Discussion

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Using epidemiology to estimate the impact and burden of exposure to air pollutants

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This paper focuses on the use of results of epidemiological studies to quantify the effects on health, particularly on mortality, of long-term exposure to air pollutants. It introduces health impact assessment methods, used to predict the benefits that can be expected from implementation of interventions to reduce emissions of pollutants. It also explains the estimation of annual mortality burdens attributable to current levels of pollution. Burden estimates are intended to meet the need to communicate the size of the effect of air pollution on public health to policy makers and others. The implications, for the interpretation of the estimates, of the assumptions and approximations underlying the methods are discussed. The paper starts with quantification based on results obtained from studies of the association of mortality risk with long-term average concentrations of particulate air pollution. It then tackles the additional methodological considerations that need to be addressed when also considering the mortality

effects of other pollutants such as nitrogen dioxide (NO₂). Finally, approaches that could be used to integrate morbidity and mortality endpoints in the same assessment are touched upon. This article is part of a discussion meeting issue 'Air quality, past present and future'.

1. Introduction

This paper provides an overview of the use of the results of epidemiological studies to quantify health effects associated with long-term exposure to ambient air pollutants. It draws particularly on experience within the UK and methods developed or used by the UK's expert advisory Committee on the Medical Effects of Air Pollutants (COMEAP). It also touches on methods that have been used for global assessments, and why different approaches might be required in different contexts.

The approach taken follows how quantification methods have developed over the last few decades. The historical context of the London smogs illustrates that attention was initially focused on the effects of short-term exposure to highly elevated concentrations of pollutants on mortality. Later, cohort studies indicated that the effects of long-term exposure to pollution posed a greater overall risk to public health and attention moved to quantifying these. Reflecting the available evidence, the mortality effects of long-term exposure to particulate air pollution were the first to be quantified. The methods used, and appropriate interpretation of the results obtained, are discussed. Next, the methodological considerations that need to be addressed when also considering the mortality effects of other pollutants such as nitrogen dioxide (NO₂) are described. The paper then touches on approaches that could be used to integrate morbidity and mortality endpoints in the same assessment.

2. Historical context

The London smogs of the early 1950s demonstrated the health effects of air pollution only too clearly. A combination of large-scale domestic burning of coal, still air and a temperature inversion—which trapped polluted air in the city—resulted in hospitals becoming overwhelmed and large numbers of people dying of acute respiratory and cardiovascular effects. Time-series plots of daily mortality statistics and the levels of smoke and sulfur dioxide during the episode show that mortality increased with rising pollution levels, and started to drop once pollution levels had peaked [1]. Various estimates have been made of the effects of this relatively short-term exposure to elevated concentrations of pollutants, ranging from 3000 deaths in the first week to 12 000 deaths including subsequent weeks, depending on assumptions made [2].

The health effects associated with other short-term episodes of elevated levels of pollutants in the UK have also been quantified (e.g. [3–6]). These were based on effects observed in studies of daily variations in air quality (time-series epidemiological studies). The first estimates of health effects attributable annually to air pollution in the UK made by COMEAP [7] also drew on the results of time-series studies.

However, evidence from cohort studies, which examine the differences in risk between individuals living in areas with different levels of air pollution, suggested that the mortality effects of long-term exposure to air pollution were higher than the risks known to be associated with short-term fluctuations in concentrations. Concentration–response coefficients¹ linking fine particulate air pollution with mortality reported from large cohort studies undertaken in the US, notably the Harvard Six Cities study and studies on the American Cancer Society (ACS) cohort [8–10], were higher than the coefficients reported in time-series studies. The Harvard Six Cities study [8] had suggested that this effect on mortality was more closely associated with

¹'Coefficient' is used in this paper to refer to that aspect of the concentration–response function which describes the association (quantitative relationship) in an epidemiological study between the change in concentration of an air pollutant and a change in mortality or morbidity risk.

fine particles smaller than $2.5\mu\text{m}$ diameter ($\text{PM}_{2.5}$)² than with larger particles. Consequently, much subsequent research—and policy attention—has focused on health effects associated with long-term average concentrations of $\text{PM}_{2.5}$.

3. Quantification to inform policy

As well as understanding the types of health effects that can be caused by exposure to air pollution, policy makers also need to be able to quantify and evaluate the size of the effects. Quantification is undertaken to meet two main needs: scoping and communicating about the size of the effect of current levels of pollution on public health (burden estimates) and the health benefits that would be expected if levels of pollution were reduced (health impact assessment). Health impact assessments of proposed interventions are also used in cost-benefit assessments, which underpin policy analysis.

There are a number of aspects that need to be considered when deciding how to quantify health effects associated with air pollution. The approach taken may differ depending upon the aim and application of the resulting estimates. Relevant considerations are summarized here and covered in more detail later:

- **Selection of the pollutant-outcome pair(s)** on which to base the estimate. This will depend upon the purpose of the quantification. The aim is to use pollutant-outcome pairs for which there is convincing evidence of a statistical association (in epidemiological studies) and plausibility of the association being causal (e.g. evidence from experimental studies).
- **Selection of an appropriate coefficient** for each pollutant-outcome pair. Considerations include whether to adopt a coefficient from a single study or a summary estimate from a meta-analysis of a number of studies. And, if a meta-analytical estimate is used, which of the available studies to include in the meta-analysis to avoid over-representation of any cohorts and to ensure that the summary estimate is appropriate for the population to which it will be applied.
- Whether coefficients reported from **single-pollutant models** will be used, or whether coefficients from **two- or multi-pollutant models** (in which the effects of other pollutants are accounted for, as far as possible) are more appropriate (if available).
- Whether or not to apply a **cut-off for quantification**. This decision could reflect whether there is evidence that suggests a threshold below which health effects are not observed, a reluctance to extrapolate beyond the range of available data, or the needs of a specific policy-relevant consideration.
- The extent to which it may be possible to quantify **uncertainties**. Statistical uncertainty around the concentration–response coefficient in epidemiological studies is usually reported using a 95% confidence interval. This is often carried through in quantification to indicate uncertainty in burden estimates or health impact assessments. Other uncertainties in the quantification process, such as uncertainty in the pollution modelling used to estimate exposure, are often not reflected quantitatively, but may be important.
- If more than one pollutant-outcome pair is to be included in the assessment, consideration needs to be given to whether to undertake a number of **separate calculations** and sum the results, **or to integrate assessment** of different health endpoints and/or pollutants within a single model.
- The **interpretation of results** of quantification is not always straightforward. Metrics such as ‘attributable deaths’ are not self-explanatory and may need to be interpreted for the intended audience [11].

² $\text{PM}_{2.5}$ is defined as the mass per cubic metre of airborne particles passing through the inlet of a size selective sampler with a transmission efficiency of 50% at an aerodynamic diameter of $2.5\mu\text{m}$. In practice, $\text{PM}_{2.5}$ represents the mass concentrations of particles of less than $2.5\mu\text{m}$ aerodynamic diameter.

- A number of other decisions also have to be made (e.g. the scale of the pollutant modelling used in the assessment) but these are not covered in this paper.

(a) Selection of a pollutant-outcome pair and coefficient

Mortality is the health endpoint which is most commonly quantified in assessments of effects associated with air pollution. In its report *Long-term exposure to air pollution: effect on mortality* COMEAP [12] came to the view that associations linking long-term exposure to particulate air pollution (represented by $\text{PM}_{2.5}$) with the effects on mortality almost certainly represented causal relationships in respect of the air pollution mixture of which $\text{PM}_{2.5}$ forms part and were highly likely to be causal in terms of particulate air pollution specifically. COMEAP noted that the evidence relating to the possible effects of long-term exposure to common gaseous air pollutants (sulfur dioxide, nitrogen dioxide (NO_2) and ozone) was less well developed. Coefficients from a study of a large cohort in the US [10] were recommended by COMEAP as expressing relative risks associated with $\text{PM}_{2.5}$ concentrations. For all-cause mortality, a relative risk from 1.06 per $10 \mu\text{g m}^{-3}$ (95% confidence interval (CI) 1.02–1.11) was recommended. COMEAP [12] also undertook an expert elicitation exercise to express Members' views on the plausibility of the coefficient, for quantifying effects of pollution in the UK, and proposed that this wider plausibility interval be used to express uncertainty around any estimates generated by using this coefficient for applications in the UK.

COMEAP reviewed its recommendations for quantification of all-cause mortality associated with $\text{PM}_{2.5}$ in 2018 [13] and recommended that a meta-analytical summary effects estimate published by Hoek *et al.* [14] be used in future. The coefficient of 1.06 is the same as the previous (2009) recommendation but, because of the additional statistical power afforded by a meta-analysis of several studies, the 95% confidence interval (1.04–1.08) is smaller than that reported by Pope *et al.* (2002) [10].

(b) Health impact assessment

Using actuarial life-table methods, COMEAP [11] used the coefficient to estimate the impact of reducing $\text{PM}_{2.5}$ pollution in the UK by $1 \mu\text{g m}^{-3}$ or of removing all particulate matter arising from human activities. A reduction of $1 \mu\text{g PM}_{2.5} \text{ m}^{-3}$ was predicted to produce a gain of 4 million years of life in the entire UK population over the next 100 years and an increase in life expectancy from birth of about 20 days. The corresponding mortality benefits of removing all anthropogenic particulate air pollution were a gain of 36.5 million life years in total population survival time over the next 100 years and an increase of 6 months in life expectancy from birth.

(c) Mortality burden estimates

The metrics commonly used in health impact assessments, such as total population survival time, are not intuitive or easily understood by some audiences. Therefore, COMEAP also estimated the mortality burden attributable to current levels of air pollution by calculating a figure of 'attributable deaths'. Such burden estimates require a number of simplifying assumptions to be made (see [11]), but can be regarded as the effect on mortality, in a given year, of long-term exposure of the current population to current levels of air pollution. They are calculated as the difference in annual deaths between a baseline scenario of actual (observed) age-specific death rates (which have been influenced by current levels of pollution) and an alternative scenario, in which age-specific death rates are reduced by an amount attributable to current levels of pollution. COMEAP [11] estimated the mortality burden of human-made particulate pollution in the UK in 2008 as: an effect equivalent to approximately 29 000 deaths associated with a loss of 340 000 years of life, or a loss of 6 months of life expectancy from birth. COMEAP noted that the estimates could vary from about a sixth to double these figures [11]. Although the calculations were undertaken using a concentration–response coefficient linking $\text{PM}_{2.5}$ concentrations with

mortality, COMEAP regarded this coefficient as likely to reflect the effects of particulate matter pollution more generally (i.e. $PM_{2.5}$ and also particles in other size fractions) [11] or perhaps even the air pollution mixture of which $PM_{2.5}$ is a part [12].

This national burden estimate stimulated interest in carrying out similar assessments at a more local level: it was suggested that local-level information may be more powerful than national data in communicating the importance of the health effects of air pollution to both elected representatives and the public. The Health Protection Agency (HPA) asked COMEAP to comment on technical considerations that might be particularly relevant to local, rather than national, assessments and to advise on the appropriateness of possible approaches to such calculations. COMEAP [15] noted that some uncertainties and assumptions were enhanced in local assessments but did not think that this made it inappropriate to undertake estimates at local authority level. (These uncertainties would need to be considered carefully at scales finer than local authority level). Public Health England (into which HPA was incorporated) therefore published estimates of mortality attributable to particulate air pollution in every local authority area in the UK [16] and the fraction of mortality attributable to long-term exposure to particulate air pollution is included in the Public Health Outcomes Framework (PHOF) for local authorities in England [17]. Based on the levels of pollution in 2018, figures for the PHOF indicator vary from less than 3% in some rural areas, to 7% or more in some London Boroughs, with the fraction of mortality attributable to long-term exposure to particulate air pollution in England being 5.2% (figure 1).

(d) Interpretation of ‘attributable deaths’

Long-term exposure to air pollution is understood to contribute to the risk of dying from certain conditions. It is one of many contributory risk factors and is unlikely to be the sole cause of deaths of individuals. This means that the mortality burden attributable to long-term exposure to air pollution should not be interpreted as air pollution causing the deaths of ‘X’ individuals equal to the calculated number of attributable deaths. The ‘attributable deaths’ represent the total mortality effect across the population, but the distribution of the mortality effect within the population, and consequently the number of individuals affected, is unknown. For this reason, COMEAP proposed that the mortality burden should be expressed as ‘an effect equivalent to ‘X’ deaths’. COMEAP [11] explored the consequences of different possible distributions of the estimated mortality burden across the population. At one extreme, the total burden of 340 000 life years lost was consistent with 29 000 individual deaths at ‘typical’ ages with an average loss of life of 11½ years. At the other extreme, if the timing of all deaths had been influenced by air pollution, the average loss of life would have been 6 months. COMEAP [11] considered that some intermediate position was much more likely and speculated that, for example, all 200 000 individuals who had died from cardiovascular causes could have been affected by air pollution, and in that case, the average loss of life attributable to air pollution for each individual affected would have been almost 2 years.

Estimates of deaths attributable to air pollution are sometimes used to compare the public health importance of air pollution with other risk factors. This might be more appropriate for some risk factors than for others. COMEAP [18] suggested that, when comparing mortality effects, it would be useful to make it clear whether risks share similar characteristics, such as whether they

- are contributory risk factors acting in combination with others, or are likely to be the sole cause of death
- mostly influence deaths at older ages (such as from cardiovascular and respiratory conditions)
- involve a delay between exposure and effect
- have effects on population dynamics, so that the size and age distribution of populations are altered.

Figure 1. Fraction of mortality attributable to long-term exposure to particulate air pollution by Local Authority area in England (and key). Taken from Public Health England's (PHE) Public Health Outcomes Framework (PHOF) datatool [17]. Contains public sector information licensed under the Open Government Licence v3.0. (Online version in colour.)

For example, long-term exposure to air pollution affects deaths from the same sorts of diseases as smoking. However, the increase in individual risk is much higher for smoking than for air pollution, whereas the number of people in the UK exposed to air pollution is much higher than the number of active smokers. For alcohol, another important risk factor, deaths from some conditions can be directly linked to alcohol consumption. However, alcohol is more likely a contributory factor for mortality from a number of other conditions.

(e) Cut-offs for quantification

Health impact assessments of policies to reduce air pollution often predict the benefits of relatively small reductions in pollutant concentrations. By contrast, burden estimates are intended to give a feel for the size of the effect attributable to current levels of pollution. The counterfactual used is typically the absence of much or all pollution. If there were evidence of a threshold for effect, below which no adverse health effects occur, this should be reflected in the choice of the counterfactual used when generating burden estimates. Relatively few of the available cohort studies linking air pollutants with mortality have formally investigated the shape of the

concentration–response curve. However, of the available studies which have investigated this very few, if any, have identified thresholds for effect [11,19].

Other reasons for implementing a cut-off for quantification might include policy relevance. For example, COMEAP [11] considered it most policy-relevant to estimate only the burden attributable to particulate air pollution arising from human activities, as there is little that can be done to control emissions from other sources. There is also an argument for restricting quantification to concentrations within the studied range. Extrapolating beyond the range of concentrations in the epidemiological study/studies which have been used to derive the concentration–response coefficients used requires an assumption that the same relationship continues at lower (or higher) concentrations than those studied and introduces additional uncertainty. COMEAP [11,19] has chosen to calculate the burden using both a cut-off for quantification representing the lower end of the studied range and also by extrapolating to zero anthropogenic pollution. The burden above the cut-off is regarded as representing the portion of the burden in which there is greatest confidence, while further extrapolation to zero estimates the additional effect that is likely under an assumption of the same concentration–response relationship down to zero anthropogenic pollution. For COMEAP’s 2010 estimates of the mortality burden attributable to particulate pollution [11], the portion of the 29 000 attributable deaths and 340 000 years of life lost above the cut-off of $7 \mu\text{g m}^{-3}$ was 11 000 attributable deaths and an associated 130 000 years of life lost.

4. Approaches to global burden estimates of mortality based on associations with $\text{PM}_{2.5}$

As well as national and local assessments, there has also been interest in estimating the global burden of mortality (and disease) attributable to long-term exposure to particulate air pollution. Approaches used for global estimates need to be applicable to all areas of the world. Until relatively recently, most of the available cohort studies investigating the health effects of air pollutants were undertaken in North America or Europe. Results from these are not directly transferable to other parts of the world, because of differences in both population health and pollution levels. Because the dominant causes of mortality in some regions of the world are very different to those in the countries in which epidemiological studies had been undertaken, projects such as the Global Burden of Disease (GBD) [20] needed to develop estimates based on coefficients for cause-specific mortality, rather than all-cause mortality. Another question regarding transferability arises because some locations, notably mega-cities in developing or middle-income countries, have very much higher pollutant concentrations than those which had been studied in North America or Europe. In order to generate concentration–response relationships across the whole range of global ambient particulate pollution concentrations, Burnett *et al.* [21] developed integrated exposure response (IER) curves which combined, on the same plot, studies linking cause-specific mortality risks of $\text{PM}_{2.5}$ exposure from ambient air pollution, environmental tobacco smoke, indoor air pollution from biomass burning and active smoking. Although the IER curve for lung cancer remains fairly linear at the high exposures represented by active smoking, those for ischaemic heart disease and stroke suggest that the slopes are much shallower at higher concentrations. These relationships were used in the GBD 2010 and 2013 estimates [22,23]. More recently, studies have been carried out in areas with higher ambient pollutant concentrations, notably China, allowing Burnett *et al.* [24] to develop new concentration–response curves (Global Exposure Mortality Models, GEMMs) across a large range of concentrations for $\text{PM}_{2.5}$, based solely on epidemiological studies of outdoor air pollution.

As well as COMEAP’s estimate of the mortality burden of particulate air pollution in the UK of an effect equivalent to 29 000 deaths, estimates have also been made using the concentration–response curves which have been primarily developed for global assessments. These include UK estimates of approximately 21 000 attributable deaths by the World Health Organization (WHO, [25]) using the IER curves and approximately 64 000 deaths by Lelieveld *et al.* [26] using

the GEMMs approach. The variations between these figures illustrate the importance of the assumptions and inputs which underpin each estimate. The burden estimates are influenced by aspects such as the method used to assess the population's exposure to pollution and the choice of the concentration used as the counterfactual (i.e. the cut-off for quantification) as well as the concentration–response function. For example, Burnett *et al.* (2018 [24]) proposed a lower counterfactual for use with the GEMMs than has usually been applied when using the IER curves.

Approaches such as these have been developed to allow consistent methods to be applied across the wide range of PM_{2.5} concentrations and population characteristics experienced around the globe. In our view, they are best used for generating global estimates or for comparisons between countries. The methods and assumptions used by COMEAP were chosen as being appropriate for quantification in the UK and we therefore consider these better for informing decision-making in the UK. We note that, although advocating the use of flexible model forms such as the IER and GEMMs, Burnett and Cohen [27] acknowledged that the use of a coefficient representing a log-linear model, such as is used by COMEAP, could also be an option when quantifying effects in countries or regions with relatively low PM_{2.5} concentrations.

5. Mortality estimates using associations with long-term average concentrations of nitrogen dioxide

While it is clear from epidemiological studies that air pollution has adverse effects on health, understanding the extent to which the different pollutants contribute to these effects is challenging. Because many pollutants are emitted from the same sources, such as traffic, their concentrations in ambient air are often correlated. This makes it difficult to interpret the associations of health effects with air pollutants, as it is not clear which component of the air pollution mixture may have caused the effect.

There is evidence from experimental toxicological studies demonstrating adverse effects of particulate matter, supporting the likelihood of a causal relationship. There is less experimental evidence investigating the effects of other correlated pollutants, such as NO₂. This made it difficult to understand whether NO₂ had direct adverse effects on health [28].

In recent years, the number of epidemiological studies reporting associations of adverse health effects, including mortality, with NO₂ has increased. In its *Review of evidence on health aspects of air pollution* (REVIHAAP) project, WHO [29] noted the large number of new time-series studies reporting associations between day-to-day variations in NO₂ concentrations and variations in mortality, hospital admissions and respiratory symptoms. REIVHAAP authors also noted that new studies had also been published showing associations between long-term exposure to NO₂ and mortality and morbidity. Given the consistent evidence from time-series studies of associations and some mechanistic support for causality, particularly for respiratory outcomes, they concluded that it was reasonable to infer that NO₂ had some direct effects on health. Because the correlations between concentrations of NO₂ and other pollutants were often high in studies which examined associations with long-term average concentrations, the authors considered that it was harder to judge the independent effects of long-term exposure to NO₂. Nonetheless, they suggested that the available evidence was suggestive of causality. In 2015, COMEAP [30] acknowledged this increasing evidence associating NO₂ with health effects and came to the view that, on the balance of probability, NO₂ itself was responsible for some of the health impact found to be associated with it in epidemiological studies.

(a) Coefficients from single-pollutant models

WHO's *Health risks of air pollution in Europe* (HRAPIE) project [31] built on the REVIHAAP review and made recommendations for concentration–response functions for cost-benefit analysis of the particulate matter, ozone and NO₂. These recommendations included an approach to quantification of mortality associated with long-term average concentrations of NO₂ using a

Figure 2. HRs (95% CI) per 10 µg m⁻³ for cohort studies reporting associations between NO₂ and all-cause mortality. (From COMEAP, 2018) [19].

summary effects estimate of relative risk (RR) of 1.055 (95% CI 1.031–1.080 per 10 µg m⁻³ from a meta-analysis of coefficients from single-pollutant models by Hoek *et al.* [14]. Based on a study by Cesaroni *et al.* [32], it was suggested that approximately 30% of the effects represented by associations with NO₂ may overlap with effects represented by associations with PM_{2.5}. The recommendation was assigned to ‘Group B’—an extended group of more uncertain pollutant-outcome pairs—to indicate that there was uncertainty about the precision of the data used for quantification of effects and to avoid double counting of effects estimated using coefficients representing associations of mortality with PM_{2.5} (designated as a more reliably quantified ‘Group A’ pollutant-outcome pair).

Because of the high economic value of willingness to pay to avoid mortality and years of life lost [33], the inclusion of this pollutant-outcome pair, as well as an estimate based on PM_{2.5} concentrations, could have a large influence on cost-benefit analyses of interventions to improve air quality. COMEAP was therefore asked to review the evidence linking long-term average concentrations of NO₂ with all-cause mortality and, if appropriate, to recommend how it should be quantified. A new systematic review and meta-analysis of associations with NO₂ obtained using single-pollutant models in cohort studies was undertaken, using an approach which ensured that only one result from each cohort was included in the meta-analysis. As the aim was to derive a summary hazard ratio considered to be representative of the risk in the general population, studies of cohorts defined by pre-existing disease or selected age ranges were excluded from the meta-analysis. A summary effects estimate of 1.023 (95% CI 1.008–1.037) per 10 µg m⁻³ was obtained from a random effect model [19] giving a lower estimate than that of Hoek *et al.* [14] recommended by HRAPIE. The coefficients of the individual studies are presented in figure 2.

This is a summary estimate derived from NO₂ coefficients obtained from single-pollutant models and so it likely reflects the effects of other pollutants and risk factors which are spatially correlated with NO₂ concentrations as well as any direct effect of NO₂ itself. COMEAP noted that correlated pollutants included PM_{2.5} as well as other components of the air pollution mixture such as ultrafine particles, black carbon and volatile organic compounds. COMEAP Members

Table 1. Types of coefficients that might be used to represent associations between long-term average concentrations of PM_{2.5} and NO₂ and mortality. Reproduced from COMEAP (2018) [19].

coefficient	possible interpretation
unadjusted coefficient for PM _{2.5}	reflects the effect of PM _{2.5} and also, to some extent, the effect of other pollutants with which PM _{2.5} is correlated. These include other fractions of PM, NO ₂ , and other components of the air pollution mixture.
unadjusted coefficient for NO ₂	reflects any causal effect of NO ₂ and also, to some extent, the effects of other pollutants with which NO ₂ is correlated. These include PM _{2.5} , other fractions of PM, and other components of the air pollution mixture (e.g. ultrafine particles, Black Carbon, Volatile Organic Compounds etc.).
coefficient for PM _{2.5} adjusted for NO ₂	reflects the effect of PM _{2.5} and also, to some extent, the effects of other pollutants with which PM _{2.5} is most closely correlated but excludes (as far as possible) effects associated with NO ₂ , and other components of the air pollution mixture which are more closely correlated with NO ₂ concentrations than with PM _{2.5} concentrations. Given the good evidence and plausibility of causality, it is reasonable to regard the majority of this effect as likely to be causally related to PM _{2.5} .
coefficient for NO ₂ adjusted for PM _{2.5}	reflects any effect of NO ₂ and also, to some extent, other pollutants with which NO ₂ is closely correlated but excludes (as far as possible) effects associated with PM _{2.5} concentrations and other components of the air pollution mixture that are more closely correlated with PM _{2.5} concentrations than with NO ₂ concentrations. Given the weaker evidence for plausibility and causality, the extent to which this effect is likely to be causally related to NO ₂ is unclear. It is unlikely to be zero, but also unlikely to be 100%.

therefore agreed that it would be appropriate to use the summary unadjusted coefficient of 1.023 (95% CI 1.008–1.037) per 10 µg m⁻³ in health impact assessments only of interventions, such as pedestrianization, that achieved reductions of other traffic-related pollutants as well as NO₂.

(b) Multi-pollutant considerations

Statistical techniques (two- or multi-pollutant models) can be used to try to separate the effects of different pollutants. In a two-pollutant regression model, the relationship between the health effect and the pollutant of interest (for example, NO₂) is estimated while the other pollutant (for example, PM_{2.5}) is held constant in an attempt to identify any independent effect of NO₂ itself. However, COMEAP’s view was that an NO₂ coefficient, even adjusted for PM_{2.5}, likely still reflects, to some extent, the effects of other pollutants more closely correlated with NO₂ than with PM_{2.5} (table 1). These other pollutants are likely to be pollutants from a traffic source e.g. carbon monoxide, ultrafine particles (which do not correlate well with PM_{2.5}) and the primary combustion particle element of PM_{2.5} (table 1). COMEAP therefore considered confounding by PM_{2.5} and other pollutants separately.

In order to investigate the extent to which the associations of mortality with NO₂ and PM_{2.5} are independent, COMEAP [19] used a sub-set of studies which had reported results from both single- and two- or multi-pollutant models for both NO₂ and PM_{2.5}. Using HRs expressed per interquartile range (IQR), HRs from single-pollutant models were compared with HRs generated by combining mutually adjusted HRs (i.e. associations with NO₂ adjusted for PM and associations

with PM adjusted for NO₂). Within each study, it was found that the combined HR estimated from coefficients each adjusted for the effect of the other was either similar to, or only a little higher than, the higher of the single-pollutant coefficients for NO₂ or PM_{2.5}. This suggests that, to a large extent, the single-pollutant associations with NO₂ and PM_{2.5} represent the same effect of a pollutant mixture (table 2, adapted from [19]). The advantage of considering combined HRs per IQR is that uncertainties in how the model allocates effects to a particular pollutant are likely to be cancelled out when they are combined.

Nonetheless, COMEAP [19] noted that the assessment of NO₂ and PM simultaneously in a two-pollutant model is not straightforward. Difficulties arise because, among other things, the effects associated with a less accurately estimated pollutant exposure can be underestimated and the effects associated with a more accurately estimated pollutant exposure overestimated—a phenomenon termed ‘effect transfer’. Effect transfer is more likely when the pollutants’ concentrations are more closely correlated with each other. If the size and direction of effect transfer is not fully understood, then the results of two-pollutant models can be complex to interpret. COMEAP summarized the statistical issues affecting the available cohort studies which had used two- or multi-pollutant models (see COMEAP 2018 [19, p. 22–24] for a more detailed explanation) as follows:

- lack of tests for an interaction between NO₂ and PM
- high correlation between pollutants arising due to common sources and meteorological conditions
- possible transfer of effect which could arise from differing levels of misclassification when estimating exposures to pollutants, together with high correlation between the pollutants and/or the magnitude of any misclassification in exposures
- confidence intervals for associations with NO₂ (adjusted for PM) overlapping substantially with those (unadjusted) from the single-pollutant models - i.e. while the central estimate after adjustment suggested an additional independent effect of NO₂, the confidence intervals did not rule out complete overlap with PM.

Despite these difficulties, the majority of Members supported the development of methods for quantification using coefficients from multi-pollutant models, albeit with the need to acknowledge the uncertainties involved. However, some COMEAP Members thought that the methodological difficulties, and the uncertainty about the extent to which even adjusted coefficients were causally related to NO₂, meant that the evidence was too uncertain to allow the use of (adjusted) NO₂ coefficients from multi-pollutant models for quantification. The views of these Members are presented fully in a Minority Report: Chapter 10 (*Views of the dissenting group*) of COMEAP’s report on this topic [19].

COMEAP acknowledged the policy need to assess the benefits of interventions which primarily target reductions of NO₂. There were two major challenges for the development of methods to do this. First, concentration–response functions recommended by COMEAP are usually based on meta-analysis of several studies, allowing use of a broad range of evidence, and Members wished to make use of the larger body of single-pollutant model evidence used in developing this summary effects estimate. However, there are no validated statistical approaches for adjusting a summary effects estimate obtained by meta-analysis of unadjusted single-pollutant coefficients, i.e. in this case the HR of 1.023 (95% CI 1.008–1.037) per 10 µg m^{−3} annual average NO₂ concentration discussed earlier. Second, the available epidemiological studies are not informative about the extent to which coefficients for NO₂ adjusted for PM_{2.5} might be confounded by other pollutants, so the extent to which the effect is likely to be causally related to NO₂ is unclear. Under these circumstances, the majority of Members considered it appropriate to informally apply expert judgement to recommend a concentration–response function intended to quantitatively represent the likely causal link between NO₂ and all-cause mortality.

Table 2. Hazard ratios (HRs) from single and two-/multi-pollutant models for NO₂ and PM_{2.5}/PM₁₀ (HRs are expressed per IQR^a). Adapted from COMEAP [19].

study	cohort	correlation NO ₂ /PM _{2.5} exposure metrics	NO ₂ IQR ($\mu\text{g m}^{-3}$)	NO ₂	NO ₂ adjusted for PM _{2.5} /PM ₁₀	PM _{2.5} / PM ₁₀ IQR ($\mu\text{g m}^{-3}$)	PM _{2.5} /PM ₁₀	PM _{2.5} /PM ₁₀ Adjusted for NO ₂	combined NO ₂ adj/PM adj HR
Cesaroni <i>et al.</i> [32]	Rome	0.79	10.7	1.029 (1.022, 1.036)	1.026 (1.015, 1.037)	5.7	1.023 (1.016, 1.031)	1.004 (0.994, 1.015)	1.030
Carey <i>et al.</i> [34] ^b	CPRD	0.85	10.7	1.022 (0.995, 1.049)	1.001 (0.959, 1.044)	1.9	1.023 (1.000, 1.046)	1.023 (0.989, 1.060)	1.024
Beelen <i>et al.</i> [35] ^c	ESCAPE	0.2–<0.7	10.0	1.015 (0.993, 1.036)	1.007 (0.967, 1.049)	5.0	1.070 (1.016, 1.127)	1.060 (0.977, 1.150)	1.067
Fischer <i>et al.</i> [36] ^d	DUELS	0.58	10.0	1.027 (1.023, 1.030)	1.019 (1.015, 1.023)	2.4	1.019 (1.016, 1.022)	1.010 (1.007, 1.013)	1.029
HEI [37] ^e	ACS CPS II	−0.08	81.4	0.95 (0.89, 1.01)	0.90 (0.84, 0.96)	24.5	1.15 (1.05, 1.25)	1.22 (1.11, 1.33)	1.09
Jerrett <i>et al.</i> [38]	ACS CPS II	0.55	7.7	1.031 (1.008, 1.056)	1.025 (0.997, 1.054)	5.3	1.032 (1.002, 1.062)	1.015 (0.980, 1.050)	1.040

^aHRs expressed per IQR (Interquartile Range) except for Beelen *et al.* [35], which used per 10 $\mu\text{g m}^{-3}$ NO₂ and 5 $\mu\text{g m}^{-3}$ PM_{2.5}.

^bPM_{2.5} results –personal communication.

^cBased on 14 cohorts in which correlation between NO₂ and PM_{2.5} was less than 0.7 (figures to 3 decimal places provided by personal communication).

^dPM₁₀.

^eHR (95% CI) for min-max range of average concentrations in fine particulate cohort (41 cities).

It was suggested that approximately 30–70% of an NO₂ coefficient adjusted for PM_{2.5} may be causally linked to NO₂. Combining this assumption with information about the extent of reduction of single-pollutant NO₂ coefficients following adjustment for PM (approximately 20% in the few available studies in which concentrations of NO₂ and PM_{2.5} were less closely correlated (less than 0.7; table 3 taken from [19])³ approximately 25–55% of the summary unadjusted coefficient was considered likely to be causally related to NO₂. Therefore, a coefficient of 1.006–1.013 per 10 µg NO₂ m⁻³ was recommended for use to assess interventions which would reduce NO_x emissions without substantially reducing emissions of other traffic-related pollutants. It was not possible to develop formal uncertainty bounds around this estimate.

Given the uncertainties involved, COMEAP did not support attempting to estimate mortality burdens attributable to NO₂ itself. However, the majority of Members supported the use of exploratory calculations to produce a range of burden estimates. Two approaches were taken. The first used the available summary single-pollutant coefficients for NO₂ and PM_{2.5}, separately, to produce separate estimates of the mortality burden. This approach regards NO₂ and PM_{2.5} as indicators of the pollution mixture. Since both of these approaches are likely to underestimate the effect of the mixture to some extent, the higher of the two estimates was regarded as the more appropriate. The second approach was also based on the available single-pollutant summary coefficients but these were adjusted, using individual results from four studies, and the resulting burden estimates combined to give another four separate burden estimates for the pollutant mixture. The extent to which single-pollutant coefficients was reduced, in each study, on mutual adjustment was used to adjust the summary single-pollutant coefficients. These four study-specific burden estimates, together with the higher of the single-pollutant-as-indicator estimates, was regarded as representing the range of likely ‘central’ estimates of the mortality burden attributable to the current air pollution mixture. It was not possible to develop formal uncertainty bounds around this estimate. Estimates were made with a quantification cut-off to avoid extrapolation beyond the range of data and without a cut-off. The range of estimates without a cut-off—an annual effect in the UK equivalent to 28 000–36 000 deaths, is used by Public Health England (e.g. [40]) to communicate about the scale of the effect of air pollution on public health.

COMEAP made a number of recommendations for future research that would help reduce uncertainties regarding the effects of long-term exposure to NO₂ on health. Research to improve understanding of the consequences of the statistical issues encountered during COMEAP’s consideration of this topic was regarded as important. COMEAP also made recommendations for new toxicological, volunteer and epidemiological studies that would help distinguish the effects of NO₂ from those of PM. These included ‘Further multi-pollutant epidemiological studies, preferably carried out in circumstances where NO₂ and PM concentrations are weakly correlated, or allowing comparison of areas with different ratios of NO₂ to PM concentrations. Examples include spatio-temporal studies and interrupted time-series studies taking advantage of the changes in NO₂ to PM_{2.5} ratios over time.’ Reductions in NO₂ concentrations experienced during the recent ‘lockdown’ implemented to reduce transmission of SARS-CoV-2, in the absence of reductions of a similar scale in PM_{2.5} concentrations, might appear to provide an opportunity for such research. Although the timescale of the reduction in transport emissions is too short to inform estimates of the effect of long-term exposure, studies might be anticipated to provide some additional insight regarding the potential independent health effects of pollutants. However, there are likely to be considerable challenges in conducting even studies of short-term exposures, for example, the many factors linked with transmission of the virus (such as population density) which are potential confounders of associations with air pollutants.

³At the time of COMEAP’s discussions, the single- and two-pollutant coefficients reported by Beelen *et al.* [35] from the 14 cohorts in which correlation was <0.7 were only available to us to two decimal places as published: unadjusted HR 1.01 (0.99–1.04) per 10 µg m⁻³ annual average NO₂; HR adjusted for PM_{2.5} 1.01 (0.97–1.05). Table 3 includes these coefficients reported to three decimal places (subsequently kindly provided to us by the study authors). These indicate a larger reduction on adjustment for PM_{2.5} than is suggested by the published coefficients.

Table 3. Hazard ratios¹ from single- and two-pollutant models for four cohorts used for quantification.

study	cohort	correlation NO ₂ /PM _{2.5} exposure metrics	NO ₂ IOR (μg m ⁻³)	NO ₂	NO ₂ adjusted PM _{2.5} /PM ₁₀	% ^b	PM _{2.5} / PM ₁₀ IQR (μg m ⁻³)	PM _{2.5} /PM ₁₀	PM _{2.5} /PM ₁₀ adjusted NO ₂	% ^b
Beelen <i>et al.</i> [35] ^c	ESCAPE	0.2–<0.7	10.0	1.015 (0.993, 1.036)	1.007 (0.967, 1.049)	53	5.0	1.070 (1.016, 1.127)	1.060 (0.977, 1.150)	14
Fischer <i>et al.</i> [36] ^d	DUELS	0.58 ^d	10.0	1.027 (1.023, 1.030)	1.019 (1.015, 1.023)	29	2.4	1.019 (1.016, 1.022)	1.010 (1.007, 1.013)	46
Jerrett <i>et al.</i> [38]	ACS CPS II	0.55	7.7	1.031 (1.008, 1.056)	1.025 (0.997, 1.054)	19	5.3	1.032 (1.002, 1.062)	1.015 (0.980, 1.050)	53
Crouse <i>et al.</i> [39] ^e	CanCHEC	0.40	15.2	1.052 (1.045, 1.059)	1.045 (1.037, 1.052)	13	5	1.035 (1.013, 1.049)	1.011 (1.003, 1.020)	68

^aHRs expressed per IQR (Interquartile Range) (Fischer *et al.*, [36], Jerrett *et al.*, [38]), mean minus 5th percentile (Crouse *et al.*, [39]) or 10 μg m⁻³ NO₂ and 5 μg m⁻³ PM_{2.5} (Beelen *et al.*, [35]).

^bThe percentage reduction in HR after adjustment for the other pollutant.

^cBased on 14 cohorts in which correlation between NO₂ and PM_{2.5} was less than 0.7. HRs provided to 3dp by the authors in December 2017.

^dPM₁₀.

^eNO₂ adjusted for PM_{2.5} and O₃. PM_{2.5} adjusted for NO₂ and O₃. From COMEAP [19].

Figure 3. Illustration of model integrating morbidity and mortality. (1) and (2): RRs taken from the literature. (3): Derived from RR for all-cause mortality (1.06 per $10 \mu\text{g m}^{-3}$) and (2).

6. Integrating mortality and morbidity endpoints

As well as quantifying mortality, there is interest in quantifying the effects of air pollution on illness and disease. Air pollution can exacerbate existing respiratory and cardiovascular conditions, and epidemiological studies also suggest associations with the incidence of new cases of the disease. Existing approaches to the quantification of morbidity endpoints (e.g. [20,31,41,42]) consider the increase in either incidence or prevalence associated with exposure to air pollutants.

COMEAP was asked to consider how to quantify effects of air pollution on cardiovascular disease and has chosen [43] to integrate effects of air pollution on mortality and CV morbidity into the same assessment as this is most appropriate to capture the dynamic effects of air pollution on the disease. The development and application of the models used for this quantification were undertaken by researchers at University College London (UCL) and the London School of Hygiene and Tropical Medicine (LSHTM). The approach models the effect of air pollution on recruitment into the pool of prevalent cases of ischaemic heart disease (IHD), using a RR for incidence, and also models the effect of air pollution on loss from the prevalent pool. This latter requires a RR for case fatality—i.e. deaths from any cause of those with IHD. The model developed for COMEAP also uses a RR for all-cause mortality in those without diagnosed IHD to ensure consistency with the overall evidence. This is derived from the RR for all-cause mortality in the general population and the RR for case fatality (figure 3).

Model simulations [43] have shown the importance of the relative sizes of the RRs for incidence and case fatality on the prevalence of the disease in this approach to modelling disease. There are few studies on IHD case fatality, but those available suggest that the RR is higher than the RR for IHD incidence, and also higher than the RR for all-cause mortality in those without IHD. Early results from this work indicate that long-term exposure to $\text{PM}_{2.5}$ increases the risk of developing IHD and also increases the risk of dying once you have IHD. Reducing $\text{PM}_{2.5}$ concentrations would therefore increase life expectancy, increase average healthy life expectancy before the development of IHD and increase survival time in those with IHD. The effect on prevalence is complex and varies with age and over time. Under some assumptions, a decrease in $\text{PM}_{2.5}$ can lead to a higher overall prevalence of IHD in the population, because of improved survival of those with the condition.

This approach to quantification seems to take appropriate account of the complex interaction between incidence, prevalence and mortality in response to reductions in air pollutant concentrations. However, studies of the effect of air pollution on IHD case fatality are scarce, meaning that this important aspect of the modelling is particularly uncertain. Information on the effect of air pollution on case fatality for other health conditions may not exist. In addition, developing a similar model which would be used to quantify multiple morbidities would likely be complicated and would likely need to include considerations such as co-morbidities. Similarly, implementation of this approach within a multi-pollutant context would not be straightforward.

This means that further development of these types of methods will be needed before they can be implemented in routine health impact analysis and cost-benefit analyses such as those used to underpin policy evaluation.

7. Concluding comments

This paper has outlined how the results of epidemiological studies have been used to quantify health effects associated with long-term exposure to ambient air pollutants. It has drawn particularly on experience in the UK and methods developed by the UK's expert advisory Committee COMEAP. Such methods are subject to a number of uncertainties, and the resulting figures should be regarded as estimates, which may vary according to the available data as well as the uncertainties in the epidemiological evidence base. The most appropriate method may depend upon the purpose of the quantification and may vary according to the geographical scale of the assessment and/or the pollutant or policy under consideration.

The increasing demand to address multiple pollutants and multiple health endpoints introduces additional uncertainties and methodological complexities. Further progress will require methodological developments and new studies, such as

- understanding the opportunities and limitations of two- and multi-pollutant models to understand effects of individual pollutants and, in particular, how differential exposure misclassification may affect the results
- modelling co-morbidities and mortality (and co-pollutants) in an integrated model
- studies on the effect of air pollutants on case fatality (i.e. mortality in those with the disease) to provide coefficients for inclusion in models

Data accessibility. This article has no additional data.

Authors' contributions. A.G. and K.E. provided Scientific Secretariat support to COMEAP during the development of the reports and statements described in the paper, and A.G. drafted the manuscript. J.F.H. and H.W. are previous and current Chairs of the Quantification Sub-group of COMEAP and contributed to the development of the reports and statements described in the paper. All authors read, revised and approved the manuscript.

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