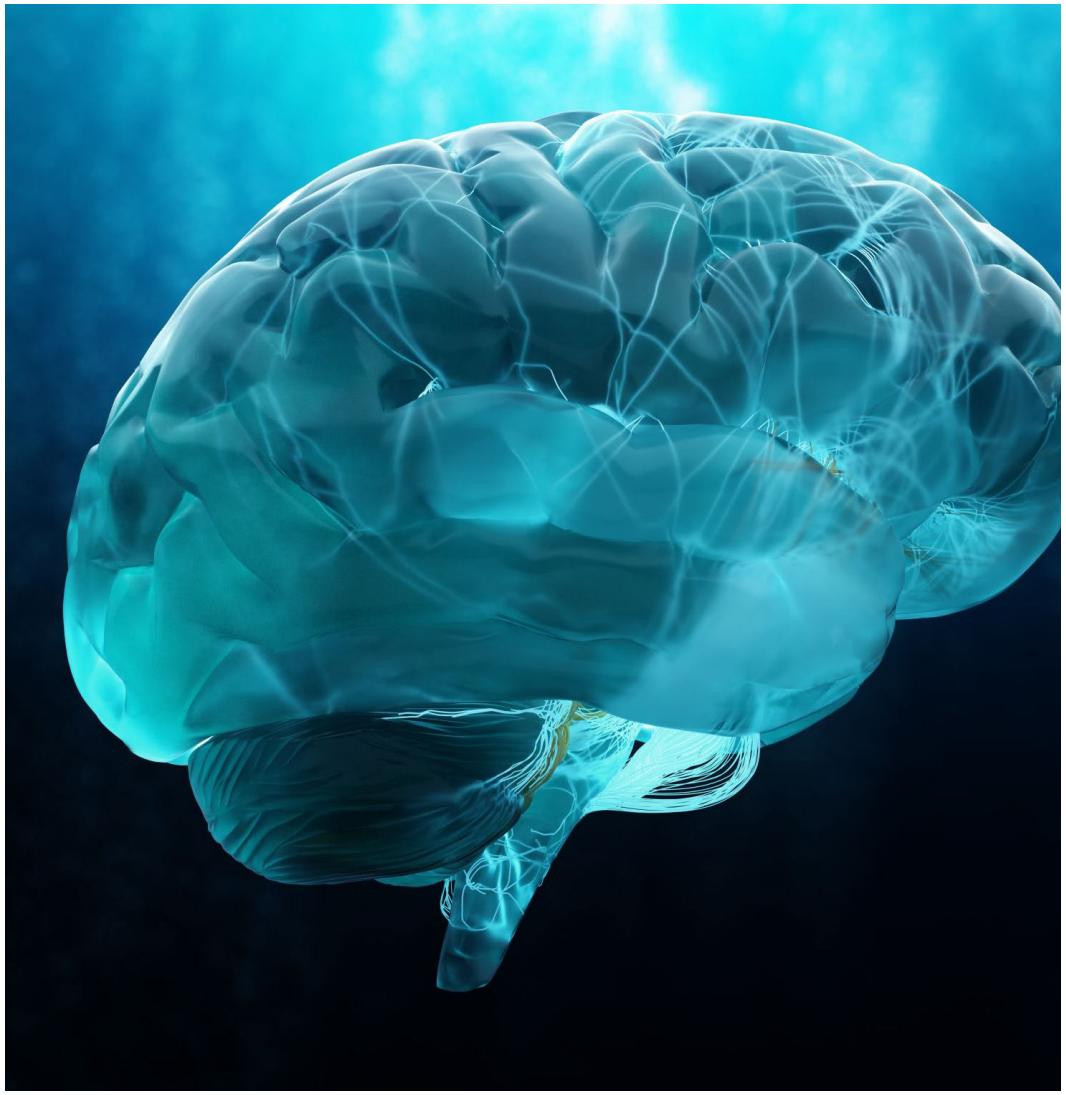
Examining the bidirectional associations between adiposity and cognitive function among middle-aged and older adults in the CLSA

Dr. Mohammad Nazmus Sakib, PhD

Dr. Peter Hall, PhD

School of Public Health Sciences

University of Waterloo



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Background

Bays et al (2013); Bazzano et al (2005); Bahadoran et al (2013); Singh et al (2014); Zilliox et al (2016)

Adiposity and obesity

- Excessive fat accumulation that presents a risk to health
- ↑ the risk of chronic diseases and deaths
  - Metabolic syndrome
  - Type 2 Diabetes Mellitus (T2DM)
  - Cardiovascular disease
  - Premature death
- Effects on cognitive function
  - ↓ Executive function (EF)
  - ↓ Memory
  - ↓ Performance on neurocognitive testing
  - ↑ Risk for dementia and Alzheimer's disease

Measures of adiposity

Body mass index
(BMI)

Waist circumference
(WC)

Waist-hip ratio
(WHR)

Dual energy X-ray
absorptiometry (DXA)

Cornier et al (2011)

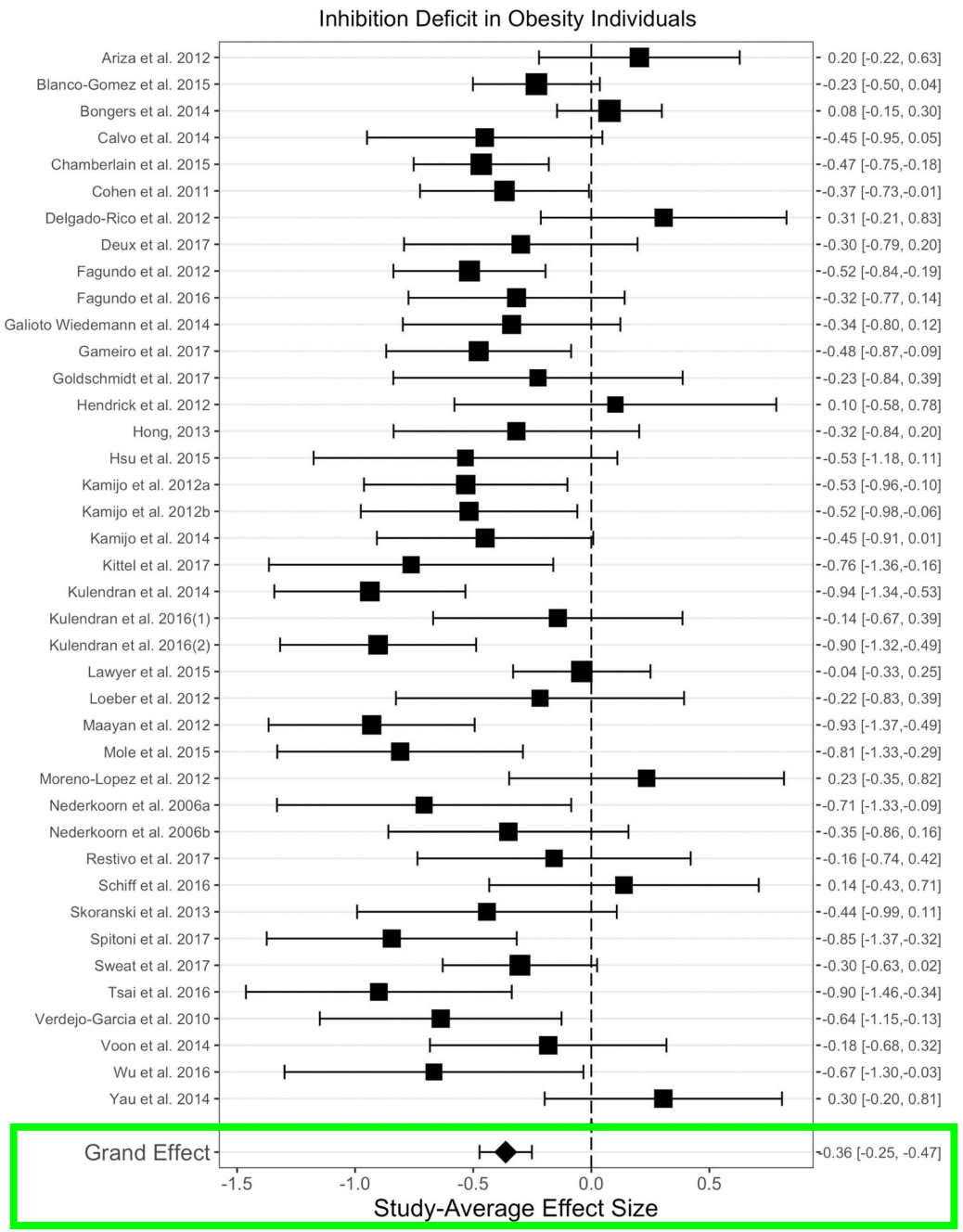
Cournot et al (2006); Whitmer et al (2005); Gunstad et al (2010); Fitzpatrick et al (2009); Anstey et al (2011)

Brain-as-outcome perspective

- Baseline obesity predicts future cognitive impairments.
- Predominantly affects:
  - Executive function
  - Attention
  - Memory
- Midlife obesity → ↑ Dementia and Alzheimer's disease in late life

https://empoweringlocallearners.weebly.com/executive-function.html

Yang et al (2018)

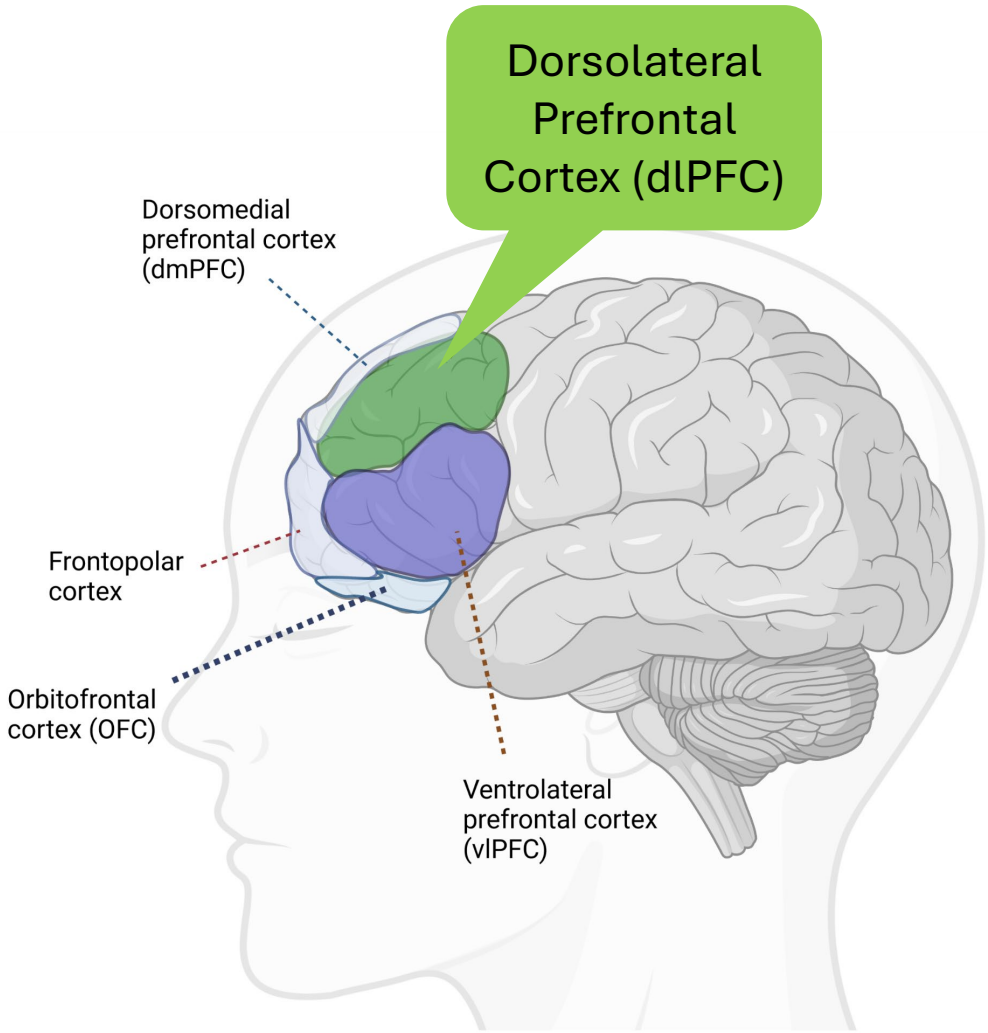


Adiposity predicts cognitive function (Brain-as-outcome)

Lowe et al. (2019); Lowe et al (2017); Safati and Hall (2019); Pieper et al (2013); Guxens et al (2009); Moffitt et al (2011)

Brain-as-predictor perspective

- Baseline cognitive impairment predicts future weight gain.
- Prefrontal cortex (PFC) plays a significant role.
- Suppression of dorsolateral PFC (dlPFC) → ↑ consumption
- ↓ Executive function → ↑ adiposity



Lowe et al (2018)

Contents lists available at ScienceDirect

NeuroImage

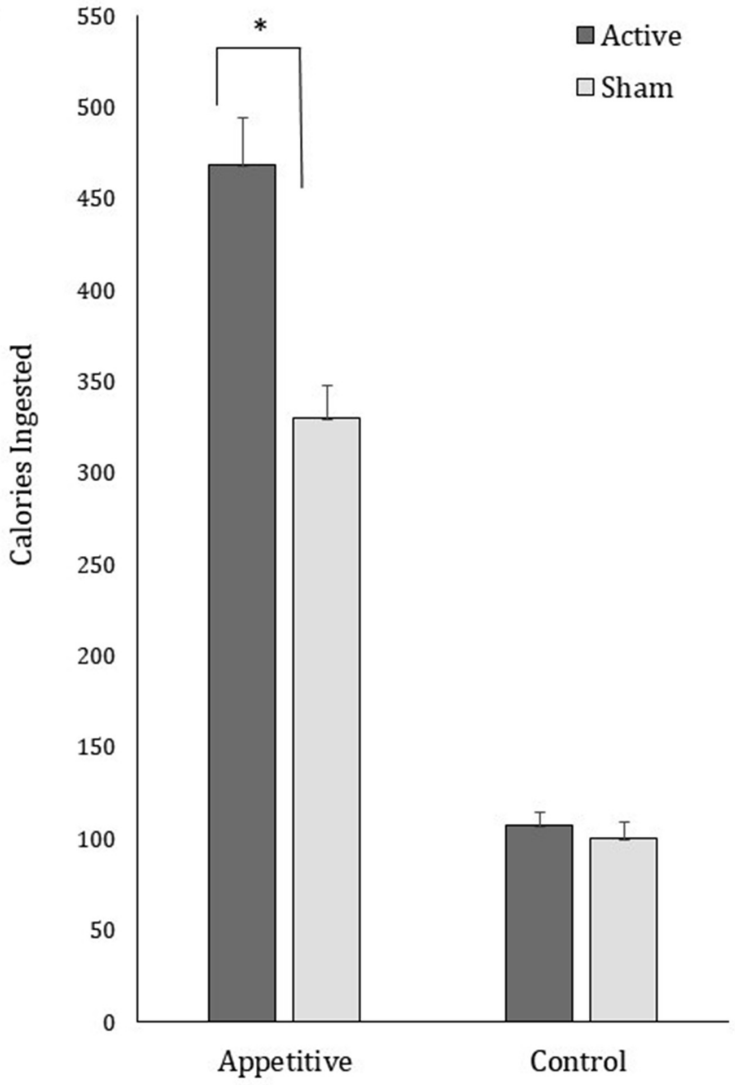
journal homepage: www.elsevier.com/locate/neuroimage

The neurocognitive mechanisms underlying food cravings and snack food consumption. A combined continuous theta burst stimulation (cTBS) and EEG study

Cassandra J. Lowe [a], William R. Staines [b], Felicia Manocchio [a], Peter A. Hall [a,*]

[a] Prevention Neuroscience Lab, School of Public Health and Health Systems, University of Waterloo, Waterloo, ON, N2L 3G1, Canada
[b] Department of Kinesiology, University of Waterloo, Waterloo, ON, N2L 3G1, Canada

- cTBS-induced attenuation of the left dlPFC increased appetitive snack food consumption.



Safati & Hall (2019)

Contents lists available at ScienceDirect

Brain Stimulation

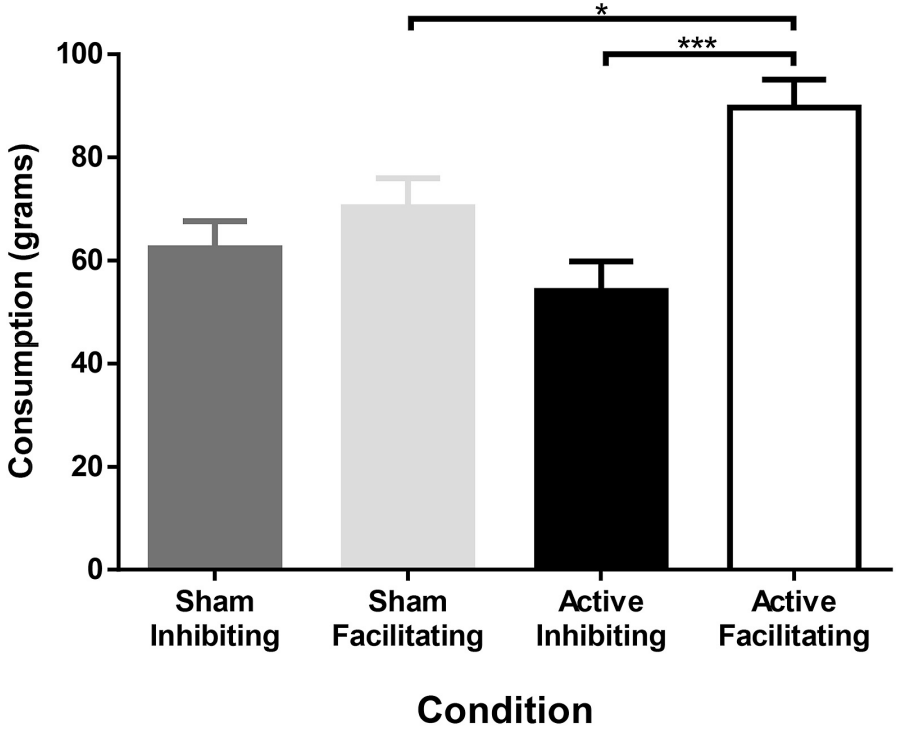
journal homepage: http://www.journals.elsevier.com/brain-stimulation

Contextual cues as modifiers of cTBS effects on indulgent eating

Adrian B. Safati [1], Peter A. Hall[*, 1]

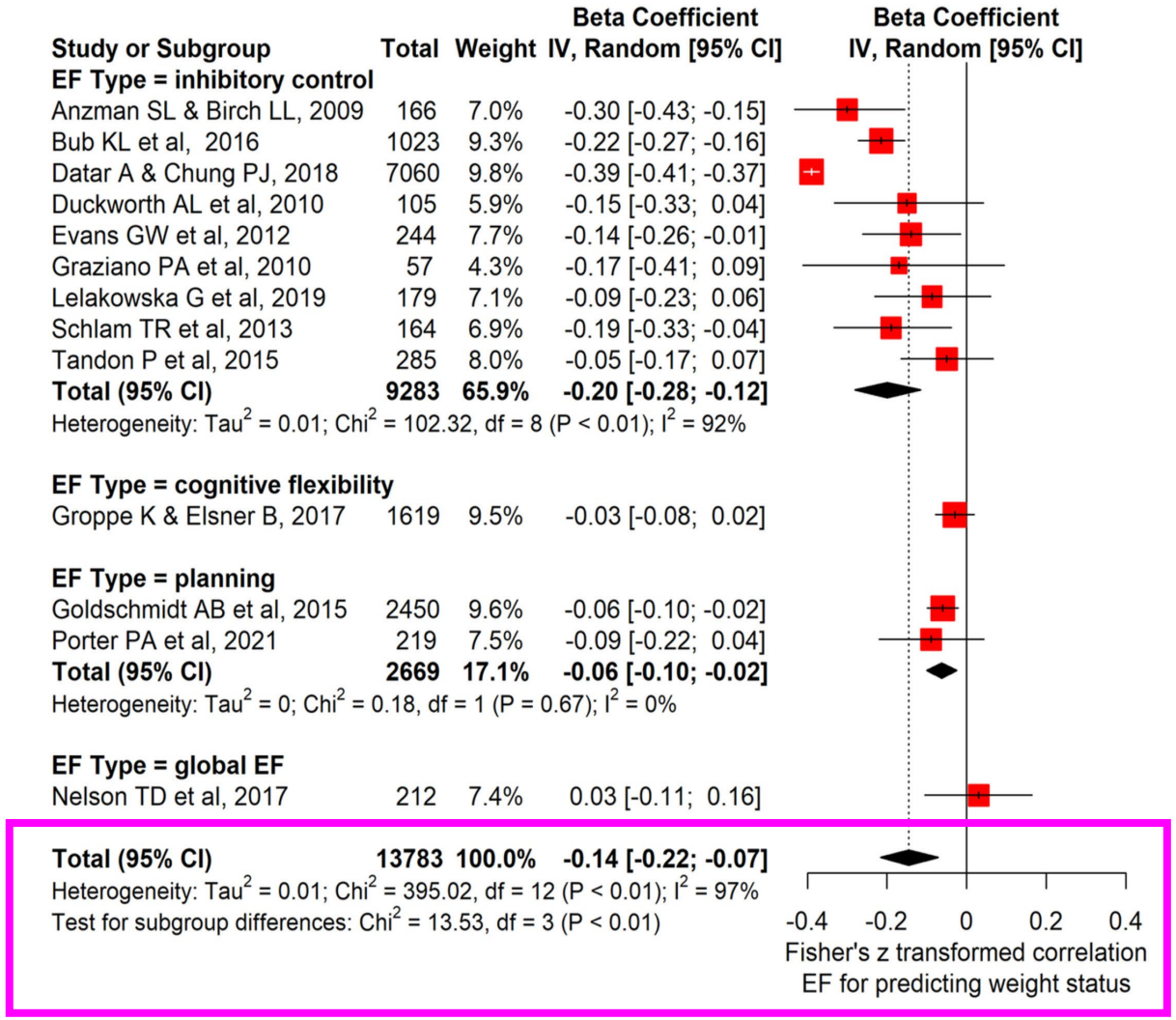
Prevention Neuroscience Laboratory, School of Public Health & Health Systems, University of Waterloo, Waterloo, Ontario, N2L 3G1, Canada

- The joint effects of contextual cues and cTBS on eating were examined.
- Findings suggested stronger cTBS effects in the presence of facilitating cues.



(Likhitweerawong et al., 2022)

Cognitive function predicts adiposity (brain-as-predictor)

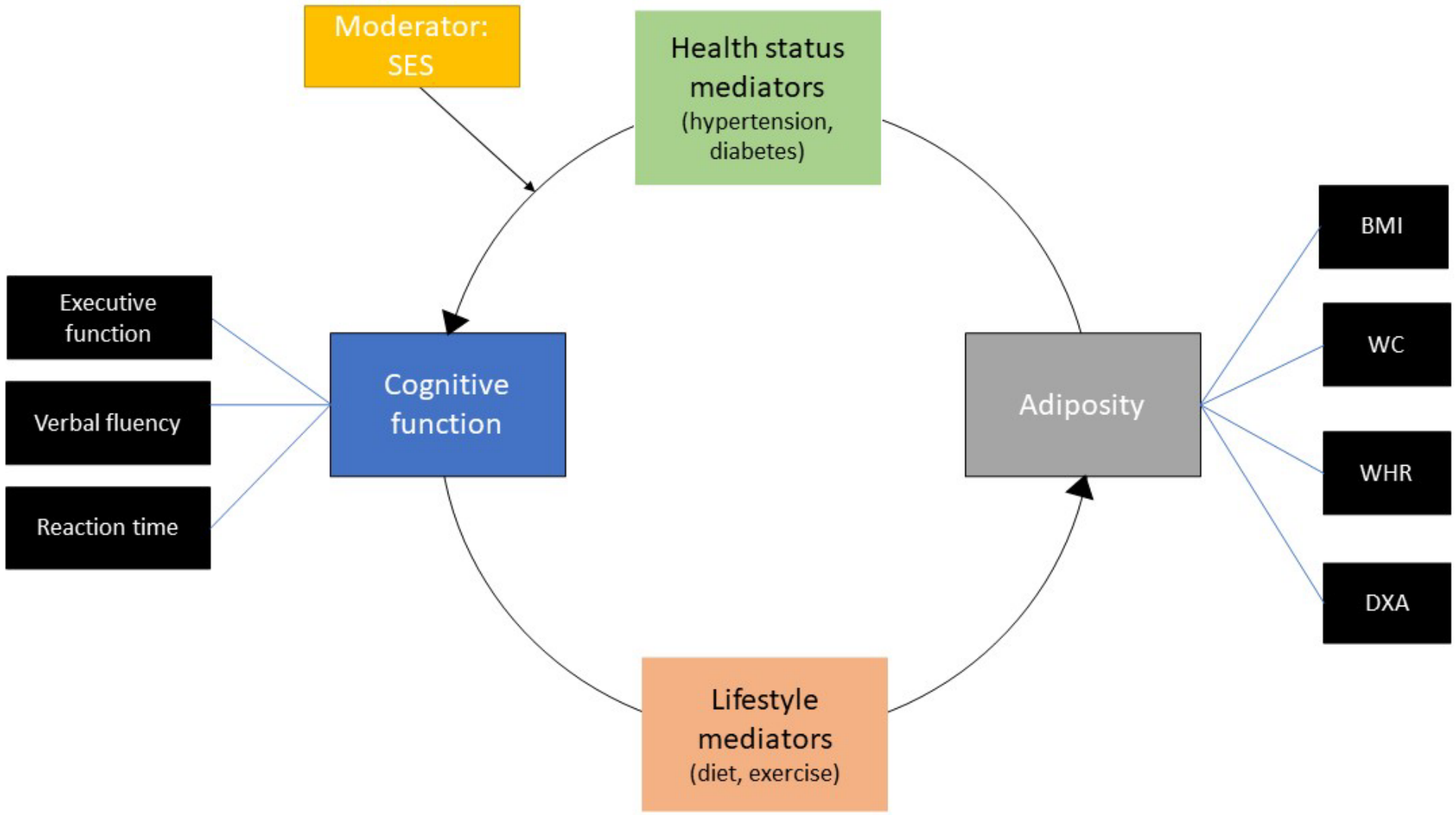


Limitations of previous research

- Lack of research using large-scale population-based datasets
- Limitation of previous research:
  - Unidirectional analyses on different samples
  - Lack of temporality
  - Small sample size
  - Insufficient measures on focal variables
  - Limited information on the potential confounders
  - Mediation paths were not explored
- Paucity of research in the Canadian context

Sakib et al (2022)

Conceptual diagram



Study 1

Cognitive Function Is Associated With Multiple Indices of Adiposity in the Canadian Longitudinal Study on Aging: A Cross-Sectional Analysis

Sakib, Mohammad Nazmus MBBS, MSc; Ramezan, Reza PhD; Thompson, Mary E. PhD; Best, John R. PhD; Hall, Peter A. PhD

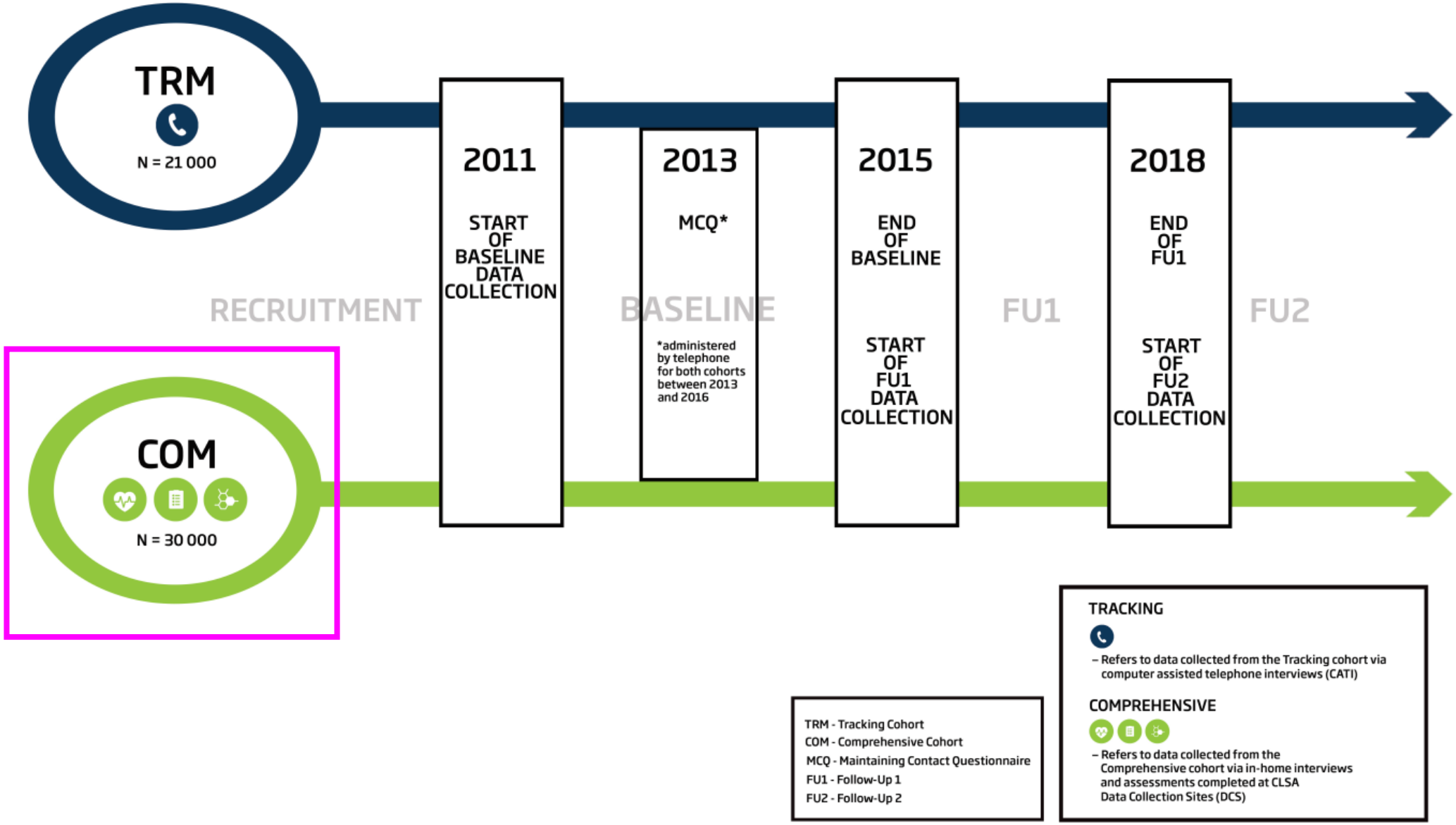
Author Information

Psychosomatic Medicine: September 2022 - Volume 84 - Issue 7 - p 773-784
doi: 10.1097/PSY.0000000000001099

Objectives and hypotheses

- To examine the association between adiposity and cognitive function and test the potential mediation paths.
- Hypothesis 1
  - Better scores on tests of cognitive function will be associated with lower adiposity.
- Hypothesis 2
  - The aforementioned associations are mediated through lifestyle behaviors and medical conditions.
- Hypothesis 3
  - The aforementioned associations will be stronger for those of higher SES.

CLSA DATA COLLECTION



(Source: https://www.clsa-elcv.ca/doc/2429)

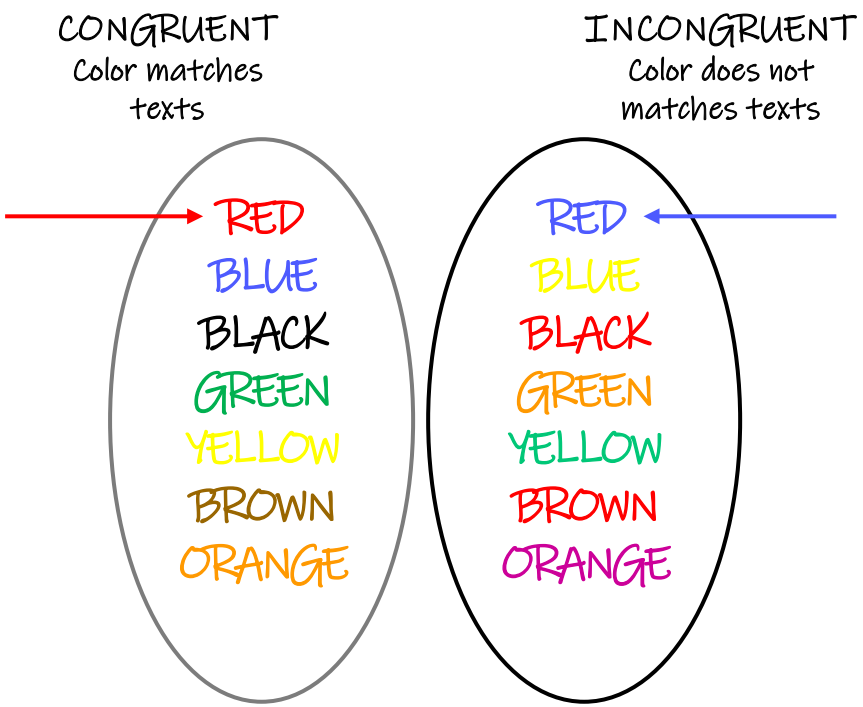
Methods

Outcome variables (Adiposity indicators)	Explanatory variables (Cognitive function)	Covariates	Mediators

• Body mass index
• Total fat mass (DXA)
• Waist circumference
• Waist-hip ratio
	• Stroop task
	• Choice reaction time (CRT)
	• Animal fluency task (AFT)
		• Age
		• Sex
		• Ethnicity
		• Income
		• Education
		• Residence
		• Physical activity
		• Comorbidity
		  • Somatic
		  • Neurologic
			• T2DM
			• Hypertension
			• Physical activity
			• Diet
			  • Healthy (legume, fruits, salad, carrot)
			  • Unhealthy (fries, pastries, snacks, chocolate)

Measures of cognitive function

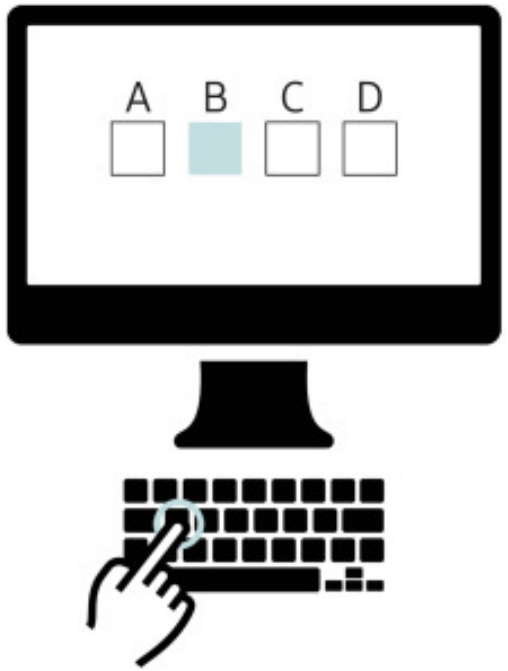
↑ Stroop interference → ↓ EF



Stroop task

(https://codepen.io/)

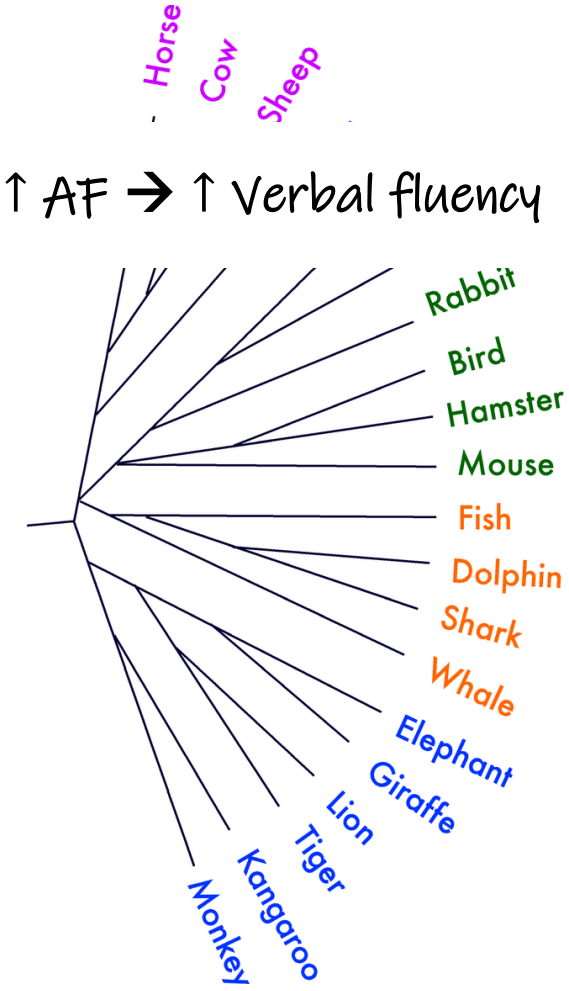
↑ RT → ↓ Processing speed



Reaction time task

(https://www.sciencedirect.com/)

↑ AF → ↑ Verbal fluency



Animal fluency task

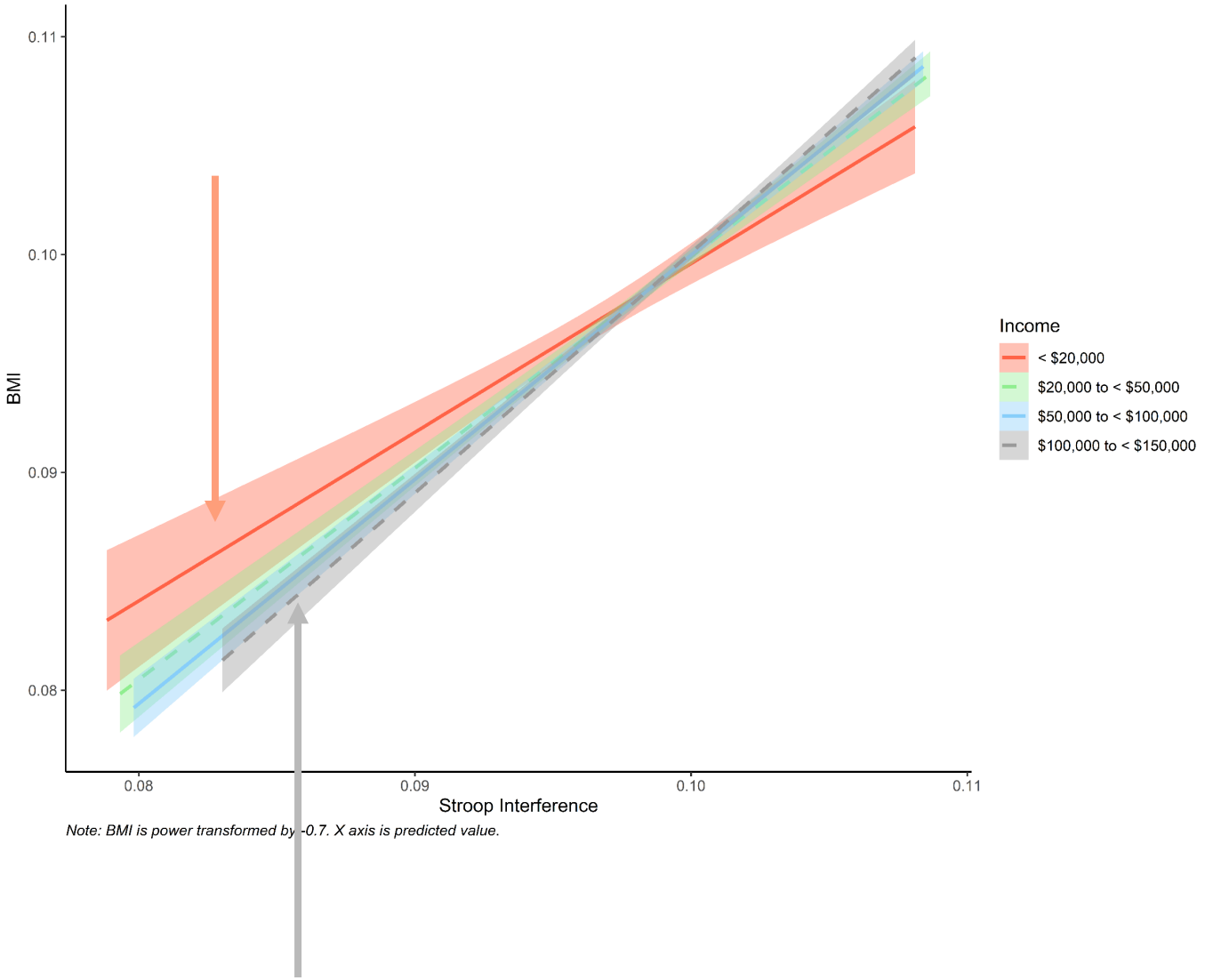
https://www.wikiwand.com/)

Statistical analyses

- Hierarchical multivariable linear regression
- Model 1: $Y_{Adiposity} = \beta_0 + \beta_1 X_{covariate} + \varepsilon$
- Model 2: $Y_{Adiposity} = \beta_0 + \beta_1 X_{covariate} + \beta_2 X_{Cog} + \varepsilon$
- Mediation analysis for lifestyle and medical conditions
  - T2DM, Hypertension, Physical activity and Diet
- Moderation analysis for income groups

Results

- ↑ Cognitive function ~ ↓ Adiposity
- Significant mediation paths:
  - Stroop → T2DM/HTN → Adiposity
  - AFT → Lifestyle/HTN → Adiposity
  - CRT → Diet/T2DM →Adiposity
- High SES (i.e., income) > Low SES



Note: BMI is power transformed by -0.7. X axis is predicted value.

Study 2

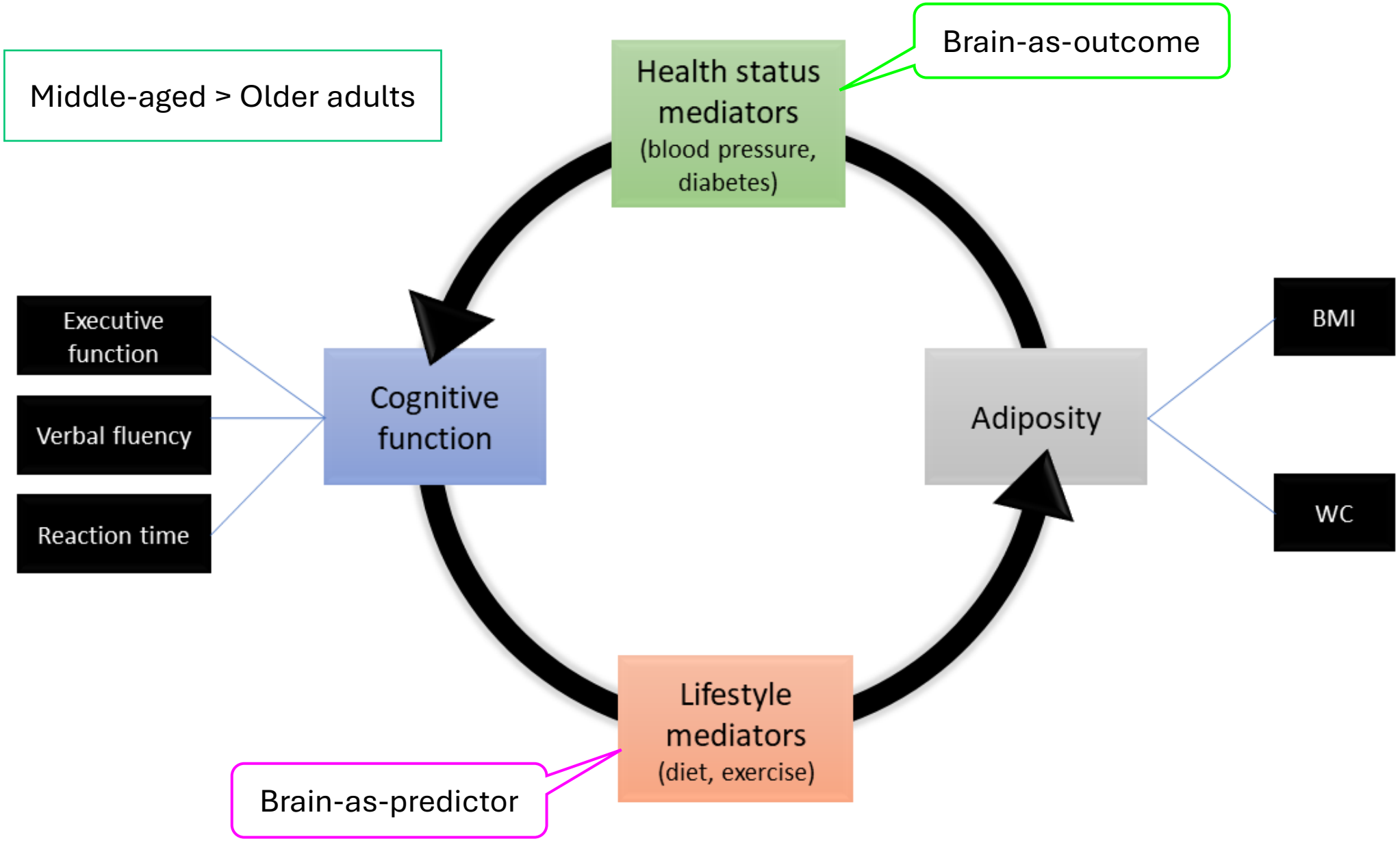
Bidirectional Associations Between Adiposity and Cognitive Function: A Prospective Analysis of the Canadian Longitudinal Study on Aging (CLSA)

Mohammad Nazmus Sakib, MBBS, MSc, John R Best, PhD, Reza Ramezan, PhD, Mary E Thompson, PhD, Peter A Hall, PhD ✉

The Journals of Gerontology: Series A, glac115, https://doi.org/10.1093/gerona/glac115

Published: 29 May 2022

Objectives and hypotheses

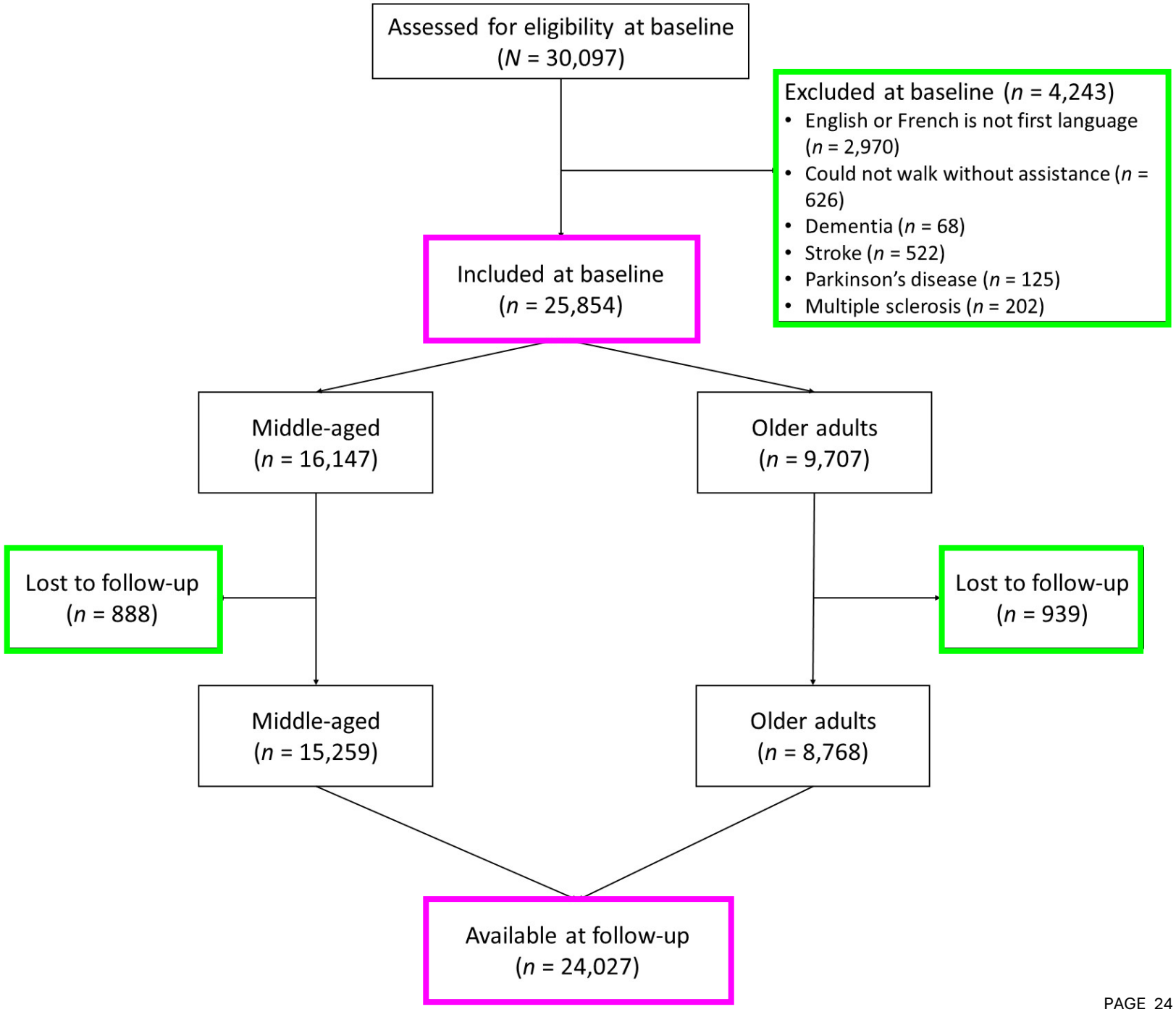


Methods

Adiposity indicators	Cognitive indicators	Covariates	Mediators

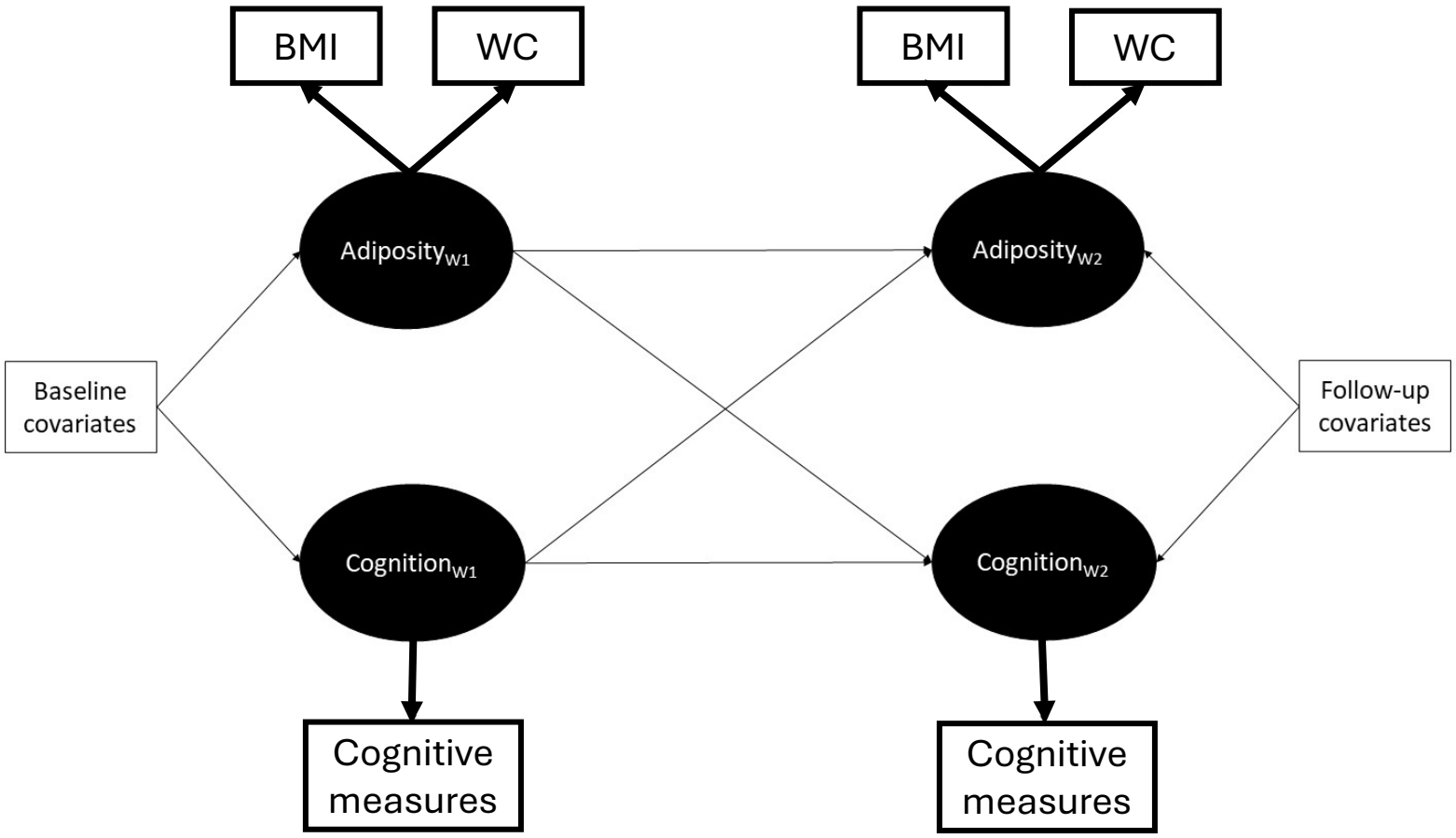
• Body mass idex
• Waist circumference
	• Stroop task
	• Choice reaction time (CRT)
	• Animal fluency task (AFT)
		• Age
		• Sex
		• Ethnicity
		• Income
		• Education
		• Residence
		• Physical activity
		• Comorbidity
		• Sleep duration
			• T2DM
			• Blood pressure
			• Physical activity
			• Diet
			  • Healthy (legume, fruits, salad, carrot)
			  • Unhealthy (fries, pastries, snacks, chocolate)

Exclusion criteria



Statistical analyses

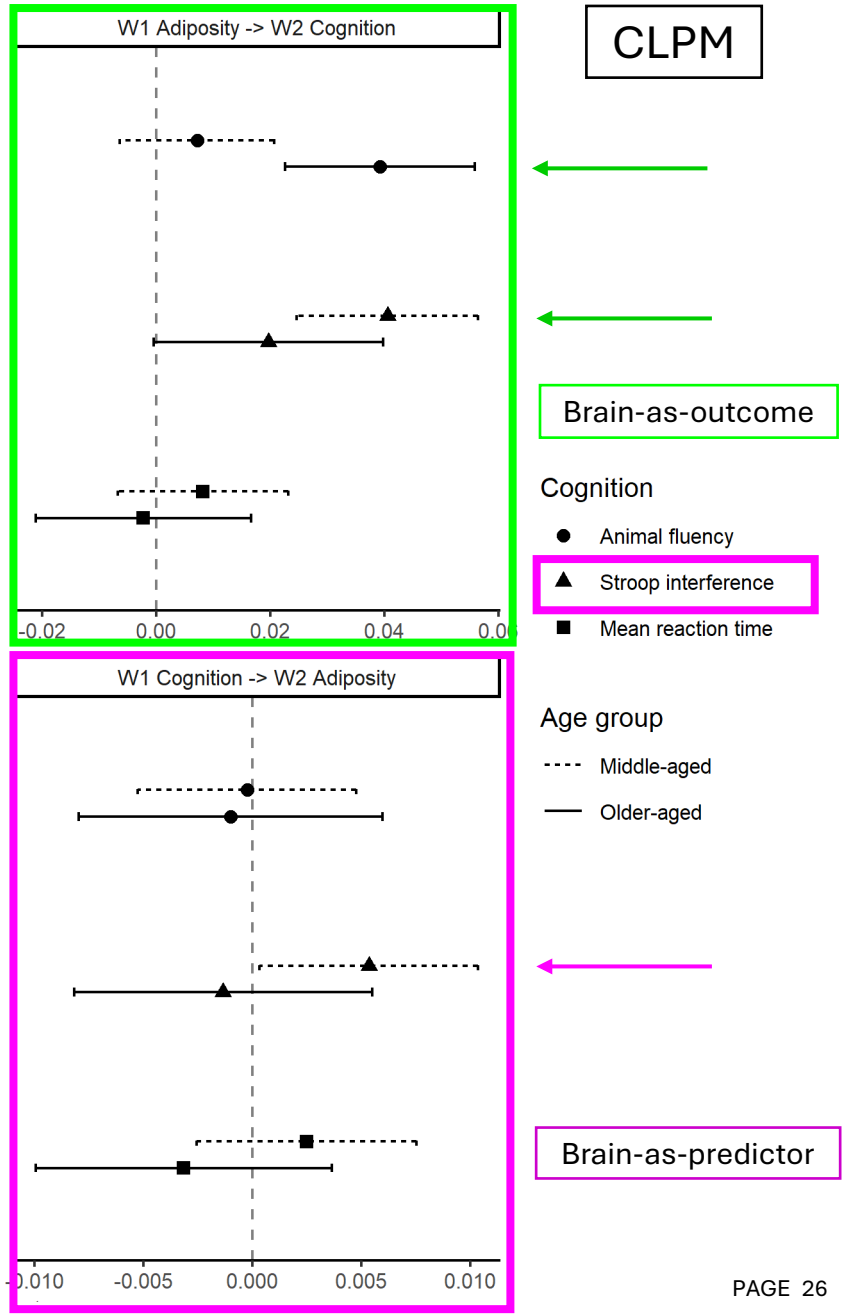
- Multivariate multivariable regressions
- Cross-lagged panel models with latent variable modeling
- Mediation analysis for lifestyle and medical condition variables
- Analyses were stratified by age group
  - Middle-aged (45-65 years)
  - Older adults (> 65 years)



Results

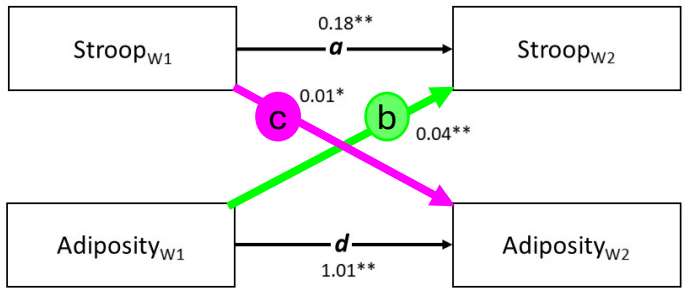
- Multivariate multivariable regressions
  - Brain-as-outcome perspective
    - Middle-aged: ↑ $Adiposity_{W1}$ → ↑ $Stroop_{W2}$, ↓ AFT_{W2}
    - Older adults: ↑ $Adiposity_{W1}$ → ↑ $Stroop_{W2}$, ↑ AFT_{W2}
  - Brain-as-predictor perspective
    - Middle-aged: ↑ $Stroop_{W1}$ → ↑ $Adiposity_{W2}$, ↑ AFT_{W1} → ↓ $Adiposity_{W2}$

- Mediation analyses
  - Brain-as-outcome perspective
    - WC_{W1} → Systolic & diastolic $BP_{Mid\text{-}age}$/$T2DM_{Mid\text{-}age\ \&\ Old\text{-}age}$ → $Stroop_{W2}$
  - Brain-as-predictor perspective
    - $Stroop_{W1}$ → $Diet_{Mid\text{-}age}$/$Pastries_{Old\text{-}age}$ → WC_{W2}

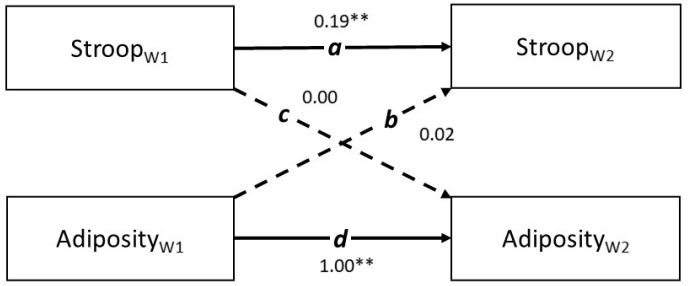


Summary of CLPM-L

- Solid lines indicate statistically significant paths
- Path b = Brain-as-outcome
- Path c = Brain-as-predictor

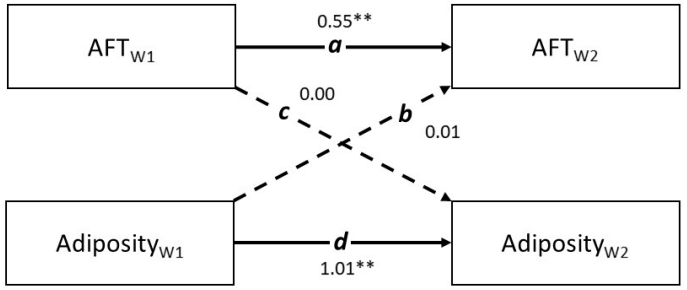


Part a: Middle-aged adults

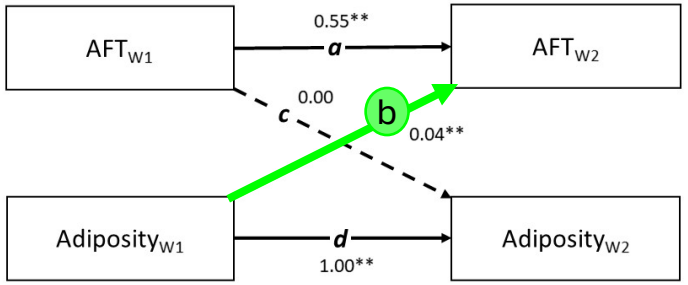


Part b: Older adults

Stroop interference

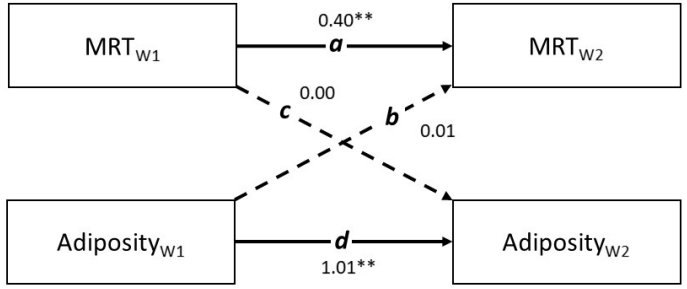


Part a: Middle-aged adults

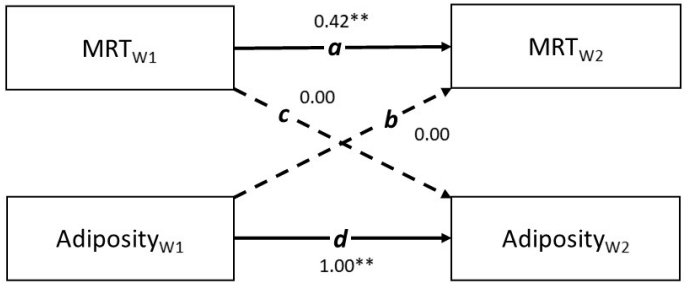


Part b: Older adults

Animal fluency



Part a: Middle-aged adults



Part b: Older adults

Mean reaction time

General discussion

Major findings

- Study 1
  - ↑ Cognition ~ ↓ Adiposity

- Study 2:
  - $\uparrow Adiposity_{mid-age} \rightleftharpoons \downarrow Executive\ function_{mid-age}$
  - $\uparrow Adiposity_{old-age} \rightarrow \uparrow Verbal\ fluency_{old-age}$

- Mediation: Lifestyle behavior and medical condition

Strengths

- Large-scale population-based datasets were utilized (Studies 1-2).
- Longitudinal analyses (Study 2)
- Multiple indices of adiposity and cognitive function (Studies 1-2)
- Rich information on potential confounders in modeling (Studies 1-2)

Limitations

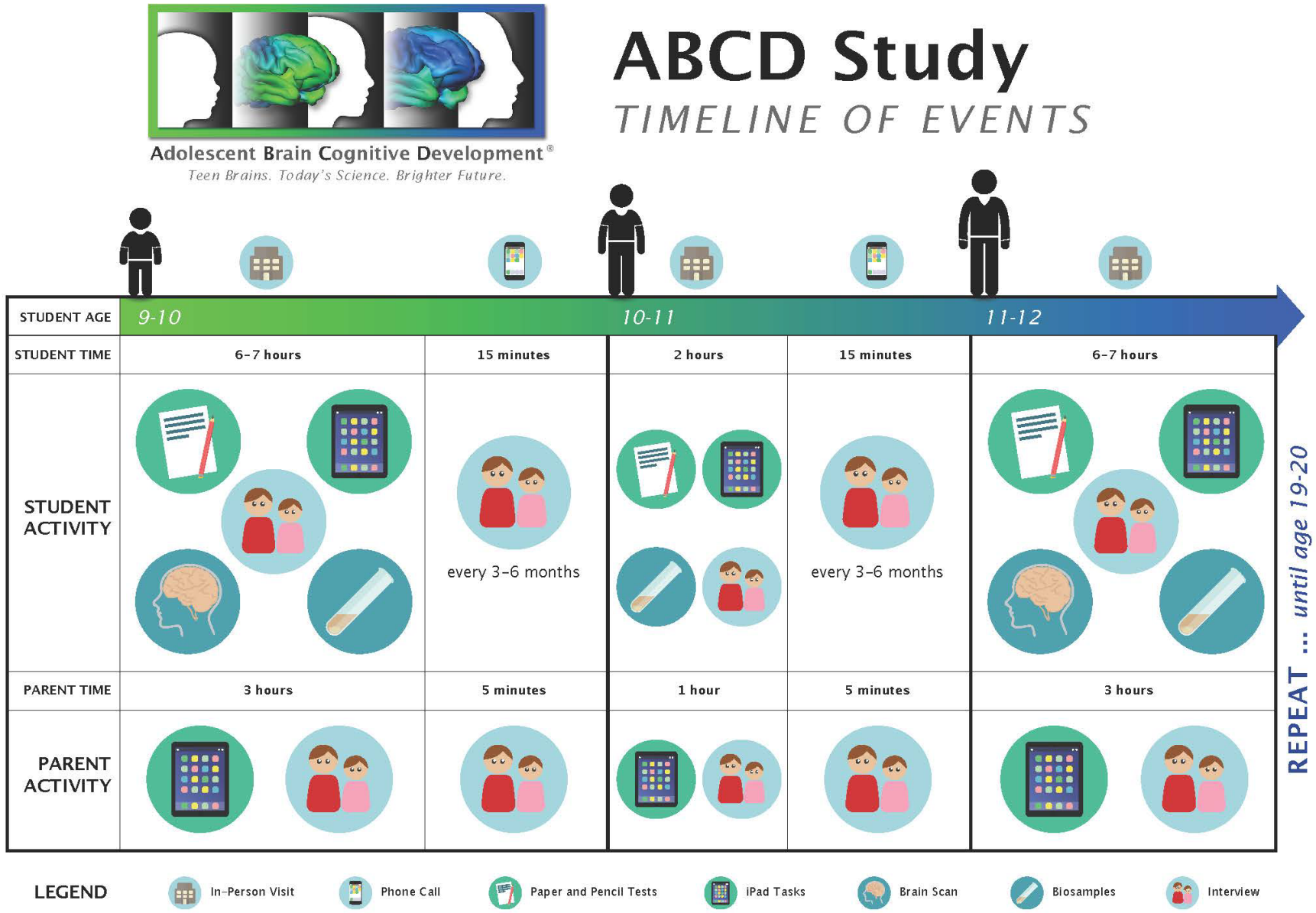
- Prospective analyses were limited to 2 waves for CLSA (Study 2)
- Short follow-up interval (3 years) likely underestimates cross-lagged effects, due to the gradual cumulative nature of the phenomena (Study 2)
- Population representativeness is not perfect despite large sample size (Studies 1-2)
- Cognitive domains examined within CLSA were not exhaustive (Studies 1-2)

Evidence from the ABCD Analyses

Title: Bidirectional associations between adiposity and cognitive function: Mediation by lateral prefrontal morphology in the ABCD Study

Authors: Sakib, M. N., Best, J. R., & Hall, P. A.

- Multisite longitudinal Study
- 11,878 children ages 9-10
- Begun in 2018
- Wave 1-3 data were available at the time of analyses.

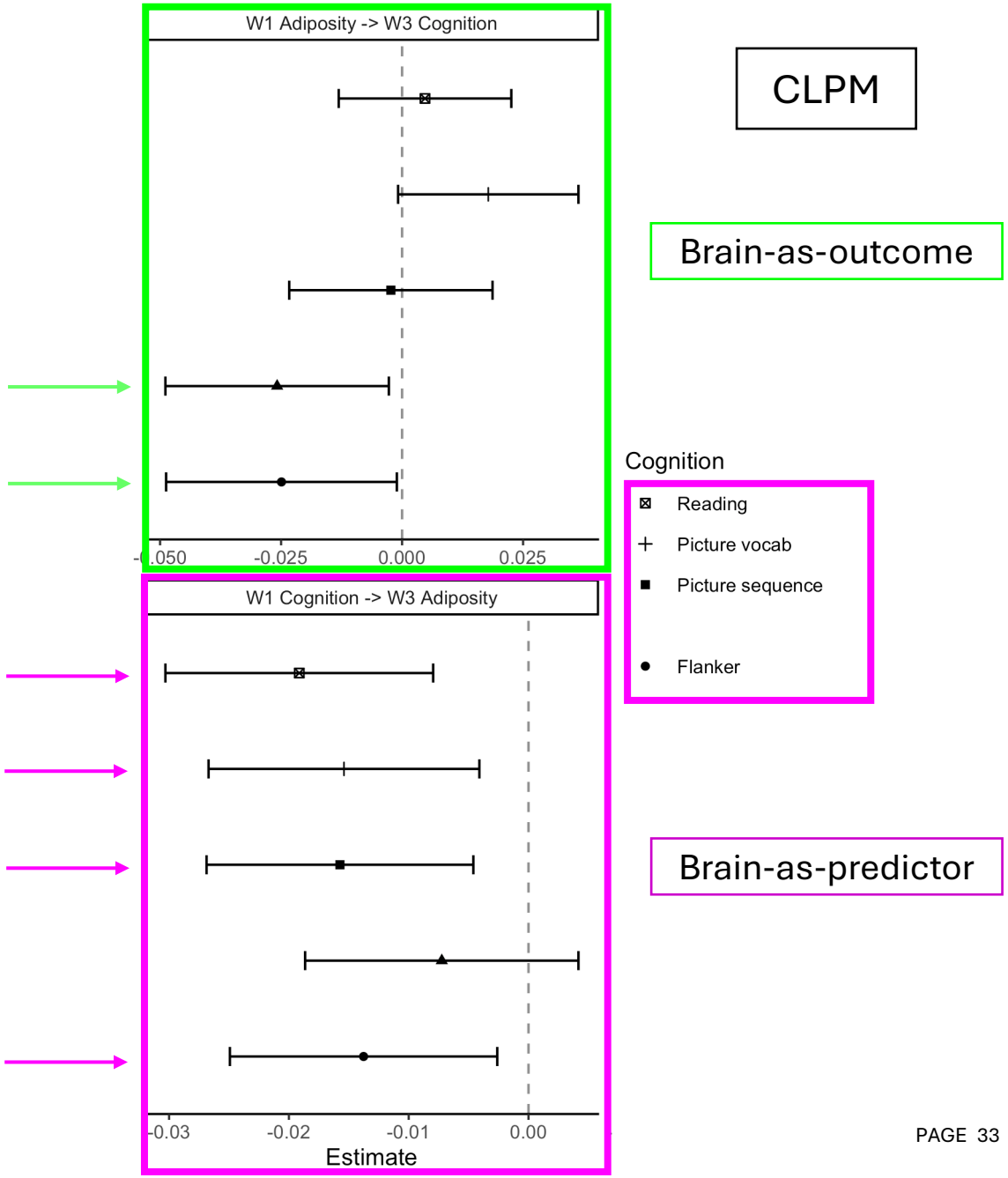


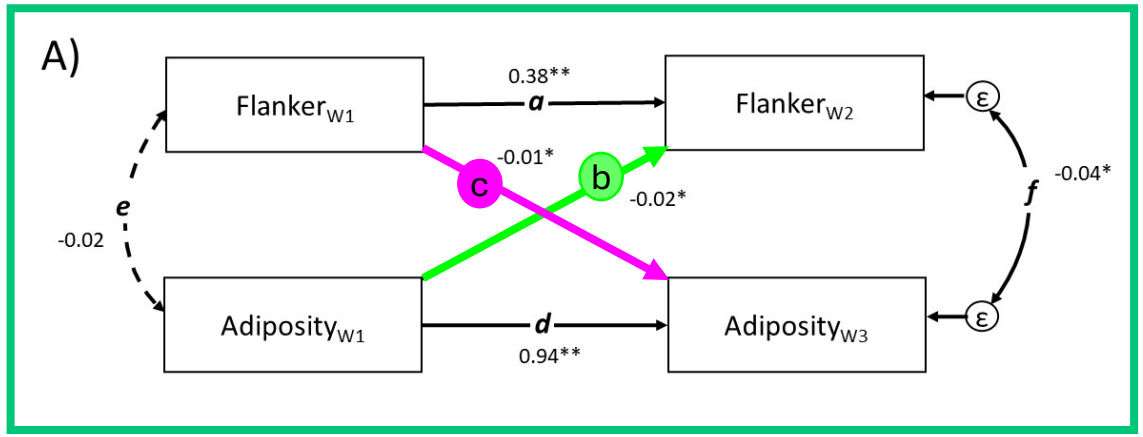
(Source: https://abcdstudy.org)

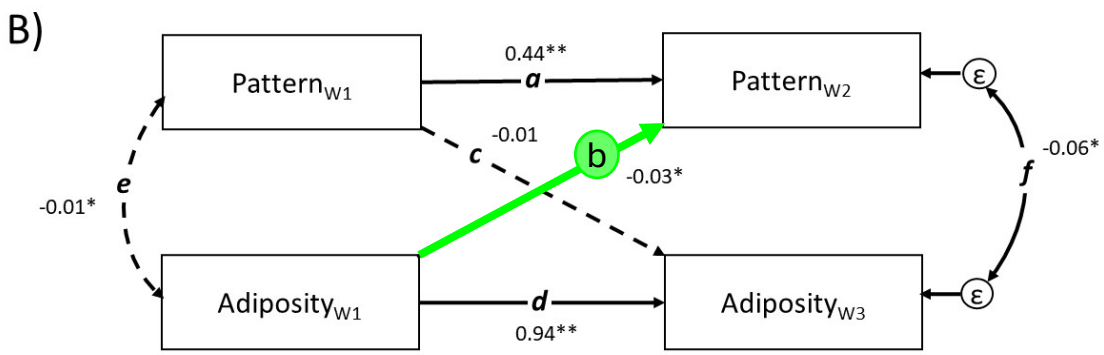
Variables and Findings

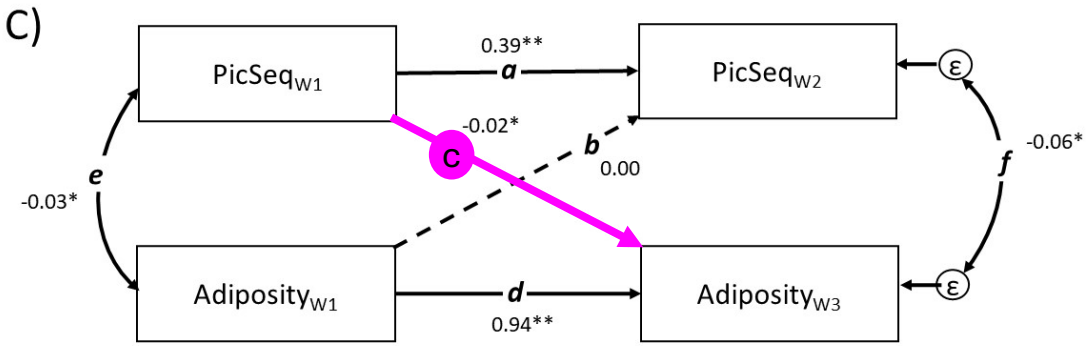
- Cognitive indicators: NIH Toolbox Cognitive Battery
  - Flanker, pattern matching, picture sequence, picture vocabulary, and oral reading
- Adiposity indicators: zBMI, WC

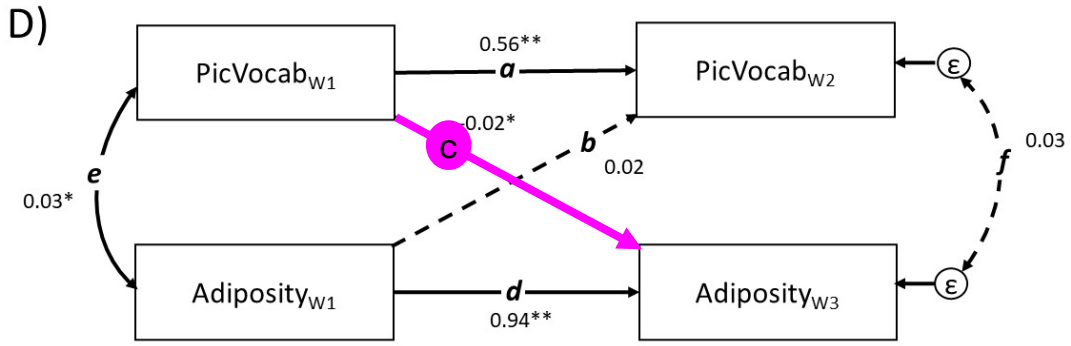
- Multivariate multivariable regressions
  - Brain-as-outcome perspective
    - $\uparrow zBMI_{W1} \rightarrow \downarrow PicSeq_{W3}$
    - $\uparrow WC_{W1} \rightarrow \uparrow PicVocab_{W3}$
  - Brain-as-predictor perspective
    - $\uparrow Flanker_{W1}, \uparrow PicSeq_{W1} \rightarrow \downarrow zBMI_{W3}, \downarrow WC_{W3}$

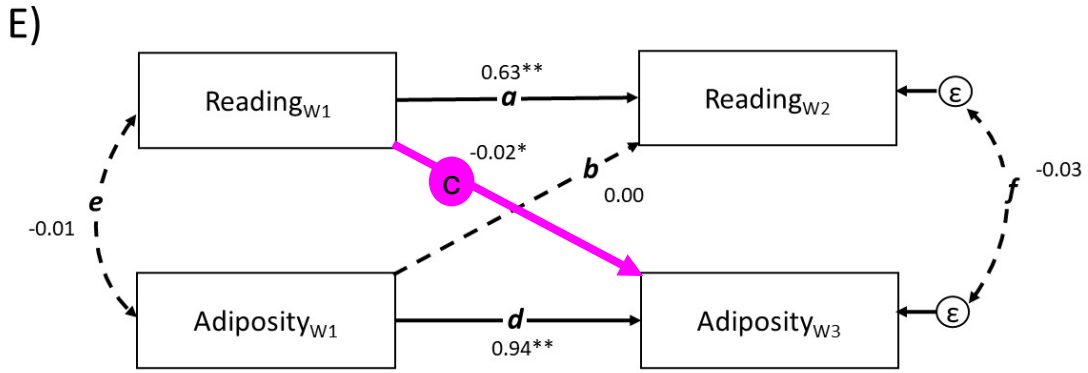












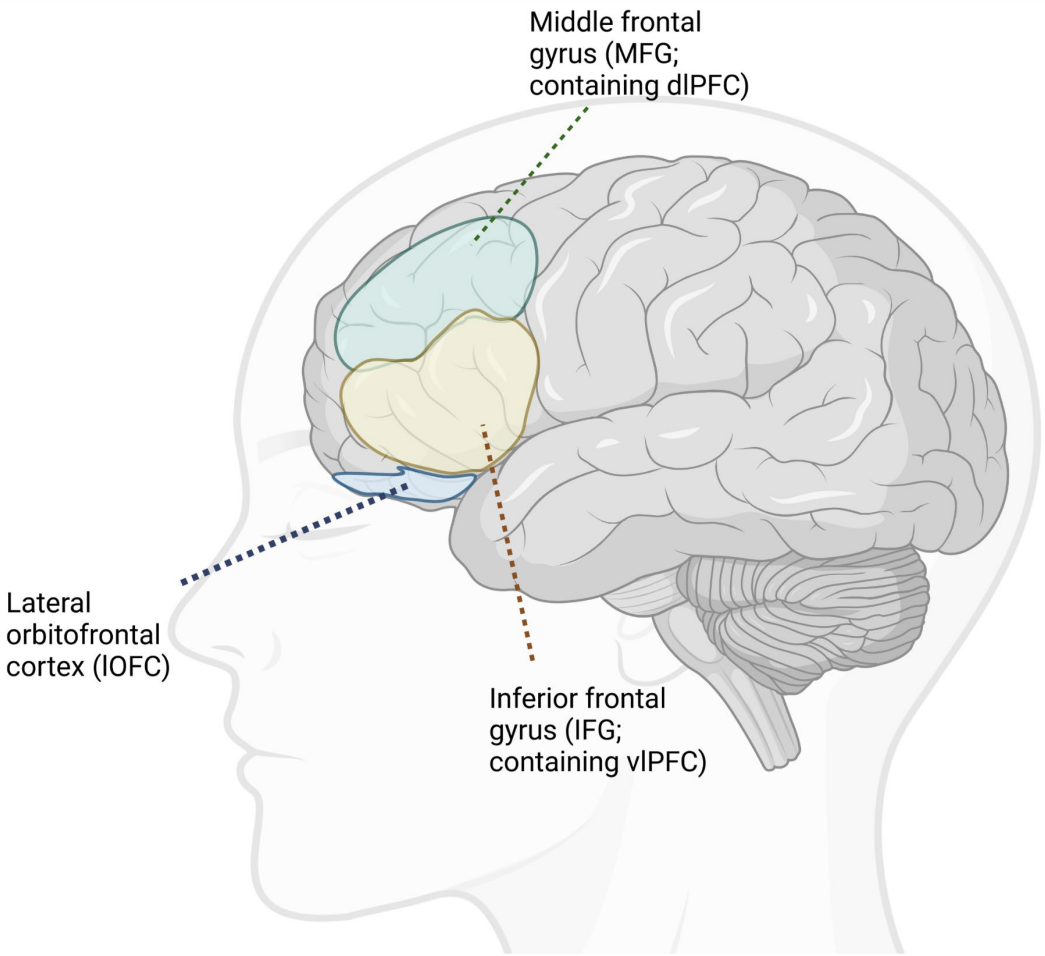
Summary of CLPM-L

- Solid lines indicate statistically significant paths
- Path b = Brain-as-outcome
- Path c = Brain-as-predictor

Mediation through brain morphology features

- Brain-as-outcome
  - Adiposity → Mediator → Cognition
    - Adiposity_{W1} → MFG_T → Pattern_{W3}
    - Adiposity_{W1} → $\text{MFG}_T/\text{IFG}_T$ → PicVocab_{W3}
    - Adiposity_{W1} → $\text{LPFC}_V/\text{MFG}_V$ → Reading_{W3}

- Brain-as-predictor
  - Cognition → Mediator → Adiposity
    - Pattern_{W1} → LPFC_T → WC_{W3}



Implications and future directions

- Future studies should employ **longer prospective data collection intervals** to more conclusively characterize the magnitude of the cross-lagged effects (ideally 10 years or more).
- Explore the **extent of bidirectionality** using other cognitive domains.
- Use a **comprehensive set** of adiposity measures in future studies.
- Utilize **brain morphology and functional imaging** data to explore bidirectionality.
- Explore the utility of **executive function training** in eating and weight loss interventions, particularly for those who have undergone bariatric surgery.
- Explore **novel methods** of enhancing executive function using **TMS**.

Thank you..

Supervisor
Dr. Peter Hall

Collaborators
Dr. Reza Ramezan
Dr. John Best
Dr. Mary Thompson

All the participants and research staffs associated with the CLSA and ABCD studies.

All the previous and current members of the Prevention Neuroscience Laboratory (Anna, Jessica, Alkarim, Adrian, Mia, Idris).

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