A Perspective of the Air Quality (PM2.5)-Premature Death Research Claim

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Introduction

PubMed is a widely used online search engine and bibliographic database that provides citations and abstracts to articles on biomedical and life sciences.[1] Currently more than 1.5 million citations on new biomedical and life science articles are added to the PubMed database each year.[2] With so many new articles occurring annually in the literature, we envision it may be challenging for physicians to be able to keep up with research relevant to their practice or interest.

Some physicians may not have the time to carefully read an article and simply look at its abstract to kept informed of current directions. Unfortunately, our experience is that—when it comes to epidemiology research—*the devil is in the details*.[3-6] In an earlier paper we noted that the way data analysis is done in many population health (observational) epidemiology studies explains why research claims in these studies do not reproduce,[7] i.e., they are false.

Here we scrutinize a false environmental health research claim—breathing air with small particles (PM2.5, diameter 2.5 microns or less) causes premature death. We use it as an example of the devilish details that physicians may wish to be aware of in epidemiology studies. It is not so much that the same type of details occurs in every epidemiology study. But it is an example of biased methods used by academic researchers to get results that are more likely to lead to a journal publication and yet unlikely to offer anything meaningful to public health.

The Air Quality-Premature Death Connection

There are three historical situations in which poor air quality has caused deaths. The best known is the London Fogs caused by temperature inversions trapping smoke, soot, and hazardous gases. The first one occurred in November 1952 and had an estimated 4,000[8] to 12,000[9] excess deaths occurring during that period and over the next several months. These fog conditions occurred again in 1956 (with 1,000 deaths) and in 1962 (with 700 deaths).[8] The other two events—with similar conditions—occurred in Meuse River Valley, Belgium, (1930) with 60 deaths and Danora, Pennsylvania, (1948) with 20 deaths.[8]

These unique conditions do not exist today because of clean-air regulations and industrial source emission controls. Yet the U.S. Environmental Protection Agency (EPA) still claims that small particulates in air (PM2.5) can cause premature deaths.[10] Further, the EPA estimated Clean Air Act compliance costs at $65 billion annually and claimed that it would prevent 230,000 annual premature deaths by 2020.[11]

Origins of Government-Funded Air Quality Epidemiology Research

In the 1990s the EPA partially funded two noteworthy investigations into possibly harmful air contaminants that were supposedly causing deaths. One was the 1993 Harvard Six Cities study.[12] This investigation followed 8,111 adults aged 25-74 for 16 years in six American cities, over which time 1,430 deaths occurred. The other was a 1995 National Institute of Statistical Science (NISS) study of more than 785,000 deaths among adults ≥65 years old in two U.S. counties over a six-year period.[13] The Harvard study claimed that PM2.5 contributed to excess deaths, increasing the death rate by 26%. The NISS study used daily deaths and found no association with PM10 (which is highly correlated with PM2.5) and deaths.

The EPA then obtained the Harvard data set and, along with industry, funded University of Ottawa epidemiologists to reanalyze it. This study—published in 2000[14]—found that if one closely followed the Harvard analysis steps, one got much the same result. The effect, however, broke down if the analysis method changed. The EPA did not approach NISS for its data set to have it reanalyzed.

The Harvard Six Cities study was published in the *New England Journal of Medicine* on Dec 9, 1993. Since then, more than 1,450 PM2.5-premature death articles and abstracts have been captured in PubMed up to the end of 2025. This is almost 47 each year over the 31-year period. But a valid question remains, given what NISS and the University of Ottawa observed: does air quality cause premature death or is the result an artifact of the way the analysis is done or the data set used?

Noteworthy Studies that Found Nothing

After Harvard Six Cities study, two large air quality-premature death studies were completed. The Six Cities data set comprised approximately 130,000 person-years with 1,400 deaths. One study in 2011[15] examined individual-level data from a population of 18.2 million (with 3.2 million deaths) across 814 US locations over the period 2000 to 2006. This data set amounted to more than 109 million person-years. Researchers found effects across locations but noted these were "likely due to unmeasured confounders." They noted from their within-location analysis that "We are not able to demonstrate any change in life expectancy for a reduction in PM2.5."

The other study[16] in 2017 used individual-level data from a population of roughly 20 million people (with more than 2 million deaths) in eight California air basins over the period 2000 to 2012. This data set amounted to approximately 200 million person-years. They too found no association between PM2.5 and daily deaths. In yet another noteworthy study, Enstrom re-analyzed data sets from the American Cancer Society Cancer Prevention Study (CPS II) cohort in 2017.[17] He too found no relationship between PM2.5 and mortality in the CPS II cohort when the best available PM2.5 data set was used.

The Data Harvard Won't Release

What is worth mentioning about the three studies discussed above[15-17] is that using different analytical methods and data sets led to null associations. In particular, the 2011 Greven study[15] showed that when individual-level data with proper spatio-temporal modeling was used, the PM2.5-premature death association disappeared. It was a gold-standard method—individual deaths, precise timing, geographic granularity, and the power of millions of observations.

So, why hasn't Harvard released its Six Cities study data set in a form that would allow other researchers to do a Greven-style analysis on it? The original data set, as far as we can tell, remains hidden. The 2000 reanalysis commissioned and funded by the EPA and industry[14] was conducted under controlled conditions with researchers having access to the original Harvard investigators. It can hardly be considered independent.

Thirty-three years later, findings of the Six Cities study—which is supposedly recognized as influential scientific research used to backstop and shape modern air quality regulations[18]—has never been independently reproduced from its raw data with modern methods. In any other situation, this would be called what it is: science by press release, sustained by data hoarding.

Big Data, Big Problems

The heart of the problem analyzing epidemiology associations between exposure topics and mortality (and morbidity) is using complex observational data sets—i.e., data sets with many variables. This problem was recognized 38 years ago. Yale researchers back in 1988 initially identified claims for 56 different medical and pharmaceutical exposure topics from published observational studies.[19,20] They then went back to the literature and looked for other similar studies for the same topics and same period and found another 136 studies supporting the claims and 127 studies contradicting the claims.

In another situation, the president of the Biometrics Society in his 2002 Presidential Address noted that when students in his statistics regression class were given the same data set and the same question, they came up with dramatically different answers.[21]

Modern research confirms this. Multiverse analysis—also called many-analyst studies—using Specification Curve Analysis (SCA) has shown that with complex data sets, there can be thousands of ways to run an analysis, all seemingly reasonable.[22,23] Here SCA researchers gave the same data set and posed the same question to independent teams. These teams consistently produce dramatically different results. In other words, any result is possible when working with complex data sets!

As a specific example, a researcher recently showed how different statistical modeling assumptions for short-term PM2.5-mortality associations in elderly people gives different results.[24] The researcher used data from the Center for Medicare and Medicaid Services, the EPA, and the National Oceanic and Atmospheric Administration. He showed that by simply removing one variable from the analysis—the previous day's temperature—PM2.5-mortality associations went from being not significant to statistically significant.

What Is Published in Literature These Days

It is useful to stand back and look at the bigger picture of what gets published in the literature. Australian researchers recently collected more than 968,000 confidence intervals extracted from abstracts and more than 350,000 other statistical intervals extracted from the full text of articles published in Medline (PubMed) from 1976 to 2019.[25] These intervals were converted to z-values by Dutch researchers, and the distribution is shown in Figure 1.[26] The z-value on the x-axis of Figure 1 is a measure of the effect (association) noted — negative effects are to the left and positive are to the right. The height of a bar gives the frequency of the effect.

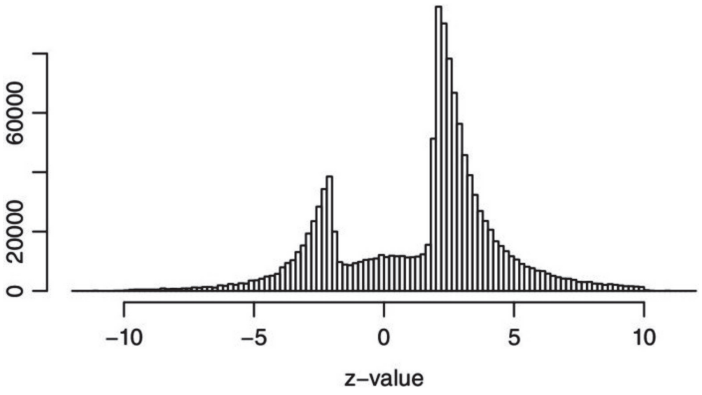


Figure 1. Distribution of more than one million z-values from Medline (1976–2019)

Source: Van Zwet and Cator,[26] with permission

There are several observations to make about Figure 1. First, there are few results between -2 and +2. These are non-significant effects. Part of what is happening in Figure 1 is the file-drawer problem.[27] Mostly, researchers will not or do not attempt to publish if nothing happened; i.e., if they get a result between -2 and +2. These studies are put into a file drawer. Also, there is the influence of researcher bias. This results in bumping what would otherwise be a non-significant effect (between -2 and +2) to a nominally significant effect (just outside the -2 to +2 range).[28]

Second, there are many more positive results than negative. Coincidentally, there are more academic opportunities for research grants by publishing positive results. So, there is incentive to *analyze* a data set until a positive result appears. Finally, the path to publishing a positive and statistically significant result for exposure topics using complex data sets appears to be in running the analysis in selective ways—to find a positive result that can lead to publication.

There are other unsettling practices hidden in the university research-journal publishing game. Professional journals prefer publishing positive studies.[29] No editor wants to headline "nothing to see here" in a study. Also, false-positive studies that are published can be canonized—endlessly cited until everyone assumes they're settled fact.[30]

Academics hold most of the peer-review and editorial positions in professional journals.[31] Further, the academic publishing and tenure process functions as natural selection of bad science.[32] Career incentives reward sensational positive results, not careful null results. The Harvard Six Cities study[12]

was a small positive study that became famous. The larger null studies[15-17] that followed were Ignored.

Follow the Money

The EPA justifies its existence and its $65 billion annual regulatory burden by claiming lives are being saved.[11] University researchers who produce studies showing that air quality harms public health get grants, publications, tenure, and prestigious appointments. Journals that publish these sensational positive studies get citations and higher impact factors. Everyone with a stake in the university-government-journal publishing-industrial complex wins. Who benefits from a null result? Nobody. Who loses? Everyone with a stake in the complex.

What It All Means

Air quality-premature death epidemiology—as currently practiced—is an artifact of analytical flexibility, unaccounted confounding, and publication bias dressed up as public health consensus. The air disasters of the mid-20th century were real. But they bear no similarity to current conditions. The Harvard Six Cities study was small. Larger, better-designed studies that followed found nothing.

Multiverse analyses show that different reasonable analytical choices produce contradictory results in research. Yet it is the studies with positive results that are most likely to get published and garner public health attention. Finally, the entire journal publication ecosystem is structurally biased toward publishing false-positive research.

A former long-time editor-in-chief of the *British Medical Journal*, Richard Smith, seems to have perfectly captured the essence of this situation in the epidemiology literature today. Smith recently proposed: "It may be time to move from assuming that research has been honestly conducted and reported to assuming it to be untrustworthy until there is some evidence to the contrary."[33]

PM2.5 and premature death has been used here as an example of a research claim in epidemiology literature that is canonized yet is false. However, there are other topics in epidemiology using observational data that fit this situation.

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AAPS Principles of Medical Policy

Medical care is a professional service, not a right. Rights (as to life, liberty, and property) may be defended by force, if necessary. Professional services are subject to economic laws, such as supply and demand, and are not properly procured by force.

Physicians are professionals. Professionals are agents of their patients or clients, not of corporations, government, insurers, or other entities. Professionals act according to their own best judgment, not government "guidelines," which soon become mandates. Physicians' decisions and procedures cannot be dictated by overseers without destroying their professionalism.

Third-party payment introduces conflicts of interest. Physicians are best paid directly by the recipients of their services. The insurer's contract should be only with subscribers, not with physicians. Patients should pay their physician a mutually agreed-upon fee; the insurer should reimburse the subscriber according to the terms of the contract.

Government regulations reduce access to care. Barriers to market entry, and regulations that impose costs and burdens on the provision of care need to be greatly reduced. Examples include insurance mandates, certificate of need, translation requirements, CLIA regulation of physician office laboratories, HIPAA requirements, FDA restrictions on freedom of speech and physicians' judgment, etc.

Honest, publicly accessible pricing and accounting ("transparency") is essential to controlling costs and optimizing access. Government and other third-party payment or price-fixing obscures the true value of a service, which can only be determined by a buyer's willingness to pay. The resulting misallocation of resources creates both waste and unavailability of services.

Confidentiality is essential to good medical care. Trust is the foundation of the patient-physician relationship. Patient confidences should be preserved; information should be released only upon patient informed consent, with rare exceptions determined by law and related to credible immediate threats to the safety or health of others.

Physicians should be treated fairly in licensure, peer review, and other proceedings. Physicians should not fear loss of their livelihood or burdensome legal expenses because of baseless accusations, competitors' malice, hospitals' attempts to silence dissent, or refusal to violate their consciences. They should be accorded both procedural and substantive due process. They do not lose the basic rights enjoyed by Americans simply because of their vocation.

Medical insurance should be voluntary. While everyone has the responsibility to pay for goods and services he uses, insurance is not the only or best way to finance medical care. It greatly increases costs and expenditures. The right to decline to buy a product is the ultimate and necessary protection against low quality, overpriced offerings by monopolistic providers.

Coverage is not care. Health plans deny payment and ration care. Their promises are often broken. The only reliable protection against serious shortages and deterioration of quality is the right of patients to use their own money to buy the care of their choice.