Low-level Lead Exposure and Mortality

The NHANES Mortality Follow-up Study

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Background

- Deaths from cardiovascular disease (CVD) have declined dramatically in the US, but it is still the leading cause of death (Mozaffarian, 2016)
- CVD accounts for ~800,000 (one in three) deaths in the U.S. (Mozaffarian, 2016)
- Lead exposure has been consistently associated with CVD mortality; it is unknown if blood lead levels < 5 µg/dL, which are typical for U.S. adults, are associated with CVD mortality

Lead and CVD

- Lead is an established risk factor for HTN and a risk factor for EKG abnormalities, peripheral arterial disease and CVD mortality (Navas-Acien, 2006; NTP, 2012)
- In laboratory studies, lead enhances atherosclerosis by inactivating NO, inhibiting endothelial repair, impairing angiogenesis and promoting thrombosis (Vaziri, 2008)
- Prior studies of lead and CVD mortality did not adjust for cadmium (EPA, 2006)
- No studies have calculated the number of premature CVD deaths in the US attributable to lead exposure using a prospective, longitudinal cohort

Objectives

- To calculate the number of premature deaths in the United States attributable to lead exposure using blood lead levels in a nationally representative, longitudinal cohort

- To test whether blood lead < 5 μg/dL are associated with cardiovascular mortality

NHANES Survey Methods

- Baseline data were collected for adults > 20 years between 1988 and 1994 and followed through December 31st, 2011
- NCHS staff linked subjects with underlying cause of death in the National Death Index (NDI) using a series of identifiers (e.g., social security number and date of birth) using probabilistic matching criteria through 2011
- The underlying cause of death was obtained using ICD-9 (1988-1998) or ICD-10 (1999-2006) codes
- A validation study using mortality-linked data from the first NHANES study (1971-1975) found that 96% of deceased participants and 99.4% of living participants were correctly classified (US Dept Health & Human Services, 2013)

Laboratory Methods

- Blood lead and other laboratory tests were measured in blood and urine samples collected during the medical exam (Gunter, et al. 1996)
- Quantification of lead in whole blood samples was done using graphite furnace atomic absorption spectrophotometry (Pirkle et al. 1994)
- The detection limit for blood lead was 1 µg/dL. For the 9.1% of participants with blood lead levels <LOD, we imputed a level of 0.7 µg/dL (Hornung, 1990)

Measurement of Key Covariates

- Smoking status was categorized as "never", "former", and "current."
- Blood pressure was measured three times during the household interview and three times during the medical exam. We used the average of all but the first blood pressure measurements to classify each participant's hypertension status, which was defined as systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg.
- We categorized physical activity by frequency of activity in the prior month: never, 1 to 14 times, or $\geq$15 times.

Statistical Methods

- We calculated continuous hazard ratios for an increase in blood lead from 10th to 90th percentile (1.0 μg/dL to 6.7 μg/dL) and 10th to 80th (1.0 μg/dL to 5.0 μg/dL) using Cox proportional-hazards models
- We calculated PAF for continuous blood lead (Vander Hoorn, 2004) and confidence intervals for the PAF estimates using Daly substitution method (Daly, 1998)
- SUDAAN version 10.0.1 was used for all statistical analyses (Shah, 2005)

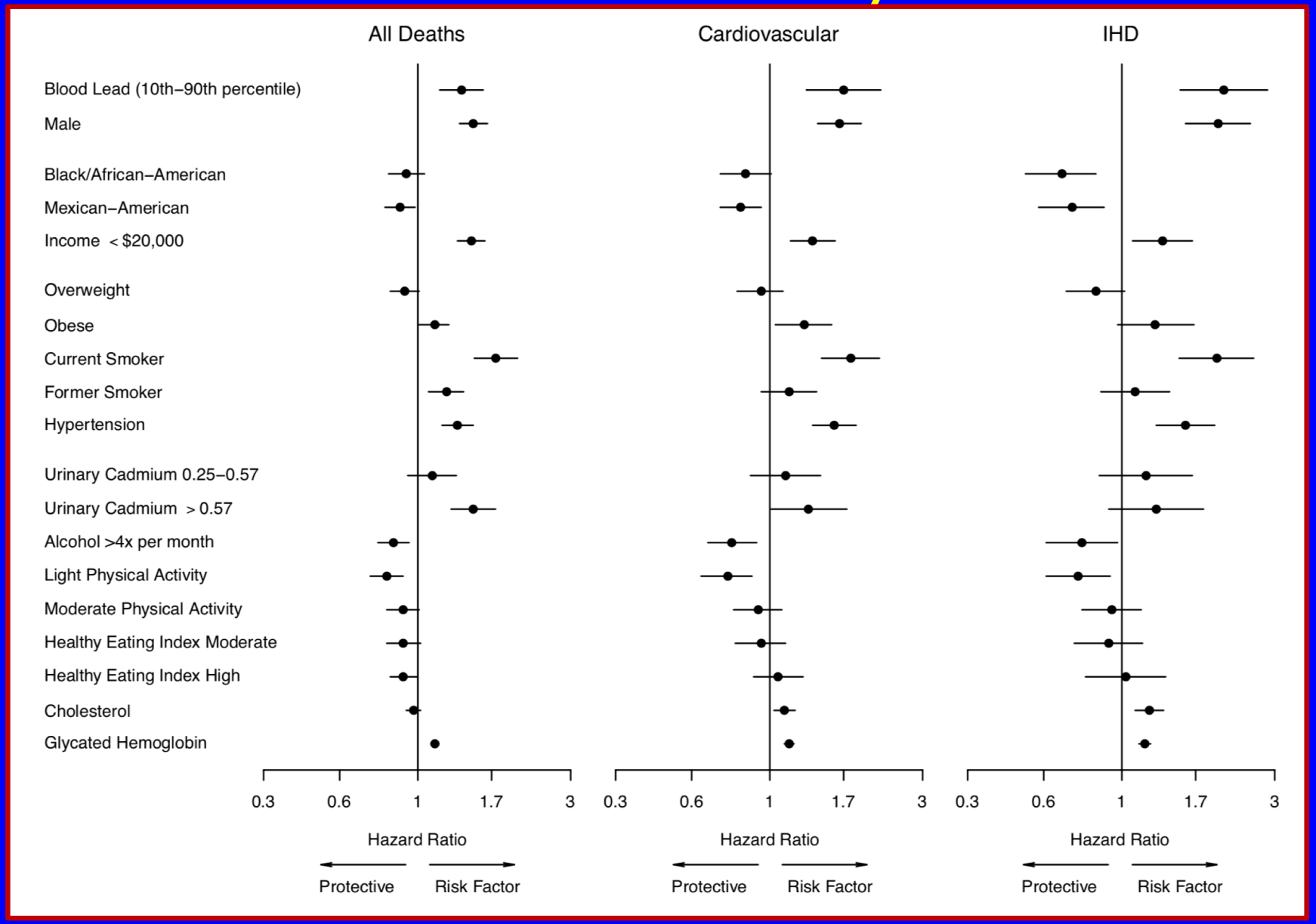
Results

There were 17,030 adults ≥20 years in the NHANES Mortality Follow-up Cohort; 1,419 (6.1%) participants were missing blood lead or urinary cadmium, 1,314 (7.0%) were missing other covariates, and 8 (0.01%) had insufficient identifiers to link with the NDI, leaving 14,289 adults for this analysis.

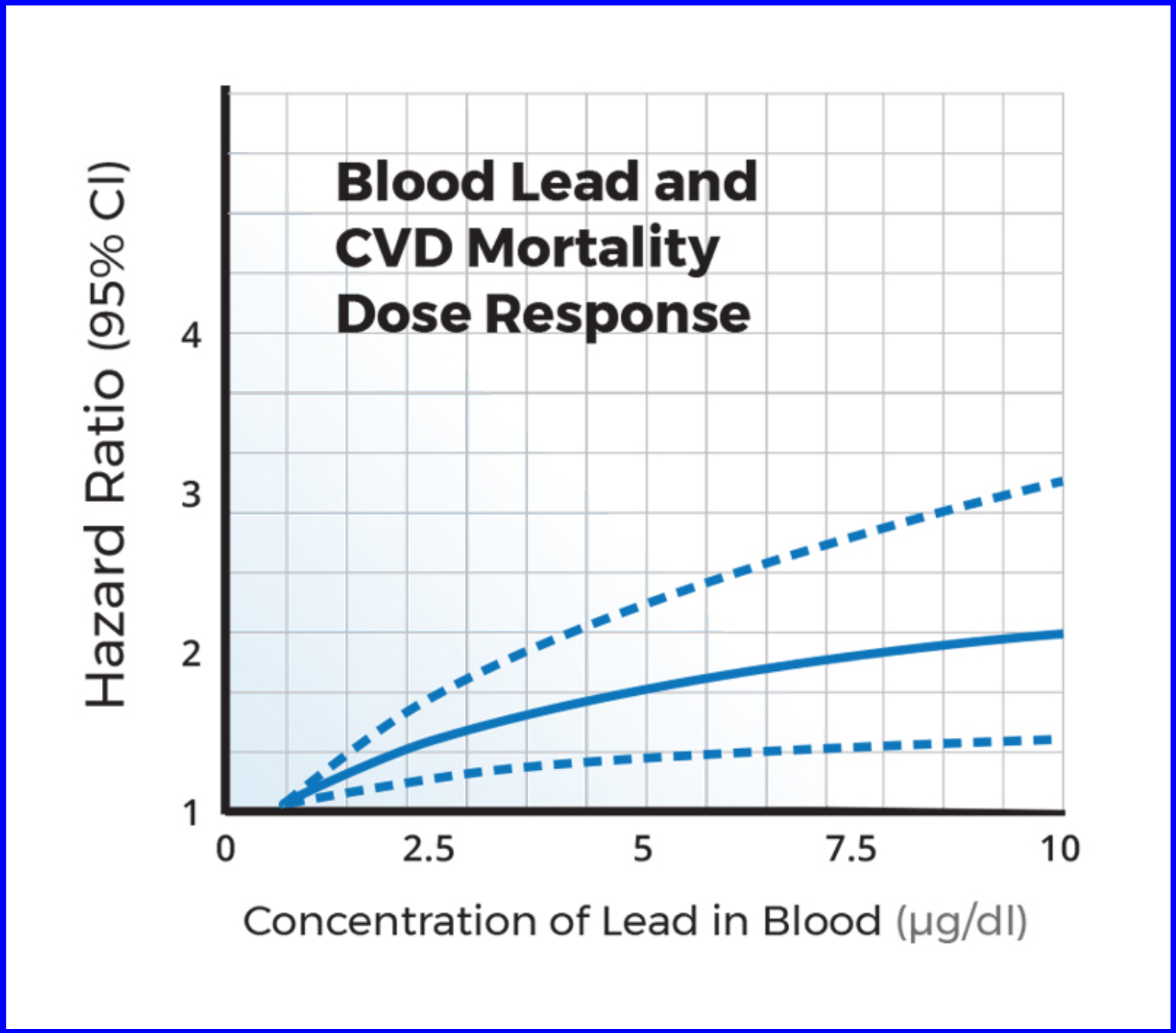
Results

- We followed 14,289 adults for a median of 19.3 years; 4,422 participants died; 1,801 (38%) were due to CVD, 988 (22%) were due to to IHD
- The geometric mean blood lead of the participants was 2.71 μg/dL; 3,632 (20%) had a blood lead >5 μg/dL
- Participants who had higher blood lead levels were older, less educated and more likely to be male. They were more likely to smoke cigarettes, consume larger amounts of alcohol, have less healthy diets, elevated serum cholesterol, higher rates of HTN and diabetes

Hazard Ratios (95% CI) for All-Cause, CVD and IHD Mortality



Lanphear B, et al. Lancet Public Health 2018;http://doi.org/10.1016/S2468-2667(18)30025-2



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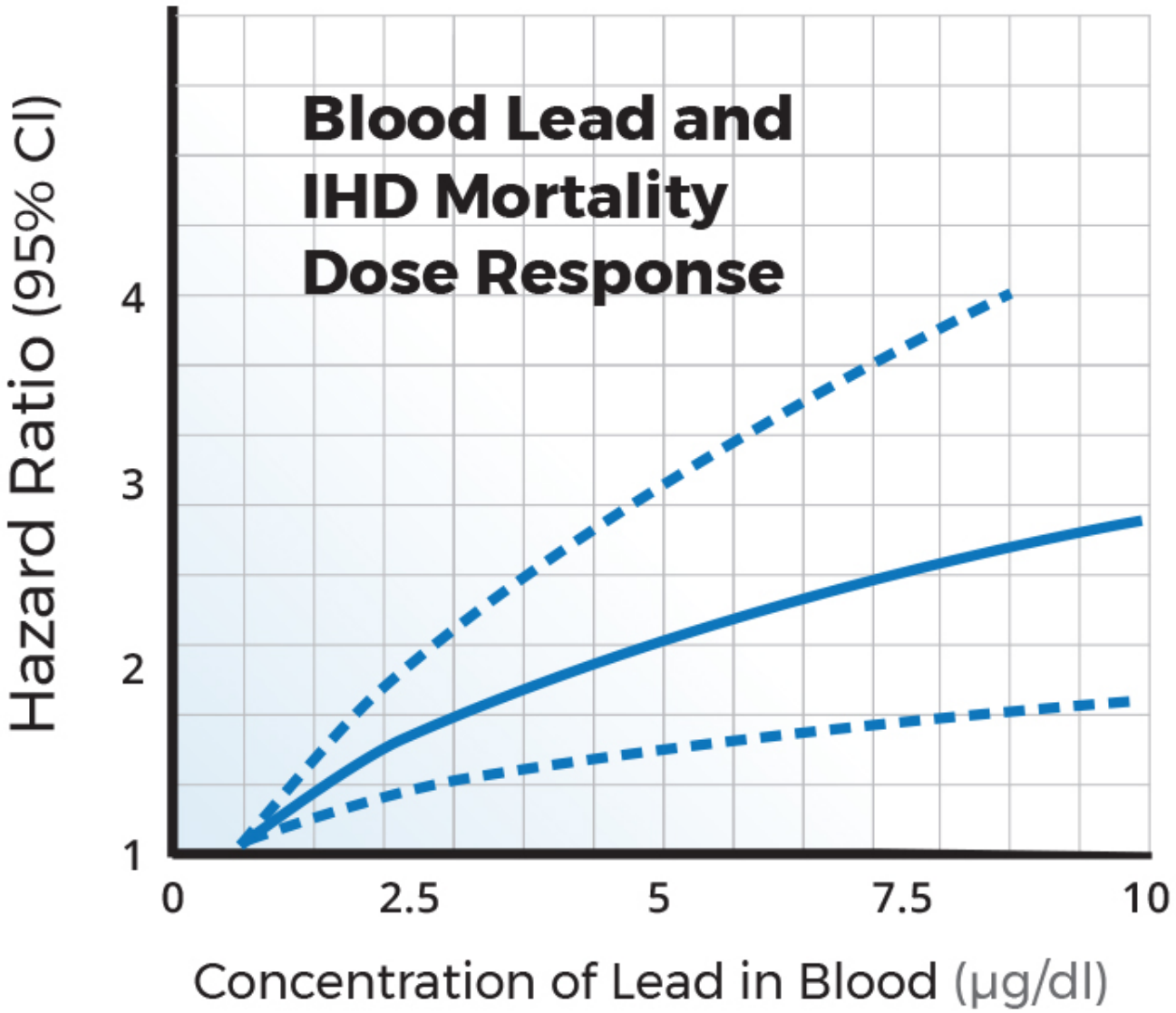

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Adjusted Hazard Ratios for All-Cause and CVD Mortality

Cause of Death	Hazard Ratio	95% CI
All-Cause Mortality	1.43	1.21-1.68
CVD Mortality	1.70	1.29-2.24
IHD Mortality	2.05	1.49-2.83

Hazard ratios for continuous blood lead represent risk for a 10th-90th percentile increase in log transformed blood lead. Adjusted for age (continuous and age-squared); sex; household income (< or > $20,000 per annum); race and ethnicity (White, Black, Mexican American); body mass index: normal (<25 kg/m^2), overweight (25-29.9 kg/m^2) or obese (≥30 kg/m^2); smoking status (current and former); hypertension; urinary cadmium (tertiles); alcohol consumption (none, 1-4, 5-29 or >30 drinks per month); physical activity in previous month (never, 1-14 time, > 15 times); Healthy Eating Index (tertiles); serum cholesterol (continuous); glycated hemoglobin (continuous).

Adjusted Hazard Ratios for All-Cause and CVD Mortality at BPb < 5 μg/dL

Cause of Death	Hazard Ratio	95% CI
All-Cause Mortality	1.38	1.15-1.66
CVD Mortality	1.95	1.46-2.60
IHD Mortality	2.57	1.56-4.52

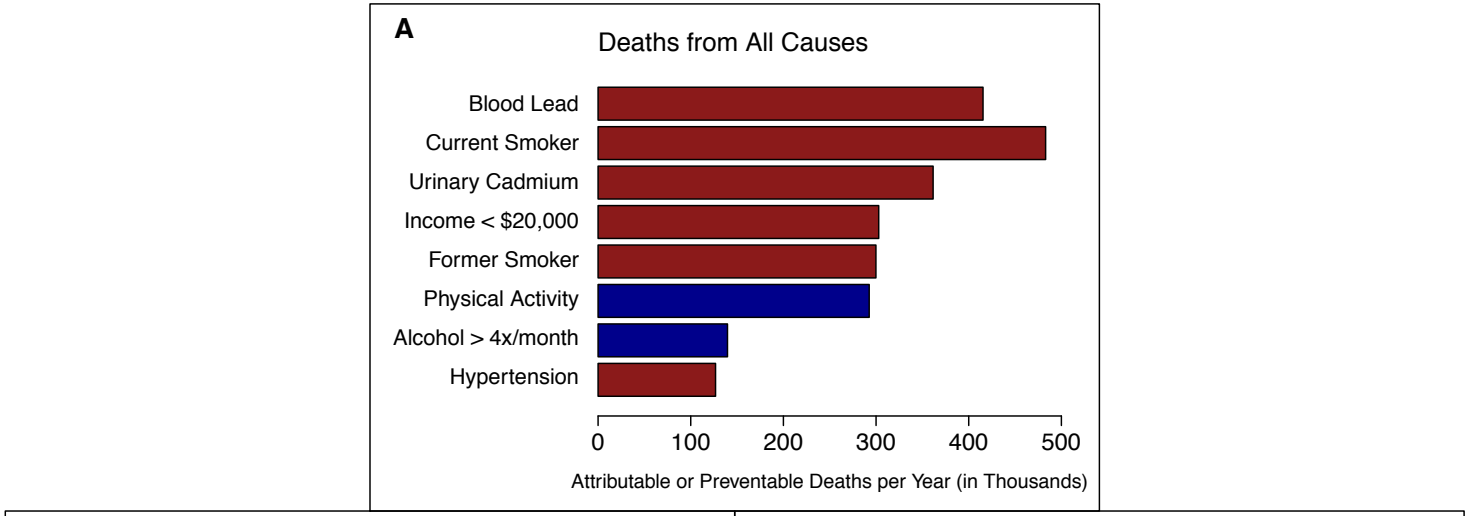
Hazard ratios for continuous blood lead represent risk for a 10th-90th percentile increase in log transformed blood lead. Adjusted for age (continuous and age-squared); sex; household income (< or > $20,000 per annum); race and ethnicity (White, Black, Mexican American); body mass index: normal (<25 kg/m^2), overweight (25-29.9 kg/m^2) or obese (≥30 kg/m^2); smoking status (current and former); hypertension; urinary cadmium (tertiles); alcohol consumption (none, 1-4, 5-29 or >30 drinks per month); physical activity in previous month (never, 1-14 time, > 15 times); Healthy Eating Index (tertiles); serum cholesterol (continuous); glycated hemoglobin (continuous).

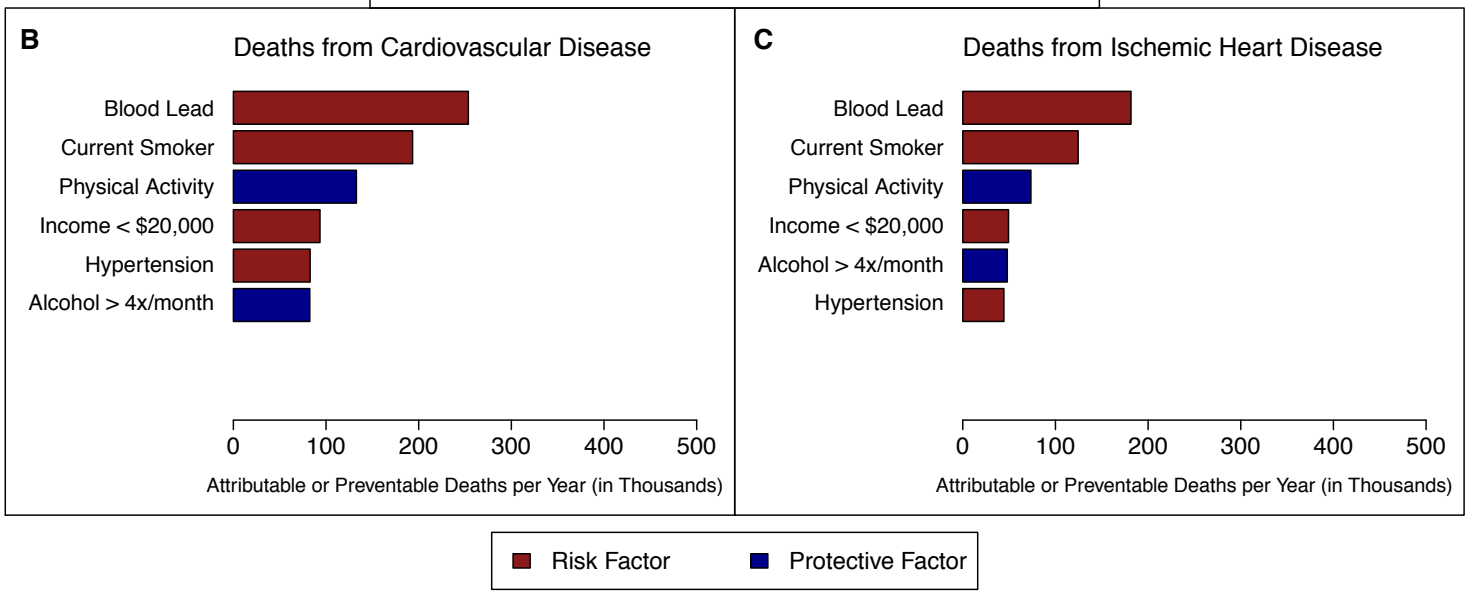
Population Attributable Fraction and Avoidable Deaths from Lead Exposure

Cause of Death	Attributable Fraction	Avoidable Deaths
All-Cause Mortality	18.0% (10.9-26.1)	412,000
CVD Mortality	28.7% (15.5-39.5)	256,000
IHD Mortality	37.4% (23.4-48.6)	185,000

Hazard ratios for continuous blood lead represent risk for a 10th-90th percentile increase in log transformed blood lead. Adjusted for age (continuous and age-squared); sex; household income (< or > $20,000 per annum); race and ethnicity (White, Black, Mexican American); body mass index: normal (<25 kg/m^2), overweight (25-29.9 kg/m^2) or obese ($\geq$30 kg/m^2); smoking status (current and former); hypertension; urinary cadmium (tertiles); alcohol consumption (none, 1-4, 5-29 or >30 drinks per month); physical activity in previous month (never, 1-14 time, > 15 times); Healthy Eating Index (tertiles); serum cholesterol (continuous); glycated hemoglobin (continuous).

Population Attributable Fractions for All-Cause and CVD Mortality from Modifiable Risk Factors





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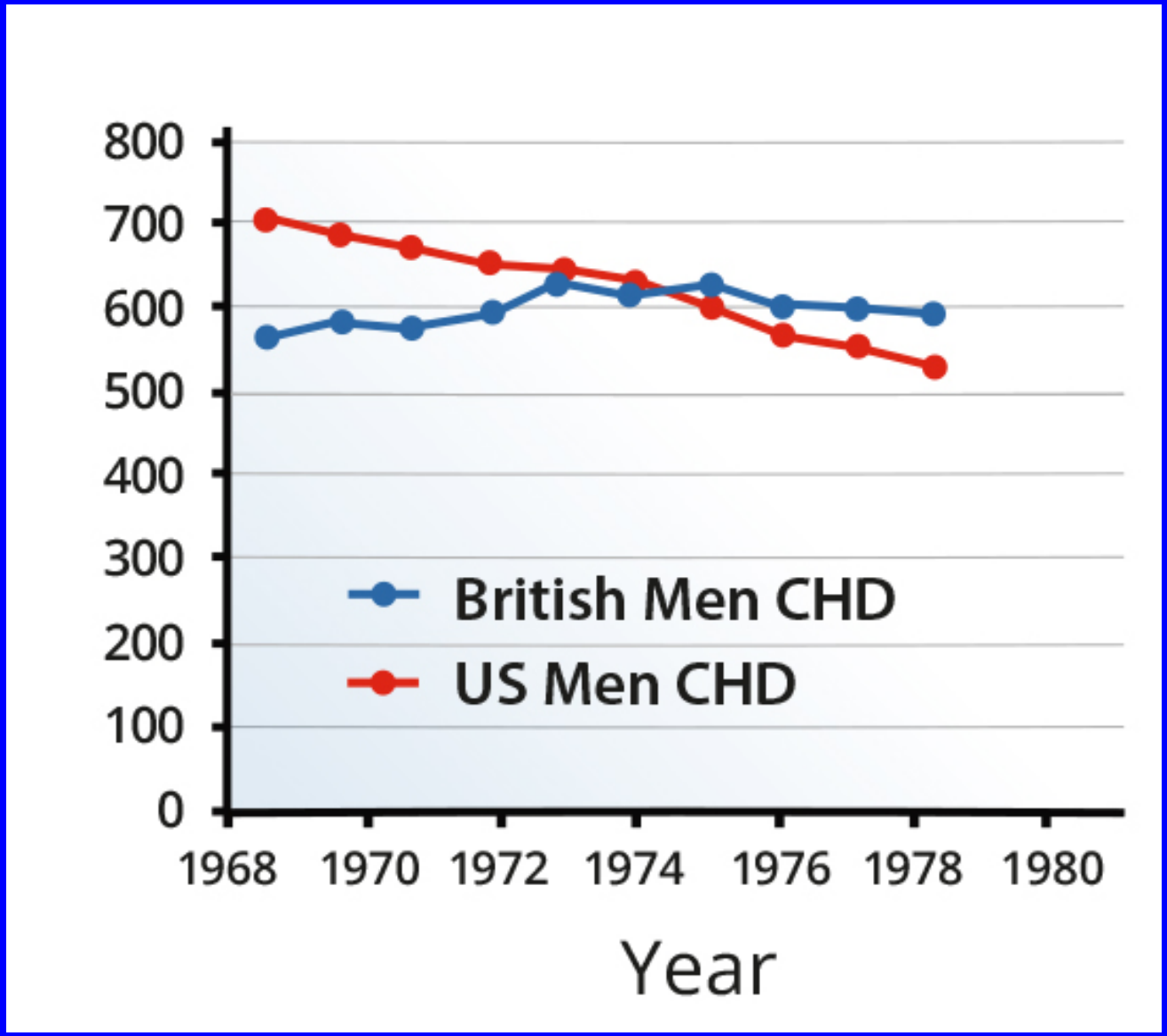
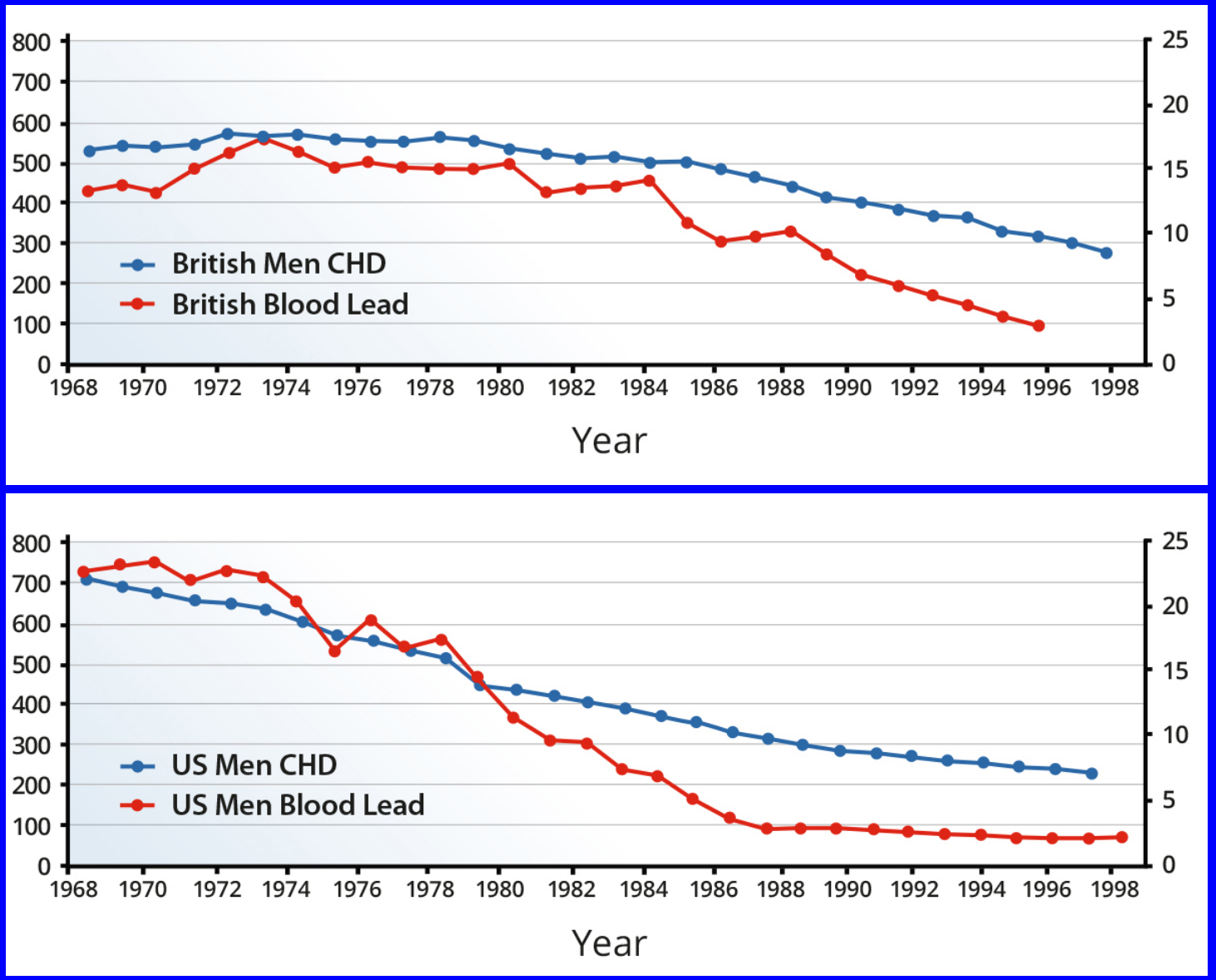
Age-Adjusted Death Rates in Britain and USA



Adapted from Rose G. BMJ 1981; 282: 1847-1851.

Age-Adjusted Death Rates and Blood Lead (μg/dL) in Britain and USA



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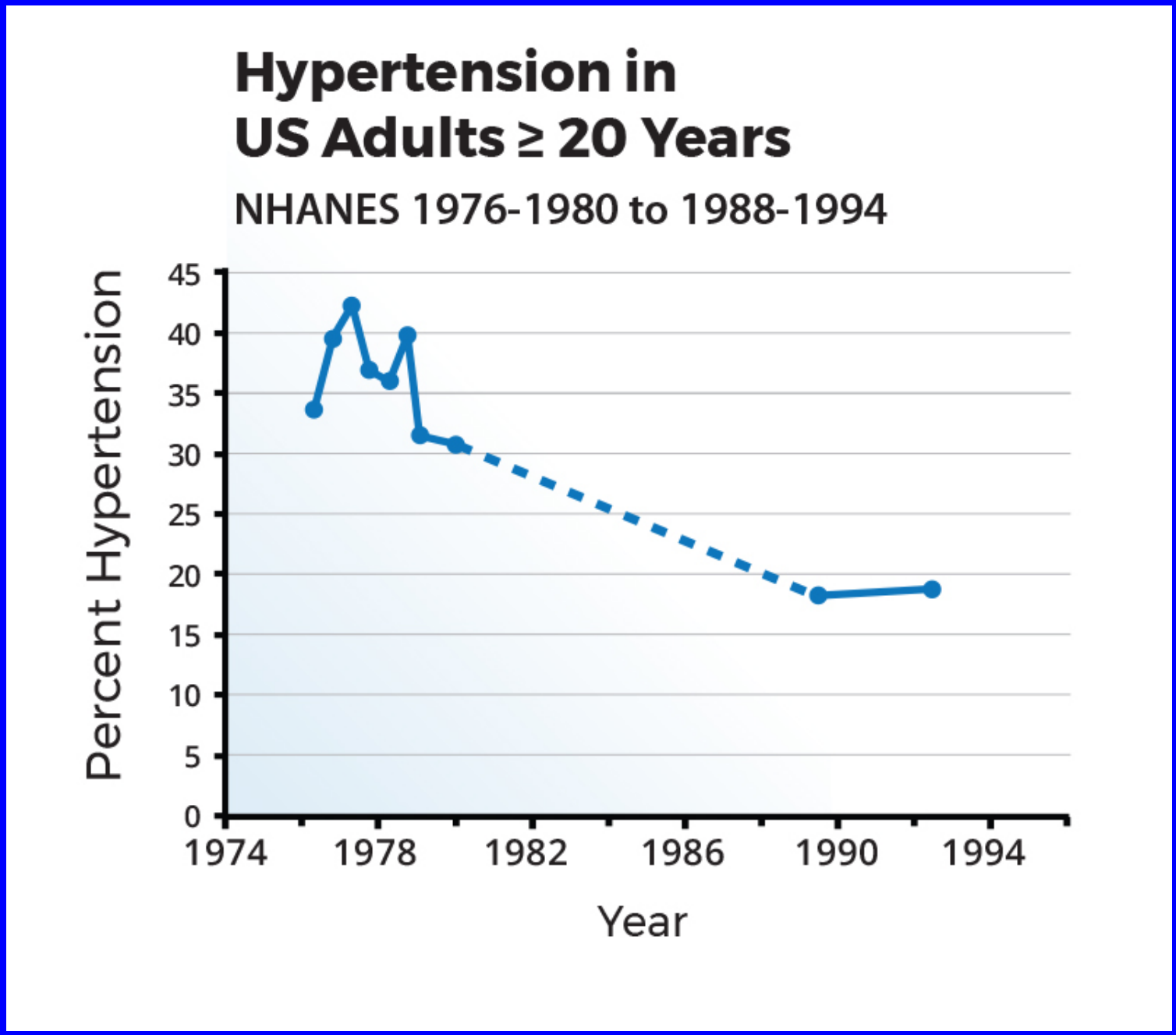

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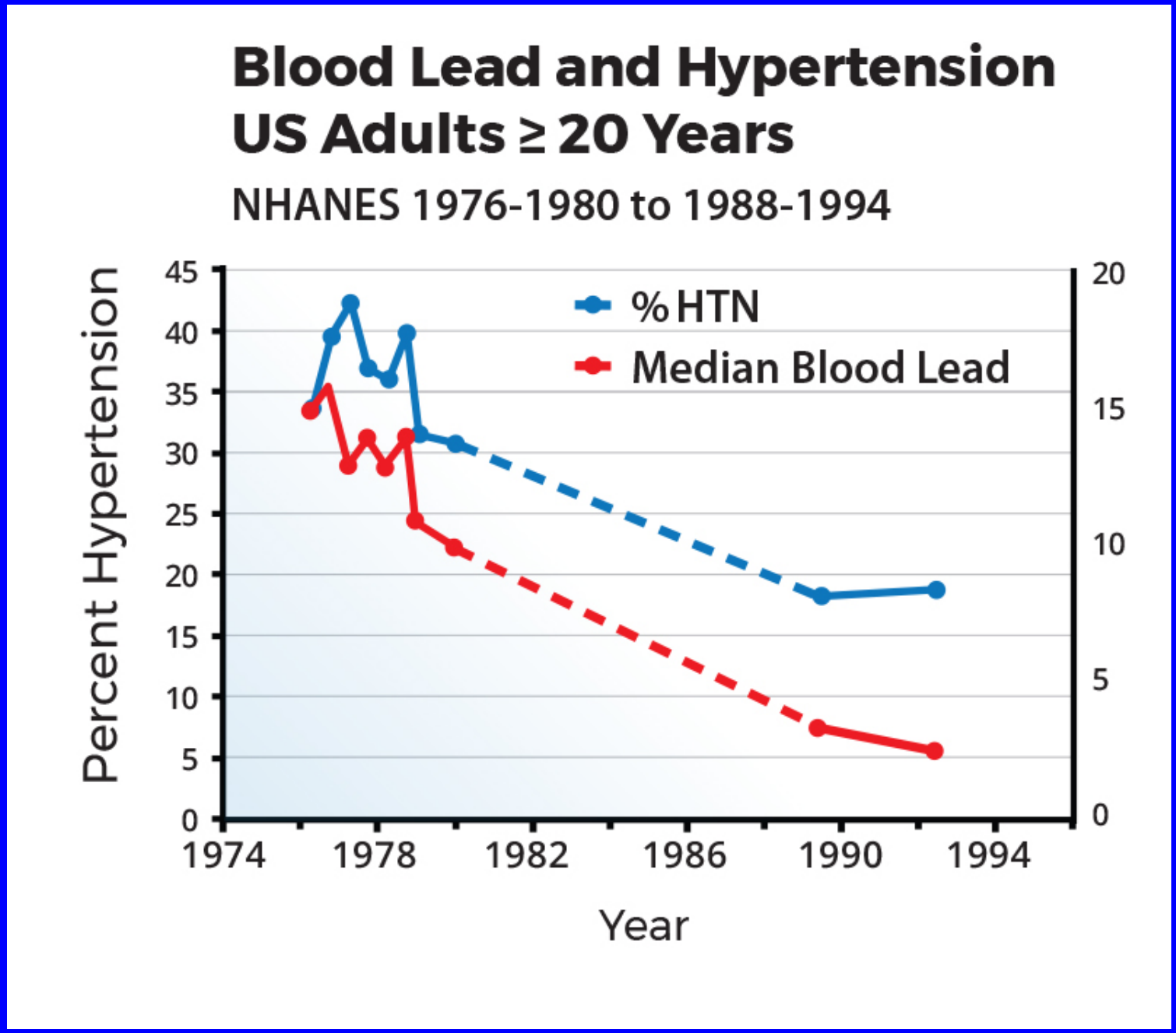

Lanphear B, et al. (unpublished data)

Discussion

- Low-level lead exposure results in 400,000 avoidable deaths annually in the United States; 250,000 from CVD
- Results are consistent with several large prospective studies, including prior analyses of the NHANES Mortality Follow-up Study through 2000 (Schober, 2006; Menke, 2006; Weisskopf, 2009; Kahlil, 2009; Aoki, 2016).
- Results are consistent with RCT of chelation therapy (Lamas, 2014) and an analysis of decline in CVD mortality in NHANES (18%) (Ruiz-Hernandez, 2017)

Key Limitations

- Reliance on baseline measures of exposure to predict mortality
- Unable to adjust for arsenic and $PM_{2.5}$ which are risk factors for CVD mortality
- May underestimate impact of lead exposure by relying on blood lead (Weisskopf, 2009)

Conclusions

- Low-level, environmental lead exposure is a leading, but largely ignored risk factor for CVD mortality in the United States
- Quantifying the contribution of lead is essential to understand trends in CVD mortality and develop comprehensive prevention strategies