



Mediation Analysis of Race and Environmental Exposures on Telomere Length

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Overview

Background: Despite racial disparities in diseases of aging and premature mortality, Black individuals in the US tend to have longer leukocyte telomere length (LTL), a biomarker of cellular aging, than White individuals. Previous findings suggest that exposure to certain persistent organic pollutants (POPs) is both racially-patterned and associated with longer LTL.

Study Aim: We examine whether Black/White differences in LTL are explained by differences in exposure to 15 POPs by estimating the indirect effect of self-reported race on LTL that is mediated through nine polychlorinated biphenyls (PCBs), three furans, and three dioxins and their mixtures.

Methods: We characterized single-pollutant mediation effects by constructing survey-weighted mediation models and consider multivariate mediation methods to account for the highly collinear nature of environmental mixtures.

Results: We found support for the hypothesis that exposure to PCBs partially mediates Black/White differences in LTL.

Background

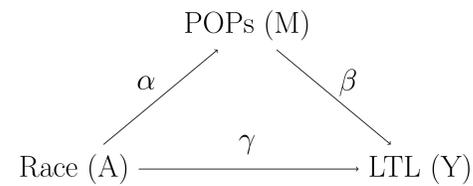
- Black individuals have longer average telomeres than White individuals (Needham et al. 2019).
- Research using nationally representative data from the National Health and Nutrition Examination Survey (NHANES) has shown that exposure to polychlorinated biphenyls (PCBs) is associated with longer LTL (Mitro et al. 2016; Patel et al. 2017; Gibson et al. 2019).
- Exposure to POPs is racially patterned, with Black individuals having higher exposures than White individuals (Pavuk et al. 2014; Xue et al. 2014).
- We hypothesize that Black individuals have longer LTL than White individuals due to greater exposure to carcinogens resulting from residential segregation (Mohai et al. 2009; Taylor 2014).

Methods: Study Population

Data Source: NHANES (1999-2000 and 2001-2002 cycles)

- Study population consisted of 1,251 adults (321 Black and 930 White)
- Outcome Variable: Telomere length relative to standard reference DNA (Y) and blood composition measured from stored DNA and whole-blood samples
- Exposure Variable: Self-reported race/ethnicity (A)
- Mediator Variables: PCB, furan, and dioxin serum concentrations (M)
- Covariates: Standardized age (linear and quadratic terms), sex, education, blood cell count and distribution variables, serum cotinine (log-scale) and lipids (log-scale)
- Due to potential batch effects across survey years, we controlled for the survey cycle (1999-2000 vs. 2001-2002) in all models

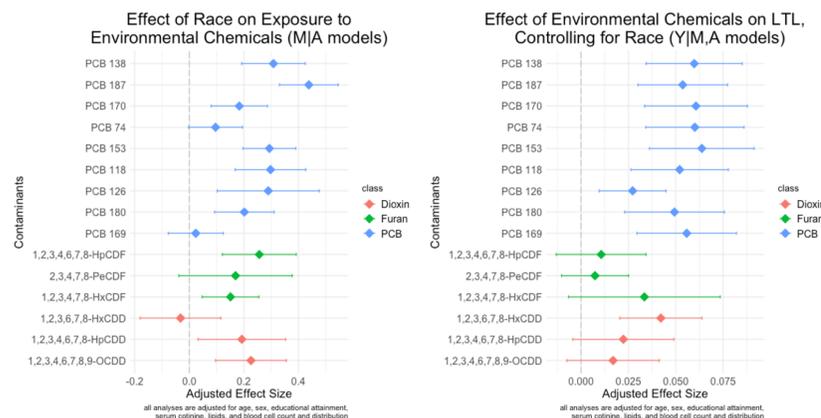
Methods: Mediation Analysis



$$\text{Total Effect} = \text{Direct Effect} + \text{Indirect Effect} = \gamma + \alpha\beta$$

- POPs with > 50% below their respective detection limits were excluded. Non-detects for the remaining POPs were multiply imputed using censored likelihood multiple imputation on the log-scale (Boss et al. 2019).
- LTL and all POPs were log-transformed for all analyses.
- Single-pollutant mediation effects were estimated from survey-weighted mediation models, to account for NHANES's stratified cluster sampling design.
- Inference for single-pollutant mediation effects was corrected for multiple testing.
- POPs were highly correlated with each other, which necessitated the utilization of multivariate mediation methods.
- Methods to characterize a global mediation effect attributable to POP mixtures:
 - (1) Unpenalized multivariate mediation regression model (OLS)
 - (2) Ridge penalized multivariate mediation regression model (Ridge)
 - (3) Exposure score with first principal component (PCA)
 - (4) Exposure score with Toxic Equivalency Quotients (TEQ)

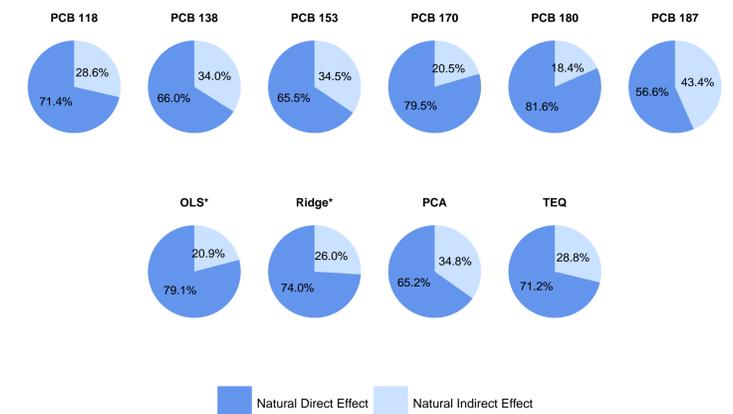
Results: Single-pollutant Mediation Models



- Total effect of race on LTL: On average, Black adults had a 0.054 higher log(T/S ratio) compared with White adults adjusted for the covariates outlined in methods section (95% CI: 0.009, 0.099).
- Black adults had higher average PCB, dioxin, and furan exposure.
- Higher PCB exposure was associated with longer LTL.

Results: Percent Mediated

Significant Indirect Effects (First Row Single-pollutant, Second Row Multivariate)



*OLS and Ridge methods do not have a clear way to determine survey adjusted standard errors and thus do not have a notion of significance.

Discussion and Conclusion

- Similar results across the methods support that PCB exposure may play a mediating role in Black/White differences in LTL. Apparent differences across methods appear to result from how variance inflation is handled and suggest that least squares-based approaches should be used with caution when high degrees of collinearity are present among candidate mediators.
- Conducted on nationally representative data, meaning that results are generalizable to US Black and White adults. Incorporating the survey design elements, when possible, is important for valid statistical inference when using nationally representative data.
- Differences in exposure to POPs help explain why Black Americans have longer LTL than their White counterparts, challenging genetic explanations for counterintuitive race differences in cellular aging.
- Future research may explore how race differences in LTL help explain race differences in cancer mortality.

Funding and References

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Funding: NIH U24 AG066528-01 (PI: Dr. Stacy Drury)