Research Needs

Resolving residual confounding through observational studies

It may be somewhat easier to identify study populations with BLLs <10 µg/dL in which socioeconomic factors are not associated with exposure as compared to populations with more widely varying blood lead levels within many low SES children, but few high SES children, may have blood lead levels above 20 or 30 µg/dL. Configuring a cohort similar to the one in Boston or assembling one from the pieces of others already studied could be helpful in isolating socioeconomic and lead effects from one another. Another formal statistical approach that could be applied to pooled data across multiple studies is the application of a hierarchical modeling approach as proposed by Schwartz et al. (2003, in press).

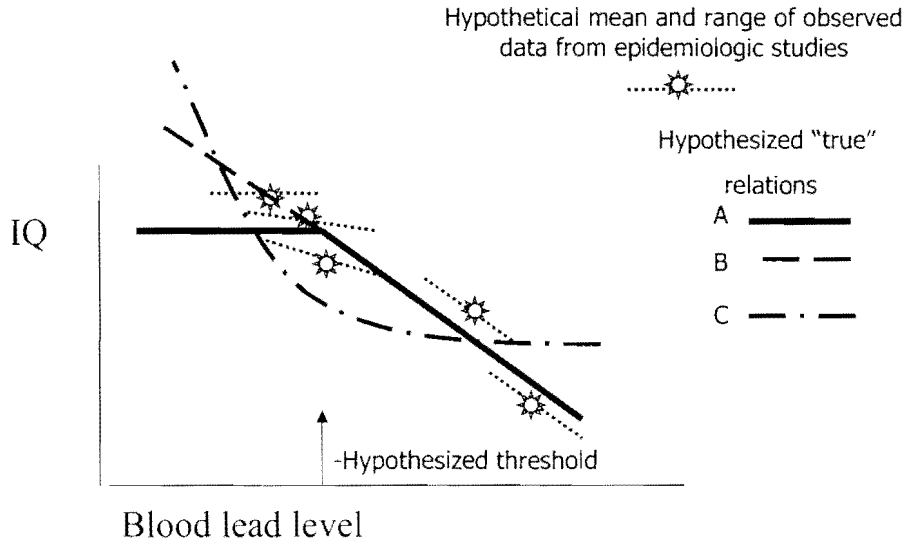
Controlled intervention trials

While experimental designs can establish causation with greater confidence than observational studies, intentionally exposing some children to higher BLLs in a randomized controlled design would be unethical. However, randomized trials in which interventions are tested for their ability to reduce BLLs <10 µg/dL or prevent their increase provide an opportunity to support or refute a causal relationship between BLLs <10 µg/dL and adverse health outcomes. Studies testing such interventions should measure covariates relevant to assessing health effects, allowing a test of the causal hypothesis should they be successful at sufficiently reducing BLLs.

Animal and in vitro studies to explore mechanisms and dose-response relations

While the overall evidence from animal or in vitro models supports the biologic plausibility of adverse effects of lead at BLLs <10 µg/dL, the WG is unaware of directly relevant animal or in vitro studies that demonstrate a steeper slope for adverse effects of lead exposure at lower BLLs than observed at higher levels. Demonstrating such a relationship in experimental studies and identifying possible mechanisms would increase confidence in a causal interpretation of the observed blood lead-response relationship in studies such as Canfield et al. (2003).

Figure 1. Expected variation in regression slopes given hypothetical "true" threshold blood lead - IQ relation (A).



Notes: Figures 2 and 3

Selected estimates of change in outcome (Full Scale IQ or McCarthy General Cognitive Index (GCI) derived from regression coefficients and listed in Table 2 and the corresponding mean BLLs of the study population are displayed in Figures 2 and 3. Figure 2 contains results from studies where the BLLs were measured at ages $\leq$2 years, and outcome measures were measured at ages $\geq$4 years. Figure 3 contains the results when both the BLLs and outcome measures were measured at ages $\geq$4 years. Both the crude (open dot) and adjusted (solid dot) coefficients are displayed in the figures when both are available. (The Kosovo and European Multicenter Study papers did not provide the crude coefficient). Although multiple models for a single study population may have been fit to results from differing ages within the defined age categories, only the regression coefficients for the highest age at which blood lead was measured (per study population) are included in the figures. (The highest outcome measure age was used as a tiebreaker when necessary.) Also, when models for both a concurrent blood lead measure and a lifetime average blood lead measure existed for the highest age at which blood lead was measured (Port Pirie and Rochester), the concurrent results were included. For the study that provided multiple models for the same highest-age blood lead versus outcome measure (Lavrion, Greece), the results from the model that included the most covariates were included. Any studies not providing both a regression coefficient and blood lead mean were excluded. Three-letter abbreviations for each study population, defined in the legends below, were used on the plots.

Legend for Figure 2

Abbreviation	Study population	Reference number	Blood lead and outcome ages
Bos	Boston, Massachusetts	7	24 months / 10 years
Cin	Cincinnati, Ohio	13	15-24 months / 6.5 years
Kos	Kosovo, Serbia	37	24 months / 4 years
Por	Port Pirie, Australia	23	24 months / 4 years
Roc	Rochester, New York	11	6-24 months / 5 years

Legend for Figure 3

Abbreviation	Study population	Reference number	Blood lead and outcome ages
Bos	Boston, Massachusetts	7	10 years / 10 years
Cin	Cincinnati, Ohio	13	51-60 months / 6.5 years
Eur	European Multicenter Study	39	6-11 years / 6-11 years
Kar	Karachi, Pakistan	28	6-8 years / 6-8 years
Kos	Kosovo, Serbia	37	48 months / 4 years
Lav	Lavrion, Greece	20	primary school / primary school
Por	Port Pirie, Australia	35	11-13 years / 11-13 years
Roc	Rochester, New York	11	5 years / 5 years

Figure 2. Cognitive Function Regression Coefficients for Blood Lead Age ≤2 years and Outcome Age ≥4 years.

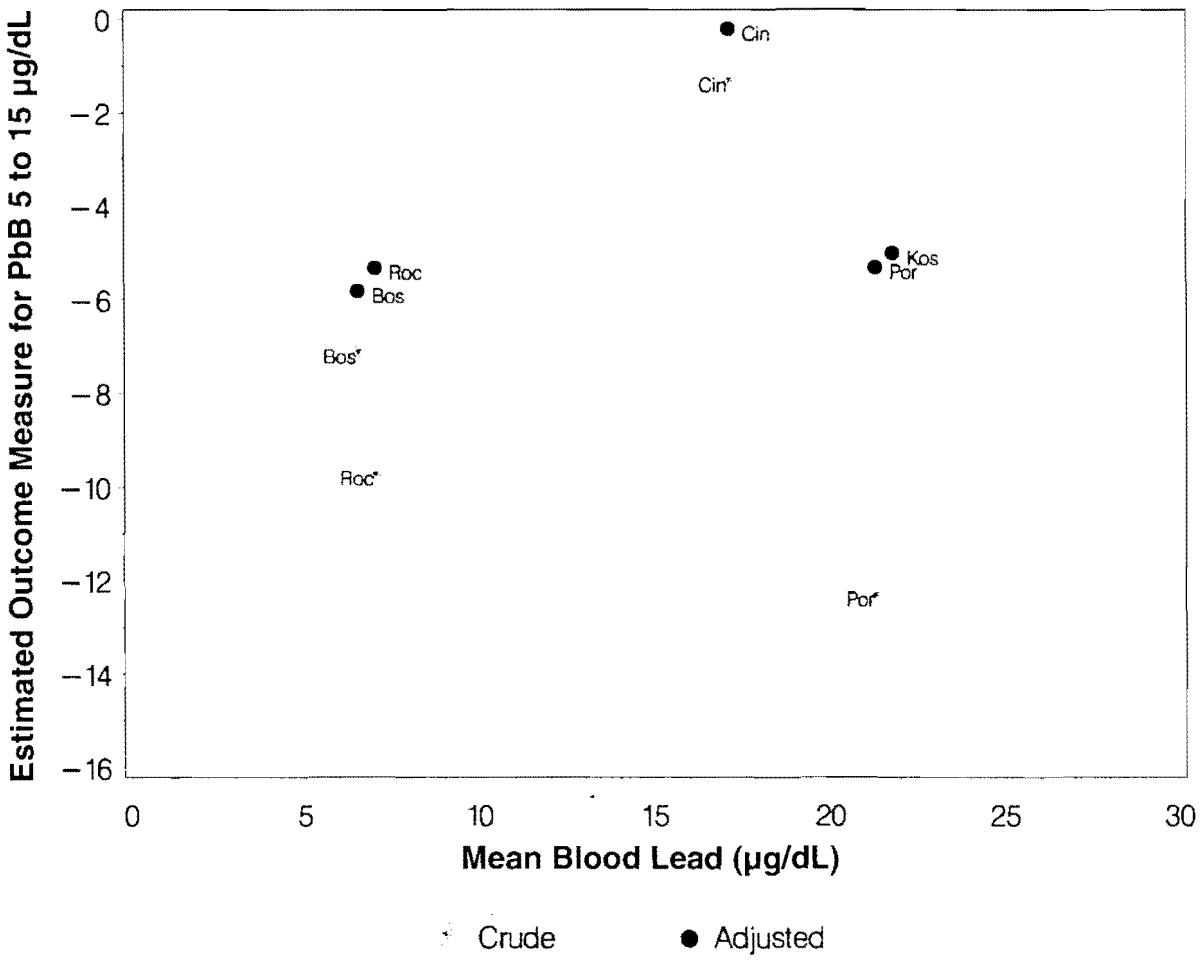


Figure 3. Cognitive Function Regression Coefficients for Blood Lead Age ≥4 years and Outcome Age ≥4 years.

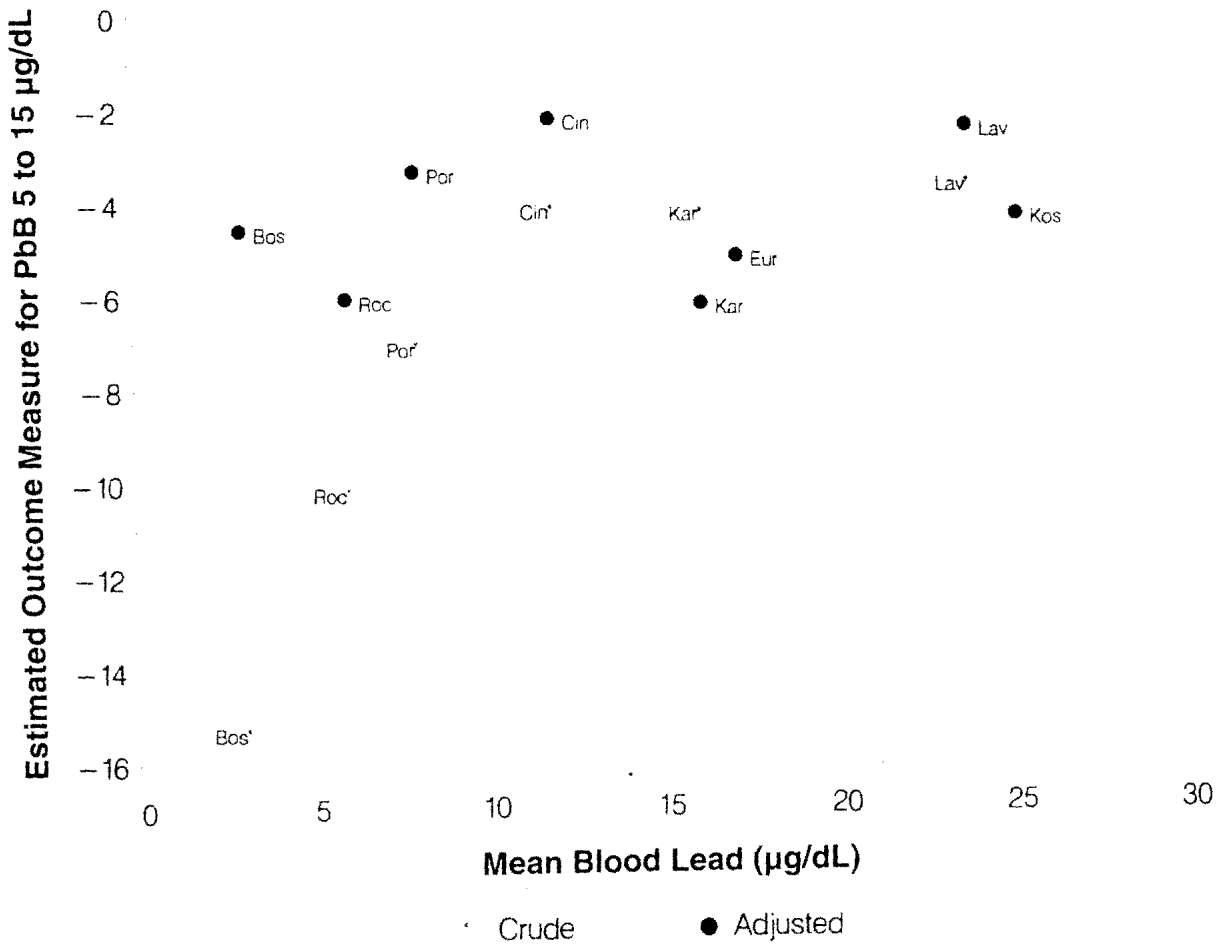
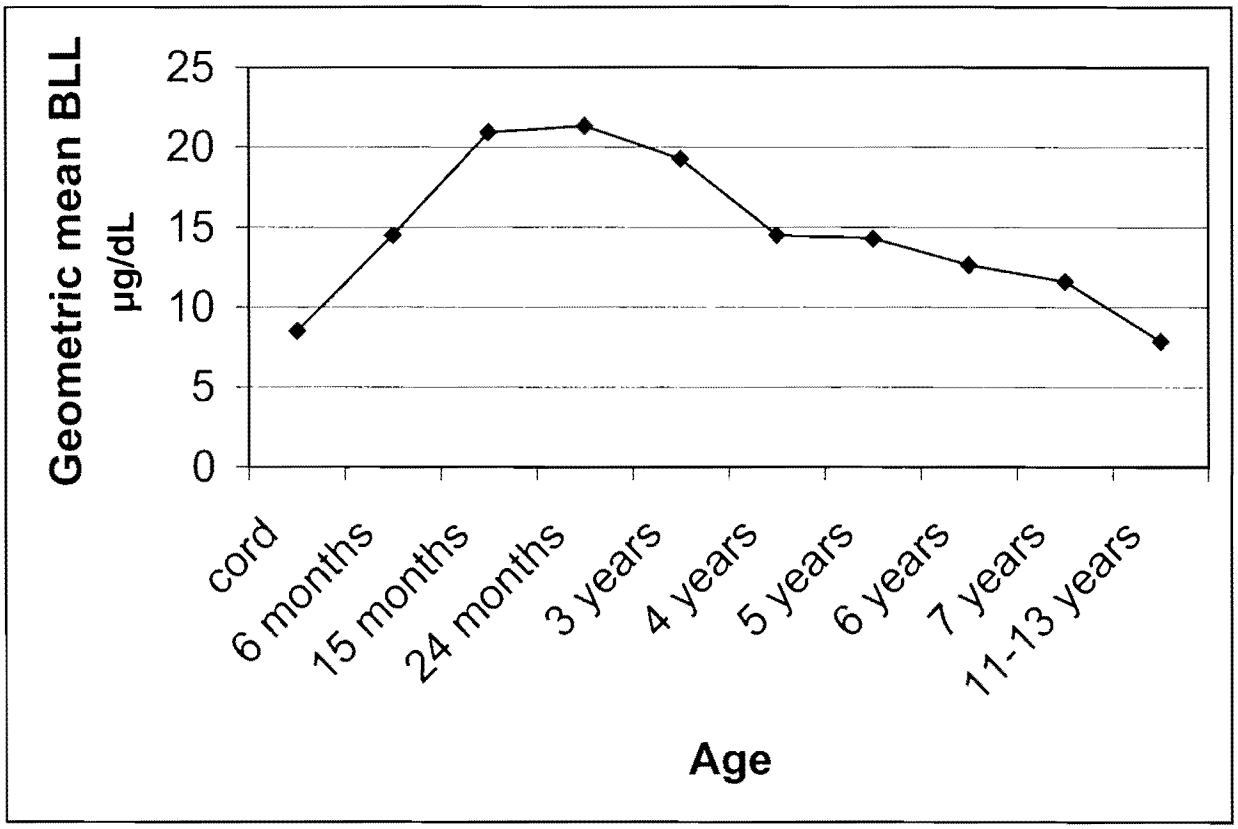


Figure 4. Age trend in blood lead levels (BLLs).



Source: Tong et al. 1996.

Figure 5. Hypothetical observed association between blood lead and IQ.

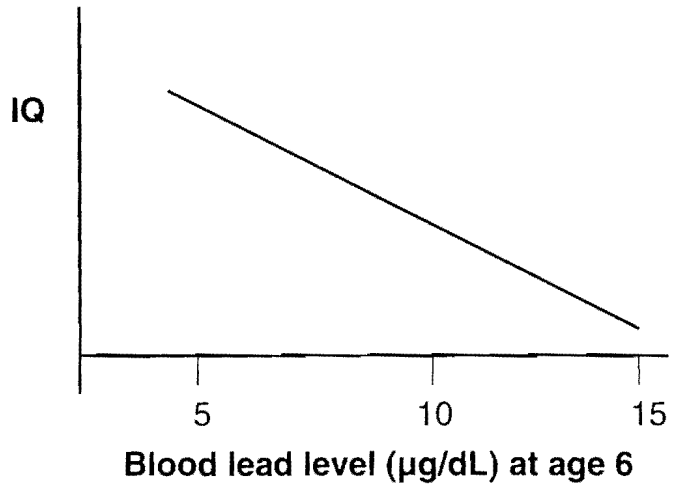


Figure 6. Hypothetical "true" association between blood lead and IQ.

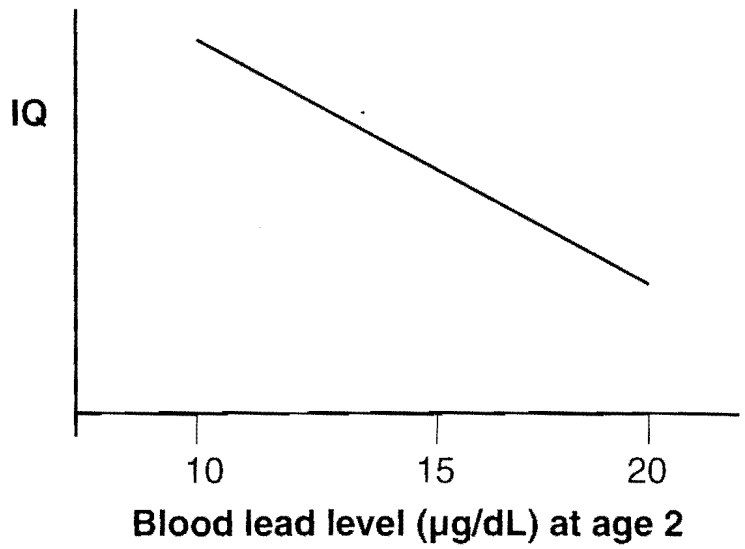
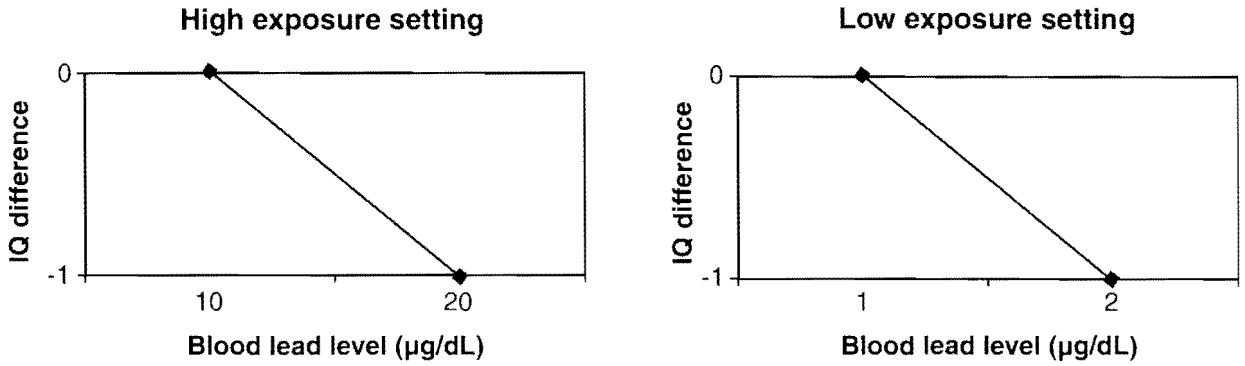



Figure 7. Hypothetical slopes of the relationship between blood lead and IQ associated with residual confounding (see Overall Conclusions).