Authors' reply

Wen-Yi Yang and colleagues were troubled that our results[1] contrast with expert opinion and concluded that hypertension is unlikely to explain the current association between concentrations of lead in blood and mortality. They also argued that, because the underlying mechanism of lead is unknown, it precludes preventive strategies and targeted allocation of resources to reduce cardiovascular disease risk.

Lead is a causal risk factor for hypertension and coronary (ischaemic) heart disease.[2] Indeed, the reduction in leaded gasoline might be key to understanding the mysterious decline in deaths from coronary heart disease that began 50 years ago.[3] Moreover, there was a precipitous but poorly understood decline in hypertension that was accompanied by a substantial drop in blood lead concentrations following the phase-out of leaded gasoline.[4] Hypertension peaked at 36% in US adults from 1976 to 1980 and then declined to 20% by 1988 to 1994, a decline that persisted after adjustment for age, sex, cuff size, body-mass index (BMI), treatment, and smoking.[4] The decline in the prevalence of hypertension was coincident with a greater than 80% reduction in median blood lead concentrations among adults, from 13 µg/dL (0·628 µmol/L) in 1976–80, to 3 µg/dL (0·145 µmol/L) in 1988–91 (figure).[5]

We should not be surprised that concentrations of lead in blood contribute less to hypertension and cardiovascular disease mortality today. The effect of risk factors, such as lead, should diminish once strategies to reduce exposures are implemented. Importantly, lead was removed from gasoline, paint, and other sources before the underlying mechanisms of lead were fully explicated; it is desirable, but not essential, to know the mechanisms before taking action.

As we reported in our Article,[1] we did not find any evidence for effect modification of the relation between concentration of lead in blood with race and ethnicity. Moreover, the design-based statistical methods in NHANES control for clustering of confounders at the primary sampling unit level. Finally, we cited and described numerous lines of evidence linking lead exposure with cardiovascular disease: laboratory studies implicating lead in the development of hypertension and atherosclerosis; prospective cohort studies; a natural history study showing an 18% decline in cardiovascular disease mortality from declining blood lead concentrations; and a reduction in cardiovascular events following chelation therapy. Most epidemics of chronic disease result from the cumulative impact of multiple risk factors, and a comprehensive prevention strategy should address all of them.

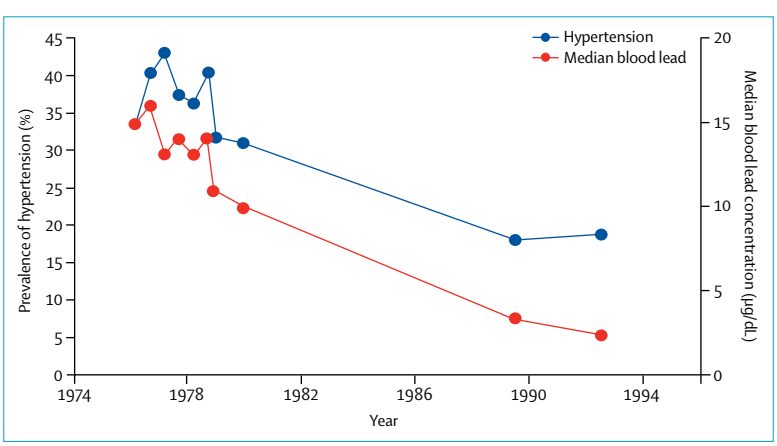

***Figure*: Decline in hypertension and concentrations of lead in blood among US adults, NHANES 1976–80 to NHANES 1988–94**

The prevalence of hypertension, defined as having a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg, among US adults older than 20 years during the phase-out of leaded gasoline was plotted with median blood lead concentration, NHANES II (1976–80) and NHANES III (1988–94). To convert values for lead from µg/dL to µmol/L, multiply by 0·0483.

We declare no competing interests. BPL serves as an expert witness in plaintiff cases of childhood lead poisoning in Milwaukee and Flint, MI, USA, but he receives no personal compensation.

Bruce Perrin Lanphear, Richard W Hornung, Peggy Auinger, Ryan Allen

blanphear@sfu.ca

Faculty of Health Sciences, Simon Fraser University, Vancouver, BC, Canada (BPL, RA); Cincinnati Children's Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati, OH, USA (RWH); and University of Rochester School of Medicine and Dentistry, Rochester, NY, USA (PA)

1 Lanphear BP, Rauch S, Auinger P, Allen RW, Hornung RW. Low-level lead exposure and mortality in US adults: a population-based cohort study. *Lancet Public Health* 2018; **3:** e177–84.

2 EPA. 2013 Final report: integrated science assessment for lead. US Environmental Protection Agency, Washington, DC, EPA/600/R-10/075F. June, 2013. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=518908 (accessed June 21, 2018).

3 Mensah GA, Wei GS, Sorlie PD, et al. Decline in cardiovascular mortality. Possible causes and implications. *Circ Res* 2017; **120:** 366–80.

4 Burt VL, Cutler JA, Higgins M, et al. Trends in the prevalence, treatment and control of hypertension in the adult US population. *Hypertension* 1995; **26:** 60–69.

5 Pirkle JL, Brody DJ, Gunter EW, et al. The decline in blood lead levels in the United States: the National Health and Nutrition Examination Surveys. *JAMA* 1994; **272:** 284–91.