Blood lead and other metal biomarkers as risk factors for cardiovascular disease mortality

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Outline

- NHANES Overview
- Blood lead-cardiovascular disease mortality study
  - Methods
  - Results & Discussion
  - Conclusions

NHANES

National Health and Nutrition Examination Survey

- Designed to assess health and nutritional status of non-institutionalized adults and children in the U.S.
- What about "exposure"?
  - Blood, urine, hair collected
  - Analyzed for various (potential) toxicants

NHANES data for Environmental Health

Three uses

1. Biomonitoring exposure
2. Tracking environmental disease
3. Investigating exposure-disease association

NHANES exposure-disease investigation: Designs

- Cross-sectional
  - NHANES data only
  - NHANES data with outside data
    - E.g., linkage through geocoding
- Longitudinal
  - NHANES with linked follow-up data
    - Mortality (National Death Index)
    - Medicaid/Medicare

Lead & cardiovascular diseases (CVD)

- Established association for morbidity
  - Hypertension
- Evidence for mortality relatively scarce
  - Previous NHANES III based studies*
    - Baseline survey more than 20 years ago

→ Update with newer data

- Additional considerations

* Schober SE *et. al.* (2006) Environ Health Perspect;114(10):1538-41.
Menke A *et. al.* (2006) Circulation;114(13):1388-94.

Methods

- Cohort design
  - Use NHANES 1999-2010 as baseline
  - Follow-up based on National Death Index thru 2011
- Main exposure variable: blood lead
- Outcome variable: CVD death
- Adjustment for: sex; race; education; smoking status
- Cox regression with age as survival time
  - Non-linearity modeled & testing using natural spline
  - Summary measure of association: relative risk (RR)
  - Proper weighting & variance estimation

(Continued)

Methods: New features

- Hematocrit-corrected blood lead as biomarker of lead exposure
- Adjustment for biomarker of exposure to non-lead metals

Hematocrit-corrected blood lead

- Lead in blood
  - Mostly (>95%) in red blood cells
  - Low concentration in plasma
- Erythrocyte lead*
  - Not affected by anemia induced by lead or other causes
  - Better than whole blood lead as exposure biomarker
- Erythrocyte lead ≈ (whole blood lead)/hematocrit
  → Rescale & call "**hematocrit-corrected blood lead**"

* deSilva PE. (1984) Ann Occup Hyg 1984;28(4):417-28.

Adjustment for biomarker of exposure to non-lead metals

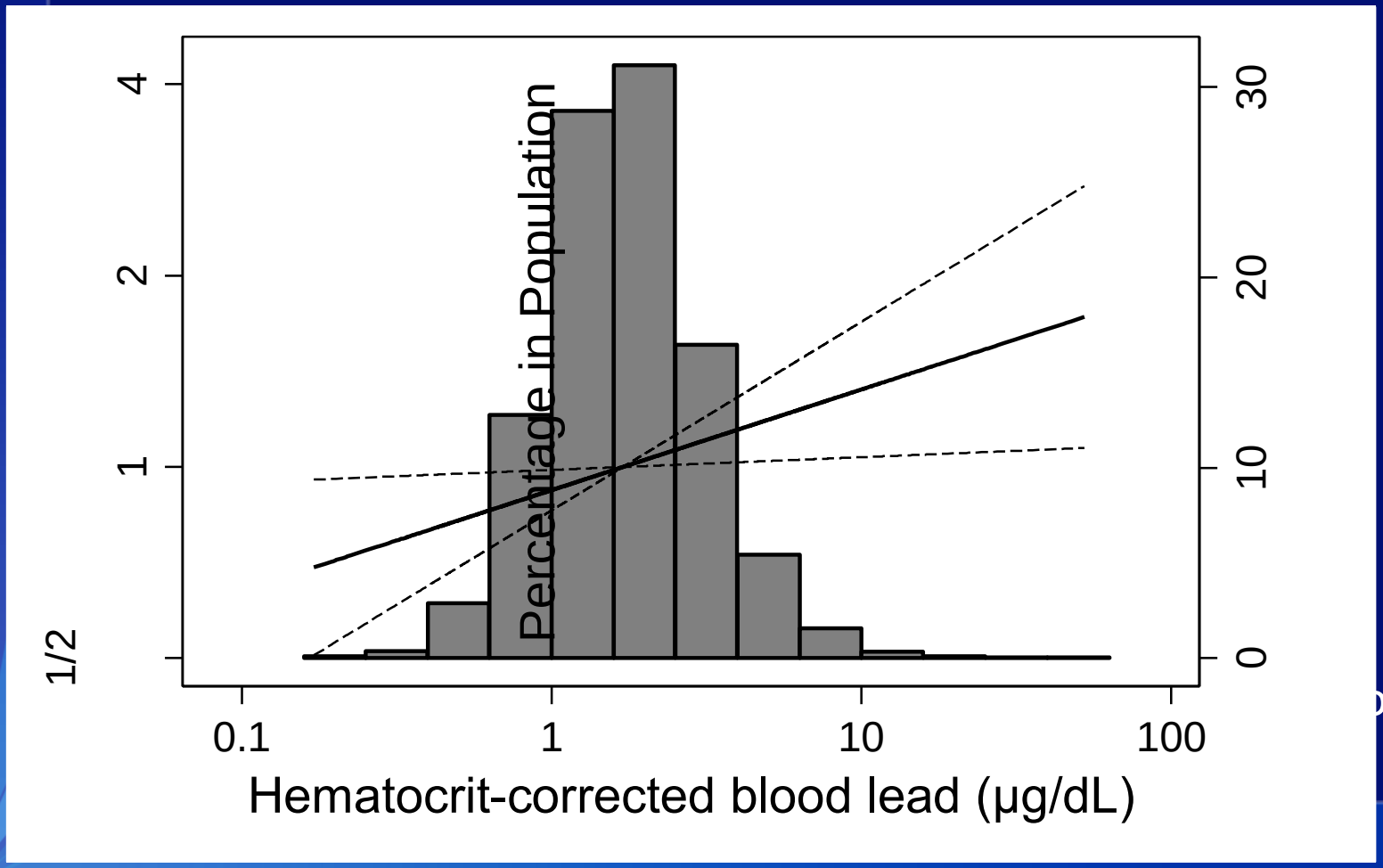
- Iron deficiency:
  - Known to increase blood lead;
  - Known to increase mortality
- Cadmium exposure:
  - Associated with higher blood lead (cigarette as common source);
  - Known to increase mortality

→ Adjusting for iron & cadmium biomarkers justified

- Also adjusted for serum calcium and serum C-reactive protein

RESULTS and DISCUSSION

Blood lead-CVD mortality association



od lead

Correct for hematocrit? Adjust for non-lead biomarkers?

	Adjusting for cadmium, iron, calcium, C-reactive protein	
	Yes	No
Correcting blood lead for hematocrit	RR = 1.44	Overestimated
Not correcting blood lead for hematocrit	Underestimated	Overestimated

- Important to:
  - Correct blood lead for hematocrit
  - Adjust for blood cadmium & serum iron

Why not *adjust* for hematocrit, instead?

	Adjusting for cadmium, iron, calcium, C-reactive protein	
	Yes	Term(s) in regression
Correcting blood lead for hematocrit	RR = 1.44	$\beta_c \frac{(whole\ blood\ lead)}{(hemacocrit)}$
Not correcting blood lead for hematocrit	Underestimated	$\beta_w(whole\ blood\ lead)$
Adjusting for hematocrit	Underestimated	$\beta_w(whole\ blood\ lead) + \beta_h(hematocrit)$

- Adjustment: add hematocrit as Cox regression covariate
  - Unsatisfactory

↓ Hematocrit in lead exposure → CVD death causal pathway

Conclusions

- Observed linear association between hematocrit-corrected blood lead and cardiovascular disease mortality with relative risk of 1.44 per 10-fold increase in blood lead.
- Correcting blood lead for hematocrit found to be preferable over:
  - No correction (use whole blood lead as biomarker of lead exposure);
  - Statistical adjustment for hematocrit.
- Adjusting for cadmium and iron biomarkers found to be important for removing confounding.

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The preliminary findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.