

BE.104

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Human health **risk** assessment
(and human health **benefit** assessment):
Collecting and weighing evidence

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Outline of lecture:

1. Jerry Avorn (2004)
2. From London, 1952 to today: evidence and beliefs about PM (and other pollutants) and mortality.
3. With what might ambient air PM (or other pollutants) covary? (That is, by what might associations between PM and mortality be confounded?)

Excerpt from *Powerful Medicines*, by Jerry Avorn, M.D.
(Knoph, 2004)

“In a former British colony, most healers believed the conventional wisdom that a distillation of fluids extracted from the urine of horses, if dried to a powder and fed to aging women, could act as a general tonic, preserve youth, and ward off a variety of diseases. The preparation became enormously popular throughout the culture, and was used widely by older women in all strata of society. Many years later modern scientific studies revealed that long-term ingestion of the horse-urine extract was useless for most of its intended purposes, and that it caused tumors, blood clots, heart disease, and perhaps brain damage.”

Excerpt from *Powerful Medicines*, by Jerry Avorn, M.D. (Knoph, 2004)

“The former colony is the United States; the time is now; the drug is the family of hormone replacement products that include Prempro and Premarin (manufactured from pregnant mares' urine, hence its name). For decades, estrogen replacement in postmenopausal women was widely believed to have ‘cardio-protective’ properties; other papers in respected medical journals reported that the drugs could treat depression and incontinence, as well as prevent Alzheimer's disease. The first large, well-conducted, controlled clinical trial of this treatment in women was not published until 1998; it found that estrogen replacement actually increased the rate of heart attacks in the patients studied. Another clinical trial published in 2002 presented further evidence that these products increased the risk of heart disease, stroke, and cancer. Further reports a year later found that rather than preventing Alzheimer's disease, the drugs appeared to double the risk of becoming senile. The studies resulted in a reduction, but not an end, to the long-term use of these products.”

How did this “shared delusion” about long-term use of hormones in postmenopausal women start, why did it persist, and how did it end?

Initial Observations:

Young women (typically) menstruate and tend to be healthy.

Old women do not menstruate, and (typically) tend to be unhealthy.

Menopause is due to decrease in estrogen production *in vivo*.

Perhaps *exogenous* estrogen can keep women young and healthy longer.

Pregnant mares secrete lots of estrogen in their urine: let's use that as a drug.

Actions:

1942: First estrogen pill, Premarin, introduced.

1963: Robert Wilson (gynecologist) and wife published (*J Am Geriatr Soc.*)

“The fate of the nontreated postmenopausal woman: a plea for the maintenance of adequate estrogen from puberty to the grave.” Popular book, *Feminine Forever*, followed in 1966.

1960's – 1990's: The pharmaceutical industry/marketers redefined menopause as a disease, “ovarian failure.”

1960's – 1990's: Physicians began “treating” “ovarian failure” chronically in the hope that it could prolong life, just as treating hypertension can. (But FDA had never approved HRT for such use).

Observational epidemiology:

Until late middle age, women have lower rates of heart disease and cardiac death than men.

Post menopause, women's rates of cardiovascular disease begin to approach those of age-matched men. (Decreased estrogen is to blame?)

Many studies: Postmenopausal women on HRT had significantly less heart disease than age-matched women who did not.

Some studies (such as those that controlled for level of education) suggest otherwise, but were largely discounted.

Stampfer & Colditz (*Prev Med.* 1991 Jan;20(1):47-63):

“Considerable epidemiological evidence has accumulated regarding the effect of postmenopausal estrogens on coronary heart disease [CHD] risk. . . . Of 16 prospective studies, 15 found decreased relative risks, in most instances, statistically significant. . . . A quantitative overview [meta-analysis] of all studies taken together yielded a relative risk [of CHD] of **0.56** (95% confidence interval **0.50-0.61**).”

Mechanistic evidence / plausibility:

Estrogens shown to lower LDL and increase HDL in blood (so they should reduce risk of cardiovascular disease); also alter other indicators of vascular function in apparently beneficial ways.

Typical **physicians' assessments:** (Ettinger, 1990, Kaiser Permanente, SF, CA):

“Since 1980, increasing epidemiologic and experimental evidence has suggested a hitherto unappreciated and **immense CHD health benefit** from use of postmenopausal estrogen therapy. . . Based on available evidence, hormone replacement therapy, appropriately administered, is both safe and beneficial. . . Although questions remain, we should not let our imperfect knowledge dissuade us from **more widespread prescribing of hormone replacement therapy.**”

Walsh BW, Schiff I. (1991), Brigham and Women's Hospital, "Menopause: advanced management strategies," *Curr Opin Obstet Gynecol*.

“Estrogen replacement therapy may offer significant benefits to nearly all postmenopausal women . . . Women at high risk for atherosclerosis, or who already have cardiovascular disease, may particularly benefit from estrogen use. The increased risk for endometrial and breast cancer seen with estrogen replacement therapy is low in comparison with its protective effect against cardiovascular disease.”

Results of controlled, randomized, placebo-controlled, clinical studies (**Experimental**, rather than observational, epidemiology)

- Heart and Estrogens/Progestin Replacement Study (**HERS**, 1998): Involved > 2,700 postmenopausal women diagnosed with coronary disease.
RR for CHD = 0.99 (0.80-1.22). Also, HRT users had more coronary events in 1st yr. of study; more blood clots throughout.
- Women's Health Initiative (WHI, 2002):
Involved > 16,000 healthy postmenopausal women
RR for CHD = 1.29 (1.02-1.63).

Why were the observational data “wrong?”

Current assessment (Grodstein, Clarkson, and Manson, “Understanding the Divergent Data on Postmenopausal Hormone Therapy,” *NEJM*, 2003):

“ . . . hormone therapy should not be initiated or continued for the purpose of preventing cardiovascular disease. Furthermore, we do not believe that long-term use (five years or more) of combined hormones should be recommended for women of any age for the prevention of chronic disease. The established increases in the risks of breast cancer, venous thromboembolism, and stroke are too high a price to pay.”

Can we apply the lessons of the HRT story to the current questions of air pollution and health?

- Cannot perform controlled, randomized, placebo-controlled, clinical studies on air pollution .
- Rely on observational data, supported by “plausibility.”
- Small signals amidst considerable noise – what do they signify?

Photo removed due to copyright considerations.

London, England, December 1952

Correlations between daily mortality and the air quality were very clear.

Meteorological inversion and fog trapped *thousands* of pollutants, *gaseous* and otherwise, from some 1,000,000 domestic stoves inefficiently burning poor quality soft coal, and from other sources.

But notice that air quality there and then is not like air quality in U.S. today.

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Deaths/day vs. daily level of air pollution.

Were “smoke”/soot and sulfur dioxide *per se* (1) the acutely toxic agents,

or instead,

(2) merely *markers* of the inversion and its associated concentrated pollution?

Sulfur dioxide : PEL = 5 ppm

IDLH = 100 ppm

Elemental carbon:

IDLH = 1,750 mg per m³

PAHs? Very little *acute* toxicity

To a first approximation, ambient air during the inversion in London *should* be considered to be like indoor air during an accidental fire.

What accounts for the acute toxicity of fire smoke?

Gaseous and vaporous products of incomplete combustion

carbon monoxide (CO), hydrogen cyanide (HCN), nitrogen dioxide (NO₂), ammonia (NH₃), hydrogen chloride (HCl), hydrogen fluoride (HF) and other gaseous fluorine compounds, sulfur dioxide (SO₂), formaldehyde, acrolein, **countless** other inorganic and organic gases and vapors, acting additively or interactively.

No one knows what killed people during this air pollution disaster.

People assume it's the particles that mattered then, and still matter today, based *not* on toxicology, but on a statistical analysis few understood . . .

Schwartz & Marcus (U.S. EPA), 1990 “Mortality and air pollution in London: a time series analysis.” *Am J Epidemiol.* Jan;131(1):185-94.

“The relation between air pollution and mortality in London was examined for the winters of **1958-1972**. The data exhibited a high degree of autocorrelation, requiring analyses using autoregressive models. There was a highly significant relation between mortality and either particulate matter or sulfur dioxide (after controlling for temperature and humidity), both overall and in each individual year. Graphic analysis revealed a nonlinear relation with no threshold, and a steeper exposure-response curve at lower air pollution levels. In models with both pollutants, particulate matter remained a significant predictor with about a 10% reduction in its estimated coefficients, while sulfur dioxide was insignificant, with a large drop in its estimated coefficient. **The authors conclude that particulates are strongly associated with mortality rates in London, and the relation is likely causal.**”

Daily PM_{2.5}
New York, NY

Graph removed for copyright reasons.

Weekly Mortality

New York, NY

Graph removed for copyright reasons.

Daily PM_{2.5} and Weekly Mortality

New York, NY

Graph removed for copyright reasons.

The National Morbidity, Mortality, and Air Pollution Study (NMMAPS: Samet *et al.*, 2000)

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Please see:

Figure 6 in Dominici, F., et al. "A Report to The Health Effects Institute: Reanalyses of the NMMAPS Database."
Johns Hopkins University, October 31, 2002.

- NMMAPS is an extensive recent analysis of daily PM levels and mortality rates.
- The figure shows the “most likely estimate” and 95% confidence interval of the % increase in mortality per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10}
- New York City (in red) is one of only two cities with a statistically positive result.
- “There is consistent evidence that the levels of fine particulate matter in the air are associated with the risk of death from all causes and from cardiovascular and respiratory illnesses. These findings strengthen the rationale for controlling the levels of respirable particles in outdoor air.”

Is the weak correlation between daily fluctuations of pollutant concentrations and daily rates of death (1) *unique* to PM?
And (2) causal?

Stieb, D., Judek, S., and Burnett, R. (2002) “Meta-analysis of time-series studies of air pollution and mortality: effects of gases and particles and the influence of cause of death, age, and season.” *J. Air Waste Manag. Assoc.* 52(4):470-84.

Synthesis of 109 daily time-series studies of air pollution and mortality.

Stieb *et al.*, 2002, *J. Air Waste Manag. Assoc.* 52(4):470-84.

Pollutant	Average ambient concentration	Increase in all-cause mortality, per conc. change = mean	95% confidence interval
NO ₂	24 ppb	2.8%	2.1%-3.5%
PM ₁₀	31.3 ug/m ³	2.0%	1.5%-2.4%
PM _{2.5}	18.3 ug/m ³	2.0%	1.2%-2.7%
CO	1.1 ppm	1.7%	1.2%-2.2%
O ₃	31.2 ppb (daily max)	1.6%	1.1%-2.0%
SO ₂	9.4 ppb	0.9%	0.7%-1.2%

Do these results mean that current levels of *all* criteria pollutants are lethal? Or are all of these time-series studies confounded? And if so, by what?

Pollutant	Average ambient concentration	Acutely lethal concentrations	
		LC ₁₀	LC ₅₀
NO ₂	24 ppb	200,000 ppb [human] 65,000 ppb [dog]	1,000,000 ppb [mouse] 315,000 ppb [rabbit] 88,000 ppb [rat] 30,000 ppb [guinea pig]
PM ₁₀	31.3 ug/m ³	not established	not established
PM _{2.5}	18.3 ug/m ³	not established	not established
CO	1.1 ppm	4,000 ppm [human; dog]	5,700 ppm [guinea pig] 2,400 ppm [mouse] 1,800 ppm [rat]
O ₃	31.2 ppb (daily max)	50,000 ppb [human]	36,000 ppb [rabbit] 34,500 ppb [cat] 24,800 ppb [guinea pig] 12,600 ppb [mouse] 10,500 ppb [hamster]
SO ₂	9.4 ppb	1,000,000 ppb [human; guinea pig]	3,000,000 ppb [mouse] 2,520,000 ppb [rat]

Major contributors to ambient PM_{2.5} in the Southeastern United States

Zheng, Cass, *et al.*

(*Environ Sci Technol.* 2002 Jun 1; 36(11):2361-71)

Source	Contribution
Secondary sulfate	30% ± 6%
Diesel exhaust	16% ± 7%
Wood combustion	15% ± 12%
Secondary ammonium	8% ± 2%
Secondary nitrate	4% ± 3%
Meat cooking	3% ± 2%
Gasoline-powered motor vehicle exhaust	2% ± 2%
Road dust	2% ± 2%

Inhaled **sulfate** : toxic at moderate levels?

1. Most bronchodilator medications used to *treat* asthma (such as albuterol) are supplied as *sulfate salts*.
2. Each puff from inhaler = 20 μg of sulfate.
3. Since a person breathes 0.0005 m^3 of air with each puff, this provides 40,000 $\mu\text{g}/\text{m}^3$ sulfate.
4. Ambient levels \approx 5 -10 $\mu\text{g}/\text{m}^3$ sulfate.

DPM: toxic at moderate levels?

- Diesel engine exhaust (DPM and gases/vapors) tested in numerous acute and chronic studies.
- 17 chronic studies, involving rats, mice, hamsters, guinea pigs, cats, and monkeys.
- LOEL for premature death due to *lifetime* exposure to DPM is 6,330 $\mu\text{g DPM/m}^3$ in F344 rats (Nikula *et al.*, 1995); 4,240 $\mu\text{g/m}^3$ in NMRI mice (Heinrich *et al.*, 1986).
- ambient concentrations of DPM $\sim 1 - 10 \mu\text{g/m}^3$.

What about other kinds of PM?

Residual oil fly ash (**ROFA**): can cause disease and death in lab rodents, but only at concentrations vastly in excess of ambient.

Concentrated ambient particles (**CAPs**):

Cause little to no toxicity in lab rodents (slight effects, reversible within 18-24 hours, poor dose-response).

Provide little support for “susceptibility factors,” such as age or pre-existing disease.

No lethality.

If, as the toxicologic and clinical data suggest, weak correlations between current air quality and current death rates are *not* causal but merely *coincidental*, what explains the coincidence?

Three factors, at least.

The *first* factor: the weather.

Meteorology has complicated, direct and indirect, short-term influences on disease and death, and it is simply not possible to “control” completely for all of the effects of weather in statistical regression analyses. Sudden cardiac death, m.i., heart failure-related morbidity and mortality, stroke, and intracranial hemorrhage *all* vary by season.

The *second* factor: fluctuations in ambient air quality are caused in part by fluctuations in human activity.

The universal risk factor for death is life; and life involves many activities which *simultaneously* put people at risk of death *and cause increases in pollution*.

Thus, there *have* to be correlations between these two things, *regardless* of whether these correlations are causal.

Example: Monday mornings and risk of m.i.

Case-crossover analysis performed as part of the Stockholm Heart Epidemiology Program (SHEEP) Möller *et al.*, (1999)

- **Hypothesis:** Triggering of myocardial infarction = f [**anger**]
- **Subjects:** 699 cases of m.i. in Stockholm County, 1993-4
- **Data on “hostile behavior” and symptoms in days/hours prior to m.i.:** gathered through detailed, structured interviews (interviewers blind to hypotheses)
- **Results:** Strongly positive. During 1 hour after an episode of anger, relative risk of m.i. = **15.7** (95% c.i. = 7.6 - 32.4)

If daily/hourly fluctuations in traffic/other activities that increase ambient PM also increase anger, the latter could confound associations between the former and m.i.

Does “stress” increase daily death rates, and could stress and traffic correlate? What determines the *timing* of one’s death?

“The *Hound of the Baskervilles* effect: natural experiment on the influence of psychological stress on timing of death.” David Phillips *et al*, *BMJ*, 2001.

Objective To determine whether cardiac mortality is abnormally high on days considered unlucky: Chinese and Japanese people consider the number 4 unlucky, white Americans do not.

Design Examination of CHD mortality on and around the fourth of each month in Chinese and Japanese subjects and white controls in U.S.

Subjects All Chinese and Japanese (n = 209 908) and white (n = 47 328 762) Americans whose computerised death certificates were recorded between the beginning of January 1973 and the end of December 1998.

Main outcome measures Ratio of observed to expected numbers of deaths on the fourth day of the month (expected number was estimated from mortality on other days of the month).

Number of deaths from chronic heart disease, by day of month, in (left) Chinese and Japanese, and (right) whites, in California

Two graphs removed for copyright reasons.

Phillips *et al.*, 2001. *BJM* **323**:1443–6

Total and Average Numbers of Deaths in the United States on
Each of the First 14 Days of the Month and the Last 14 Days
of the Preceding Month, 1973 through 1988.

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Phillips *et al.*, 1999. *NEJM* **341**:93-98

A *third* factor: these correlations may be more a reflection of the statistical regression methods used to detect them than of any genuine and robust association.

As explained by Chock *et al.* (2000) :

“Depending on how one deals with the choice of weather variables, co-pollutants, smoothing schemes, seasonal consideration, and so forth, it is possible and in fact not surprising that different best-effort models applied to the data sets of the same urban areas can reach different or even contradictory conclusions.”

As Samet *et al.* (2003) now note:

“Of course, there is no ‘correct’ model.”

Overall, then, the overall weight of evidence suggests that:

(i) *high* levels of *pollution* correlate with mortality because they *cause* mortality; whereas

(ii) *low* levels of pollution *correlate* with mortality *not* through cause-and-effect, but instead, either largely or entirely, *through coincidence*.

Moreover, PM, as soot, can be a *marker* for acutely lethal air pollution (when such pollution is dominated by inefficient combustion), but is not known or expected to be a *cause*, even at high concentrations, let alone at low.

Current U.S. EPA policy, however, assumes that >10,000 lives per year are lost due to ambient PM: Cost-benefit justification for many Clean Air Act regulations. Health Canada and agencies within the EU predict the same.