EXPANSION of the multi-city mortality and morbidity study

Environment Protection and Heritage Council

FINAL REPORT

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Project description and methods used

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Chapter 1 Introduction

This report details results from the Environment Protection and Heritage Council (EPHC) funded project: 'Expansion of the multi-city mortality and morbidity study'. The study examines the effects of air pollution on health in Australian and New Zealand cities for a four-year period from January 1998 to December 2001, and estimates the associations between daily outdoor concentrations of the major air pollutants and the health outcomes: daily hospital admissions and daily mortality. The cities considered are Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth and Sydney.

1.1 Background to the project

In 1998, the National Environment Protection Council (NEPC) made a National Environment Protection Measure (NEPM) for ambient air quality which sets national air quality standards for the six major pollutants - nitrogen dioxide (NO_2), particles (as PM_{10}), carbon monoxide (CO), ozone (O_3), sulfur dioxide (SO_2), and lead (Pb). In 2003 the NEPM was varied to incorporate standards for $PM_{2.5}$. The NEPM (ambient air quality) standards have been set to be protective of human health. These standards are based primarily on studies conducted overseas. Whether these findings can be extrapolated to the Australian situation has been the subject of much debate. There has been relatively little work carried out in Australia: in Sydney (Morgan et al. 1998a, 1998b), Brisbane (Simpson et al. 1997; Petroeschevsky et al. 2001), Melbourne (Simpson et al. 2000; EPA Victoria 2000; EPA Victoria 2001) and in Perth (DoE 2003). These studies indicate that current levels of ambient air pollution in these cities are making significant contributions to variations in daily mortality and hospital admissions for cardiovascular and respiratory disease, and that the effects observed overseas may occur in Australia as well.

However, a number of questions remain about these studies regarding (a) the robustness of the statistical techniques used (would a different technique give a different result), (b) whether all confounding effects were included, (c) how important are the impacts on public health (for example, is the effect on acute mortality only a 'harvesting' effect where only sick elderly people are dying days or weeks earlier, with no impact on annual mortality rates) and (d) how applicable are these few studies to all the major Australian cities. There was a commitment in the NEPM to undertake a full review of the NEPM, including the standards for all pollutants, commencing in the year 2005. An important part of this review was to be the expansion of the local database relating to air quality and health issues.

Given NEPC has had to set national air quality standards based primarily on overseas epidemiological studies, a comprehensive Australian study was warranted which would address the issues of the robustness of the statistical techniques, the control for confounding effects, the significance of the impacts, and the general applicability of these studies in Australia. A project was designed to develop a research protocol, using

international benchmarking with USA and European groups, to address these issues in estimating the associations between air pollution and daily mortality and morbidity in Melbourne, Sydney, Perth and Brisbane (the only cities where there were comprehensive data sets available for air pollution for about 3-4 years). A submission was made in 1999 to the Strategic Partnerships with Industry - Research and Training (SPIRT) Scheme (now referred to as the Australian Research Council (ARC) Linkage Scheme). The NSW Health Department, EPA Victoria, Queensland Health and WA Department of Environmental Protection were involved in this project. The research protocol developed for the use of health and environmental data in the statistical modelling undertaken were subjected to international benchmarking by exchanging information and data with an international group of scientists from the APHEA project (short-term effects of air pollution on health - European approach; included scientists from Greece, UK, France, Germany, the Netherlands, among others) and the NMMAPS study in the USA, conducted by the Health Effects Institute (HEI).

In late 1999, the SPIRT scheme funded the project, which was entitled 'The assessment of the impact of air pollution on daily mortality and morbidity in Australian cities using a protocol based on international benchmarking' (Simpson et al. 2001). The project commenced in late 2000 and was completed in early 2003 and results are set out in published papers (Simpson et al. 2005a; 2005b). The study examined the short-term health effects of air pollution on daily mortality and daily hospital admissions in four Australian cities — Brisbane, Melbourne, Perth and Sydney — for the period 1996 to 1999, and used a similar protocol to APHEA2 multi-city studies overseas. Given the limitations on the data sets available, the only air pollutants considered were: NO_2, particles (as measured by nephelometry) and ozone. The conclusions from this study can be summarised as follows:

Mortality
There are significant associations between all non-accidental mortality counts and NO_2, particles and ozone, and the estimates for Australian cities were similar to the findings in other studies overseas. No significant heterogeneity was found, but the NO_2 and particle effects may refer to the same impacts.

Hospital admissions
Similar to overseas studies, air pollution has an impact on hospital admissions in Australian cities, but there can be significant differences between cities. Fine particles (measured by nephelometry) and NO_2 have a significant impact on cardiovascular admissions, and particles, NO_2 and ozone have a significant impact on respiratory admissions. In all analyses, the particle and NO_2 impacts appear to be related. However, the results for respiratory admissions were sensitive to the time series model used.

1.2 Rationale for current study

A meeting was convened on 24-25 July 2002 in Melbourne by the EPHC to discuss the health effects of air pollution and to make recommendations to the EPHC on which future research projects should be supported to inform the review of the Ambient Air

Quality NEPM. Preliminary results for the SPIRT study were presented and the recent results of the overseas studies (APHEA, NMMAPS) presented by Professor Ross Anderson, School of Medicine, University of London. The meeting highlighted a number of issues:

- It was clear from overseas studies that the results differed in different regions of the USA and in different regions of Europe. The preliminary SPIRT results in Australia also showed different results for different localities.

- Overseas, there was an ongoing re-analysis of studies as new data and new statistical techniques became available. It was clear this was necessary in the Australian studies. In particular, the use of new statistical techniques, such as a multi-city pooled analysis, would allow both a study of why different cities yield different results, as well as an estimate of a mean effect for Australian cities.

- All the overseas studies emphasised the importance of the health impacts of fine particles ($PM_{2.5}$). The SPIRT study spanned 1996-1999 and extensive $PM_{2.5}$ data sets were not available for that period, but are now for later periods so another study to investigate the impact of $PM_{2.5}$ was considered, with the number of Australian cities contributing expanded if possible.

- New Zealand cities could also be included in any new multi-city analysis.

1.3 Current project

The two types of studies most commonly used to examine effects of pollution on health are clinical and epidemiological investigations. Each type of study has a role in determining the effects of pollutants on health.

Clinical investigations
The main advantage of clinical studies is that the subjects (whether human or animal) are exposed to controlled doses (and exposure times) in laboratory chambers, so the averaging time and type of air pollution exposure is strictly controlled. Since many of the health problems associated with air pollution are multi-factorial, clinical studies have proven quite useful as they control for variables such as temperature, relative humidity, passive smoking and exercise, allowing the effect of one or possibly a combination of pollutants to be examined. Major limitations of such studies are that they do not represent true exposures to ambient air pollution, nor do they give any indication of the effects of long-term exposure. Small sample sizes are common and, as a result, variations in effects between individual subjects can be an important limitation, and the application of the results to the total population can be problematical.

Epidemiological investigations

These studies are based on the exposure of a population to a pollutant. The main types of epidemiological investigations used are longitudinal/temporal studies (such as time series) and cross-sectional/geographical studies:

- Longitudinal/temporal studies examine the effect of a pollutant on a population over time. The major advantage of this type of epidemiological study is that the confounding effects of variables such as smoking and workplace environment are not such a problem provided they do not vary over the time period in the study.

- Cross-sectional/geographical studies examine the health status of populations in different geographical locations. They typically involve comparing the health of people residing in a location with high air pollutant concentrations with the health of people living in an area with low concentrations of the same air pollutant, and then assessing whether any differences in health status arise solely due to the different air pollution exposures.

This EPHC study is an epidemiological time series study. The major advantages of epidemiological investigations are that exposure is studied under natural conditions, with large numbers of individuals and for long periods of time. Probably the major limitation of this type of study is that the population as a whole is examined, with no knowledge of individual exposures to pollutants and little understanding of other confounding factors. Because an individual's health is dependent on a number of factors associated with the individual's environment and behaviour, studies that examine the effect of a pollutant on the population as a whole are inadequate in measuring any individual's true exposure. Alternatives, such as personal monitoring, are expensive and must involve willing and reliable subjects and, as a consequence, sample sizes become small, reducing statistical power. Another problem is that there are limited studies on exposures to pollutants difficult to measure (for example, aromatic hydrocarbons).

1.3.1 Aims

In this EPHC study, a research protocol was developed to examine the association between air pollution concentrations and daily mortality and morbidity in Australian cities. Cities with available data were included; Brisbane, Canberra, Melbourne, Perth and Sydney in Australia; and Auckland and Christchurch in New Zealand. International benchmarking was carried out in collaboration with Professor Joel Schwartz, Professor of Environmental Epidemiology in the Harvard School of Public Health in the United States. Professor Schwartz is an international expert in the fields of air pollution and epidemiology who has worked on statistical modelling for multi-city studies in the NMMAPS study in the USA and the APHEA studies in Europe. Professor Schwartz was also involved with the APHENA study (air pollution and health in Europe and North America), which focused on cities in the USA, Canada and Europe.

1.3.2 Research design

The study used all available data sets from 1998 to 2001 for daily mortality, daily hospital admissions and air pollution data for all available pollutants for the seven Australian and New Zealand cities under study. All pollutants were included as they are often correlated with each other and studying one in isolation may lead to misleading results. The results are to be used in the review of the NEPM, as well as to identify any regional differences in impacts.

Pooling the estimates from individual city results produces an overall estimate for all cities for the impact of the pollutants, as well as estimating whether these effects differed from city to city. This approach also attempted to identify factors that may lead to different effects in different cities, for example, different climates and different lifestyles. It was important that there were complete data sets for each pollutant in each city; for example, in the previous SPIRT study, ozone, nitrogen dioxide and particles (as nephelometer measurements) were common to the four cities studied. In particular, $PM_{2.5}$ was of interest for this EPHC study and there are complete data sets from 1998-2001 in a number of Australian cities.

The study designs used in the APHENA study were also used in this study for international benchmarking. Professor Schwartz collaborated with the research team and advised on the appropriate statistical methods to be used in the multi-city Australian and New Zealand study so that it could be benchmarked against the APHENA study.

1.3.3 Rationale for multi-city studies

There have been a number of single city studies in Australia and New Zealand examining the impacts of air pollution on health outcomes; for example, for Brisbane (Simpson et al. 1997; Petroeschevsky et al. 2001), Sydney (Morgan et al. 1998a; 1998b), Melbourne (EPA Victoria 2000; EPA Victoria 2001), Christchurch (Hales et al. 2000), and Perth (DoE 2003).

A quantitative meta-analysis of published results can be applied to combine information across single-city results to estimate an overall effect. However, as Bell et al. (2005) point out, this approach has some problems:

- the single city studies generally differ in the statistical approaches used so some of the differences found will arise from these different models

- meta-analysis studies of separate single city studies are subject to publication bias and an overestimation of the overall effect, as a positive association is more likely to be published.

With regard to this last point Goodman et al. (2005) notes that 'depending on published, single-estimate, single-site analyses is an invitation to bias' as 'investigators tend to report, if not believe, the analysis that produces the strongest signal'. Goodman et al. (2005) also note that epidemiologists are trained to report the largest or the statistically strongest estimates, and meta-analyses of single city results for ozone and mortality (for example, Bell et al. 2005; Ito et al. 2005; Levy et al. 2005) have clearly shown this.

A multi-city approach is preferable. In this approach, a uniform analytical framework is applied to the time-series data for a number of single cities, and city-specific estimates are pooled to derive an overall estimate. Uniformity gives this approach more statistical power than meta-analyses and allows the better exploration of heterogeneity between cities. This approach has now been in adopted in Europe (APHEA) and the US (NMMAPS). Bell et al. (2005) conclude:

> We recommend caution against using the results of single city studies, whether individually or pooled, for impact assessment. Multi-city approaches such as NMMAPS or APHENA offer a now-feasible alternative that is less subject to publication bias.

One strong recommendation from such analyses (for example, Bell et al. 2005) is to adopt a multi-city approach with an a priori lag or lags adopted and the same statistical models used for each city analysis.

The approach adopted in this EPHC study is to reduce bias by using a multi-city approach similar to that used in NMMAPS and APHEA, and similar to that being proposed for APHENA. This approach has the following advantages:

- the averaging time for the air pollution exposure is set a priori to avoid the bias of looking for the lags or averages that give the highest value (here the period chosen is the 2-day average of the pollution on the same day and the day previous to the health outcome, following the APHEA approach)

- the same statistical modelling is carried out for each city; this avoids the error in combining results from studies using different methodologies.

Chapter 2 Statistical methods

The raw data used for the presented analyses are in the form of multivariate time series, that is, daily measures of air pollution exposure, and daily counts of health outcome events. The earliest statistical approach to this type of data was to calculate an array of correlation coefficients that measured the tendency for health outcome counts to increase with rising pollutant levels. However, this simplistic approach was rapidly abandoned, in anticipation of potential complications related to the following issues:

Seasonal variation in both health outcomes and air pollution – meteorological effects
The rate of occurrence of adverse health outcomes depends on season (possibly in response to temperature change, although changes in diet and habits may also be influences). For example, rates of cardiovascular and respiratory illnesses consistently show a peak in winter.

Air pollution levels also show seasonal patterns - an increase in particulate matter, for example, associated with an increase in the use of wood fires in some cities. Thus, the rate of cardiovascular illness may vary synchronously with levels of particulates, because each is being influenced separately by season. This phenomenon is known as 'confounding' - temperatures are lower when pollutant levels increase and cause increased rates of illness, creating the impression that increased air pollutant levels lead to more adverse health outcomes.

This is not to say that all of the observed effect of air pollution on health can be attributed to temperature. The statistical challenge is to estimate how much of the effect is attributed to season and temperature, and how much to air pollution.

Interference of other time-dependent confounding effects
While the effects of season and temperature described above provide the strongest examples of confounding in air pollution time series analyses, any variable which changes over time and which potentially influences air pollutant levels and health outcomes in similar ways may have the same effect. Thus it is important to consider the effects of day of the week, which may influence vehicle use and therefore total volume of emissions, as well as being weakly related to health outcomes (decreased hospital admissions on Sunday, increased mortality and admissions on Mondays). Any variable that does not change over time (for example, sex) does not have the potential to produce a time-dependent confounding effect.

Lagged effects
While time series data are most effective for discerning short-term effects, an appropriate definition of 'short-term' is problematic. Should we examine the air pollutant level on the same day, the day before, or averaged over the week prior to the health outcome counts? In practice, the lag time will depend on the specific pollutant and health outcome, and the putative mechanism by which they are associated.

Mortality displacement or 'harvesting'
Early findings of correlations in time between mortality and air pollution levels were interpreted by some as simply indicating the bringing forward (by a few days or weeks) of an inevitable and imminent death, due to exposure to a bad pollution day. Methods for detecting this phenomenon are complex and comparatively recent.

Combined effects of air pollutants
Just as it is necessary to disentangle the effects of a single air pollutant and, say, temperature, it is also important to try to separate the effects of individual pollutants. For example, nitrogen dioxide and particle levels often show very similar daily patterns, and hence their independent effects may be difficult to separate.

Differing effects of air pollutants in different cities: effect modification by city factors.
In combining the results of multi-city studies, it is sometimes observed that the effects of air pollutants vary across cities. This phenomenon is known as effect modification. Some of this variability may be due to chance, but it can be postulated that, particularly where the variability is large, some is due to differences in the sources and distributions of air pollutants, quality of the air pollution monitoring, prevailing meteorological conditions, or demographic characteristics. There are statistical techniques for identifying non-chance variability, leading then to an examination of the differences between cities that might account for this.

Differing effects of air pollutants in different season: effect modification by season
It may be hypothesised that pollutants could have differing effects with differing prevailing meteorological conditions, even within the same city. Of particular interest, given the importance of temperature, is the differentiation of effects in warm and cool periods. This is dealt with by stratifying the model.

Technical issues

- Most time series data exhibit autocorrelation; that is, days close together are more likely than days far apart to exhibit similar levels of health outcomes. This is not associated with the air pollutant levels of interest, and violates the independence assumption of many statistical procedures.

- To deal adequately with confounding (detailed above), it is crucial to understand the nature of the relationships in detail. For example, cardiovascular events are most frequent on very hot and very cold days, and the time lag of these effects is different to respiratory events. Many standard approaches do not allow for these complexities. If confounding is not properly dealt with, then estimated effects can be incorrect.

- The separation of the effects of two pollutants that are highly correlated poses a technical problem known as collinearity. The consequence of this is that statistical models may become very unstable and produce incorrect estimates.

These complexities have led researchers to develop sophisticated statistical approaches to try to discern the specific health effects attributable to air pollution and the form of the relationship. By far the most important analytical issue is to ensure that confounding is controlled, so that the inference of a causal relationship between air pollution and health outcome may be justified. The approaches that have been developed use statistical models, which often incorporate many explanatory variables, but which have appropriate, and not unnecessarily complex, forms. This then enables the separation of the effects of each variable and, in particular, the assessment of the independent role of air pollution. The model achieves this by predicting the number of health events that are associated with a particular change in the level of a pollutant, when other influential variables (temperature, etc.) do not change.

Analytical responses to the above issues have been many and varied. As a consequence, comparability and coherence of findings have been hampered. An evidence-based conclusion as to the health effects of air pollution has emerged only with the recognition of the need for a standardised analytical approach, with well-understood theoretical underpinnings. Professor Joel Schwartz has been at the forefront of many of these developments, particularly in relation to the APHENA study and provided much advice to this EPHC study. As a result of his advice, a case-crossover analysis was used to examine the short-term effects of air pollution and distribute lag models to examine the long-term effects. Some comparisons for the short-term analyses were made with the Poisson regression time series models using generalised additive models (GAMs), the approach adopted in previous studies.

2.1 Case-crossover analysis (short-term effects)

The conventional case-crossover design is used to investigate risk factors for illness; it is particularly useful when a risk factor is transient and operates close in time to the illness it supposedly causes. The analysis compares the level of the risk factor at the time of the illness (or at the time when the risk factor exerts its effect) with the level in a nearby period when the event did not occur (Maclure 1991). The advantage of such a design is that factors which do not change over time (for example, sex), or which change only slowly over time (for example, age, diet, blood pressure, tobacco smoking) cannot act as confounding variables.

The case-crossover approach has been adapted to the analysis of the acute effects of environmental exposures, especially air pollution (Neas et al. 1999; Sunyer et al. 2000). It is particularly appropriate because of the focus on short-term or transient risk factors (air pollutant levels), and because it effectively eliminates confounding by season (Bateson & Schwartz 2001). The adaptation of the method to time-series data involves the selection, for each event day, of a 'control' day (another nearby day). The analysis then compares the distributions of air pollution levels on the event days and the control days.

The method compares air pollution on days there were events (hospital admissions or deaths) to air pollution on days when there was no event. The case-crossover is a case-control method and as such the inference does start with individual cases. The fact that these individuals are aggregated over a day makes no difference to the description of the method (or its interpretation). Every population is made up of individuals and every statistical analysis depends on aggregating over individual results. The case-crossover approach is an adaptation of the case-control method and infers that cases act as their own controls; that is, the individuals with health events on a given day are assumed to have been equally likely to have events on other days, and any differences in health events between case and control days may be explained by differences in variable factors such as air pollution and weather.

A number of different control selection strategies have been investigated for their effectiveness in dealing with or inducing bias and confounding (Levy et al. 2001). In this study, the fixed 28-day window method was used, as this has been shown to minimise bias and maximise the number of controls. A one-day exclusion period around the case days was used, so that case and control days were always separated by at least two days. This exclusion period is used to prevent over-matching, as adjacent daily pollutant levels are often correlated (tomorrow's air pollution is somewhat dependent on today's).

The control selection and lag selection are separate processes. The control selection is done first and breaks the entire length of data into consecutive 28-day long windows. Cases are only compared to controls in the same window. The exposure variable on which they are compared is dependent upon the aim of the analysis. They may be compared using the same day air pollution (looking for short-term associations) or a lagged value, such as three days (looking for slightly longer-term associations).

A variant of the case-crossover analysis occurs when control days are further restricted to match the case day on a particular variable. This further eliminates confounding by that variable. This approach was used to deal with temperature and other pollutants (Schwartz 2004a). While seasonal effects are eliminated by the design of the analysis, and other confounding effects can be eliminated by matching, it remains necessary to take into account the remaining confounding variables. In particular, the model additionally controlled for average temperature (if not matched), average temperature difference (current minus previous day), extremes of hot and cold (coldest and warmest 1% of days), average relative humidity, average pressure, day of the week, public holiday (yes/no) and day after a public holiday(s) (yes/no) (models of admissions only).

To incorporate the possibility of a short-term delay between air pollution exposure and its health effect, we reported results for pollutant concentrations that were averaged over the two days — the same day as the event and the previous day — often referred to as the average of same day (zero lag) and lag 1 concentrations – (0-1).

The case-crossover models were run in the SAS statistical package Version 8.1 (SAS 2001), and used conditional logistic regression (PROC PHREG).

2.1.1 Case-crossover sensitivity analyses and effect modifiers

Differences between the effect estimates for each city were examined using a hierarchical regression model involving two levels of measurement: within-city measures (daily pollutants etc.), and between-city measures (potential effect-modifiers) (Dominici et al. 2002a). The between-city measures used by APHEA studies included average pollutant level, number of monitors, average temperature, average humidity, average pressure, average rainfall, per cent of the population under 15 and over 65, total population and average mortality. We have used some of these effect modifiers (Tables 1.1 and 1.9 in *Volume 2: Project results and conclusions*). The regression models incorporated weights (the inverse standard error of the estimate) so that cities with more precise estimates — usually the larger cities) were more influential.

To test whether any pollutant effects were dependent on season, case-crossover analyses were done separately for the cool season (May to October) and the warm season (November to April).

Matched case-crossover analyses were used to investigate whether some pollutant effects were related to those of other pollutants (Schwartz 2004b) and this avoids the assumption of linearity in the associations.

Closeness of the matching is necessary to minimise confounding, but should not be so close that no controls are available. Matched control days were defined as:

- PM_{10} 24-hour average within 3 $\mu g.m^{-3}$
- $PM_{2.5}$ 24-hour average within 2 $\mu g.m^{-3}$
- NO_2 24-hour average within 1 ppb
- NO_2 1-hour average within 1 ppb
- CO 8-hour average within 0.5 ppm
- O_3 8-hour average within 2 ppb.

For some pollutant and health outcomes a matching to temperature was performed, where matched control days were defined as:

- temperature within 1 degree Celsius.

2.2 Comparison with previous approaches

2.2.1 The SPIRT study approach

The SPIRT project was a multi-city study examining the impacts of air pollution on mortality and morbidity in four Australian cities — Brisbane, Melbourne, Perth and Sydney (see Simpson et al. 2005a; 2005b). The approach adopted in the SPIRT project was similar to the APHEA2 studies where daily average temperature and relative humidity were used to control for the confounding effects of meteorological variables (Atkinson et al. 2001; Le Tertre et al. 2002; Katsouyanni et al. 2001). The influence of events such as day of the week, public and school holidays, influenza epidemics, and bushfire or control burn events (a particular problem in Australian cities) were included

when necessary. The analysis proceeded in two stages. In the first stage, time series models predicting daily mortality were developed for each city and each pollutant, with the effects of long-term trends, seasonality, weather and other potential confounders controlled. In the second stage, a meta-analysis of the parameter estimates derived from the single city models was performed for each health outcome to provide multi-city estimates. Included in this stage were formal tests for heterogeneity between single city estimates.

Poisson regression modelling was conducted for each city using modelling approaches within the APHEA2 framework. Given the problems with using such techniques (especially with the S+ plus package) (Dominici et al. 2002b), a number of techniques were used. Each utilised a GAM (Insightful Corporation 2002) with nonparametric smoothers to correct for time (both seasonality and long term trends), and other variables such as the weather variables. The approach preferred follows the APHEA2 sensitivity analysis (Katsouyanni et al. 2003) and uses a GAM model with a penalised spline algorithm for smoothing and the default option of thin plate regression splines within the R statistical analysis program in conjunction with the MGCV package (Wood 2003; R Development Core Team 2002).

Single city analyses were conducted according to a standard model-building protocol based on APHEA2. This protocol mandates the inclusion of certain confounding variables and allows others to be selected based on the Akaike's information criterion (AIC) (Katsouyanni et al. 2001). Long-term or seasonal trends were removed first and the next step considered the influence of weather. The weather terms considered were: same day average temperature, lags of up to 3 days, the average of lags 1-3 for average temperature, same day average relative humidity, lags of up to 3 days for average relative humidity, the average of lags 1-3 for average relative humidity, and same day average pressure. The same day average temperature and same day average relative humidity were always included. If significant, other weather terms were then included, as well as variables for week days, public and school holidays, outliers, and influenza epidemics. Any remaining serial correlation was removed by introducing autoregressive terms to the model when needed, based on the methodology by Brumback et al. (2000).

The above step produced the base model, to which linear terms for each pollutant variables were added in separate models. The APHEA2 approach considered the average of lags 0 and 1 for all pollutants while the NMMAPS study examined lags 0, 1 and 2 (Samet et al. 2000; Dominici et al. 2002a). In this EPHC study, a combination of both approaches has been used, that is, lags 0, 1, 2, 3 and average of days 0-1). Only nephelometer measurements (bsp), NO_2 and ozone concentrations were used as measures of air pollution, as these were the only complete data sets available for all cities. Bushfires are a particular problem near Australian cities and periods of control burns are carried out regularly, with the highest nephelometer readings usually found over these periods. These effects were excluded by removing all days with nephelometer readings above the high 24-hour average value of $3x10^{-4}.m^{-1}$.

In the second stage of the analysis, the single city results were pooled to estimate the overall effects for the cities under study. In the context of a study such as the APHEA2 project, a multi-city approach which combines all results would appear to be beneficial as it maximises the precision with which common effect estimates can be made. As mentioned previously, problems such as differing study designs, exposure and outcome measures and data gathering processes are minimised, since a common protocol is followed. Similarly, contributions to inter-study heterogeneity arising from differing study designs, exposure and outcome measures and data gathering processes are also minimised. The research hypothesis (in this case, that there is an association between health and air pollution) can be studied across a range of settings with differing exposure and covariable distributions (air pollution and meteorological variables). This should improve generalisability of findings, if effect magnitudes are consistent, or provide a means to explore variability in findings, if they are not.

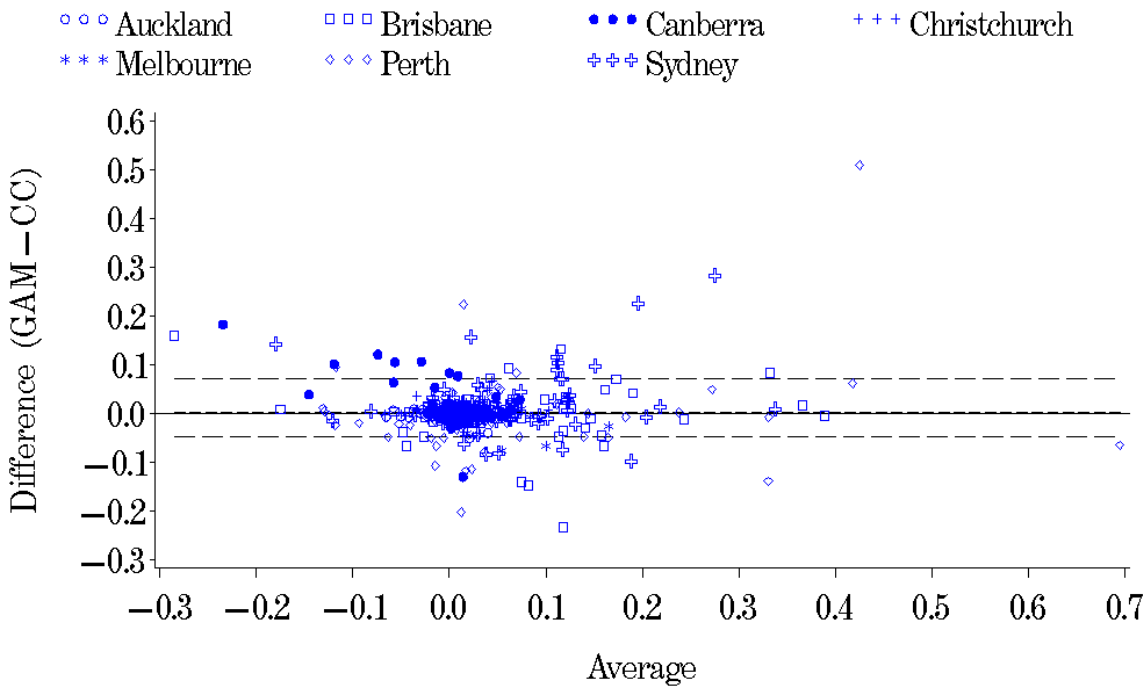
As this EPHC study is an extension of the SPIRT study, then comparison is made, where possible, between SPIRT results and results derived here (referred to as EPHC results). Here, we do not use nephelometer readings for particles, but rather focus on $PM_{2.5}$ and PM_{10}. However, it is possible that some of the differences found may be because of the different statistical approaches used, so GAMs were run on the data sets used here for comparison with the results from the case-crossover models.

2.2.2 Comparison of methods

As with the previous SPIRT study, in this EPHC study, every GAM controlled for long-term trend, season, average temperature, average temperature difference (current minus previous day), average humidity, average pressure, extremes of hot and cold (coldest and warmest 1% of days), flu epidemics, day of the week and public holiday (yes/no). Models of admission variables also included an indicator variable for the day after a public holiday. Models in Canberra included an indicator for the 15th of the month. Pollutant effects are the average over lagged days 0 and 1. A random effects meta-analysis was used to combine the effects across cities (Normand 1999). A test of heterogeneity was used to find differences across cities, as was the related I-squared, which is interpretable as the proportion of total variation in the relative risks that is due to heterogeneity between cities (Higgins & Thompson 2002).

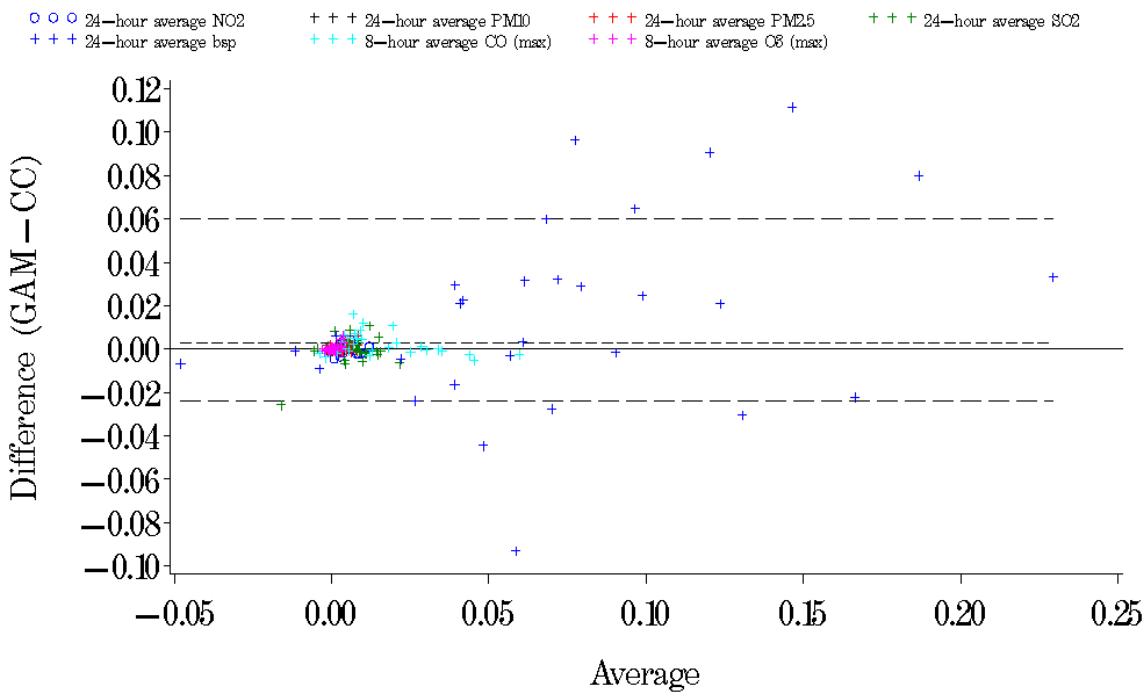
Comparisons between estimates derived from the case-crossover method and from the GAM method are displayed in Figures 2.1 for single cities and Figure 2.2 for pooled estimates. Most estimates fall within the expected range of the comparable method. In Figure 2.2, it is clear that a number of differences have arisen for bsp, so the emphasis on $PM_{2.5}$ and PM_{10} as measures for particles here should avoid these effects. In general, it would appear the GAM results are slightly higher than the case-crossover results.

Figure 2.1: Agreement between city-level GAM and case-crossover (CC) estimates (Bland-Altman plot)



Long dotted lines show central 95th percentile, short dotted lines show mean, solid line at zero (perfect agreement). The plot is based on n=1012 estimates. Average difference between methods=0.014, t-statistic=8.04, p-value<0.0001. Some evidence that GAM estimates are, on average, greater than case-crossover estimates, but the difference is small. The biggest difference is in Perth for cardiac failure admissions 65+ yrs and 24-hour bsp, GAM=0.68, CC=0.17.

Figure 2.2: Agreement between pooled GAM and case-crossover (CC) estimates (Bland-Altman plot)



Long dotted lines show central 95th percentile, short dotted lines show mean, solid line at zero (perfect agreement). Based on n=210 estimates. Biggest differences for bsp. Average difference between methods=0.0028, t-statistic=2.33, p-value=0.02. So some evidence that GAM estimates are, on average, greater than case-crossover estimates, but the difference is very small.

Tables 2.1, 2.2 and 2.3 shows comparisons between GAM and case-crossover results for this EPHC study for the same four cities (Brisbane, Melbourne, Perth and Sydney) as in the previous SPIRT study for NO_2, bsp, and ozone respectively. There are some small differences between the results for respiratory admissions.

Table 2.1: Comparison of GAM and case-crossover (CC) results for Brisbane, Melbourne, Perth and Sydney for a one-unit (ppb) increase in average 24-hour NO_2 (average of lags 0-1)

	EPHC study CC	EPHC study GAM
	% increase (95% CI)	% increase (95% CI)
Total mortality all ages		
Brisbane	0.9 (0.3,1.4)*	0.8 (0.3,1.3)*
Melbourne	-0.0 (-0.3,0.2)	0.0 (-0.2,0.3)
Perth	0.2 (-0.4,0.7)	0.2 (-0.3,0.8)
Sydney	0.4 (0.1,0.7)*	0.3 (0.0,0.6)*
Respiratory admissions 65 + yrs		
Brisbane	0.6 (-0.1,1.4)	0.4 (-0.4,1.2)
Melbourne	0.3 (-0.1,0.6)	0.1 (-0.3,0.4)
Perth	-0.4 (-1.2,0.3)	-1.0 (-1.7,-0.2)
Sydney	0.5 (0.2,0.9)*	0.7 (0.3,1.1)*
Cardiac admissions 65+ yrs		
Brisbane	0.7 (0.2,1.3)*	0.7 (0.1,1.3)*
Melbourne	0.8 (0.5,1.0)*	0.8 (0.5,1.1)*
Perth	1.0 (0.4,1.6)*	0.8 (0.2,1.4)*
Sydney	0.9 (0.6,1.2)*	0.9 (0.6,1.2)*
Meta-analysis	0.6 (0.4,0.9)*	0.7 (0.5,0.9)*

** Statistically significant increase at 5%*

Table 2.2: Comparison of GAM and case-crossover (CC) results for Brisbane, Melbourne, Perth and Sydney for a one-unit ($10^{-4}.m^{-1}$) increase in average 24-hour bsp (average of lags 0-1)

	EPHC study CC	EPHC study GAM
	% increase (95% CI)	% increase (95% CI)
Total mortality all ages		
Brisbane	16.2 (5.5,27.9)*	20.5 (9.8,32.1)*
Melbourne	0.8 (-2.7,4.4)	1.2 (-2.5,5.0)
Perth	-0.7 (-11.7,11.6)	-0.8 (-12.4,12.0)
Sydney	6.7 (0.0,13.8)*	7.5 (0.5,15.0)*
Respiratory admissions 65 + yrs		
Brisbane	17.1 (3.3,32.7)*	18.8 (4.1,35.6)*
Melbourne	5.5 (0.4,10.8)*	2.7 (-2.5,8.3)
Perth	3.6 (-10.8,20.4)	-6.5 (-20.3,9.6)
Sydney	10.9 (2.5,20.0)*	13.1 (6.9,19.7)*
Cardiac admissions 65+ yrs		
Brisbane	2.9 (-7.2,14.1)	2.6 (-7.4,13.7)
Melbourne	9.6 (5.2,14.2)*	8.3 (3.7,13.2)*
Perth	20.5 (6.9,35.9)*	19.7 (5.9,35.4)*
Sydney	12.3 (4.9,20.2)*	10.4 (5.4,15.5)*
Meta-analysis	9.8 (5.2,14.7)*	9.4 (4.7,14.3)*

** Statistically significant increase at 5%*

Table 2.3: Comparison of GAM and case-crossover (CC) results for Brisbane, Melbourne, Perth and Sydney for a one-unit (ppb) increase in maximum 8-h ozone (average of lags 0-1)

	EPHC study CC	EPHC study GAM
	% increase (95% CI)	% increase (95% CI)
Cardiovascular mortality all ages		
Brisbane	0.2 (-0.1, 0.6)	-0.0 (-0.3, 0.3)
Melbourne	0.2 (-0.0, 0.5)	0.1 (-0.2, 0.3)
Perth	0.1 (-0.3, 0.6)	0.2 (-0.3, 0.6)
Sydney	0.3 (0.1, 0.5)*	0.3 (0.1, 0.5)*
Respiratory mortality all ages		
Brisbane	0.5 (-0.3, 1.2)	0.4 (-0.3, 1.1)
Melbourne	0.0 (-0.5, 0.6)	0.1 (-0.5, 0.7)
Perth	0.0 (-1.0, 1.0)	0.5 (-0.5, 1.5)
Sydney	0.4 (-0.0, 0.8)	0.3 (-0.1, 0.8)

** Statistically significant increase at 5%*

The two methods adopted to model the associations with short-term health outcomes for air pollution both attempt to identify the associations with day-to-day variability in the health outcomes with air pollution data. However, health outcomes may change with season, even over years; for example, death counts usually show a seasonal cycle with peaks in winter, and are usually decreasing over time (per capita). These seasonal cycles need to be filtered out in the analysis as, even though air pollutant concentrations often increase in winter, so do other variables such as the number of very cold days. The day-to-day variability in the death counts, however, is not related to smoking habits as these do not change on a day-to-day basis, while other variables such as air pollution and weather do. Therefore, filtering techniques are needed to control for such long-term factors.

Using GAMs, the temporal changes in the health outcome greater than 60 days (for example, with season and year) are filtered out using fitting procedures for functions or splines; however, the choice of the number of degrees of freedom and the decision rule is subjective and it is not possible to be sure whether there is over-correcting (variability in the data is introduced by the filtering) or under-correcting (not all variability in the data due to seasonal change, for example, has been filtered out). Also, when multiple pollutants have been examined, the independent effect of each pollutant is usually addressed in multi-pollutant models, but these are sensitive to the assumptions inherent in GAMs. Another problem is that, if the association with one pollutant is nonlinear, or varies by season, then a two-pollutant model assuming a linear relationship with each pollutant might not give the independent effect of the second pollutant.

In case-crossover, each day is compared to a nearby control day (or days). The exposures on the case day are compared with exposures in (possibly multiple) control days. These matched pairs are analyzed using conditional logistic regression. Because daily groups of people serve as their own control (that is, the same people are assumed to be vulnerable to having an adverse health outcome on case and control days), the use of a nearby day as the control period means that all confounders and covariates that change slowly over time (such as season, trend, age, usual diet) are controlled. The case-crossover method can therefore potentially control for long-term trend, seasonal changes, and influenza epidemics (over weeks or months) by design. In GAM modelling, flu epidemics are controlled for by using filters based on respiratory admissions data, which tend to over-correct when the health outcomes being tested are the respiratory admissions themselves; this may account for some of the differences between the GAM and case-crossover results for respiratory admissions health outcomes.

2.3 Distributed lag (long-term effects) models

It is expected that air pollutants exert their effects over a number of days preceding the health event (chronic effects) and not just due to short-term exposure over the previous few days (acute effects). Distributed lag models are developed to examine such effects. These effects may differ in strength on differing days, reducing to zero a certain number of days out from the event.

Several key studies have found a long delay between exposure to air pollutants and increases in mortality. A multi-city study in Europe found associations between particulate matter and all-cause (non-external) mortality that lasted for forty days, although the largest increases were in the first seven days (Zanobetti et al. 2002). A study in Ireland found significant increases in respiratory deaths three to four weeks after exposure to black smoke (Goodman et al. 2004). A study in the US found increases in deaths in the elderly that lasted for five days after exposure to particulate matter (Schwartz 2000). These investigations of the delayed health effects of air pollution focused on deaths have yielded consistent results.

The approach adopted in this EPHC study used the analysis protocol of the air pollution and health European approach - APHEA (Zanobetti et al. 2003). For the air pollution analysis, effects were lagged up to 40 days prior to the event, and distributed lag models were constructed within the general framework of generalized additive models (Zanobetti et al. 2003). For each city, pollutant and outcome combination, a Poisson regression model was fitted with independent (unconstrained) pollutant effects from lags zero (same day effect) to 40 days. The overall effect of pollution was estimated using the sum of the unconstrained parameters, which is an unbiased estimate of the total effect (Zanobetti et al. 2003). It should be noted that Goodman et al. (2004) also included a distributed lag model for temperature, but this was not used in this EPHC study, or in the APHEA study.

The categorical covariates of day of the week and public holiday were included in all models. The day after a public holiday was also included in models of admissions. The daily admission and mortality counts were assumed to follow a possibly over-dispersed Poisson distribution. Model residuals were checked for serial independence using the cumulative periodogram test (Fuller 1996). This residual test is particularly important for assessing if the seasonality in the health outcome has been adequately modelled, and is similar to the APHEA2 approach.

Missing pollutant data is a much bigger problem for analyses that examine long-term compared to short-term effects. This is because a missing day causes only two days to be lost from an analysis that looks at short-term effects (average of days 0 and 1), but causes 41 days to be lost from an analysis that looks at the effects over 40 days. Hence, a few missing days can cause a dramatic loss of power and generalisability. To overcome this problem, the small number of missing pollutant results (no more than five per cent) were imputed using a linear regression model including covariates for the weather, other related pollutants, lagged observations of the same pollutant, day of the week and season. These regression models had a very high R-squared (greater than 90%). Because of the sensitivity to missing data for the method, pollutants that were only recorded one day in six could not be used.

2.3.1 Effect modifiers

Differences in the results between cities were investigated using a hierarchical model (Dominici et al. 2002a). The effect estimates in each city were regressed against the potential city-level effect modifiers of average pollutant level, number of monitors, average temperature, average humidity, average pressure, average rainfall, per cent of the population under 15 and over 65, total population and average mortality (see Tables 1.1 and 1.9 in *Volume 2: Project results and conclusions*). The regression models used to estimate the impact of effect modifiers incorporated weights (the inverse standard error of the estimate) so that cities with more precise estimates — usually the larger cities — were more influential in investigating the impact of effect modifiers.

The distributed lag models were run using the R statistical package (Ihaka & Gentlemen 1996) and plots were made using SAS/GRAPH® software.

2.4 Pooled estimates

The estimates across cities were combined using a random effects meta-analysis method (Normand 1999). This method creates an overall estimate of the pollution effect whilst controlling for differences between cities. The I-squared statistic was used to quantify heterogeneity, and is the percentage of total variation due to heterogeneity between cities (Higgins & Thompson 2002). I-squared values range from 0 to 100 per cent, where 0 indicates the same pollutant effect across cities, and 100 indicates maximum variability. I-squared values greater than 80% are considered high, greater than 50% are notable, greater than 20% are mild, and below 20% are small (Higgins & Thompson 2002).

Statistical tests were used to test the significance of the I-squared results, in order to identify whether or not there was evidence of heterogeneity between the results for each city (at 5% level of significance).

To test whether one city had an undue influence on the meta-analysis, a leave-one-city-out sensitivity analysis was used (Normand 1999). To look for differences between countries, separate meta-analyses were run for the Australian and New Zealand cities. These sensitivity analyses were run for both the case-crossover and distributed lag models.

The random effects meta-analysis was performed in R (Ihaka & Gentlemen 1996).

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