $PM_{2.5–10}$ were associated with increases in asthma symptoms and the need for rescue medication use in both the non-atopic and the atopic subgroups. The magnitude of the effect was similar between groups.

In a case-control study in Czech Republic in 2008, Choi et al. (2021) investigated the associations between ambient Benzo[a]pyrene (B[a]P), a polycyclic aromatic hydrocarbon (PAH), and non-atopic and atopic asthma in children. While this paper did not assess the impact of the air pollutants that are within the scope of our rapid review, we included it since PAHs come from similar sources to criteria pollutants, such as emissions from vehicles, domestic heating or cooking, and might have similar health impacts. The less volatile PAHs are carried on PM so may contribute to effects of PM.

- 191 asthmatic and 194 control children were recruited from industrial and semi-rural areas and medical records, blood and urine samples and confounder data were collected. Exposure windows of 30-days periods for measured ambient B[a]P levels were assigned to study participants, and the mean levels were 11.4 ng/m^3 for industrial and 2.5 ng/m^3 for background regions.
- Non-atopic cases were exposed to higher B[a]P concentrations compared to non-atopic controls, while atopic asthmatic and control children had similar exposures.
- Adjusted odds ratios comparing asthmatic and control children per ln-unit increase in B[a]P were found to be higher in non-atopic children (4.7 [1.9-11.5] for boys and 44.8 [4.7-428.2] for girls) compared with atopic (2.0 [0.4-11.1] and 3.0 [0.7-12.7] respectively).
- However, sample sizes were very limited in this study and the results showed high uncertainty.

Mild intermittent and mild persistent asthma

In a controlled human exposure study, Vagaggini et al. evaluated airway inflammatory response of ozone in subjects with different degrees of asthma severity (Vagaggini et al., 1999).

- Two groups of asthmatic subjects were studied: 7 subjects with mild intermittent asthma, asymptomatic and without regular treatment (mean age: 24 years; Group A)

and 7 with mild persistent asthma, requiring regular treatment to control asthma symptoms (mean age: 29.7 years; Group B). Patients in this latter group withdrew from regular treatment 72 h before each exposure.
- All subjects were exposed, in a randomized crossover design, to air or ozone (0.26 ppm for 2 h with intermittent exercise).
- Questionnaire based total symptom score and FVC and FEV_1 (measured at the end of 1 and 2 hours of exposure and 6 hours after the end of ozone exposure) were significantly increased and decreased respectively in Group A, whereas no changes were observed in Group B except for a significant decrement of FEV_1 2 hours after the beginning of ozone exposure.
- Sputum (collected 6 hours post exposure) neutrophil percentage was significantly higher post ozone than post air exposure in both groups whilst IL-8 was higher after ozone exposure versus air, only in Group A. No ozone-induced change in sputum eosinophil percentage and eosinophil cationic protein concentration were observed in either group.
- Explanations given over the mild effect on regularly treated asthmatic subjects included the need for a longer withdrawal of anti-asthma drugs prior to ozone exposure, greater antioxidant activity in the airway mucosa in subjects with more severe airway inflammation and a blunted perception of dyspnoea and other irritant symptoms of the upper airways in subjects with mild persistent asthma in comparison with patients with mild intermittent asthma.

Late- and early-onset asthma

In an observational population-based study of adults from Southern Taiwan, Wu et al. (2016) assessed whether ambient air pollution (PM_{10}, NO_2, SO_2) could have a differential effect on late- (onset > 12 years) and early- (≤ 12 years) onset asthma (Wu et al., 2016).

- A cross-sectional questionnaire survey about respiratory health was conducted among 703 schoolchildren's parents (aged 26 to 50 years) ever having typical asthma symptoms.
- 253 were defined as having early-onset and 450 as having late onset disease.
- Individual exposure to ambient air pollution (PM_{10}, NO_2, SO_2) was estimated for the preceding year before the asthma severity survey.
- Using the median of PM_{10} (66 µg/m3) as a cut-off, those exposed to higher PM_{10} were more likely to have higher severity scores (OR = 1.74; 95 % CI, 1.13 – 2.70) only for asthmatics with asthma onset at > 12 years.
- In two pollutant models, the effect of 1-year average of PM_{10} remained significant after adjusting for other pollutants.

Lau et al. (2020) utilised data from a cohort of Canadian children (n = 770,776) to assess the effect of NO_2 exposure on early onset (defined as 0 – 3 years old) and late onset (4 – 9 years) asthma. A sensitivity analysis was also conducted in which the cut-offs were modified for both early onset (0 – 5 years) and late onset (6 – 9 years).

- Increased ORs observed for early onset asthma at higher levels of NO_2 in comparison to late onset (2.16 [1,27, 3.68] and 1.43 [0.91, 2.26], respectively, at the fourth quartile (17.87 ppb) in comparison to the first quartile (6.31 ppb) of NO_2), with no disparity observed at the lowest concentrations.

- Smaller disparities between subtypes were observed in the sensitivity analysis with modified onset age cut-offs.

Sbihi et al. (2017) conducted a population-based birth cohort study in Canada using administrative data from 1999 to 2002 to identify trajectories of childhood asthma and characterize the potential impact of residential greenness and air pollution on different asthma subtypes. Despite the fact that this study examined the effects of long-term exposure to pollution, it provided some insight into the differential impact of air pollution on different asthma subtypes:

- Mothers with a residential history throughout their pregnancy in the metropolitan area of Vancouver, British Columbia, Canada, were included in the study and children born were followed for 10 years (n = 68,195).
- The authors applied group-based trajectory modeling (GBTM), a modelling approach that identifies groups of individuals following similar developmental asthma trajectories, to classify children who belong to a distinct disease trajectory (Nagin and Odgers 2010).
- They identified non-asthmatics (88.8% of the study population) and three different asthma groups: (a) Late-onset chronic asthma, i.e. children who start developing asthma by age 3 with peak prevalence by age 6 that is sustained until the end of follow-up (4.1%), (b) Early-onset chronic asthma, i.e. children who start developing asthma by age 3 with peak prevalence by age 4 that is sustained until the end of follow-up (1.5%), and (c) Transient asthma, i.e. children who start developing asthma by age 1 with peak prevalence by age 2, and no asthma activity after age 6 (5.6%).
- Multinomial logistic regressions showed that an interquartile range increase in NO_2 (exact value not reported, median levels were 33 $\mu g/m^3$) increased the risk of chronic asthma trajectory relative to non-asthma trajectory, and the risk was higher for late- (30% [11-52%]) compared with early-onset asthma (20% [0-51%]). For transient asthma, the risk estimates were considerably lower and not statistically significant (6% [-70-22%]).
- For $PM_{2.5}$, an interquartile range increase (exact value not reported, median levels were 12.5 $\mu g/m^3$) was associated with increased risks of chronic asthma trajectory relative to non-asthma trajectory, but higher risks were observed for late-onset and transient asthma (24% [7-45%] and 24% [8-42%] respectively) compared with early-onset asthma (-1% [-20-23%]).
- Two pollutant model estimates showed similar associations. Odds ratios for higher exposure quartiles were non-significant likely because of the small number of children in each trajectory experiencing these levels.

Other asthma classifications

Mamessier et al assessed the effect, ex vivo, of DEP on T-cell activation in severe uncontrolled asthmatics during and outside exacerbations (Mamessier et al., 2006).

- Nineteen blood samples were obtained at distance from an exacerbation and 13 samples were obtained during an exacerbation. Five patients were studied both during and outside of an exacerbation. Results were compared with data obtained in healthy controls (n =14)

- Peripheral blood mononuclear cells were cultured in the presence of low-dose DEP-PAH (SRM 1650; 8 μg/ml for 7 days).
- DEP increased T-cell activation in asthmatics, enhancing activation marker expression, cytokine production and proliferation.
- The effect was statistically more pronounced in samples taken during an exacerbation for cytokine production and proliferation.

In a cross-sectional study of 4,209 French schoolchildren (aged 10–12 years) conducted between March 1999 and October 2000, Zhou et al. (2013) investigated whether emotion and conduct problems (ECPs) modify the relationships between ambient air pollutants (NO_2 and PM_{10}) and childhood asthma, classified as current wheezing (n = 289) or doctor-diagnosed (n = 196), and eczema. Although the main focus of the study was to assess the role of ECPs in outcome-exposure relationships, the analysis reported adjusted ORs for both asthma subtypes without an interaction term for ECPs.

- No statistically significant associations reported for any pollutant on either asthma subtype.
- No difference in exposure-outcome associations between subtypes observed.

Zhang et al. (2020a) conducted a time-series analysis in Shenyang, China, from 2011 to 2018 to explore the associations between hospital admissions for asthma and multiple environmental exposures, including air quality and meteorological factors.

- In total, 173,747 outpatient hospital visits were included in the analysis, and were categorised into acute bronchial (n = 124,616) and chronic cough-variant asthma (n = 24,144). The cumulative (lag days 0-10) effects of short-term exposure to air pollution on hospital admissions were assessed by using distributed-lag models and pollutant-specific daily air quality indices (AQI).
- Chronic cough-variant asthma patients were found to have higher risk of hospitalization (14.5%) compared with acute bronchial asthmatics (1.6%) when assessing increases from the minimum hospitalization AQI value to the 95th percentile. However, both risks were not statistically significant (p-values >0.05, confidence intervals not reported) and the statistical significance of their difference was not assessed.

5.2.2 Animal studies

No studies were identified that employed animal models to investigate differential susceptibility to air pollution among different subtypes of asthma.

Although animal models of asthma only partially capture the multitude of pathways underlying human asthma and species specific limitations need to be considered when extrapolating results to humans (Holmes et al., 2011), calls continue for more complex models of novel asthmatic subtypes to better define biomolecular pathways (Wenzel, 2016, Harkema et al., 2017, Martin et al., 2014).

Examples include a murine model, developed using combinations of infectious and allergic stimuli, that demonstrates corticosteroid refractory inflammation and airway

hyperresponsiveness, with possible involvement of the type-1 cytokine, IFN-γ and secretory leukocyte protease inhibitor (Raundhal et al., 2015).

Strain-dependent differences in the pulmonary response to repeated ozone exposures in non-atopic mice include greater eosinophilic inflammation, mucous cell metaplasia and expression of genes related to type 2 immunity and airway mucus hypersecretion in lungs of C57BL/6NTac mice compared to BALB/cNTac mice (Harkema et al., 2017).

The identification of gene-environment interactions has evolved with the advent of new mouse genetic reference populations such as the Collaborative Cross (CC), a panel of recombinant inbred strains derived from 8 inbred strains (Srivastava et al., 2017). Smith et al. have surveyed CC strains to identify phenotypes with heightened susceptibility to ozone (0.8 ppm 4 hours/day for 9 days) (Smith et al., 2021). Across 12 strains evaluated, CC002/Unc (referred to as CC002) exhibited extreme eosinophilic inflammation. BAL fluid from CC002 mice contained nearly 40% eosinophils versus 0–7% across the other strains and 0–2% in the classical C57BL/6NTac and BALB/cNTac inbred strains, prompting the researchers to suggest it may represent a new model of nonatopic asthma for studying novel mechanisms that underlie the association between ozone exposure and nonatopic asthma.

Summary of studies investigating potential susceptibility to the effects air pollution exposure by asthma subtype

- Observational studies:
    - Varied asthma subtype categorisation and further mechanistic work is required to define asthma phenotypes.
    - Allergic asthma attribution also varied, with studies attributing allergic asthma in the presence of any or specific co-allergens.
    - Mixed results observed for susceptibility by allergic or non-allergic phenotype for PM-associated endpoints, with two studies suggesting greater risk for asthma hospitalisation for allergic asthmatics in relation to O_3 and PM exposure.
    - Findings across studies investigating late- and early-onset asthma age cut-offs varied.
    - Increased risk of developing early onset asthma in relation to NO_2 exposure suggested in one North American study, whilst a study from Asia suggests greater vulnerability in late onset individuals.

- Experimental studies:
    - Ex vivo, that DEP has a more pronounced effect on T-cell cytokine production and T-cell proliferation when samples are taken during an exacerbation than outside of one.
    - In a CHE study, the response to ozone exposure is greater in untreated mild intermittent asthmatic subjects compared to treated mild persistent asthmatic subjects, both in terms of clinical/functional response and biochemical and cellular changes in induced sputum.

5.3 Discussion

The limited research conducted to date confirms that it is too early to make a judgement as to whether individuals with certain subtypes of asthma may be more susceptible to adverse health effects attributed to poor air quality. As stated previously, the most relevant definitions of subtypes of the disease continue to be debated and it will take time for sufficient studies to accumulate on potentially differential effects of air pollution exposure, despite the convincing evidence for increased susceptibility as a whole for asthmatics in comparison to non-asthmatics.

Of the few published studies, heterogeneity exists with respect to study design, disease distinctions (e.g., allergic versus non-allergic, early-versus late onset) and the clinical endpoints investigated. Greater focus has been on a comparison of responses between allergic and non-allergic asthma where there seems to be some suggestive evidence for differential risks for certain asthma subtypes. Two epidemiological studies reported largest risk of hospitalization (i.e., emergency room visit or admission) in relation to short-term air pollution exposure for patients with current or a history of allergic asthma compared with non-allergic asthmatics (Noh et al. 2016, Rosenquist et al. 2020). Mixed evidence was observed with differential impacts on early- and late-onset asthmatic children. Two studies reported higher risk for late- compared with early- onset asthma in relation to air pollution exposure, while another showed the opposite direction (Wu et al. 2016, Sbihi et al. 2017, Lau et al. 2020). These results were based on long-term rather than short-term exposures to NO_2 (Sbihi et al. 2017, Lau et al. 2020) and PM_{10} (Wu et al. 2016) and the definition of early/late-onset was not consistent across studies.

A notable limitation of these identified studies was the omission of (a) variables thought to be key in influencing air pollution-induced exacerbations (e.g., type of medication, adherence in taking medication) or (b) biologic measurements to investigate mechanistic differences between responses to pollutant exposure. A potentially helpful biomarker in predicting an asthmatic's response to air pollution is an eosinophil count, given the central proinflammatory role of these cells in the pathogenesis of both allergic and non-allergic asthma and that they are associated with asthma exacerbations. It is of note here, that initial findings of a retrospective analysis of two controlled human exposure to DE studies in asthmatic volunteers have shown no association between a subject's baseline blood eosinophil count and health outcomes reported (unpublished findings from Chris Carlsten, University of British Columbia).

For allergic phenotypes, acute exposure to air pollution may exacerbate asthma by directly stimulating an inflammatory response by altering innate and adaptive immunity (Miller and Peden, 2014). Alternatively, pollutants could enhance a response to allergens (Guarnieri and Balmes, 2014, Gandhi and Vliagoftis, 2015). Studies in animals and man supports this, with evidence for such an effect on lung function and inflammatory responses to ozone, nitrogen dioxide, sulphur dioxide, and diesel-exhaust particles (D'Amato et al., 2002, Diaz-Sanchez et al., 2006, Devalia et al., 1994). Mechanisms through which air pollutants could enhance sensitisation to airborne allergens include increased deposition in the airways via carriage by particles, heightened epithelial permeability due to oxidative injury, increased antigenicity of proteins by chemical modification and a direct adjuvant effect (Diaz-Sanchez et al., 1999).

In the absence of atopy, aeroallergens may still have a role in pollutant-induced exacerbations in a manner similar to atopic asthmatics. In support of this, Burney and colleagues reported that exacerbations, in both non-atopic and atopic asthmatics, were associated with increases in the patient's IgE binding to outdoor airborne particles collected during the weekend preceding the exacerbation as compared to control weekends (Burney et al., 2008).

Table 18 - Are certain subtypes of asthma at increased risk? Overall evidence.

Study	**Pollutant**	**Main findings**
Epidemiological observational	PM, NO_2, ozone	Very limited and inconsistent evidence for differences in the risk of asthma-related endpoints by different subtypes
Controlled human exposure	Ozone	Greater response in mild intermittent asthma compared with treated mild persistent asthma
Ex vivo	DEP	More pronounced effect on T-cell proliferation & cytokine production during an exacerbation versus outside of one

Chapter 6 – Life-stage

6.1 Introduction

It is known that the health effects of short-term exposure to air pollution differ among individuals based on their specific biological, demographic or lifestyle characteristics, which undergo substantial changes throughout various life stages (Hooper and Kaufman 2018, O'Neill et al. 2012). Infants and young children due to the ongoing development of their lungs and their higher inhalation rates, as well as the elderly due to pre-existing conditions and pregnant women, are particular groups that can be more susceptible to the health impacts of air pollution exposure. Recognising and strengthening the evidence for these differential impacts is important for informing policy interventions and communicating the evidence to these subpopulations and the general public.

The World Health Organisation recently updated the Air Quality Guideline values and used epidemiological evidence to support these limits (Velasco and Jarosińska 2022). In particular, multiple systematic reviews and meta-analyses were commissioned to investigate the associations between short- and long-term exposure to air pollution and mortality (Chen and Hoek 2020, Orellano et al. 2020). In relation to the health effects of short-term exposure to air pollution in specific age groups, Orellano et al. (2020) reported limited evidence on statistically significant effect modification by life-stage for cause-specific mortality. We sought to identify mortality and morbidity studies that support the evidence of potential effect modification of the health effects of short-term exposure to air pollution by different life-stage.

6.2 Epidemiological studies assessing certain age groups as potentially more susceptible to the effects of air pollution

The present review identified studies assessing whether certain age groups represent potentially vulnerable subpopulations to the harmful effects of ambient air pollution. The pollutants investigated were NO_2, PM_{10}, $PM_{2.5}$, SO_2 and ozone. A total of 15 studies assessing the effect of life-stage on all-cause/cause-specific mortality, hospital admissions, emergency room visits (ERVs) or outpatient visits were included from the 149 epidemiological studies identified through database searching (Appendix 1). More than half of the identified studies included for review were conducted in Asia, with three in Europe, two in North America and two in South America. For inclusion in the present review, a study had to have investigated potential effect modification by age within the association between exposure to ambient air pollution and the aforementioned outcome categories.

6.2.1 All-cause mortality studies

Several studies assessed potential effect modification by age on the association between air pollution exposure and all-cause mortality.

- Cai et al. (2019) conducted a time-series study investigating associations between $PM_{2.5}$ exposure and all-cause mortality (n = 41,815 deaths), cause-specific mortality and respiratory diseases in Shenzen, China, although effect modification by age was

only reported for all-cause mortality. The study suggested an increased excess risk in those aged 65 years and older compared to those younger than 65, however, the findings did not reach the nominal level of statistical significance.

- A second study in China was conducted in Shanghai by Kan et al. (2008), which similarly observed non-statistically significant effect modification for 65 years & older rather than 5-44 / 45-54 years old, in associations between PM_{10}, NO_2 and SO_2 and all-cause mortality. However, the effect estimates for PM_{10} and NO_2 in those >65 years of age were higher and statistically significant (percent increase in mortality was 0.26% [0.15, 0.38] and 1.01% [0.69, 1.34] respectively for 10μg/m^3 increase in exposure.
- Cakmak et al. (2007) investigated age group susceptibility in non-accidental mortality in relation to air pollution using a time-series design in Chile from 1997 to 2003. They compared the risks of mortality for people <64, 65-74, 75-84 and >85 years of age and found that those >85 years of age were observed to be over twice as likely to die from acute increases in PM_{10} and > 50% more likely to die from increases in O_3 and SO_2 compared to those <64 years of age. The increases in the reported risks were generally monotonic with increasingly older age groups.
- Forastiere et al. (2008) conducted a case-crossover study to investigate exposure to PM_{10} in relation to all-cause mortality and reported strong signals of effect modification of the association by age. Pooled estimates across the nine Italian cities reported statistically significant ($p < 0.05$) increased risk of all-cause mortality in relation to a 10μg/m^3 increase in exposure to PM_{10} for those aged 75-84 (0.59% [0.20, 0.97] percent increase in risk) and 85 years and older (0.97% [0.53, 1.42]), in comparison to those aged 35-64 (-0.20% [-0.77, 0.37]).
- A follow-up (to Forastiere et al 2008) study by Alessandrini et al. (2016) conducted across 12 Italian cities found increased risks of all-cause mortality in relation to PM exposure for those aged 85 years and older compared to those aged 65-84 years, but the results were not statistically significant.

6.2.2 Cause-specific mortality studies

- As well as investigating non-accidental mortality, Yap et al. (2019) assessed effect modification by age in the association between exposure to PM_{10}, $PM_{2.5}$, NO_2, O_3 and SO_2 and cardiovascular mortality in Singapore. The study reported statistically significant increased cardiovascular mortality associated with 10μg/m^3 increments of PM_{10} (<65 ER: -0.706 [-2.083, 0.645]; ≥65 ER: 1.236 [0.436, 2.042]) and $PM_{2.5}$ (<65 ER: -1.145 [-2.872, 0.613]; ≥65 ER: 1.478 [0.437, 2.530]) for those aged 65 years and older in comparison to those aged younger than 65 at lag 0-5 days. The study also reported statistically significant protective effects of the older age group for both PM_{10} and $PM_{2.5}$ at lag 0-30 days, with the authors concluding that such findings could be attributed to a “mortality displacement” or “harvesting” effect.
- Shin et al. (2020) observed a statistically different effect of gender but not age (all ages vs those aged 65 years and older) when investigating exposure to ozone on circulatory mortality in a multi-city study conducted in Canada for the years 1984 to 2012.

6.2.3 Hospital admissions studies

- Park et al. (2013) investigated effect modification by age in the associations between exposure to NO_2, PM_{10}, SO_2, ozone and hospital admissions for asthma in a multi-city time-series study conducted in South Korea for the years 1999 to 2003. The investigation classified the study population into three age groups: 0-14 years, 15-64 (reference category) and those age 65 years and older. Statistically significant differences were observed in both the younger and older age groups in comparison to those aged 15-64 years. A 10µg/m^3 increase of PM_{10} was associated with a 1.5% [0.1, 2.8] decrease in relative risk (RR) of asthma hospital admissions for children and a 1.3% [0.7, 1.9] increase for the elderly. Additionally, an increase of 1 part per billion (ppb) of NO_2 was associated with a 0.5% [0.3, 0.7] RR increase in the elderly. No significant age group differences in RR were observed for SO_2 or ozone.
- A meta-analysis of studies assessing the relationship between exposure to NO_2 and $PM_{2.5}$ on asthma hospital admissions (excluding emergency room visit studies) in London that reported findings by age group was conducted by the Environmental Research Group of Imperial College London (Evangelopoulos et al. 2022). A total of 19 studies published up to August 2021 were included and the results of the meta-analysis found that associations for $PM_{2.5}$ were higher in children (aged 0 to 14 years: 3.2% [1.9, 4.5] percent change in risk per 10µg/m^3 increment) and in the elderly (aged 65 years and older, including COPD: 3.9% [1.1, 6.9]), in comparison to those aged 15 to 64 years (-0.1% [-2.9, 2.8]). Similarly, a 10µg/m^3 increase in exposure to NO_2 was associated with a statistically significant increase in risk for children (3.9% [1.5, 6.4]), however the suggested increase in risk observed in the elderly was non-statistically significant.

These studies assessed asthma as an umbrella term and looked at effect modification by age which can further refine the group of asthmatics that is already included on the DAQI, e.g., by defining asthmatic children as a group in higher risk compared to asthmatics in general. The papers did not assess potential effect modification by specific subtypes of asthma which was the main objective of Chapter 5 – Asthma subtypes.

Three studies identified in the present review investigated respiratory disease hospital admission and potential susceptibility differences by age group in relation to air pollution exposure:

- Yang et al. (2003) found increased ozone exposure (by 9.74µg/m^3) to be associated with increased odds ratios (ORs) of respiratory disease hospital admissions in children under 3 years old (1.22 [1.15, 1.30]) and those aged over 65 years (1.13 [1.09, 1.18]), however, the study did not report on the statistical significance of the difference between the two age groups.
- Similarly, a study conducted in Leeds, UK, by Namdeo et al. (2011) failed to report on the statistical significance of differences between age groups (0-59, 60-69, 70-79, 80 and older), despite finding PM_{10} and ozone to be positively associated with respiratory hospital admissions in the elderly, particularly in the 70-79 age group, as well as NO_2 displaying the opposite age-related effect, with lower effects on the more elderly.
- Coker et al. (2022) investigated the use of low-cost sensors in epidemiological study through a time-series analysis undertaken in Rio Branco, Brazil. The study utilised a single monitor located in the urban centre of the city. US EPA correction factors were

applied to raw $PM_{2.5}$ concentration measurements and the associations between a 10μg/m^3 increase in corrected concentration measurements and respiratory disease hospital admissions were reported by age group (0-10, 11-18, 19-64, 65 years and older). No statistically significant differences in relative risk were observed between age groups.

6.2.4 Emergency room visits studies

Three of the identified studies investigated the role of age in modification of the effect of air pollution exposure on emergency room visits (ERVs):

- Lin and Kuo (2013) conducted a case-control study based in Taoyuan, Taiwan, aimed at assessing the effects of PM_{10} exposure on ERVs for ischaemic heart disease (IHD; 1,881 visits) and hypertension heart disease (HHD; 904 visits), with the modification of effect by age and gender assessed. A group consisting of emergency patients with gastrointestinal (GI) diseases (24,756 visits) was chosen as a control group. A formula devised by the Taiwan Environmental Protection Agency was used to convert monitoring station measurements of PM_{10} into the pollution standard index (PSI). The only difference in associations were reported for women, in which IHD admissions in age group 65+ were increased when exposed at >=50 on the PSI scale when compared to women of the same age group exposed to <50 on the PSI. The study presents several problems in interpreting the results fully and may not provide much insight into the impacts of age on susceptibility in the exposure-ERV association, given that the study only compared sex-age groups, used a calculated exposure index and used a very specific control group.
- Strosnider et al. (2019) collected data on ERVs for all respiratory diseases; acute respiratory infection (ARI) including upper respiratory infections, bronchitis, and bronchiolitis; asthma; COPD; and pneumonia from 17 US states for 2000 through 2014. They investigated the associations between the aforementioned health outcomes and ambient ozone and $PM_{2.5}$ levels in three specific age-groups, i.e. 0-18, 19-64 and 65 years and older, as well as all ages combined. They used a two-stage time-series analysis framework applying unconstrained distributed lag models for lag days 0 to 6 at county level the estimates of which were combined with Bayesian hierarchical models to obtain nationally relevant effect estimates. In total, they included 38.4 million respiratory ED visits from 869 counties and reported heterogeneous relative risks by outcome and age group. In particular, for ozone they found statistically significant, positive associations for each outcome for all age groups except for asthma among older adults. Relative risks were highest among those aged 19-64 except for ARI (effect estimates for those 19-64 and 65+ year old were similar). For $PM_{2.5}$, less variation was observed in the relative risks by age group for asthma, ARI and COPD. The effect estimates for all respiratory disease was higher for children (1.024 [1.018, 1.029] per 10 μg/m^3 increase), while for pneumonia it was higher and only significant for adults 19–64-year-old (1.017 [1.006, 1.029]). Results were very similar between single- and two-pollutant models.
- Zhang et al. (2020b) conducted a case-crossover study of associations between PM concentrations and all-cause emergency department visits across two cities in China (2015 – 2016; 292,806 ERVS in Guanzhou and 331,386 in Shenzhen). Increasing PM_{10} and $PM_{2.5}$ exposure was found to be associated with statistically significant increased

ORs in children (0-14 years) in comparison to other age groups (15-34, 35-64, 65 years and older).

6.2.5 Notable excluded studies

In the present review, the reported effect of age on the exposure-outcome association is reported where possible. A number of studies did not report results of comparisons between all age groups/for all associations and some reported effect modification in age groups that were too refined for comparison and inclusion for the present review. For example, Liang et al. (2021 and 2022) reported the difference in associations between PM exposure and lower respiratory infections outpatients visits for those under 5 and 5-14 years old. Additionally, three identified studies assessed different outcomes by age group, preventing any real comparisons. Andersen et al. (2007 and 2008) assessed cardiovascular disease (CVD) and respiratory disease (RD) admissions in those aged 65 years and older but investigated asthma admissions in children. Similarly separate analyses were undertaken by Gouveia and Fletcher (2000) and although the study did provide total RD mortality for those under 5 and over 65 years, the use of such a refined younger age group precluded the present review from drawing meaningful comparisons.

6.2.6 Multi-city studies

In an older multi-city European project entitled "Air Pollution and Health: a European Approach" (APHEA project) effect modification by age (as well as other variables) was investigated using second stage meta-regression models (Samoli et al., 2005). In the analysis based on daily data (in the 1990s) from 29 cities across Europe, including London and Birmingham from the UK, it was found that the effect of PM_{10} and black smoke (a reflectometry measurement corresponding to small carbonaceous particles that was usual at that time period) on mortality was smaller in cities with a smaller proportion of individuals older than 65 years of age. Specifically in cities where the proportion of over 65s was relatively low (at the 25th percentile), increasing PM_{10} concentrations were associated with a 0.54% increase in natural cause mortality, whilst in cities where the proportion of persons over 65 was relatively high (at the 75th percentile), the corresponding increase in mortality was 0.76% ($p < 0.05$ for the effect modification). In an extended analysis within the APHENA collaboration including data from European, US and Canadian cities, it was also found in second stage regression models that a higher percentage of persons over 65 and over 75 years of age was associated with higher PM_{10} effects both in Europe and the U.S., as shown in the Table below (adapted from Katsouyanni et al., 2009).

Table 19 - Percentage change in all-cause mortality associated with an increase of 10μg/m³ in PM_{10} (lag 0–1) at the 25th and 75th percentile of the centre-specific distribution of selected effect modifiers (adapted from Katsouyanni et al., 2009).

	Europe		**United States**	
Effect Modifier	25th Percentile Estimate [95% CI]	75th Percentile Estimate [95% CI]	25th Percentile Estimate [95% CI]	75th Percentile Estimate [95% CI]
% Population ≥65 years	0.25 [0.12, 0.38]	0.31 [0.18, 0.45]	0.06 [-0.11, 0.24]	0.23 [0.08, 0.37]
% Population ≥75 years	0.25 [0.12, 0.38]	0.32 [0.18, 0.47]	0.03 [-0.17, 0.22]	0.24 [0.09, 0.39]

Separate analyses for daily deaths among people younger and older than 75 years revealed the same pattern, i.e., the increase in mortality related to a 10µg/m^3 increase in PM_{10} (lags 0-1) was larger among the older population (0.44% increase in the number of deaths among those older than 75 years of age compared to 0.25% among those younger than 75 in European cities with corresponding numbers equal to 1% and 0.63% for Canadian cities and 0.47% and 0.12% in US cities; Samoli et al. 2008). The results remained robust after adjusting for O_3 concentrations.

In a paper reporting time-series study results of $PM_{2.5}$ associations with total mortality in 10 Mediterranean cities of Europe (Med-particles project; Samoli et al., 2013) it was found that associations between a 10µg/m^3 increase in $PM_{2.5}$ and mortality appeared to be limited to the older age group (0.77% [0.43, 1.10] compared with 0.02% [–0.51, 0.55] for those younger than 75, p = 0.02). In contrast, the opposite pattern was observed for $PM_{2.5-10}$ (0.10% [–0.47, 0.68] among those older than 75 years in comparison to 0.76 [0.03, 1.49] for those younger than 75 years, p = 0.16).

6.2.7 Pregnant women as another group at-risk

Pregnant women are another under-recognised vulnerable subpopulation that have been studied in epidemiological studies. Multiple studies have assessed the relationships between exposure to air pollution during pregnancy and maternal health outcomes such as gestational hypertension, pre-eclampsia and gestational diabetes.

A recent review by Decrue et al. (2023) presented an overview of the associations between outdoor air pollution and maternal cardiometabolic health during pregnancy. As the authors suggest, this group is of particular public health importance as "*it is susceptible to the effects of air pollution due to the delicate balance of feto-placental circulation, rapid fetal development and physiological changes in pregnancy such as increased minute ventilation and altered inflammatory profile*". They concluded that there is enough evidence to support links between particulate matter or nitrogen dioxide with the development of multiple pregnancy outcomes, such as hypertensive disorders, particularly pre-eclampsia and gestational diabetes mellitus. More specifically, they identified studies that support robust associations between particulate matter exposure during the entire gestational period and the development of hypertensive disorders. A large cohort study from Denmark (Pedersen et al. 2017), also supported similar findings for NO_2 exposure. The review also discussed potential mechanisms through which air pollution exposure may contribute to cardiometabolic disease during pregnancy (Decrue et al 2023). These include oxidative stress and with that, vascular inflammation as well as endothelial dysfunction and subsequently hypertension. An imbalance in the oxidative stress response could also accelerate B-cell dysfunction, leading to insulin resistance. Air pollution-induced epigenetic changes such as alterations in placental and mitochondrial DNA methylation could lead to altered gene expression and as a consequence, compromised placental function and hypertensive disorders.

However, these type of studies refers to medium- to long-term air pollution exposure, assessing either trimester or whole pregnancy exposure estimates and their relationship with the development of pregnancy outcomes. This is not within the main focus of our report,

which is on the impacts of short-term exposure to air pollution (e.g., daily or the average of a few days of exposure). With regards to short-term exposure to air pollution the evidence was limited:

- We identified one study that investigated the associations between exposure to air pollution up to 7 days prior to delivery with cardiovascular events during labour (Männistö et al. 2015). They assessed data from 228,562 deliveries, 687 of which (0.3%) suffered from a cardiovascular event during pregnancy and found significant associations with nitrogen oxides. There were also some trends of associations for mainly $PM_{2.5}$ and PM_{10}, but the results were not statistically significant, probably due to the low number of counts which did not provide enough statistical power.

Finally, a plethora of studies have assessed the impacts of air pollution on birth outcomes, including pre-term birth and low birthweight. We decided not to review this literature because other comprehensive systematic reviews for various birth outcomes already exist (Li et al. 2020), but most importantly because an umbrella review on the subject has been conducted by COMEAP and will be published soon. In addition, these studies share similar design characteristics with the studies on pregnancy outcomes, and mainly focus on trimester or whole pregnancy, and not short-term exposures.

Summary of epidemiological studies assessing certain age groups as potentially more susceptible to the effects of air pollution: effect modification studies

- Some evidence from Asia and South America identified an increased risk of non-accidental mortality in relation to exposure to PM and O_3 in older populations.

- One study from Italy reports a statistically significant excess risk of all-cause mortality associated with PM_{10} exposure in populations aged 75 years and older, with no significant associations reported for any pollutants across other identified studies.

- Limited evidence on effect modification of age in cause-specific mortality air pollution studies. Results from a study in Singapore suggest increased susceptibility in those aged 65 years and older but findings are inconsistent across lag structures.

- Suggestive evidence for increased risk of asthma hospitalisation attributable to NO_2 and $PM_{2.5}$ exposure in children (<15 years old) and older populations (65 years and older).

- Limited evidence on ERVs with one study from Asia and one from the US reporting increased susceptibility in children for respiratory disease ERVs.

- Substantial evidence from multi-city studies in Europe and the US to suggest that older populations are more susceptible to the effects of increased short-term exposure to PM.

- Suggestive evidence for links between air pollution and pregnancy outcomes, such as hypertensive disorders, but the exposure windows assessed are usually for trimester or the whole pregnancy period.

6.3 Biological basis for an increased susceptibility among older adults to the health effects induced by exposure to air pollutants

Ageing is a continuous process of progressive decline of the body's function, stress resistance and physiological reserves, leading to increased vulnerability, frailty and sensitivity of elderly people. With fewer newborns and people living longer, older people are making up an increasing fraction of the total population. As a consequence, the elderly are the fastest growing population who appear to be particularly susceptible to adverse health effects attributed to poor air quality.

Explanations are likely to be several, have not been examined fully and moreover, it is a view of some that this notion is too simplistic, arguing that individual factors (e.g., chronic disease) may play a greater role in the frailty of subjects than simply age (Pope 2000). Attributing increased sensitivity to the higher prevalence of underlying clinical conditions (e.g., respiratory, cardiovascular, metabolic, neurological) clearly gives rise to some overlap between potentially susceptible groups of older adults and people with, for example, heart or lung diseases. For instance, chronic obstructive pulmonary disease (COPD) is common in older populations. Patients with COPD have a diminished capacity to clear inhaled material from their lungs and may, as a result, incur a higher-than-normal 'dose' at any level of air pollution. In response to elevated levels of pollution, individuals with COPD experience a greater fall in lung function and a higher risk of admission to hospital than healthy persons of the same age.

Older adults may represent a susceptible population because of the natural and gradual decline in physiological processes over time. Most elderly individuals have reduced lung capacity and the imposition of a further reduction in lung function by air pollution may cause them to exceed a critical threshold. Dosimetric studies show reduced clearance of particulate matter in all regions of the respiratory tract with increasing age beyond young adulthood (US EPA 2009).

Susceptibility to air pollution in the elderly may also be related to an age-related loss of antioxidant defence mechanisms in the lung and elsewhere in the body or, the loss of other compensatory mechanisms in the cardio-respiratory system (Kelly et al., 2003). Support for the concept that respiratory tract lining fluid (RTLF) antioxidant defences are altered in the elderly comes from animal studies that indicate that glutathione, the most abundant intracellular and extracellular nonprotein thiol, decreases with age. Studies of the airways in asymptomatic elderly humans suggest that inflammatory cell numbers are increased in comparison with younger volunteers (Meyer et al 1996). This low-grade inflammation may influence RTLF antioxidant concentrations through increased free radical fluxes in the airways. Bronchoalveolar lavage studies in healthy individuals of differing ages have also revealed increasing cell numbers, interleukin-6 concentrations and superoxide production in older subjects. These findings have been interpreted to indicate that low-grade inflammation does indeed exist in the lower respiratory tract of many asymptomatic, clinically normally healthy volunteers of advanced age. Given this, in the absence of compensatory antioxidant changes, it is feasible that RTLF antioxidant status is compromised in the elderly.

Evidence from controlled human exposure studies, examining older adults, and animal toxicology, utilising models of senescence, provides further biological plausibility for health effects observed in epidemiological studies:

- Controlled human exposure studies revealed decreased heart rate variability in older adults with or without COPD after $PM_{2.5}$ concentrated ambient particle exposure (Devlin et al. 2003; Gong et al. 2004).
- Using an animal model of terminal senescence, Tankersley et al. (2008) demonstrated altered baseline autonomic tone, reductions in cardiac fractional shortening, and pulmonary vascular congestion after carbon black exposure.
- Arrhythmias have been observed in older, but not younger, rats exposed to $PM_{2.5}$ CAPs (Nadziejko et al. 2004).
- It should be noted that earlier controlled human exposure studies have demonstrated a decrease in ozone-induced decrements in lung function with age (McDonnell et al 1999; Hazucha et al 2003). A more recent controlled human exposure study (restricted to subjects 59.9 ± 4.5 years old) conducted at a lower ozone delivery rate more representative of that likely to occur in ambient air, however, shows that small lung function decrements, airway inflammation and epithelial injury may occur in older healthy adults (Arjomandi et al., 2018).

The advent of geroscience and the utilisation of metabolomic and proteomic assessments in different phases of life is a new approach aimed at predicting and understanding age-related health conditions and risk factors, as well as biological responses of exposures to environmental pollutants (Sierra 2016; Hoffman et al 2017; Gruzieva et al 2022). For example, differential perturbations of air pollution-related metabolites and pathways by age have been detected, providing further evidence on mechanisms for susceptible subpopulations (Chen et al 2017).

6.4 Biological basis for increased susceptibility among children to the health effects induced by exposure to air pollutants

Stronger associations observed in epidemiological studies between ambient air pollution exposure and health effects amongst children can be explained by several factors that differ compared to adults. These include less developed organ systems and higher frequency and duration of exposures due to more physical activity and time spent outside and the potential for those exposures to deliver higher doses that may remain in the lung for a greater duration.

The number of alveoli in the human lung increases from around 24 million at birth to 257 million at the age of 4 years and 600 million by adulthood. This significant period of lung growth, which includes the development of respiratory bronchioles, the epithelium and immune cell populations, is guided by a complex and precisely timed sequence of chemical messages. Air pollution has the potential to interfere with these signalling pathways, and as a consequence, developmental processes.

The developing airway epithelium of growing children is also more permeable to air pollutants. Defences against particulate pollution and gaseous pollution are not fully evolved.

As a consequence, children also have a differential ability to metabolise, detoxify and excrete environmental agents.

In addition, children have narrower airways, thus irritation (and subsequent inflammation and obstruction) caused by air pollution that would produce only a slight response in an adult can result in potentially significant obstruction in the airways of a young child.

Children spend more time outside, where concentrations of combustion-generated air pollution are generally higher, and exercise more than adults. Time spent undergoing physical activities significantly increase breathing rates and with that, the intake of air and pollution into the lung. Added to this, on a per body weight basis, the intake of air, hence atmospheric pollutants, of a resting infant is twice that of a resting adult.

Children also have different patterns of breathing than adults that may alter the deposition of inhaled pollutants. At rest, adults typically breathe predominantly through the nose, which partially filters toxic particles and gases, while children are more commonly mouth breathers.

Children may also present with more severe symptoms associated with air pollution exposure because unlike, adults, they may not cease activity even when they are symptomatic.

6.5 Discussion

The studies identified in the present rapid review assessing potential effect modification by age on the association between exposure to ambient air pollution and related health endpoints are limited but provide some indications and suggestive evidence for increased susceptibility in older and younger populations in comparison to adults (generally categorised as being aged 15 to 64 years). Evidence from epidemiological studies is limited per outcome-pollutant association and comparison between studies becomes problematic when sample populations are divided into non-matching age categories.

For older populations, some evidence exists for PM and O_3-related mortality (all-cause and cause-specific) and asthma hospitalisation, however, the number of studies in each geographic region remains small and further work is required to fully quantify the suggested increases in susceptibility in relation to the health effects attributable to these pollutants. The few relevant multi-city studies undertaken across Europe and in the US to date have provided inconsistent evidence for effect modification by age on PM-related mortality, however the evidence does point towards increased susceptibility in populations comprised of higher proportions of older individuals (Katsouyanni et al., 2001; Samoli et al., 2008 and 2013). As discussed in Section 6.3, the degradation of physiological, metabolic and compensatory processes that occur with age and the increased prevalence of underlying disease in this population may provide a basis for the suggestive evidence drawn from epidemiological studies and further study may help to establish such links, e.g., further investigation into respiratory disease mortality and hospital admissions in older populations compared to those younger. The controlled human exposure and animal toxicology studies generally support the theory that older populations are more susceptible to the harmful effects of gaseous and particulate air pollutants.

Of the two studies identified in the present review investigating asthma hospital admissions and effect modification in children (one of which was a meta-analysis), both identified an increased risk in children (aged 0 to 14 years) in relation to PM exposure, with the meta-analysis (Evangelopoulos et al., 2022) also finding an increased risk for NO_2 exposure. This finding is supported by Fan et al. (2016) who conducted a similar systematic review, but on ERVs, and also strengthens the evidence of a higher association between short-term exposure to $PM_{2.5}$ and asthma in children compared with adults, but without looking at specific subtypes (see Chapter 5). The evidence for respiratory disease hospital admissions as a whole was inadequate, with one study (Yang et al., 2003) finding suggestive evidence for an increased risk in children, however a large multi-city study conducted in the US found increased risk for respiratory disease ERVs in children in relation to $PM_{2.5}$ exposure (Strosnider et al., 2019). Zhang et al. (2020b) also found increased respiratory disease ERV risk for children across two cities in China. As discussed in Section 6.4, factors underdeveloped pulmonary, immune and defence systems, a higher frequency and duration and the potential for those exposures to deliver higher doses that may remain in the lung for a greater duration may explain the increased risk observed in a number of epidemiological studies included in the present review.

Further epidemiological work aimed at assessing increased susceptibility to pollution-related health effects by life-stage should benefit from maintaining more consistency across studies in the selection of age cut-offs for each sub-population in the study sample. A small number of identified studies attempted to assess the differential effects of pollutants by 10-year age bands, which may be too fine in resolution to fully identify differences. Further experimental and epidemiological work is required to more accurately define life-stages at which exposure to ambient air pollutants may be of greater risk for specific health endpoints. Geographic heterogeneity must also be increased in epidemiological studies and large-scale multi-city studies may provide the statistical power needed to detect differential effects that remain inconsistent across smaller scale studies to date.

Chapter 7 – Discussion

Summary boxes are provided at the end of individual results sections describing the evidence, stemming from a given study type (e.g., epidemiological time-series/case-crossover/panel, CHE, animal), regarding increased susceptibility to air pollution among people with metabolic stressors and different subtypes of asthma as well as at different life stages. In addition, individual chapter discussions (Sections

4.6 Discussion: are subjects with metabolic disorders at increased risk from short-term exposure to air pollution?, 5.3 Discussion and 6.5 Discussion) include an overall appraisal of the evidence for each susceptibility factor by synthesising the evidence, when available, from epidemiological and experimental studies.

7.1 Conclusions from the previous chapters

Is the overall body of evidence sufficient to come up with firm conclusions with respect to the potentially susceptible groups evaluated? The text below summarises the findings of our rapid review and the implications of the latter with regards to the DAQI.

- Overall, for ambient air pollution as a whole, the evidence base could not be regarded as adequate to conclusively characterise diabetics, the obese or asthmatics with a specific subtype as groups at greater risk to the effects of short-term exposure to ambient air pollution.

- The limited evidence for PM-related effect modification does indicate greater susceptibility in diabetics. Evidence of biological plausibility includes particle induced (a) heart rhythm disorders, in line with epidemiological observations of increased hospital admissions for cardiac arrythmia and (b) thrombotic effects, supportive of epidemiological observations of increased hospital admissions for cardiovascular disease and myocardial infarction.

- The lack of evidence for greater susceptibility of diabetics to gaseous pollutants should be taken with caution and studied further, bearing in mind in prioritising this work that not all pollutants generally provide high or very high concentration days (Walton et al. 2020).

- Evidence suggests that obese (or even overweight but not obese) individuals are potentially more susceptible to ozone-related respiratory health effects. This evidence stems from human studies that have observed a greater lung function decline in

obese/overweight subjects in response to acute ozone exposure and animal data demonstrating increased susceptibility to ozone-associated pulmonary resistance and inflammation and airway hyperresponsiveness in obese mice.

- Mechanisms that may contribute towards an exaggerated respiratory response to ozone exposure with increasing BMI include mechanical factors (e.g., lower lung volumes, smaller tidal volumes, increased breathing frequency) and/or mediation via inflammatory adipokines and the gut microbiome.

- The consequences of such susceptibility are significant when one considers the prevalence of obesity (in England 63.8% of adults are either overweight or obese) and projected increases in ambient ozone concentrations under the changing climate.

- While there are many studies supporting adverse effects of short-term exposure to air pollution on asthma as an umbrella term, there is very limited and inconclusive evidence about potentially differential effects by specific asthma subtypes. Increased susceptibility to PM-related health effects in asthmatics was not evaluated by the US EPA and the present review finds the evidence to be inadequate to infer increased susceptibility for specific asthma subtypes at present, with current findings varying across studies.

- Evidence suggests increased susceptibility in older and younger populations in comparison to adults indicating that these life-stages should continue to be regarded as at-risk. The present review concludes that the evidence for PM-related health effects in older populations is adequate to suggest increased susceptibility in this group (particularly in large multi-city studies), in contrast to the US EPA ISA in which the evidence was deemed inadequate (EPA, 2019).

- It is likely that individuals may be at increased risks of a health effect due to a combination of concurrent factors. However, knowledge about such interactions is currently limited. Additionally, it is worth mentioning that the effects of air pollutants may vary depending on the type of disease, its severity, and management, yet only a few studies delve into this level of specificity.

- Further epidemiological and experimental work is required, as specified in our research recommendations below about specific subpopulations that can be regarded as at greater risk than others.

Implications of these conclusions for the DAQI advice

- Based on the findings of this report, we would not recommend any changes to the groups already mentioned in the recommended actions and health advice accompanying the DAQI[6].

- However, it would still be useful to communicate the state of the evidence on the potential susceptible groups we considered to the public. This could either be in the

[6] https://uk-air.defra.gov.uk/air-pollution/daqi

Additional information on the short-term effects to air pollution page that is linked to from the DAQI page[7] or in similar background material. The phrases below repeat our conclusions above in a shorter form to aid in developing such materials.

- Even though the evidence was insufficient at this stage to strongly support diabetics being especially sensitive to air pollution, cardiovascular disease, which is already known to make people susceptible to the health effects of air pollution, is very common in this subgroup.

- Asthmatics should continue to be regarded as a susceptible subgroup, but the evidence is not yet clear about whether susceptibility might potentially vary by asthma subtype. Clarification of this awaits further developments in the field defining these subtypes and understanding the effects of air pollution on them.

- It could be argued that for the DAQI, attempts should not be made to identify specific asthmatics that may be more responsive to the adverse effects of air pollution, in order to keep the messaging concise and clear and guard against any complacency within the susceptible asthmatic population as whole.

- Obese and overweight individuals may be a susceptible group especially with respect to ozone and a compromised respiratory function, but these findings need further investigation before formally appearing in the DAQI. Communication via alternative channels (e.g., Weight Watchers) may wish to be considered in the interim.

- The elderly and the children should continue be regarded as groups at-risk for particular health outcomes, but there is not always evidence available to demonstrate whether or not these differences are shown in formal tests of statistical significance.

7.2 General discussion points on defining susceptible groups and advice accompanying the DAQI

Principles for defining susceptible groups

Here we outline what may constitute the ideal evidence base for defining a group as susceptible.

To provide epidemiological evidence, investigation into a potentially susceptible group should be clearly defined, with the effect of exposure to a given pollutant estimated for the susceptible group in question and a reference non-susceptible group or the general population independently, as well as the difference in effect quantified and tested for statistical significance. A large proportion of the epidemiological studies identified for this review (across all posited susceptible groups, pollutants and across numerous health outcomes) were inconsistent in the comparisons being assessed between studies, as well as many not reporting on the statistical significance of the difference in effect of exposure between groups. For example, studies assessing the difference in diabetic sub-populations

[7] https://uk-air.defra.gov.uk/air-pollution/effects?view=short-term

tended to either investigate diabetics in comparison to non-diabetics or the total study sample which included diabetics; and asthma subtypes continue to be redefined, with age onset subtypes displaying inconsistencies in age cut-offs between studies. This is important because different background incidence rates of the disease under investigation might apply for the groups that are compared with those potentially at-risk. In many studies, differential effects between sub-populations were not the primary focus of investigation and were included as sensitivity analyses or in supplementary materials. In some cases where the statistical significance in the difference between groups was not reported, it may be possible to infer such information through the reported effect estimates and confidence intervals (either in provided tables and/or plots). However, for the purposes of the present review, statistically significant differences were considered only for those studies that reported them.

Such inconsistencies hinder the ability to definitively characterise a sub-population as at-risk, particularly when the evidence base is limited as a whole for many pollutant-outcome associations per potentially susceptible group. Rather, for a group to be defined as at-risk, the epidemiological evidence should provide multiple studies (contributing a reasonable proportion of the total relevant studies) assessing consistent group comparisons and report higher effect estimates (or increased risk) for one or more health outcomes that are statistically significant.

In terms of the reporting of statistically significant differences between a potentially susceptible group and a non-susceptible one or the general population, strict benchmarks should be in place as the characterisation of susceptible populations for the DAQI has very large ramifications with respect to the target population and behavioural change. However, these strict benchmarks also need to be applied in findings from systematic reviews that have collated all the evidence in the scientific literature. Our report is a rapid review, and even though we followed standard approaches for reviewing the literature, we cannot rule out the possibility of studies being missed by our search strategy (e.g., as outlined above, the identified panel studies that evaluated effects in obese and diabetic populations appeared in the output of literature searches tailored to identify controlled human exposure studies or were identified from hand searching the reference lists thereof). Thus, we did not formally compare every element of our evidence against the different aspects of the aforementioned strict benchmarks, but we bore them in mind when drawing our overall conclusions given above.

A further point to consider is whether an at-risk group should be characterised when the evidence of increased susceptibility is adequate for one or more air pollutants but not others. For example, upon reviewing the available evidence, the present report concludes that suggestive or adequate evidence exists for increased susceptibility to the effects of exposure to one or more pollutants in older and younger populations, however the evidence is inadequate for a number of pollutant-outcome relationships. Where the evidence for a pollutant-outcome association within a group is adequate to determine increased susceptibility but other associations are not, it may be sufficient to utilise the adequate albeit not comprehensive evidence base to provide a more general view of overall susceptibility within the group in question. This approach somewhat contradicts the stricter benchmark of statistically significant findings for an at-risk group previously discussed, but in practice may provide a safer characterisation of at-risk groups whilst keeping abreast and reviewing new

studies at regular intervals, that may provide a more conclusive determination of susceptibility over time. Overall, our conclusions need to be (a) understood in relation to the DAQI and (b) given further consideration with respect to the wider discussion to which this report contributes, taking into account issues such as which pollutants are more or less likely to drive the definition of high or very high days within the index.

In addition to the epidemiological evidence, defining an at-risk population also requires supporting evidence for the plausibility of increased susceptibility from other studies such as panel or controlled human exposure, or relevant animal studies. Although we cannot be confident that the panel studies reviewed represent a comprehensive evidence base, they were generally of good quality and all studies all included a susceptible and non-susceptible reference group. The controlled human exposure studies were all of good quality, however, a number did not include a healthy control group and it is possible that compromised participants (e.g., those with metabolic disturbances) are not representative of those within the general population. The animal studies were again generally of good quality and in the main included a control group. Limitations that hinder interpretation of the results include the small number of very heterogeneous studies and possible species (mice versus rats) differences in responses to exposures.

The aim of this rapid review was to investigate whether particular subpopulations are especially sensitive to air pollution. Any lack of evidence to support this for a given group does not mean that it is not at risk at all. For example, according to the at-risk population groups in the current DAQI, diabetics with cardiovascular disease (many of whom will be older) are still at risk, irrespective of the underlying reason for this increased susceptibility. Similarly, asthmatics should continue to be considered as a sensitive subpopulation even though the evidence for increased susceptibility for specific asthma subtypes is too limited at present to introduce more refined advice within the overall asthmatic population.

Guidance on short-term versus long-term exposures

We focused our work on the effects of short-term exposure to air pollution, which is directly related to the DAQI and short-term variability of the air pollution mixture. However, there are spatial contrasts in air pollution, especially for pollutants such as NO_2 which are less homogeneous than others (PM). These spatial contrasts are also important as they can drive environmental injustice and potential synergies with other spatially variable factors, such as poverty, access to health care, etc. Air quality indices based on long-term air pollution levels can be used to communicate the issue to the general public and used in combination with temporal indices.

Potential caveats associated with advice provided by air quality messaging services

Even when an alert service provides a recommended action that people at-risk can take in the event of increased short-term exposures to air pollution, it may not be as simple to follow as it might at first appear. For example:

- Too regular use of broncho-dilators in reliever inhalers can lead to tolerance, for example, as consequence of a down regulation of relevant receptors, and a less effective broncho-dilator response (Appendix 2, Wraight et al 2003) although this

depends on the type of inhaler (e.g., it does not apply to MART inhalers which combine preventer and reliever treatment in one inhaler)[8].

- Should clinicians tell people to stay indoors if they have serious problems with damp and mould in their house?
- Recommending low pollution transport routes seems to be reasonable common sense and often would be but what if a recommendation to walk through a green space simply traded traffic-related pollution exposure for pollen exposure, which could itself trigger symptoms?

Intervention studies based on air quality messaging services

Ideally, intervention studies around messaging services should be conducted to determine if actions taken by a given susceptible group in response to alerts are of benefit. However, this can be difficult to do – in particular areas, there may be insufficient statistical power (Walton et al, 2014), although there are some studies of this type (Kelly et al 2012; McDermott et al 2006; Wen et al 2009). They will be most effective if the susceptible groups were clearly identified (with increased effect size giving greater statistical power). Hopefully, research such as that conducted for this report will help to do this. This is not to say that patients are not benefiting, particularly if those that feel they are affected by air pollution may be more likely to use the DAQI.

The wider issues in the preceding paragraphs are not specifically within the remit of this report. They are mentioned to give our findings context rather than to come to definitive conclusions on these broader points.

Concentration response relationships

Findings evaluated and discussed in this report were related to continuous changes in concentrations not air quality index bands. The former is generally more robust overall, even if it less easy to communicate. Controlled human exposure studies may suggest thresholds below which adverse symptoms do not occur. A recent review examining PM concentration-responses after controlled human air pollution exposures to identify potential effect thresholds included 31 studies of concentrated ambient particles, engineered carbon nanoparticles, diesel exhaust, and woodsmoke (Orach et al 2021). Despite a dearth of eligible publications, considerable variability in methodology, and inconsistent reporting standards between studies, concentration-dependent effects on oxidative stress markers, inflammation, and cardiovascular function were identified that overlapped across different pollutants. Findings from studies of DE exposure indicate an estimated threshold for effects on brachial artery diameter (in both healthy and metabolic syndrome subjects) below 200 $\mu g/m^3$. Adverse symptoms may however still be relevant at lower concentrations in the general population, where numbers are much larger and those with more severe disease are included. Thus, the breakpoints in the DAQI represent a continuum of increasing probabilities of adverse effects rather than an instant major change.

Knowledge of susceptibility in the real world and within research studies

Identification of a susceptible group within this report does not automatically mean that they could be specifically highlighted within the messaging linked with the DAQI. There are other

[8] https://www.asthmaandlung.org.uk/symptoms-tests-treatments/treatments/combination

issues to consider that are outside the scope of this report. These include whether the general public will actually know they are in a susceptible group if characterisation of susceptibility was based on biomarkers that are not routinely measured (for example eosinophil count to define a particular subtype of asthma). Although for diabetics, the obese, children and the elderly, it would be known. Conversely, protocols used clinically to stage disease may not be easily available for epidemiological study if clinical tests are not easily used in the field or not available in routine statistics. In addition, there may be no obvious way for those in a susceptible group to take any action to reduce their symptoms, for example while asthmatics may change their medication in response to a change in symptoms, other disease groups may not be able to do the same. Actions taken to reduce air pollution exposure would plausibly still be useful but current studies do not necessarily quantify this directly (e.g., using monitoring site concentrations rather than identifying peaks in personal exposure).

7.3 Future research recommendations

As a result of our rapid review assessment of the literature, we identified some knowledge gaps for the identification of specific subpopulations that are greater at-risk with regards to their short-term exposure to ambient air pollution. These gaps can be further investigated and addressed in future research based on the recommendations below:

- Larger epidemiological studies (i.e., longer time-series or bigger samples for case-crossover design) that provide enough statistical power to assess effect modification for less common factors, such as diabetes status or specific asthma subtypes, to identify susceptible populations.

- More harmonised (i.e., greater inter-study homogeneity in methodology and reporting) CHE studies of sensitive populations to improve our understanding of concentration–response relationships between air pollutants and acute health effects.

- Specific pollutant-outcome pairs are not well-studied compared to others and firm conclusions cannot be drawn. Especially for ozone and respiratory disease (mortality and morbidity), more epidemiological studies should be conducted.

- In relation to the above, the health effects of air pollutants other than the criteria pollutants assessed in this review, such as ultrafine particles, should be considered. In addition, potentially differential effects for different PM components should also be assessed.

- Further epidemiological and experimental studies to assess potentially increased susceptibility among diabetics compared to non-diabetics or the general population with regards to short-term exposure to air pollution.

- For obesity, in particular, more experimental and observational studies (epidemiological, CHE and animal) to evaluate effects of air pollution exposure on cardiorespiratory function.

- Controlled human exposure studies of obese and normal weight individuals with asthma, i.e. those with both a greater baseline airway reactivity/inflammation and response to ozone, should be considered.

- Better definition of asthma subtypes and identification of the health effects of air pollution associated with each subtype from observational and experimental studies is needed in order to facilitate clinicians provide personalised environmental medicine to their patients.

- If long-term exposures to air pollution are planned to be taken into account for air quality indices and communication to the public, more epidemiological, spatiotemporal studies assessing simultaneously the effects of short- and long-term exposure to pollution should be conducted.

- Greater characterisation of the effects of air pollution on maternal health including cardiovascular and respiratory parameters (e.g. does air pollution have a greater effect on a pregnant asthmatic woman compared to a non-pregnant woman?) throughout pregnancy, ideally using measurements of personal exposure.

- Intervention studies focusing on the communications and messaging services of air quality to the general public and specific subgroups should be conducted to determine if actions taken by a given susceptible group in response to alerts are of benefit.

- Full systematic reviews that comprehensively assess the experimental and epidemiological literature, including proper quality and risk of bias assessments, can provide better insight on the identification of subpopulations that can be regarded as at risk.

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Appendix 1 – Literature review search strings, results and search protocol

ASTHMA BY SUBTYPE SEARCH STRATEGY: Controlled human exposure studies

Category 1 – the air pollutant
Keywords (for **Searches 1, 2 & 3**): "air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone

Category 2 – controlled human exposure
Keywords (for **Searches 1, 2 & 3**): "controlled human exposure" OR "human exposure" OR exposure

Category 3 – asthma
Keyword (for **Searches 1 & 2**): asthma
Keywords (for **Search 3**): ("allergic asthma" OR "atopic asthma") AND ("non-allergic asthma" OR "non-atopic asthma"

Category 4 – subtypes
Keywords (for **Search 1**): phenotype* OR endotype* OR subtype*
Keyword (for **Search 2**): eosinophil*
NB **Search 3** does not have a Category 4 search term

Search String	Pub Med Hits (relevant)	Web of Science Hits (relevant)
Search 1. ("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND ("controlled human exposure" OR "human exposure" OR exposure) AND (asthma) AND (phenotype* OR endotype* OR subtype*)	**162**	**259**
Search 2. ("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND ("controlled human exposure" OR "human exposure" OR exposure) AND (asthma) AND (eosinophil*)	**244**	**333**
Search 3. ("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND ("controlled human exposure" OR "human exposure" OR exposure) AND ("allergic asthma" OR "atopic asthma") AND ("non-allergic asthma" OR "non-atopic asthma")	**10**	**12**

ASTHMA BY SUBTYPE SEARCH STRATEGY: Animal studies

Category 1 – the air pollutant

Keywords (for **Searches 1, 2 & 3**): "air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone.

Category 2 – animal study

Keywords (for **Searches 1, 2 & 3**): Animal* OR mice OR mouse OR rat OR rats OR "guinea pig*" OR cat OR cats OR dog OR dogs OR pig OR pigs OR monkey* OR horse*.

Category 3 – asthma

Keyword (for **Searches 1 & 2**): asthma

Keywords (for **Search 3**): ("allergic asthma" OR "atopic asthma") AND ("non-allergic asthma" OR "non-atopic asthma"

Category 4 – subtypes

Keywords (for **Search 1**): phenotype* OR endotype* OR subtype*

Keyword 2 (for **Search 2**): eosinophil*

NB **Search 3** does not have a Category 4 search term

Search String	Pub Med Hits (relevant)	Web of Science Hits (relevant)
Search 1. ("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND (animal* OR mice OR mouse OR rat OR rats OR "guinea pig*" OR cat OR cats OR dog OR dogs OR pig OR pigs OR monkey* OR horse*) AND (asthma) AND (phenotype* OR endotype* OR subtype*)	**94**	**231**
Search 2. ("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND (animal* OR mice OR mouse OR rat OR rats OR "guinea pig*" OR cat OR cats OR dog OR dogs OR pig OR pigs OR monkey* OR horse*) AND (asthma) AND (eosinophil*)	**204**	**502**
Search 3. ("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND (animal* OR mice OR mouse OR rat OR rats OR "guinea pig*" OR cat OR cats OR dog OR dogs OR pig OR pigs OR monkey* OR horse*) AND ("allergic asthma") AND ("non-allergic asthma")	**5**	**11**

ASTHMA BY SUBTYPE SEARCH STRATEGY: Epidemiological studies

Category 1 – the air pollutant
Keyword options:
"air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone

Category 2 – epidemiological studies
Keywords: epidemiolog* OR "health effect*" OR "short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover"

Category 3 – asthma
Keyword: asthma

Category 4 – subtypes
Keywords: phenotype* OR endotype* OR subtype* OR "pathological pathway*"

Search String	Pub Med Hits (relevant)	Web of Science Hits (relevant)
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND (epidemiolog* OR "health effect*" OR "short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover") AND (asthma) AND (phenotype* OR endotype* OR subtype* OR "pathological pathway*")	**91**	**83**

ASTHMA BY SUBTYPE SEARCH STRATEGY: Systematic reviews of epidemiological studies (excluding the subtype component)

Category 1 – the air pollutant
Keyword options:
"air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone

Category 2 – epidemiological studies
Keywords: epidemiolog* OR "health effect*" OR "short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover"

Category 3 – asthma
Keyword: asthma

Category 4 – reviews
Keywords: review* OR "meta-analysis"

Search String (in bold are the changes from the original search)	Pub Med Hits (relevant)	Web of Science Hits (relevant)
(“air pollution” OR “diesel exhaust” OR “particulate matter” OR “sulphur dioxide” OR “nitrogen dioxide” OR ozone) AND (epidemiolog* OR “health effect*” OR “short-term exposure*” OR “panel stud*” OR “time-series” OR “time series” OR “case-crossover” OR “case crossover”) AND (asthma) AND (review* OR “meta-analysis”)	**838**	**785**
(“air pollution” OR “diesel exhaust” OR “particulate matter” OR “sulphur dioxide” OR “nitrogen dioxide” OR ozone) AND (epidemiolog* OR “health effect*” OR “short-term exposure*” OR “panel stud*” OR “time-series” OR “time series” OR “case-crossover” OR “case crossover”) AND (asthma) AND (review***[Title and Abstract]** OR “meta-analysis”**[Title and Abstract]**)	**542**	**534**
(“air pollution” OR “diesel exhaust” OR “particulate matter” OR “sulphur dioxide” OR “nitrogen dioxide” OR ozone) AND (epidemiolog* OR “health effect*” OR “short-term exposure*” OR “panel stud*” OR “time-series” OR “time series” OR “case-crossover” OR “case crossover”) AND (asthma) AND (review***[Title]** OR “meta-analysis”**[Title]**)	**155**	**190**
(“air pollution” OR “diesel exhaust” OR “particulate matter” OR “sulphur dioxide” OR “nitrogen dioxide” OR ozone) AND (epidemiolog* OR “health effect*” OR “short-term exposure*” OR “panel stud*” OR “time-series” OR “time series” OR “case-crossover” OR “case crossover”) AND (asthma**[Title]**) AND (review***[Title and Abstract]** OR “meta-analysis”**[Title and Abstract]**)	**200**	**128**
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND (epidemiolog* OR "health effect*" OR "short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover") AND (asthma**[Title]**) AND (review***[Title]** OR "meta-analysis"**[Title]**)	**68**	**45**

METABOLIC SYNDROME SEARCH STRATEGY: Controlled human exposure studies

Category 1 – the air pollutant
Keyword options:
"air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone

Category 2 – controlled human exposure
Keyword options:
"controlled human exposure" OR "human exposure" OR volunteers OR subjects OR participants

Category 3 – metabolic syndrome
Keywords: "metabolic syndrome" OR diabetes OR diabetic* OR obes*

Search String (in bold are the changes from the previous search)	Pub Med Hits (relevant)	Web of Science Hits (relevant)
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND ("controlled human exposure" OR "human exposure" OR volunteers OR subjects OR participants) AND ("metabolic syndrome" OR diabetes OR diabetic* OR obes*)	**719**	**828**

METABOLIC SYNDROME SEARCH STRATEGY: Animal studies

Category 1 – air pollutant
Keywords:
"air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone

Category 2 – animal study
Keywords: animal* OR mice OR mouse OR rat OR rats OR "guinea pig*" OR cat OR cats OR dog OR dogs OR pig OR pigs OR monkey* OR horse*

Category 3 – metabolic syndrome
Keywords: ("metabolic syndrome" OR "metabolic disorders" OR "metabolic dysfunction" OR diabetes OR diabetic* OR obes* OR "insulin resistance" OR "insulin sensitivity" OR adiposity OR "adipose inflammation" OR "energy metabolism" OR "glucose metabolism" OR "lipid metabolism" OR "glucose tolerance" OR "energy homeostasis"

Search String (in bold are the changes from the previous search)	Pub Med Hits (relevant)	Web of Science Hits (relevant)
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND (animal* OR mice OR mouse OR rat OR rats OR "guinea pig*" OR cat OR cats OR dog OR dogs OR pig OR pigs OR monkey* OR horse*) AND ("metabolic syndrome" OR "metabolic disorders" OR "metabolic dysfunction" OR diabetes OR diabetic* OR obes* OR "insulin resistance" OR "insulin sensitivity" OR adiposity OR "adipose inflammation" OR "energy metabolism" OR "glucose metabolism" OR "lipid metabolism" OR "glucose tolerance" OR "energy homeostasis")	**665**	**550**

METABOLIC SYNDROME SEARCH STRATEGY: Epidemiological studies

Category 1 – the air pollutant
Keyword options:
"air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone

Category 2 – epidemiological studies
Keywords: **epidemiolog* OR "health effect*"** OR "short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover"

Category 3 – metabolic syndrome
Keyword: "metabolic syndrome" OR diabetes OR diabetic* OR obes*

Search String	Pub Med Hits (relevant)	Web of Science Hits (relevant)
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND (epidemiolog* OR "health effect*" OR "short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover") AND ("metabolic syndrome" OR diabetes OR diabetic* OR obes*)	**1,360**	**1,155**
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND ("short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover") AND ("metabolic syndrome" OR diabetes OR diabetic* OR obes*)	**164**	**290**

AGE SEARCHES STRATEGY: Epidemiological studies

Category 1 – the air pollutant
Keyword options:
"air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone

Category 2 – epidemiological studies
Keywords: **epidemiolog* OR "health effect*"** OR "short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover"

Category 3 – age
Keyword: age OR aged OR ageing OR elderly OR old OR older OR oldest OR young* OR child*

Category 4 – health outcome
Keyword: mortality OR deaths OR "hospital admissions" OR "emergency room visits"

Search String	Pub Med Hits (relevant)	Web of Science Hits (relevant)
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND (epidemiolog* OR "health effect*" OR "short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover") AND (age OR aged OR ageing OR elderly OR old OR older OR oldest OR young* OR child*) AND (mortality OR deaths OR "hospital admissions" OR "emergency room visits")	**3,676**	**4,437**
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND ("short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover") AND (age OR aged OR ageing OR elderly OR old OR older OR oldest OR young* OR child*) AND (mortality OR deaths OR "hospital admissions" OR "emergency room visits")	**1,006**	**2,255**
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND ("short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover") AND (age**[Title and Abstract]** OR aged**[Title and Abstract]** OR ageing**[Title and Abstract]** OR elderly**[Title and Abstract]** OR old**[Title and Abstract]** OR older**[Title and Abstract]** OR oldest**[Title and Abstract]** OR young***[Title and Abstract]** OR child***[Title and Abstract]**) AND (mortality OR deaths OR "hospital admissions" OR "emergency room visits")	**770**	**1,859**
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND ("short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover") AND (age**[Title]** OR aged**[Title]** OR ageing**[Title]** OR elderly**[Title]** OR old**[Title]** OR older**[Title]** OR oldest**[Title]** OR young***[Title]** OR child***[Title]**) AND (mortality OR deaths OR "hospital admissions" OR "emergency room visits")	**149**	**413**

PREGNANCY OUTCOMES SEARCHES STRATEGY: Epidemiological studies

Category 1 – the air pollutant
Keyword options:
"air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone

Category 2 – epidemiological studies
Keywords: **epidemiolog* OR "health effect*"** OR "short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover"

Category 3 – age
Keyword: "pregnancy" OR "gestational diabetes" OR preeclampsia OR "blood pressure" OR "gestational hypertension" OR "dam weight gain" OR "dam body weight" OR "maternal weight"

Search String	Pub Med Hits (relevant)	Web of Science Hits (relevant)
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND (epidemiolog* OR "health effect*" OR "short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover") AND ("pregnancy" OR "gestational diabetes" OR preeclampsia OR "blood pressure" OR "gestational hypertension" OR "dam weight gain" OR "dam body weight" OR "maternal weight")	**2,368**	**1,861**
("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND ("short-term exposure*" OR "panel stud*" OR "time-series" OR "time series" OR "case-crossover" OR "case crossover") AND ("pregnancy" OR "gestational diabetes" OR preeclampsia OR "blood pressure" OR "gestational hypertension" OR "dam weight gain" OR "dam body weight" OR "maternal weight")	**235**	**483**

Literature Search Protocol

Introduction

The Environmental Research Group (ERG), Imperial College London, has been commissioned to provide an expert rapid review of studies that have attempted to identify subgroups of the general population that are more likely to have higher risks of experiencing a health outcome associated with their short-term exposure to air pollution. This document describes the literature search strategy that ERG will follow.

Review Question

Is there enough evidence from experimental and epidemiological studies to support that specific subtype(s) of asthma or diabetes/metabolic syndrome (including obese individuals) may increase an individual's susceptibility to air-pollution-related health effects? If so, what are the risks associated with short-term exposure to air pollution for these potentially susceptible subgroups of the population?
Is age a potential effect modifier of the association between short-term exposure to air pollution and various health outcomes such as all-cause and cause-specific mortality or hospital admissions?

Searches

The search strategy aims to retrieve peer-reviewed, published studies from anytime up to October 2022. The searches will be performed on PubMed and Web of Science and studies only in English will be assessed. Additional studies will be gathered by reviewing the reference lists of the articles retrieved. In the appendix, we present the search strategy for each at risk group /study type pair, the final search strings to be used and the number of hits from each search string. All the search strings are built using three main components, i.e., one for air pollution, one for the type of study and one for the at risk group under investigation. An example can be seen below:

("air pollution" OR "diesel exhaust" OR "particulate matter" OR "sulphur dioxide" OR "nitrogen dioxide" OR ozone) AND ("controlled human exposure" OR "human exposure") AND ("metabolic syndrome" OR diabetes OR diabetic OR obes*)*

Specific health outcomes will not be included in the initial search strategy to avoid missing relevant studies for the full range of effects in at risk groups, although these will be extracted and discussed once studies have been identified.

Types of studies to be included

This study will review both experimental and epidemiological studies. For the former, we will perform separate searches for animal and controlled human exposure studies, while for the latter, we will identify studies on short-term exposure to pollution, such as time-series, case-crossover and panel studies. Studies that are case reports, case series or only available as abstracts will be excluded.

Condition or domain being studied

Short-term exposure to ambient air pollution (i.e., particulate matter, nitrogen dioxide, sulphur dioxide, and ozone) and its effect on asthmatics with specific subtypes of the disease, people with diabetes/metabolic syndrome (including obese individuals) and different age groups including children, the elderly or pregnant women.

Participants/population

The study population depends on the research question under investigation. We have three main areas of research; thus, the population will be:

- Asthmatics with specific subtypes of the disease
- People with diabetes/metabolic syndrome (including obese individuals)
- People of specific age, i.e., children, elderly and pregnant women

Exposures

Short-term exposure to ambient levels of $PM_{2.5}$, PM_{10}, NO_2, O_3 and SO_2. The review of experimental evidence will also include traffic-related exposures, because many controlled human exposure and animal studies have employed whole vehicle exhaust, diesel exhaust particles and these pollutants dominate exposures in urban environments where most people live, work and commute.

Comparators

Health outcomes (based on the research question) associated with higher levels of exposure compared to those occurring in response to lower levels of exposure and also between persons 'at-risk' compared to those not 'at-risk', e.g., persons with and without diabetes or persons with one type of asthma versus another etc.

Main Outcomes

Based on the research question:

- A particular focus will be placed on studies of asthma-related outcomes which have information about the asthma subtype of the population under investigation. However, the health outcomes will not be restricted to this, as the main aim is to assess whether there are potentially differential risks for people with specific asthma subtype compared with other asthmatics or the general population. For example, some studies might look at, say, lower respiratory infections in asthmatics
- Similarly, while diabetic outcomes will be covered, we will not restrict our searches to specific health outcomes for diabetics. For example, we will investigate whether the results support a greater risk of a respiratory or cardiovascular effect in people with diabetes/metabolic syndrome from short-term exposure to air pollution
- All-cause, respiratory and cardiovascular mortality and hospital admissions occurring in people of specific age groups as defined above
- Experimental studies will collect all relevant outcomes (e.g., organ function, cellular changes, molecular alterations, biomarkers of effects) that may shed light on a mechanism, or set of mechanisms, by which air pollution may damage human health to a greater extent within at-risk groups.

Data Extraction

The process of this rapid review will follow standard approaches for reviewing the scientific literature in many respects but not necessarily all aspects of formal systematic review guidelines. For example, there are insufficient resources for duplicate screening – instead researchers will discuss with the wider team specific studies that seem unclear in some way. Duplicated studies will be removed after the search. Then, the reviewers will independently apply the eligibility criteria and select the studies to be included in the review. They will begin with the screening of titles, then abstracts, then finally full texts for those that satisfy the eligibility criteria of the review. Author, year of publication, source of the publication, study design, location, period, pollutant studied, methods of exposure assessment, number of participants/animals, health outcome(s) (or for experimental studies: endpoints such as organ function, cellular changes, molecular alterations) under investigation, effect estimates, covariate adjustment will be extracted using a bespoke data-extraction form. All studies retrieved will be maintained and recorded.

Risk of bias assessment

Owing to time restraints, a systematic evaluation of the literature has been agreed to be outside of the remit of this work, ruling out formal methods of appraising for quality and bias. Expert commentary on the quality of the studies will nonetheless be provided where relevant to the narrative discussion. We will not be able to conduct our own meta-analyses that would provide pooled health effect estimates either. Instead, this rapid review will be a mixture of a qualitative, albeit critical in nature, review of the evidence, and quantitative pooled estimates from previous meta-analyses that will be discussed extensively.

Strategy for data synthesis

Narrative synthesis will be conducted for the eligible studies.

Depending on the number of hits, the total number of studies for review may be constrained using logical approaches e.g., for modification by age addressing core health outcomes such as all cause, respiratory and

cardiovascular mortality/respiratory and cardiovascular admissions rather than rare health outcomes or emphasising multi-city studies.

Analysis of subgroups or subsets

If we identify factors that potentially cause heterogeneity between studies, such as study location, exposure assessment etc., we will discuss them in the project report.

Review team members

Drs Heather Walton, Julia Fussell, Dimitris Evangelopoulos and Dylan Wood, Environmental Research Group (ERG), Imperial College London

Type and method of review

Narrative synthesis of epidemiological and experimental evidence.

Funding sources/sponsors

Department for Environment, Food and Rural Affairs

Actual start date and Anticipated completion date

04 October 2022 – 31 March 2023

Appendix 2 – Personal communication with Dr. Paul Pfeffer regarding asthma subtypes

Identifying and Defining "At Risk" Groups to Better Target Air Quality Information – A Rapid Evidence Assessment of the Health Evidence Base – Literature Search Protocol.

Conversation via Microsoft Teams with Paul Pfeffer to discuss air pollution and asthma subtypes.

Date: Thursday 1st December 14:00 - 15:00
Present: Dimitris Evangelopoulos, Julia Fussell, Paul Pfeffer, Heather Walton, Dylan Wood

Stratification of asthma into different types is controversial.

Current definitions (e.g., by phenotype or endotype) are different to what they were a decade or so ago and future definitions will undoubtedly be different from those used today.

A good definition to use:

- Allergic asthma versus non-allergic asthma i.e., asthma that is or is not allergen driven. And these are static characteristics (e.g., irrespective of treatment).

Other definitions:

- Type 2 (T2) asthma versus non-T2 asthma.
    - 'T2 low asthma' should be considered synonymous with non-T2 asthma.
    - The classical schema is of pathologic T helper lymphocyte type 2 (Th2) responses to aeroallergens in the airways causing inflammation and also compromising antiviral immune responses.
    - However, the problem with categorising patients this way is that the Th status changes with treatment so that with medication, an asthmatic can change from being T2 high to T2 low.

- Asthma with or without nasal polyps
- Aspirin-exacerbated asthma
- Perimenstrual asthma

The last 3 can be regarded as 'fine print' when considering the overall asthma population.

Definitions that are not useful for targeting air quality information:

- Severe asthma as is reflective of the amount of treatment needed to get the asthma under control.
- Brittle asthma – no longer used and has been replaced with severe asthma.
- Childhood versus late-onset asthma owing to controversy that exists about the existence of adult-onset asthma as a separate entity.
- Neutrophilic asthma because it is now thought that this is related to overuse of corticosteroids leading to susceptibility to infections and therefore neutrophilia. Treatments targeting neutrophils do not work for asthma.

Q: What would be helpful in predicting an asthmatic response to air pollution?
A: An asthmatic's eosinophil count

- This is because eosinophils have a central proinflammatory role in the pathogenesis of asthma and are associated with asthma exacerbations.

N.B. eosinophilia is common in both allergic and non-allergic asthma.

What needs to be done (what Paul is planning to do):

- A study on how the following variables influence the effect of air pollution on asthma exacerbations:
    - Eosinophil count
    - Allergic history
    - Type of medication
    - Adherence in taking medication

Thereby determining which of the above infer greater susceptibility.
N.B. Data on the above variables resides in primary care, allowing easy access.

Paul doubts that we will find many existing epidemiological studies that have looked at how the short-term effects of air pollution asthma may differ by asthma type/management

- Heather mentioned 2 previous studies: one that looked at effects on severe asthmatics (https://www.sciencedirect.com/science/article/abs/pii/S0013935102943574) that has since been forwarded to Paul and another that looked at the modifying effect of bronchial hyper-reactivity on the relationship between air pollution and asthma symptoms https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(98)06311-9/fulltext
- Julia has also forwarded to Paul a study that looked at effects on allergic v non-allergic asthma (https://www.tandfonline.com/doi/abs/10.1080/02770903.2021.1955133?journalCode=ijas20)

Heather has subsequently brought to our attention additional studies reporting that:

- Children with BHR and relatively high concentrations of serum total IgE are susceptible to air pollution https://pubmed.ncbi.nlm.nih.gov/10093979/

- The relation between symptoms and measures of exposure to (truck) traffic-related air pollution were almost entirely restricted to children with BHR and/or sensitization to common allergens, indicating that these are a sensitive subgroup among all children for these effects https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1241655/

- An association of PM_{10} and ozone with uncontrolled asthma in adults https://pubmed.ncbi.nlm.nih.gov/21690606/

Problems in gleaning information from controlled human studies

- Most studies have focused on surrogate markers such as a drop in lung function, which is not representative of an exacerbation (cf Chris Carlsten study of ozone & AOE supplementation)

Problems in gleaning information from animal studies

- Issues in extrapolating findings from animal models, in which allergic airway disease must be induced by a short period of antigen exposure, to humans, that have a complex, heterogeneous syndrome that is rarely due to a single allergen and that often presents in the absence of atopy.

Air Quality alerts

- Are they doing anything/do they work? Paul referred to the study in Toronto (https://www.sciencedirect.com/science/article/pii/S2542519617301857), the findings of which suggested that issuing air quality alerts alone has a limited effect on public health.
- Heather referred to a study she did in Sussex that looked at whether there would be sufficient power to do a study of the effectiveness of the air pollution information service. The study concluded there was not in this case. Walton H, Fuller G, Baker T and Atkinson R (2014) Air Pollution Alert Services Evidence Development Strategy – Prediction Of Possible Effectiveness And Assessment Of Intervention Study Feasibility http://www.erg.ic.ac.uk/Research/home/aspire-project.html
- We discussed whether such a study would have more power if done in London. It was thought it probably would but care would need to be taken to define a control group in such a study.
- Should not necessarily be telling people to stay indoors (e.g., re mould)
- Problems in telling patients to (a) take more medication when this could be detrimental or (b) walk through a green space that may simply trade traffic-related pollution exposure for pollen exposure. For a) some reliever inhalers down-regulate relevant receptors which can be detrimental, it depends on which reliever inhalers patients are taking. (The MART inhaler was mentioned as a combined reliever and preventer inhaler which might be expected to pre-empt an exacerbation at the start; others do not work that way).
- Difficult to give clinical advice because we have not done the studies.

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