Working Paper for COMEAP Report "Associations of long-term average concentrations of nitrogen dioxide with mortality" published July 2018

Working Paper 3: Exploratory burden calculations of mixtures of $PM_{2.5}$ and NO_2

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EXPLORATORY BURDEN CALCULATIONS OF MIXTURES OF $PM_{2.5}$ AND NO_2

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1. Introduction

Burden calculations are used as an approximate snapshot of the general size of the public health problem posed by air pollution. They are intended to be simpler to do than impact calculations used in policy analysis. Policy analysis may require detailed analysis of the effect of specific pollutants because regulations are on a pollutant by pollutant basis and it is thought that policies that target these specific pollutants may be more efficient. This is not required to the same degree for burden calculations. As has been discussed earlier in the report, it is very challenging to disentangle the effects of specific pollutants in epidemiological studies. In some respects, the epidemiological studies are better suited to estimating effects on health of mixtures of air pollutants. This Working Paper explores the potential ways in which previous calculations of burden by the Committee on the Medical Effects of Air Pollutants, COMEAP (2010), might be changed by the new understanding developed in the process of preparing this report.

In areas of uncertainty, it is appropriate to derive calculations in a variety of ways and compare the results. This does not mean any one option is the 'right' way but the options scope the bounds of where the answer might lie. The main COMEAP report on associations of long-term average concentrations of nitrogen dioxide with mortality (COMEAP, 2018) considers the application and interpretation of coefficients and discusses the uncertainties and reasoning for choosing specific approaches. More details are found in Working Paper 2 and several chapters of the main report including Chapter 10, which sets out the contrasting views against calculating burden.

a) Single pollutant associations with '$PM_{2.5}$' or 'NO_2' may appear to relate to these specific pollutants but are actually representing the air pollution mixture from two different angles,

b) Single pollutant associations with '$PM_{2.5}$' probably reflect the general air pollution mixture, as well as $PM_{2.5}$ itself but may miss the full effect of the traffic mixture (or other local combustion sources) ,

c) Single pollutant associations with 'NO_2', probably reflect the local traffic or combustion source mixture, as well as (possibly or probably) NO_2 itself but may miss the full effect of the overall air pollution mixture,

d) In principle, coefficients from associations adjusted for other pollutants would be used for each specific pollutant and the results added up. There is wide agreement with this principle.

e) In practice, there is substantial uncertainty as to the interpretation of the multipollutant model results (NO_2 adjusted for $PM_{2.5}$ and *vice versa*).

f) Comparison of the sum of the coefficients per IQR for NO_2 adjusted for $PM_{2.5}$ and *vice versa* **within the same study** suggests the total is a little more than for the unadjusted coefficients for either pollutant, although the confidence intervals mean this is not fully confirmed.

g) The above conclusion relies on the possible overestimation of one adjusted coefficient (with less exposure misclassification) and underestimation of the other (with more exposure misclassification) partially cancelling each other out, leading to a more reliable total.

h) Application of the adjusted coefficients in circumstances where the relative inter-quartile ranges (IQRs) are different from the original studies no longer ensures the total is more reliable, because the over- or under-estimation may be exaggerated or ameliorated by different concentration ranges in different localities. The reliability of the adjusted coefficient for each pollutant has to be considered in its own right. Even after adjustment these coefficients still represent mixtures to some extent.

i) Views on this in the discussions in the main report ranged all the way across (i) considering the results cannot be used (Chapter 10) (ii) considering the results can be used to illustrate possible answers and (iii) that, while acknowledging uncertainty, it is reasonable to use results when the correlation between pollutants was not too high.

j) The adjusted coefficient aspects of this working paper are compatible with (ii) and (iii). It is wise nonetheless to bear the possibility of (i) in mind.

k) The number of studies using multi-pollutant models is relatively few and even fewer when excluding studies with close correlations between pollutants.

l) Therefore, it was decided to use a range of % reductions in the size of the unadjusted coefficient on adjustment for other pollutants derived from different studies and apply this to the meta-analysis summary estimate of single pollutant model associations, based on a larger number of studies.

m) This relies on pairing % reductions applied to meta-analysis summary estimates of single pollutant associations for both NO_2 and $PM_{2.5}$. Studies with pairs of adjusted coefficients ($PM_{2.5}$ coefficients adjusted for NO_2 and *vice versa*) will have been identified through the literature search for studies on NO_2. Single pollutant associations for $PM_{2.5}$ have not, however, been updated.

1.1 Detailed approach

The sequence of calculations is set out in Table 1, followed by a table of coefficients and the population-weighted concentrations used. Confidence intervals are discussed in text at the end, due to the particular problems with deriving confidence intervals for percentage reductions. More on the methods can be found in Chapter 8 of the report.

Table 1. Calculation sequence for range of options for approximate burden calculations

Calculation sequence for each constituent country		Option 1 Unadjusted coefficient for $PM_{2.5}$[a]	Option 2 Unadjusted coefficient for NO_2[a]	Option 3a-d Paired adjusted NO_2 and adjusted $PM_{2.5}$ coefficients from each of studies a to d
1	Meta-analysis of single-pollutant associations to give a pooled summary estimate (HR) per 10 µg/m^3.	Not reviewed here, use past recommendation	See Chapter 2 of the main report (COMEAP, 2018)	n/a
2	Derive % reduction[b] per 10 µg/m^3 from (lnHRunadj – lnHRadj)/lnHRunadj per µg/m^3 for both NO_2 and $PM_{2.5}$ for each of the 4 individual selected studies providing multi-pollutant model results. See Table 2 for hazard ratios and % reductions for steps 1-3.	n/a	n/a	See Working Paper 2 and Table 2 below. Comment on possible confidence intervals.
3	Apply the paired % reductions for both NO_2 and $PM_{2.5}$ from each individual study to the relevant pooled summary estimate for NO_2 and $PM_{2.5}$ to provide a range of pairs of reduced summary estimates (HR) per 10 µg/m^3. % reduction x ln(pooledHRunadj) then exponentiate to give 4 pairs of reduced pooled HR per 10 µg/m^3	n/a	n/a	See Table 2 below Derive for selected confidence intervals (not possible in all cases); not necessary if within the range of central estimate options.
4	Scale the pooled unadjusted HR and pairs of reduced pooled HRs by the relevant population-weighted mean concentration 'x' with or without the relevant cut-off (see Table 3) $\ln HR^{(x/10)}$= scaled lnHR exp(scaled lnHR) = scaled HR	Use pooled unadjusted HR for $PM_{2.5}$	Use pooled unadjusted HR for NO_2	Use pairs of NO_2 and $PM_{2.5}$ reduced pooled HRs
5	Derive the attributable fraction from the scaled HRs (scaledHR-1)/scaled HR=Attributable fraction (AF)	Use scaled pooled unadjusted HR for $PM_{2.5}$	Use scaled pooled unadjusted HR for NO_2	Use pairs of NO_2 and $PM_{2.5}$ reduced pooled HRs

6	Derive attributable deaths AF*baseline deaths=attributable deaths (AD)	Use attributable fraction from scaled pooled unadjusted HR for $PM_{2.5}$	Use attributable fraction from scaled pooled unadjusted HR for NO_2	Use pairs of attributable fractions from NO_2 and $PM_{2.5}$ reduced pooled HRs
7	Derive life-years lost AD*baseline expected .remaining life expectancy	Use attributable deaths from scaled pooled unadjusted HR for $PM_{2.5}$	Use attributable deaths from scaled pooled unadjusted HR for NO_2	Use pairs of attributable deaths from NO_2 and $PM_{2.5}$ reduced pooled HRs
8	Sum attributable deaths and life-years lost across each pair of pseudo-adjusted pooled results.	n/a	n/a	Sum paired results for NO_2 and $PM_{2.5}$ derived from paired % reductions from each of studies a-d
9	Sum from constituent countries to the UK			
10	Repeat steps 4 - 9 for upper and lower confidence intervals.			Not possible in all cases and not necessary if within the range of central estimate options
11	Summarise across options as range of possible answers.	While results for $PM_{2.5}$ alone and NO_2 alone were derived as internal stages in these calculations, they are subject to even greater uncertainty than the overall totals. It is not suggested that they are highlighted separately, although views in the main report COMEAP (2018) varied on this from omitting the calculations in Option 3 entirely through to considering that, if appropriate for impact calculations, this was equally appropriate for burden calculations.		

Note: Unadjusted: single pollutant model. Adjusted: multi-pollutant (two-pollutant) model result.

a A further set of options could use concentration-response functions from meta-analyses of time-series results for NO_2 unadjusted in place of option 2 and an NO_2 time-series coefficient adjusted for $PM_{2.5}$ for the NO_2 portion of Option 3. Using the time-series coefficient was suggested in Chapter 10 of the main report COMEAP (2018)..

b Results from the Cox proportional hazard models used in the cohort studies are linear for the log of the hazard ratio (beta coefficient) against concentration. Therefore, scaling by concentration or % reduction needs to be done on the log scale.

Calculations for loss of life expectancy from birth were not calculated due to time-constraints.

Table 2. Various illustrative coefficients for use in approximate burden calculations

Indicator Pollutant	**Unadjusted coefficient from meta-analysis** (NO$_2$ Chapter 2 of COMEAP (2018); PM$_{2.5}$ COMEAP, 2010 and Hoek *et al* 2013). Robustly established	**Various options for adjusted coefficients** (NO$_2$ adjusted for PM$_{2.5}$ and *vice versa* (derived as paired NO$_2$ and PM$_{2.5}$ % reductions from unadjusted to adjusted coefficients from each study). Issues with derivation of confidence intervals for ratios for correlated variables so Cis not given			
		Jerrett *et al*, 2013	Fischer *et al* 2015 (PM$_{10}$)	Beelen *et al* 2014	Crouse *et al* 2015 (with O$_3$)
% reduction on adjusting NO$_2$ single pollutant coefficient for PM$_{2.5}$	n/a	19%[a]	29%)	53%	13%
NO$_2$ single pollutant model summary estimate (far columns - summary estimate reduced by the relevant % reductions from each study).	1.023 (1.008, 1.037)	1.019	1.016	1.011	1.020)
% reduction on adjusting PM$_{2.5}$ single pollutant coefficient for NO$_2$	n/a	53%	46%	14%	68%
PM$_{2.5}$ single pollutant model summary estimate (with % reduction applied – far columns)	1.06 (1.04, 1.08) Also 1.01,1.12	1.029	1.033	1.053	1.019

Table 3: Population-weighted mean NO_2 and $PM_{2.5}$ concentrations in 2013 (µg/ m³)

Country	Population-weighted annual mean concentration (µg/m³)			
	NO_2		$PM_{2.5}$	
	Total	Above 5	Anthropogenic	Above 7
England	18.63	13.64	9.39	4.52
Wales	12.28	7.29	7.66	2.91
Scotland	10.92	6.14	5.79	0.95
Northern Ireland	8.53	3.76	6.52	1.85
UK	17.39	12.42	8.92	4.07

See Chapter 8 in the main report (COMEAP, 2018) for how concentrations were derived.

1.2 Commentary on confidence intervals

Calculating the percentage reduction involves subtracting the unadjusted coefficient from the adjusted one and dividing by the unadjusted coefficient. Both the adjusted and unadjusted coefficients have confidence intervals around them, so there is a need to propagate the statistical uncertainty from these inputs through to the percentage reduction. It turns out that this is not at all straightforward.

Leaving aside the actual equation for combining the variables for the moment, in any case where the variables are correlated, this needs to be taken into account. Confidence intervals describe the spread of answers that could be obtained when a population is sampled repeatedly. If a population was sampled for both height and weight, you would not get a random spread of height and weight in each sampled group of people, because a group that had more tall people by chance would have a higher average height and tend to have a higher average weight as well. In our case, we would need to know the covariance[1] between the adjusted coefficient and the unadjusted coefficient, as both are used in calculating the percentage reduction. We do not know what this covariance is for each study, although we did explore how the results would vary according to the covariance (see below). We considered that it was less likely (although not impossible) that there was a negative covariance and more likely the covariance was positive. This was because a larger unadjusted coefficient might be expected to be split into larger adjusted coefficients, compared with another study with a smaller unadjusted coefficient, assuming the split between the pollutants remained similar. This was approximately the case for the studies in Table.1.

The second problem is that it is difficult to derive confidence intervals for ratios (Franz, 2007, Cox, 1990). Some methods (e.g. Fieller method, Delta method) are available but several have specific assumptions. In particular, if the denominator is anywhere near zero, the results may become unstable. There may also be problems if a zero intercept cannot be assumed. (A zero intercept would imply that if the unadjusted coefficient was zero, then the difference between the adjusted and unadjusted coefficient would also be zero, this is not guaranteed).

We explored some of the possible behaviour of the confidence intervals using the Delta method (Franz, 2007; Oehlert, 1992 and Dortman, 1938, quoted in verHoef, 2012). We did indeed find problems, with implausibly wide confidence intervals for Jerrett et al (2013) and Beelen et al (2014). We also tried using the log of the difference between the adjusted and unadjusted coefficient as a step in the calculations before transforming the answer back, but this did not improve the result. For both Jerrett et al and Beelen et al, at least some of the set of unadjusted and adjusted coefficients for NO_2 and $PM_{2.5}$ were not statistically significant. The method worked better for Fischer et al (2015) and Crouse et al (2015) (aside from the more general issue that the Fischer paper used PM_{10} and the Crouse paper also controlled for ozone). There was still the problem that the covariance was unknown but it was possible to get an idea of the range of possible values for the confidence intervals and to show that the range of the confidence intervals decreases as covariance increases.

Even after getting an idea of the confidence intervals around the % reduction, further steps are needed. These confidence intervals need to be combined with the confidence intervals for the single pollutant model summary estimates for each pollutant separately and then across the estimates for $PM_{2.5}$ and NO_2 when they are

[1] Both covariance and correlation express the degree to which random variables tend to deviate from their expected values (mean values) in a similar way. For covariance the individual values of each variable at a particular point on the graph are subtracted from their mean, multiplied together and divided by the number in the sample minus 1. It is thus in combined units of both variables. Correlation divides the covariance by the standard deviations of each variable, making it easier to compare with other relationships because it is unit-less. If X is a random variable with mean μ and G() is a differentiable function, we have

$G(X) = G(\mu) + (X-\mu)G'(\mu)$ (based on an one-step Taylor approximation) and so

$Var(G(X)) = Var(X)*[G'(\mu)]^2$ (approximately) summed. Again, covariance information is needed and is not available. Moreover, for combining the % reduction with the single pollutant summary estimate, it is unclear whether it would necessarily be positive. It might actually be negative for adding across the pollutants (a smaller value for the summary estimate after applying a % reduction for one pollutant might imply a larger value for the other pollutant). As the unknowns accumulate across the steps and there were already problems with the starting point, the exploration of possible values for the confidence intervals was not pursued further.

Overall, it may be that a better approach would be to use computationally intensive statistical methods (e.g. bootstrap or simulations) rather than a formal analytical method that does not apply in all circumstances. It is suggested that this is explored further, subsequent to publication of the report.

Although it did not prove possible to define the confidence intervals exactly, some of the insights gained from considering the issue will be used to comment on the likelihood of the confidence intervals overlapping with the results found using the single pollutant model estimates.

2. Results

2.1. Worked example using Fischer et al (2015)

It is not obvious which study to use as a worked example as Jerrett *et al* (2013) and Beelen *et* al (2014) have large confidence intervals, Fischer *et* al (2015) used PM_{10} rather than $PM_{2.5}$, and Crouse *et al* (2015) controlled for ozone as well (this is a good thing but complicates comparisons with other studies and we did not include ozone in our calculations. There is uncertainty over whether there are effects of long-term exposure to ozone (COMEAP, 2015) although the Crouse study supports it.). We have used estimates from Fischer *et al* as this is a large study, which would have considerable weight in a meta-analysis of % reductions were it possible to do this (see 4.2 of the report). The example only uses the central estimates.

The hazard ratios (HRs) for NO_2 unadjusted and NO_2 adjusted for PM_{10} are 1.027 and 1.019 per 10 µg/m^3 respectively. The % reduction is calculated on the log scale using the beta coefficients (as the study results are linear for the log of the hazard ratio against concentration). The natural logs of these hazard ratios gives 0.027 and 0.019 per 10 µg/m^3 and a percentage reduction of (0.019 – 0.027)/0.027 = -29% (negative for a reduction). This % reduction was then applied to the single pollutant meta-analysis central estimate of 1.023 (again using the log scale). Ln1.023 is 0.023 per 10 µg/m^3 or 0.0023 per µg/m^3. 29% of this is 0.0007. This is then subtracted from 0.0023 (as it is a reduction) giving a new beta coefficient of 0.0016, and, taking the antilog, a new HR of 1.016. This new 'reduced' HR was then used in the normal way to calculate the attributable deaths and life years lost using the population-weighted mean concentrations with or without a cut-off. This gave a figure for the UK of 126,566 to 177,008 life years lost equivalent to 10,967 – 15,329 attributable deaths at typical ages. (Note that while apparently labelled as a burden figure for NO_2, it in fact still probably reflects other traffic pollutants too, perhaps to a greater extent than would have been the case with adjustment for $PM_{2.5}$ rather than PM_{10}).

An analogous process gives a 46% reduction on adjustment of the PM_{10} coefficient for NO_2 and a new 'reduced' HR of 1.03344 (from applying the % reduction to the Hoek et al (2013) meta-analysis coefficient for $PM_{2.5}$). Note that it is the % reduction that is transferred further down the calculations not the Fischer et al PM_{10} coefficient itself. The new HR gives a result for the UK of 84,731 – 185,913 life years lost equivalent to 7348 – 16,098 attributable deaths at typical ages.

The two results are then added to give a total of 211,298 – 362,921 life years lost and 18,315 – 31,4272 attributable deaths rounded to 211,000 to 363,000 life years lost equivalent to 18,300 to 31,4009 attributable deaths at typical ages.

2.2. Full tables of results

Full tables of results for the various different methods are given in Table 4 (life-years lost) and 5 (attributable deaths). The results from Tables 4 and 5 are also presented visually in Figures 1 and 2. These figures make it easier to compare the results across approaches.

It can be seen from these tables and figures that using single pollutant models for NO_2 or $PM_{2.5}$ as indicators of the mixture gave estimates of 151,000- 330,000 life years lost (13,000 – 29,000 attributable deaths) whereas for the central estimates of pairs of adjusted coefficients from 4 different studies values from around 222,000 – 372,000 life years lost (20,000 to 32,000 attributable deaths) if choosing values compatible with the range of results for at least three of the studies. The range for the latter was within the range of the confidence intervals for the calculations using single pollutant model estimates (64,000 – 432,000 life years lost; 6,000 – 37,000 attributable deaths) but towards the upper end. If it is assumed that the multi-pollutant model results can be taken at face value (i.e. there is not too much bias due to exposure misclassification), then this suggests that there is not complete overlap of the associations of NO_2 and $PM_{2.5}$ and that previous burden calculations have underestimated the burden to some extent. Note that this conclusion does not require that NO_2 itself is responsible for this increase, although it may contribute. It may simply be that the NO_2 associations are picking up an aspect of the effects of the air pollution mixture (perhaps traffic pollutants) that are less well picked up by studies using $PM_{2.5}$.

The full range across all 4 studies using pairs of adjusted coefficients is 207,000 to 416,000 life years lost, equivalent to 18,000 to 36,000 attributable deaths. This wider range still does not go as low as the lower end of 13,000 attributable deaths (151,000 life years lost) for the central estimate with cut-off single pollutant calculations. It does, however, extend above the upper end of 29,000 attributable deaths (330,000 life years lost).

The discussion above has only considered the central estimates for the approach using pairs of adjusted coefficients. Unfortunately, as discussed earlier, the confidence intervals around the estimates from pairs of adjusted coefficients are hard to estimate and probably wide. The key question is whether the confidence intervals would suggest that the results using pairs of adjusted coefficients would be compatible with full overlap between the NO_2 and $PM_{2.5}$ associations i.e. no increase over and above the burden estimate for $PM_{2.5}$ alone, as used currently. Conversely, several of the results using the central estimates of the paired coefficients do not reach as high as the upper confidence interval for the single pollutant summary estimate. More specifically, could any of the possible confidence intervals for the paired coefficient explored using the Delta method, and a variety of covariances, be compatible with results of 5,000, 13,000 or 38,000 attributable deaths (the lower confidence interval for the NO_2 single pollutant calculation with a cut off of 5 µg/m^3; the central estimate for the $PM_{2.5}$ single pollutant calculation with a cut-off of 7 µg/m^3 and the upper confidence interval of the $PM_{2.5}$ single pollutant calculation with no cut-off)?

The confidence intervals for Beelen et al (2014) and Jerrett et al (2013), while unknown, are likely to be wide. One or more of the sets of adjusted and unadjusted coefficients in each study had lower confidence intervals below 1. Thus the results using these studies are likely to be compatible with a wide range of possible results, including those for the single pollutant calculations specified above. On the other hand, wide confidence intervals would give these studies less weight were it to be possible to do a meta-analysis of these studies.

With no covariance, the 95% confidence intervals around the % reductions for Fischer et al (2015) were 12% - 47% for NO_2 adjusted for PM_{10} and 29% - 65% for PM_{10} adjusted for NO_2. For Crouse et al (2015) the equivalent figures were -5% - 30% for NO_2 adjusted for $PM_{2.5}$ and ozone (-5% being an increase on adjustment) and 43% - 93% for $PM_{2.5}$ adjusted for NO2 and ozone. These are not definite answers as we think there is likely to be positive covariance (but we also know this would narrow the range of the confidence intervals to some degree). Also, as discussed previously, there are other potential issues with the methods for deriving confidence intervals.

Using these values as possible answers with some plausibility, we can compare possible results for attributable deaths with those specified above for single pollutant calculations. The first calculation applied the largest reductions to adjust the lower confidence intervals of the single pollutant model estimate using a cut off and *vice versa* (small reduction/upper confidence interval/no cut-off) as possible outer ends of ranges were being investigated.

Could the possible confidence intervals for the results from the paired coefficients extend lower than 5000 attributable deaths (the lower confidence interval for the NO_2 single pollutant calculation with a cut off of 5 µg/m^3)?

Yes, results for Crouse et al. could extend a bit lower than 5000 attributable deaths but only using the upper possible values for the % reduction for both NO_2 and $PM_{2.5}$ applied to the lower confidence intervals of the single pollutant model estimates for both pollutants with their relevant cut-offs. Results for Fischer et al. were similar to but not lower than 5000 attributable deaths.

Could the possible confidence intervals for the results from the paired coefficients applied to the single pollutant central estimate extend lower than 13,000 *attributable deaths (the central estimate for the $PM_{2.5}$ single pollutant calculation with a cut-off of 7 µg/m^3)?*

Yes, results for Crouse et al., could extend a bit lower than 13000 attributable deaths using the upper possible values for the % reduction for both NO_2 and $PM_{2.5}$ applied to the central estimates of the single pollutant model estimates for both pollutants with their relevant cut-offs. Results for Fischer et al. were very similar to 13,000 attributable deaths.

Could the possible confidence intervals for the results from the paired coefficients applied to the single pollutant central estimate extend higher than 38,000 attributable deaths (the upper confidence interval of the $PM_{2.5}$ single pollutant calculation with no cut-off)?

Yes, , for both Crouse et al and Fischer et al., the possible confidence interval giving the smaller reduction applied to the central estimate of the single pollutant model estimates is sufficient to exceed 38,000 by a reasonable margin. The results could be even higher applying the smallest reduction to the upper confidence intervals of the single pollutant model estimates.

In other words, for the two studies likely to have more weight in a meta-analysis, the possible confidence intervals can give answers a bit lower than the lowest single pollutant central estimate ($PM_{2.5}$ with a cut-off) and, for one study, just lower than the lower confidence interval of the single pollutant model estimates. However, both studies can give answers higher than the upper confidence interval for $PM_{2.5}$ with no cut-off and substantially higher if applied to the upper confidence interval rather than central estimate of the single pollutant model estimate. So, while precise confidence intervals cannot be derived, there are indications that it cannot be ruled out that there is no effect additional to that obtained using the single pollutant estimates for either pollutant but overall the results from the possible confidence intervals with paired coefficients extend into a higher upper range than the single pollutant estimates.

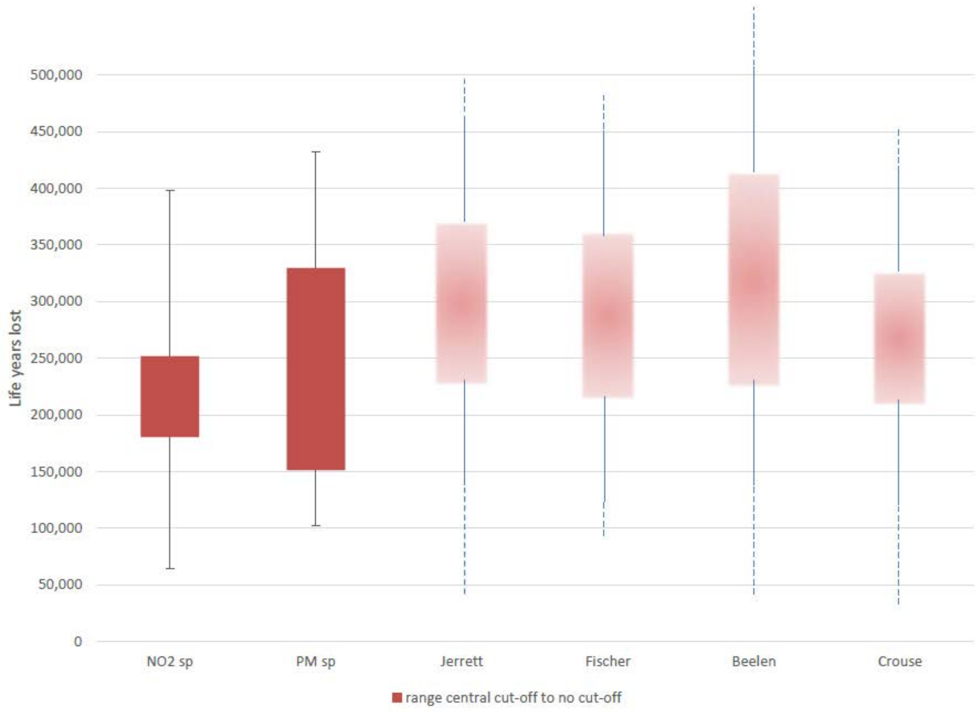
Table 4. Various illustrative calculations for burden of long-term exposure to the air pollution mixture in the UK (life years lost)

	Burden of air pollution (life years lost) in the UK (range with and without cut-offs)					
General method for approximating burden of air pollution mixture	**Single-pollutant (sp) summary estimate for NO_2 or $PM_{2.5}$**		**Combining pairs of mutually-adjusted coefficients (NO_2 adjusted for $PM_{2.5}$ and *vice versa*)**			
Specific method (concentration-response functions (and 95% confidence intervals where possible)) for approximating burden of air pollution mixture	**NO_2 sp summary estimate (this report) HR 1.023 (1.008, 1.037)**	**$PM_{2.5}$ sp summary estimate (Hoek et al, 2013) HR 1.06 (1.04, 1.08)**	**Jerrett *et al*, 2013 Adj NO_2 HR 1.019 Adj $PM_{2.5}$ HR 1.029**	**Fischer *et al* 2015 (PM_{10}) Adj NO_2 HR 1.016 Adj PM_{10} HR 1.033**	**Beelen *et al* 2014 Adj NO_2 HR 1.011 Adj $PM_{2.5}$ HR 1.053**	**Crouse *et al* 2015 (+O_3) Adj NO_2 HR 1.020 Adj $PM_{2.5}$ HR 1.019**
Comment on each general approach	Robustly established with appropriate 95% CIs, overestimate for specific pollutant, but may underestimate for the mixture.		Central estimates more uncertain than unadjusted ones – single studies and possible issues with bias in either direction due to measurement error. CIs hard to derive for ratios for correlated variables (see text).			
Central estimate with and without cut-off (5 µg/m³ for NO_2; 7 µg/m³ for $PM_{2.5}$)	180,511 – 252,041[a]	151,222 – 329,826	224,459 – 373,323	211,298 – 362,921	221,727 – 415,717	206,761 – 328,499
Result using 95% confidence intervals of CRF for no cut-off	89,479 – 397,909	223,906 – 432,013[b]	Not possible to derive precise confidence intervals – see commentary in text.			
Result using 95% confidence intervals of CRF for cut-off (5 µg/m³ for NO_2; 7 µg/m³ for $PM_{2.5}$)	63,865 - 285,894	102,207 – 198,928[b]				

a Results in this table given with more significant figures than appropriate given uncertainties, for the purposes of later rounding.

b For the COMEAP plausibility interval of HR 1.01 – 1.12 per 10 µg/m3, 57,557 – 625,963 for no cut-off and 26,095 – 290,645 down to 7 µg/m3.

Figure 1 Possible ranges for burden calculations (life years lost)



NOTE This is not a standard box plot.

Sp = single pollutant (as indicator of a mixture). PM refers to anthropogenic $PM_{2.5}$.

The remaining 4 columns are for the combination of results for pairs of adjusted coefficients for the studies from the specified authors (see text). The paler colour reflects the additional uncertainty as to whether there is bias due to measurement error in the presence of close correlations.

Blocks show ranges from the cut-off (5 $\mu g/m^3$ for NO_2, 7 $\mu g/m^3$ for $PM_{2.5}$) to the higher result for no cut-off. Error bars (solid line with cap) are for the lower confidence interval for the cut-off to the upper confidence interval for no cut-off. There are technical issues with deriving confidence intervals for the results combining adjusted coefficients. The dotted lines reflect the fact that there will be confidence intervals around these estimates (which cannot be precisely defined) and that these will be wider for Beelen and Jerrett. (giving both the possibility of a wider range of answers but also suggesting less weight on the result than for Fischer and Crouse).

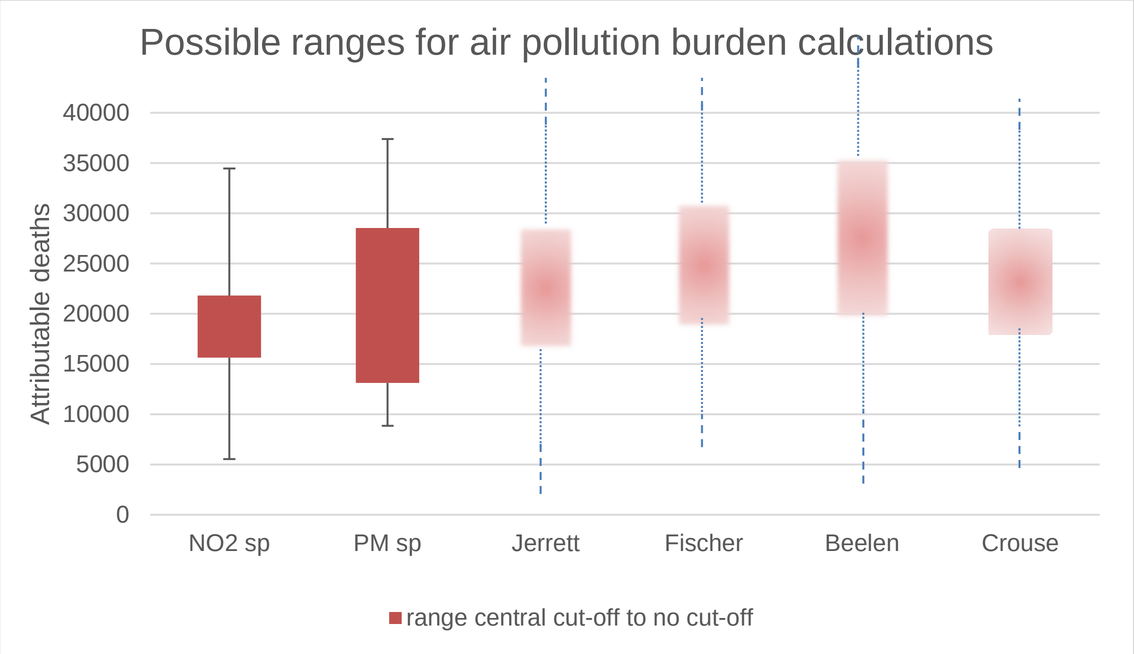
Table 5. Various illustrative calculations for burden of long-term exposure to the air pollution mixture in the UK (attributable deaths)

	Attributable deaths aged 30 years and over (range with and without cut-offs)					
General method for approximating burden of air pollution mixture	**Single-pollutant (sp) summary estimate for NO_2 or $PM_{2.5}$**		**Combining pairs of mutually-adjusted coefficients (NO_2 adjusted for $PM_{2.5}$ and *vice versa*)**			
Specific method (concentration-response functions (and 95% confidence intervals where possible)) for approximating burden of air pollution mixture	**NO_2 sp summary estimate (this report) HR 1.023 (1.008, 1.037)**	**$PM_{2.5}$ sp summary estimate (Hoek et al, 2013) HR 1.06 (1.04, 1.08)**	**Jerrett *et al*, 2013 Adj NO_2 HR 1.019 Adj $PM_{2.5}$ HR 1.029**	**Fischer *et al* 2015 (PM_{10}) Adj NO_2 HR 1.016 Adj PM_{10} HR 1.033**	**Beelen *et al* 2014 Adj NO_2 HR 1.011 Adj $PM_{2.5}$ HR 1.053**	**Crouse *et al* 2015 (+O_3) Adj NO_2 HR 1.020 Adj $PM_{2.5}$ HR 1.019**
Comment on each general approach	Robustly established with appropriate 95% CIs, overestimate for specific pollutant, but may underestimate for the mixture.		Central estimates more uncertain than unadjusted ones – single studies and possible issues with bias in either direction due to measurement error. CIs hard to derive for ratios for correlated variables (see text).			
Central estimate with and without cut-off (5 μg/m³ for NO_2; 7 μg/m³ for $PM_{2.5}$)	15,641-21,827[a]	13,114 – 28,558	19,454 – 32,329	18,315 – 31427	19,222 – 35,997	17,919 – 28,447
Result using 95% confidence intervals of CRF for no cut-off	7,749 – 34,460	19387 – 37,406[b]	Not possible to derive precise confidence intervals – see commentary in text.			
Result using 95% confidence intervals of CRF for cut-off (5 μg/m³ for NO_2; 7 μg/m³ for $PM_{2.5}$)	5538 – 24,772	8864 – 17,251[b]				

[a] Results in this table given with more significant figures than appropriate given uncertainties for the purposes of later rounding.

[b] For the COMEAP plausibility interval of HR 1.01 – 1.12 per 10 μg/m³, 4983 – 54198 for no cut-off and 2263 – 25205 down to 7 μg/m³.

Figure 2 Possible ranges for air pollution burden calculations (attributable deaths)



NOTE This is not a standard box plot.

Sp = single pollutant (as indicator of a mixture). PM refers to anthropogenic $PM_{2.5}$.

The remaining 4 columns are for the combination of results for pairs of adjusted coefficients for the studies from the specified authors (see text). The paler colour reflects the additional uncertainty as to whether there is bias due to measurement error in the presence of close correlations.

Blocks show ranges from the cut-off (5 µg/m^3 for NO_2, 7 µg/m^3 for $PM_{2.5}$) to the higher result for no cut-off. Error bars (solid line with cap) are for the lower confidence interval for the cut-off to the upper confidence interval for no cut-off. There are technical issues with deriving confidence intervals for the results combining adjusted coefficients. The dotted lines reflect the fact that there will be confidence intervals around these estimates (which cannot be precisely defined) and that these will be wider for Beelen and Jerrett. (giving both the possibility of a wider range of answers but also suggesting less weight on the result than for Fischer and Crouse).

2.3 Discussion and conclusions

This Working Paper has explored possible answers for the burden of the air pollution mixture as a whole. The perspective was based on exploring the implications of the evidence considered in this report, given specific assumptions that are of uncertain validity:

a) That the multi-pollutant model results can be taken at face value, or at least that any bias due to measurement error is sufficiently small that it does not affect the results unduly. (We do not know one way or the other if this is true, but have reduced the likelihood somewhat by using studies with lower correlations between pollutants. However, this is not the only factor that contributes to bias in the results).

b) That, if the multi-pollutant model results cannot be taken at face value, that summing across NO_2 and $PM_{2.5}$ may cancel out the biases to some extent. This only applies to the same relative inter-quartile ranges for NO_2 and $PM_{2.5}$ as in the original studies. This may not always be the case.

c) That the variation in PM components at given concentrations of NO_2 are similar to those in the original studies (this affects the way in which control for $PM_{2.5}$ controls for traffic pollutants).

d) That the more limited control for individual confounders in the administrative cohorts (Fischer et al (2015) and Crouse et al (2015) does not affect the results too much.

e) That the fact that Fischer et al (2015) used PM_{10} rather than $PM_{2.5}$ and that Crouse et al (2015) also controlled for ozone does not affect the results too much (noting that, for the PM_{10} issue, it is the % reductions that are transferred down the calculations rather than the absolute coefficients).

f) That the overall conclusions would not change significantly if possible effects of long-term exposure to ozone were included in the process (studies are somewhat contradictory and results are probably smaller, given the effect is thought to be on respiratory rather than all-cause mortality).

Given the above assumptions, this perspective suggests that previous estimates of burden may be an underestimate and that the studies of associations with NO_2 are detecting effects of the air pollution mixture less well captured by studies using $PM_{2.5}$. This conclusion does not require that NO_2 itself is responsible, although it may contribute. Even given the specific assumptions above, it is not proven that there is a larger effect given the likely overlap in confidence intervals.

A summary of the conclusions from this Working Paper is given in Table 6. In overall summary, those considering effects of air pollution on public health should be aware that current burden estimates may be an underestimate. While not certain, it would be wise to take this possibility into account when considering options for improving public health in the future.

Table 6. Summary of various illustrative calculations for burden of long-term exposure to the air pollution mixture in the UK in 2013

	Burden of air pollution (life years lost) in the UK (range with and without cut-offs)	
General method for approximating burden of air pollution mixture	**Single-pollutant (sp) summary estimate for NO_2 or $PM_{2.5}$**	**Combining pairs of mutually-adjusted coefficients (NO_2 adjusted for $PM_{2.5}$ and *vice versa*)**
Comment on each general approach	Robustly established with appropriate 95% CIs, overestimate for specific pollutants, but may underestimate for the mixture.	Central estimates more uncertain than unadjusted ones – single studies and possible issues with bias in either direction due to measurement error. CIs hard to derive for ratios for correlated variables (see text).
Central estimate with and without cut-off (5 µg/m³ for NO_2; 7 µg/m³ for $PM_{2.5}$)	Using single-pollutant model central estimates for <u>either</u> NO_2 or $PM_{2.5}$ suggests that the burden of the air pollution mixture in the UK in 2013 is around: 151,000- 330,000 life years lost equivalent to 13,000 – 29,000 attributable deaths at typical ages. This may be an underestimate if both pollutants (or the pollutants they best represent) have independent effects.	Using the central estimates of pairs of adjusted coefficients for NO_2 and $PM_{2.5}$ from 4 different studies gave a range compatible for the burden of the air pollution mixture in the UK in 2013 of around: 222,000 – 372,000 life years lost equivalent to 20,000 to 32,000 attributable deaths at typical ages, if choosing a range compatible with results for at least three of the studies. <u>If</u> it is assumed that the multi-pollutant model results can be taken at face value, this suggests that there may not be complete overlap of the associations of NO_2 and $PM_{2.5}$ and that previous burden calculations may have underestimated the burden to some extent. Note that this conclusion does not require that NO_2 itself is responsible for this increase, although it may contribute. It could simply be a better reflection than $PM_{2.5}$ of effects of some traffic pollutants.

Range from lowest 95% confidence intervals for a cut-off to highest 95% confidence interval for no cut-off (Hoek et al confidence intervals for $PM_{2.5}$)	64,000 – 432,000 life years lost, equivalent to 8,000 – 38,000 attributable deaths at typical ages	The range above is compatible with the range of confidence intervals from the single pollutant model calculations i.e. compatible with full overlap at a smaller probability than the central estimates. The full range of central estimates using this method is 207,000 – 416,000 life years lost equivalent to 18,000 – 36,000 attributable deaths. The confidence intervals around this range of central estimates cannot be defined but probably extends below the lower confidence interval of the single pollutant model estimates in at least some cases. The confidence intervals around this range of central estimates probably would extend above 432,000 life years lost equivalent to 38,000 attributable deaths in some cases.
Range from lowest plausible interval for a cut-off to highest plausible interval for no cut-off (COMEAP plausible intervals for $PM_{2.5}$)	26,000 – 626,000 life years lost equivalent to 2,000 – 54,000 attributable deaths (Note these outer ends of the range have low probabilities.]	The confidence intervals around this range of central estimates cannot be defined. Unclear if these would extend down to 26,000 life years lost equivalent to 2,000 attributable deaths but may do so. Unclear whether the confidence intervals around this range of central estimates would extend up to 626,000 life years lost equivalent to 55,000 attributable deaths but could do so in some cases.

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