CHILDHOOD LEAD EXPOSURE AND LONG-TERM TELOMERE EROSION

Evidence from adult follow-up in the New Zealand Dunedin Study

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Telomere Research Network
Annual Meeting
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Duke UNIVERSITY

This talk will cover

1. Background to the study
2. The New Zealand Dunedin Study
3. Preliminary findings

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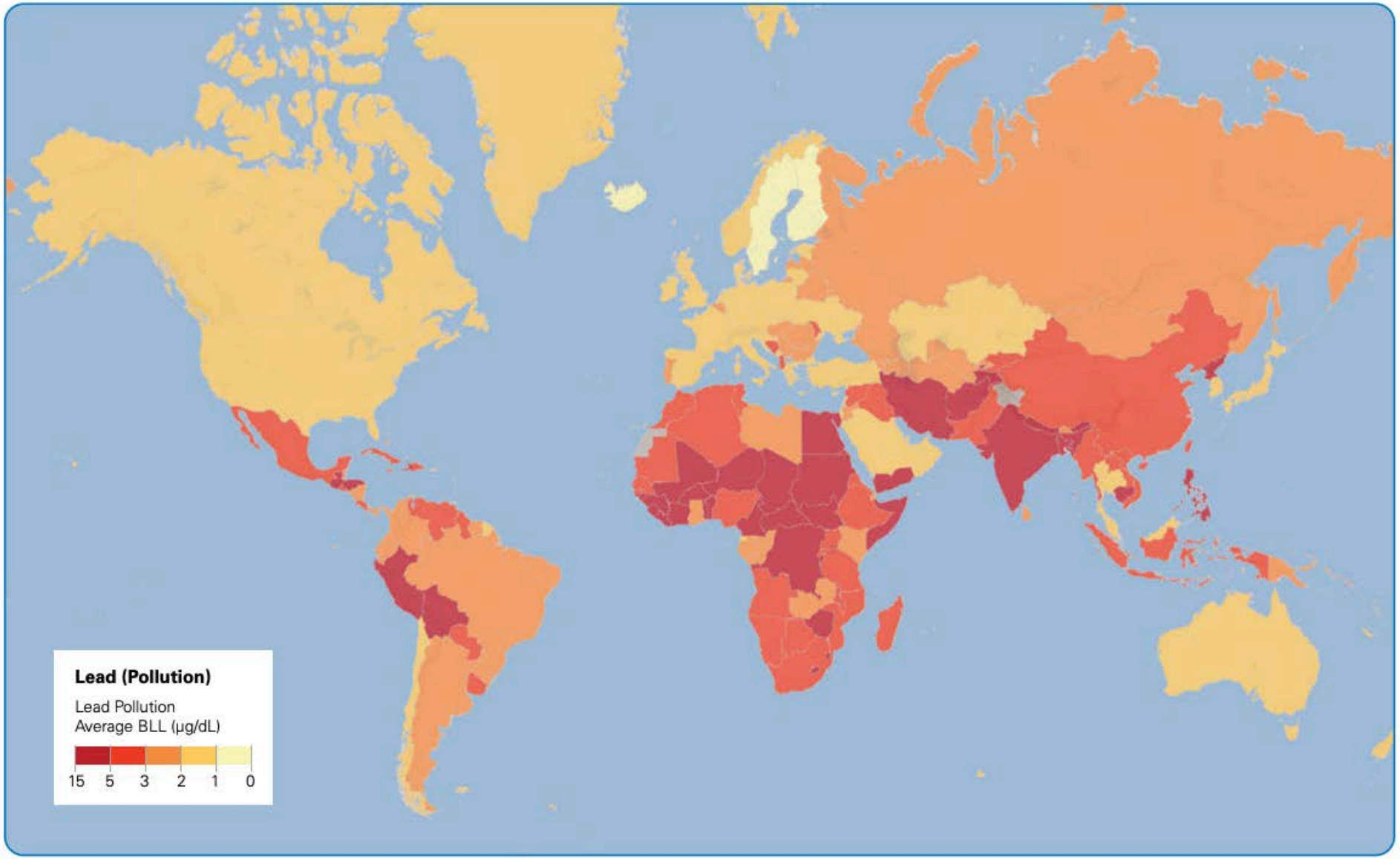
Lead is a environmentally ubiquitous neurotoxicant

Children's average blood lead levels by country (in ug/dL)



Source: IHME 2019. See Annex for full list by country. Lead exposure and health data is also visualized at www.lead.pollution.org

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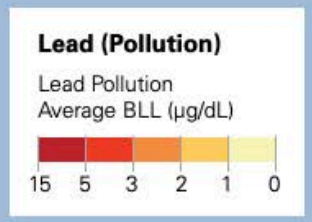

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Lead exposure disrupts child brain development

- Children exposed to lead develop lower:
  - Cognitive ability
  - Fine motor skills
  - Emotion regulation capacity

Long-term consequences are poorly understood

- Dysregulation of telomere length has been proposed as one mechanism for long-term harm.

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- Dysregulation of telomere length has been proposed as one mechanism for long-term harm.
- But:
  - To date, only 5 studies have considered telomere length following early life lead exposure.
  - Findings have been decidedly mixed.

Our motivating research question now is:

WHAT ARE THE LONG-TERM IMPLICATIONS OF EARLY LEAD EXPOSURE FOR TELOMERE LENGTH?

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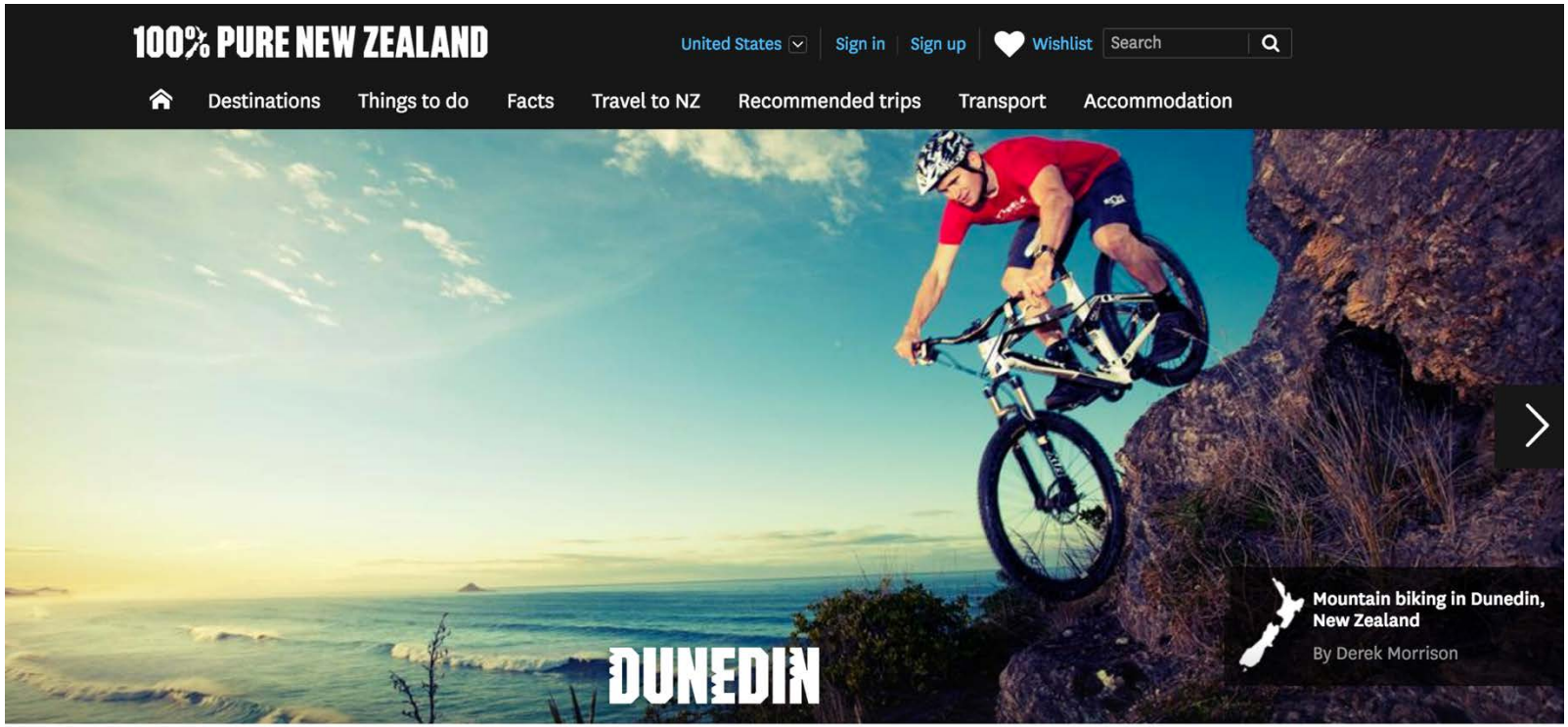
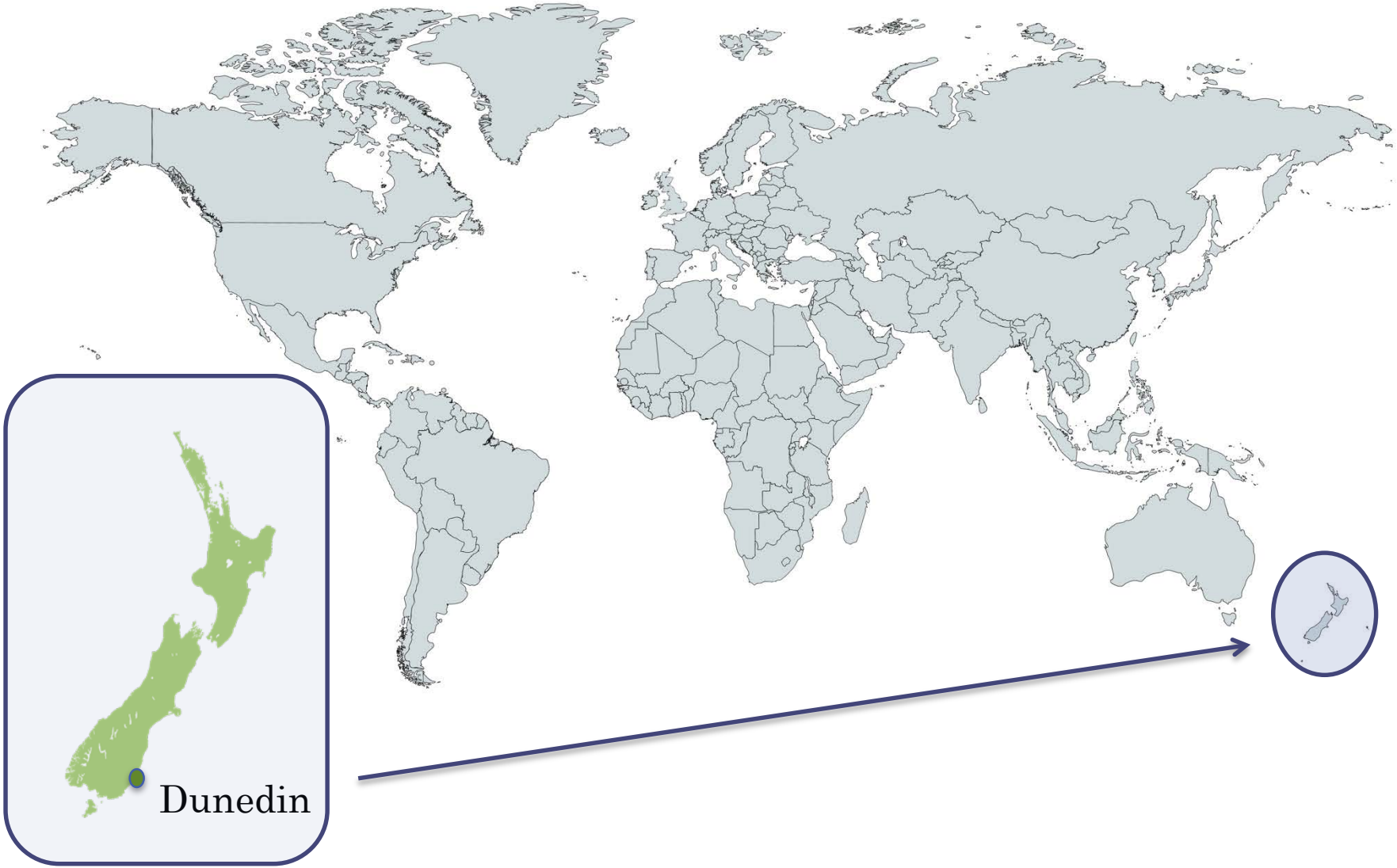


The Dunedin Study



The Dunedin Study

All births from April 1972 to March 1973

N=1,037

Represents the full range of socioeconomic status of the South Island of New Zealand

Dunedin Longitudinal Study

Age	Year	Number	Percent*
Birth	1972-73		
3	1975-76	1037	100%
5	1977-78	991	96
7	1979-80	954	92
9	1981-82	955	92
11	1983-84	925	90
13	1985-86	850	82
15	1987-88	976	95
18	1990-91	993	97
21	1993-94	992	97
26	1998-99	980	96
32	2004-05	972	96
38	2010-12	961	96%

* Percent of cohort members alive at assessment wave

Dunedin Longitudinal Study

Blood-lead level tested

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N = 579 (63%) with blood-lead data

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Telomere length measured

LTL measured via qPCR

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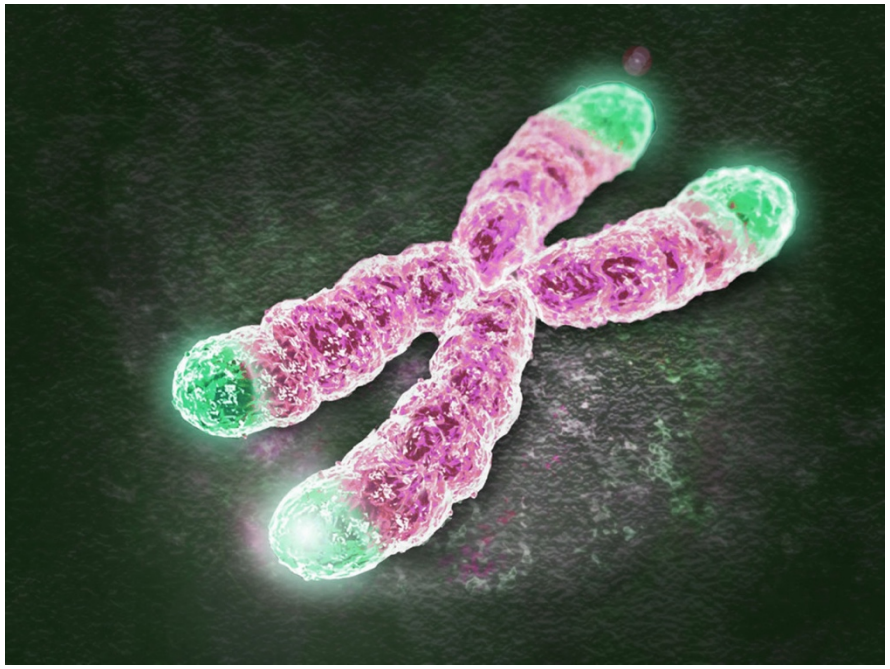

STUDY AIMS

Test the hypothesis that children with greater blood-lead level will:

1) Display shorter telomere length at age 38.
2) Display greater decline in telomere length from age 26 to 38.

Aim 1: Do children with greater lead exposure show shorter telomere length at age 38?

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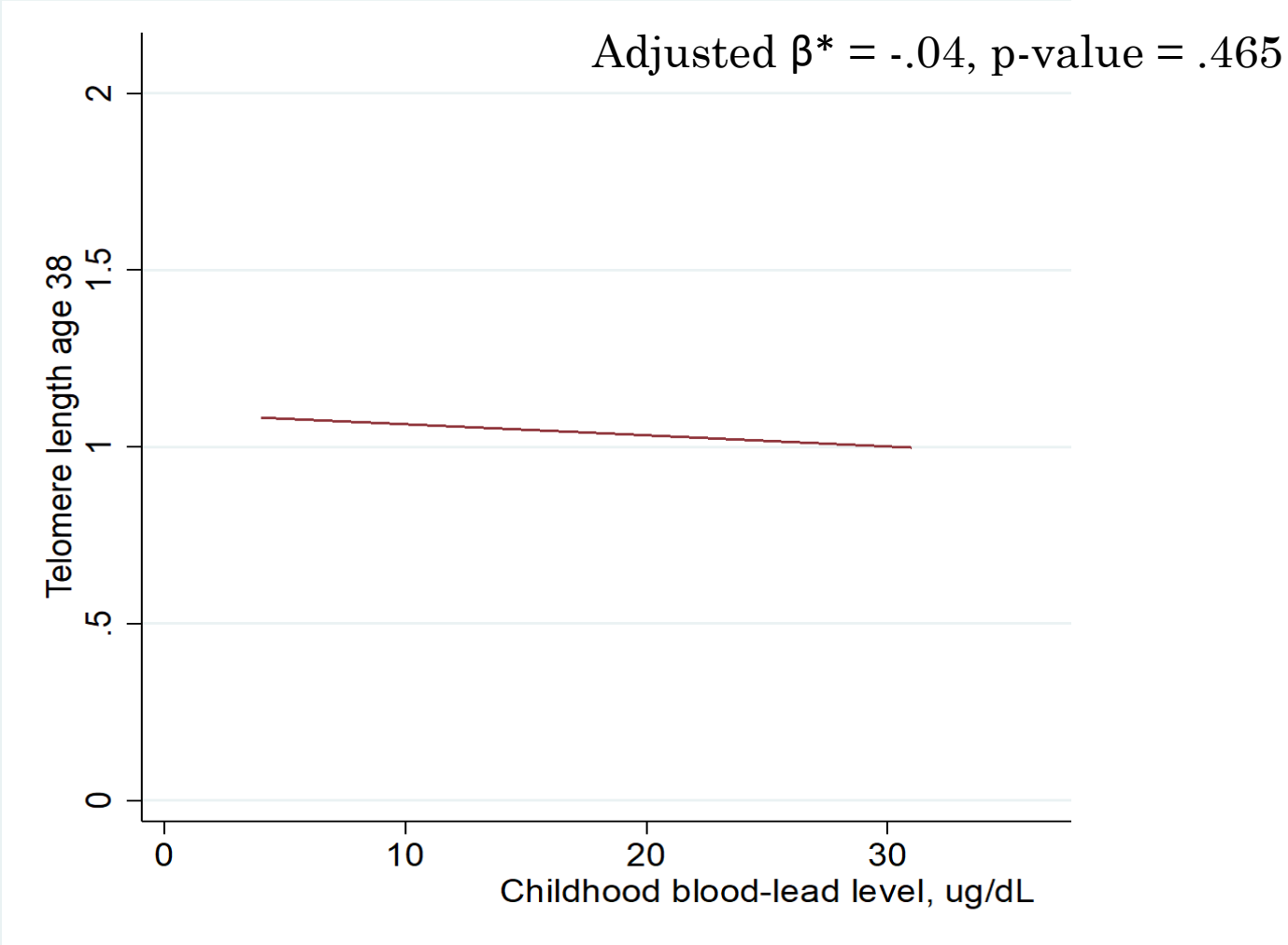

*Adjusted for sex, BMI, smoking, family SES, and white blood cell count

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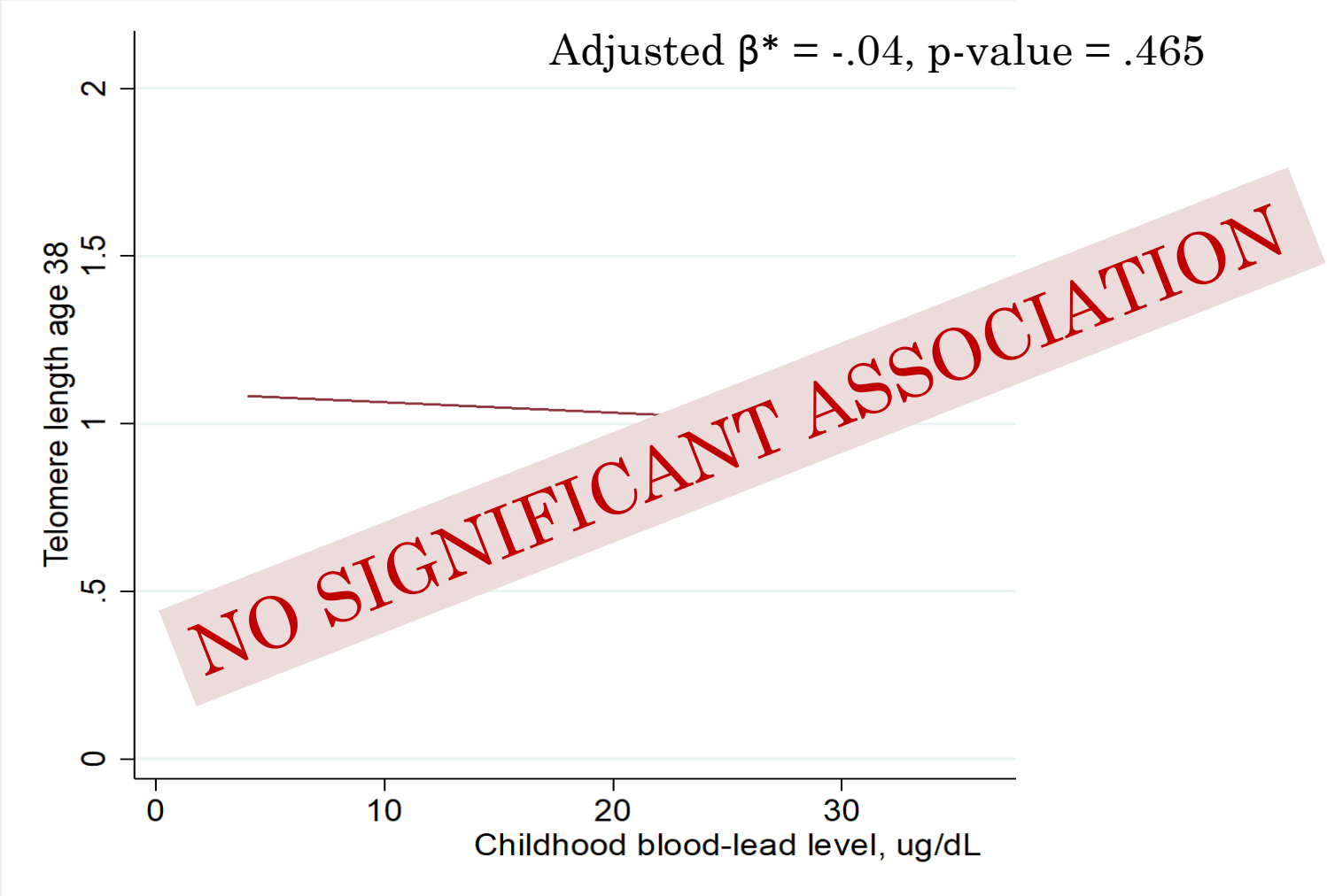

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Aim 2: Do children with greater lead exposure show greater decline in telomere length from age 26 to 38?

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	Adjusted [illegible] value	[illegible]
Association of childh[illegible] with telomere [illegible] 38	-.07	.200
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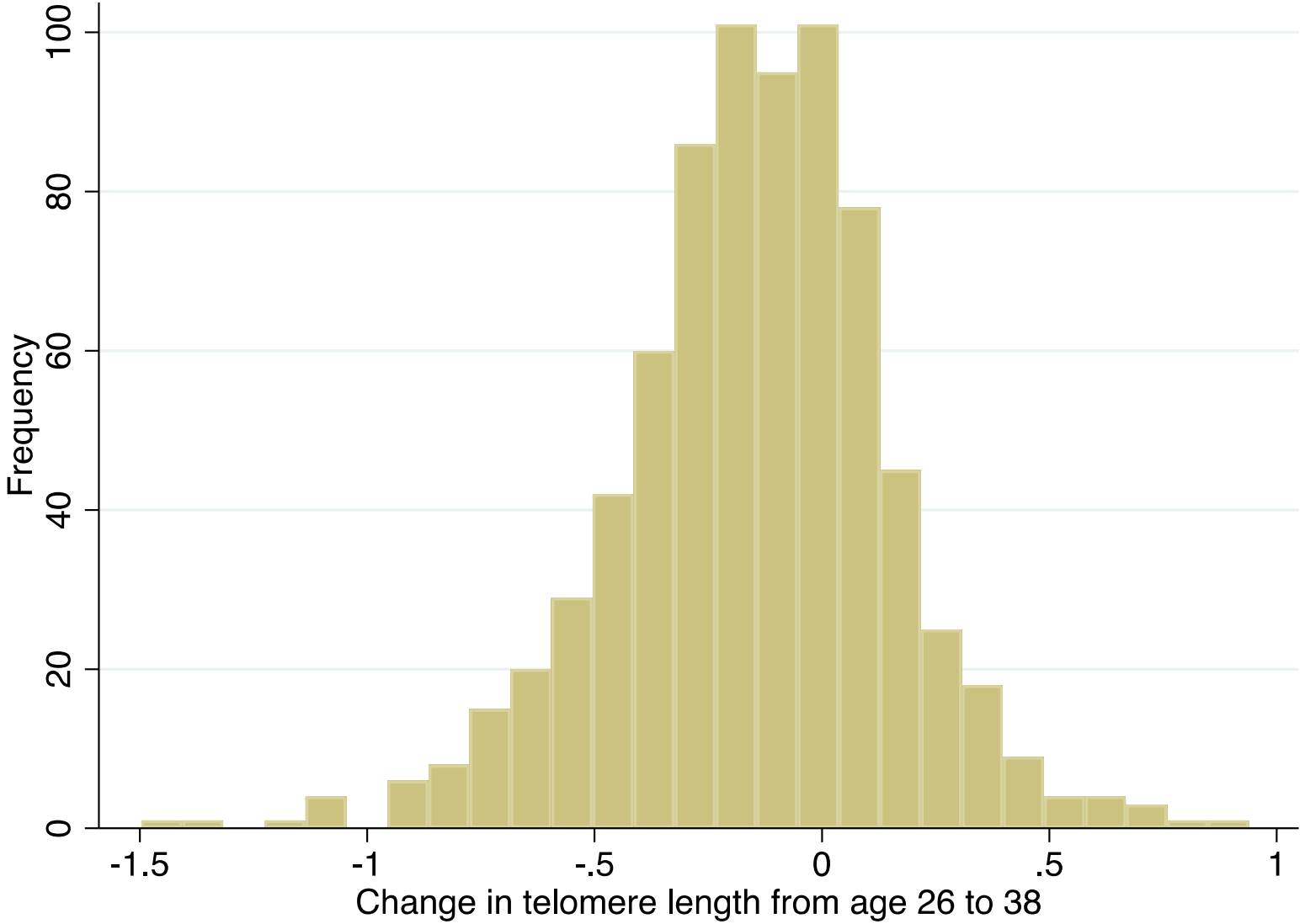
NO SIGNIFICANT ASSOCIATION

Pre-specified Sensitivity tests

Removing those who experienced telomere growth over adulthood

- "Given uncertainty about the interpretation of telomere lengthening we will also conduct sensitivity tests excluding Study members whose telomeres lengthened from age 26 to 38."

Telomere growth in the Dunedin Cohort



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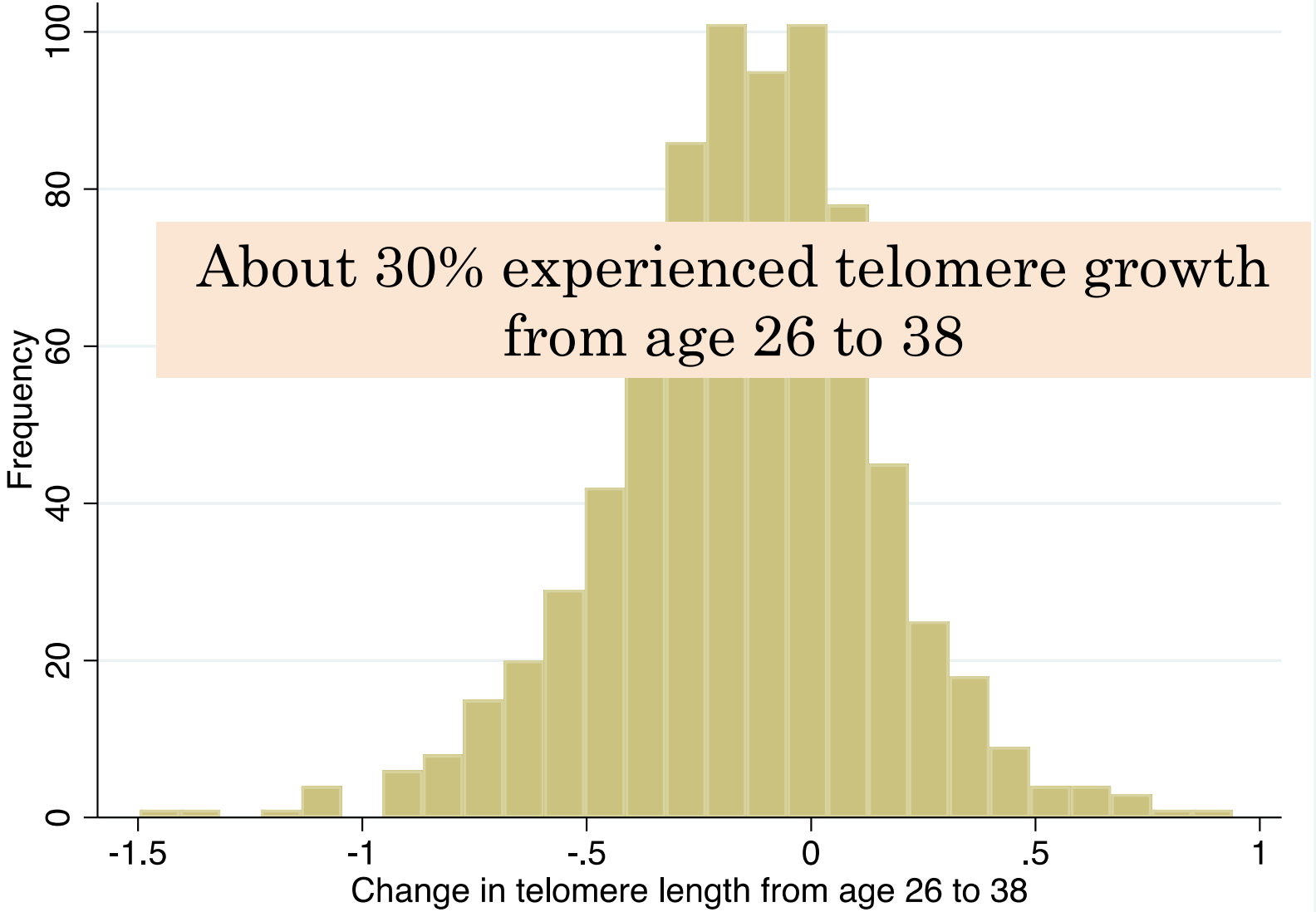

Association of lead and telomere length among those with no growth (N=321)

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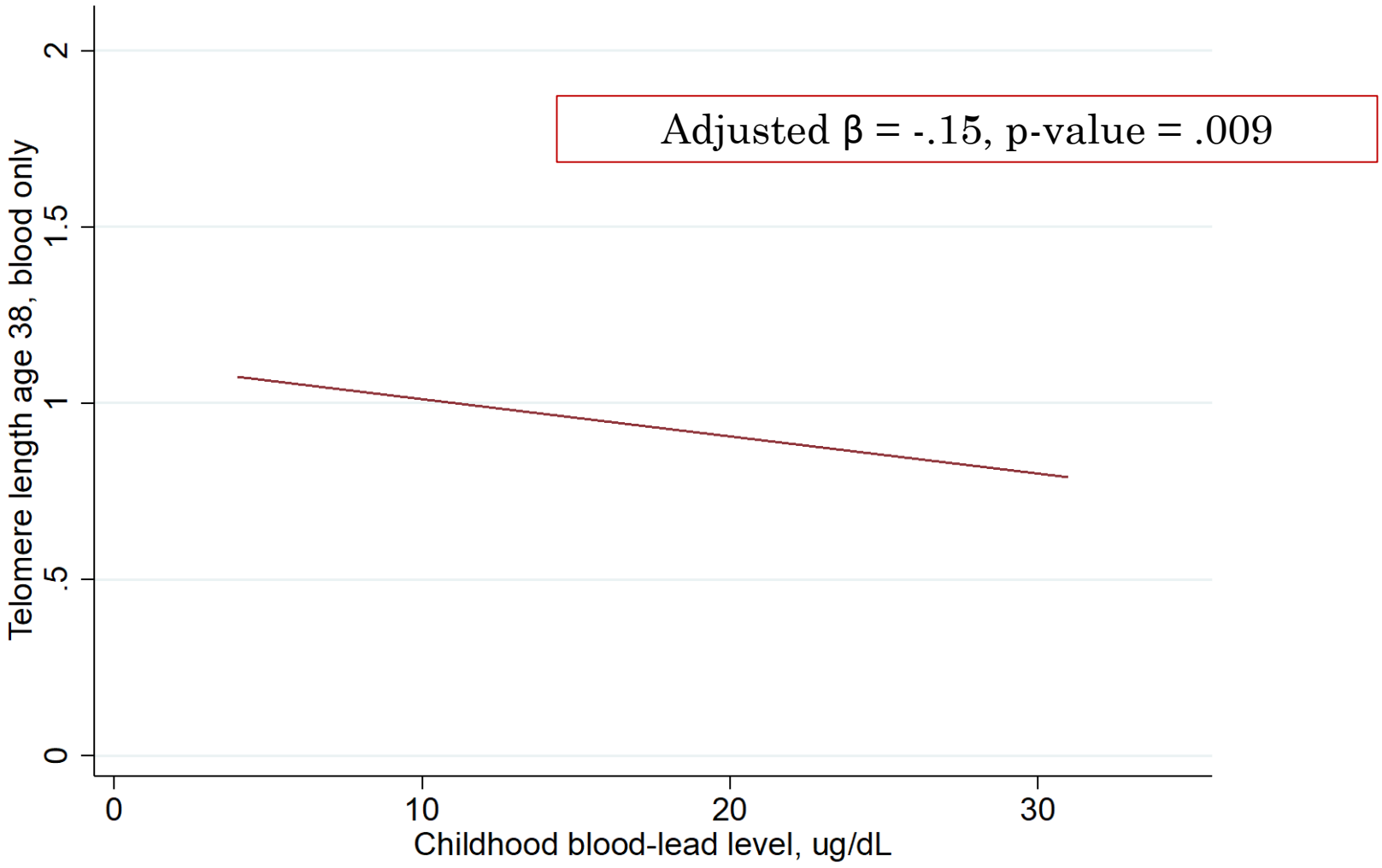

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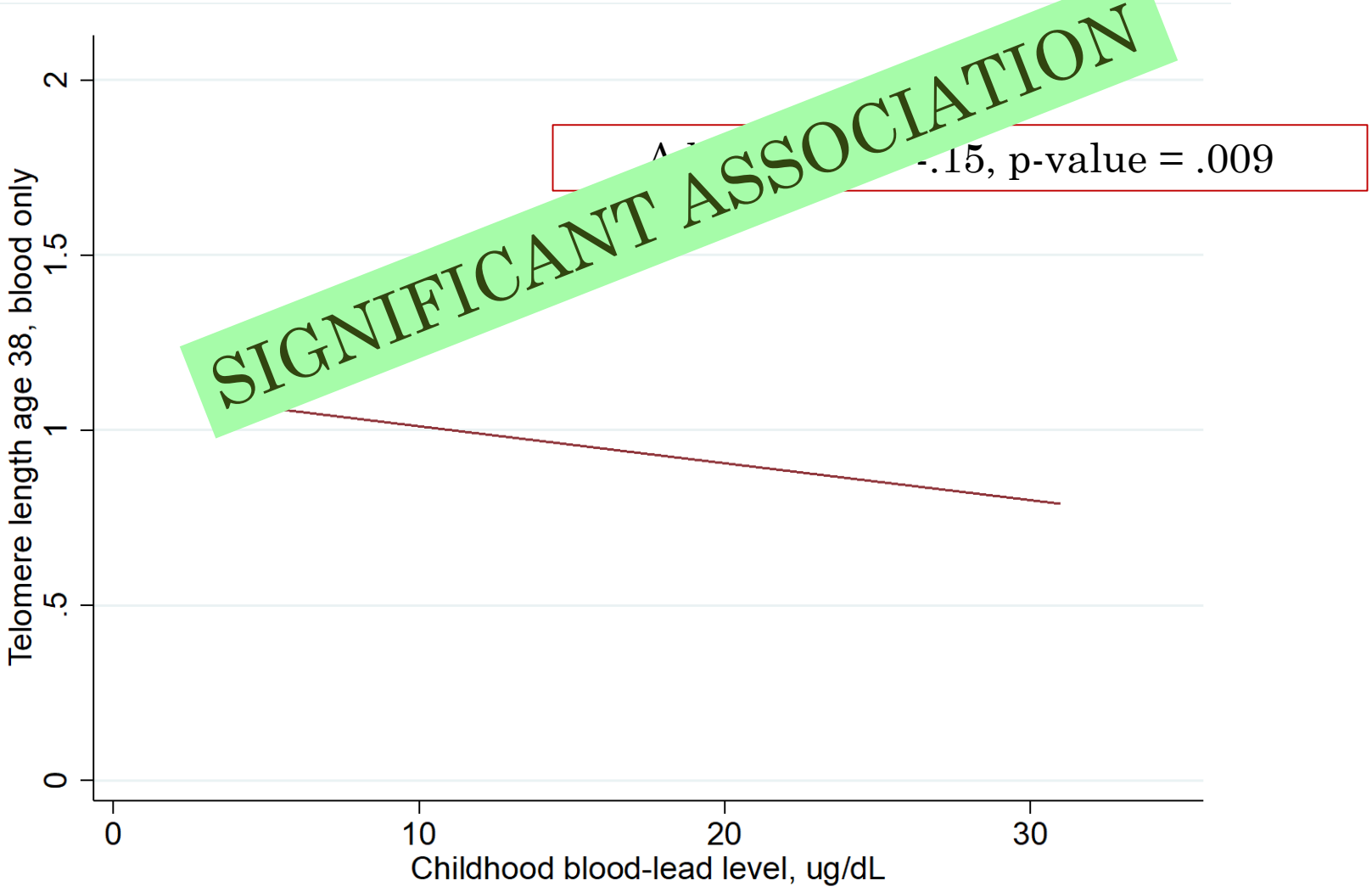

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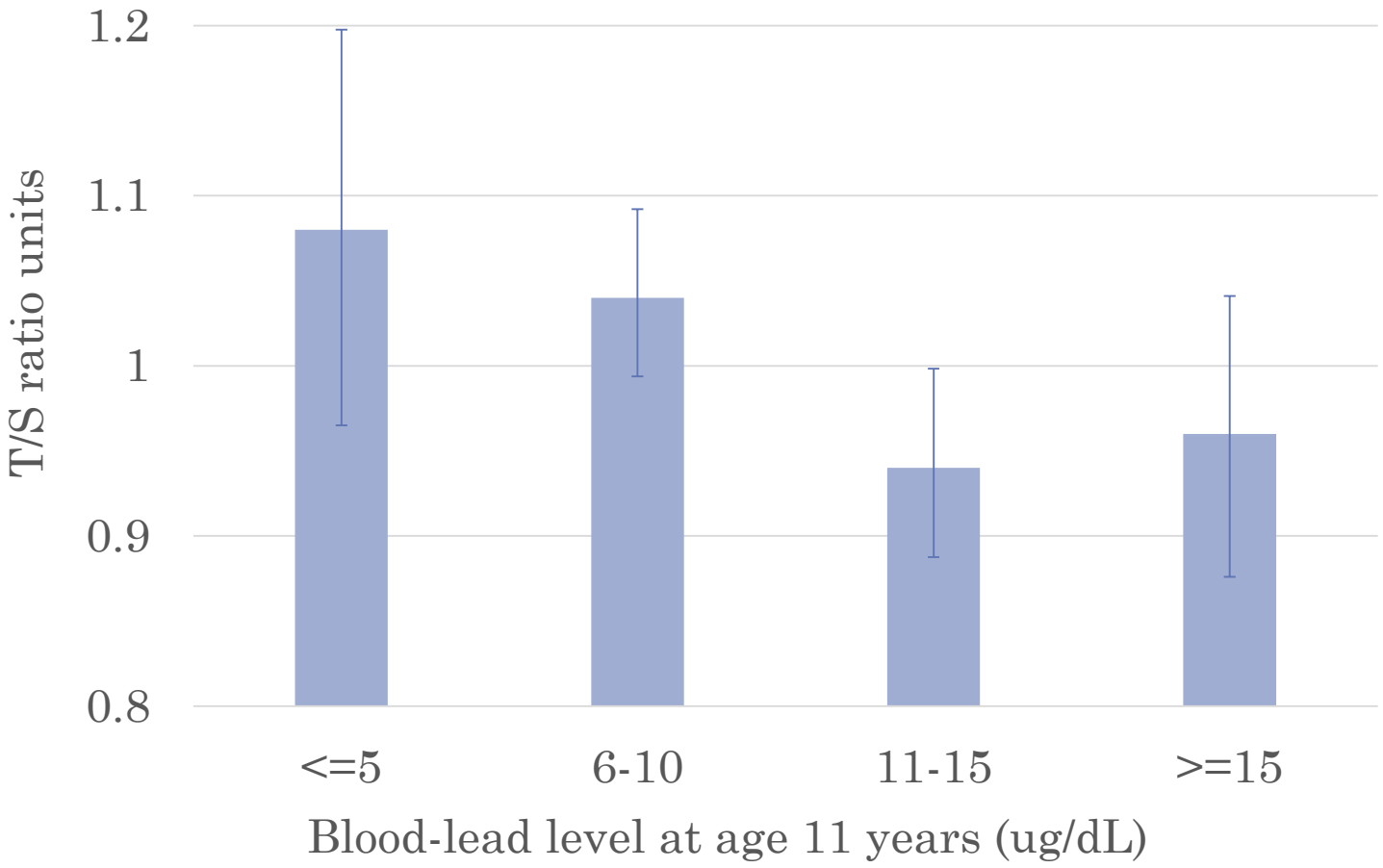
Telomere length at age 38 (among those with no growth)



Aim 2 excluding those with "growth"

	Fully adjusted β	p-value
Association of childhood lead with telomere length at age 38	-.15**	.009

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MODEST ASSOCIATION

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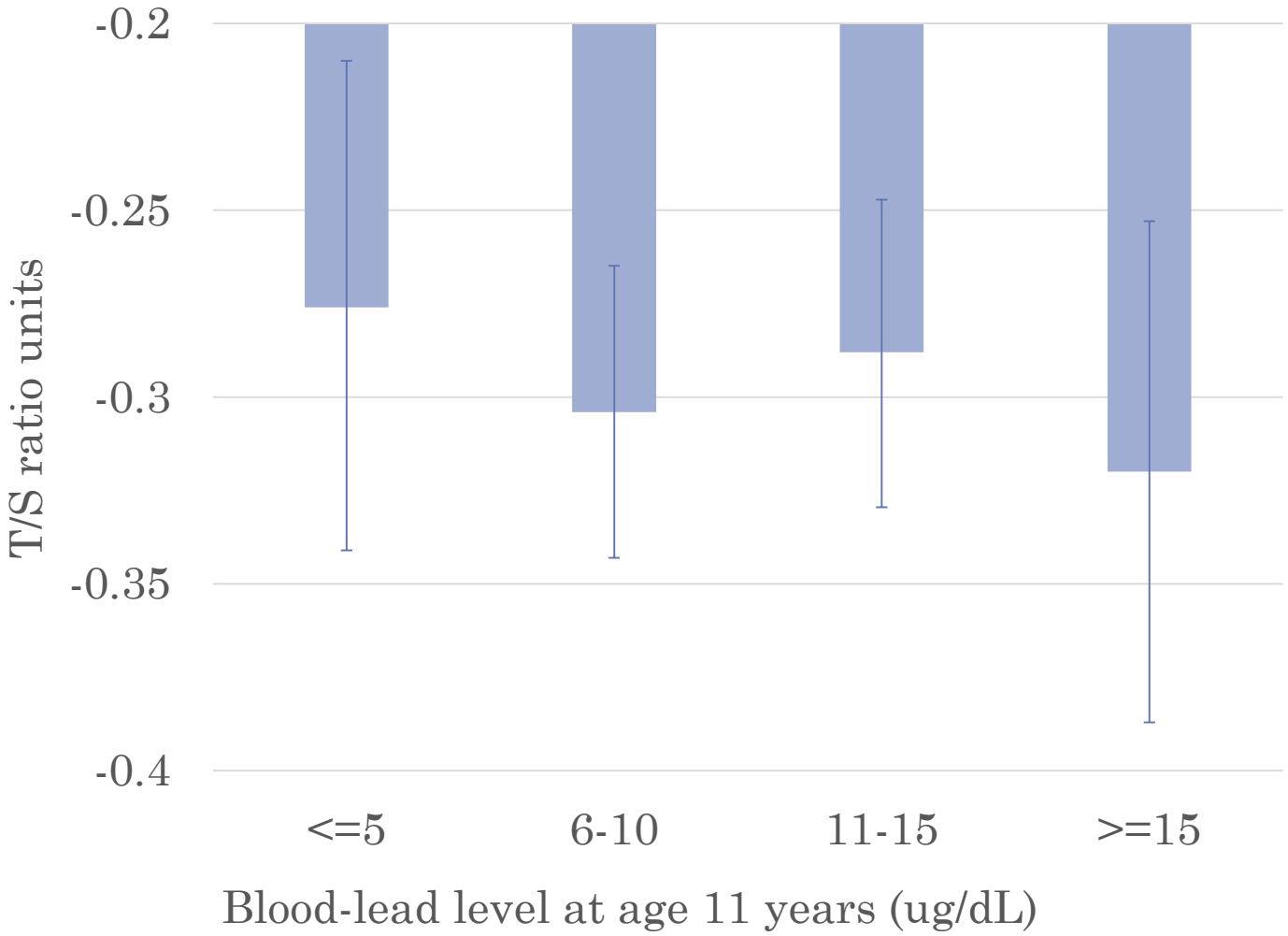
Association of childhood lead with telomere length at age 38	-.15**	.009
Association of childhood lead with telomere length at age 38 **adjusted for age 26 length**	-.06*	.033

Change in telomere length over adulthood (among those with no growth)

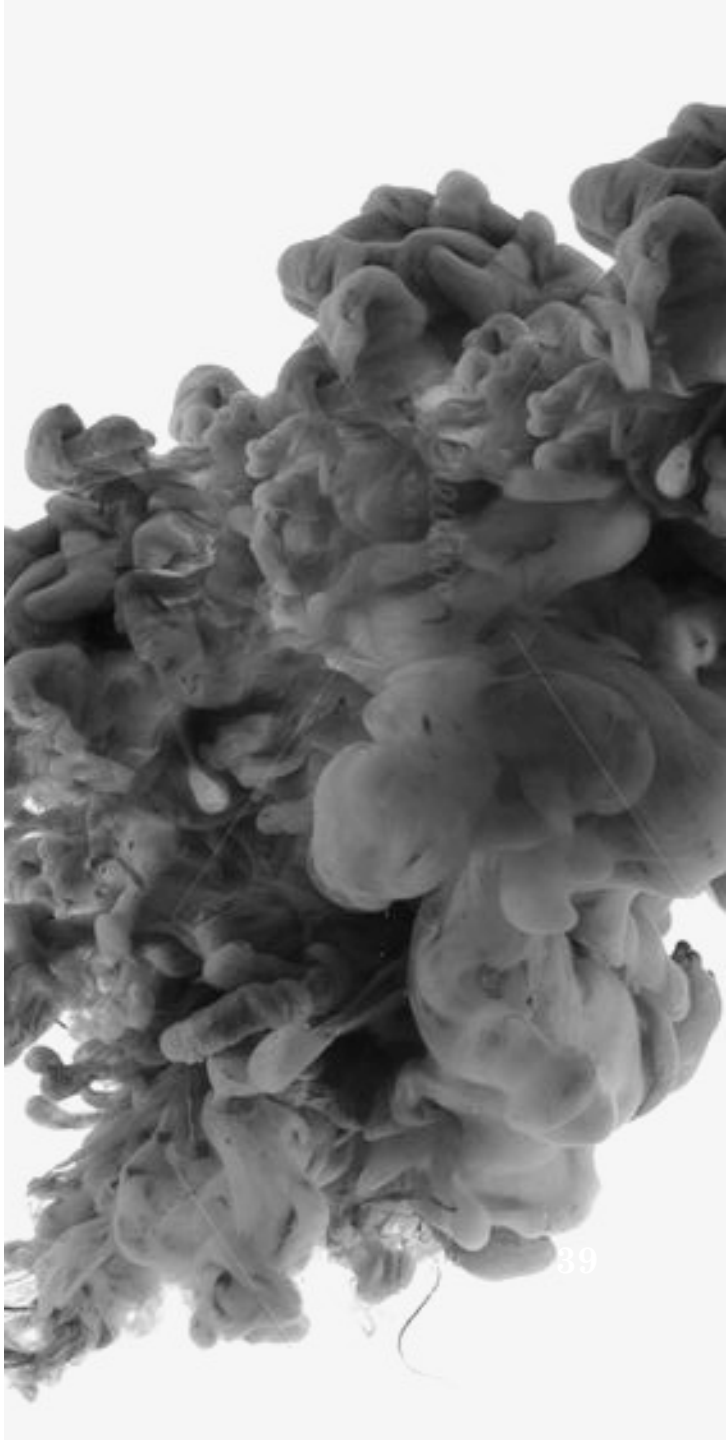


Preliminary Take-home findings

- Across all tested individuals, childhood lead exposure does not predict telomere length at midlife.
  - Or decline across adulthood.

Preliminary Take-home findings

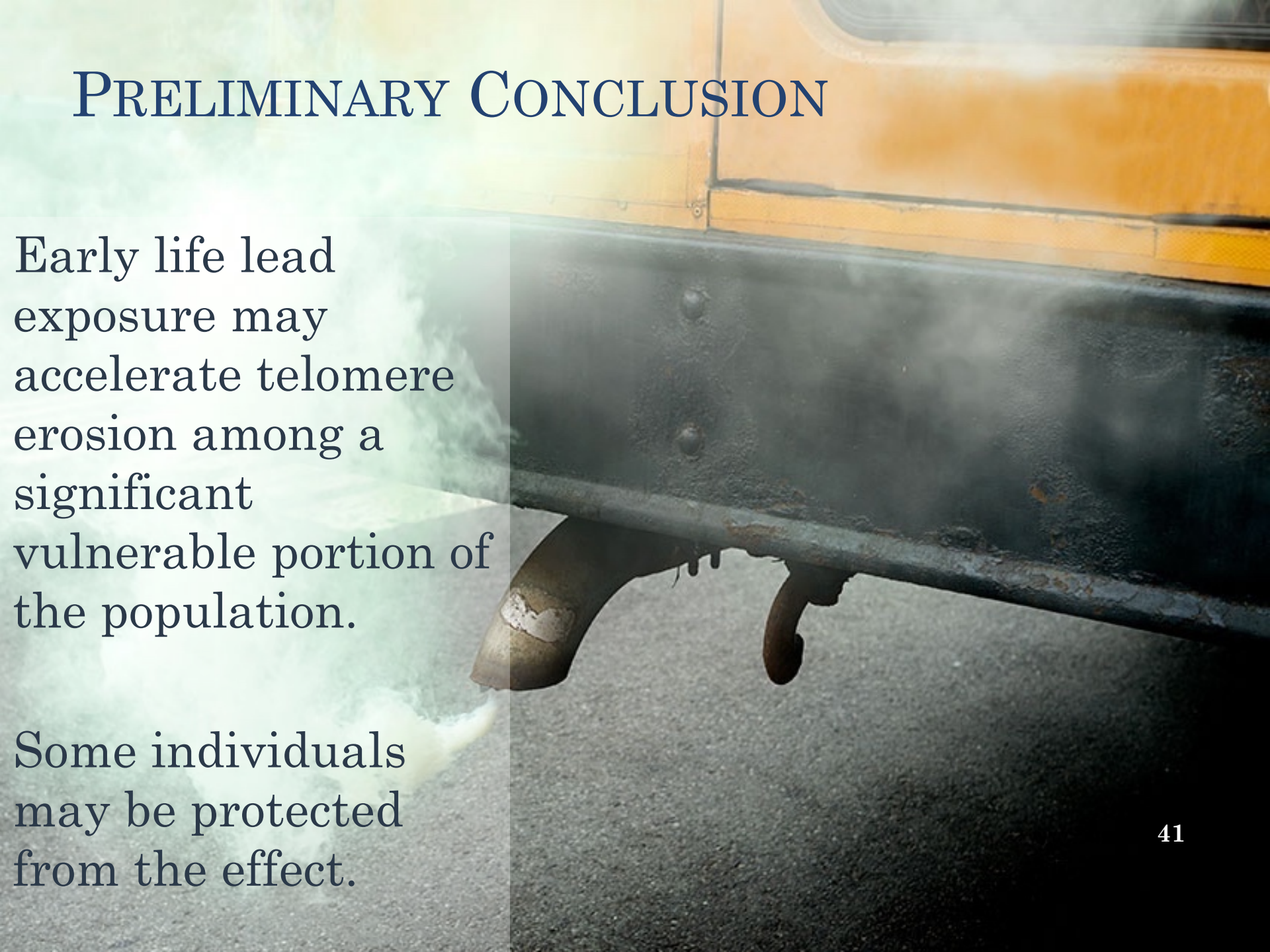
- And yet….
  - Among individuals who do not experience telomere growth, lead is modestly associated with shorter telomeres at midlife.
  - And weakly associated with telomere erosion across adulthood.



Preliminary Take-home findings

- Emerging research question:
  - Are telomere repair mechanisms in 30% of the cohort negating lead-effects on telomere erosion (telomerase?)?

Preliminary Conclusion



Early life lead exposure may accelerate telomere erosion among a significant vulnerable portion of the population.

Some individuals may be protected from the effect.

THANKS TO THE MOFFITT & CASPI LAB

PI's Terrie Moffitt & Avshalom Caspi

Co-authors and collaborators:

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- Benjamin Williams
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- Annchen Knodt
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- Ahmad Hariri
- Jonathan Broadbent
- Richie Poulton
- Sandhya Ramrakha
- David Ireland
- Maxwell Elliott

https://moffittcaspi.trinity.duke.edu/

& the Dunedin study team

Dunedin Multidisciplinary Health & Development Research Unit

DMHDRU

University of Otago

Te Whare Wānanga o Otāgo

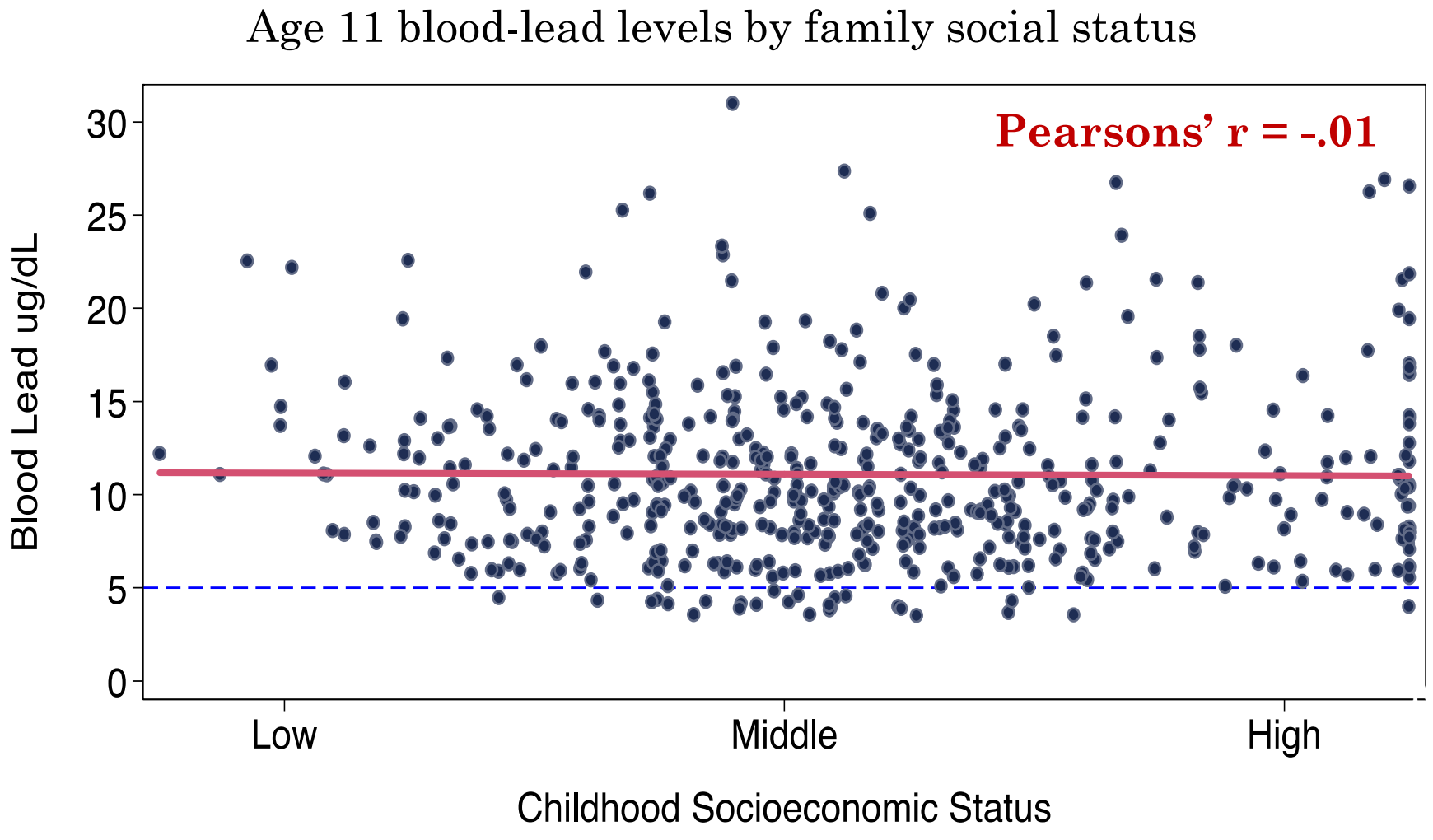
New Zealand

Additional slides

These studies have produced mixed findings

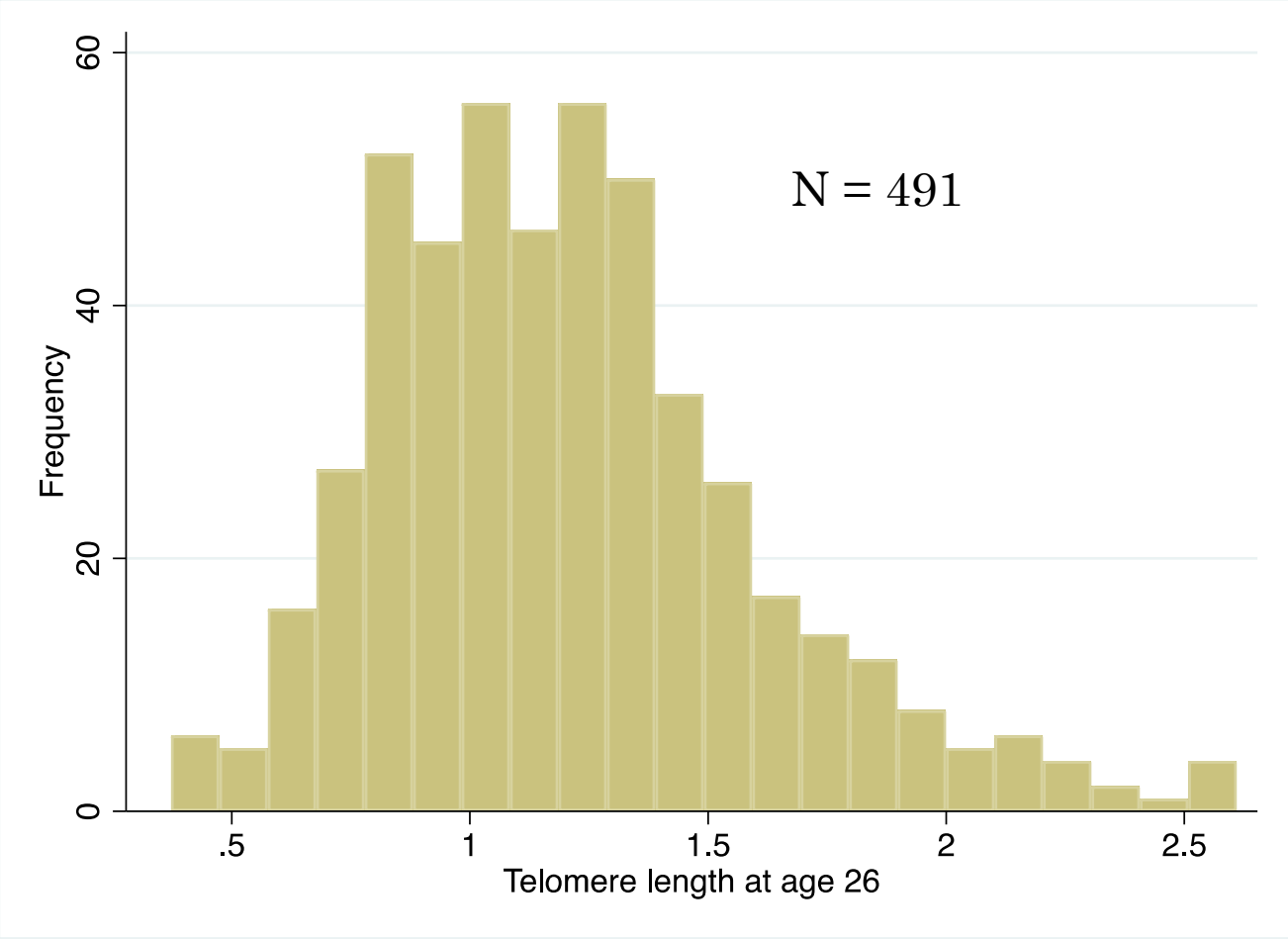
Study	Age (location)	Sample Size	Effect?
Lin et al. 2013	Pre-natal (China)	309	No effect
Pawlas et al. 2015	8 y.o. (Poland)	99	Shorter telomeres (β = -.13)
Wai et al. 2018	Pre-natal (Myanmar)	409	No effect
Herlin et al. 2019	Pre-natal (Argentina)	169	Shorter telomeres
Alegría-Torres et al. 2020	10 y.o. (Mexico)	88	Shorter telomeres (Pearson's r = -.21)

Uniquely, Study member exposure showed no socioeconomic gradient



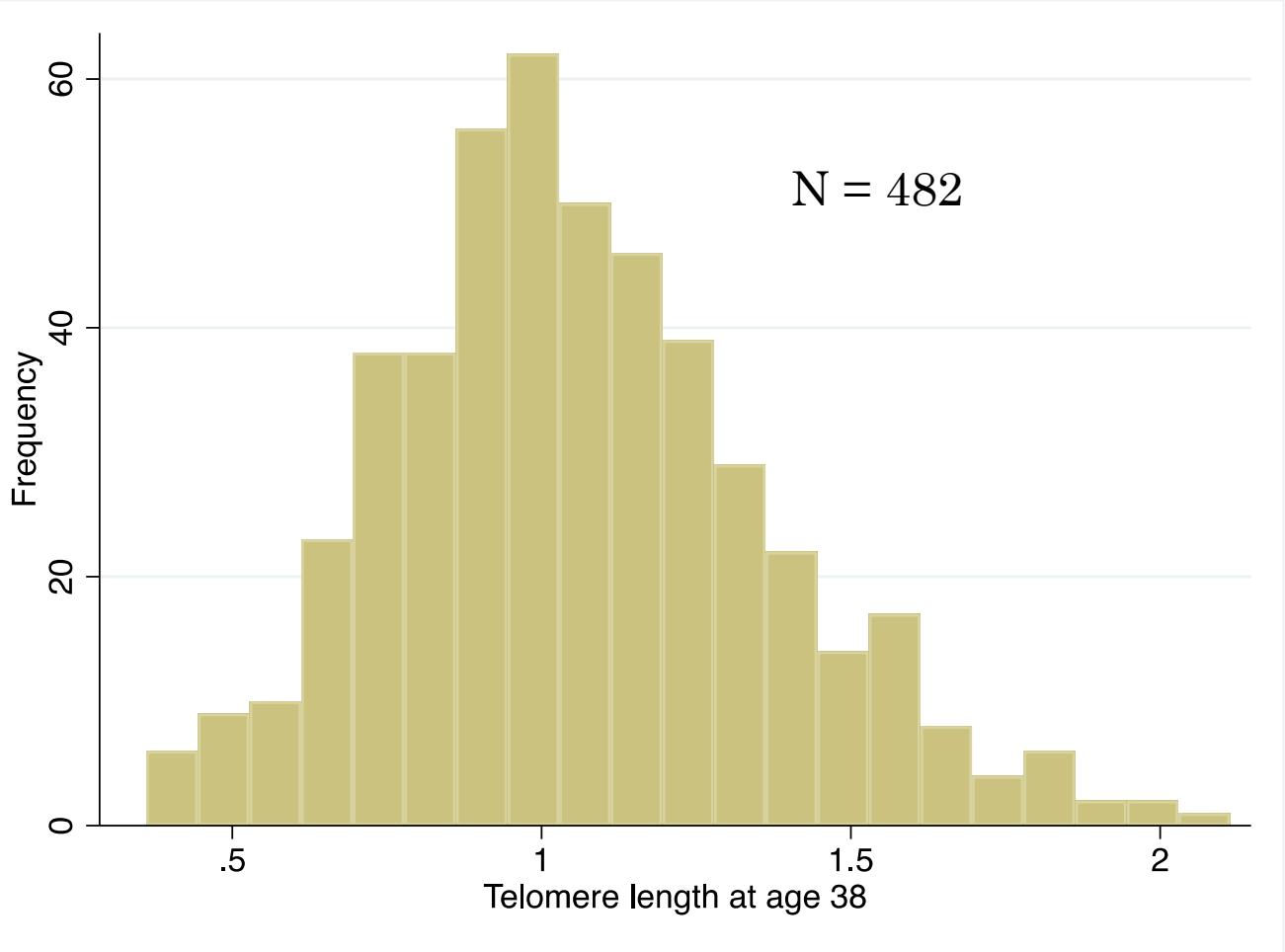
Mean relative leukocyte Telomere length in the Dunedin study (T/S ratio)

Age 26 telomere length (in T/S ratio units): mean 1.21, SD 0.40

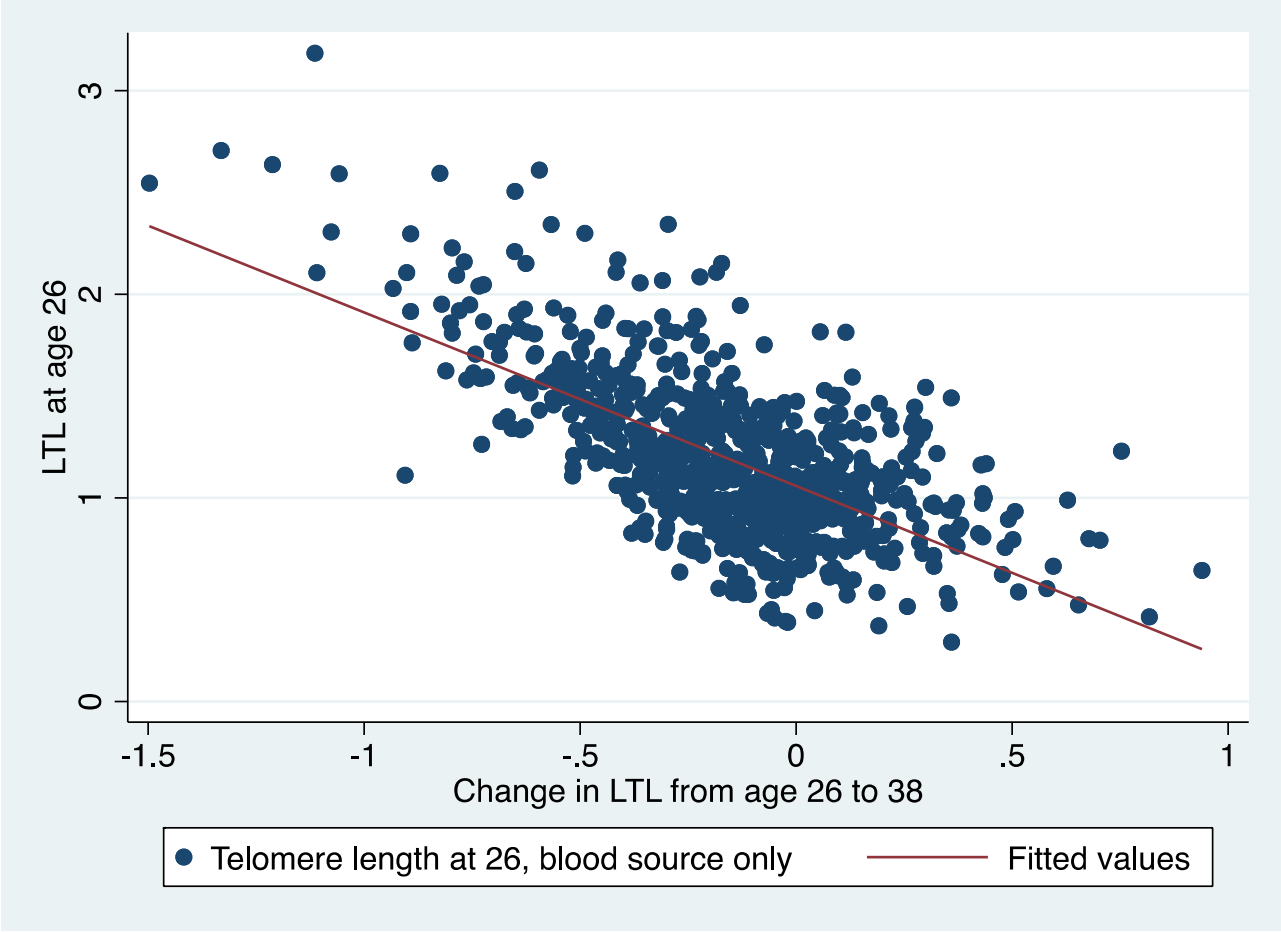


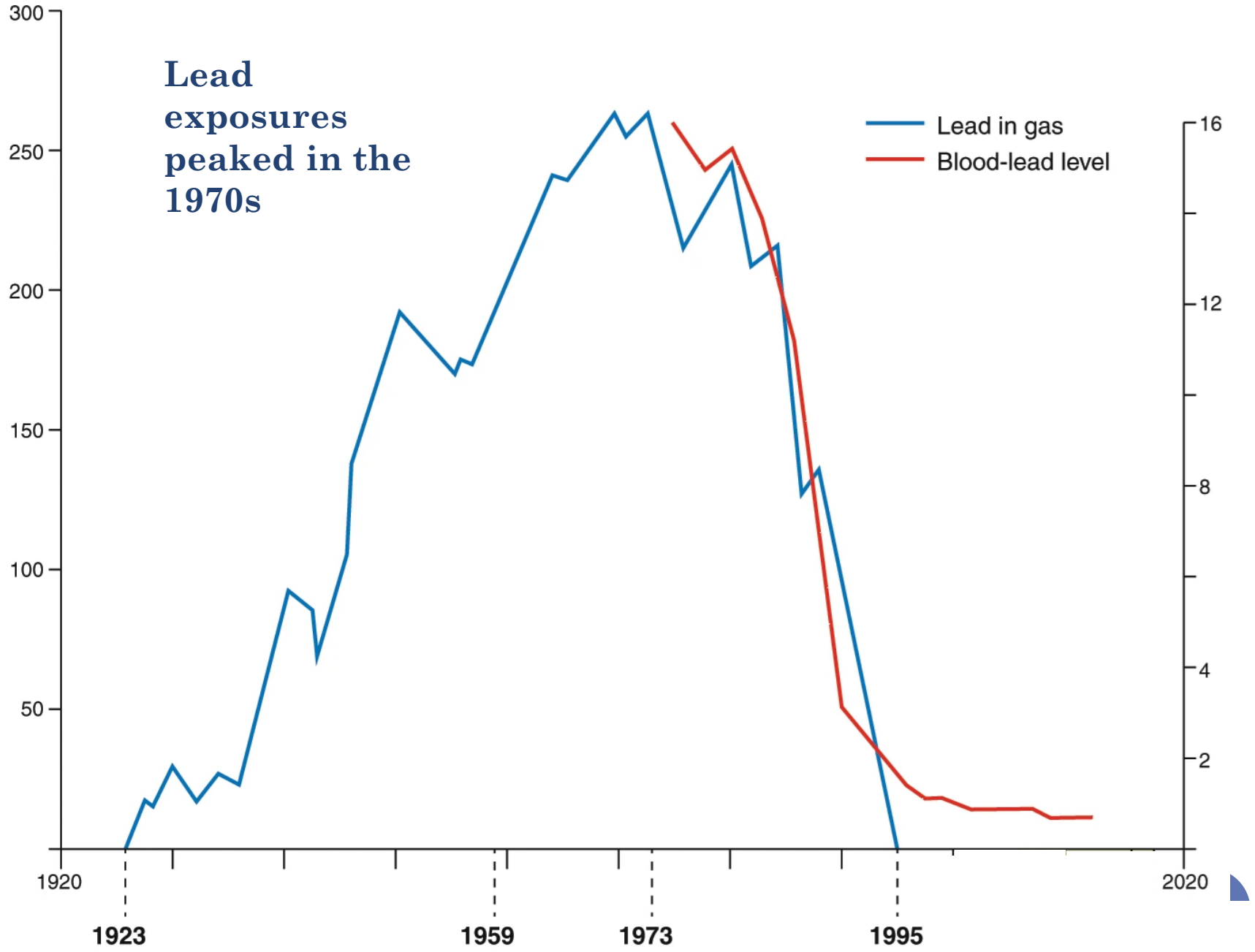
Mean relative leukocyte Telomere length in the Dunedin study (T/S ratio)

Age 38 telomere length (in T/S ratio units): mean 1.06, SD 0.31



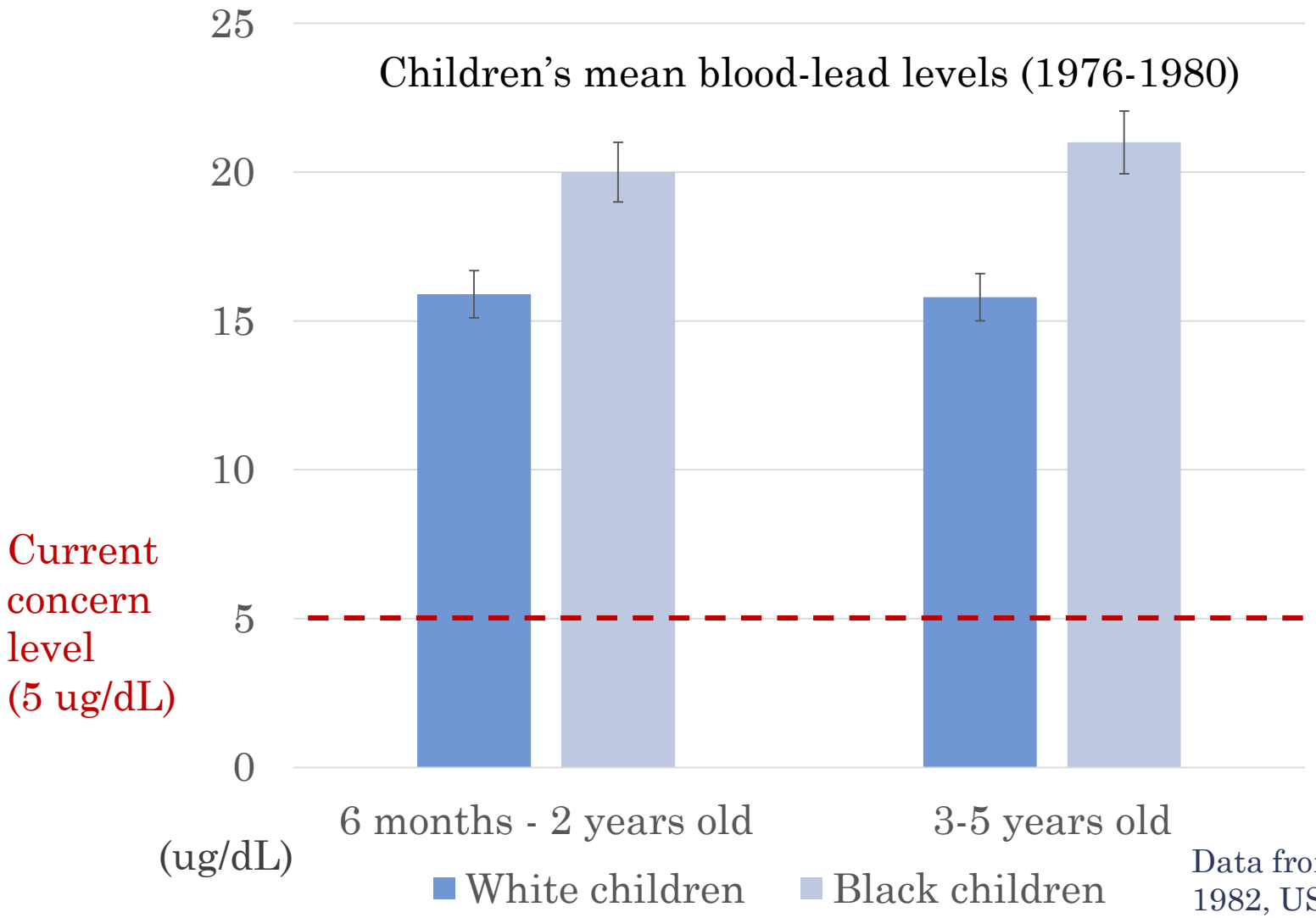
Notably change in LTL is predicted by LTL at baseline (age 26)





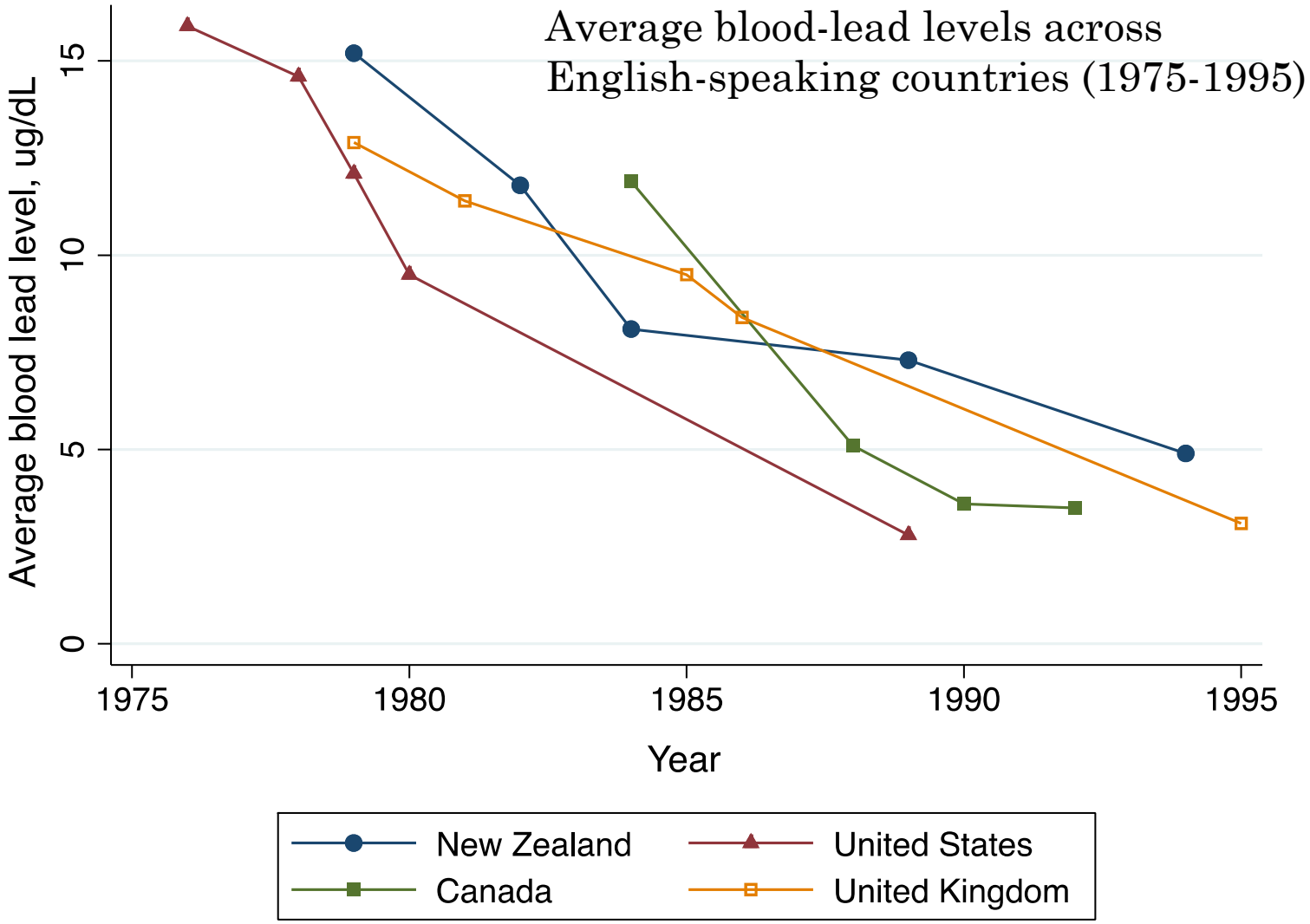
Phase out of lead complete

Take away: peak exposures were 3-4x higher than current levels for clinical attention

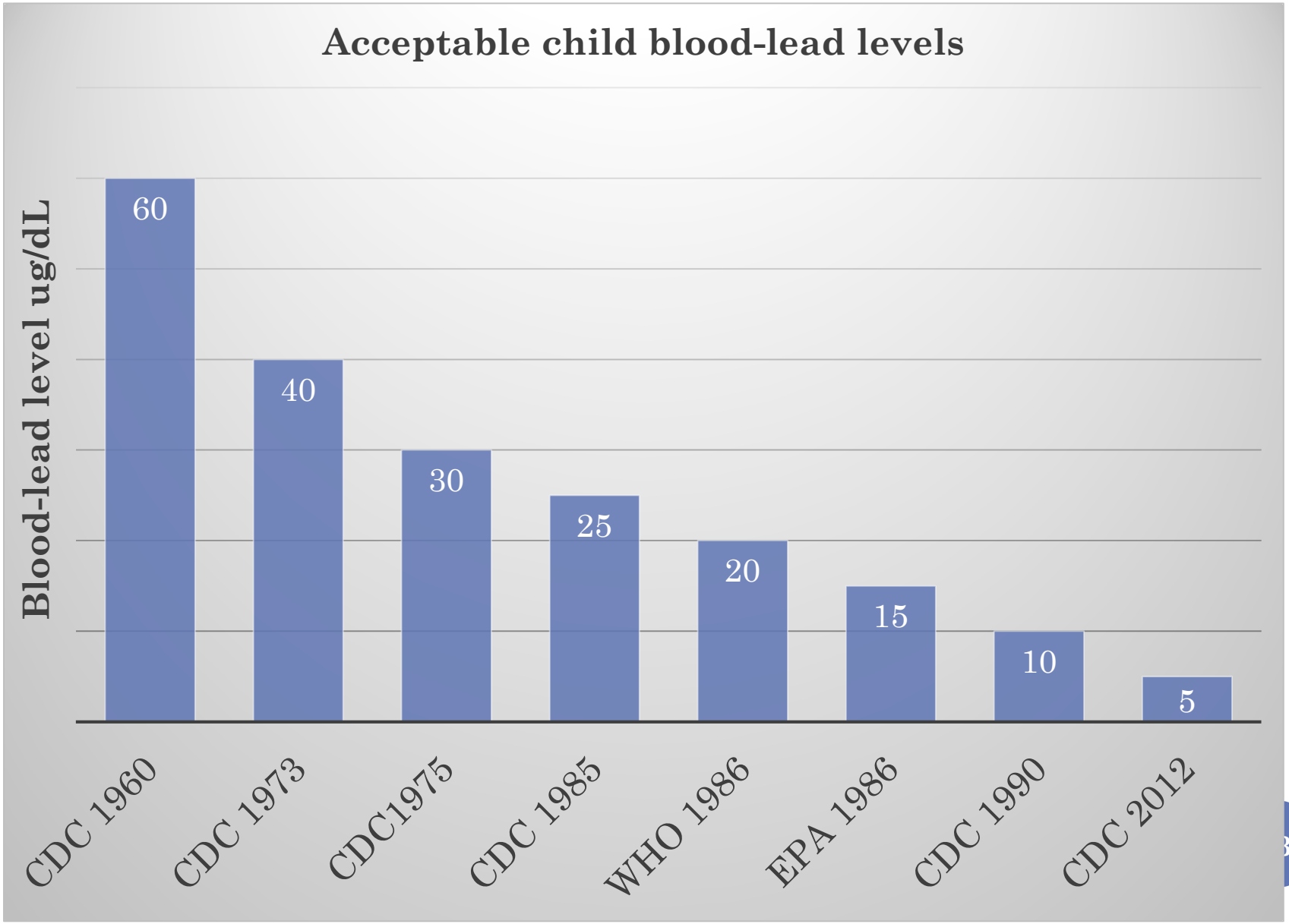


Data from Annest et al. 1982, US health statistics

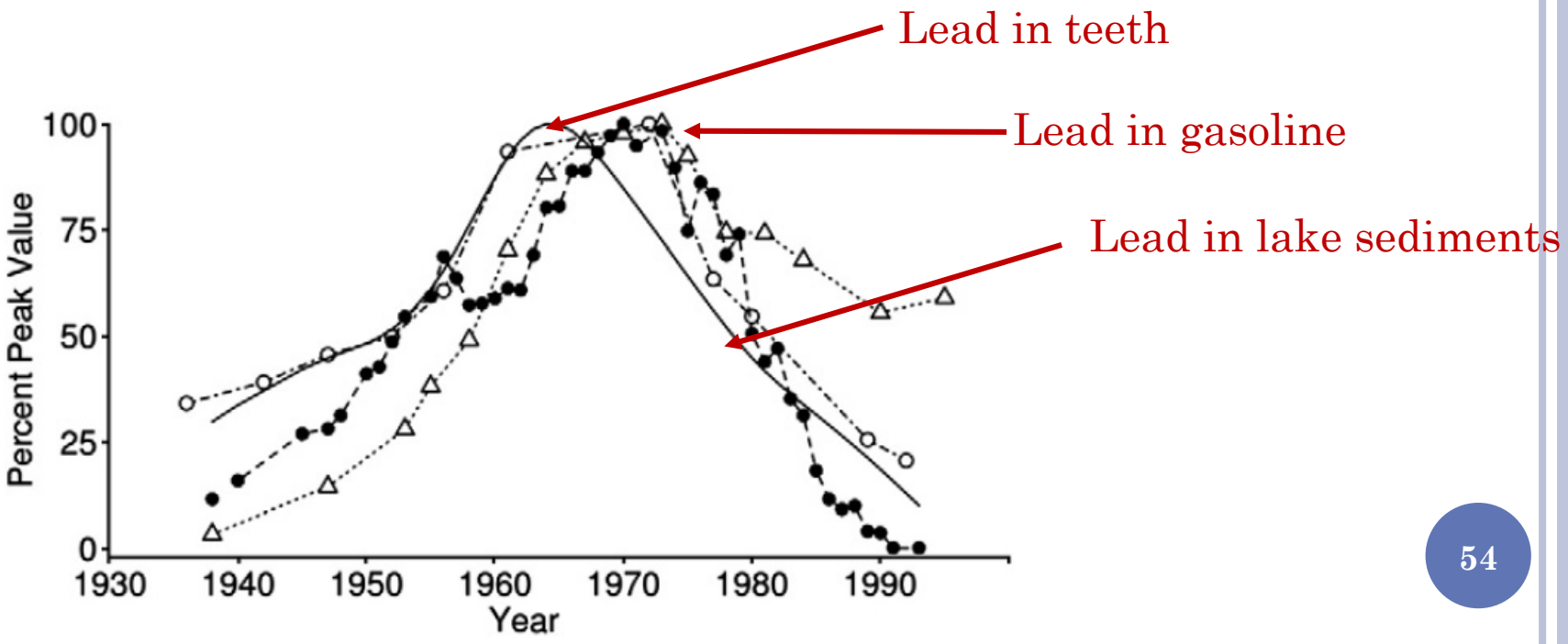
These trends were similar across the developed world.



Data from Thomas et al, 1999


Acceptable child blood-lead levels
Blood-lead level ug/dL
60
40
30
25
20
15
10
5
CDC 1960
CDC 1973
CDC1975
CDC 1985
WHO 1986
EPA 1986
CDC 1990
CDC 2012

In developed countries, lead exposures likely peaked in the early 1970s



(Robbins et al., 2010)