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

Yutaka Aoki, PhD, MS, MHS
Senior Service Fellow

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Acknowledgments

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- Debra J. Brody, NCHS
- Katherine M. Flegal, NCHS
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- Jennifer Parker, NCHS
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

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”

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
Blood lead-CVD mortality association

- RR = 1.44 (95% CI = 1.05, 1.98) per 10-fold increase in blood lead
- $p$ for non-linearity = 0.97

![Graph showing hematocrit-corrected blood lead (µg/dL) with percentage in population and relative risk.](image)
### Correct for hematocrit? Adjust for non-lead biomarkers?

<table>
<thead>
<tr>
<th>Correcting blood lead for hematocrit</th>
<th>Adjusting for cadmium, iron, calcium, C-reactive protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>RR = 1.44</td>
</tr>
<tr>
<td>No</td>
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</tr>
<tr>
<td>Not correcting blood lead for hematocrit</td>
<td>Underestimated</td>
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- **Important to:**
  - Correct blood lead for hematocrit
  - Adjust for blood cadmium & serum iron
Why not *adjust* for hematocrit, instead?

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- 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.
Acknowledgement

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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.