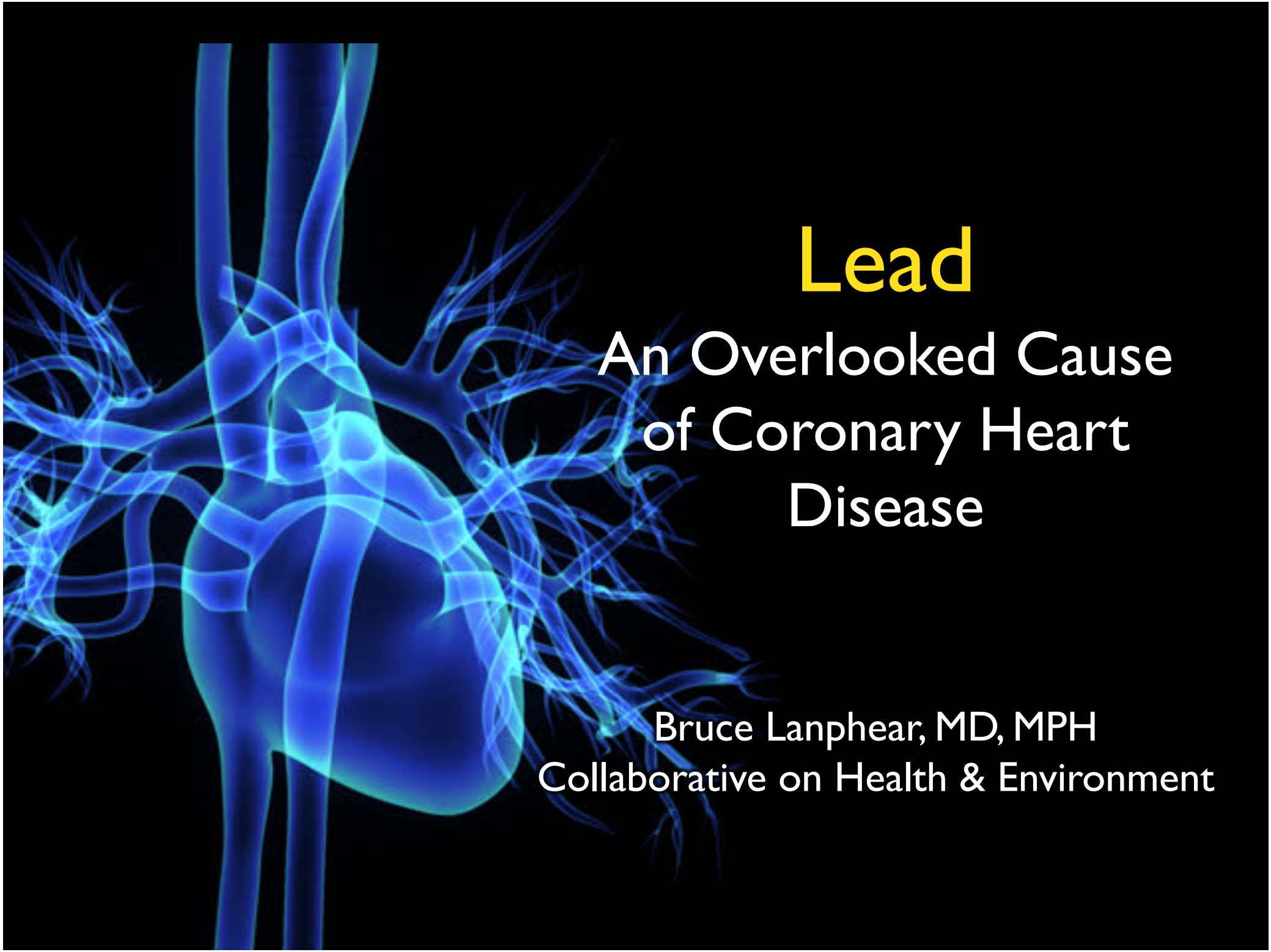


Lead

An Overlooked Cause of Coronary Heart Disease

Bruce Lanphear, MD, MPH
Collaborative on Health & Environment

Background

- CVD accounts for ~800,000 (one in three) deaths in the U.S. (Mozaffarian, 2016)
- Deaths from coronary heart disease (CHD) have declined by 70% in the US, but it is still the leading cause of death (Mozaffarian, 2016)
- Lead is an causal risk factor for HTN and coronary heart disease (NTP, 2012; EPA, 2013)

Lead and CVD

- Five of six prospective studies found a significant association of lead and CVD mortality (Moller, 1992; Lustberg 2002; Menke, 2006; Weisskopf, 2009; Kahlil, 2009; Aoki, 2016)
- In laboratory studies, lead enhances atherosclerosis by inactivating NO, inhibiting endothelial repair, impairing angiogenesis and promoting thrombosis (Vaziri, 2008)
- No studies have calculated the number of CVD deaths in the US attributable to lead using a national cohort
- Unknown if blood lead levels < 5 µg/dL, which are typical for U.S. adults, are associated with CVD 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)

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 using Daly substitution method (Daly, 1998)
- SUDAAN version 10.0.1 was used for all statistical analyses (Shah, 2005)

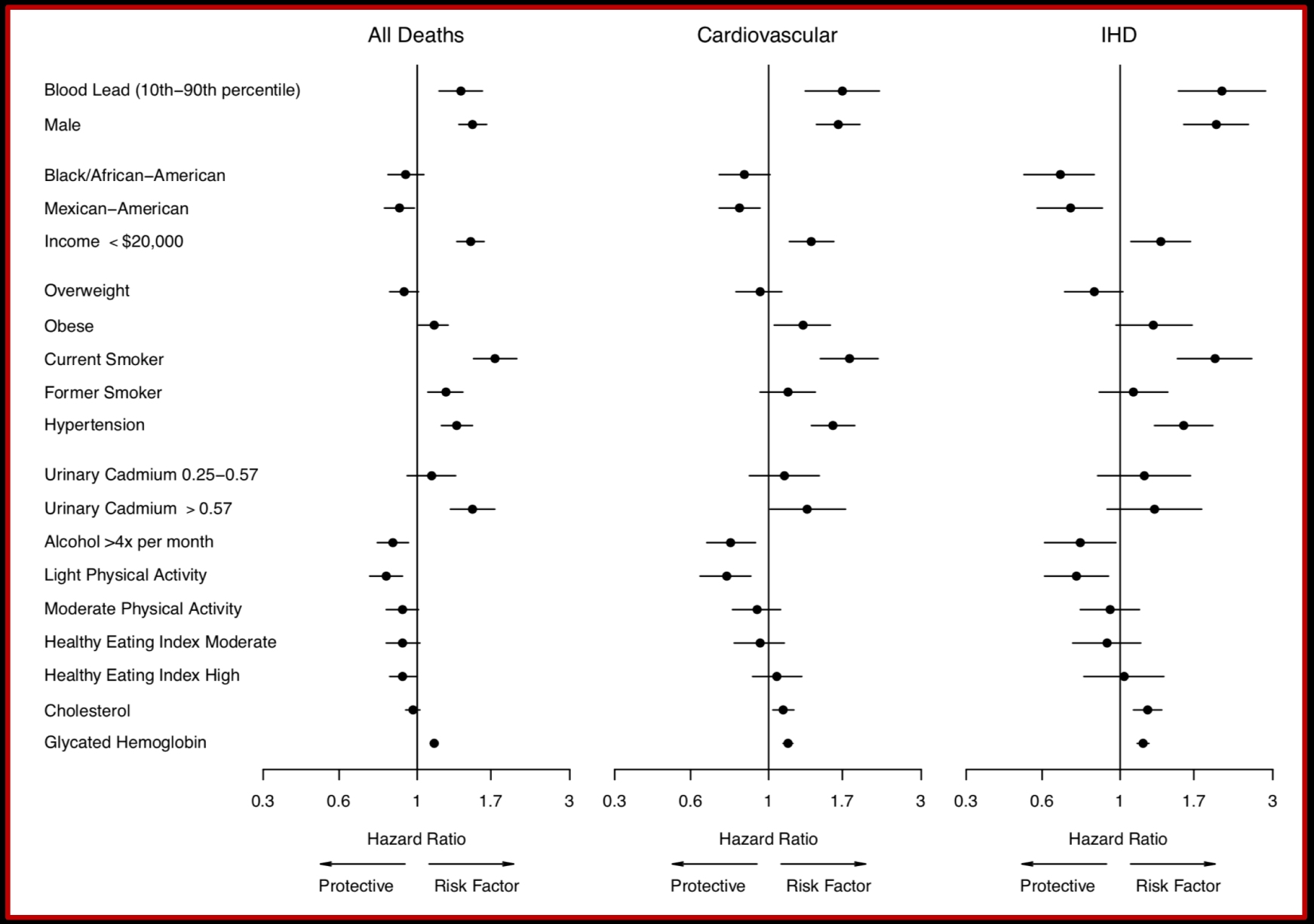
Results

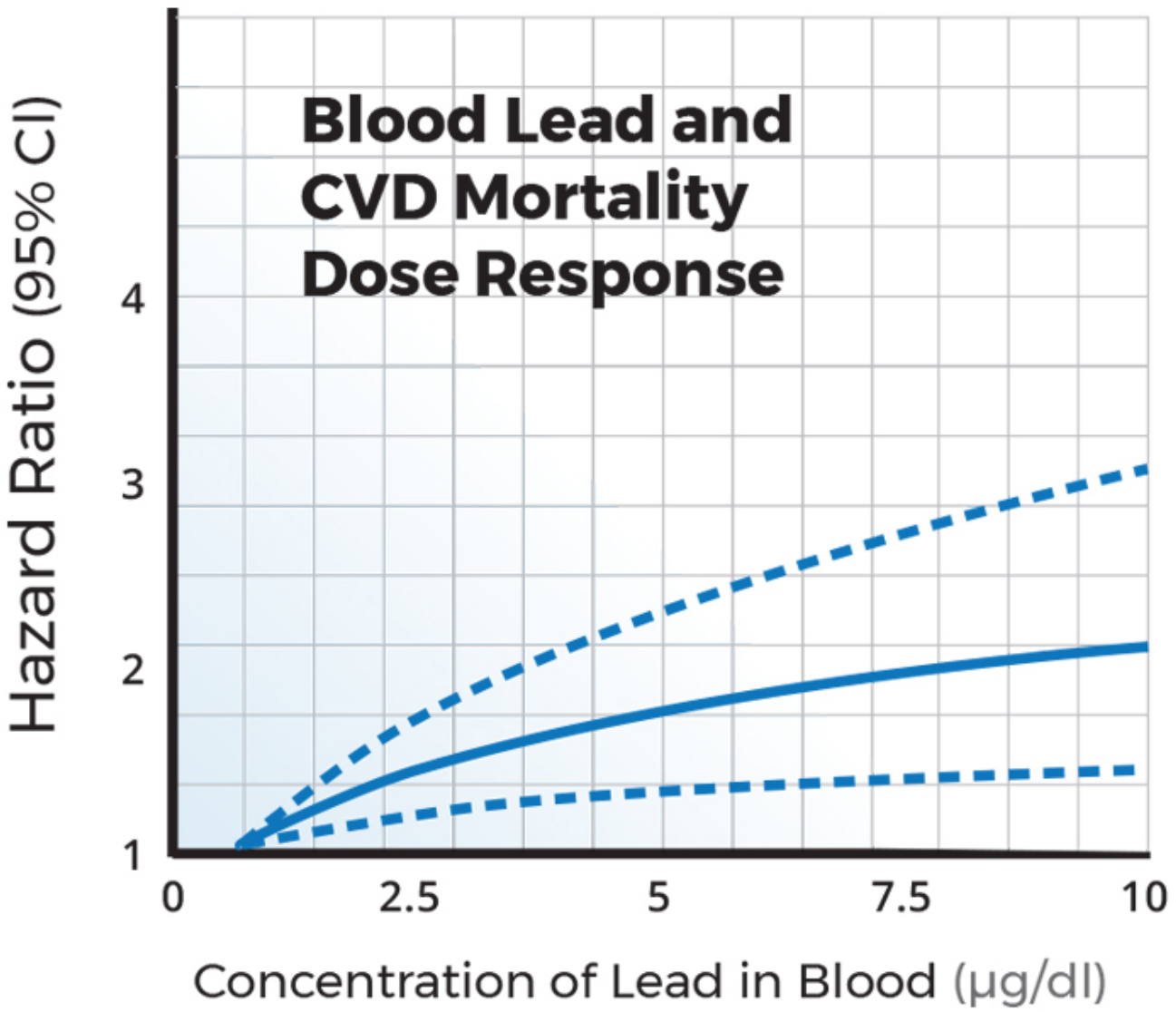
- 14,289 adults were followed for a median of 19.5 years; 4,422 participants died; 1,801 (38%) were due to CVD, 988 (22%) were due to IHD (CHD)

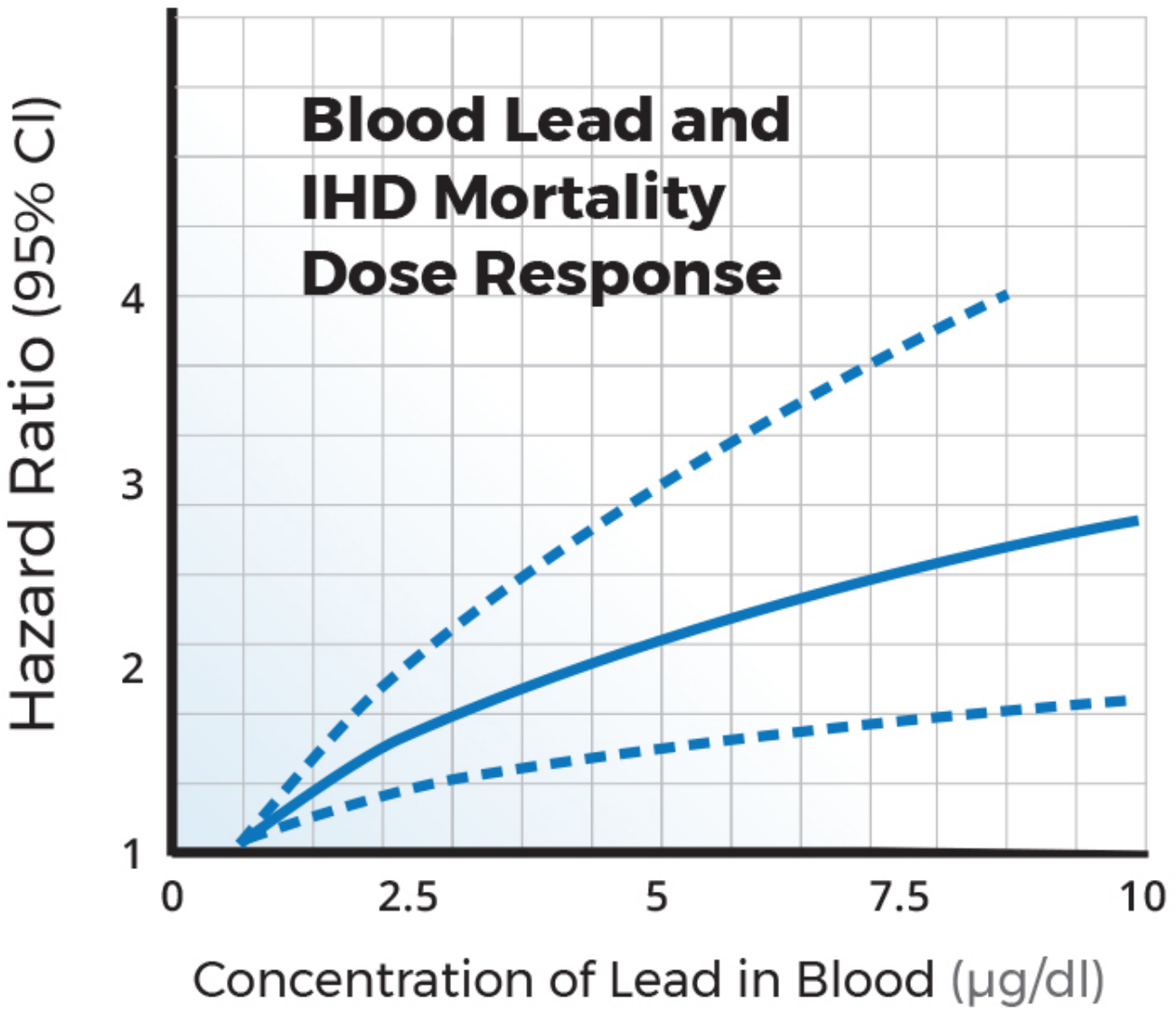
- The geometric mean blood lead of the participants was 2.71 μg/dL; 3,632 (20%) had a blood lead >5 μg/dL

- 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




Blood Lead and
CVD Mortality
Dose Response
Hazard Ratio (95% CI)
4
3
2
1
0
2.5
5
7.5
10
Concentration of Lead in Blood (µg/dl)


Blood Lead and
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4
3
2
1
0
2.5
5
7.5
10
Concentration of Lead in Blood (µg/dl)

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 > $20,000 per annum); race and ethnicity (White, Black, Mexican American); body mass index: normal (<25 kg/m^2), overweight (25-29.9 kg/m^2) or obese ($\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).

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

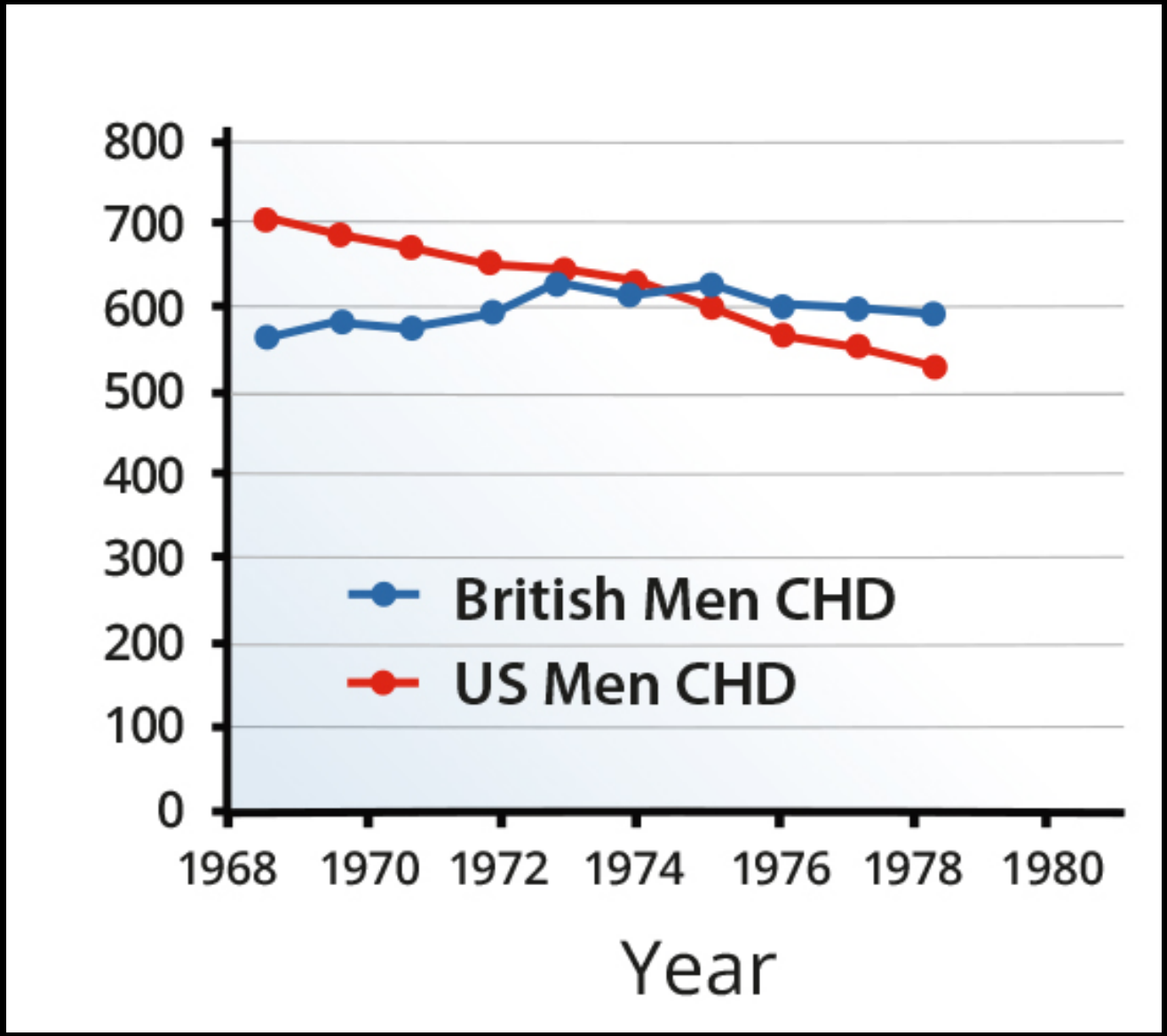
Hazard ratios for continuous blood lead represent risk for a 10th-90th percentile increase in log transformed blood lead. Adjusted for age (continuous and age-squared); sex; household income (< or > $20,000 per annum); race and ethnicity (White, Black, Mexican American); body mass index: normal (<25 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

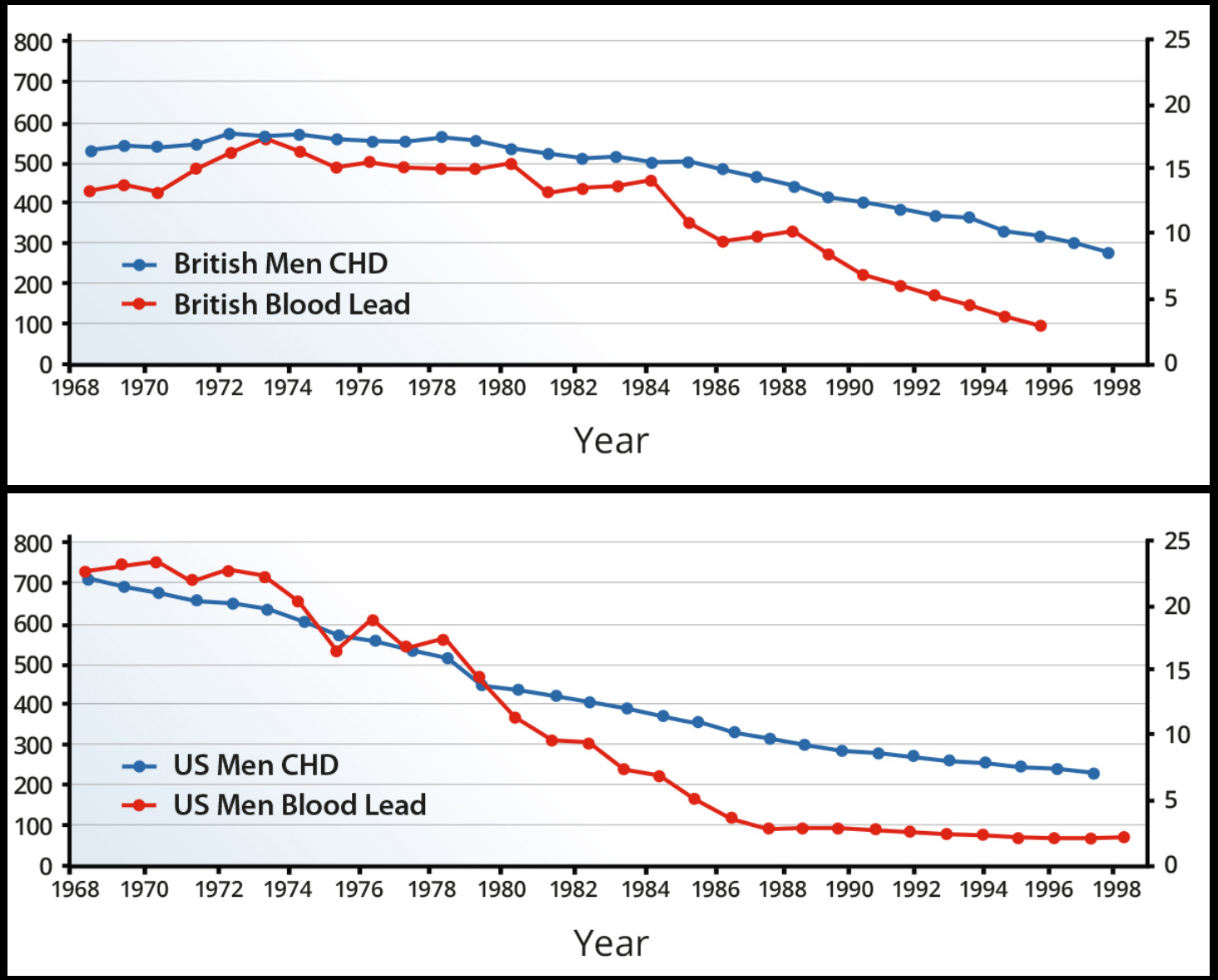
Hazard ratios for continuous blood lead represent risk for a 10th-90th percentile increase in log transformed blood lead. Adjusted for age (continuous and age-squared); sex; household income (< or > $20,000 per annum); race and ethnicity (White, Black, Mexican American); body mass index: normal (<25 kg/m^2), overweight (25-29.9 kg/m^2) or obese ($\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).

Age-Adjusted Death Rates in Britain and USA

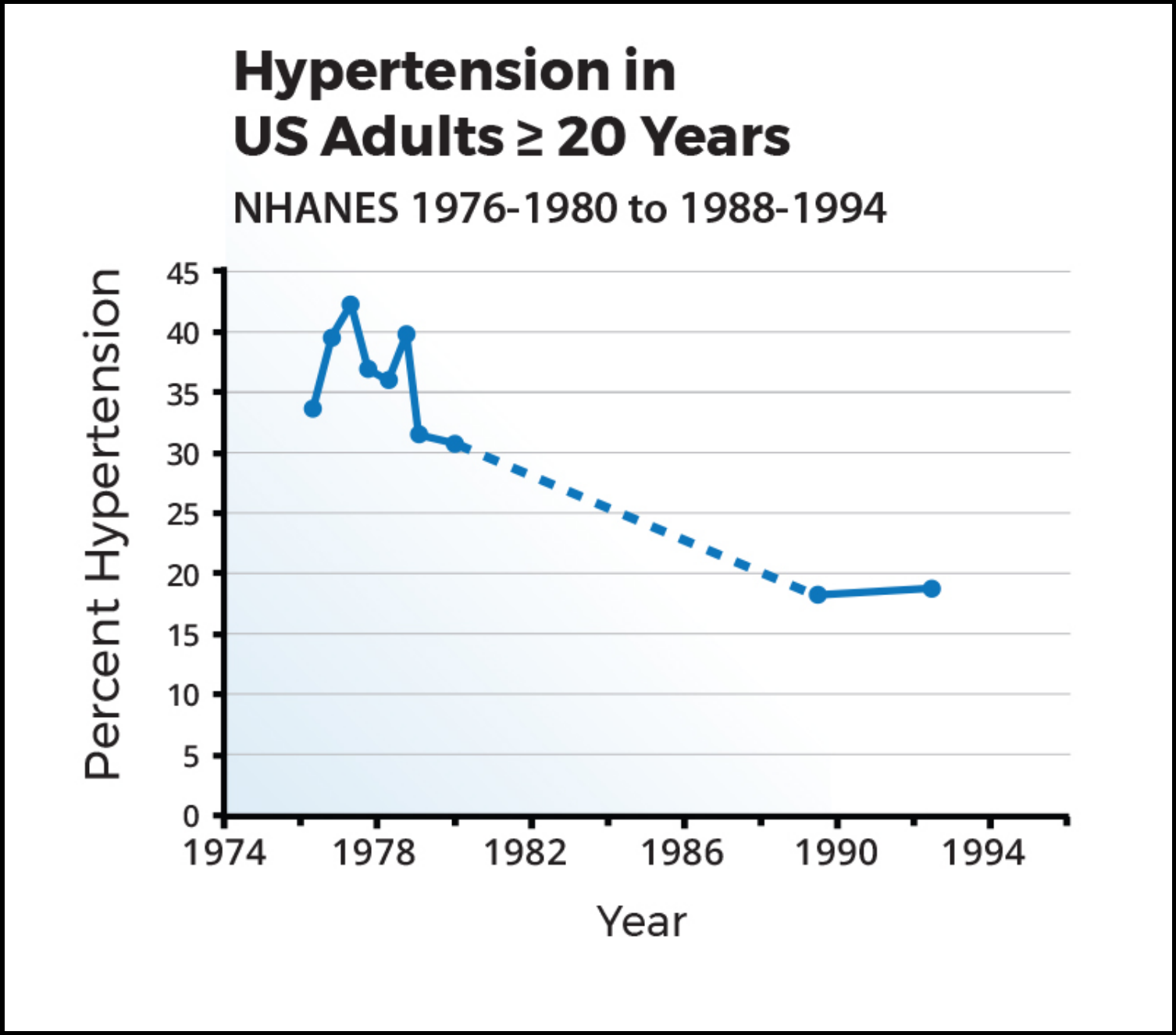


Adapted from Rose G. BMJ 1981; 282: 1847-1851.

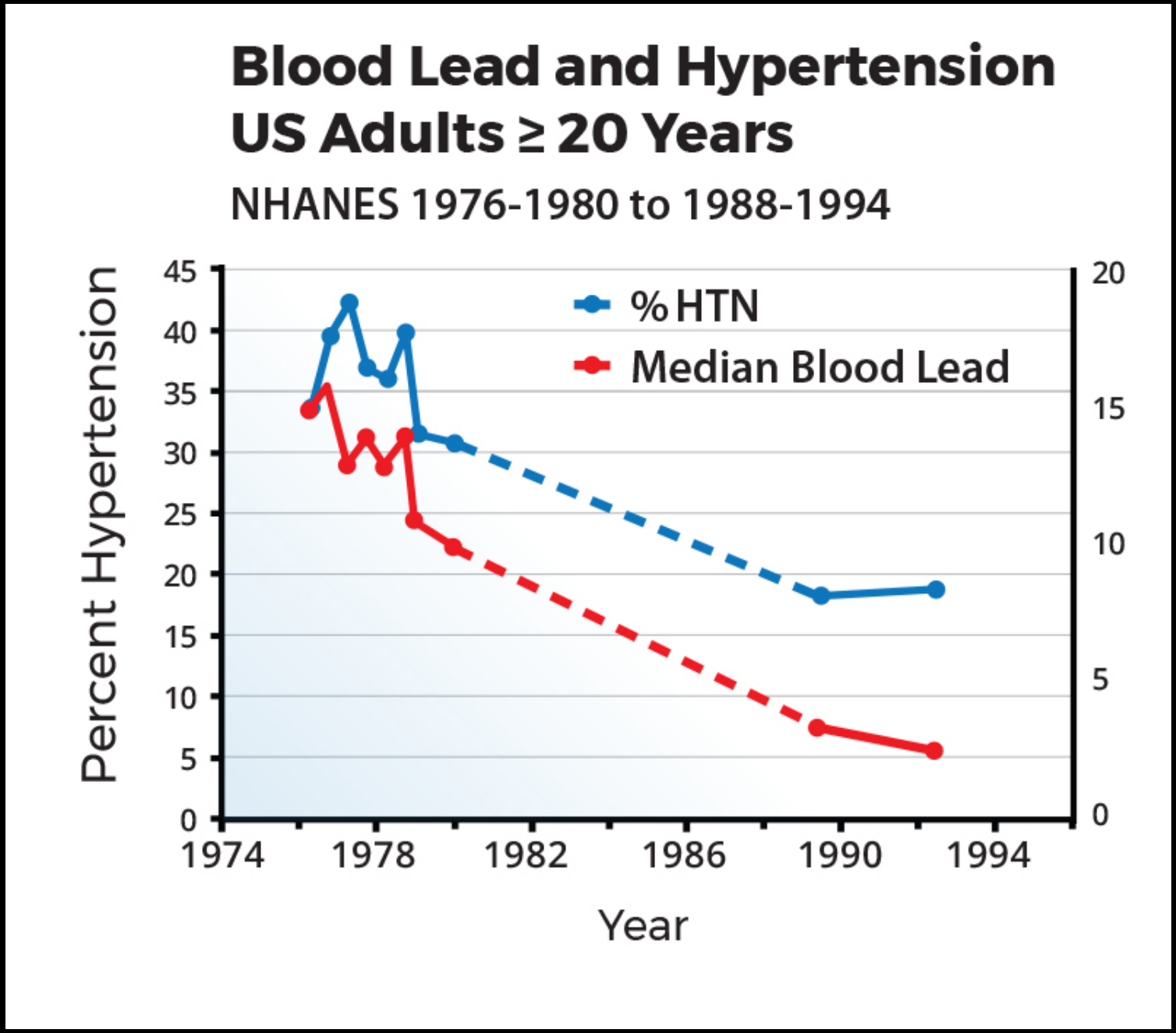
Age-Adjusted Death Rates and Blood Lead (μg/dL) in Britain and USA



Nevin R (unpublished data)



Lanphear B, et al. (unpublished data)



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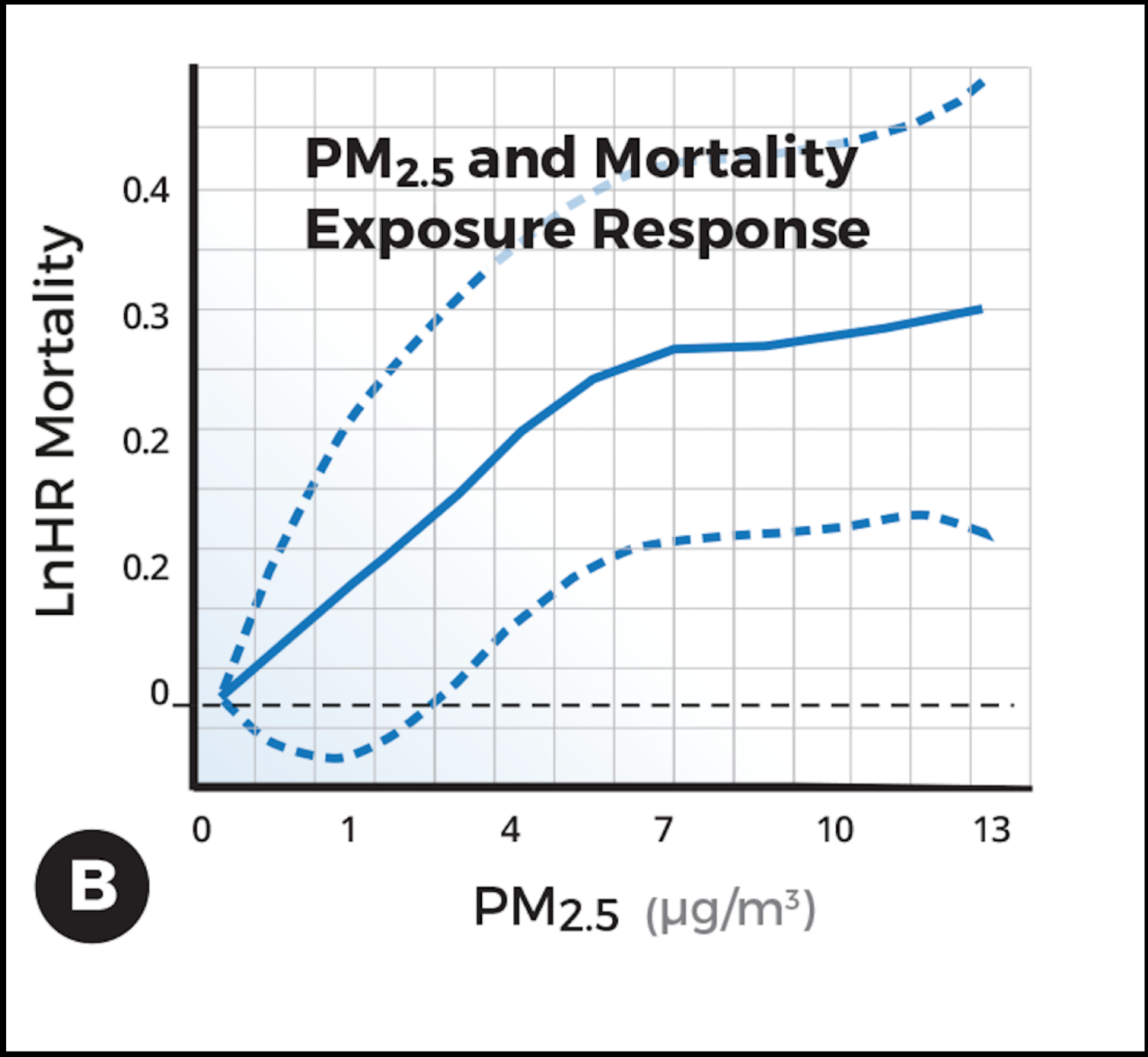
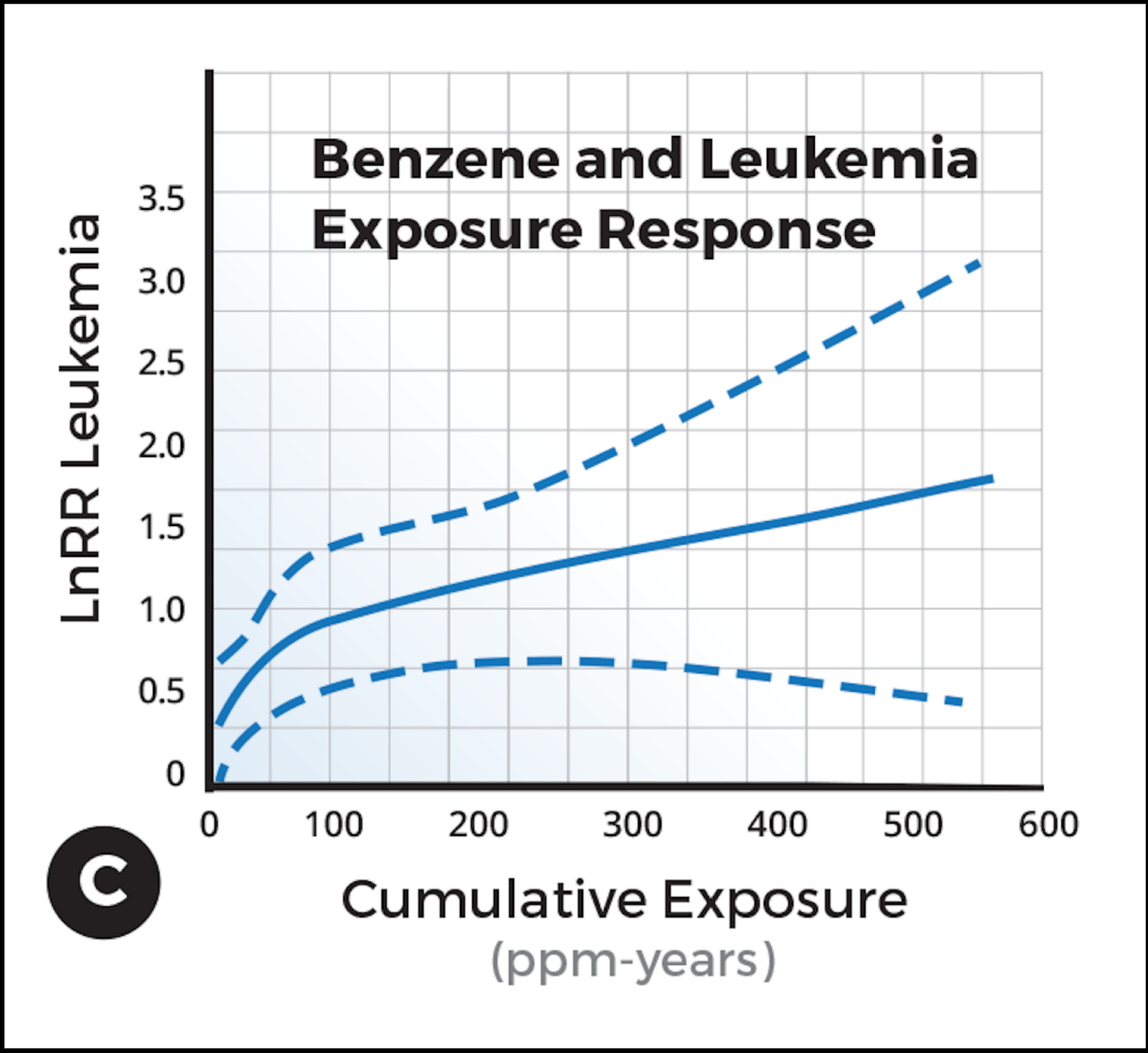


Pinault L, et al. Environ Health 2016 DOI: 10.1186/s12940-016-0111-6



Vlaanderen J, et al. Environ Health Perspect 2010;118:526-532.

Smoking Ban

Pell J, et al. NEJM 2008;359:482-491.

Smoking Ban

20% Reduction AMI

Pell J, et al. NEJM 2008;359:482-491.

Discussion

- Lead exposure results in 250,000 CVD deaths and 185,000 CHD deaths annually in U.S.
- Blood lead concentrations < 5 μg/dL, which are typical for U.S. adults, are associated with CVD mortality; there is no apparent threshold
- The decline in lead exposure, which is intertwined with air pollution, is linked with mysterious decline in coronary heart disease

Key Limitations

- Reliance on baseline measures - including one blood lead test - to predict mortality
- Unable to adjust for arsenic and $PM_{2.5}$ which are both 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 and develop prevention strategies
- Sufficient evidence to lower allowable blood lead concentrations for workers