Statistical Review of Competing Findings in Fine Particulate Matter and Total Mortality Studies

By Jacob Kohlhepp

Introduction

Intrepid Insight is a not-for-profit corporation focused on providing free consulting services to non-profits, local governments, and good causes. Intrepid Insight's areas of focus include but are not limited to statistics, data science, economics, and internal software development. Intrepid Insight is managed by a group of volunteer directors and contributors.

My name is Jacob Kohlhepp, and I am the founder and economic director of Intrepid Insight. I am an incoming PhD student in economics at UCLA with experience as a statistical analyst. While I am not an expert in epidemiology, I have done research at the intersection of economics and epidemiology, specifically the impact of overtime on workplace injury (paper forthcoming). This research makes me uniquely familiar with the statistical tools employed in the research in question: Cox proportional hazards regression. I am also familiar with the statistical principals and calculations that undergird research across all disciplines. One such type of analysis is meta-analysis: the process of pooling together results from different experiments to come up with a combined effect. Being aware of the limitations of my knowledge, I will focus my comments and findings on the statistical and data-related aspects of the research in question, and will not give any opinions on the underlying epidemiology.

Research on the relationship between particulate matter and mortality is related to the public policy debate surrounding air pollution regulations. It should be noted that Intrepid Insight takes no position on political issues that are inherently tied to the research in question.

Even though we do not take a position, it is worth acknowledge the importance of the question being debated. The relationship between PM2.5 and mortality is used to justify air pollution regulations. In a 2014 regulatory impact report, in a discussion assessing the benefits of the Clean Air Act, the EPA states "Avoided premature deaths account for 98 percent of monetized PM-related co-benefits and over 90 percent of monetized ozone-related co-benefits."[1] Because regulations are never costless, it is important to balance the cost and the benefits. This is why the EPA and other regulatory bodies release reports, like the one quoted above, analyzing the net economic impact. It follows that it is extremely important to careful evaluate research that seeks to answer the question: does PM2.5 cause premature deaths and increase total mortality?

Task

I was contacted by Dr. James Enstrom in my capacity as economic director and founder of Intrepid Insight. Dr. Enstrom requested that I conduct a review of the statistical evidence and arguments presented in his 2017 paper "Fine Particulate Matter and Total Mortality in Cancer Prevention Cohort

[1] EPA. Regulatory Impact Analysis for the Proposed Carbon Pollution Guidelines for Existing Power Plants and Emission Standards for Modified and Reconstructed Power Plants. June 2014. 4-21. https://www.epa.gov/sites/production/files/2014-06/documents/20140602ria-clean-power-plan.pdf.

Reanalysis,"[2] the response letter to the editor by Pope et al,[3] and Enstrom's response to criticism letter to the editor. Because all of these articles and letters are focused on Pope et al's 1995 paper "Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults," I also reviewed it.[4] In addition, because there is an argument about what the body of research says in general about the association between fine particulate matter and total mortality risk, I was asked to review two sets of meta-analysis calculations performed by Enstrom and Burnett.

Intrepid Insight was not paid at all to perform this investigation. As is our policy, we provide our services for free to problems that we deem to be "good." Following our provision of assistance, our clients may voluntarily donate to our organization. None of this funding is used to pay staff or directors – I and all other Intrepid Insight team members are volunteers. Because reproducibility and sound statistical and scientific methods are issues that we deem to be important to the public good, we decided to perform this work.

Summary of Conclusions from Reviewing the Series of Articles

After reviewing the statistical evidence and arguments presented in Enstrom's 2017 paper "Fine Particulate Matter and Total Mortality in Cancer Prevention Cohort Reanalysis,"[2] the response letter to the editor by Pope et al,[3] and Enstrom's response to criticism letter to the editor,[5] I have concluded that while both Enstrom and Pope et al make valid criticisms of each other's analyses, only two criticisms can be evaluated without the release of additional data.

The first is Pope et al's claim that "He [Enstrom] controls for a relatively limited number of individual-level covariates and does not control for any ecologic covariates." Although Enstrom is up front about his use of fewer covariates in his paper, he should provide additional reasoning for why he did not use these covariates as controls. His current reasoning that they are excluded because "[they] had a lesser impact on the age-sex adjusted RR" is not sufficient justification. The reasoning for exclusion should be rooted in theory or additional statistical tests.

The second is Enstrom's claim that "without explanation, Pope 1995 and HEI 2000 omitted from their analyses, 35 cities with CPS II participants and IPN PM2.5 data." This omission is likely because PM 2.5 measurements were not available for these locations in the sources Pope et al and HEI used. However, as Enstrom explains, there did exist additional data that could have prevented the exclusion of these cities (IPN PM2.5 data). Pope et al does not provide any defense of why this data was ignored, or whether this exclusion has any bearing on his results or the representativeness of the original findings.

Beyond these two points, the other criticisms require the release of the original data.

To be specific, Pope et al present the following criticisms of Enstrom's paper in the section titled "Deficiencies in Enstrom's Reanalysis":

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[2] Enstrom JE. Fine particulate matter and total mortality in cancer prevention study cohort reanalysis. Dose-Response. 2017;15(1): 1-12. https://www.ncbi.nlm.nih.gov/pubmed/28473741

[3] Pope CA III, Krewski D, Gapstur SM, Turner MC, Jerrett M, Burnett RT. Fine particulate air pollution and mortality: response to Enstrom's re-analysis of the American Cancer Society Cancer Prevention Study II cohort (letter). Dose-Response. 2017;15(4). doi:10.1177/1559325817746303.

[4] This article is freely available on Enstrom's website: http://www.scientificintegrityinstitute.org/Pope1995.pdf.

[5] Enstrom JE. Response to Criticism --- Dose-Response May 29, 2018 (complete).

1. “The Enstrom’s analysis uses a data set with a shorter follow-up period, fewer participants, and fewer deaths than any previous PM2.5–mortality analyses that used the CPS-II cohort, including the original 1995 analysis.”
2. “Moreover, the key deficiency in the Enstrom’s reanalysis is the absence of advanced modeling approaches for exposure assessment that have been developed over the last 2 decades. Estimates of PM2.5–mortality associations are affected by the quality of the PM2.5 data and the accuracy of matching participants and exposures.”
3. “Furthermore, Enstrom’s PM2.5 exposure assessment is likely subject to greater exposure misclassification because of inadequate assignment of geographic units of exposure. Although other published ACS CPS-II studies assigned geographic areas of exposure based on participants’ residence information, the Enstrom’s analysis used the ACS Division and Unit numbers to assign PM2.5 exposures (see letter from ACS).

All of these points are valid. However, Enstrom, and any other independent analyst, are constrained by the data that is available. As Enstrom explains in the last portion of his “Introduction” section, despite subpoenas by the US House Science, Space, and Technology Committee, the American Cancer Society has refused to release the underlying CPS II data used in Pope 1995. Enstrom also explains that the ACS has refused to work with him and “3 other highly qualified investigators” in a “collaborative analysis of the CPS II data.” As a result, Enstrom used an older, “original” version of the CPS II data, which he readily admits is limited.[6] He obtained this data from an anonymous source with appropriate access, and not through formal channels. This is the reason Enstrom’s analysis has a “a shorter follow-up period, fewer participants, and fewer deaths than any previous PM2.5–mortality analyses.” It is also the reason why Enstrom used the ACS division and unit numbers to assign exposure rather than residential addresses: the limited data set he has does not contain residential addresses.[7]

In a similar manner, Enstrom’s criticisms of Pope et al could be easily evaluated with the release of the underlying data. Specifically, his claims that the analyses conducted by Pope et al are sensitive to data exclusions and that the findings vary dramatically based on location, could all be resolved with the underlying data.

It is finally worth noting that Pope et al have possession or access to the underlying data, while Enstrom does not. As a result, regardless of whether the data is released publicly, they have the ability to refute or verify Enstrom’s claims. They could perform Enstrom’s analyses themselves using the underlying CPS II data used in Pope 1995, fixing the issues they identify. Pope et al’s response to Enstrom’s criticism does not perform this analysis, and instead presents additional studies performed on different data. While these studies may support a relationship between fine particulate matter and mortality, they do not address the underlying claim that Enstrom makes: namely, that the Pope 1995 findings are not robust.

Intrepid Insight Statement of Support for Greater Data Transparency

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[6] “This article presents my initial analysis of the CPS II cohort and it is subject to the limitations of data and documentation that is not as complete and current as the data and documentation possessed by ACS” (Enstrom 2017).

[7] “Since this deidentified data file does not contain home addresses, the Division number and Unit number assigned by ACS to each CPS II participant have been used to define their county of residence” (Enstrom 2017).

Because so much rests on the release of the source data, I have asked all nine of Intrepid Insight's directors and contributors to vote on whether to support data transparency as a principle (in this case and in all others). The vote was unanimously in favor.

Because the Pope 1995 paper is used to support public policies, there is an even greater justification for releasing the underlying data. Whether a person supports or opposes greater particulate matter regulations, one can still stand for reproducibility and transparency. These principles are in line with the same transparency we demand from the press and from politicians. Indeed, they seem like a natural extension of American democratic values to the world of public policy research.

There are many options for how the data could be released: it can be deidentified and completely open source, or it can be left in a secured portal with a vetting process for users. Both of these methods are used by government, nonprofit and corporate entities alike.

To practice what we preach, I the underlying Excel workbooks used to perform all of these analyses are available on Intrepid Insight's website, at this link: https://www.intrepidinsight.com/pm25_statreview/

Results of Replicating Burnett's Meta-Analysis

I was also asked to replicate Dr. Richard Burnett's meta-analyses presented in his talk "Reproducibility and Air Pollution Epidemiology" at the Health Effects Institute's 2018 Annual Conference.[8] Intrepid Insight's director of statistics, James Lepore, and I completed these calculations which are presented in Appendix A. We do not take a position on whether the studies Dr. Burnett selected are meaningful or representative studies.

We calculated both random and fixed effects meta-analyses for three continents and globally. To do this, we first converted the hazard ratios and confidence intervals back to the original coefficients from the regressions by taking the natural logarithms.[9] We derived standard errors from these confidence intervals by dividing the difference between the upper and lower bounds by 3.92.[10] We proceeded with the fixed and random effects analyses using formulas and procedures that are broadly accepted.[11]

Although it is not stated in the slides, we believe that Dr. Burnett is using a random effects model to pool the hazard ratios into a combined hazard ratio. The random effects model seems most appropriate based on the rejection of the null hypothesis in the Cochrane's Q Test for Homogeneity.[12]

Comparing our numbers (Table A1) to Burnett's slides, our North America random effects relative risk point estimate is the same when rounded to two decimal places (1.10), as is our confidence band upper bound (1.13). However, our lower bound is slightly higher (1.07) than his (1.06). In general, this small difference does not change the interpretation. In both his and our analysis, the result is statistically

[8] The slides which contain the numbers used are available online: https://www.healtheffects.org/sites/default/files/burnett-reproducibility-hei-2018.pdf.

[9] The reason for this is outlined here: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm.

[10] This procedure is outlined here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm.

[11] See here: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf and here: https://newonlinecourses.science.psu.edu/stat509/node/143/.

[12] We followed the NIH's procedures to compute the I^2 and the Q test statistic: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/.

significant, in that the 95% confidence intervals do not cross 1 (the null result). We also performed similar analyses on his global, Europe, and Asia cohorts (see tables A2 through A4). We found similar slight differences, all of which did not change the overall interpretations.

The reason for these differences may be rounding: Dr. Burnett may be using relative risk and confidence interval estimates from the underlying studies that are carried out to more than 2 decimal places, and then rounding the results to two decimal places in his slides. It could also be that Burnett is using a statistical package, like R or SAS, to perform the meta-analysis. Sometimes these packages include additional adjustments or slightly different approaches than the standard formulas we used.

Our final conclusion is that assuming the relative risks and confidence intervals in Burnett's slides match the underlying studies, and the studies he chose are a representative of the literature, his North America meta-analysis appears accurate.

Results of Performing Random Effects Meta-analyses of US Studies Selected by Enstrom

I also conducted fixed and random effects meta-analyses on groups of US studies selected by Enstrom, and on one group of California-only studies. In all US groups, statistical tests suggest the use of random effects models. For the California-only group, the random effects analysis reduces to the fixed effects analysis because the Q-statistic was less than the degrees of freedom. As with Burnett's analyses, I do not take a position on whether Enstrom's selections are meaningful or representative, or on whether the fixed or random effects model is most appropriate for calculating aggregate effects for these groups. The results are reported in Appendix B.

Enstrom analyses first divide Burnett's original North America studies into two groups: Canada and the United States.

The results for Canada are listed in Table B1. A random effects model appears most appropriate based on the Cochrane's Q Test, and under this model I estimate the pooled relative risk to be 1.160, with a 95% confidence interval of (1.124, 1.198). As this confidence interval does not cross 1, it is statistically significant.

For the United States, Dr. Enstrom requested several different versions. Before presenting those results, we also present the results of only excluding the Canada studies from Burnett's original meta-analysis, but making no other changes. This analysis is presented in full in Table B2. The random effects pooled relative-risk point estimate is 1.064, with a 95% confidence interval of (1.043, 1.085).

The studies Enstrom requested are listed in Tables B3 through B7. A random effects model appears most appropriate in all cases based on the Cochrane's Q Test. These additional analyses, with their associated pooled relative risk and 95% confidence intervals:

1. Table B3: A version using nine cohort studies, including the Medicare 2008 study broken into three regions rather than the Medicare 2017 study. 1.031 (0.997, 1.066)
2. Table B4: A version using eight cohort studies, omitting the Medicare studies entirely (Table B3). 1.014 (0.973, 1.057)
3. Table B5: A version using eight cohort studies, omitting the Medicare studies entirely with CPS II and H6CS results limited to the most recent follow-up period. 0.997 (0.958, 1.038)

4. Table B6: A version using eight cohort studies, omitting the Medicare studies entirely, using the Enstrom 2017 CPS II reanalysis results and the most recent H6CS follow-up results. 0.997 (0.954, 1.043)

Although relative risk point estimates for fine particulate matter exposure vary for each analysis, all of the 95% confidence intervals cross 1. As a result, none of the summary RRs for Enstrom's United States meta-analyses are statistically significant.

Finally, Enstrom requested that I perform a meta-analysis using six California studies he selected. As mentioned previously, this is the only meta-analysis where Cochrane's Q-test suggests using a fixed effects meta-analysis. Even if the random effects model is used, the results are the same, as the degrees of freedom is greater than the Q-statistic. The full calculations and results are presented in Table B7. Under a fixed-effects model I estimate the pooled relative risk to be 0.999, with a 95% confidence interval of (0.988, 1.009). As this confidence interval crosses 1, it is not statistically significant.

The last table, Table B8, was provided by Enstrom as additional information about the studies he selected in his meta analyses versions for the United States.

The Excel workbook used to perform all these calculations are publicly available on Intrepid Insight's website at this link: https://www.intrepidinsight.com/pm25_statreview/

Conclusion

Intrepid Insight and I do not take a position on whether fine particulate matter causes premature deaths and increases total mortality, as this is outside our area of expertise. However, we stand firmly behind the proposition that data transparency, especially in issues of public policy debate, is necessary. In this particular case, it would aid both sides in resolving questions of methodology and robustness.

Regarding Dr. Burnett's meta-analyses, I find that while his calculations vary slightly from mine, the differences are not large and do not significantly change the interpretation. Specifically, it is possible the differences are only due to rounding differences or variations in the methods used by different software packages. I also present the results from the meta-analyses requested by Dr. Enstrom. These are in Appendix B.

Robust debate requires robust scientific inquiry. Resolving any methodological conflicts and publishing underlying data will help lawmakers and the public make informed decisions when it comes to important matters like air pollution regulations.

Appendix A

Table A1: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis
Global Cohorts of Ambient Fine Particulate Matter and Non-Accidental Mortality
North America

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from Slide 12 of Richard T. Burnett's presentation at the HEI 2018 Annual Conference (April 30, 2018).
2. Methodology for the fixed and random effects meta analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
3. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
4. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
5. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
6. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

	Relative Risk Results		
North American Studies	**RR**	**95%CI(L)**	**95%CI(U)**
Male Health Professionals	0.860	0.720	1.020
Agricultural Health Study	0.940	0.780	1.130
California Teachers Study	1.010	0.940	1.080
AARP Diet and Health	1.030	1.010	1.060
National Health Interview Survey	1.060	1.010	1.110
American Cancer Society CPS-II	1.070	1.060	1.090
AHSMOG	1.080	0.970	1.210
MEDICARE	1.080	1.080	1.090
Census Health & Environment (1991)	1.120	1.100	1.130
Breast Screening	1.120	1.050	1.200
Nurses' Health Study	1.130	1.050	1.220
Six City Study	1.140	1.070	1.220
Census Health & Environment (2001)	1.150	1.120	1.170
Census Health & Environment (1996)	1.180	1.160	1.200
Community Health Survey	1.260	1.190	1.340
Intrepid Insight Fixed Effects Meta-Analysis	**1.089**	**1.085**	**1.093**
Intrepid Insight Random Effects Meta-Analysis	**1.101**	**1.074**	**1.128**
Burnett Meta-Analysis (Methodology Not Provided)	**1.100**	**1.060**	**1.130**

Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	**Q Test Statistic**	**P-Value**
	207.7096	0.0000

I^2	**93.26%**

Table A2: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis
Global Cohorts of Ambient Fine Particulate Matter and Non-Accidental Mortality
Europe

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from Slide 12 of Richard T. Burnett's presentation at the HEI 2018 Annual Conference (April 30, 2018).
2. Methodology for the fixed and random effects meta analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
3. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
4. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
5. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
6. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

	Relative Risk Results		
European Studies	**RR**	**95%CI(L)**	**95%CI(U)**
Rome Census Cohort	1.040	1.030	1.050
Dutch Study of Diet and Cancer	1.060	0.970	1.160
DUELS	1.130	1.110	1.150
National Health Interview Surveytional English	1.130	1.000	1.270
Escape	1.140	1.030	1.270
France	1.150	0.980	1.350
Intrepid Insight Fixed Effects Meta-Analysis	**1.061**	**1.052**	**1.070**
Intrepid Insight Random Effects Meta-Analysis	**1.098**	**1.039**	**1.160**

Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	**Q Test Statistic**	**P-Value**
	69.1226186	1.56017E-13

I^2	**92.77%**

Table A3: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis
Global Cohorts of Ambient Fine Particulate Matter and Non-Accidental Mortality
Asia

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from Slide 12 of Richard T. Burnett's presentation at the HEI 2018 Annual Conference (April 30, 2018).
2. Methodology for the fixed and random effects meta analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
3. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
4. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
5. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
6. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

	Relative Risk Results		
Asian Studies	**RR**	**95%CI(L)**	**95%CI(U)**
Taiwan Civil Servants	0.920	0.720	1.170
Chinese Male Cohort	1.090	1.090	1.100
Hong Kong	1.140	1.070	1.220
Intrepid Insight Fixed Effects Meta-Analysis	**1.090**	**1.085**	**1.095**
Intrepid Insight Random Effects Meta-Analysis	**1.098**	**1.047**	**1.151**

Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	**Q Test Statistic**	**P-Value**
	3.6656329	0.159962404

I^2	**45.44%**

Table A4: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis
Global Cohorts of Ambient Fine Particulate Matter and Non-Accidental Mortality
Global - "All Cohorts"

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from Slide 12 of Richard T. Burnett's presentation at the HEI 2018 Annual Conference (April 30, 2018).
2. Methodology for the fixed and random effects meta analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
3. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
4. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
5. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
6. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

	Relative Risk Results		
All Studies	**RR**	**95%CI(L)**	**95%CI(U)**
Male Health Professionals	0.860	0.720	1.020
Agricultural Health Study	0.940	0.780	1.130
California Teachers Study	1.010	0.940	1.080
AARP Diet and Health	1.030	1.010	1.060
National Health Interview Survey	1.060	1.010	1.110
American Cancer Society CPS-II	1.070	1.060	1.090
AHSMOG	1.080	0.970	1.210
MEDICARE	1.080	1.080	1.090
Census Health & Environment (1991)	1.120	1.100	1.130
Breast Screening	1.120	1.050	1.200
Nurses' Health Study	1.130	1.050	1.220
Six City Study	1.140	1.070	1.220
Census Health & Environment (2001)	1.150	1.120	1.170
Census Health & Environment (1996)	1.180	1.160	1.200
Community Health Survey	1.260	1.190	1.340
Rome Census Cohort	1.040	1.030	1.050
Dutch Study of Diet and Cancer	1.060	0.970	1.160
DUELS	1.130	1.110	1.150
National Health Interview Surveytional English	1.130	1.000	1.270
Escape	1.140	1.030	1.270
France	1.150	0.980	1.350
Taiwan Civil Servants	0.920	0.720	1.170
Chinese Male Cohort	1.090	1.090	1.100
Hong Kong	1.140	1.070	1.220
Intrepid Insight Fixed Effects Meta-Analysis	**1.086**	**1.083**	**1.089**
Intrepid Insight Random Effects Meta-Analysis	**1.100**	**1.082**	**1.117**

	Q Test Statistic	**P-Value**
Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	315.1367701	3.94967E-53

I^2	**92.70%**

Appendix B

Table B1: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis
Cohorts of Ambient Fine Particulate Matter and Total Mortality
Canada Subset

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from Slide 12 of Richard T. Burnett's presentation at the HEI 2018 Annual Conference (April 30, 2018).
2. Cohorts were selected by James Enstrom, and not by Intrepid Insight. Intrepid Insight does not take a position on whether these are methodologically relevant subsets.
3. Methodology for the fixed and random effects meta analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
4. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
5. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
6. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
7. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

	Relative Risk Results		
Canada Studies (Subset Selected by Enstrom)	**RR**	**95%CI(L)**	**95%CI(U)**
Census Health & Environment (1991)	1.120	1.100	1.130
Breast Screening	1.120	1.050	1.200
Census Health & Environment (2001)	1.150	1.120	1.170
Census Health & Environment (1996)	1.180	1.160	1.200
Community Health Survey	1.260	1.190	1.340
Intrepid Insight Fixed Effects Meta-Analysis	**1.146**	**1.136**	**1.157**
Intrepid Insight Random Effects Meta-Analysis	**1.160**	**1.124**	**1.198**

Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	**Q Test Statistic**	**P-Value**
	32.9583	0.0000

I^2	**87.86%**

Table B2: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis
Global Cohorts of Ambient Fine Particulate Matter and Non-Accidental Mortality
North America - Excluding Canadaian Studies

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from Slide 12 of Richard T. Burnett's presentation at the HEI 2018 Annual Conference (April 30, 2018).
2. Methodology for the fixed and random effects meta analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
3. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
4. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
5. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
6. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

	Relative Risk Results		
North American Studies	**RR**	**95%CI(L)**	**95%CI(U)**
Male Health Professionals	0.860	0.720	1.020
Agricultural Health Study	0.940	0.780	1.130
California Teachers Study	1.010	0.940	1.080
AARP Diet and Health	1.030	1.010	1.060
National Health Interview Survey	1.060	1.010	1.110
American Cancer Society CPS-II	1.070	1.060	1.090
AHSMOG	1.080	0.970	1.210
MEDICARE	1.080	1.080	1.090
Nurses' Health Study	1.130	1.050	1.220
Six City Study	1.140	1.070	1.220
Intrepid Insight Fixed Effects Meta-Analysis	**1.077**	**1.073**	**1.082**
Intrepid Insight Random Effects Meta-Analysis	**1.064**	**1.043**	**1.085**
Burnett Meta-Analysis (Methodology Not Provided)	**1.100**	**1.060**	**1.130**

Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	**Q Test Statistic** 32.0044	**P-Value** 0.0002

I^2	**71.88%**

Table B3: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis

Cohorts of Ambient Fine Particulate Matter and Total Mortality

US Subset: Nine Cohorts with complete follow-up period as tabulated by Enstrom

Medicare (2008) included rather than Medicare (2017), as per October 12, 2017 NEJM Letter by Enstrom

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from Slide 12 of Richard T. Burnett's presentation at the HEI 2018 Annual Conference (April 30, 2018).
2. Cohorts were selected by James Enstrom, and not by Intrepid Insight. Intrepid Insight does not take a position on whether these are methodologically relevant subsets.
3. Methodology for the fixed and random effects aeta-analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
4. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
5. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
6. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
7. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

			Relative Risk Results		
US Subset 1 Studies	**Acronym**	**Years**	**RR**	**95%CI(L)**	**95%CI(U)**
Veterans' Study	Vets	1986-1996	0.890	0.850	0.950
Medicare (2008) Eastern	MCAPS	2000-2005	1.068	1.049	1.087
Medicare (2008) Central	MCAPS	2000-2005	1.132	1.095	1.169
Medicare (2008) Western	MCAPS	2000-2005	0.989	0.970	1.008
ACS Cancer Prevention Study (CPS II)	CPS II	1982-2000	1.028	1.014	1.043
Nurses' Health Study	HNHS	1992-2002	1.260	1.020	1.540
Health Professionals FU Study	HHPS	1989-2002	0.860	0.720	1.020
Harvard Six Cities Study	H6CS	1974-2009	1.140	1.070	1.220
Agricultural Health Study	AHS	1993-2009	0.950	0.760	1.200
NIH-AAPR Diet and Health Study	NIH-AARP	2000-2009	1.025	1.000	1.049
National Health Interview Survey	NHIS	1997-2011	1.016	0.979	1.054
Intrepid Insight Fixed Effects Meta-Analysis			**1.033**	**1.024**	**1.041**
Intrepid Insight Random Effects Meta-Analysis			**1.031**	**0.997**	**1.066**

	Q Test Statistic	**P-Value**
Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	109.5100704	6.69843E-19

I^2	**90.87%**

Table B4: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis
Cohorts of Ambient Fine Particulate Matter and Total Mortality
US Subset: Eight Cohorts with complete follow-up periods as tabulated by Enstrom
Medicare (2008) and Medicare (2017) are both omitted

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from Slide 12 of Richard T. Burnett's presentation at the HEI 2018 Annual Conference (April 30, 2018).
2. Cohorts were selected by James Enstrom, and not by Intrepid Insight. Intrepid Insight does not take a position on whether these are methodologically relevant subsets.
3. Methodology for the fixed and random effects aeta-analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
4. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
5. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
6. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
7. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

			Relative Risk Results		
US Subset 2 Studies	**Acronym**	**Years**	**RR**	**95%CI(L)**	**95%CI(U)**
Veterans' Study	Vets	1986-1996	0.890	0.850	0.950
ACS Cancer Prevention Study II	CPS II	1982-2000	1.028	1.014	1.043
Nurses' Health Study	HNHS	1992-2002	1.260	1.020	1.540
Health Professionals FU Study	HHPS	1989-2002	0.860	0.720	1.020
Harvard Six Cities Study	H6CS	1974-2009	1.140	1.070	1.220
Agricultural Health Study	AHS	1993-2009	0.950	0.760	1.200
NIH-AAPR Diet and Health Study	NIH-AARP	2000-2009	1.025	1.000	1.049
National Health Interview Survey	NHIS	1997-2011	1.016	0.979	1.054
Intrepid Insight Fixed Effects Meta-Analysis			**1.023**	**1.012**	**1.035**
Intrepid Insight Random Effects Meta-Analysis			**1.014**	**0.973**	**1.057**

	Q Test Statistic	P-Value
Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	43.3307	0.0000

I^2	**83.85%**

Table B5: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis
Cohorts of Ambient Fine Particulate Matter and Total Mortality
US Subset: Eight Cohorts with latest follow-up periods for CPS II & H6CS by Enstrom
Medicare (2008) and Medicare (2017) are both omitted

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from Slide 12 of Richard T. Burnett's presentation at the HEI 2018 Annual Conference (April 30, 2018).
2. Cohorts were selected by James Enstrom, and not by Intrepid Insight. Intrepid Insight does not take a position on whether these are methodologically relevant subsets.
3. Methodology for the fixed and random effects aeta-analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
4. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
5. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
6. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
7. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

			Relative Risk Results		
US Subset 2 Studies	**Acronym**	**Years**	**RR**	**95%CI(L)**	**95%CI(U)**
Veterans' Study	Vets	1986-1996	0.890	0.850	0.950
ACS Cancer Prevention Study II	CPS II	1990-2000	1.020	1.003	1.037
Nurses' Health Study	HNHS	1992-2002	1.260	1.020	1.540
Health Professionals FU Study	HHPS	1989-2002	0.860	0.720	1.020
Harvard Six Cities Study	H6CS	2000-2009	1.190	0.910	1.550
Agricultural Health Study	AHS	1993-2009	0.950	0.760	1.200
NIH-AAPR Diet and Health Study	NIH-AARP	2000-2009	1.025	1.000	1.049
National Health Interview Survey	NHIS	1997-2011	1.016	0.979	1.054
Intrepid Insight Fixed Effects Meta-Analysis			**1.014**	**1.002**	**1.027**
Intrepid Insight Random Effects Meta-Analysis			**0.997**	**0.958**	**1.038**

	Q Test Statistic	P-Value
Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	31.8163	0.0000

I^2	**78.00%**

Table B6: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis
Cohorts of Ambient Fine Particulate Matter and Total Mortality
US Subset: Eight Cohorts with Enstrom CPS II Reanalysis and latest follow-up periods for H6CS
Medicare (2008) and Medicare (2017) are both omitted

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from Slide 12 of Richard T. Burnett's presentation at the HEI 2018 Annual Conference (April 30, 2018).
2. Cohorts were selected by James Enstrom, and not by Intrepid Insight. Intrepid Insight does not take a position on whether these are methodologically relevant subsets.
3. Methodology for the fixed and random effects aeta-analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
4. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
5. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
6. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
7. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

			Relative Risk Results		
US Subset 2 Studies	**Acronym**	**Years**	**RR**	**95%CI(L)**	**95%CI(U)**
Veterans' Study	Vets	1986-1996	0.890	0.850	0.950
ACS Cancer Prevention Study II Reanalysis (Enstron	CPS II	1982-1988	1.023	0.997	1.049
Nurses' Health Study	HNHS	1992-2002	1.260	1.020	1.540
Health Professionals FU Study	HHPS	1989-2002	0.860	0.720	1.020
Harvard Six Cities Study	H6CS	2000-2009	1.190	0.910	1.550
Agricultural Health Study	AHS	1993-2009	0.950	0.760	1.200
NIH-AAPR Diet and Health Study	NIH-AARP	2000-2009	1.025	1.000	1.049
National Health Interview Survey	NHIS	1997-2011	1.016	0.979	1.054
Intrepid Insight Fixed Effects Meta-Analysis			**1.012**	**0.997**	**1.028**
Intrepid Insight Random Effects Meta-Analysis			**0.997**	**0.954**	**1.043**

	Q Test Statistic	**P-Value**
Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	31.7506	0.0000

I^2	**77.95%**

Table B7: Intrepid Insight Computation of Fixed and Random Effects Meta-Analysis

Cohorts of Ambient Fine Particulate Matter and Total Mortality

US Subset: Six California Cohorts as tabulated by James Enstrom

Notes

1. Hazard ratios, confidence intervals, and studies included were taken from James Enstrom titled "Burnett Hei Reproducibility & AP Epi Meta-Analysis 040318 080918.xlsx."
2. Cohorts were selected by James Enstrom, and not by Intrepid Insight. Intrepid Insight does not take a position on whether these are methodologically relevant subsets.
3. Methodology for the fixed and random effects aeta-analysis was derived from this source: https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.
4. This methodology was confirmed using this second source: https://newonlinecourses.science.psu.edu/stat509/node/143/.
5. Logarithms of Reported RRs are taken because this returns them to the original coefficient values from the Cox regression: https://www.statsdirect.com/help/survival_analysis/cox_regression.htm
6. The methodology for deriving the standard errors from the confidence intervals was found here: https://handbook-5-1.cochrane.org/chapter_7/7_7_7_2_obtaining_standard_errors_from_confidence_intervals_and.htm
7. Formulas for I^2 and Q are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/

			Relative Risk Results		
US Subset CA Studies	**Acronym**	**Years**	**RR**	**95%CI(L)**	**95%CI(U)**
Adventist Health Study SMOG	CA AHSMOG	1977-1992	1.000	0.950	1.050
CA ACS Cancer Prevention Study I	CA CPS I	1983-2002	0.997	0.978	1.016
Medicare Air Pollution Cohort Study	MCAPS 'West'	2000-2005	0.989	0.970	1.008
CA ACS Cancer Prevention Study II	CA CPS II	1982-2000	0.968	0.916	1.022
California Teachers Study	CA Teachers	2001-2007	1.010	0.980	1.050
CA NIH-AARP Diet and Health Study	CA NIH-AARP	2000-2009	1.017	0.990	1.040
Intrepid Insight Fixed Effects Meta-Analysis			**0.999**	**0.988**	**1.009**
Intrepid Insight Random Effects Meta-Analysis			**0.999**	**0.988**	**1.009**

	Q Test Statistic	**P-Value**
Cochrane's Q Test for Homogeneity of Studies (Null Hypothesis: Studies are Homogenous)	4.7683	0.4448

I^2	**-4.86%**

Table B8: Information on Nine US Cohort Studies and Six California Cohort Studies as provided by Enstrom

US Cohort Studies	Acronym	FU Years	Author Organizations	Geographic Location	Lead Author+Article Year+Journal+RR Table
Veterans' Study	Vets	1986-1996	Lipfert & WashU & EPRI	32 VA Clinics in 28 States & PR	Lipfert 2000 IT Table 6 [see Enstrom 2005 Table 10
Medicare (2008) Eastern	MCAPS	2000-2005	JHU SPH	613 Counties in Eastern US States	Zeger 2008 EHP Table 3
Medicare (2008) Central	MCAPS	2000-2005	JHU SPH	185 Counties in Central US States	Zeger 2008 EHP Table 3
Medicare (2008) Western	MCAPS	2000-2005	JHU SPH	62 Counties in 3 US States (CA+OR+WA)	Zeger 2008 EHP Table 3
ACS Cancer Prevention Study (CPS II)	CPS II	1982-2000	BYU & ACS & HEI & H TH Chan SPH	50 & 58 US Metro Areas	Krewski 2009 HEI Report 140 Table 34
ACS CPS II Reanalysis	CPS II	1982-1988	UCLA & Scientific Integrity Institute	50 & 85 US Counties	Enstrom 2017 D-R Table 2
Nurses' Health Study	HNHS	1992-2002	USoCar SPH & H TH Chan SPH	13 NE & MidWestern States (CA Omitted)	Puett 2009 EHP Table 3
Health Professionals FU Study	HHPS	1989-2002	USoCar SPH & H TH Chan SPH	13 NE & MidWestern States (CA Omitted)	Puett 2011 EHP Table 2
Harvard Six Cities Study	H6CS	1974-2009	H TH Chan SPH	6 Eastern & MidWestern Cities	Lepeule 2012 EHP Table 2
Agricultural Health Study	AHS	1993-2009	Health Canada & NIEHS	NC & IA	Weichenthal 2015 EHP Table 2
NIH-AAPR Diet and Health Study	NIH-AARP	2000-2009	NYU & UCB & NCI	6 States & 2 Metro Areas	Thurston 2016 EHP Table 2 & Figure 3
National Health Interview Survey	NHIS	1997-2011	NCHS/CDC & NCEH/CDC	Representative US Sample	Parker 2018 Circ Table 3 (corrected)

US Subset: CA Cohort Studies					
Adventist Health Study SMOG	CA AHSMOG	1977-1992	LLU & EPA	SoCal+SanDiego+SanFran Air Basins	McDonnell 2000 JEAEE Table & Text
CA ACS Cancer Prevention Study I	CA CPS I	1983-2002	UCLA	11 & 25 CA Counties	Enstrom 2005 IT Table 7
Medicare Air Pollution Cohort Study	MCAPS 'West'	2000-2005	JHU SPH	62 Counties in 3 US States (CA+OR+WA)	Zeger 2008 EHP Table 3
CA ACS Cancer Prevention Study II	CA CPS II	1982-2000	HEI & U Ottawa	4 CA Counties	HEI Krewski Special Analysis 2010
California Teachers Study	CA Teachers	2001-2007	CoH & OEHHA & UCB	58 CA Counties	Ostro 2015 EHP Table S3
CA NIH-AARP Diet and Health Study	CA NIH-AARP	2000-2009	NYU & UCB & NCI	58 CA Counties	Thurston 2016 EHP Table 2 & Figure 3