International Lead Association

SPHERL – Key Findings from the 8-Year Longitudinal Workplace Epidemiology Study

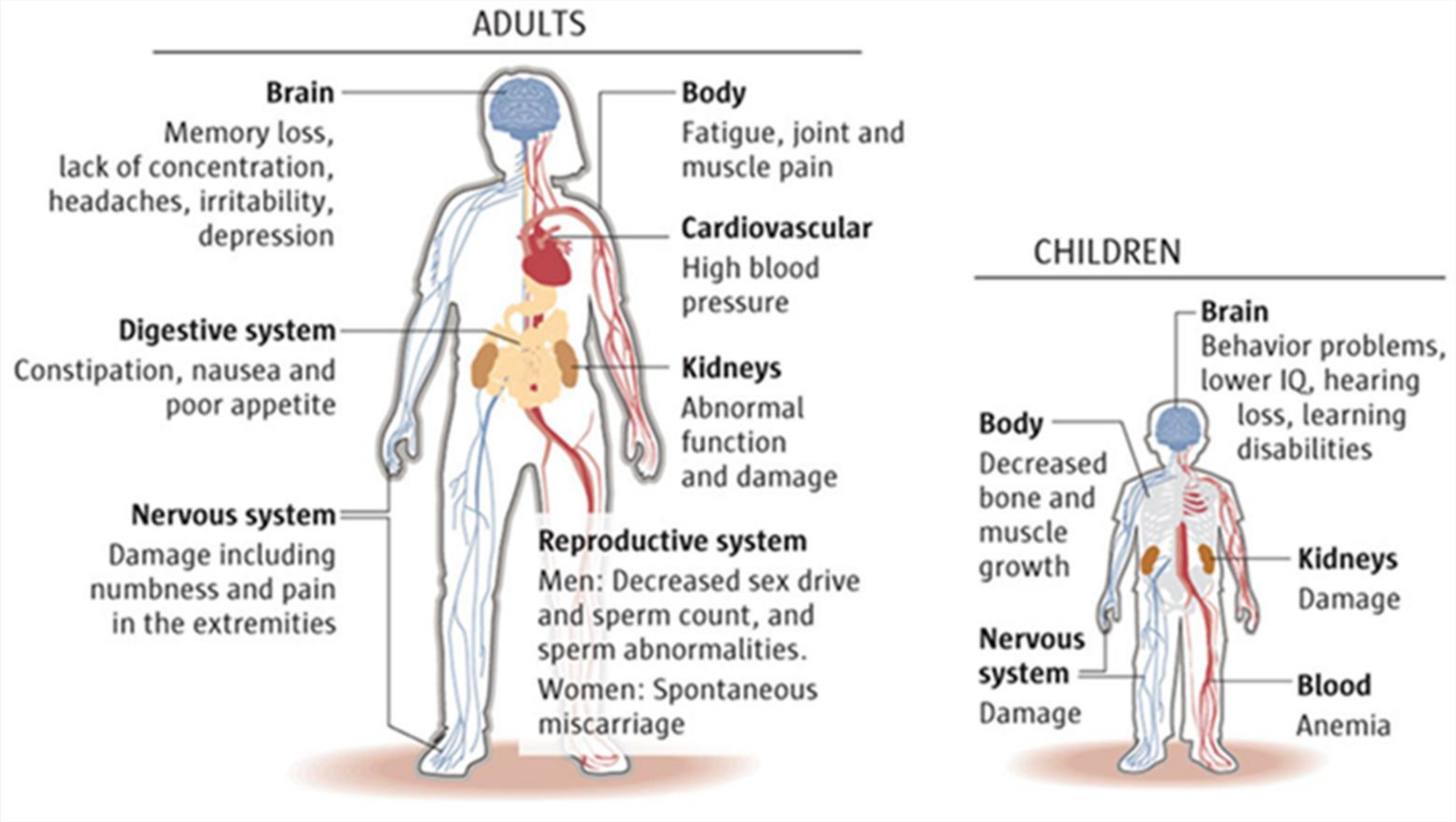
Lead Workplace Exposure Management Workshop
25 June 2025

AGENDA

- Study purpose and objectives
- Health endpoints
- Study results
- Publications
- Use in regulatory defense
- Using the SPHERL cohort for follow-on study and regulatory defense

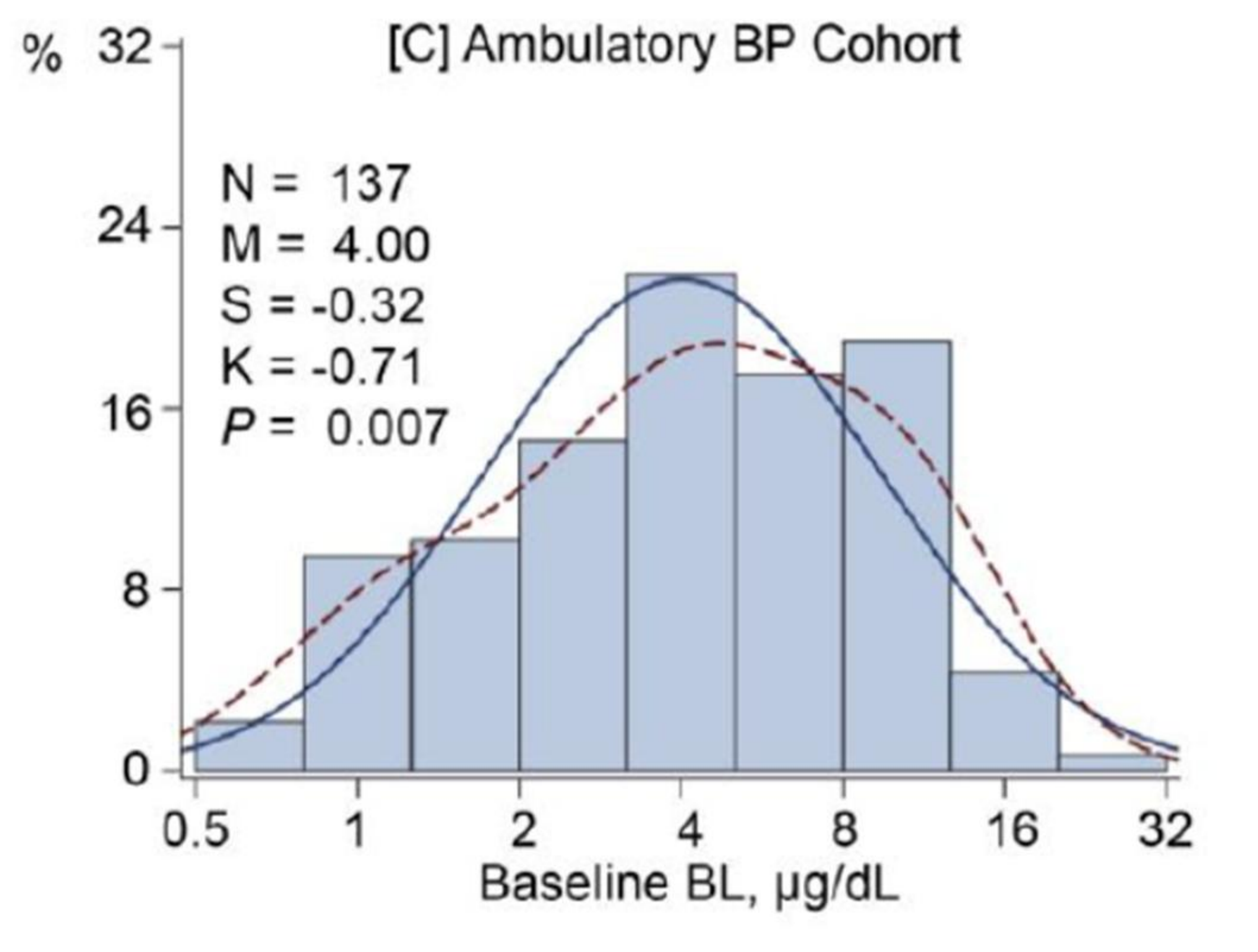
STUDY PURPOSE

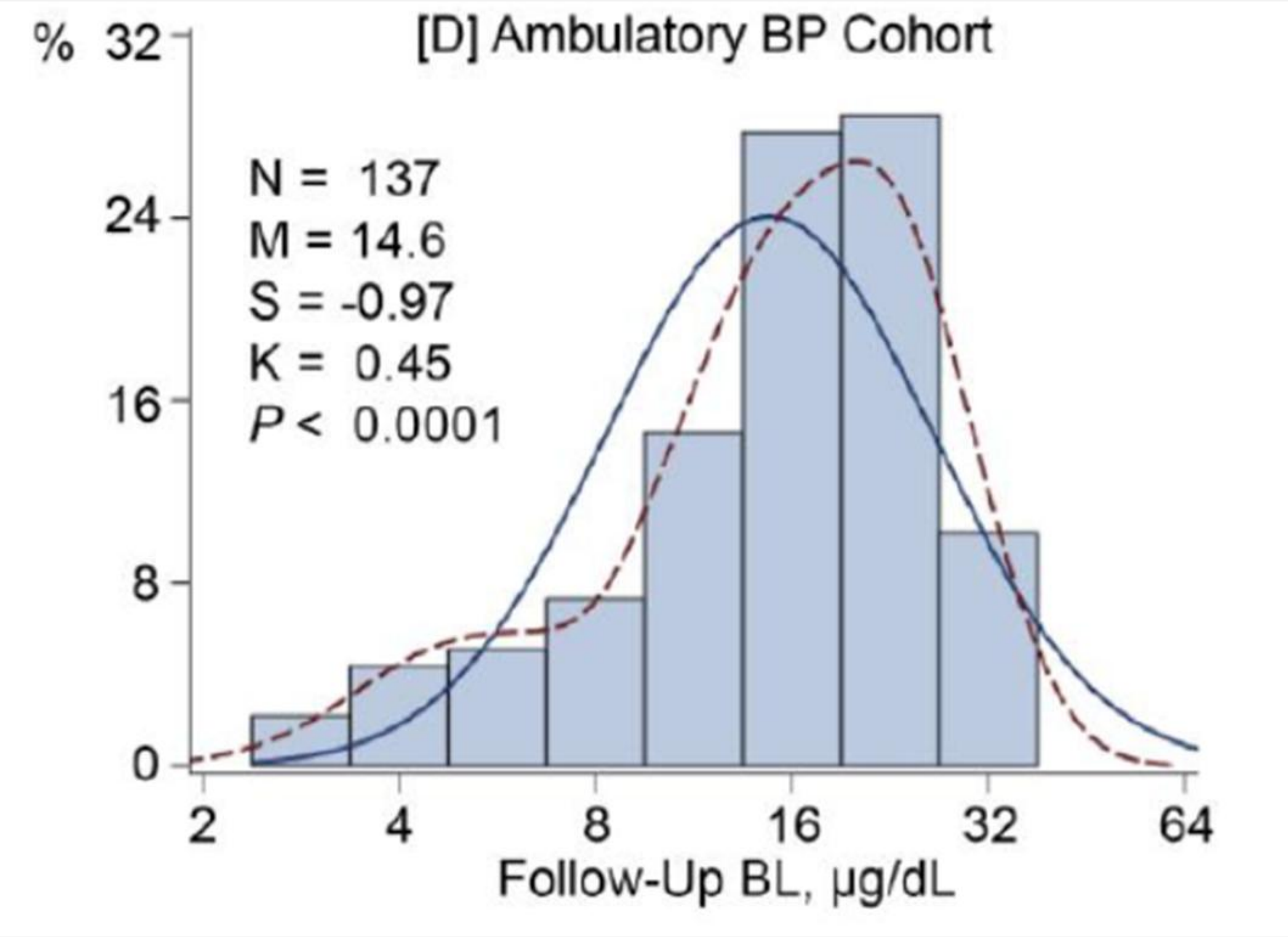
- To pinpoint the BLLs at which known health effects of Pb appear after chronic occupational exposure
  - Existing studies of occupational exposure is from short-term (cross-sectional) studies in which the influence of previous lead exposure (high bone lead) on the health effect of interest is difficult to ascertain
  - Existing studies also suffer from insufficient control for confounders or lifestyle factors and the use of insufficiently precise and/or sensitive measures of physiological function
- Launched in pilot form in 2014 as independent research project undertaken by the University of Leuven (Belgium)
- Completed in 2022



STUDY OBJECTIVES

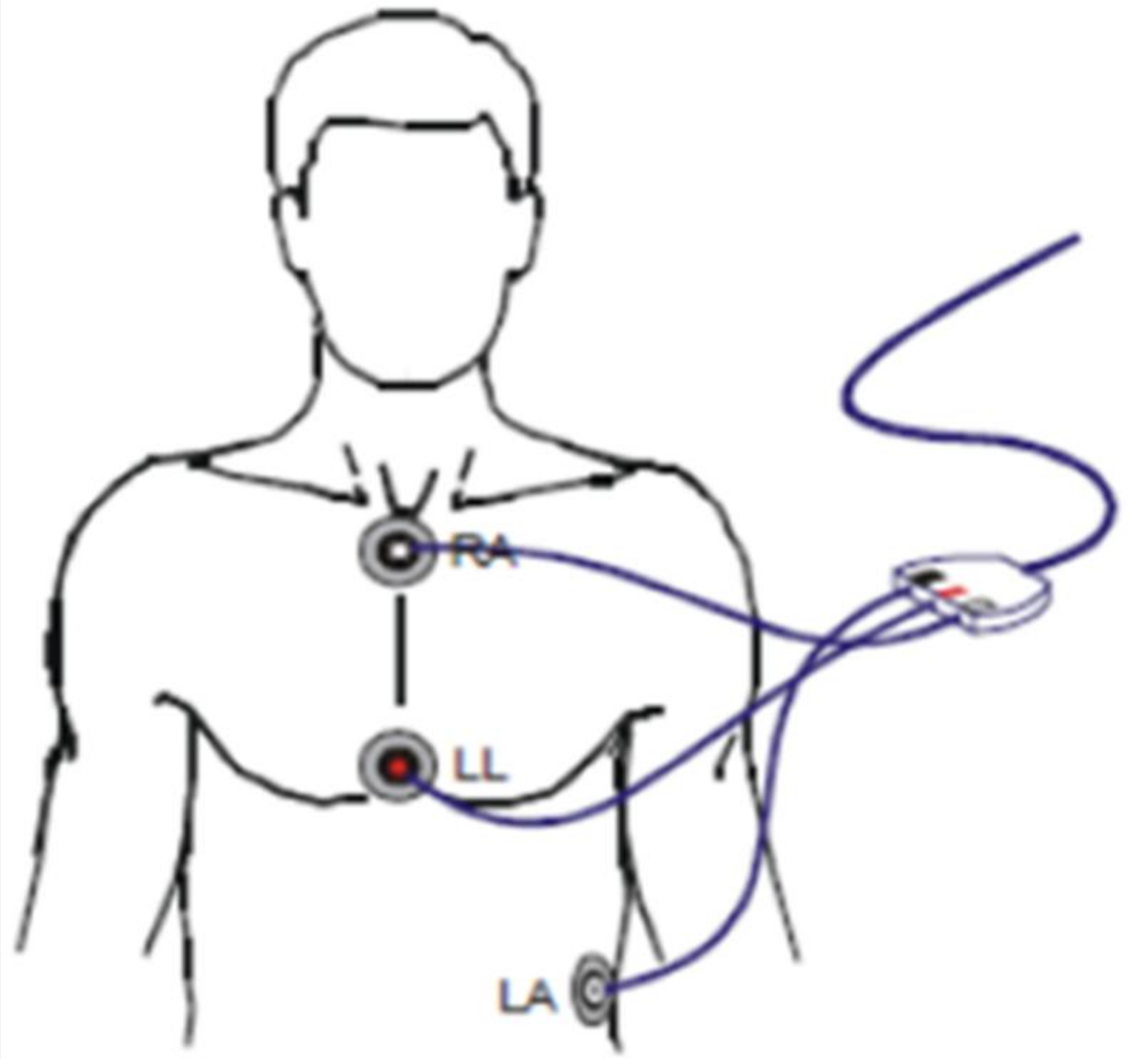
- To address – in a prospective, follow-up study of Pb workers – the extent to which changes in Pb exposure may have a measurable effect on blood pressure and other cardiovascular endpoints, autonomic nervous system function (heart rate variability), neuro-cognitive function, and renal function
- To evaluate effects of increases in blood lead from background to concentrations of regulatory importance (15 to 20 µg/dL) on all major Pb-induced health endpoints of medical significance at baseline and at 1-, 2-, and up to 6-year intervals
- **To inform regulatory decisions regarding blood lead limits**

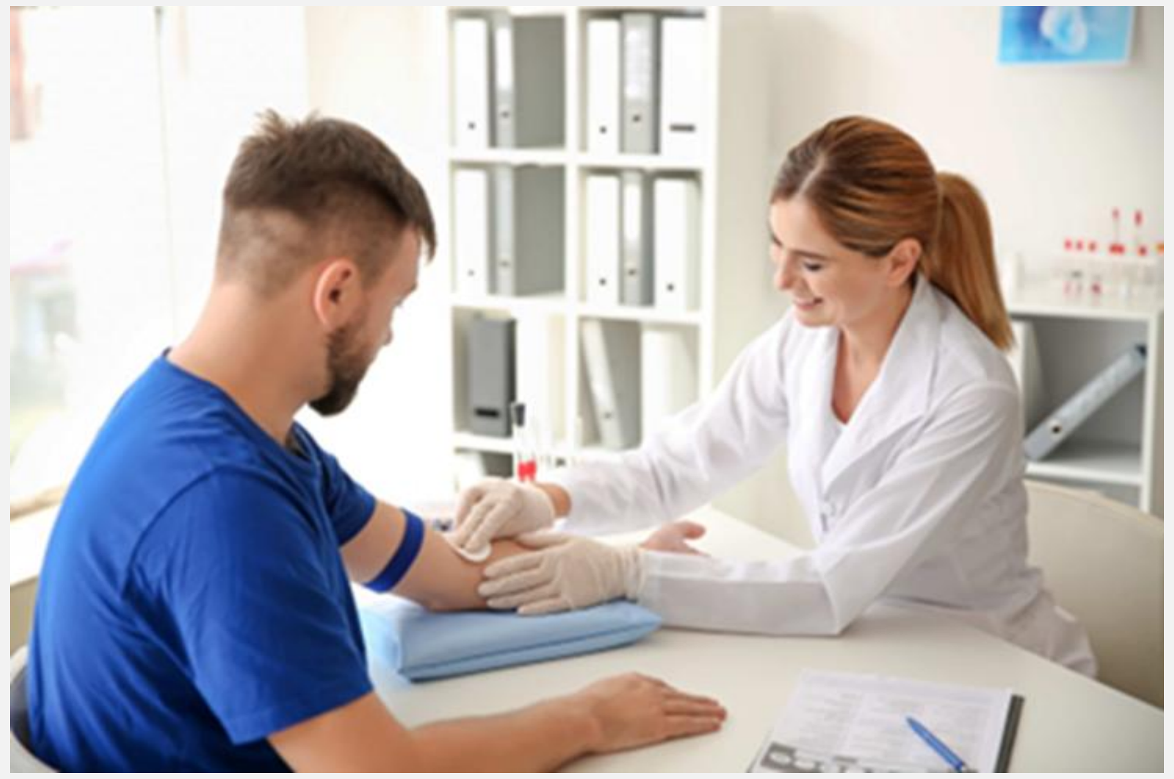




HEALTH ENDPOINTS

- Cardiovascular
  - Office blood pressure
  - 24-hr ambulatory blood pressure
- Neurological
  - Neurocognition – Digit Symbol Test (DST) and Stroop Test (ST)
  - Nerve conduction velocity
  - Heart rate variability (autonomic nervous system)
- Renal (kidney) – (estimated) glomerular filtration rate (eGFR)
  - eGFRcrt = eGFR from serum creatinine
  - eGFRcys = eGFR from serum cystatin C
  - eGFRcc = eGFR from serum creatinine + cystatin C





STUDY RESULTS

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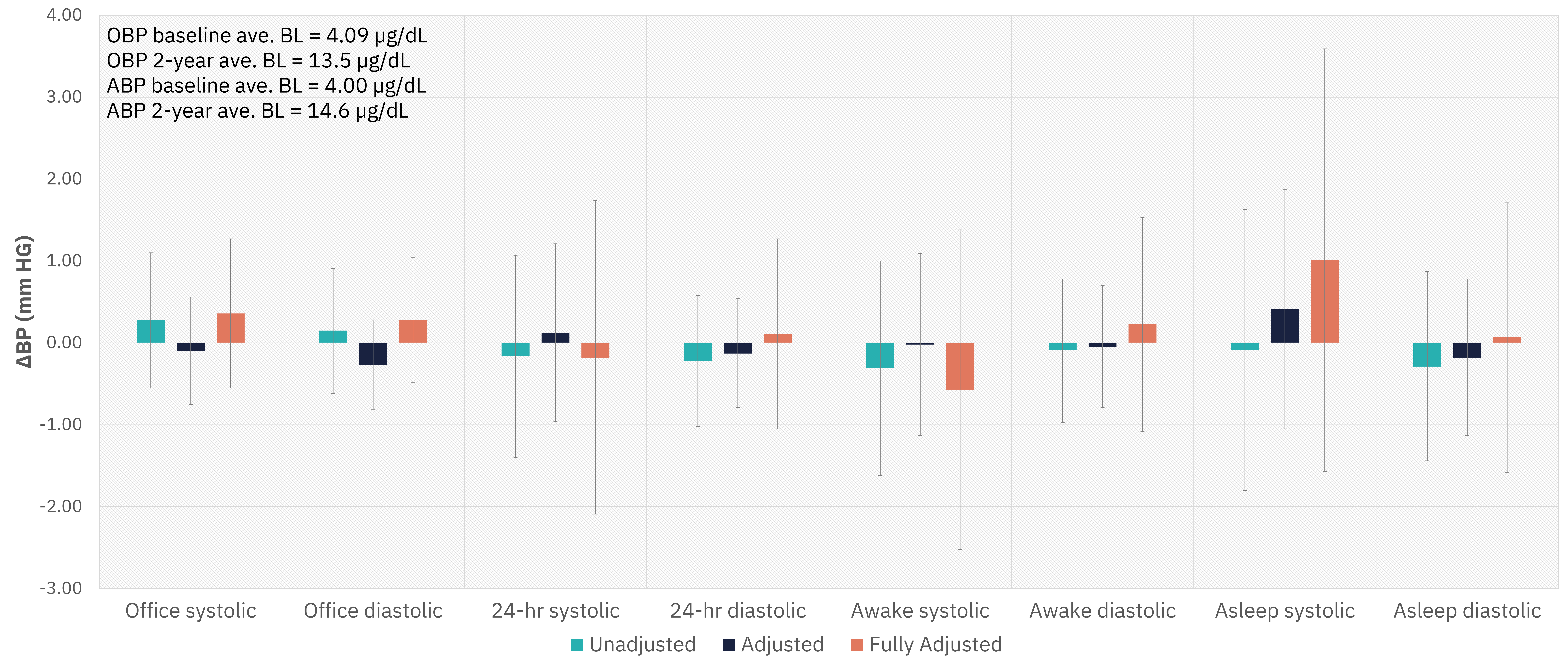

STUDY RESULTS

Endpoint	Baseline[1]	Year 1[2]	Year 2[3]	Up to Year 6[4]
Cardiovascular				
Office BP	**No effect**	**No effect**	**No effect**	**No effect**
Ambulatory BP	**No effect**	**No effect**	**No effect**	**ND**
Neurological				
Digit Symbol Test	**No effect**	**No effect**	**No effect**	**No effect**
Stroop Test	**No effect**	**No effect**	**No effect**	**No effect**
Nerve conduction velocity	**No effect**	**No effect**	**No effect**	**ND**
Heart rate variability	**No effect**	**No effect**	**No effect**	**No effect**
Renal				
eGFR from serum creatinine	**No effect**	**No effect**	**No effect**	**No effect**
eGFR from serum cystatin C	**No effect**	**No effect**	**No effect**	**No effect**
eGFR from serum creatinine + cystatin C	**No effect**	**No effect**	**No effect**	**No effect**

[1]Condition upon enrollment in study; i.e., background BLL; [2]After one year of occupational Pb exposure compared to baseline; [3]After two years of occupation Pb exposure compared to baseline; [4]After up to six years of occupational exposure compared to baseline.

STUDY PUBLICATIONS

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Publication Number	Year of Publication	Citation
1	2015	Hara, A., Gu, Y.M., Petit, T., Liu, Y.P., Jacobs, L., Zhang, Z.Y., Yang, W.Y., Jin, Y., Thijs, L., Wei, F.F., Nawrot, T.S., and Staessen, J.A. 2015. Study for Promotion of Health in Recycling Lead - Rationale and design. Blood Press. 24(3):147-157.
2	2018	Yang, W-Y., Mujaj, B., Efremov, L., Zhang, Z-Y., Thijs, L., Wei, F.F., Huang, O-F., Luttun, A., Verhamme, P., Nawrot, T.S., Boggia, J., and Staessen, J.A. 2018. ECG Voltage in Relation to Peripheral and Central Ambulatory Blood Pressure. Am J Hypertens. 31(2):178-187.
3	2018	Yang, W-Y., Efremov, L., Mujaj, B., Zhang, Z-Y., Wei, F-F., Huang, Q-F., Thijs, L., Vanassche, T., Nawrot, T., and Staessen, J.A. 2018. Association of office and ambulatory blood pressure with blood lead in workers before occupational exposure. Journal of the American Society of Hypertension 12(1):14-24.
4	2019	Mujaj, B., Yang, W-Y., Zhang, Z-Y., Wei, F-F., Thijs, L., Verhamme, P., and Staessen, J.A. 2019. Renal function in relation to low-level environmental lead exposure. Nephrology Dialysis Transplantation 34(6):941-946.
5	2018	Yang, W-Y., Staessen, J.A. 2018. Blood pressure, hypertension and lead exposure. Environ Health. 2018 Feb 19;17(1):16.
6	2018	Yang, W-Y., Zhang, Z-Y., Mujaj, B., Thijs, L., and Staessen, J.A. 2018. Environmental exposure to lead: old myths never die. Lancet Public Health 3(8):e362.
7	2018	Lanphear, B.P., Hornung, R.W., Auinger, P., and Allen, R. 2018. Environmental exposure to lead: old myths never die - Authors' reply. Lancet Public Health 3(8):e363.
8	2019a	Yu, C-G., Wei, F-F., Yang, W-Y., Zhang, Z-Y., Muja, B., Thijs, L., Feng, Y-M., and Staessen, J.A. 2019. Heart rate variability and peripheral nerve conduction velocity in relation to blood lead in newly hired lead workers. Occup Environ Med. 76(6):382-388.
9	2019b	Yu, C-G., Yang, W-Y., Saenen, N., Wei, F-F., Zhang, Z-Y., Mujaj, B., Thijs, L., Feng, Y-M., Nawrot, T.S., and Staessen, J.A. 2019. Neurocognitive function in relation to blood lead among young men prior to chronic occupational exposure. Scand J Work Environ Health 45(3):298-307.
10	2019c	Yu, C-G., Wei, F-F., Yang, W-Y., Zhang, Z-Y., Mujaj, B., Thijs, L., Feng, Y-M., Boggia, J., Nawrot, T.S., Struijker-Boudier, H.A.J., and Staessen, J.A. 2019. Central hemodynamics in relation to blood lead in young men prior to chronic occupational exposure. Blood Press. 28(5):279-290.
11	2020	Staessen, J.A., Thijs, L., Yang, W-Y., Yu, C-G., Wei, F-F., Roels, H.A., Nawrot, T.S., and Zhang, Z-Y. 2020. Interpretation of Population Health Metrics: Environmental Lead Exposure as Exemplary Case. Hypertension 75(3):603-614.
12	2020a	Yu, Y-L., Yang, W-Y., Thijs, L., Melgarejo, J.D., Yu, C-G., Wei, D.M., Wei, F-F., Nawrot, T.S., Zhang, Z-Y., and Staessen, J.A. 2020. Two-Year Responses of Office and Ambulatory Blood Pressure to First Occupational Lead Exposure. Hypertension. 76(4):1299-1307.
13	2020b	Yu, Y-L., Thijs, L., Yu, C-G., Wen-Yi Yang, W-Y., Melgarejo, J.D., Wei, D-M., Wei, F-F., Nawrot, T.S., Verhamme, P., Roels, H.A., Staessen, J.A., and Zhang, Z-Y. Two-Year Responses of Heart Rate and Heart Rate Variability to First Occupational Lead Exposure. Hypertension. 2021 May 5;77(5):1775-1786.
14	2021	Yu, Y-L., Thijs, L., Saenen, N., Melgarejo, J.D., Wei, D-M., Yang, W-Y., Yu, C-G., Roels, H.A., Nawrot, T.S., Maestre, G.E., and Staessen, J.A. Two-year neurocognitive responses to first occupational lead exposure. Scand J Work Environ Health. 2021 Apr 1;47(3):233-243.
15	2022	Yu, Y-L., Thijs, L., Yu, C-G., Melgarejo, J.D., Wei, D-M., Wei, F-F., Yang, W-Y., Roels, H.A., Nawrot, T.S., Zhang, Z-Y., and Staessen, J.A. Two-Year Responses of Renal Function to First Occupational Lead Exposure. Kidney Int Rep. 2022 Mar 26;7(6):1198-1209.
16	2023a	Yu YL, Yang WY, Hara A, Asayama K, Roels HA, Nawrot TS, Staessen JA. Public and occupational health risks related to lead exposure updated according to present-day blood lead levels. Hypertens Res. 2023 Feb;46(2):395-407.
17	2023b	Yu YL, An DW, Yang WY, Verhamme P, Allegaert K, Nawrot TS, Staessen JA. Blood Pressure and Renal Function Responses in Workers Exposed to Lead for up to Six Years. J Clin Hyperten, 2023 Dec; 25 (12): 1086-1095.
18	2023c	Yu YL, An DW, Chori BS, Nawrot TS, Staessen JA. Blood pressure and hypertension in relation to lead exposure updated according to present-day blood lead levels. Kardiol Pol. 2023;81(7-8):675-683.

SPHERL AND REGULATORY DEFENSE

- SPHERL was specifically designed in anticipation of informing major regulatory decisions regarding appropriate, science-based blood lead limits for the contemporary workplace
  - EU/RAC
  - Cal/OSHA
  - MNOSHA
  - ACGIH
  - U.S. FEDERAL OSHA

SPHERL COHORT AND FOLLOW-ON STUDY

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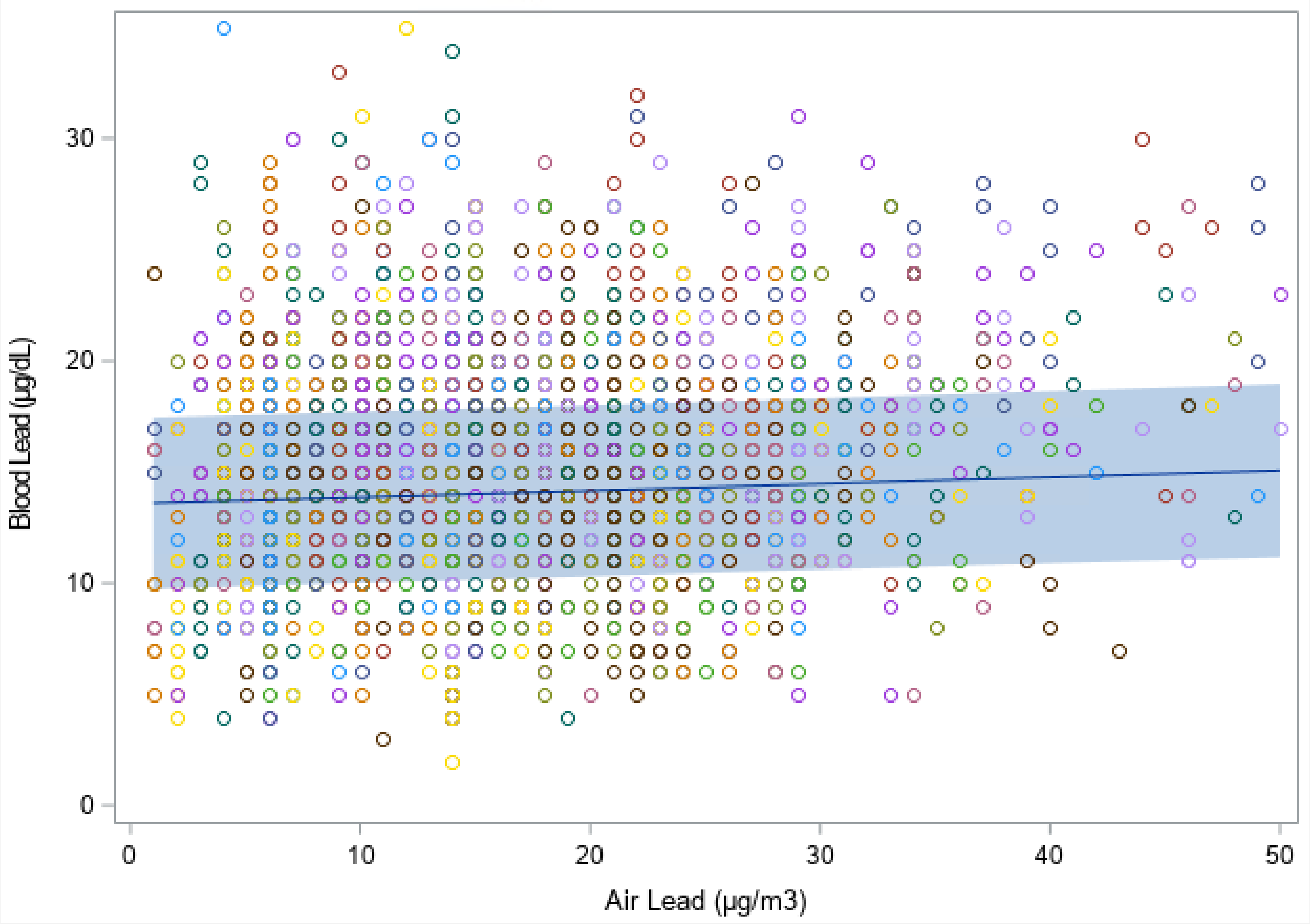
Study	Study Population	PbA sample type and measurement period	PbA (µg/m³)	Respiratory Protection	PbB (µg/dL)	Repeated PbA and/or Pb measurements	Results
Williams et al. (1969)	39 battery workers, UK (dates NR)	Personal 8-hour	AM: 9-218 Range: 1-300	None	AM: 27.2-74.2 Range: 22-90	Yes, both	**β = 0.201 per µg/m³**
King et al. (1979)	101 workers (battery, pigment, smelter), UK (1974-1985)	Personal 8-hour	Mean NR Range: 25-1200	Unknown	Mean NR Range: 22-91	Yes, both	**β = 0.014 to 0.068 per µg/m³**
Gartside et al. (1982)	94 battery workers, US (1974-1976)	Area and personal 8-hour	AM: 115 Range: 5-350	Unknown	AM:43 Range: 22-73	Yes, both	**β = 0.0536 per µg/m³**
Bishop and Hill (1983)	233 battery workers, US (1975-1981)	Personal 8-hour	Mean NR Range: 10-170 (Plant C only; others NR)	None before 1979; some after 1979	Mean NR Range: 22-62 (Plant C only; others NR)	Yes, both	**β = 0.02 to 0.06 per µg/m³** (cross-sectional) **β = 0.02 to 0.08 per µg/m³** (longitudinal)
Hodgkins et al. (1992)	44 battery workers, US (1983-1985)	Personal 8-hour	6-month average: AM: 5-33 2.5-year average: AM: 11-19 Range NR	None	6-month: AM: 21-40 Range NR	Yes, both	**β = −0.01 to 2.35 per µg/m³** (cross-sectional; univariate) **β = −0.37 to 1.80 per µg/m³** (cross-sectional; multivariate) **β = 1.50 per µg/m³** (longitudinal; univariate) **β = 1.14 per µg/m³** (longitudinal; multivariate)
Kentner and Fischer (1993)	134 battery workers, Germany (1982-1991)	Area 40 minute	AM: 94 Range: 15-289	Unknown	AM: 9.44 Range: 1-98	Yes, both	PbA in mg/m³: **β = 21.242**
Lai et al. (1997)	219 battery workers, Taiwan (dates NR)	Personal (time period NR)	AM: 190; GM: 82 Range NR	None (some workers self-reported wearing cloth masks)	AM: 56.9 Range NR	No	PbA in mg/m³: **β = 0.2356** (simple regression); **β = 0.1294** (multiple regression)
Park and Paik (2002)	117 workers (smelter, radiator, battery, powder), Korea (dates NR)	Personal 8-hour	AM: 641; GM: 118 Range: <10-8000	Unknown	AM: 38.6 Range: 7.3-113.5	No	**β = 15.3**
Pierre et al. (2002)	131 crystal manufacturing workers, France (dates NR)	Personal 8-hour	AM: 228; GM: 111 Range: 1-2131	Unknown	AM: 21.9; GM: 27.2 Range: 10.9-61.3	No	PbB in µg/L: **β = 0.181**
Rodrigues et al. (2010)	84 bridge painters, USA (1994-1995)	Personal varied by task	2-week average of daily TWA: GM: 58.8 Range: 1.2-396	Yes, some workers	First day GM: 16.1; Range: 3-49.5 Last day GM: 18.2: Range: 3-42	Yes, both	PbA: **β = 0.10** (univariate); **β = 0.11** and **β = 0.05** (multivariate)
Wu et al. (2016)	1,745 smelter workers, China 1988-2008)	Area 8-hour	1-year average: Dust AM: 20-730; Fumes AM: 60-130 Range NR	Unknown	Not reported	Yes, both	N/A; however, authors reported significant correlation between cumulative exposures and PbB
Ono and Horiguchi (2021)	32 battery workers, Japan (2017-2020)	Personal 8-hour	AM: 6.88 Range: 1.61-17.74	None	AM: 10.2 Range: 3.1-18	No (except for 2 workers)	Simple regression: **β = 0.156 per µg/m³** Multiple regression: **β=0.410 per µg/m³**

SPHERL COHORT AND FOLLOW-ON STUDY

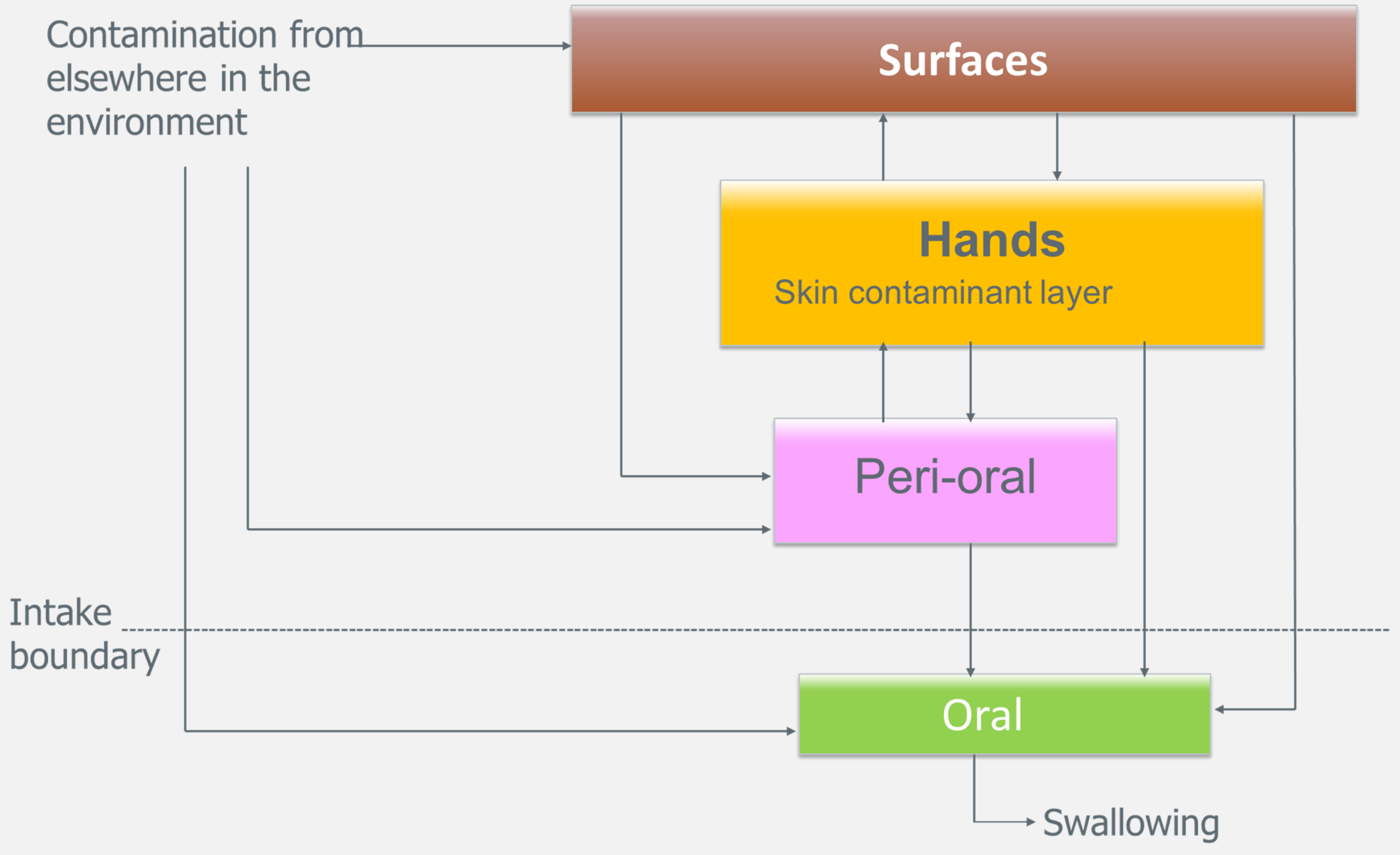
- Air Pb:blood Pb study
  - Phase I
    - Use of SPHERL study participants to fill data gaps in the existing evidence from the literature regarding the nature and magnitude of the air Pb:blood Pb relationship
    - Established evidence for lack of a relationship and demonstrated that PBPK modeling to set air Pb limits is not scientifically supportable
  - Phase II
    - Additional analyses with an expanded cohort from same study site for the purpose of producing a more scientifically robust study for publication/better inform regulatory decisions
    - A 1 µg/m^3 increment in PbA was associated with a 0.042 µg/dL higher PbB – a "slope" far lower than the slope derived from existing studies of the relationship
    - **Conclusion: reducing air lead levels alone is not a scientifically-supported exposure mitigation strategy to reduce PbB; regulators should focus on other means of exposure reduction when considering new lead standards**

PbA and PbB Data Points with Regression Line



SPHERL COHORT AND FOLLOW-ON STUDY

- Non-respiratory exposures to Pb in the workplace
  - ***To address anticipated lowering of US federal OSHA air Pb limits by showing that exposure to sources of Pb in the workplace other than air – e.g., via dermal contact, hand-to-mouth activity – are more important and easier to control compared to reducing Pb exposure through, e.g., increased ventilation***
  - Working with U.S. NIOSH and/or academic partner in U.S. PNW to develop protocol that quantifies dermal contact and incidental exposures to Pb via hand-to-mouth activity
  - Aim is to use study results to influence OSHA to codify in the Pb standard low-cost worker hygiene and workplace housekeeping measures ***instead of mandating reduced air lead limits***
  - Preliminary study protocol calls for use of workers from at least 2 sites in U.S. – one possibly being the SPHERL study site



Thank you – and farewell from me!

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