Examining mechanisms underlying the association between adverse childhood experiences and health outcomes in mid-to-older age adults in the CLSA

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clsa élcv
Canadian Longitudinal Study on Aging
Étude longitudinale canadienne sur le vieillissement

McMaster University

Adverse Childhood Experiences (ACEs)

Abuse

Physical

Emotional

Sexual

Neglect

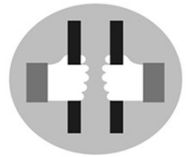
Physical

Emotional

Intimate Partner Violence

Other Household Adversities

Mental Illness



Incarcerated Relative

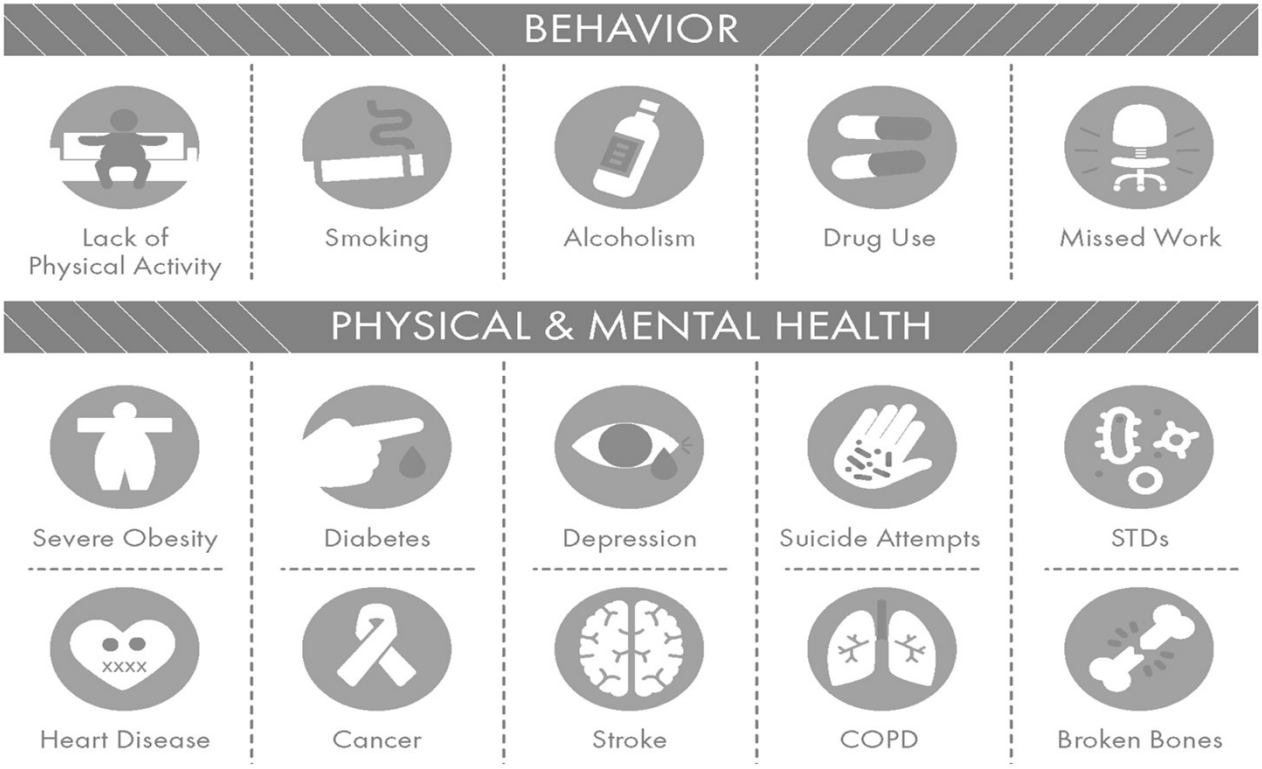
Death, multiple and traumatic loss

Substance Abuse

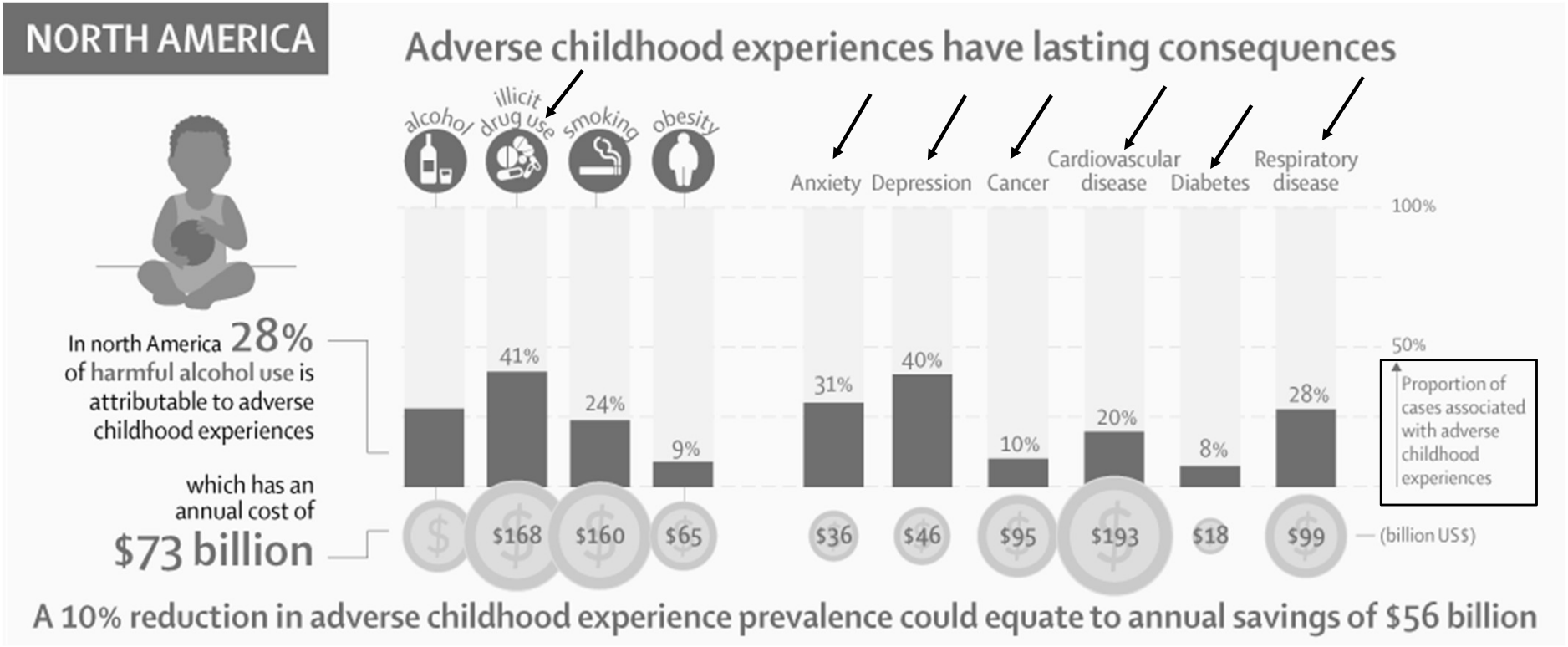
Divorce

ACE EFFECT

ACEs, individually and in combination, are linked to the delay of early developmental milestones, early- and late-life psychiatric outcomes, chronic physical disease, and premature mortality.

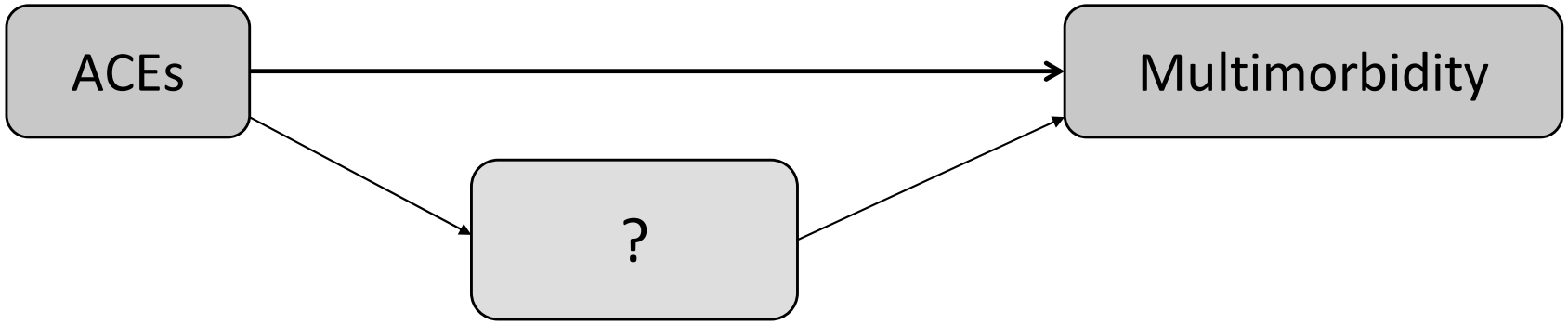


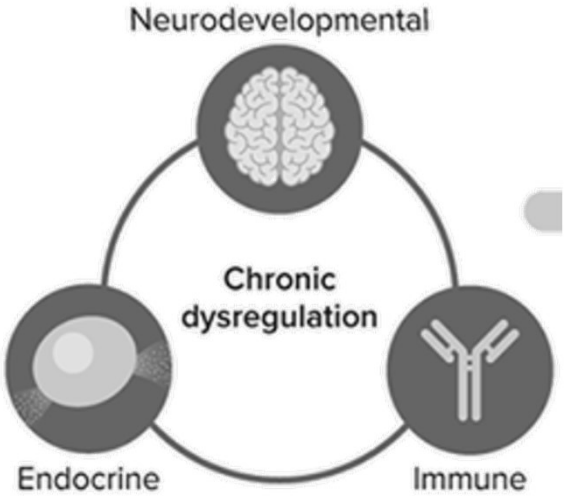
Background



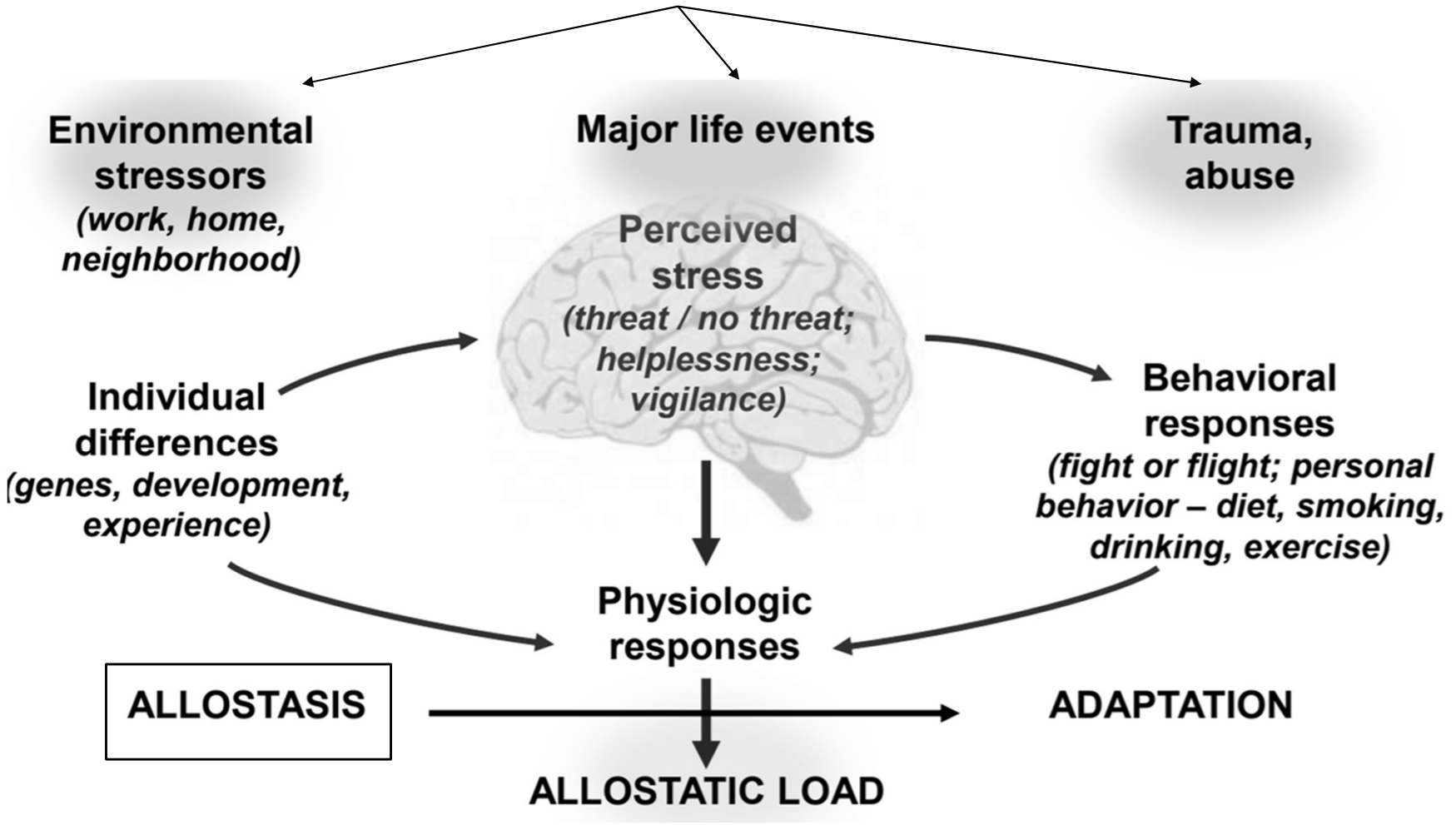
Bellis et al., Lancet Public Health, 2019

Mechanisms linking ACEs to health outcomes



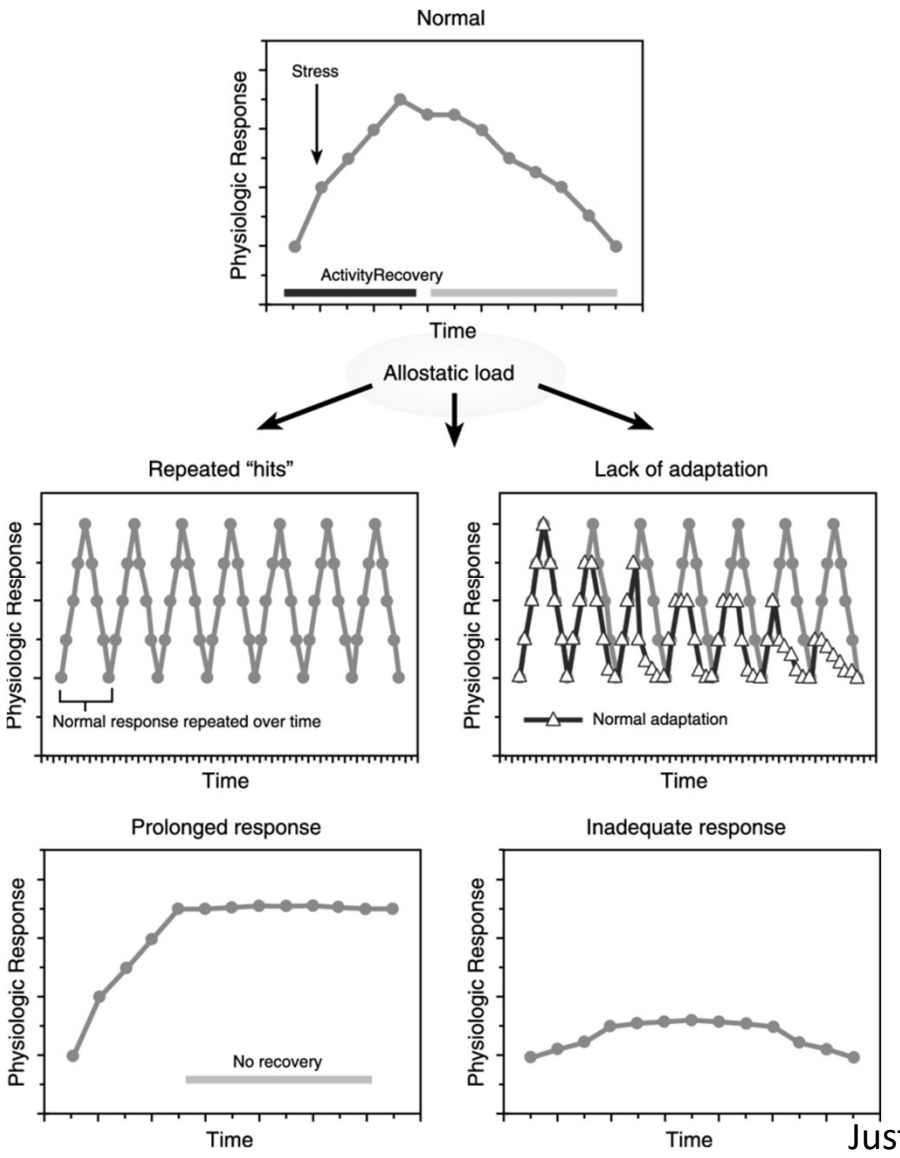


ACEs become biologically embedded


Environmental stressors
(work, home, neighborhood)
Major life events
Trauma, abuse
Perceived stress
(threat / no threat; helplessness; vigilance)
Individual differences
(genes, development, experience)
Behavioral responses
(fight or flight; personal behavior – diet, smoking, drinking, exercise)
Physiologic responses
ALLOSTASIS
ADAPTATION
ALLOSTATIC LOAD

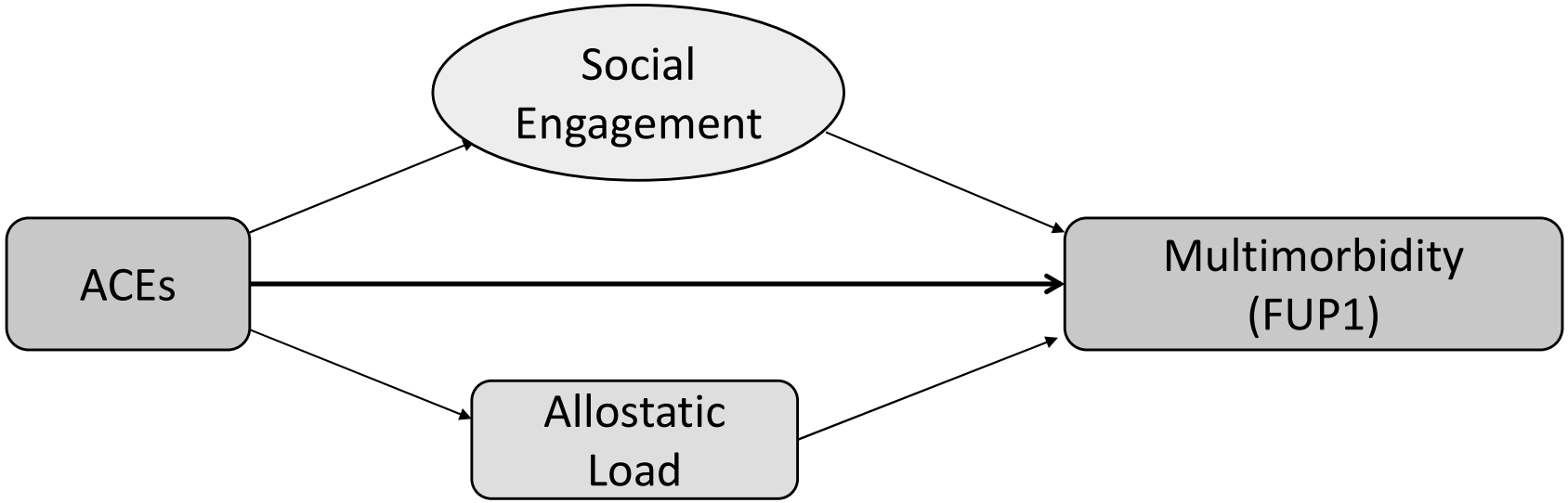
McEwen, 2000

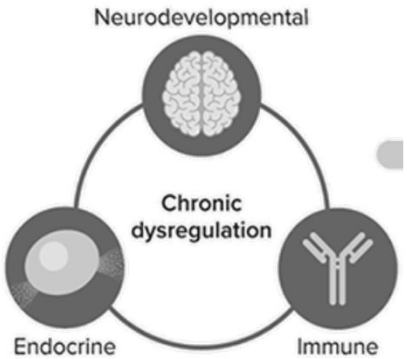
Allostatic states



Juster et al., 2010

Mechanisms linking ACEs to health outcomes





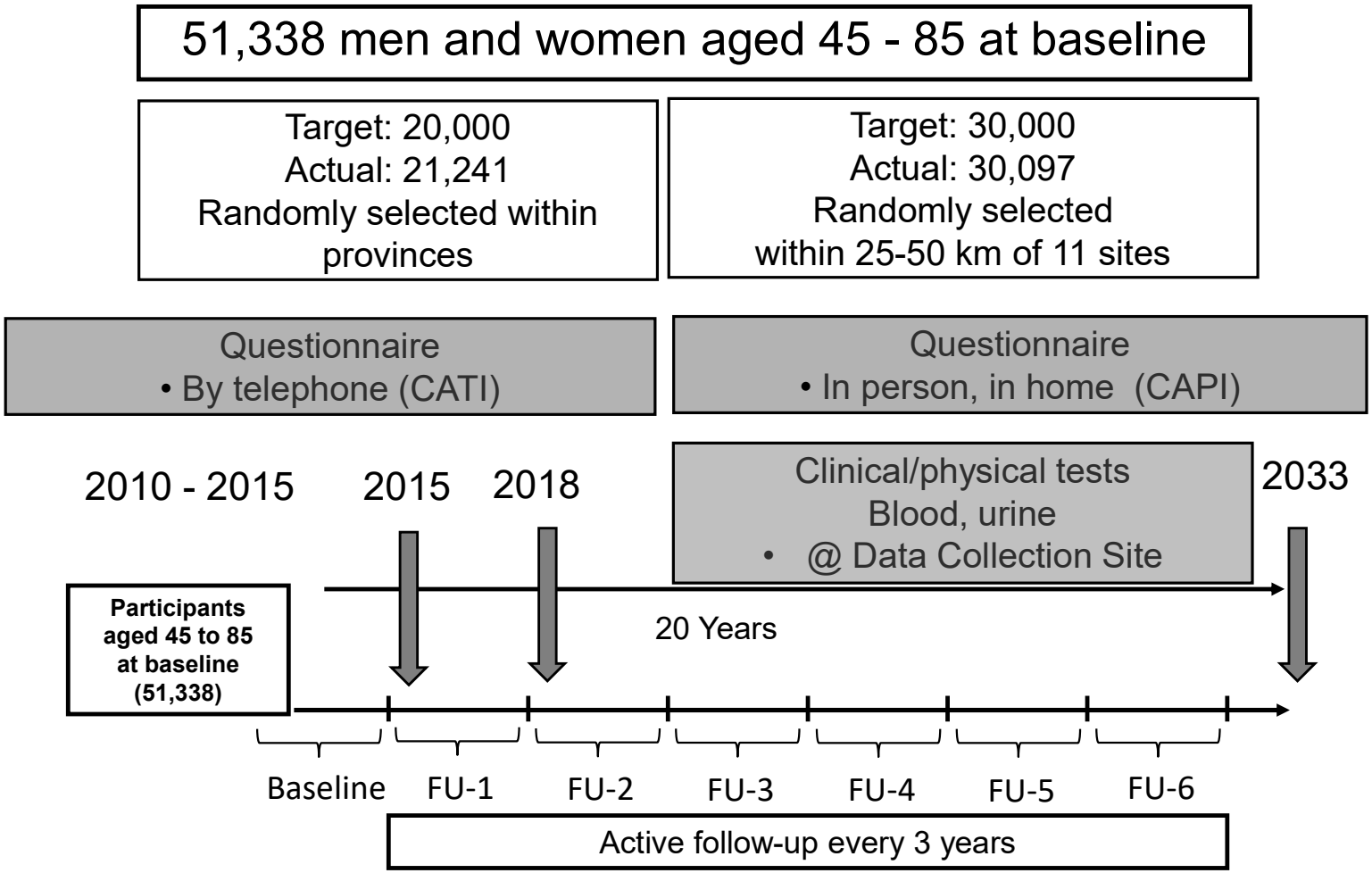
Objectives

1. Estimate the prevalence of individual ACEs by sociodemographic characteristics among middle-aged and older adults in Canada.

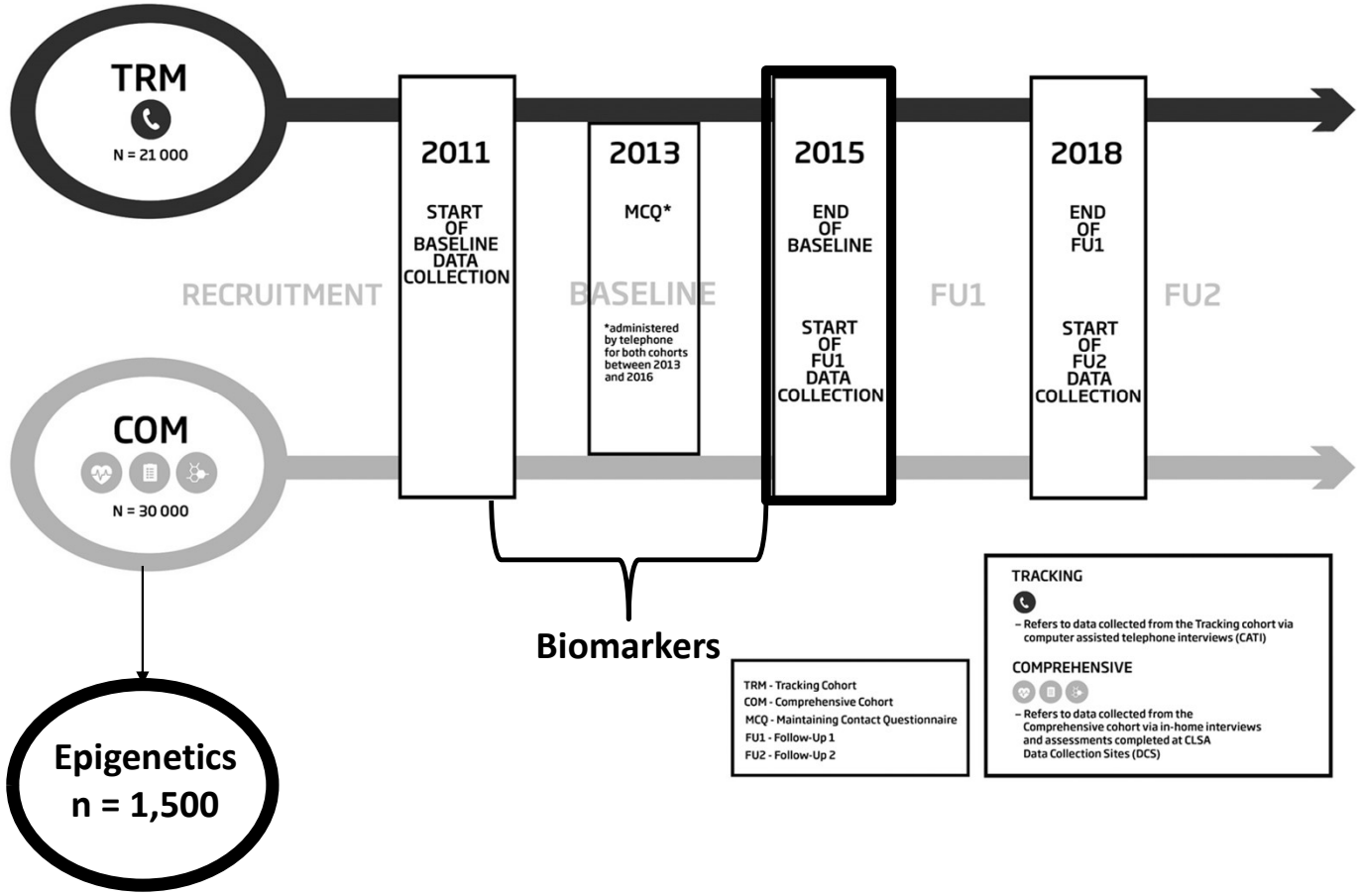
2. Determine whether allostatic load and social engagement mediate the association between ACEs and multimorbidity after adjusting for covariates.

3. Examine whether the mediation model varies by sex and age groups.

Canadian Longitudinal Study on Aging Research Platform



CLSA Data Collection



Measures: ACEs

Physical abuse
Slap-hit (3+)
Push-grab (3+)
and/or Kick-bit

Sexual abuse
Forced sexual touch
or activity

Emotional abuse
Parents/guardians
saying hurtful or
Insulting things (3+)

Neglect
Parents/guardians not
take care of basic
needs

Intimate Partner Violence
Verbal abuse (6+)
and/or Physical
violence (3+)

Parental Separation
Yes vs. No

Parental Death
Yes vs. No

Family Mental Health Problems
Yes vs. No

Total ACEs score

Measures: Allostatic Load

White blood cells
HbA1c
Albumin
Alanine amino transferase
Creatinine
Hemoglobin
Ferritin
CRP

Total cholesterol
HDL cholesterol
LDL cholesterol
Triglycerides

Systolic blood pressure
Diastolic blood pressure
Heart rate

BMI
Waist circumference
Waist hip ratio

High-risk category for each biomarker was defined using the age- and sex-specific upper or lower quartile of the sample's distribution of a specific biomarker variable

Allostatic load index: total number of biomarkers falling within the high-risk categories

Measures: Social Engagement

Social support

Medical Outcomes Study and Social Support Survey

Measures perception of emotional support, instrumental assistance, information, guidance and feedback, personal appraisal support, and companionship

Scores were calculated by averaging responses and transforming them to range from 0 to 100

Social participation

Frequency of participation
- at least daily
- weekly
- monthly
- or yearly

in community-related activities

A latent variable for social engagement was created from social support and participation scales.

Measures: Multimorbidity

Musculoskeletal
(osteoarthritis, rheumatoid arthritis, osteoporosis, and back problems)

Cardiovascular
(heart disease, angina, myocardial infarction and peripheral vascular disease)

Respiratory
(asthma, chronic obstructive pulmonary disease)

Endocrinological
(thyroid disorders, diabetes)

Neurological
(stroke/cerebral vascular event, transient ischemic attack, Parkinson's disease, multiple sclerosis, epilepsy, and migraine headaches)

Psychological
(Depression and other mood disorders)

Gastrointestinal
(ulcer, bowel disorder, and bowel and urinary incontinence)

Renal
(kidney disease)

Ophthalmological
(cataracts, glaucoma, and macular degeneration)

Cancer
(all cancers other than non-melanoma)

Each condition was assessed for presence or absence and summed up to create a total score

Measures: Statistical Analysis

Prevalence Analysis

Logistic regression was used to obtain the adjusted prevalence estimates of ACEs within groups formed by the sociodemographic characteristics

Mediation Analysis

Structural equation modeling with Full Information Maximum Likelihood (FIML)
Covariates: age, sex, income, physical activity, nutrition, smoking, and alcohol consumption

The path models

Direct effect of ACEs on allostatic load, social engagement, and multimorbidity
Direct effect of allostatic load and social engagement on multimorbidity
Indirect effect of ACEs on multimorbidity via allostatic load index and social engagement
A covariance between the two mediators – social engagement and allostatic load

Results: Distribution of ACEs (n=44,817)

At least 1 ACE
62%

2 or more ACEs
36%

3 or more ACEs
20%

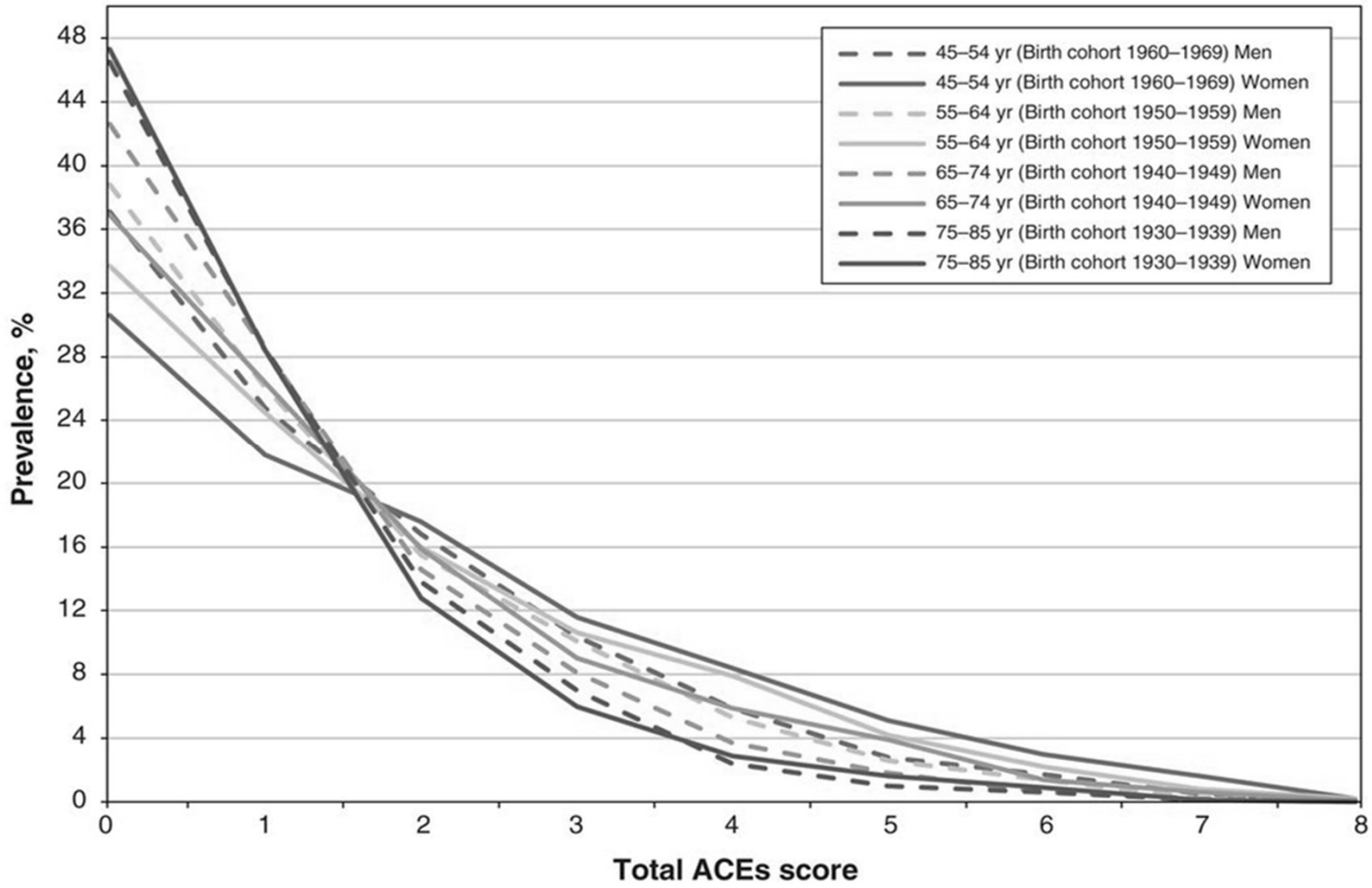
Physical abuse
26%

Intimate partner violence
22%

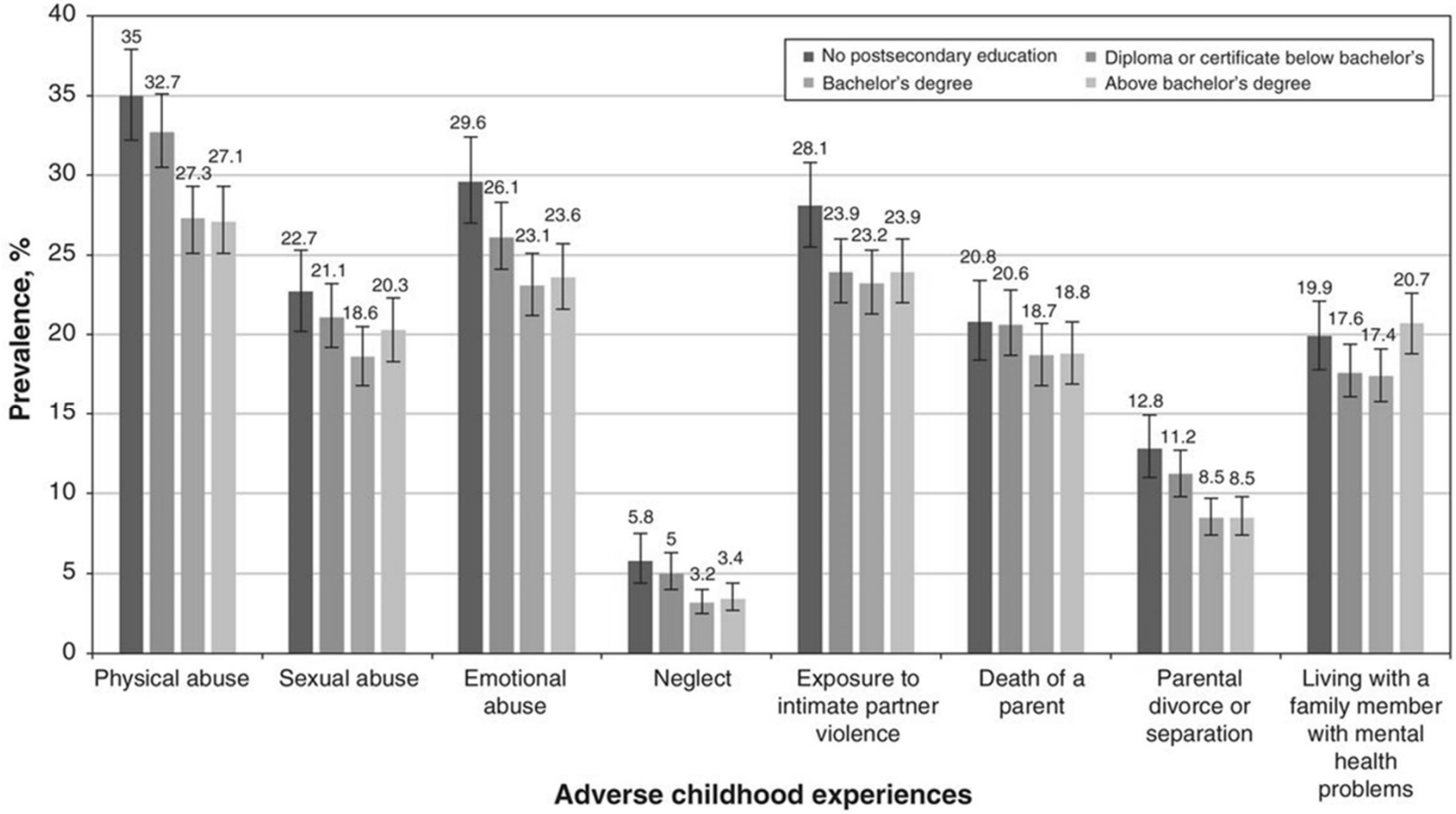
Emotional abuse
22%

Joshi D., Raina P., Tonmyr L., MacMillan H.L., & Gonzalez A. CMAJ open. 2021

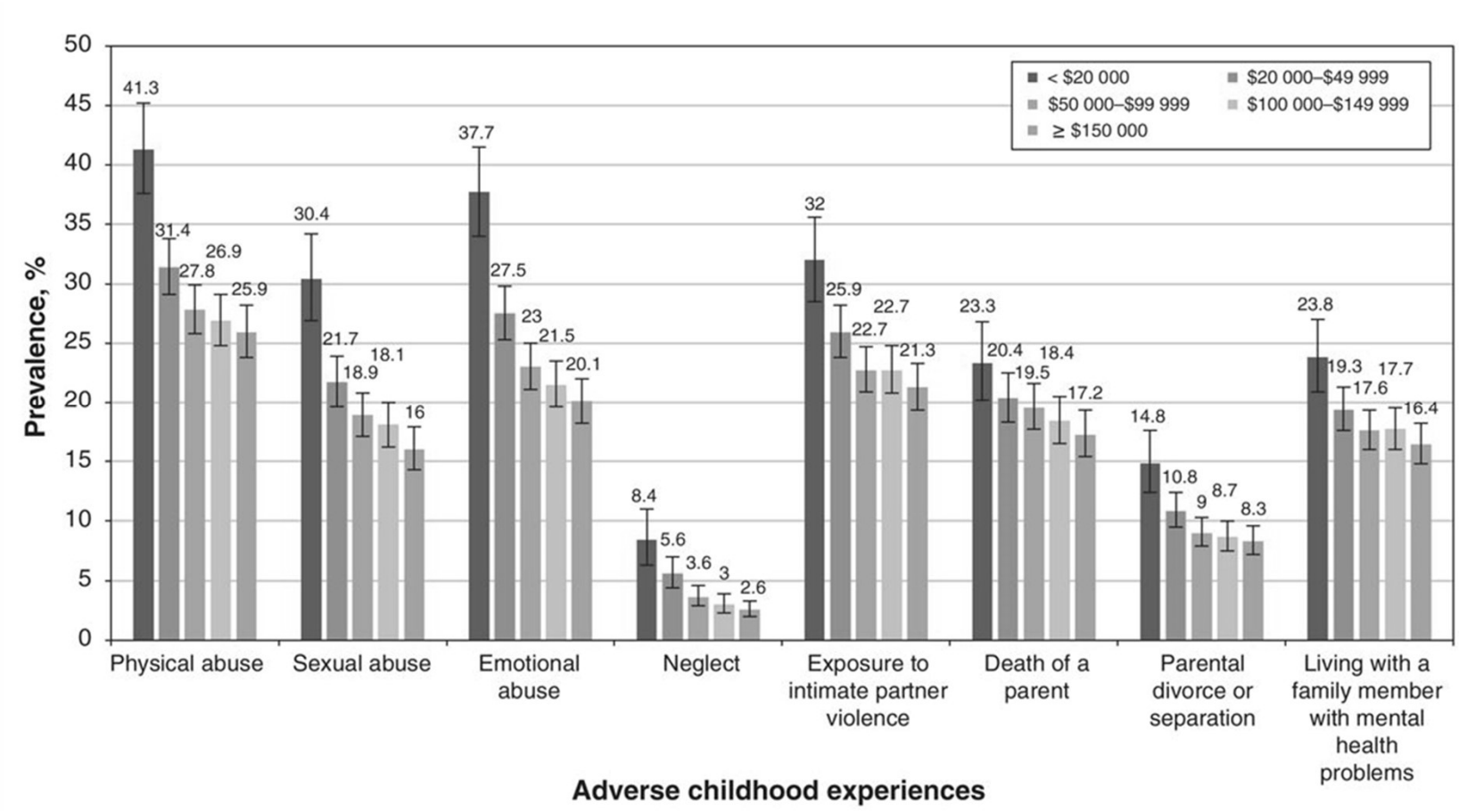
Weighted prevalence for total ACEs score by age and sex groups



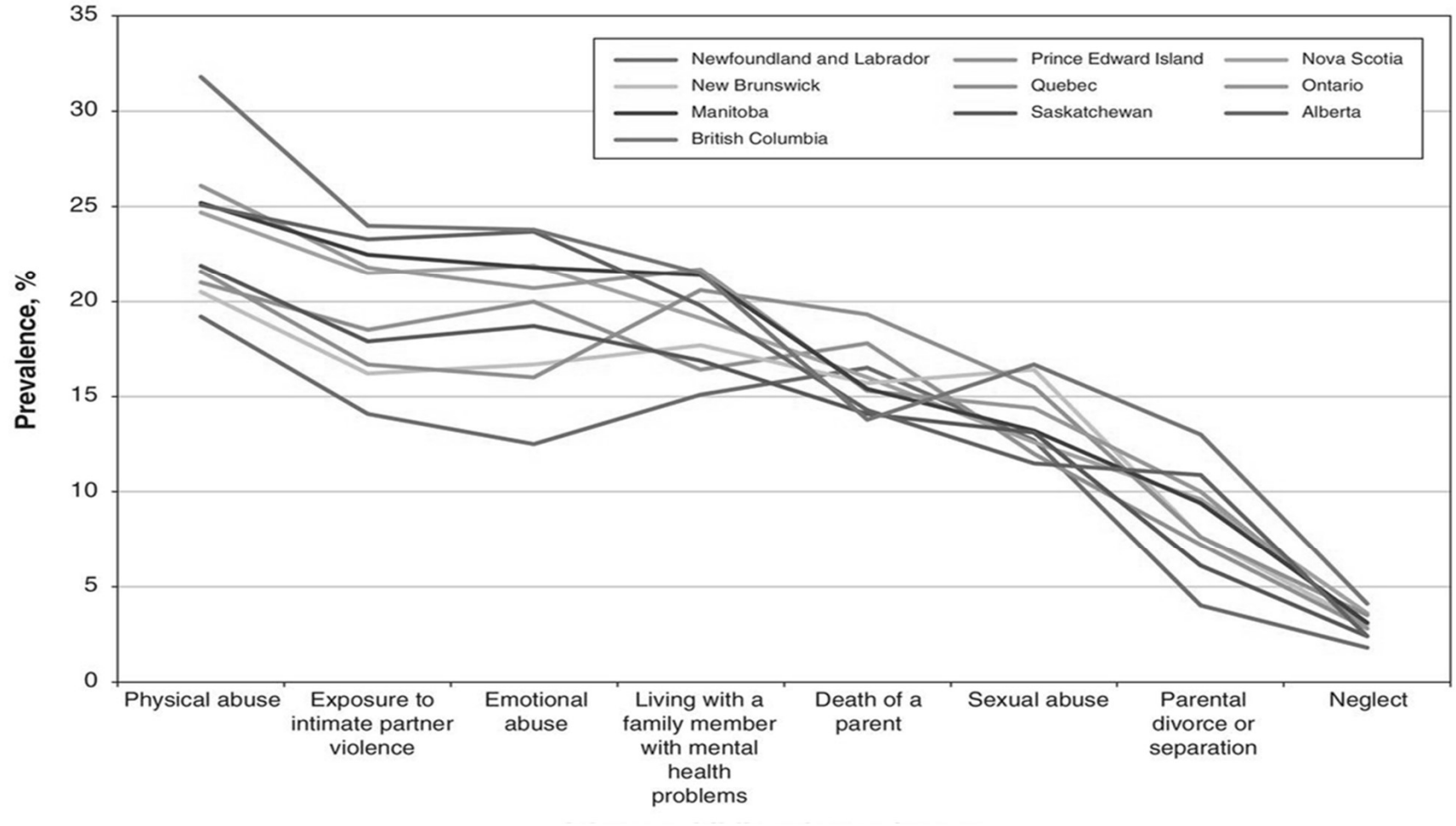
Individuals with no postsecondary education or education below a bachelor's degree had higher prevalence of ACEs



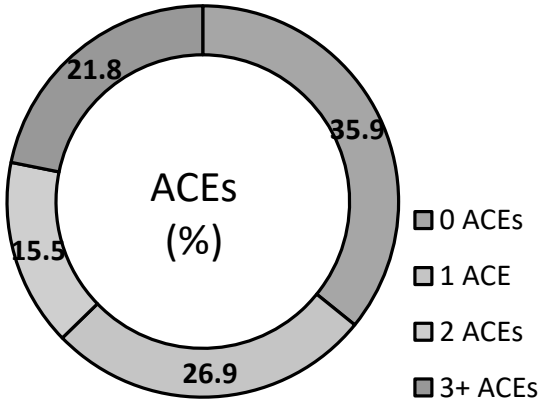
Individuals who had household income less than $20000 had higher prevalence of ACEs

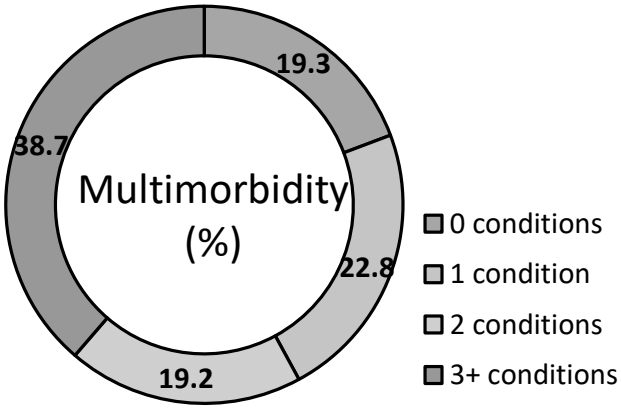


Higher proportions of ACEs were reported for BC, Alberta, Manitoba, Ontario and Quebec.



Distribution of ACEs, mediators, and multimorbidity (n=27,765)



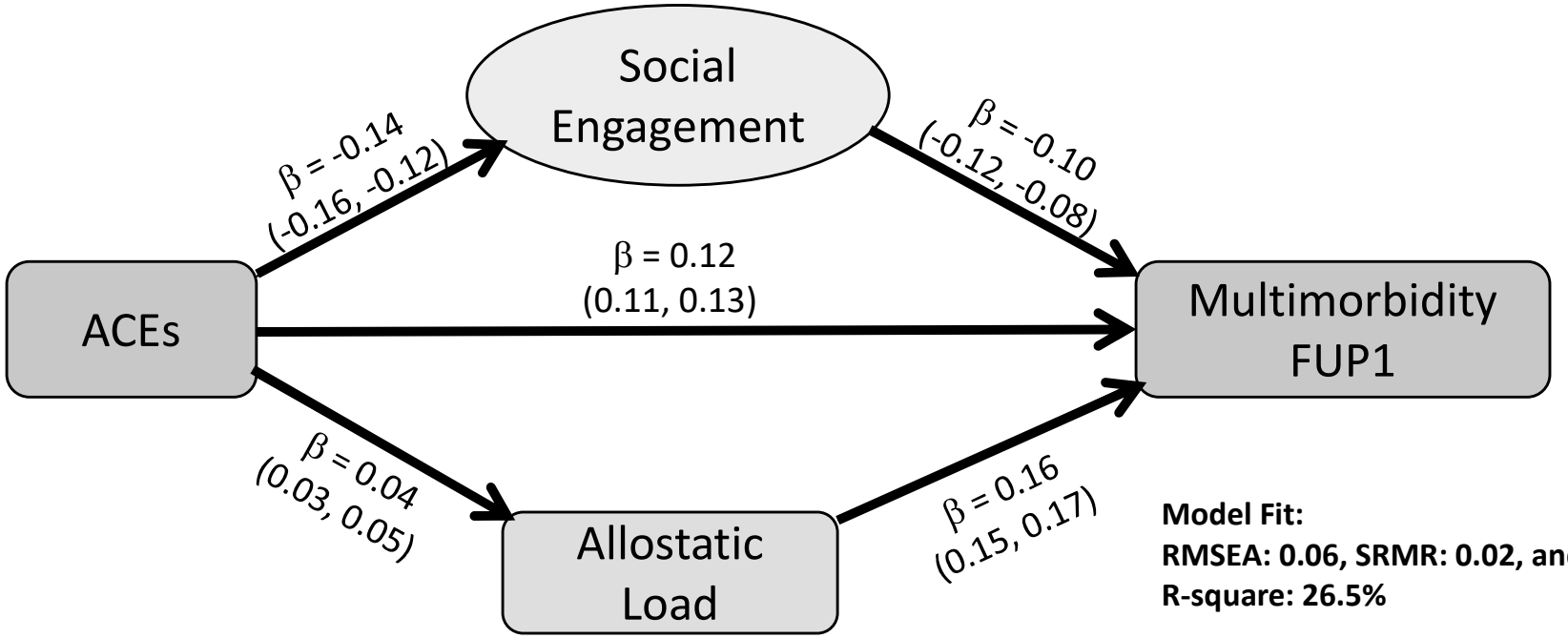


Allostatic load index, mean (S.E.)	4.2 (0.02)
Social participation, mean (S.E.)	3.0 (0.01)
Social support, mean (S.E.)	82.6 (0.10)

Total annual household income, *n* (%)	
<$ 20 000	1303 (4.2)
$20 000–<50 000	5617 (17.8)
$50 000–<100 000	9286 (33.5)
$100 000–<150 000	5218 (22.6)
$150 000 or more	4617 (21.8)
Low physical activity, *n* (%)	20 585 (72.9)
Low nutritional intake, *n* (%)	11 302 (39.6)
Smoking, *n* (%)	
Never smoker	16 568 (87.1)
Occasional smoker	447 (2.6)
Current smoker 0–15 cigarettes/day	1089 (6.4)
Current smoker 15+ cigarettes/day	690 (3.9)
Alcohol consumption, mean (S.E.)	3.9 (0.01)

Atkinson L., Joshi D., Raina P., Griffith L.E., MacMillan H., & Gonzalez A. Psychological Medicine. 2021

Mechanisms linking ACEs to health outcomes (overall Comp. sample)



Model Fit:
RMSEA: 0.06, SRMR: 0.02, and CFI: 0.97
R-square: 26.5%

Model was adjusted for age, sex, income, smoking, nutrition, and alcohol consumption.
Covariance between social engagement and allostatic load was included.
All paths are statistically significant, $p < .0001$.

The direct effect of ACEs and the indirect effect of ACEs through social engagement and allostatic load on multimorbidity were stronger in females than males.

Pathway	Males	Females
ACEs→multimorbidity	0.10 (0.08, 0.12)	0.13 (0.11, 0.15)
Indirect	0.01 (0.01, 0.01)	0.03 (0.02, 0.04)
Total	0.11 (0.09, 0.13)	0.15 (0.13, 0.17)
ACEs→allostatic load	0.04 (0.02, 0.06)	0.05 (0.03, 0.07)
ACEs→social engagement	−0.11 (−0.13, −0.09)	−0.17 (−0.20, −0.14)
Allostatic load→multimorbidity	0.15 (0.13, 0.17)	0.16 (0.14, 0.18)
Social engagement→multimorbidity	−0.07 (−0.10, −0.04)	−0.12 (−0.15, −0.09)

R-square males: 23% **R-square females: 28%**

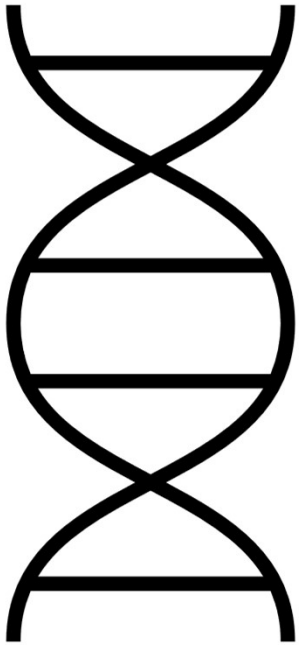
Model was adjusted for age, sex, income, smoking, nutrition, and alcohol consumption.

Covariance between social engagement and allostatic load was included.

The direct and indirect effects of ACEs on multimorbidity were stronger in the younger age group (45–54 years) and weakened with increasing age.

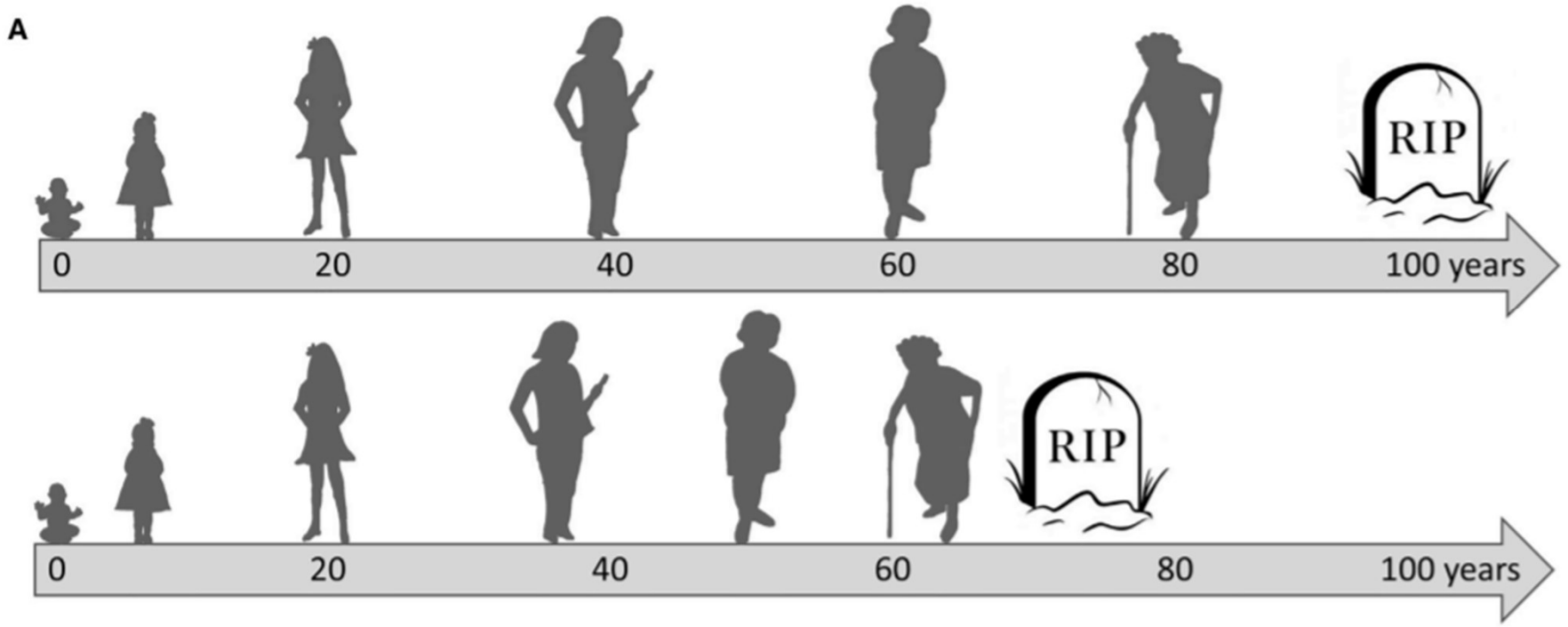
Pathway	45–54 years	55–64 years	65–74 years	75–85 years
ACEs→multimorbidity	0.15 (0.13, 0.17)	0.13 (0.11, 0.15)	0.11 (0.08, 0.14)	0.11 (0.08, 0.14)
Indirect	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.02 (0.01, 0.03)	0.006 (N.S.) (−0.002, 0.01)
Total	0.18 (0.16, 0.20)	0.16 (0.14, 0.18)	0.13 (0.10, 0.16)	0.10 (0.07, 0.13)
ACEs→allostatic load	0.06 (0.04, 0.08)	0.03 (0.01, 0.05)	0.03 (0.00, 0.06)	0.004 (N.S.) (−0.03, 0.04)
ACEs→social engagement	−0.14 (−0.17, −0.11)	−0.17 (−0.20, −0.14)	−0.14 (−0.18, −0.10)	−0.09 (−0.14, −0.04)
Allostatic load→multimorbidity	0.24 (0.21, 0.27)	0.21 (0.19, 0.23)	0.14 (0.11, 0.17)	0.10 (0.06, 0.14)
Social engagement→multimorbidity	−0.12 (−0.17, −0.07)	−0.13 (−0.17, −0.09)	−0.10 (−0.13, −0.07)	−0.06 (−0.12, 0.001)
	R-square: 15%	**R-square: 15%**	**R-square: 9%**	**R-square: 6%**

Model was adjusted for age, sex, income, smoking, nutrition, and alcohol consumption.
Covariance between social engagement and allostatic load was included.



Epigenetics: DNA Methylation Age (DNAmAge)

Biological Aging



DNA Methylation

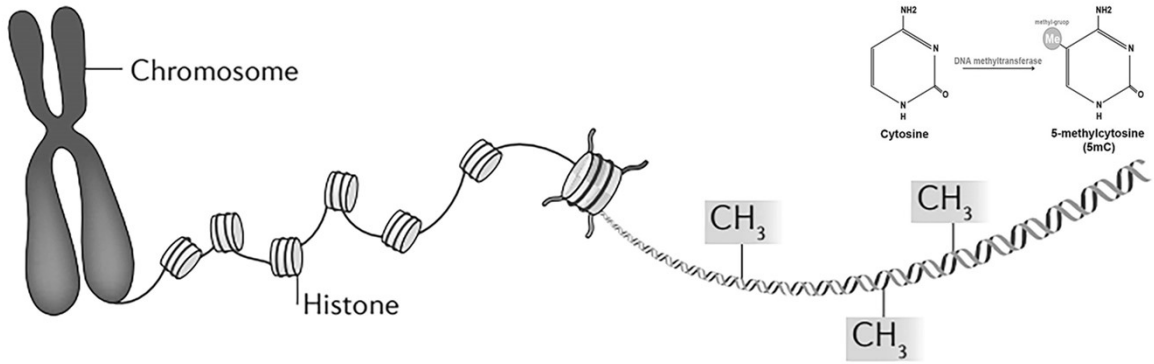
An epigenetic mark

Involved in gene regulation

Occurs across the genome

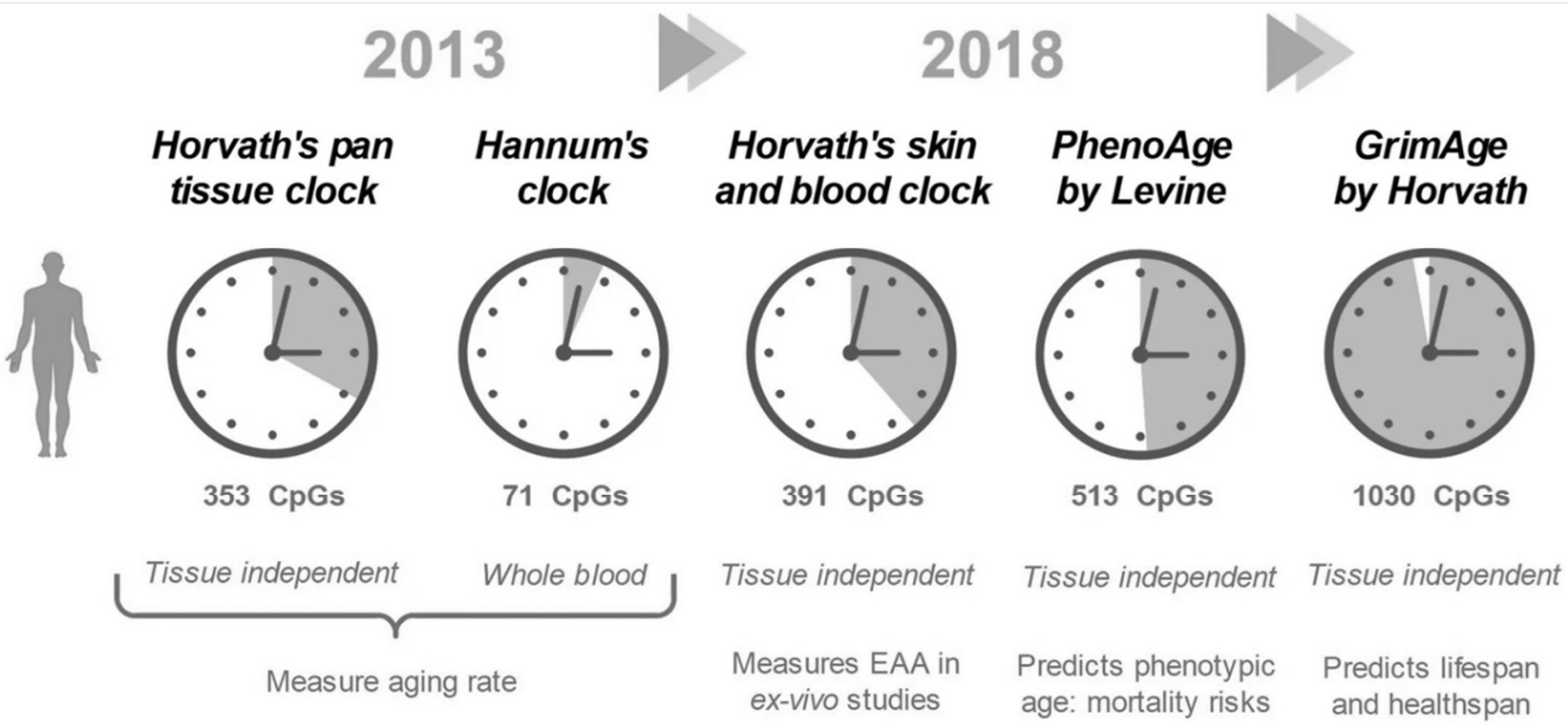
Addition of methyl group to C nucleotide (CpG)

Changes over time



DNA modification through methylation may help to explain the lasting effects of early life adversity on health

Epigenetic Clocks



Topart, 2020

DNA methylation and adverse health outcomes

Studies have shown individuals who had childhood exposure to sexual abuse, intimate partner violence, and poor parental mental health displayed epigenetic age acceleration, where the DNAm age was greater than their chronological age.

A meta-analysis showed childhood exposure to traumatic stress was associated with epigenetic age acceleration, with each additional exposure to a new type of trauma being associated with a 6-month age acceleration (only for Hannum DNAm Age but not for the Horvath DNAm Age)

Objective

1) Examine the association of ACEs with epigenetic age acceleration assessed using the DNAm GrimAge and DNAm PhenoAge epigenetic clocks in middle and older-aged adults.

2) Examine the association between each adversity domain and epigenetic age acceleration.

Measures: DNA methylation

Extracted genomic DNA from the frozen PBMC samples
Proportion of methylation on CpG nucleotide base pairs was measured using the EPIC arrays

The EPIC array quantitatively measures DNA methylation at 862,927 CpG sites and 2,932 CHH sites across the genome

Perform bisulfite conversion

For Quality control purposes, these raw array data were preprocessed using the GenomeStudio software (Illumina, CA, USA), which transformed the raw methylation values into beta values

The beta values range from 0 to 1 and indicate the proportion of methylation at each CpG loci present in the sample

Each clock was derived using weight and beta values that were normalized using the Noob normalization approach

Measures: Epigenetic Age Acceleration

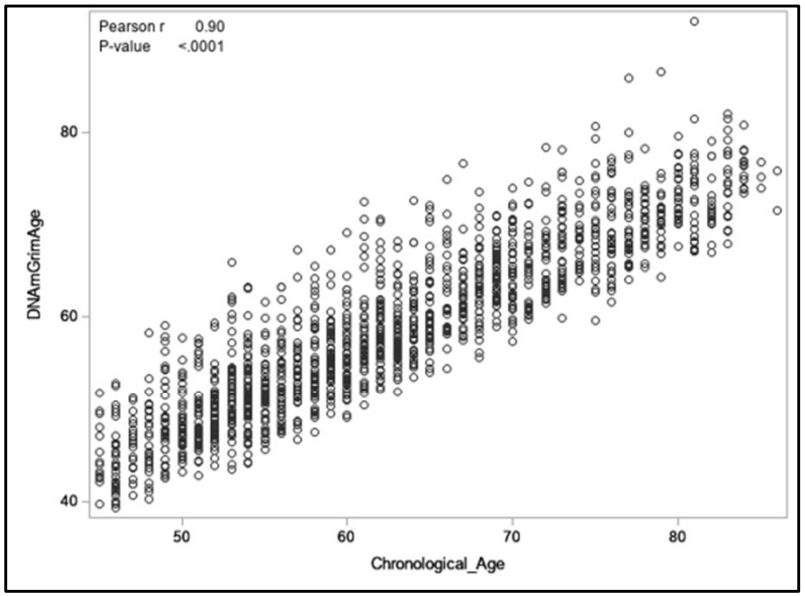
DNAm GrimAge
7 age-related plasma biomarkers + smoking
These biomarkers were combined into a composite biomarker

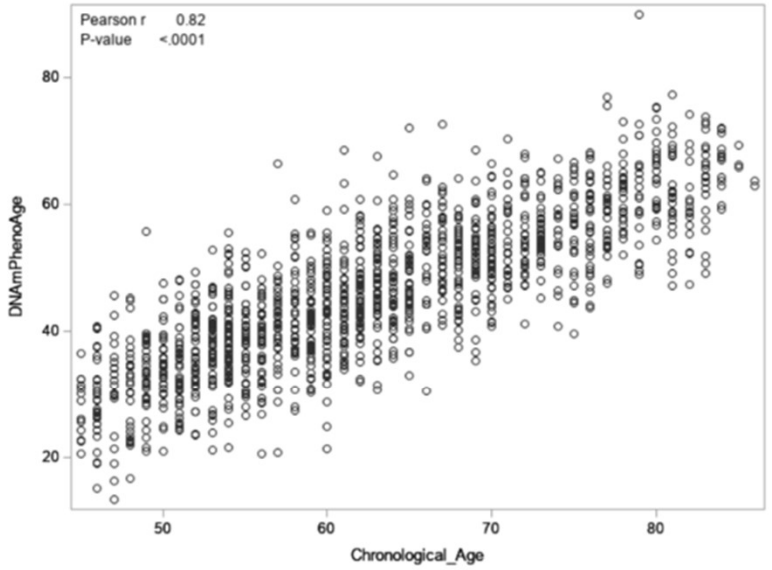
DNAm PhenoAge
Chronological age + nine clinically relevant blood biomarkers

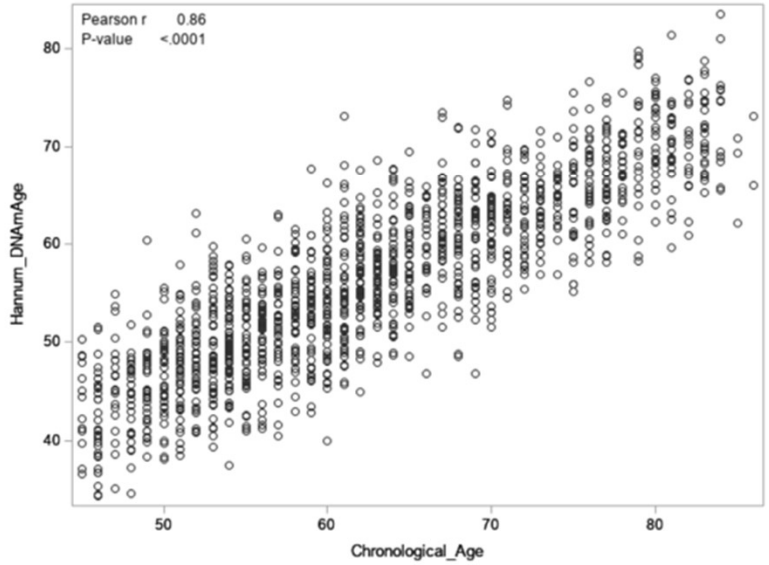
The DNAm age acceleration - residuals were estimated for each participant by regressing the biological clock estimate on chronological age.

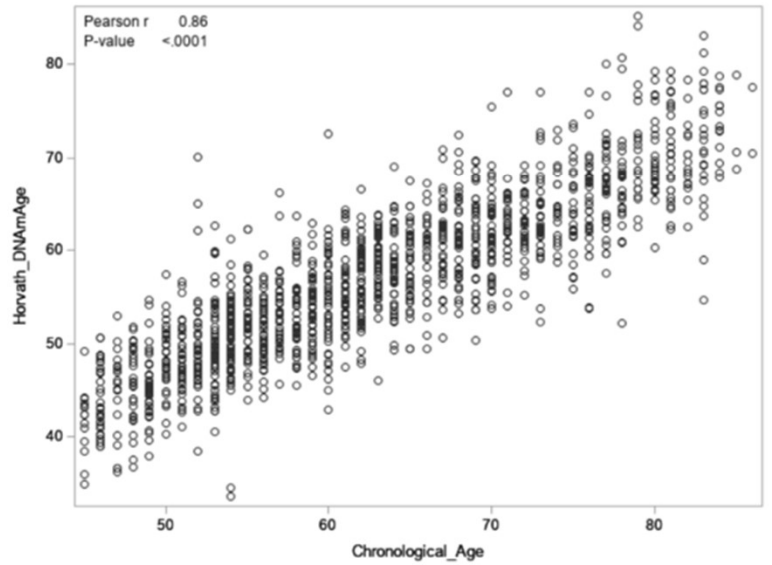
Chronological and biological age of participants (n=1,445)

Age measures	Mean	SE
Chronological age (years)	59.7	(0.3)
Horvath DNAm age (years)	54.6	(0.3)
Hannum DNAm age (years)	43.0	(0.3)
DNAm PhenoAge (years)	42.8	(0.4)
DNAm GrimAge (years)	56.3	(0.3)

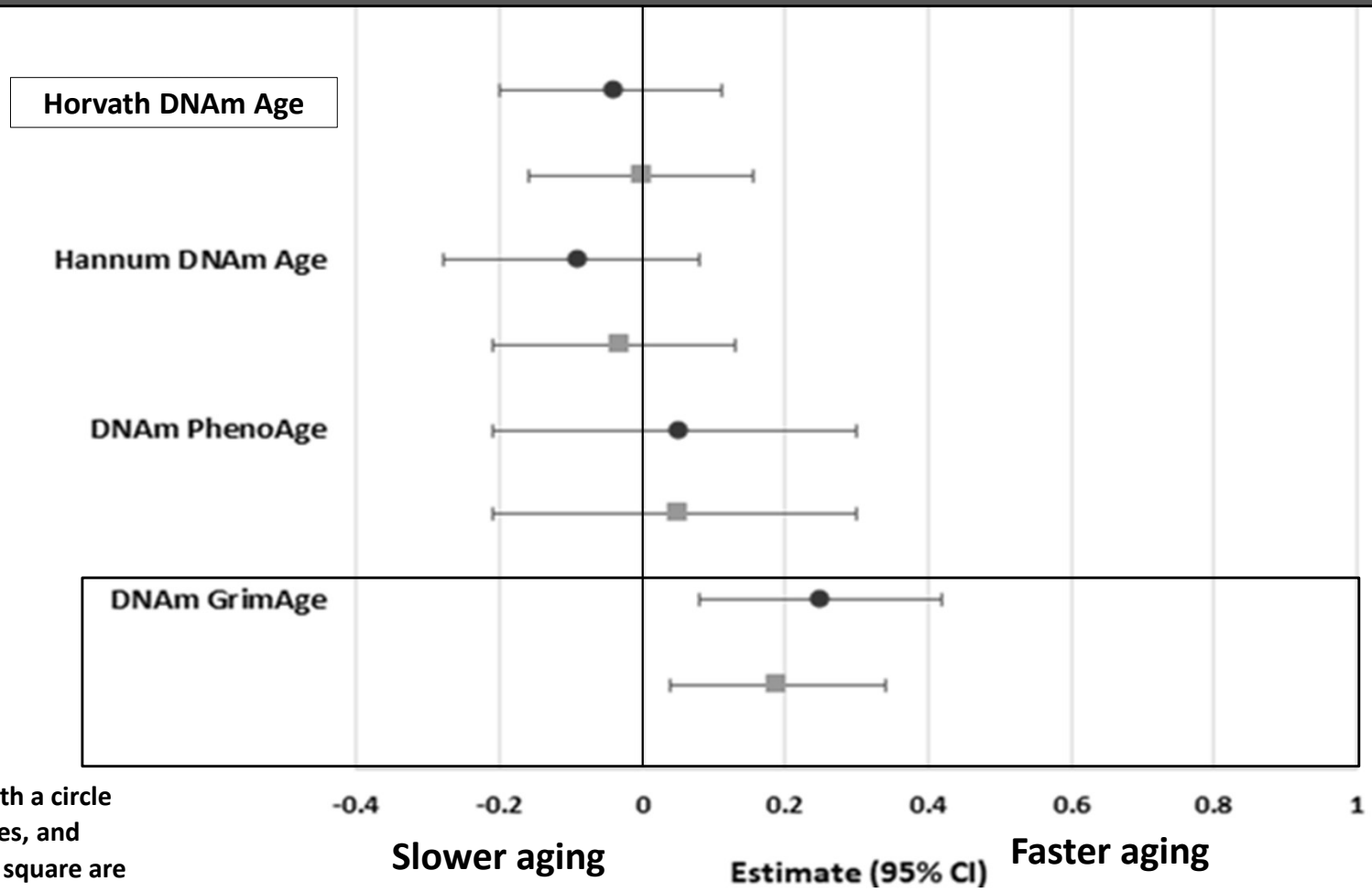

Pearson r 0.90
P-value <.0001
DNAmGrimAge
Chronological_Age


Pearson r 0.82
P-value <.0001
DNAmPhenoAge
Chronological_Age


Pearson r 0.86
P-value <.0001
Hannum_DNAmAge
Chronological_Age


Pearson r 0.86
P-value <.0001
Horvath_DNAmAge
Chronological_Age

Association between ACEs and the four epigenetic age acceleration measures



Estimates presented with a circle are unadjusted estimates, and those presented with a square are fully adjusted for covariates.

Co-occurrence of poor health behaviours & DNAm GrimAge acceleration

Any two health behaviours: 1.33 years (95% CI: 0.02, 2.66)

Any three health behaviours: 2.8 years (95% CI: 1.44, 4.15)

Any all four health behaviours: 3.69 years (95% CI: 2.04, 5.35)

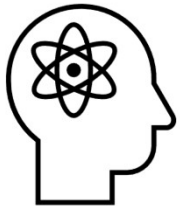
Limitations

- Exposure to ACEs was reported retrospectively and may be prone to recall and reporting biases.

- Prevalence of ACEs may be underestimated as the CLSA sample only included community participants from the 10 provinces.

- Cross-sectional design precludes claims about temporal associations.

Conclusions



ACEs increases stress, lowering social engagement and contributing to allostatic load, thereby resulting in multimorbidity.

Social engagement facilitated at any age for those at high risk of multimorbidity may lower or delay negative health outcomes.

Exposure to ACEs may induce DNAm changes that may be persistent across the life course, especially in the absence of health behaviour and lifestyle interventions

Increase awareness of ACEs, support positive parenting, promote healthy child development and improve overall quality of household environments

In addition, trauma-informed approaches need to be developed and promoted to assist individuals affected by ACEs

Clinicians can play an important role by being cognizant about ACEs and implementing trauma informed care to alleviate the harms caused by ACEs

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Questions?