Examining the bidirectional associations between adiposity and cognitive function using population-level data

by

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Author’s Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

The manuscripts presented in this thesis, including two that have been in press or published, are the work of Mohammad Nazmus Sakib, in collaboration with his co-authors and committee members. Exceptions to sole authorship include:

Chapter 5: Sakib MN, Ramezan R, Thompson ME, Best JR, and Hall PA. Cognitive function is associated with multiple indices of adiposity in the Canadian Longitudinal Study on Aging (CLSA): A cross-sectional analysis. *Psychosomatic Medicine*. 2022. In press. https://doi.org/10.1097/PSY.0000000000001099

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As the lead author of these three chapters (Chapters 5 to 7), I was responsible for conducting background research, ethics application, data acquisition, data cleaning and analyses, interpretation of the results, writing the manuscript and submission to the refereed journal for publication. My co-authors provided guidance during each step of the research, reviewed the analytic approach, assisted in data analyses, and provided feedback on manuscript drafts. Dr. Hall provided substantial guidance and direction throughout the process.

Under Dr. Hall's supervision, I also prepared the remaining chapters of this thesis, which were not written for publication.

Abstract

Background

The association between adiposity and cognitive function has been extensively explored in previous literature, and numerous cross-sectional and longitudinal analyses suggest a reliable association. However, most previous studies on this topic were predominantly executed with a narrow, unidirectional assumption that baseline adiposity predicts future cognitive function (i.e., the "brain-as-outcome" perspective). Literature within neuropsychology, the cognitive neurosciences and cognitive epidemiology suggests that baseline cognitive function may also predict the development of adiposity (i.e., the "brain-as-predictor" perspective), although this reverse directionality has not been extensively explored to date using population-level datasets. Instead, relatively small-scale experimental studies have shown that temporary attenuation of some facets of cognitive function, particularly the executive control domain, could result in disinhibited eating. Therefore, it is plausible that impaired cognitive function affects the implementation of behaviors that confer downstream risk for adiposity. Taken together, these findings suggest that the association between adiposity and cognitive function could be reciprocal, but bidirectional effects have not been explored systematically in previous literature. This dissertation aimed to examine the hypothesized bidirectional associations between adiposity and cognitive function and their possible mediation paths using population-level datasets in three age groups: older adults, middle-aged adults, and adolescents.

Methods

Studies 1 and 2 were conducted using the Canadian Longitudinal Study on Aging (CLSA) datasets. Study 1 was a cross-sectional analysis of the baseline CLSA comprehensive cohort (N = 30,097), whereas Study 2 was a prospective analysis of the baseline and first follow-

up datasets. The bidirectionality hypotheses were examined using three indicators of cognitive function (animal fluency, Stroop interference, and mean reaction time) and four indicators of adiposity (body mass index [BMI], total fat mass, waist circumference [WC] and waist-hip ratio [WHR]). Hierarchical multivariable regression, multivariate multivariable regression and cross-lagged panel model with latent variable modeling (CLPM-L) were employed to test the study hypotheses. Mediation analyses were conducted for lifestyle (e.g., diet, physical activity) and physical health status (e.g., hypertension, blood pressure and diabetes) variables.

Study 3 was a prospective analysis of the Adolescent Brain Cognitive Development (ABCD) dataset (N = 11,878). The above-mentioned bidirectional hypotheses were examined using two indicators of adiposity (e.g., BMI z score [zBMI] and WC) and five indicators of cognitive function included in the NIH Toolbox Cognitive Battery (e.g., Flanker, pattern recognition, picture sequence, picture vocabulary and oral reading tasks). Multivariate multivariable regression and CLPM-L were employed to test the study hypotheses. Mediation analyses were conducted for lifestyle (e.g., diet, physical activity) variables, physical health status (e.g., blood pressure) variables, and lateral prefrontal cortex (PFC) morphology features (volume and thickness).

Results

Study 1 showed that measures of cognitive functions were significantly associated with adiposity after controlling for confounders in cross-sectional analysis of the CLSA baseline datasets. In general, superior performance on animal fluency, Stroop, and reaction time tasks was associated with lower adiposity by most metrics. These associations were more substantial for moderate- and high-income sub-populations and mediated through lifestyle behavior (e.g., diet and physical activity) and physical health conditions (e.g., diabetes and diet).

Study 2 suggested that higher baseline adiposity was associated with higher Stroop interference at follow-up for both middle-aged and older adults. Similarly, higher baseline Stroop interference was associated with higher follow-up adiposity, but only in middle-aged adults. Effects involving semantic fluency and processing speed were less consistent. The above effects persisted following covariate adjustments and when used latent variable modeling of the adiposity variable. Significant mediation effects were observed for blood pressure, diabetes, and diet.

Study 3 revealed that higher baseline zBMI and WC were associated with worse follow-up picture sequence and better picture vocabulary task performance, respectively. Likewise, superior baseline performance on Flanker and picture sequence tasks was associated with better follow-up adiposity status. A bidirectional association was observed between episodic memory and zBMI. Latent adiposity modeling showed a bidirectional association with executive function (measured by Flanker task) but not with other cognitive domains. Significant mediation effects were observed for blood pressure, physical activity, and lateral PFC volume/thickness.

Conclusion

This dissertation examined the possibility of bidirectional associations between adiposity and cognitive function among older adults, middle-aged adults, and adolescents. Findings suggested that bidirectional associations between adiposity and cognitive function exist among adolescents and middle-aged individuals. In contrast, findings involving older adult population supported primarily a “brain-as-outcome” perspective on the association between adiposity and cognitive function.

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This dissertation was made possible by the data acquired for the Canadian Longitudinal Study on Aging (CLSA) and the Adolescent Brain Cognitive Development (ABCD) Study. I want to extend my sincere gratitude to all the researchers, staff members, and participants involved in those studies. Additionally, I want to thank the present (Anna, Jessica, Alkarim) and previous (Adrian, Idris, Mia) members of the Prevention Neuroscience Laboratory. Each of you are/were valuable members of the group and I want to thank you all for your support and for the good memories we have shared.

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Dedication

This dissertation is dedicated to my mother, Nazma Khatun,
and father, Mohammad Fazlur Rahman,
for their unwavering love, support, and encouragement.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

ABCD	Adolescent Brain and Cognitive Development
AD	Alzheimer's Disease
ADI	Area Deprivation Index
AFT	Animal Fluency Task
BMI	Body Mass Index
BP	Blood Pressure
CAT	Computerized Adaptive Testing
CLPM	Cross-Lagged Panel Models
CLSA	Canadian Longitudinal Study on Aging
CRT	Choice Reaction Time
CVD	Cardiovascular Disease
dlPFC	Dorsolateral Prefrontal Cortex
DXA	Dual-energy X-ray Absorptiometry
IFG	Inferior Frontal Gyrus
LOFC	Lateral Orbitofrontal Cortex
LPFC	Lateral Prefrontal Cortex
MET	Metabolic Equivalent of Task
MFG	Middle Frontal Gyrus
MMR	Multivariate Multivariable Regression
MRT	Mean Reaction Time
MVPA	Moderate-to-Vigorous Physical Activity
NHANES	National Health and Nutrition Examination Survey
NHES	National Household Education Surveys Program
NIH	National Institutes of Health
PFC	Prefrontal Cortex
SEM	Structural Equation Modeling
SNST	Stroop Neurological Screen Test
T2DM	Type 2 Diabetes Mellitus
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist-Hip Ratio
zBMI	Body Mass Index z-scores

1 Chapter 1: Background

1.1 Adiposity and obesity

The term adiposity indicates the degree of body fat accumulation in an individual (1). It is typically considered an indicator of positive energy balance. Accumulation of excess fat leads to overweight and obesity. Obesity is considered a chronic condition and is defined as "abnormal or excessive fat accumulation that presents a risk to health" (2). Obesity represents a major public health concern as it substantially increases the risk of developing other comorbidities by promoting insulin resistance, such as metabolic syndrome, T2DM and cardiovascular disease (CVD) (3, 4). The health consequence of obesity is not only limited to physical health problems but also extends to affect brain function (e.g., cognitive functions) (5). Obesity is also associated with an increased risk of premature death and higher all-cause mortality (6-9).

1.2 Measures of adiposity

There are a number of accepted methods for assessing adiposity (e.g., body mass index [BMI], waist circumference [WC], waist-hip ratio [WHR], Dual-energy X-ray absorptiometry [DXA] and others), and each method has advantages and limitations.

1.2.1 Body mass index (BMI)

The use of BMI as a measure of adiposity is ubiquitous in both research and clinical setting (10-12). It is a measure of weight adjusted for height and calculated as weight in kilograms divided by the square of height in meters (10). Among adults, a BMI between 18.5 and 24.9 kg/m^2 is considered a healthy weight, whereas a BMI between 25.0 and 29.9 kg/ m^2 is deemed overweight, and a BMI of 30.0 kg/m^2 or higher is regarded as obese (Table 1).

The use of the absolute values of BMI may not be appropriate in children and adolescents because of growth trajectories, which vary considerably in early life. For this reason, BMI tends to vary substantially with age and sex in youth, but the cut-off values are not adjusted for age and sex (10). Therefore, percentiles and z-scores of BMI are usually recommended to assess youth's

nutritional status and growth (10, 13). Among children and adolescents 2 to 19 years, a BMI < 5^{th}, 5 to < 85^{th}, 85 to <95^{th} and ≥ 95^{th} percentiles are considered underweight, healthy, overweight, and obese, respectively (Table 1) (10, 14). This BMI-for-age percentile growth charts were developed based on the sample of five cross-sectional, nationally representative health examination surveys in the United States (US): (1) National Household Education Surveys Program (NHES) II (1963–65), (2) NHES III (1966–70), (3) National Health and Nutrition Examination Survey (NHANES) I (1971–74), (4) NHANES II (1976–80), and (5) NHANES III (1988–94) (15). Children ages 6–11 years from NHES II, 12–17 years from NHES III, 1–19 years from NHANES I, six months–19 years from NHANES II, and 2 months–19 years from NHANES III were included in constructing the percentile growth chart (15). As this growth chart was developed based on the US sample, caution is needed when applying these criteria to the non-US population because of the limitation in generalizability.

Table 1: Classification of weight status based on BMI and BMI percentile (16-20).

Weight Status	**BMI (kg/m^2) / BMI percentile**
Adults	
Underweight	< 18.5
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obese	≥ 30
Obesity class I	30.0–34.9
Obesity class II	35.0–39.9
Obesity class III	> 40
Children and adolescents	
Underweight	< 5th percentile
Normal weight	≥ 5th percentile to < 85th percentile
Overweight	≥ 85th percentile to < 95th percentile
Obese	≥ 95th percentile
Obesity class I	≥ 95th percentile to < less than 120% of the 95th percentile
Obesity class II	≥ 120% of the 95th percentile < 140% of the 95th percentile or BMI ≥ 35
Obesity class III	≥ 140% of the 95th percentile or BMI ≥ 40

Although percentiles are easier to understand and useful for clinical settings, BMI z-scores are recommended for research purposes (13, 21). As a standardized measure, z-scores have superior comparability across age and sex groups (13). Further, it can be analyzed as a continuous variable, and conversion to percentile is also possible if required (13). For BMI z-scores, the cut-offs of -2.0, 1.0, 2.0 and 3.0 represent underweight, overweight, obesity, and severe obesity, respectively (Table 2). The interpretation of the z-scores, however, could be challenging for general public and has limited utility in clinical settings (13).

Table 2: Cut-offs BMI-z score for children 5-19 years old (12, 22)

Z-score cut points	**Weight**
Severe thinness	<-3SD
Thinness	-3SD to <-2SD
Normal	-2 SD to +1SD
Overweight	>+1SD to +2SD
Obese	>+2SD to +3SD
Very obese	>+3SD

Although BMI has emerged as the most widely accepted non-invasive anthropometric measure for classifying overweight and obesity (10-12), it has several limitations. For example, BMI calculation does not take into account muscle mass, bone density, and overall body composition. Therefore, it tends to underestimate adiposity level in the population (e.g., subside actual prevalence) and overestimate fatness in individuals with high muscle mass, such as athletes (17-19, 23). Overall, BMI is an excellent surrogate measure of adiposity, but its strengths and limitations should be carefully considered when used for clinical and research purposes.

1.2.2 Waist circumference (WC)

WC is a simple but effective technique to assess centralized obesity. It can be measured using a simple measuring tape while a patient is standing, wearing light clothing, and at end-expiration. The simplicity of the measurement makes it an inexpensive and easily applicable tool

to use in research and clinical settings. WC shows an excellent correlation with abdominal obesity assessed by imaging methods (24) and a high association with CVD risk factors (e.g., hypertension or blood lipid levels) and mortality (25). WC cut points for overweight and obesity have been established based on their correspondence to a BMI of 25 kg/m2 or 30 kg/m2: 80 and 88 cm for women and 94 and 102 cm for men, respectively (26, 27). It was observed that the cut-offs could vary depending on the ethnic background of the individuals. For example, those of South Asian descent tend to have higher body fat levels and abdominal adipose tissue, and they reported increased metabolic risk at lower waist circumference (28). Therefore, different cut-offs are usually recommended for different ethnic groups; for example, 102 cm for men and 88 cm for women in the United States; 94 cm for men and 80 cm for women in Europe; 90 cm for men and 80 cm for women South Asians and Chinese; and 85 cm for men and 90 cm for women (26, 29-31).

One major limitation of WC is the lack of consensus on the measurement site. At least eight different measurement locations were reported in the literature, and the variability in measurements due to using different locations could be problematic (32-39). The measurement location immediately above the iliac crest is often recommended as bony structures are stable landmarks and usually are not affected by changes in weight (17). The World Health Organization (WHO) recommends the use of the midpoint between the lowest rib and the iliac crest as the measurement site; however, this method requires the identification of two separate locations (e.g., iliac crest and the lowest rib) followed by locating the midpoint between these two structures. Therefore, this method could require more skill and time commitment when implemented in a research study compared to the measurement that relies on only one structure (e.g., iliac crest) (17).

Despite the measurement issues, WC was reported to be a better indicator of abdominal fatness and CVD risks compared to BMI and WHR (30). Altogether, WC is an effective tool to assess central fat deposition and CVD risks, but it is of utmost importance for the research community to establish and adopt the most appropriate measurement site for central adiposity.

1.2.3 Waist-hip ratio (WHR)

Various ratios can be computed from anthropometric data. One of the most commonly used ratios to assess adiposity is WHR. WHR has been used as a proxy measure for abdominal fat distribution. An increase in WHR indicates increased visceral adipose tissue, which strongly correlates with CVD risks. Elevated WHR is associated with a several-fold increase in CVD risk even in the presence of normal BMI (17, 30, 40-42). Therefore, the measurement of body fat distribution by WHR carries important information in identifying people at higher risk of mortality.

According to the US Department of Health and Human Services, the WHR cut-off points to detect obesity are ≥ 0.95 and ≥ 0.80 for males and females (43). Similar to WC, the optimal cut-off values for WHR in detecting CVD risks can differ among different populations (44). Because WHR is a ratio of two different measures in the same individual, it adjusts for ethnic differences in body shape to some extent when determining metabolic risk (17).

1.2.4 Body composition using DXA

One of the widely used imaging techniques for assessing body composition is DXA (12, 17, 45, 46). It can assess fat mass, bone mass, and lean mass of an individual. Because of the high precision and accuracy, DXA is often considered a “gold standard” for body fat assessment. It requires very little radiation exposure, making it appropriate for repeated measures in a clinical setting.

DXA also has several limitations. It was reported that DXA might underestimate body fat at low body fat percentage and overestimate body fat at higher body fat percentage in both adults and children (17). Furthermore, DXA cannot differentiate between subcutaneous and visceral fat adiposity. There could also be inter-manufacturer and intra-manufacturer differences in the DXA devices; therefore, these discrepancies could induce variability in body fat measurement in longitudinal and multicenter research settings.

1.3 Epidemiology of adiposity

The prevalence of obesity and associated complications have reached an epidemic proportion worldwide. According to a report by the WHO, approximately 39% and 13% of adults aged ≥18 years were overweight and obese in 2016, respectively, corresponding to 1.9 billion overweight and 650 million obese people worldwide (2). While undernutrition was eliminated in most developed nations, overnutrition has emerged as a serious public health concern. It was reported that approximately 73.6% of the adults 20 years and older in the United States live with excess adiposity, among which 31.1% are overweight and 42.5% are obese (47). According to the Statistics Canada, the prevalence of overweight and obesity were 36.3% and 26.8%, respectively, in 2018 (48). Although undernutrition is still prevalent in many corners of the world, an upward trend of excess adiposity is becoming evident in many developing nations because of improved nutrition (49).

Childhood obesity has also emerged as a growing concern in recent decades. The WHO reported that approximately 340 million (18%) children and adolescents aged 5-19 years are either overweight or obese (2). The prevalence of obesity among children and adolescents was estimated to be 19.3% and 13% in the United States and Canada, respectively (50-52), and a similar trend is also evident in developing regions (53).

1.4 Evidence for bidirectional associations between adiposity and cognitive function

1.4.1 Adiposity predicts cognitive function

The proposition of "adiposity-to-cognition" (i.e., "brain-as-outcome" approach) is predominant in the medical literature and has been extensively studied in previous research. This hypothesis makes a unidirectional assumption suggesting that baseline adiposity predicts future cognitive function. In such empirical studies, the effects of baseline adiposity on later cognitive function are predominantly observed in the domains of executive functioning, attention, memory, and impulsivity (5, 8, 54-64).

Previous studies showed that higher adiposity is generally associated with poor cognitive function. Although most of the analyses on this topic are cross-sectional in nature, longitudinal assessments suggested a reliable association between midlife obesity and risk for poor neurocognitive function in late life (65-71). For example, Cournot and colleagues reported that a higher baseline BMI was associated with cognitive decline over 5 years (65). Similarly, Gunstad and colleagues noted a decline in general cognitive and executive function among those with higher body composition at baseline (67). This pattern has also been reiterated in meta-analytic reviews. To illustrate, Yang and colleagues reported that obese individuals exhibited less control in major executive function domains, including inhibition, cognitive flexibility, working memory, decision making, verbal fluency, and planning (54). In contrast, this association was only evident in inhibition and working memory domains in the case of overweight individuals (54).

The "brain-as-outcome" perspective is also supported by other longitudinal studies showing that midlife obesity poses a substantial risk of developing dementia and Alzheimer's disease in old age (66, 68-72). Consistent with this, meta-analytic reviews revealed a substantial

and reliable association between obesity and the later development of Alzheimer's disease (AD) and other dementias (72, 73). In terms of magnitude, it appears that obesity in midlife doubles the risk of AD (70, 73). Together these findings suggest that obesity is not only associated with short-term cognitive dysfunction but also significantly increases the risk of neurodegenerative diseases later in life (74).

1.4.2 Cognitive function predicts adiposity

The "brain-as-predictor" perspective is less well explored in previous investigations pertaining to adiposity and cognitive function. This proposition assumes that baseline cognitive function is predictive of future adiposity, and as such, impaired cognitive function predicts weight gain over time. It is believed that the prefrontal cortex (PFC), a part of the brain located at the front of the frontal lobe of the brain, is primarily responsible for "brain-as-predictor" association. This cortical region appears to support core executive processes—i.e., inhibition, working memory, mental flexibility, and planning—which in turn enable a wide variety of higher cognitive functions (75). For instance, the PFC and its subregions have been implicated in planning, sequencing of behaviors over time, personality expression, decision-making processes, and the modulation of complex social behavior (55, 75, 76).

In theory, the role of dorsolateral PFC (dlPFC) is particularly important in regulating dietary behavior in environments characterized by oversupply and visibility of calorie-dense food options (77, 78). Given that the North American food environment largely matches this milieu profile, it is not surprising that the empirical evidence from laboratory experimentation supports this theoretical proposition. A growing body of experimental studies supports the causal role of the dlPFC in calorie-dense food consumption (79, 80). For example, temporary suppression of the dlPFC by continuous theta burst stimulation (a suppressive variant of rTMS) results in increased consumption of calorie-dense foods (81, 82). This indicates that attenuated

function in dlPFC may increase the likelihood of food indulgence, binge eating, and unhealthy food choice more broadly. Consequently, such behaviors in the long term could lead to weight gain, obesity, and the development of associated comorbidities (e.g., hypertension, diabetes) (78).

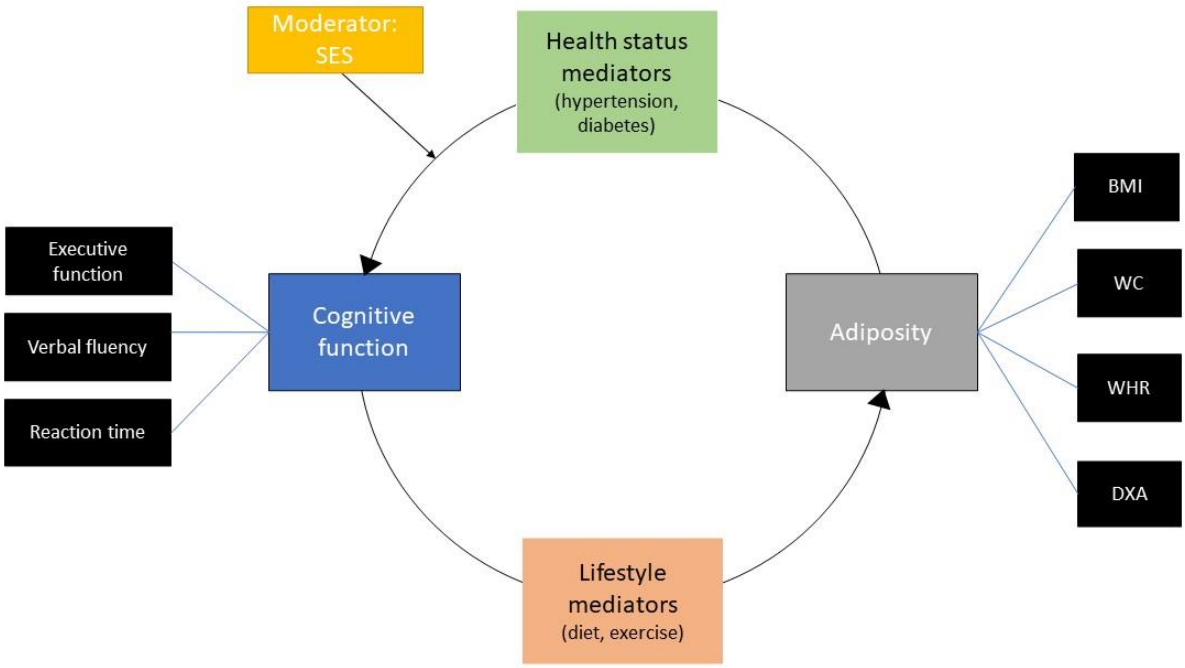

Figure 1: Bidirectional associations model between adiposity and cognitive function.

Besides experimental study findings, this "cognition-to-adiposity" association has also been demonstrated in epidemiological studies. For example, it was reported that executive function in early childhood correlated with dietary behavior in cross-sectional analyses (83) as well as predicted a range of late-life health outcomes, including BMI (84, 85). Guxens and colleagues found that preschool children with higher cognitive function scores were less likely to be overweight at 2-year follow-up (84). Similarly, Moffitt and colleagues reported that children and adolescents with lower scores on an index of cognitive control (based on nine measures of

self-control) were more likely to present with greater health concerns, including weight-related issues in adulthood (85). Overall, despite the limited evidence to date, the above-mentioned findings suggest that the association between adiposity and cognitive function could be bidirectional (Figure 1). The bidirectionality hypothesis remains to be more comprehensively tested in large scale datasets involving a wide range of ages however.

2 Chapter 2: Study Rationale and Objectives

2.1 Study rationale

Although previous studies have shown the existence of both "brain-as-predictor" and "brain-as-outcome" paths using cross-sectional and longitudinal datasets, the bidirectionality proposition has not been comprehensively explored using large-scale population-based datasets. Furthermore, the bidirectionality proposition has not been examined in the same sample. Previous studies mostly examined unidirectional path that is either "brain-as-predictor" path or "brain-as-outcome" path, and bidirectionality has been assumed based on the findings of those unidirectional analyses. Therefore, it is not entirely evident whether such bidirectionality can happen in the same population and timeframe in parallel. In addition, the proposed bidirectionality could be far more complex than simple direct associations between the two. For example, when considering the associations between cognitive function and adiposity, it is not clear whether these associations are independent of obesity-related comorbidities or not (61, 86).

Second, it is also possible that the bidirectional associations are mediated through indirect paths. For example, poor executive control has been associated with higher levels of unhealthy food consumption, more sedentary behavior, less physical activity, and lower levels of fruit and vegetable consumption (83, 87-90). It indicates the presence of indirect paths mediates the association between baseline cognitive function and follow-up adiposity through lifestyle factors, such as diet and physical activity. Likewise, the association between baseline adiposity and follow-up cognitive function could be mediated through obesity-related complications, such as diabetes and hypertension. It should be noted that both diabetes (91-94) and hypertension (95, 96) have been reported to have deleterious effects on cognitive function. These potential mediation paths have not been explored in previous research.

Third, the association between adiposity and cognitive function has been examined using small-scale datasets in previous research. Furthermore, those studies encountered several methodological issues, such as lack of temporalty, small sample size, insufficient measures of focal variables (e.g., cognitive function and adiposity), limited information on the potential confounders, and others. Further research is needed to overcome these issues and preferably conduct research using large-scale population-level data, with sufficient power to detect small-to-medium size effects.

Finally, there is a paucity of research in this field in the Canadian context. Therefore, the associations described previously may not be generalizable to the Canadian population. Understanding the dynamic interrelationship between brain health and adiposity is vital considering the huge demographic of older people in Canada who are at higher risk of developing cognitive impairments.

2.2 Study objective

To address the knowledge gaps mentioned above, three studies were conducted for this dissertation. The objective of Study 1 was to examine the association between cognitive function and adiposity (the "brain-as-predictor" path) using a cross-sectional analysis as well as to determine the existence of any mediational effects of lifestyle factors (e.g., diet and physical activity) and medical conditions (e.g., diabetes and T2DM).

Study 2 aimed to explore the bidirectional associations between adiposity and cognitive function longitudinally in a prospective dataset of middle-aged and older adults as well as to test any mediational effects of lifestyle factors and medical conditions. Finally, Study 3 aimed to examine the bidirectional associations between adiposity and cognitive function longitudinally in

a prospective dataset of adolescents and to test any mediational effects of lifestyle factors, medical conditions, and lateral PFC volume/thickness.

3 Chapter 3: Manuscript 1

3.1 Cognitive function is associated with multiple indices of adiposity in the Canadian Longitudinal Study on Aging (CLSA): A cross-sectional analysis

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3.2 Abstract

3.2.1 Objectives

Prior studies have suggested reciprocal associations between cognitive function and adiposity, but this has not been investigated with population representative datasets. The purpose of this study was to examine the association between cognitive function and adiposity in a large population-based sample of middle-aged and older adults. It was hypothesized that better scores on tests of cognitive function would be associated with lower adiposity and this association would be primarily mediated through lifestyle behavior and physical health status.

3.2.2 Methods

Using baseline data from the Canadian Longitudinal Study on Aging (*N*=30,097), we tested our hypotheses using three indicators of cognitive function (animal fluency, Stroop interference, and mean reaction time) and four indicators of adiposity (body mass index [BMI], total fat mass, waist circumference and waist-hip ratio). Hierarchical multivariable linear regression modeling was conducted followed by tests for moderation by socioeconomic status and mediation through diet, physical activity, hypertension and diabetes status.

3.2.3 Results

All measures of cognitive indicators were significantly associated with adiposity after controlling for confounders. In general, superior performance on animal fluency, Stroop and reaction time tasks were associated with lower adiposity by most metrics. Stroop interference was associated with adiposity across all metrics, including BMI ($b = -0.04, 95\%\ CI\ -0.06, -0.01$), total fat mass ($b =\ 19.35, 95\%\ CI\ 8.57, 30.12$), waist circumference ($b =\ 33.83, 95\%\ CI\ 10.08,\ 57.58$), and waist-hip ratio ($b =\ 0.13, 95\%\ CI\ 0.01, 0.24$). These associations were more substantial for moderate- and high-income sub-populations. Mediation

analyses suggested that the above effects were mediated through lifestyle behavior (e.g., diet and physical activity) and physical health conditions (e.g., diabetes and hypertension).

3.2.4 Conclusions

Reliable associations exist between cognitive function and adiposity in middle-aged and older adults. The effects appear to be mediated through lifestyle behavior and physical health conditions.

3.3 Introduction

The prevalence of obesity has been rising for several decades in Canada and worldwide (2, 97). It is a risk factor for the development of other chronic conditions, such as type 2 diabetes mellitus (T2DM) (98) and heart disease (99). It has been reported that more than 1.9 billion people (18 years and older) worldwide are overweight, and over 650 million of them are obese (2). In Canada, 63.1% of the adults are either overweight (36.3%) or obese (26.8%) (48), exposing them to a heightened risk of developing life-threatening chronic diseases.

The deleterious effect of obesity extends beyond endocrine and cardiovascular systems to include the central nervous system. A number of previous studies have reported an association between cognitive function and body mass index (BMI) (100, 101). Specifically, a high BMI is found to be associated with cognitive decline, and obese individuals tend to perform sub-optimally on formal neuropsychological tests compared to those with a normal range BMI (100, 101). It is believed that eating behavior plays a crucial role in mediating the association between cognition and BMI. Diet is not only an important contributor to obesity (9) but also associated with cognitive health (102). Prior studies have reported an association between unhealthy diet (e.g., high-fat diet) and memory deficits (102-104); healthy eating (e.g., fruits and vegetables), on the other hand, is associated with reduced age-related cognitive decline (105-107).

Recent experimental findings indicate that the association between eating and brain health could be bidirectional (78). For instance, experimentally attenuating the brain regions that support executive function (e.g., left dorsolateral prefrontal cortex; dlPFC) results in disinhibited eating (79), an effect particularly strong in the presence of facilitative cues to consume (82). As such, cognitive resources have a causal influence on capacities for self-restraint, buttressing an argument for bidirectional associations between cognitive function (especially executive function) and weight gain over time, mediated through eating indulgence (77).

In terms of other putative mediators, physical activity, hypertension and diabetes have also received attention. Findings suggest that physically active individuals are less likely to develop cognitive decline, all-cause dementia, vascular dementia and Alzheimer's disease when compared to individuals with a sedentary lifestyle (108-111). Likewise, patients with cognitive deficits tend to lead a more sedentary life and perform less physical activity than cognitively healthy individuals (112). Therefore, it is plausible that impaired cognition leads to obesity through this indirect path of reduced activity level.

Hypertension is also an important risk factor for cognitive decline, and its association has been widely explored in cross-sectional and longitudinal studies (91-94). The association is somewhat inconclusive in cross-sectional studies ranging from no correlation to J- or U-shaped associations (91). However, most prospective studies have revealed a positive association between elevated blood pressure and the later development of cognitive dysfunction (91). In one study, midlife hypertension was associated with a 1.19- to 1.55-fold increased risk of cognitive disorders (93). In terms of mechanisms, hypertension has the capability to cause pathological alterations in cerebral microvessels (e.g., microhemorrhages, lacunar infarcts and white matter injury), which can ultimately lead to cognitive deficits (94). Similarly, T2DM is also known to be associated with cognitive dysfunction and increases the risk of dementia and Alzheimer's disease in older adults, possibly through the same mechanisms (95, 96).

To date, a limited number of studies have explored the associations between cognitive function and adiposity using large-scale population data, and fewer still have examined mediators of such associations systematically. The Canadian Longitudinal Study on Aging (CLSA) data provides an opportunity to assess the above associations and mediational processes in a large, nationally representative sample of the Canadian population (113). In this study, we

examined the association between adiposity and cognitive function and assessed whether or not this association was mediated by eating behavior, physical activity level, hypertension and diabetes status. We hypothesize that better scores on tests of cognitive function will be associated with lower adiposity after controlling for demographics and comorbidities, and the effects of cognitive function on adiposity are primarily mediated through lifestyle behaviors and adverse physical health status. We also hypothesize that the association between cognitive function and adiposity will be stronger for those of higher socioeconomic status (SES), given the more minimal constraints placed on eating selection by environment and financial resources.

3.4 Method

3.4.1 Procedures

This study utilized baseline data from the Canadian Longitudinal Study on Aging (CLSA), which is the only wave containing all 4 indicators of adiposity: BMI, waist-hip ratio (WHR), waist circumference (WC) and total fat mass. The CLSA is a long-term, national, prospective study comprising 51,338 participants who were between the ages of 45-85 years during recruitment (113, 114). The CLSA commenced its recruitment process in 2010 and completed baseline data collection in 2015. Exclusion criteria for CLSA were residing in one of the three territories of Canada, living on a federal First Nations reserve or other First Nation settlement in the provinces, serving as a full-time member of the Canadian Armed Forces, living in a long-term care institution, cognitive impairment at the time of contact, and not being able to communicate in one of the two national languages (English or French) (113-115).

The CLSA consists of two cohorts: tracking and comprehensive. The tracking sample is the smaller cohort and consists of 21,241 participants who were randomly selected (within age/sex strata) from across 10 Canadian provinces and underwent only a 60-minute telephone interview (113-115). The comprehensive cohort, on the other hand, comprises 30,097

participants randomly selected within age/sex strata from among individuals residing within a 25-50 km radius of one of the 11 data collection sites (Vancouver, Victoria, Calgary, Winnipeg, Hamilton, Ottawa, Montréal, Sherbrooke, Halifax, and St. John's) in 7 provinces (113-115). The comprehensive cohort participants underwent a 90-minute in-person interview at home with computer-assisted interview instruments. In addition, they visited a data collection site for physical assessments and provided a biological sample (i.e., blood and urine). Baseline participants were recruited from the following sources: Canadian Community Health Survey–Healthy Aging (for CLSA tracking cohort only), Provincial Health Registries and Telephone Sampling-Random Digit Dialing (113, 114, 116). The CLSA is expected to continue for at least 20 years, with follow-up data collection every three years. Detailed information about the sampling strategy and study design has been published elsewhere (113, 114).

CLSA participants provided a core set of information on demographic and lifestyle/behavior measures, social measures, physical/clinical measures, psychological measures, economic measures, health status measures, and health services use (113, 117). All participants provided written consent to participate in the CLSA. The present study received ethics approval from the Office of Research Ethics, University of Waterloo (ORE# 41434). The data access application was approved by the CLSA Data and Sample Access Committee.

3.4.2 Participants

This study used the baseline data of the comprehensive cohort only as some of the cognitive variables of interest (i.e., Stroop Neurological Screen Test and Choice Reaction Time Test) were not available for the tracking cohort participants. Therefore, this cross-sectional study included a total of 30,097 men and women aged 45-85 years, representing over 3.7 million Canadians. There were some missing values (n = 1,488) associated with our variables of interest.

Accordingly, our analytic sample included 28,609 participants from CLSA comprehensive cohort.

3.4.3 Measures

3.4.3.1 Adiposity indicators

BMI. Each participant's height (m) and weight (kg) were measured as part of CLSA data collection (118). A BMI variable was created as kg/m^2. Conventional BMI cutoffs were used to create the following BMI original categories: underweight (BMI < 18.5), normal (BMI = 18.5-24.9), overweight (BMI = 25-29.9), and obese (BMI $\geq$ 30). In statistical modeling, BMI was used as a continuous variable.

Total fat mass. At baseline, the CLSA utilized dual-energy X-ray absorptiometry (DXA) to measure total fat mass (in kg), including all the fatty tissue in the body (i.e., fatty tissue found within the organs of the body and also the subcutaneous fat found under the skin) (119). Body fat percentage was calculated and provided in the dataset as a continuous variable.

Waist circumference (WC). This measurement was taken around the abdomen at the level of the umbilicus. It is a reliable measure of fat around the midsection. Excessive abdominal fat may put an individual at a higher risk of chronic diseases (120). Ideally, WC should be less than 40 and 35 inches for men and women, respectively (121).

Waist-hip ratio (WHR). WHR is a measure of fat distribution calculated by dividing the circumference of the waist by the hip circumference. According to the World Health Organization, a healthy WHR is 0.9 or less for men and 0.85 or less for women (28).

3.4.3.2 Cognitive Function

Cognitive function was assessed based on the performance on three cognitive tasks: Stroop Neurological Screen Test (SNST) and Choice Reaction Time (CRT) Test and Animal Fluency Test (AFT).

Stroop Neurological Screen Test (SNST). This task is frequently used to assess executive function, selective attention, and cognitive flexibility (122, 123). As this task requires subjects to inhibit an overlearned response in favor of an unusual one; it is a good measure of the "behavioral inhibition" facet of executive function. In the task, participants are instructed to identify the color of the font in which a word is presented whilst ignoring the meaning of the word itself (122, 123). When the written word is incongruent with the font color (e.g., *red* written in *green* ink), the time it takes to identify the color increases relative to a baseline condition. The Victoria Stroop version used in the CLSA presented the participants with three stimulus cards sequentially: (i) neutral: a list of neutral words printed with different ink colors, (ii) congruent: a number of "X"s printed with different ink colors, and (iii) incongruent: a number of color words printed in a manner that the color word and ink color do not match (e.g., "blue" word is written in "green" ink) (124-126). For the first card, participants were asked to read the list of neutral words, from left to right, for each of the successive rows. For the second card, participants were asked to name the ink color of the printed "X"s. For the final card, participants were asked to quickly name the color of the ink in which the words are written, ignoring the meaning of the words (119). The participants' responses were recorded for each block. The Stroop interference, defined as the delay in completion time between congruent and incongruent blocks, was calculated by taking the differences in the completion time between the incongruent and congruent blocks.

Choice Reaction Time (CRT) Test. This test requires participants to respond to one stimulus but to not respond to another (127). It assesses participants' ability to maintain attention and vigilance for the target stimulus and the ability to inhibit responses to the nontarget stimuli. The CRT was administered on a computer with a touch screen which displayed four horizontal

plus signs and four keys, with one key underneath each plus sign (124). The touch screen would have one plus sign turn into a box and the participants were instructed to press the touch key on the screen underneath the box as quickly as possible. The exercise was repeated 52 times (124). Participants' scores were generated automatically by the computer software. The mean reaction time was calculated as the average of the correct answers, excluding incorrect answers and timeouts.

Animal Fluency Test (AFT). This is a brief cognitive screening test that requires participants to name as many animals as possible in 60 seconds, with one point given for each unique animal (124). If a patient named 15 or fewer animals within the 60-second time frame, this may indicate early stages of dementia or the development of cognitive impairment (128). For the purpose of the CLSA, the participants' responses were recorded and the data were entered into a database. Animal names provided by the participants that met the CLSA animal definition were considered primary and coded based on their scientific taxonomic classification (124). Then using a validated algorithm, test scores were determined.

3.4.3.3 Covariates

Age. Participants' age was calculated from their date of birth and provided as a numerical variable. It was also converted into an ordinal variable with the following age groups for descriptive analyses: 45-54, 55-64, 65-74, and 75+ (129).

Sex. Participants were asked to report their biological sex at birth; men coded as 1 and women coded as 0 (129).

Ethnicity. This variable was coded as 1 and 0 where 1 denotes Caucasian and 0 denotes non-Caucasian ethnicities (129).

Income: Income was assessed based on total household income. Participants were asked: "What is your best estimate of the total household income received by all household members, from all sources, before taxes and deductions, in the past 12 months?" (129). This variable was categorized as follows: < $20,000; $20,000-$50,000; $50,000-$100,000; $100,000-$150,000; and ≥ $150,000. Missing values (n = 1393) were recoded as "No Response".

Education. The level of education was obtained from two variables. After first responding to whether they had graduated from high school, participants were asked: "Have you received any other education that could be counted towards a degree, certificate, or diploma from an educational institution?" (129). Respondents who said "No" were considered as having an education which was "high school or less". Participants who said "Yes" were further asked the following question to know the level of education achieved: "What is the highest degree, certificate, or diploma you have obtained?" (129). An ordinal variable was derived from these variables with the following categories: high school or less; certificate or degree below bachelor; and bachelor or above.

Residence. Area of residence was defined as rural or urban. This variable was provided in the dataset as: rural; urban core; urban fringe; urban population centre outside a census metropolitan area and census agglomeration; secondary core; and postal code link to dissemination area (129). This variable was recoded as rural and urban, with the latter including all non-rural categories.

Somatic comorbidity. A comorbidity index variable was created by summing across following 22 chronic conditions: diabetes, chronic obstructive pulmonary disease, asthma, heart disease, heart attack, hypertension, peripheral vascular disease, epilepsy, migraine, rheumatoid arthritis, osteoarthritis, other arthritis, back problems, hyperthyroidism, hypothyroidism,

depression, mood disorder, anxiety disorder, cancer, bowel disorder, stomach ulcer, and kidney disease (118, 130). An ordinal comorbidity variable was also created for descriptive analyses based on the sum number of chronic conditions: 0, 1-2, 3-4, and ≥ 5. When a target mediator contained within the somatic comorbidity index was tested in mediational analyses, it was temporarily removed and the index recalculated for use in that analysis only.

Neurologic comorbidity. This variable was coded as 0 and 1, where 0 indicates no neurologic comorbidity and 1 indicates the presence of any one of the following neurologic conditions: stroke, Parkinson's disease, multiple sclerosis and dementia.

3.4.3.4 Putative Mediators

Healthy foods. The variables for food consumption behavior were derived from the "Short Diet Questionnaire" (129, 131). More frequent consumption of legumes, fruits, green salad and carrot were used as an indicator of healthy food choice habits. Participants were asked the following questions: (i) "How often do you usually eat legumes: beans, peas, lentils?", (ii) "How often do you usually eat fruit (fresh, frozen, canned)?", (iii) "How often do you usually eat green salad (lettuce, with or without other ingredients)?", and (iv) "How often do you usually eat carrots (fresh, frozen, canned, eaten on their own or with other food, cooked or raw)?" (129). The responses for each healthy food item were an ordinal scale as follows: per day, per week, per month and per year. These variables were recoded as "daily", "weekly", and "rarely". The average caloric density of these items was 54 kcal per 100 gm, according with standardized estimates (132).

Hyperpalatable foods. More frequent consumption of fries, snacks, pastries and chocolate were used as an indicator of unhealthy, hyperpalatable food choice habits. Participants were asked the following questions: (i) "How often do you usually eat French fries or pan-fried

potatoes, poutine?", (ii) "How often do you usually eat salty snacks (regular chips, crackers, …)?", (iii) "How often do you usually eat cakes, pies, doughnuts, pastries, cookies, muffins…?" and (iv) How often do you usually eat chocolate bars? (129). The response scale for each hyperpalatable food item was an ordinal scale as follows: per day, per week, per month and per year. These variables were recoded as "daily", "weekly", and "rarely". The average caloric density of these items was 434 kcal per 100 gm, according with standardized estimates (132).

Physical Activity (mild): Participants were asked: "Over the past 7 days, how often did you take a walk outside your home or yard for any reason? For example, for pleasure or exercise, walking to work, walking the dog, etc." (133). This variable was recoded as follows: never, seldom (1-2 days), sometimes (3-4 days), often (5-7 days), and no response.

Physical Activity (moderate): Participants were asked: "Over the past 7 days, how often did you engage in moderate sports or recreational activities such as ballroom dancing, hunting, skating, golf without a cart, softball or other similar activities?" (133). This variable was recoded as follows: never, seldom (1-2 days), sometimes (3-4 days), often (5-7 days), and no response.

Hypertension status. Participants were asked: "Has a doctor ever told you that you have high blood pressure or hypertension?" This variable was recoded as 0 and 1 where 1 denotes the presence of hypertension.

Diabetes status. The diabetic status was derived from two variables. At first, participants were asked: "Has a doctor ever told you that you have diabetes, borderline diabetes or that your blood sugar is high?" (118). Then, a follow-up question was asked to those who responded "yes" to know the type of diabetes. Finally, the diabetic status was recoded as "Type 2", "other type" and "none".

3.4.4 Statistical analyses

Data management and statistical analyses were performed using R statistical software package, version 4.1.0 (134). Data were analyzed using survey weights provided by the CLSA. As recommended by the CLSA, we used inflation weights in descriptive analyses and analytic weights in inferential analyses (116). First, we conducted descriptive analysis for the study variables. Weighted percentages and means were calculated for each of the categorical and continuous variables, respectively. In addition, the mean scores for the cognitive tasks and BMI were calculated for each subgroup.

For the inferential statistics, hierarchical multivariable linear regressions were conducted to assess the association of adiposity with all other study variables. We used a power transformation of the BMI variable (-0.7) in the regression models for variance stabilization and/or non-normality of the residuals of the model. No power transformation was used for other outcome variables. A total of 2 models were assessed. Two-way interaction terms among variables were tested in all models. Model 1 examined the association between each adiposity indicator and potential confounders/covariates (i.e., age, sex, ethnicity, income, education, residence, physical activity, somatic comorbidity and neurologic comorbidity). Model 2 assessed the association between adiposity indicators and cognitive function while controlling for the effects of confounders/covariates.

Next, we conducted separate mediation analyses with diet, physical activity, hypertension, and diabetes status as mediating variables to assess whether the association between adiposity and cognitive function is mediated through other variables. While hypertension and diabetes status were represented as single variables, diet and physical activity were each measured by several variables, hence we used models with multiple mediators in (at

least two of) our analyses. A simple mediation model with statistical control and multiple mediators uses the following two regression models:

1) Model A:

$$Y = a_A + a_1X_1 + \cdots + a_kX_k + b_1M_1 + \cdots + b_mM_m + f_1C_1 + \cdots + f_pC_p + \varepsilon_A$$

2) Model B:

$$Y = a_B + a'_1X_1 + \cdots + a'_kX_k + f'_1C_1 + \cdots + f'_pC_p + \varepsilon_B$$

where $X_1, \ldots, X_k$ are the exposure variables (cognitive function, hence k=3 in our study), $M_1, \ldots, M_m$ are the mediators, and $C_1, \ldots, C_p$ are the confounders. The indirect or mediated effects are the effects of X_1 , X_2, and X_3 (i.e., cognitive function) on Y (i.e., adiposity) through $M_1, \ldots, M_m$ (i.e., mediators), calculated by the difference between total effects (a'_1, a'_2, a'_3) and direct effects (a_1, a_2, a_3). A non-parametric bootstrap method was used to compute 95% confidence intervals for indirect effects. Using the above-mentioned models, the effects were calculated manually. Finally, we conducted a moderation analysis by income groups to test whether the association between cognitive function and adiposity is moderated by SES stratum.

3.5 Results

3.5.1 Sample characteristics

Socio-demographic, lifestyle and health-related characteristics of the CLSA comprehensive cohort participants (n = 30,097) are summarized in Table 1. The majority of the participants were middle-aged (71.73%), Caucasian (94.7%) and residents of an urban area (91.53%). The sample had a similar proportion of males (49.64%) and females. In terms of socioeconomic status, 46.43% of the participants possessed at least a bachelor's degree and 72% had an annual household income of $50,000 or more. Although about half of the participants reported engaging in walking outside the home frequently (50.70%), most did not participate in sports or recreational activities (82.36%). In addition, 67.45% of the participants were found

either overweight or obese, and a substantial proportion had three or more somatic comorbidities (41.78%). However, relatively small proportion of participants reported of having neurologic comorbidity (2.5%). In terms of eating behaviors, healthy foods were consumed on a daily (fruits [71.76%]) or weekly basis (legume [59.32%]; green salad [68.82%]; carrot [73.30%]) whereas hyperpalatable foods were consumed mainly weekly (snacks [50.74%]; pastries [50.57%]) or rarely (fries [74.41%]; chocolate [67.79%]).

3.5.2 Primary analyses

Model 1 revealed that BMI was significantly associated with sex, income, education, and somatic comorbidity (Table 2). Indicators of cognitive function were significantly associated with BMI after controlling for the effects of confounders and covariates (Model 2). More specifically, a unit increase in animal fluency score was associated with average $BMI^{-0.7}$ increase by 0.04 units whereas a unit increase in Stroop interference was associated with average $BMI^{-0.7}$ decrease by 0.04 units.

A similar association was observed between cognitive function indicators and other adiposity indicators (Table 3). Animal fluency score was associated with adiposity indicators such that one unit increase in animal fluency score was associated with a total fat mass, WC and WHR decrease of 45.85, 31.69 and 0.21 units, respectively (Table 3). Similarly, in the case of Stroop interference scores, a unit increase was associated with an increase in total fat mass, WC and WHR by 19.99, 35.38 and 0.13 units, respectively (Table 3). Although the effects of mean reaction time on WC and WHR were found in the expected direction, the coefficient for total fat mass was negative. It suggests that one unit increase in mean reaction time was associated with average total fat mass decrease by 0.87 units, and average WC and WHR increased by 1.61 and 0.02 units, respectively.

Moderation analyses revealed that above associations were generally stronger for people in higher SES categories. Those with an annual household income of "$50,000 to < $100,000" and "$100,000 to < $150,000" showed a significantly higher reduction of average $BMI^{-0.7}$ by 0.06 and 0.09 units respectively for each unit increase in Stroop interference (Table 4). This pattern of association was evident across all adiposity indicators.

Some evidence for mediation of adiposity-cognition associations was found for lifestyle behaviors and physical health status; however, the findings were not consistent across all cognitive and adiposity indicators (Table 5). For example, the association between adiposity and Stroop interference was found to be mediated through hypertension (-0.33, 95% CI -1.25, -0.15) and T2DM (-0.04, 95% CI -0.05, -0.02; Table 5). But the association between adiposity and animal fluency was found to be mediated through diet, physical activity, and hypertension (Table 5). Finally, diet and T2DM status emerged as significant mediators of the association between adiposity and mean reaction time (Table 5).

3.6 Discussion

This investigation examined associations between three indicators of cognitive function (Stroop interference, animal fluency and mean reaction time) and four indicators of adiposity (BMI, WC, WHR and total fat mass assessed by DXA) in covariate-adjusted models, followed by mediation and moderation analyses. Findings revealed that lower scores on animal fluency, higher scores on the Stroop interference and higher mean reaction time were associated with increasing adiposity, in fully adjusted models. Such findings were evident across all adiposity indicators, the sole exception being the association between BMI/total fat mass and reaction time.

Using mediation analysis, it was found that the indirect effect of Stroop interference on adiposity in middle-aged and older adults was not mediated through lifestyle behaviors but was

mediated by two common chronic conditions: hypertension and Type 2 diabetes. However, lifestyle behaviors did emerge as significant mediators for effects involving reaction time and animal fluency. When examining associations as a function of socioeconomic status, it was found that stronger effects of cognitive function were evident at moderate- and high-income levels, regardless of which type of indicator was used. This may be a function of less choice available to those in lower SES strata, such that food choice is more dictated by the environment and financial constraints than decision-making or successfully navigating decision implementation challenges. Additionally higher stress levels and lower access to healthcare resources may play a stronger contributing role to health outcomes than individual choice at lower SES levels.

Our findings are largely in line with prior work in the field using smaller samples. For example, previous studies reported that a higher BMI is associated with cognitive decline (135, 136), and obese individuals tend to perform poorly in neuropsychological tests (100, 137). We included four indicators of adiposity in our analysis, and the measures of centralized obesity (e.g., WC) are often considered superior compared with BMI because of their higher predictive validity (138). However, previous studies reported that regardless of the adiposity measures, adiposity showed an inverse association with cognitive function (139, 140). In accordance with previous research, we found a similar inverse association between adiposity and cognition across all adiposity indicators.

Mediational effects varied across cognitive and adiposity indicators, and generally suggested the possibility of both lifestyle and health status mediation. Ultimately, the directionality of such effects can only be determined with future research using prospective data; for now we can conclude only that lifestyle (eating, activity) and health status (hypertension,

T2DM) hold promise as putative mediators of reciprocal associations between adiposity and cognitive function. Longitudinal analyses with multiple years of follow-up data over sufficiently long periods of time—that is, years to decades—could potentially disambiguate mediational mechanisms.

The current study has several strengths. First, we utilized a large and nationally representative sample of Canadians consisting of 30,097 participants. This large sample was sufficiently powered to detect even small magnitude effects. Second, we were able to control for a number of chronic diseases that might have an association with adiposity by creating a comorbidity index. Third, instead of using a single measure of cognitive function and adiposity, we used multiple indicators of each: three indicators of cognitive function and four indicators of adiposity. This allows us to make broader statements about our findings, because they are not specific to a particular measure of cognitive function or adiposity.

Despite several strengths, this study is not without limitations. Although CLSA is a national dataset of middle-aged and older Canadians, the representativeness is somewhat limited for the specific cohort used for the present analysis. Unlike tracking cohort where the sample was collected from across all Canadian provinces, comprehensive cohort participants were recruited only from seven Canadian provinces and within a certain radius of the data collection sites in eleven cities. Therefore, the generalizability of this study is limited to those living in the vicinity of major urban centres. Like most survey data, this study also encountered the issue of missing values. Considering the large sample size and a relatively small proportion of missing values (5%), we conducted complete case analyses for all regression models and mediation analyses. Many CLSA variables were derived from survey questionnaires. Although these questionnaires were validated (e.g., Short Diet Questionnaire), self-reported natures of these measures could

lead to social desirability biases (e.g., exaggeration or under-reporting). Finally, this study is cross-sectional in nature and, as such, we cannot infer causality or temporality based on our findings. The use of the baseline data, however, did allow us to maximize the number of adiposity indicators available, given that DXA was measured only at baseline within the CLSA.

The mediational analyses undertaken provided some evidence for adiposity-cognition associations mediated through lifestyle behavior and physical health status. However, given the cross-sectional nature of the data, such mediation effects are difficult to interpret in absolute terms. An analysis of prospective associations with multi-year follow-up data will more conclusively identify the reliability and directionality of mediational processes hypothesized here. Similarly, the observed effects of cognition on adiposity—though highly reliable—were relatively small in absolute terms across all adiposity indicators. Therefore, inferring clinical and societal value for these findings should be undertaken with this in mind. Based on the current findings, we can only state that cognition is associated with adiposity, but the actual effect size should be investigated using prospective data with multi-year follow-up over time periods long enough to expect cumulative temporal effects to emerge.

Future research should also examine the extent to which the associations between adiposity and cognitive function are evident in earlier age cohorts. Given that older cohorts present a larger possibility that cognition is affected by decades of adiposity and its associated physiological conditions (e.g., hypertension), it is more likely that cognitive differences are pre-existing if they are already evident in early life, before adiposity has emerged. Future research should address this knowledge gap by examining datasets of adolescents and young adults. We included three measures of cognitive function in our analysis. Future research might benefit as well from using a broader range of cognitive constructs to examine in relation to effects of

adiposity. Finally, this study is solely a neuropsychological test-based study, and such associations should also be explored using brain imaging data.

3.7 Conclusion

In conclusion, our findings indicate that lower performance on several measures of cognitive function is associated with increased adiposity. This remains true whether the latter is measured by BMI, WHR, WC or total fat mass assessed using DXA. Mediational analyses suggest a mediational path through lifestyle behavior and physical health status, and moderation analyses suggested that the effects were stronger for those in higher SES strata, at least in the case of Stroop interference effects. Future longitudinal investigations will be potentially useful to further disentangle the nature and directionality of the associations observed here, particularly in the case of mediational pathways. The current and future findings may assist researchers and policy makers to view obesity as both a predictor and outcome of brain health if the current findings prove reliable across datasets and in longer-term prospective studies.

3.8 Acknowledgments

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3.9 Tables and Figures

3.9.1 Table 1: Sample characteristics

Variables	Percentage (weighted)	Stroop Interference (Mean, 95% CI)	Mean Reaction Time (Mean, 95% CI)	Animal Fluency Score (Mean, 95% CI)	BMI (Mean, 95% CI)
Total Sample	100	9.95 (9.86, 10.05)	797.29 (794.89, 799.68	20.33 (20.24, 20.41)	27.80 (27.72, 27.88)
Age					
45-54	41.97	8.03 (7.90, 8.17)	742.23 (738.46, 746.00)	21.91 (21.76, 22.06)	27.56 (27.42, 27.70)
55-64	29.76	9.80 (9.66, 9.94)	795.94 (792.11, 799.78)	20.63 (20.50, 20.75)	28.15 (28.03, 28.27)
65-74	17.16	11.77 (11.57, 11.96)	857.85 (852.98, 862.72)	18.60 (18.46, 18.74)	28.13 (28.00, 28.27)
75+	11.11	14.90 (14.56, 15.24)	916.86 (909.92, 923.79)	16.21 (16.05, 16.37)	27.27 (27.11, 27.43)
Sex					
Male	49.64	10.00 (9.87, 10.13)	784.28 (780.86, 787.70)	20.56 (20.44, 20.68)	28.15 (28.05, 28.25)
Female	50.36	9.91 (9.78, 10.04)	810.14 (806.80, 813.48)	20.10 (19.99, 20.21)	27.46 (27.35, 27.57)
Ethnicity					
Non-Caucasian	5.30	10.39 (9.88, 10.90)	862.53 (848.90, 876.16)	17.47 (17.06, 17.87)	27.00 (26.70, 27.30)
Caucasian	94.70	9.93 (9.84, 10.02)	793.62 (791.21, 796.02)	20.49 (20.40, 20.57)	27.85 (27.77, 27.92)
Income					
No response	5.60	10.75 (10.38, 11.13)	825.41 (815.60, 835.23)	18.88 (18.55, 19.22)	27.68 (27.37, 27.99)
< $20,000	4.42	12.63 (12.06, 13.19)	868.17 (856.23, 880.12)	17.60 (17.26, 17.94)	28.77 (28.38, 29.16)
$20,000 to < $50,000	17.69	12.08 (11.81, 12.35)	847.07 (841.16, 852.98)	18.10 (17.92, 18.27)	28.27 (28.10, 28.44)
$50,000 to < $100,000	31.43	9.95 (9.80, 10.11)	800.00 (795.82, 804.18)	20.01 (19.87, 20.15)	27.92 (27.78, 28.05)
$100,000 to < $150,000	20.94	8.98 (8.82, 9.15)	770.78 (765.76, 775.80)	21.54 (21.36, 21.73)	27.58 (27.41, 27.76)
< $150,000 or more	19.92	8.31 (8.14, 8.47)	753.70 (748.63, 758.78)	22.53 (22.34, 22.73)	27.26 (27.09, 27.43)
Education					
High school or less	13.85	12.17 (11.87, 12.47)	833.00 (826.29, 839.71)	17.61 (17.41, 17.81)	28.75 (28.54, 28.96)
Below bachelor	39.73	10.17 (10.02, 10.32)	798.77 (794.96, 802.58)	19.60 (19.48, 19.73)	28.27 (28.15, 28.39)
Bachelor or above	46.43	9.11 (9.00, 9.23)	785.41 (781.95, 788.87)	21.76 (21.63, 21.88)	27.12 (27.01, 27.22)
Residence					
Urban	91.53	9.93 (9.84, 10.03)	799.87 (797.33, 802.40)	20.35 (20.26, 20.44)	27.82 (27.74, 27.90)
Rural	8.47	10.19 (9.89, 10.49)	769.57 (762.62, 776.52)	20.08 (19.81, 20.36)	27.61 (27.37, 27.85)
Physical activity (mild)					
No response	3.88	11.42 (10.77, 12.08)	842.55 (828.28, 856.81)	18.10 (17.68, 18.53)	28.31 (27.90, 28.72)
Never	12.82	10.41 (10.15, 10.66)	805.32 (798.65, 812.00)	19.37 (19.15, 19.59)	29.08 (28.85, 29.31)
Seldom (1-2 days)	14.78	9.82 (9.58, 10.06)	789.93 (783.71, 796.14)	20.19 (19.97, 20.41)	28.29 (28.08, 28.50)

Sometimes (3-4 days)	17.86	9.70 (9.49, 9.91)	790.47 (784.83, 796.11)	20.48 (20.28, 20.67)	28.00 (27.82, 28.19)
Often (5-7 days)	50.70	9.86 (9.74, 9.98)	796.43 (793.09, 799.78)	20.73 (20.61, 20.84)	27.23 (27.13, 27.33)
Physical activity (moderate)					
No response	3.82	11.40 (10.74, 12.06)	842.36 (828.01,856.71)	18.10 (17.67, 18.53)	28.32 (27.91, 28.72)
Never	82.36	9.98 (9.88, 10.08)	797.95 (795.29, 800.60)	20.33 (20.24, 20.42)	27.92 (27.84, 28.01)
Seldom (1-2 days)	8.76	9.25 (8.97, 9.53)	774.54 (767.26, 781.83)	20.86 (20.57, 21.14)	27.01 (26.79, 27.24)
Sometimes (3-4 days)	3.35	9.43 (9.02, 9.85)	791.70 (780.24, 803.16)	20.79 (20.35, 21.23)	26.68 (26.32, 27.05)
Often (5-7 days)	1.70	10.21 (9.48, 10.93)	794.42 (776.27, 812.56)	21.43 (20.81, 22.04)	26.91 (26.34, 27.49)
Somatic comorbidity					
None	16.76	8.75 (8.55, 8.95)	765.47 (759.33, 771.62)	21.34 (21.12, 21.55)	26.25 (26.09, 26.40)
1-2	41.46	9.65 (9.52, 9.79)	788.80 (785.11, 792.49)	20.53 (20.40, 20.67)	27.21 (27.10
3-4	25.90	10.44 (10.25, 10.63)	808.10 (803.44, 812.75)	20.02 (19.86, 20.18)	28.33 (28.17, 28.48)
> 4	15.88	11.20 (10.97, 11.44)	835.08 (829.26, 840.91)	19.25 (19.06, 19.45)	30.14 (29.92, 30.37)
Neurologic comorbidity					
No	97.50	9.87 (9.77, 9.96)	795.25 (792.83, 797.67)	20.40 (20.31, 20.48)	27.80 (27.72, 27.87)
Yes	2.50	13.34 (12.55, 14.14)	874.72 (858.15, 891.30)	17.83 (17.36, 18.30)	28.00 (27.56, 28.44)
Hypertension					
No	68.06	9.36 (9.26, 9.47)	783.17 (780.25, 786.08)	20.86 (20.76, 20.97)	26.84 (26.76, 26.93)
Yes	31.94	11.19 (11.02, 11.36)	826.91 (822.72, 831.10)	19.22 (19.08, 19.36)	29.84 (29.70, 29.99
BMI					
Normal	31.85	9.56 (9.40, 9.71)	795.43 (791.01, 799.85)	19.47 (18.52, 20.43)	22.75 (22.71, 22.79)
Underweight	0.70	10.83 (9.74, 11.92)	827.56 (799.27, 855.85)	20.81 (20.66, 20.96)	17.49 (17.31, 17.67)
Overweight	39.98	9.89 (9.75, 10.03)	796.19 (792.44, 799.93)	20.24 (20.11, 20.37)	27.35 (27.31, 27.38)
Obese	27.47	10.44 (10.26, 10.63)	799.11 (794.60,803.62)	19.96 (19.81, 20.12)	34.58 (34.46, 34.70)
Legume					
Per day	5.16	10.23 (9.84, 10.61)	819.11 (807.47, 830.74)	19.96 (19.56, 20.35)	27.21 (26.90, 27.53)
Per week	59.32	9.63 (9.52, 9.75)	795.76 (792.64, 798.88)	20.73 (20.62, 20.83)	27.60 (27.50, 27.70)
Rarely	35.52	10.44 (10.28, 10.61)	796.48 (792.50, 800.45)	19.73 (19.59, 19.87)	28.22 (28.09, 28.35)
Fruits					
Per day	71.76	9.95 (9.84, 10.06)	801.16 (798.34, 803.99)	20.36 (20.26, 20.46)	27.52 (27.43, 27.61)
Per week	24.78	9.86 (9.67, 10.04)	785.75 (780.92, 790.58)	20.41 (20.24, 20.58)	28.49 (28.33, 28.65)
Rarely	3.46	10.72 (10.21, 11.22)	799.36 (785.99, 812.74)	19.06 (18.66, 19.46)	28.74 (28.30, 29.17)
Salad					
Per day	20.94	10.08 (9.86, 10.30)	809.00 (803.67, 814.33)	20.18 (19.99, 20.36)	27.25 (27.09, 27.41)
Per week	68.82	9.75 (9.65, 9.86)	791.43 (788.54, 794.33)	20.56 (20.46, 20.66)	27.88 (27.79, 27.97)

Rarely	10.24	11.05 (10.75, 11.35)	812.54 (805.29, 819.80)	19.09 (18.84, 19.34)	28.40 (28.16, 28.64)
Carrot					
Per day	9.49	10.55 (10.22, 10.88)	810.33 (802.33, 818.33)	19.69 (19.42, 19.97)	27.32 (27.06, 27.58)
Per week	73.30	9.92 (9.81, 10.02)	796.40 (793.60, 799.21)	20.44 (20.35, 20.54)	27.77 (27.68, 27.85)
Rarely	17.21	9.77 (9.56, 9.98)	793.59 (787.87, 799.31)	20.19 (19.99, 20.40)	28.22 (28.02, 28.41)
Fries					
Per day	0.17	13.27 (9.91, 16.63)	792.02 (688.50, 895.55)	20.22 (18.33, 22.11)	27.91 (26.05, 29.76)
Per week	25.42	10.09 (9.90, 10.28)	788.10 (783.16, 793.03)	20.15 (19.99, 20.32)	28.88 (28.72, 29.04)
Rarely	74.41	9.90 (9.80, 10.00)	800.41(797.66, 803.15)	20.39 (20.29, 20.49)	27.43 (27.35, 27.52)
Snacks					
Per Day	4.74	10.34 (9.88, 10.80)	803.38 (791.30, 815.46)	20.07 (19.70, 20.45)	27.84 (27.47, 28.20)
Per Week	50.74	9.48 (9.36, 9.60)	782.13 (778.86, 785.39)	20.82 (20.71, 20.94)	27.88 (27.77, 27.99)
Rarely	44.52	10.46 (10.31, 10.60)	813.91 (810.24, 817.58)	19.79 (19.66, 19.91)	27.71 (27.60, 27.82)
Pastries					
Per Day	13.67	11.40 (11.12, 11.68)	821.86 (815.23, 828.48)	19.22 (18.99, 19.45)	27.43 (27.23, 27.63)
Per Week	50.57	9.72 (9.60, 9.84)	790.15 (786.88, 793.43)	20.62 (20.50, 20.73)	27.81 (27.70, 27.91)
Rarely	35.76	9.72 (9.57, 9.87)	797.83 (793.68, 801.98)	20.35 (20.22, 20.49)	27.93 (27.80, 28.06)
Chocolate					
Per Day	3.12	10.12 (9.54, 10.69)	798.37 (784.99, 811.75)	20.63 (20.18, 21.07)	27.07 (26.70, 27.45)
Per Week	29.10	9.60 (9.44, 9.76)	790.93 (786.58, 795.28)	20.68 (20.52, 20.84)	27.84 (27.69, 27.98)
Rarely	67.79	10.10 (9.98, 10.21)	799.90 (796.95, 802.86)	20.17 (20.07, 20.26)	27.82 (27.73, 27.91)

3.9.2 Table 2: Hierarchical multivariable linear regression with $BMI^{-0.7}$ as criterion variable.

Variables	Model 1		Model 2	
	b (95% CI)	p	b (95% CI)	p
Age	0.02 (-0.06, 0.11)	0.59	0.03 (-0.06, 0.12)	0.517
Sex				
Female	Ref		Ref	
Male	-8.43 (-10.55, -6.31)	<0.001	-8.44 (-10.56, -6.32)	<0.001
Ethnicity				
Non-Caucasian	Ref		Ref	
Caucasian	0.45 (-3.81, 4.71)	0.826	0.15 (-4.12, 4.41)	0.946
Income				
No response	-7.79 (-12.9, -2.68)	0.003	-7.81 (-12.93, -2.7)	0.003
< $20,000	-7.1 (-13.12, -1.08)	0.021	-7.11 (-13.13, -1.09)	0.021
$20,000 to < $50,000	-5.47 (-9.42, -1.52)	0.007	-5.46 (-9.41, -1.52)	0.007
$50,000 to < $100,000	-5.97 (-9.44, -2.51)	0.001	-5.96 (-9.43, -2.5)	0.001
$100,000 to < $150,000	-5.37 (-9.13, -1.6)	0.005	-5.26 (-9.03, -1.49)	0.006
$150,000 or more	Ref		Ref	
Education				
High school or less	-6.8 (-10.69, -2.91)	0.001	-6.68 (-10.57, -2.79)	0.001
Below bachelor	-5.18 (-7.55, -2.81)	<0.001	-5.18 (-7.55, -2.81)	<0.001
Bachelor or above	Ref		Ref	
Residence				
Urban	Ref		Ref	
Rural	-0.19 (-4.83, 4.46)	0.938	-0.19 (-4.84, 4.46)	0.936
Somatic comorbidity	-3.06 (-3.61, -2.5)	<0.001	-3.07 (-3.63, -2.51)	<0.001
Neurological comorbidity				
No	Ref		Ref	
Yes	2.36 (-4.89, 9.62)	0.523	2.43 (-4.83, 9.68)	0.512
Animal fluency	-	-	0.04 (0.01, 0.07)	0.004
Stroop interference	-	-	-0.04 (-0.06, -0.01)	0.001
Mean reaction time	-	-	0 (0, 0)	0.121

Note: Coefficients were multiplied by 10^3 in order to facilitate readability of the table

3.9.3 Table 3: Multivariable linear regression with other adiposity indicators as criterion variables (total fat mass, waist circumference and waist-hip ratio)

Variables	Total fat mass (%)		Waist circumference		Waist-hip ratio	
	b (95% CI)	p	b (95% CI)	p	b (95% CI)	p
Age	148.21 (105.23, 191.18)	<0.001	98.09 (3.2, 192.97)	0.043	1.15 (0.68, 1.63)	<0.001
Sex						
Female	Ref		Ref		Ref	
Male	-8070.17 (-9099.88, -7040.46)	<0.001	13988.54 (11713.81, 16263.27)	<0.001	168.48 (157.11, 179.85)	<0.001
Ethnicity						
Non-Caucasian	Ref		Ref		Ref	
Caucasian	1065.83 (-997.81, 3129.47)	0.311	989.82 (-3582.6, 5562.25)	0.683	-28.06 (-50.92, -5.21)	0.015
Income						
No response	5475.81 (2967.63, 7983.98)	<0.001	3719.79 (-1752.99, 9192.58)	0.183	9.28 (-18.07, 36.64)	0.506
< $20,000	6113.41 (3179.76, 9047.06)	<0.001	7832.68 (1365.39, 14299.98)	0.018	5.54 (-26.79, 37.86)	0.737
$20,000 to < $50,000	4786.65 (2874.37, 6698.94)	<0.001	4770.87 (538.16, 9003.57)	0.027	16.96 (-4.2, 38.12)	0.116
$50,000 to < $100,000	4735.59 (3055.94, 6415.24)	<0.001	3744.44 (29.06, 7459.81)	0.048	12.45 (-6.12, 31.03)	0.189
$100,000 to < $150,000	3532.49 (1704.61, 5360.38)	<0.001	5812.6 (1772.49, 9852.72)	0.005	17.18 (-3.02, 37.37)	0.095
$150,000 or more	Ref		Ref		Ref	
Education						
High school or less	1932.71 (51.88, 3813.53)	0.044	7672.6 (3505.71, 11839.49)	<0.001	43.5 (22.67, 64.33)	<0.001
Below bachelor	1924.13 (775.13, 3073.13)	0.001	5072.39 (2531.06, 7613.73)	<0.001	21.54 (8.83, 34.24)	0.001
Bachelor or above	Ref		Ref		Ref	
Residence						
Urban	Ref		Ref		Ref	

Rural	-842.75 (-3073.49, 1387.99)	0.459	202.2 (-4778.82, 5183.22)	0.937	4.74 (-20.16, 29.64)	0.709
Somatic comorbidity	1332.76 (1062.63, 1602.9)	<0.001	3366.69 (2772.29, 3961.1)	<0.001	12.17 (9.2, 15.14)	<0.001
Neurologic comorbidity						
No	Ref		Ref		Ref	
Yes	-679.4 (-4251.2, 2892.39)	0.709	2663.85 (-5094.41, 10422.1)	0.519	22.31 (-16.47, 61.09)	0.263
Animal fluency	-45.85 (-58.85, -32.86)	<0.001	-31.69 (-60.48, -2.91)	0.030	-0.21 (-0.35, -0.06)	0.005
Stroop interference	19.99 (9.22, 30.77)	<0.001	35.38 (11.62, 59.13)	0.003	0.13 (0.01, 0.25)	0.031
Mean reaction time	-0.87 (-1.29, -0.46)	<0.001	1.61 (0.69, 2.52)	0.001	0.02 (0.01, 0.02)	<0.001

Note: Coefficients were multiplied by 10^3 in order to facilitate readability of the table

Table 4: Stroop interference associations with adiposity indicators by income category in fully adjusted models.

Income categories	*b* (95% CI)	*p* value
	BMI$^{-0.7}$	
No response	-0.04 (-0.13, 0.05)	0.378
< $20,000	-0.08 (-0.16, 0)	0.063
$20,000 to < $50,000	0.02 (-0.02, 0.06)	0.289
$50,000 to < $100,000	**-0.06 (-0.1, -0.02)**	**0.003**
$100,000 to < $150,000	**-0.09 (-0.15, -0.03)**	**0.002**
< $150,000 or more	-0.02 (-0.08, 0.05)	0.632
	Total body fat	
No response	0.16 (-43.22, 43.54)	0.994
< $20,000	20.88 (-13.98, 55.73)	0.24
$20,000 to < $50,000	0.77 (-17.75, 19.28)	0.935
$50,000 to < $100,000	**35.97 (17.05, 54.89)**	**<0.001**
$100,000 to < $150,000	**42.59 (13.52, 71.66)**	**0.004**
< $150,000 or more	7.87 (-28.11, 43.84)	0.668
	Waist circumference	
No response	43.11 (-48.99, 135.21)	0.359
< $20,000	82.9 (-2.59, 168.4)	0.057
$20,000 to < $50,000	-36.73 (-78.63, 5.17)	0.086
$50,000 to < $100,000	**71.89 (29.44, 114.33)**	**0.001**
$100,000 to < $150,000	**97.48 (33.38, 161.58)**	**0.003**
< $150,000 or more	3.09 (-71.36, 77.53)	0.935
	Waist-hip ratio	
No response	0.36 (-0.1, 0.83)	0.126
< $20,000	0.16 (-0.2, 0.52)	0.38
$20,000 to < $50,000	-0.06 (-0.26, 0.14)	0.553
$50,000 to < $100,000	**0.31 (0.1, 0.52)**	**0.003**
$100,000 to < $150,000	0.18 (-0.14, 0.5)	0.278
< $150,000 or more	-0.03 (-0.43, 0.38)	0.897

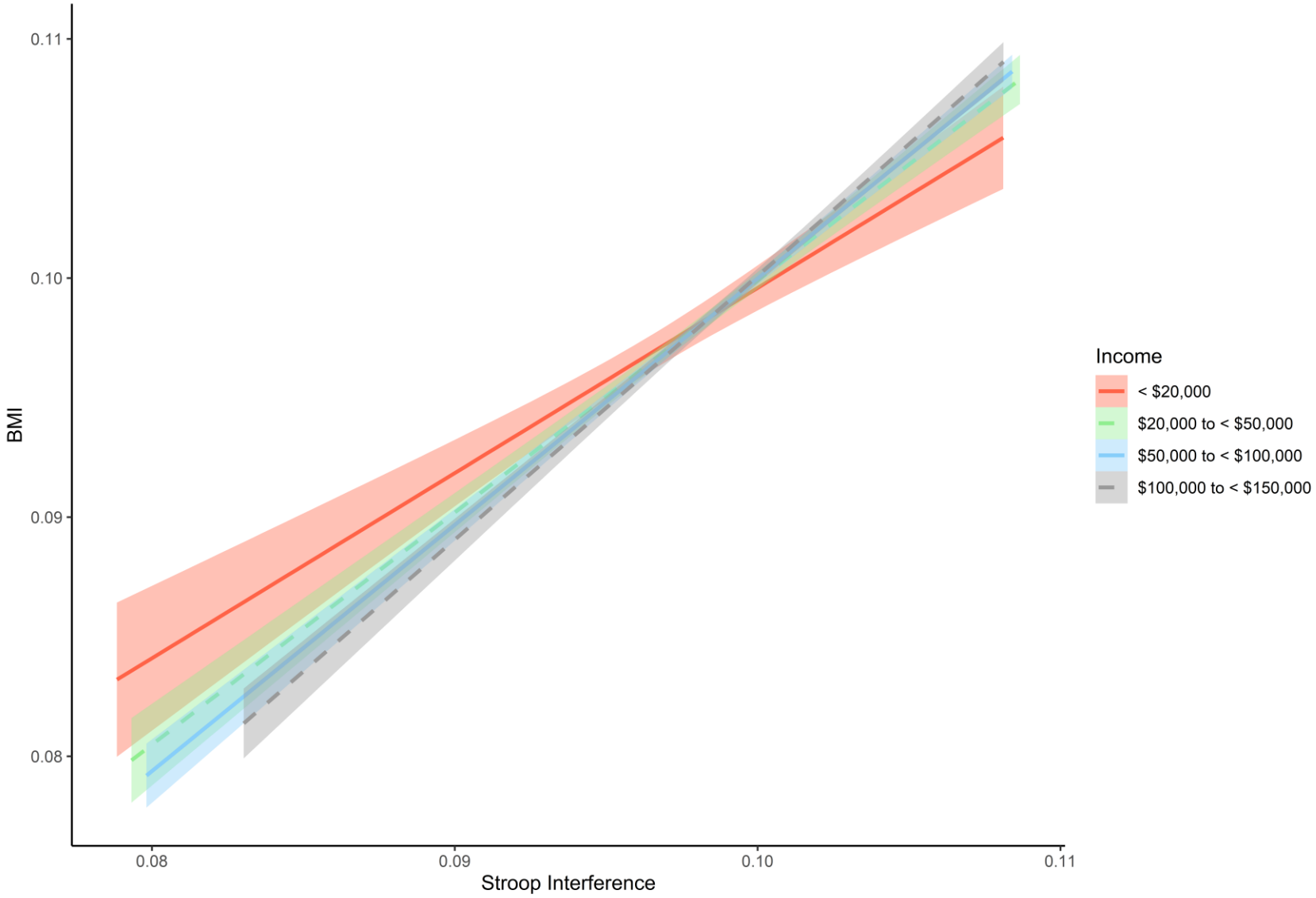
Note: Coefficients were multiplied by 10^3 in order to facilitate readability of the table

3.9.4 Table 4: Indirect effects of lifestyle variables and physical health status for each cognitive and adiposity indicator.

Outcome variable	Animal fluency (95% CI)	Stroop interference (95% CI)	Mean reaction time (95% CI)
		Diet as mediator	
$BMI^{-0.7}$	**0.24 (0.09, 0.89)**	-0.19 (-0.38, 0.27)	**0.01 (0.00, 0.03)**
Total body fat	**-280.31 (-589.48, -140.03)**	116.25 (-62.19, 283.11)	**-9.17 (-16.82, -3.38)**
Waist circumference	**-728.6 (-1198.01, -308.08)**	-12.03 (-109.87, 615.71)	**-26.12 (-32.16, -5.68)**
Waist-hip ratio	**-3.40 (-5.55, -1.49)**	2.65 (-0.16, 3.08)	**-0.11 (-0.14, -0.02)**
		Hypertension as mediator	
$BMI^{-0.7}$	**1.64 (0.62, 1.97)**	**-0.33 (-1.25, -0.15)**	-0.02 (-0.04, 0.00)
Total fat mass	**-674.66 (-719.70, -230.85)**	**423.67 (45.47, 451.04)**	4.71 (-0.46, 15.41)
Waist circumference	**-1393.33 (-2108.69, -711.42)**	**715.29 (144.61, 1282.76)**	21.06 (-2.91, 42.19)
Waist-hip ratio	**-4.77 (-7.24, -2.39)**	**2.45 (0.47, 4.53)**	0.07 (0.00, 0.15)
		Physical activity as mediator	
$BMI^{-0.7}$	**0.85 (0.57, 1.29)**	0.14 (-0.07, 0.41)	0.00 (-0.01, 0.01)
Total fat mass	**-388.98 (-579.91, -244.24)**	-97.27 (-215.70, 22.00)	5.44 (-2.94, 6.16)
Waist circumference	**-1494.76 (-1616.42, -758.10)**	-380.82 (-470.01, 100.49)	3.45 (-10.81, 11.16)
Waist-hip ratio	**-2.95 (-4.76, -1.92)**	0.51 (-1.09, 0.70)	0.01 (-0.02, 0.05)
		Type 2 diabetes as mediator	
$BMI^{-0.7}$	0.27 (-0.37, 0.67)	**-0.04 (-0.05, -0.02)**	**-0.88 (-1.39, -0.34)**
Total fat mass	32.78 (-183.81, 128.14)	**235.95 (90.67, 395.20)**	**8.89 (4.77, 15.89)**
Waist circumference	191.39 (-818.84, 483.42)	**1243.61 (463.44, 1773.69)**	**34.19 (21.85, 67.64)**
Waist-hip ratio	0.17 (-2.89, 1.66)	**3.73 (1.73, 6.46)**	**0.16 (0.08, 0.25)**

Note: Coefficients were multiplied by 10^5 in order to facilitate readability of the table.

3.9.5 Figure 1: Fitted regression lines predicting BMI from Stroop interference by income subgroups.



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

4 Chapter 4: Manuscript 2

4.1 Bidirectional associations between adiposity and cognitive function: A prospective analysis of the Canadian Longitudinal Study on Aging (CLSA)

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4.2 Abstract

4.2.1 Objectives

Theoretical perspectives suggest that adiposity and cognitive function may be bidirectionally associated, but this has not been examined in a large-scale dataset. The current investigation aims to fill this gap using a large, representative sample of middle-aged and older adults.

4.2.2 Methods

Using data from the Canadian Longitudinal Study on Aging (CLSA; N = 25,854), the bidirectional hypothesis was examined with three indicators of cognitive function (i.e., executive function, processing speed and verbal fluency) and adiposity (i.e., waist circumference [WC], body mass index [BMI] and total fat mass). We used multivariate multivariable regression and structural equation modeling to assess the prospective associations between adiposity and cognitive indicators.

4.2.3 Results

Analyses revealed that higher baseline WC was associated with higher Stroop interference at follow-up for both middle-aged (standardized estimate, β = 0.08, 95% CI 0.06, 0.10) and older adults (β = 0.07, 95% CI 0.04, 0.09). Similarly, higher baseline Stroop interference was also associated with higher follow-up WC in middle-aged (β = 0.08, 95% CI 0.06, 0.10) and older adults (β = 0.03, 95% CI 0.01, 0.06). Effects involving semantic fluency and processing speed were less consistent. The above effects were similar to those observed using other adiposity indicators (e.g., BMI, total fat mass) and were robust to adjustment for demographics and other cofounders, and when using latent variable modeling of the adiposity variable.

4.2.4 Conclusion

Evidence for a bidirectional association between adiposity and cognitive function exists, though the associations are most reliable for executive function and primarily evident at mid-life.

4.3 Introduction

The prevalence of obesity is rising sharply around the world because of increasingly sedentary lifestyles and excess intake of calorie-dense foods (141). The World Health Organization (WHO) reported that more than 1.9 billion people (≥18 years) worldwide are overweight and over 650 million of them are obese (2). Based on a report of Statistics Canada, approximately 63.1% of the adult Canadians were either overweight (36.3%) or obese (26.8%) in 2018 (48); in the United States, corresponding figures were 31.1% for overweight and 42.5% for obesity (142). Excess adiposity is recognized as a risk factor for numerous chronic diseases, including type 2 diabetes mellitus (T2DM), heart diseases, and cancer (143). Beyond effects on the endocrine, cardiovascular and immune systems, obesity may also affect the central nervous system adversely (78). Promoting optimal brain health is a public health priority considering the growing number of older adults and an associated increase in neurodegenerative disease incidence globally (144).

A significant body of research suggests a negative association between obesity and cognitive performance (8, 145). The detrimental effects of obesity are especially evident in the domains of short-term memory and executive function (8, 65, 146). For example, individuals with higher body mass index (BMI) perform poorly on verbal learning tasks (e.g., delayed recall and recognition of words) compared to those with lower BMI (56, 65). Performance decrements are also observed among obese individuals for tasks that require significant executive control requirements to complete, such as concept formation and set shifting in Wisconsin card sorting test (147). On a structural brain level, obesity is associated with reduced white matter integrity in prefrontal cortex tracts involved in executive control (148). Beyond executive control, obesity adversely affects other domains including psychomotor function, selective attention, decision making, planning and problem solving (8). Finally, clinical epidemiology studies document

reliable associations between obesity and cognitive decline (e.g., dementia) among older adults (72).

Studies examining the link between obesity and cognitive function are typically undertaken with the assumption of a unidirectional association between the two, such that obesity pre-dates—and contributes to—future cognitive dysfunction. However, there remains the possibility of a bidirectional influence (149). To illustrate, executive function, a cognitive process strongly linked with the lateral prefrontal cortex (PFC) (150), enables individuals to control thoughts, actions, and emotions (151). Impaired lateral prefrontal function can lead to increased impulsivity and reduced inhibitory control; it has been shown to be predictive of eating tendencies (152), emotional eating (153) and binge eating (154) among members of the general population. A causal role of lateral PFC on eating indulgence has also been demonstrated in experimental studies. For example, experimentally attenuating the dorsolateral prefrontal cortex (dlPFC) using suppressive brain stimulation results in disinhibited eating in the laboratory context (79), which can be enhanced further in the presence of facilitative cues to consume (82). Likewise, large-scale population studies have demonstrated a correlation between lateral prefrontal morphology and body composition in early life, long before the brain could register the cumulative impact of decades of adiposity (155). The above experimental and epidemiological findings underscore the possibility that the associations between executive function and obesity may be bidirectional, when considered over extended periods of time (78, 149). However, this proposition has not been tested in an explicit manner in a large, population-representative dataset with sufficient statistical power to detect subtle, cumulative effects.

Aside from eating behaviour, several other factors could influence or mediate the hypothesized bidirectional association, including physical activity, hypertension, and T2DM, as

each of these are also associated with cognitive performance (156, 157). Similarly, an argument can also be made that people with lower executive function may find it disproportionately challenging to consistently enact an active lifestyle (112), given the inherent requirements for self-organization, planning, and inhibiting indulgence in distracting sedentary activities (e.g., screen time). Accordingly, it is plausible that both eating and physical activity may mediate brain health associations with adiposity, and further that this could occur with or without the development of clinical mediating conditions (i.e., hypertension and T2DM).

The current investigation aims to test bidirectional associations between adiposity and cognitive function, using a population representative sample of middle-aged and older adults in Canada. Consistent with prior research, we anticipate that higher adiposity at baseline will be associated with lower follow-up cognitive function; conversely, however, we also anticipate that lower baseline cognitive function will be associated with significantly higher follow-up adiposity. Given that older adulthood involves longer exposure to potential adverse effects of obesity on the brain, we expect that any bidirectional associations between adiposity and cognitive function would be more prominent in the middle-aged subsample than the older adult sample. We also hypothesize that the above-mentioned bidirectional associations would be mediated through lifestyle behavior (e.g., physical activity and diet) and adverse health conditions (e.g., high blood pressure and diabetes).

4.4 Method

4.4.1 Data source and study settings

This study involved a 3-year prospective analysis of the baseline and first follow-up data from the Canadian Longitudinal Study on Aging (CLSA) (113). The recruitment process of the CLSA commenced in 2010 and completed baseline data collection in 2015. The current analysis used the comprehensive cohort from within the CLSA, which includes 30,097 Canadians aged

between 45-85 years. These participants were interviewed both at home and at hospital based data collection sites for comprehensive assessments. The comprehensive cohort participants were recruited from provincial health registries and by telephone sampling (Random Digit Dialing). The CLSA exclusion criteria were as follows: (1) inability to communicate in one of the two national languages, English or French; (2) cognitive impairment at time of recruitment; (3) resident of the three territories; (4) full-time member of the Canadian Armed Forces; (5) resident in a long-term care institution; and (6) living on Federal First Nations reserves or other First Nations settlements. As initially planned, the follow-up data for the CLSA will be collected every three years for a period of 20 years. Currently, baseline and first follow-up data collection have been completed and released; second follow-up data were not yet available to the researchers. The details of the study design and recruitment process have been published elsewhere (113). The present study received ethics approval from the Office of Research Ethics, University of Waterloo (ORE# 41434). The data access application was approved by the CLSA Data and Sample Access Committee (Application# 1906024).

Any CLSA participants who could not walk without assistance or for whom English or French was a second language were excluded from the present statistical analyses, in order to remove these confounds from the measurement of the language-mediated cognitive tests (i.e., Stroop task and Animal naming). Likewise, individuals diagnosed with clinical conditions that might affect cognitive function trajectories (i.e., multiple sclerosis, dementia, stroke and Parkinson's disease) were excluded from the analysis. Exclusion criteria were applied on the baseline measures. Following the earlier exclusions, the effective sample for the present analyses comprised 25 854 participants from the CLSA comprehensive cohort (Supplementary Figure B-2, Supplementary Table B-1 and B-2).

4.4.2 Measures of adiposity

Waist circumference (WC). WC was measured around the position of the natural indent in the waist area (halfway between the last floating rib and the iliac crest) (118, 119). This measurement was taken at the data collection sites. A higher WC indicates excess fat deposition around the midsection. According to the Centers for Disease Control and Prevention, an ideal WC for men is less than 40 inches, and for women is less than 35 inches (121). In general, the measures of centralized obesity (i.e., WC) are considered preferred measures of adiposity because of their superior predictive validity, as compared with BMI (138).

Body mass index (BMI). Weight and standing (shoeless) height of the CLSA comprehensive cohort participants were measured at each data collection wave. Two measurements were taken for each variable and then averaged together (119). BMI was calculated as weight in kg/height in m^2. A BMI ranging between 18.5-24.9 is considered "normal" whereas a BMI between 25-29.9 is deemed "overweight," and over ≥ 30 is classified as "obese".

Total fat mass. This measure of adiposity was assessed only at the CLSA baseline data collection using dual-energy X-ray absorptiometry (DXA) (119). Body fat percentage was calculated and provided in the dataset as a continuous variable.

4.4.3 Measures of cognitive function

Stroop Neurological Screen Test (SNST). The SNST was identified as the primary indicator for executive function within the CLSA. Stroop paradigms assess the ability to inhibit cognitive interference that arises when the processing of one stimulus is impeded by concurrent processing of another stimulus (125, 126). This task is typically presented in three consecutive blocks. The first "neutral" block requires the participants to read neutral words (e.g., chair, table, boat, window, etc.). The second block is a "congruent" block where the participants are provided

with a list of color words written in a manner that the font color and the name of the color are identical, such as Green is written in Green font. In the final "incongruent" block, a list of color words is provided, but the color words are printed in a manner that mismatches with the font color, such as Green is written in Red font. When the color word and font color mismatch, the time required to identify the font color increases considerably because people tend to read the color names automatically (125, 126). This is denoted as the "Stroop interference effect," and is calculated by taking the difference of completion times between incongruent and congruent blocks. Higher Stroop interference is taken as an indicator of weak executive control. The CLSA implemented the Victoria version of the Stroop task (113, 119, 125, 126). In the first block, participants were provided with a card that contained a list of neutral words written in different fonts. Participants were instructed to read the words. In the next block, participants were provided with a card containing a list of "X"s printed in different font colors. Participants were instructed to name the color of the font in which "X"s were printed. Finally, participants were provided with a card containing the name of color words printed in incompatible font color in the third block. Participants were instructed to name the color of the font while ignoring the meaning of the color words. The completion time was calculated in seconds for each block and provided in the dataset. Among the three cognitive tasks included in this investigation, Stroop task is considered as the most robust measure of executive function (158).

Choice Reaction Time (CRT). Choice reaction time primarily assesses speed of information processing (159), but performance on this task largely depends on several executive control components, such as working memory and attention (160, 161). CLSA participants performed the CRT task at the data collection sites on a computer with a touch screen. Participants were presented with is a horizontal row of four plus signs on the computer screen

(119, 124). One of the plus signs changed to a box after 1,000 milliseconds and the participants were required to press the box on the touch screen as soon as possible (119, 124). There were 10 practice trials in the task followed by 52 test trials (119, 124). The reaction time (in milliseconds) of the participants was recorded automatically by the computer software. The mean reaction time was calculated as the average of the correct response of the test trials, excluding incorrect answers and timeouts. Higher reaction time indicates poor speed visual information processing.

Animal Fluency Test (AFT). Semantic fluency tasks are commonly used to measure memory store integrity, thereby facilitating diagnosis of disorders of aging, such as Alzheimer's disease and other dementias (162). Such tasks involve verbally naming as many words as possible from a particular thematic category (e.g., animals, fruits or phonemic) in a specified period of time. The AFT assesses semantic fluency by asking individuals to name as many animals as they can in 60 seconds. One point is rewarded for mentioning each unique animal. As this task requires word retrieval (e.g., animal names) while meeting certain constraints (e.g., only animals, avoid repetition and proper nouns), people with sound cognitive function tend to produce more correct words (163). A score below 15 is generally taken to indicate impaired cognitive function (162). Beyond semantic fluency, performance on the AFT also requires some secondary demands involving executive control (164), but less so than the Stroop paradigm.

Within the CLSA, the comprehensive cohort participants performed the AFT during their in-home interview, and their responses were recorded (119, 129). The recording was transcribed, and the animal names were coded based on scientific taxonomic classification. Animals with the same scientific taxonomic classification with variant names (e.g., cougar and puma or salmon and salmon fish) were labeled with the same code. Animals with different scientific taxonomic classifications were labeled with unique codes. Scoring was conducted using a validated

algorithm such that all unique codes received 1 point after excluding any matched lower taxonomic classifications. For instance, where participants mentioned “bird, parrot, pheasant”, only parrot and pheasant received a point but bird did not, because bird is the category that includes both parrot and pheasant (124).

4.4.4 Covariates and mediators

Age. The CLSA participants were asked about their exact date of birth (129). Age was calculated using the date of birth and provided as integer values in the dataset. For the purpose of this study, the analyses included examination of two age groups, corresponding with working age (45-65 years, n = 16,147) and retirement age (> 65 years, n = 9,707). This approach was taken given the considerably different daily demands—in terms of exercise opportunities and eating constraints—between the two age groups, as well as the higher age-related cognitive deficits that would tend to selectively affect the latter age group.

Sex. Participants were asked to report their biological sex using the following item: “What was your sex at birth?”. This variable was coded as 1 and 0, where 1 denotes male sex (129).

Ethnicity. The CLSA participants were asked about their cultural and racial backgrounds, such as Caucasian, Chinese, South Asian, Black, etc. This variable was coded as 1 and 0, where 1 denotes Caucasian and 0 denotes all non-Caucasian ethnicities (129).

Income: The annual household income of the participants was used to assess income status. The participants were asked: “What is your best estimate of the total household income received by all household members, from all sources, before taxes and deductions, in the past 12 months?” (129). This was an ordinal variable with the following categories: < $20,000; $20,000-$50,000; $50,000-$100,000; $100,000-$150,000; and ≥ $150,000 (129). The missing values were coded as “No Response”.

Education. The level of education was measured at baseline, using two separate questions. At first, the participants were asked: "Have you received any other education that could be counted towards a degree, certificate, or diploma from an educational institution?" (129). Those individuals who answered "No" were considered to have education level "high school or less". Those participants who answered "Yes" were asked a follow-up question: "What is the highest degree, certificate, or diploma you have obtained?" (129). The education variable was recoded with the following categories: "high school or less", "certificate or degree below bachelor", and "bachelor or above".

Residence. The area of residence was classified as: rural, urban core, urban fringe, urban population centre outside a census metropolitan area and census agglomeration, secondary core, and postal code link to dissemination area (129). This variable was recoded as "rural" and "urban," where urban included all the non-rural categories.

Comorbidity index. To adjust for the comorbidity load, we created a comorbidity index. Participants were asked whether a doctor ever told them that they have chronic conditions (129, 130). From the list of chronic conditions, we included 22 in the comorbidity index (see Appendix B). The index was created by summing across all chronic conditions included in the index. The comorbidity index was recomputed as required for the mediation analyses to exclude diabetes or hypertension when these chronic diseases were the target mediators.

Sleep duration. The participants were asked "During the past month on average how many hours of actual sleep did you get at night?". The number of hours spent on sleeping provided in the dataset as a numeric variable.

Physical Activity. The CLSA participants were asked: "Over the past 7 days, how often did you take a walk outside your home or yard for any reason? For example, for pleasure or

exercise, walking to work, walking the dog, etc." (133). This was an ordinal variable with the following categories: "never", "seldom (1-2 days)", "sometimes (3-4 days)", and "often (5-7 days)". The missing values were coded as "no response".

Diet. The variables related to dietary behaviours were derived from the "Short Diet Questionnaire" (129, 131). The intake of legumes, fruits, green salads and carrot was selected as the surrogate of healthy food choice. The CLSA participants were asked: (i) "How often do you usually eat legumes: beans, peas, lentils?", (ii) "How often do you usually eat fruit (fresh, frozen, canned)?", (iii) "How often do you usually eat green salad (lettuce, with or without other ingredients)?" and (iv) "How often do you usually eat carrots (fresh, frozen, canned, eaten on their own or with other food, cooked or raw)?" (129). These variables were coded as: per day, per week, per month and per year. The variables were recoded with the following categories: "daily," "weekly," and "rarely". The average caloric density of these items is 54 kcal per 100 gm, according with standardized estimates (132). On the other hand, the intake of fries, snacks, pastries, and chocolate were selected to represent unhealthy food choices. Participants were asked: (i) "How often do you usually eat french fries or pan-fried potatoes, poutine?" (ii) "How often do you usually eat salty snacks (regular chips, crackers, …)?", (iii) "How often do you usually eat cakes, pies, doughnuts, pastries, cookies, muffins, …?" and (iv) How often do you usually eat chocolate bars? (129). These variables were also recoded as "daily," "weekly," and "rarely". The average caloric density of these items is 434 kcal per 100 gm, according with standardized estimates (132).

Blood pressure (BP). BP (systolic and diastolic) was measured 6 times for each participant using the BpTRU™ BPM200 Blood Pressure Monitor (119). The average of systolic

blood pressure and the average of diastolic blood pressure (excluding first reading) were provided separately in the dataset as in units of millimeters of mercury (mmHg).

Diabetes. To know about diabetic status, participants were asked: "Has a doctor ever told you that you have diabetes, borderline diabetes or that your blood sugar is high?" (118). Participants who responded "yes" were asked a follow-up question about their type of diabetes, i.e., Type 1, Type 2, or neither. The diabetes variable was derived from these questions and recoded as "Type 2", "other type" and "none".

4.4.5 Statistical analyses

Statistical analyses were performed using R statistical software version 4.1.0 (134). To assess bidirectional associations, we used multivariate multivariable regression and structural equation modeling (SEM). The statistical analyses were adjusted for analytic weight as per the recommendation of the CLSA (116). The BMI variable was power transformed by -0.7 for variance stabilization and/or non-normality of the residuals of the model.

The brain-as-outcome path (adiposity → cognition) was assessed using baseline WC or $BMI^{-0.7}$ or DXA as an independent variable and three follow-up cognitive tasks (i.e., Stroop, AFT, MRT) as dependent variables in the multivariate multivariable regression analyses. The brain-as-predictor path (cognition → adiposity) was assessed using baseline Stroop interference/AFT/MRT as an independent variable and two follow-up adiposity measures (i.e., WC and $BMI^{-0.7}$) as dependent variables. A total of 3 models were assessed for each regression path. Model 1 was the unadjusted model; Model 2 was adjusted for major sociodemographic characteristics (e.g., age, sex, income and education); and Model 3 was fully adjusted model controlled for all included covariates (e.g., age, sex, income, education, ethnicity, residence, physical activity, comorbidity load and sleep duration) (Table 1, 2).

For SEM analysis, cross-lagged models were constructed using the 'lavaan' and "lavaan.survey" R packages (165). The correlations among cognitive measures at baseline and correlations among cognitive measures at follow-up were small ($r = -0.27$ to 0.22) (Supplementary Table B-3). Furthermore, cognitive variables included in this study measure different aspects of cognitive function despite the fact all tasks require some cognitive control requirements. On the other hand, correlations among adiposity measures at baseline and follow-up were relatively strong ($r = \sim 0.8$). For these reasons, cognitive variables were examined as a sole outcome or predictor in separate identical models, whereas WC and BMI were used as a latent construct in the SEM model. Figure 1 and Supplementary Figure B-1 illustrate the cross-lagged paths constructed for the SEM. The diagonal lines in the figure indicate the primary paths of interest. Path b estimated the strength of the association between latent adiposity measure (i.e., WC and $BMI^{-0.7}$) at baseline and cognition at follow-up, controlling for the effects of baseline cognition and of the covariates. Path c estimated the strength of the association between cognition at baseline and latent adiposity measure at follow-up, controlling for the effects of baseline adiposity and of the covariates. The primary set of models used full information maximum likelihood estimation, which means that all participants with at least baseline values on the variables of interest were included in the analysis regardless of whether those participants also have complete data at follow-up. This approach is suitable under the assumption that the data are missing at random (166). The standardized coefficients of the age subgroups (e.g., middle-aged vs. older adults) were compared by calculating z-score and corresponding p values (supplement Table B-6).

Next, we conducted mediation analysis using lavaan R package (165). Mediation analysis was performed only for the cross-lagged paths of interest (path b and c). For path b (adiposity →

cognition), blood pressure and T2DM were examined as mediators whereas for path c (cognition → adiposity), physical activity and diet were analyzed as mediators. Parallel mediation models were used where the mediator constitutes multiple variables (e.g., diet and blood pressure). Mediation analyses were adjusted for all covariates with appropriate survey weights applied to the analyses.

4.5 Results

Sample characteristics at baseline (Wave 1) and 3-year follow-up (Wave 2) are presented in Table 1. In general, middle-aged participants performed better on cognitive tasks at baseline, as compared with older adults. For example, older adults received statistically significantly lower scores on AFT (17.74, 95% CI 17.61, 17.86 vs. 21.67, 95% CI 21.57, 21.78) and higher scores on Stroop interference (12.90, 95% CI 12.72, 13.08 vs. 8.78, 95% CI 8.69. 8.87) and MRT (871.96, 95% CI 867.91, 876 vs. 759.48, 95% CI 756.79, 762.17) compared to middle-aged participants (Table 1). A similar trend was also evident at follow-up (Table 1). Both cohorts showed a statistically significant drop in Stroop interference scores (e.g., 8.78 vs. 2.66 in middle-aged and 12.90 vs. 4.73 in older adults) from baseline to follow-up, likely reflecting a practice/familiarity effect or dropout bias (Table 1, Supplementary Table B-2). In terms of adiposity measures, older adults had slightly higher WC (94.07, 95% CI 93.74, 94.40 and 93.64, 95% CI 93.27, 94) at both waves of data collection compared to the middle-aged sub-sample (92.32, 95% CI 92.04, 92.60 and 92.77, 95% CI 92.47, 93.07). There was no statistically significant difference in BMI between middle-aged and older adults at baseline; however, a slightly higher BMI was observed for the middle-aged sub-sample at follow-up (28, 95% CI 27.89, 28.11) compared to older adults (27.49, 95% CI 27.36, 27.62) (Table 1). When comparing baseline and follow-up adiposity measures, none of the age groups showed statistically significant difference in BMI or WC at follow-up (Table 1).

Multivariate multivariable regression models with WC as an independent variable and three cognitive tests as outcome variables (path b; adiposity → cognition) showed that higher baseline WC was statistically significantly associated with higher follow-up Stroop interference in unadjusted, partially adjusted and fully adjusted models in both middle-aged (standardized estimate, $\beta_{model\ 1} = 0.08$, 95% CI 0.06, 0.10; $\beta_{model\ 2} = 0.04$, 95% CI 0.03, 0.06; $\beta_{model\ 3} =$ 0.03, 95% CI 0.01, 0.05) and older adults ($\beta_{model\ 1} = 0.07$, 95% CI 0.04, 0.09; $\beta_{model\ 2} = 0.05$, 95% CI 0.03, 0.08; $\beta_{model\ 3} = 0.03$, 95% CI 0.01, 0.06), whereas higher baseline WC was associated with better animal fluency scores in older adults only in partially adjusted and fully adjusted models ($\beta_{model\ 2} = 0.03$, 95% CI 0.00, 0.05; $\beta_{model\ 3} = 0.03$, 95% CI 0.00, 0.06) (Table 2). In addition, higher baseline WC was significantly associated with higher follow-up reaction time in middle-aged adults in fully adjusted model ($\beta_{model\ 3} = 0.02$, 95% CI 0.00, 0.04), but not in older adults. A similar pattern of findings was observed when other adiposity indicators were used in the model (i.e., $BMI^{-0.7}$, DXA) (Table 2).

Multivariate multivariable regression for path c (cognition → adiposity) indicated that higher baseline Stroop interference was associated with higher follow-up WC ($\beta_{model\ 1} = 0.08$, 95% CI 0.06, 0.10; $\beta_{model\ 2} = 0.04$, 95% CI 0.02, 0.05; $\beta_{model\ 3} = 0.03$, 95% CI 0.02, 0.05) and lower follow-up $BMI^{-0.7}$ ($\beta_{model\ 1} =$ -0.06, 95% CI -0.08, -0.04; $\beta_{model\ 2} =$ -0.04, 95% CI -0.05, -0.02; $\beta_{model\ 3} =$ -0.03, 95% CI -0.05, -0.01) in middle-aged adults in all models. In the case of older adults, the only statistically significant association was between baseline Stroop interference and follow-up WC in the unadjusted model ($\beta_{model\ 1} = 0.03$, 95% CI 0.01, 0.06) (Table 2). Higher baseline AFT and lower baseline MRT were primarily associated with lower follow-up adiposity in middle-aged adults (Table 2).

To probe the presence of bidirectional associations in a more parsimonious manner, we undertook SEM using a latent adiposity variable formed from both prospectively measured adiposity indicators (BMI and WC), predicting separately each cognitive construct (one indicator each). Supplementary Table B-4 and B-5 summarize the SEM models examining prospective associations between cognitive function and the latent adiposity variable. One of the primary paths of interest (path b; Figure 1) indicated that higher baseline adiposity was associated with higher follow-up Stroop interference, and this association was statistically significant for middle-aged adults (standardized estimate, β = 0.04, 95% CI 0.02, 0.06). However, in the case of the AFT in older adults, higher baseline adiposity was associated with significantly better AFT performance (0.04, 95% CI 0.02, 0.06) at follow-up, suggesting an advantage to verbal fluency conferred by adiposity (Supplementary Figure B-3). Similarly, in the middle-aged sub-sample, higher baseline Stroop interference was associated with higher follow-up adiposity (path c) (0.01, 95% CI 0.00, 0.01). Additional statistically significant associations were observed between baseline and follow-up adiposity and cognitive function indicators, which are presented in Supplementary Table B-4 and B-5, Figures 1 and 2, and Supplementary Figure B-3 and B-4. Overall, irrespective of the modeling approach, the bidirectional association between Stroop interference and adiposity was observed in the middle-aged subsample.

Mediation analyses indicated that the association between baseline WC and follow-up Stroop interference (path b) was mediated through T2DM for both middle-aged (standardized estimate, β = 0.0090, 95% CI 0.0054, 0.0126) and older (0.0066, 95% 0.0021, 0.0110) adults (Table 3). Although systolic (0.0195, 95% CI 0.0094, 0.0297) and diastolic (−0.0148, 95% CI −0.0231, −0.0066) BP showed statistical significance as individual mediators in the middle-aged, the total indirect effects of BP were not found statistically significant in either group. For path c,

the association between baseline Stroop interference and follow-up WC was mediated by total caloric consumption for middle-aged adults (-0.0006, 95% CI -0.0011, -0.0001), and pastries consumption for older adults (-0.0006, 95% CI -0.0011, -0.0001).

4.6 Discussion

The purpose of this investigation was to probe for the possibility of a bidirectional association between adiposity and cognitive function using a large, representative sample of middle-aged and older adults. Using multivariate multivariable regression and cross-lagged latent variable modelling, we observed that higher baseline adiposity was associated with lower executive function at 3-year follow-up, with reliable associations observed for both age subgroups. In contrast, the association between baseline executive function and follow-up adiposity was statistically significant only in the middle-aged subsample. As such, our findings support a bidirectional association between cognition and adiposity, but primarily among midlife individuals, and with specific reference to executive function.

The above findings were robust following adjustment for a wide variety of confounders, including sociodemographic, medical and lifestyle variables. The current findings significantly augment our knowledge about the association between adiposity and cognitive function and provide some information on the boundary conditions for any potential bidirectional associations. Specifically, from a brain-as-outcome perspective, middle-aged adults showed evidence of an inverse association between obesity on executive function; from a brain-as-predictor perspective, worse executive function at baseline was shown to be associated with the accumulation of adiposity over a 3-year period for the same age group. The mediation analyses suggested that lifestyle behaviors and physical health conditions can be critical when considering the long-term bidirectional effects of adiposity and cognition. Diet and T2DM were emerged as

statistically significant mediators for the brain-as-predictor path and brain-as-outcome path, respectively.

The current findings are consistent with previous studies documenting negative associations between obesity and brain health outcomes. Indeed, many prior cross-sectional and longitudinal studies have reported an association between obesity and cognitive dysfunction, as well as an association between obesity and brain pathologies that implicate the prefrontal cortex (65, 72, 145-148). Evidence of bidirectional association between executive function and adiposity also supports prior theorizing (78). It is not clear why the bidirectional relationship was found only in the middle-aged subsample, but not in the older adults. However, it is possible that in older adults, much more of the variability in executive function is absorbed by medical comorbidities.

Despite our finding that higher adiposity at baseline was associated with lower performance on executive function at 3-year follow-up, the opposite was true for animal fluency in the older adult sub-sample. That is, obesity appeared to have a protective effect in relation to verbal fluency. Although this seems counter-intuitive, it could be consistent with the literature on the so-called "obesity paradox" where it has been argued that weight gain at old age is protective from cognitive decline (167). The protective effects of mild adiposity can also be explained by prodromal weight loss in dementia. It has been documented that dementia and Alzheimer disease are usually preceded by years of unintentional weight loss (168, 169). It is also possible that the animal naming effect is a selection bias or survivorship effect; this interpretation is supported by the fact that baseline associations between animal naming and adiposity were in the theoretically expected direction in a prior cross-sectional study conducted using CLSA baseline data (170).

Although the brain-as-predictor view was inadequately explored in previous research, there is evidence of indirect paths through which impaired cognition can lead to adiposity. One such potential mechanism is the association between prefrontal function and food consumption. Executive function deficit is associated with poor decision-making related to food choice and consumption (152-154). Accordingly, people with cognitive deficits tend to gain weight over time, a potent indicator of the bidirectional association reported in previous studies (78). Experimental studies further confirm this association using noninvasive brain stimulation where suppression of the lateral prefrontal cortex results in increased consumption of calorie-dense food (78, 79, 82). Our analysis suggests that such associations exist at the population level, at least in middle-aged people.

Likewise, T2DM was found as a statistically significant mediator for the association between baseline adiposity and follow-up cognition. As reported in previous studies, T2DM is associated with cognitive dysfunction, dementia and Alzheimer's disease in older adults (171, 172). Therefore, it is highly plausible that obesity together with T2DM hasten the progression of cognitive decline (173). Overall, mediation analysis suggests that the hypothesized bidirectional association could be influenced by modifying lifestyle behavior and physical health status.

Strengths of the current investigation include the use of a large-scale population dataset, with substantial power to detect subtle effects. Likewise, given that the dataset was representative of the general population to some extent, the findings may be generalized to the larger Canadian population, with the caveat that the sample was disproportionately urban. Further, the analysis was adjusted for several important covariates, including comorbidity load. Finally, unlike most survey data, the adiposity measures were not self-reported, so there was less reporting bias associated with these measures.

There are several limitations of the present study. First, the CLSA lacks structural and functional brain imaging data in the waves available for this analysis. Imaging data is useful to examine for older adults as several reliable changes happen in brain structure within this age range (e.g., gradual grey and white matter atrophy) (174); future CLSA waves will include such data, and will enable questions about brain structure and function to be addressed directly. Second, some adiposity indicators within CLSA, such as total fat mass measured by DXA and waist-hip ratio, were not measured at the 3-year follow-up; therefore, we could not include these in our path c (cognition → adiposity) analysis. A prior study examining cross-sectional data from the CLSA baseline did include such measures (170), and found similar patterns of findings across all adiposity indicators. Third, as the CLSA comprehensive cohort participants were recruited from areas within 25-50 km radius of the data collection sites and some participants were excluded based on exclusion criteria, our findings primarily represent those who live near the major urban centers, functionally mobile and do not have major neurological disorders (113, 119). Fourth, we stratified our analysis using two broad age groups based on retirement age; however, it should be noted that the strategy of using only two age groups might affect the ability to identify other differences associated with age within each broad category (i.e., individuals in their 80s might have significant differences in cognitive capabilities and adiposity status compared to those in their 60s). Fifth, a sizable number of the participants in the analytic sample were French speakers (n = 6,090); therefore, the possibility of differences in task performance because of different psychometric properties of English and French versions of the tasks cannot be excluded. Sixth, although the findings of cross-lagged analyses were consistent with regression-based analyses, it should be noted that the cross-lagged panel modeling depends on a number of assumptions (e.g., synchronicity, stationarity, stability, and others) that are often

violated or cannot be entirely met (175, 176). Seventh, as expected in the longitudinal studies, one primary challenge for the CLSA is participant engagement and retention. Approximately 7% (n = 1,827) of the participants in our analytic sample were lost to follow-up. Although baseline characteristics of the retained and lost to follow-up individuals were quite similar and the attrition rate was low in absolute terms, it is possible that some findings are influenced by survivorship bias.

Next, survey questionnaires were used to derive many CLSA variables. Despite the fact that these survey questionnaires were validated (e.g., Short Diet Questionnaire), the possibility of social desirability bias due to exaggeration or under-reporting cannot be excluded. Finally, although the cross lagged associations were reliable, they were very subtle. This implies the need for more extended follow up intervals over which to properly assess the gradual and cumulative hypothesized reciprocal effects of brain and adiposity. A lag of 3 years between measurements within the current dataset was minimally sufficient to detect the presence versus absence of statistically reliable cross-lagged effects. However, a minimum time lag of 10 years may be more ideal in order to properly assess the magnitude of such effects in absolute terms. This will be possible to examine with future waves of CLSA follow-up data, and with other population level datasets.

Despite the above-mentioned limitations, the current study provides some evidence for bidirectional associations between adiposity and cognitive function, particularly for middle-aged adults. Further studies are needed to confirm these associations with other measures, populations and longer follow-up intervals. Future studies should also examine adiposity-cognition associations using structural and functional brain imaging data. Other cognitive variables could be considered in future studies to understand to what extent bidirectional associations exist in

other cognitive domains. Finally, although the pattern of findings supports a bidirectional association between adiposity and executive function, the absolute magnitude of the associations is small over the 3-year window of the existing analysis. Given the high degree of stability in adiposity metrics over the 3 years follow up window (r = ~ 0.9), relatively little variability in adiposity remained to be predicted by variables in the model, including executive function and other cognitive variables. It is expected that future waves of follow up data over longer intervals will allow for a more statistically powerful test of the cumulative effects of both focal variables upon each other over time.

4.7 Conclusion

In summary, this investigation examined evidence for bidirectional associations between indicators of cognitive function and adiposity from middle age to late life. Findings suggested modest but reliable evidence of a prospective association between baseline adiposity and follow-up executive function among middle-aged and older adults. There was evidence of bidirectional associations, such that baseline executive function was associated follow-up adiposity, although this was specific to middle-aged individuals. As such, the bidirectional association model was supported at middle age for executive function, but not other cognitive functions or in late life. Findings are largely consistent with prior theory proposing bidirectional association between prefrontal function and adiposity (78). Overall, the findings suggest that researchers, healthcare providers and policymakers should consider the complexity of adiposity-cognition association beyond the dominant unidirectional assumption.

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4.9 Tables and Figures

4.9.1 Table 1: Descriptive statistics of the sample.

Variables	Overall Weighted mean/percentage (95% CI)	Middle-aged Weighted mean/percentage (95% CI)	Older adults Weighted mean/percentage (95% CI)
Baseline assessment			
Animal fluency	20.69 (20.60, 20.77)	21.67 (21.57, 21.78)	17.74 (17.61, 17.86)
Stroop interference	9.81 (9.72, 9.89)	8.78 (8.69, 8.87)	12.90 (12.72, 13.08)
Mean reaction time	787.60 (785.23, 789.97)	759.48 (756.79, 762.17)	871.96 (867.91, 876.00)
Body mass index	27.77 (27.69, 27.86)	27.80 (27.70, 27.91)	27.69 (27.57, 27.80)
Waist circumference	92.76 (92.53, 92.98)	92.32 (92.04, 92.60)	94.07 (93.74, 94.40)
Total fat mass	33.47 (33.34, 33.60)	32.76 (32.60, 32.92)	35.61 (35.42, 35.81)
Age	59.31 (59.16, 59.45)	54.61 (54.51, 54.71)	73.32 (73.19, 73.44)
Comorbidity	2.44 (2.41, 2.47)	2.22 (2.18, 2.25)	3.11 (3.06, 3.16)
Sleep duration	6.82 (6.80, 6.84)	6.78 (6.75, 6.80)	6.94 (6.91, 6.98)
Sex			
Female	50.51 (49.74, 51.28)	49.14 (48.19, 50.09)	54.59 (53.41, 55.77)
Male	49.49 (48.72, 50.26)	50.86 (49.91, 51.81)	45.41 (44.23, 46.59)
Ethnicity			
Non-Caucasian	2.09 (1.87, 2.31)	2.22 (1.94, 2.50)	1.68 (1.39, 1.98)
Caucasian	97.91 (97.69, 98.13)	97.78 (97.50, 98.06)	98.32 (98.02, 98.61)
Income			
No response	5.27 (4.95, 5.60)	4.23 (3.86, 4.59)	8.40 (7.73, 9.07)
< $20,000	4.00 (3.73, 4.26)	3.36 (3.05, 3.67)	5.90 (5.36, 6.44)
$20,000 to < $50,000	16.79 (16.27, 17.31)	11.74 (11.18, 12.31)	31.86 (30.74, 32.98)
$50,000 to < $100,000	31.62 (30.91, 32.32)	30.26 (29.40, 31.12)	35.69 (34.54, 36.83)
$100,000 to < $150,000	21.52 (20.86, 22.18)	24.57 (23.74, 25.41)	12.39 (11.60, 13.17)
< $150,000 or more	20.80 (20.14, 21.47)	25.84 (24.99, 26.69)	5.76 (5.22, 6.30)
Education			
High school or less	13.94 (13.42, 14.45)	11.19 (10.60, 11.78)	22.12 (21.11, 23.13)
Below bachelor	39.95 (39.19, 40.70)	40.60 (39.67, 41.53)	38.00 (36.84, 39.16)
Bachelor or above	46.12 (45.35, 46.88)	48.21 (47.26, 49.15)	39.88 (38.72, 41.04)

Residence			
Urban	90.98 (90.53, 91.42)	90.55 (90.00, 91.10)	92.26 (91.57, 92.94)
Rural	9.02 (8.58, 9.47)	9.45 (8.90, 10.00)	7.74 (7.06, 8.43)
Physical Activity			
No response	3.42 (3.16, 3.68)	3.19 (2.89, 3.50)	4.10 (3.64, 4.56)
Never	12.31 (11.81, 12.80)	11.58 (10.98, 12.19)	14.46 (13.64, 15.29)
Seldom (1-2 days)	14.70 (14.15, 15.26)	15.03 (14.34, 15.71)	13.73 (12.89, 14.58)
Sometimes (3-4 days)	18.13 (17.52, 18.73)	18.13 (17.39, 18.87)	18.11 (17.18, 19.04)
Often (5-7 days)	51.45 (50.68, 52.21)	52.06 (51.12, 53.01)	49.60 (48.40, 50.79)
Three-year follow-up			
Animal fluency	20.56 (20.47, 20.65)	21.53 (21.42, 21.63)	17.48 (17.35, 17.61)
Stroop interference	3.15 (3.11, 3.19)	2.66 (2.62, 2.70)	4.73 (4.64, 4.81)
Mean reaction time	803.71 (800.92, 806.49)	772.55 (769.50, 775.59)	905.18 (899.93, 910.44)
Body mass index	27.88 (27.79, 27.97)	28.00 (27.89, 28.11)	27.49 (27.36, 27.62)
Waist circumference	92.98 (92.74, 93.22)	92.77 (92.47, 93.07)	93.64 (93.27, 94.00)
Change scores			
Animal fluency	-0.34 (-0.42, -0.26)	-0.30 (-0.41, -0.20)	-0.46 (-0.58, -0.34)
Stroop interference	-6.48 (-6.57, -6.40)	-6.06 (-6.15, -5.96)	-7.85 (-8.04, -7.67)
Mean reaction time	21.98 (19.29, 24.67)	15.72 (12.60, 18.83)	42.42 (37.18, 47.65)
Body mass index	0.15 (0.12, 0.18)	0.24 (0.21, 0.27)	-0.14 (-0.19, -0.09)
Waist circumference	0.40 (0.30, 0.51)	0.61 (0.49, 0.73)	-0.25 (-0.41, -0.08)
Age	62.05 (61.90, 62.20)	57.56 (57.46, 57.67)	76.07 (75.94, 76.20)
Comorbidity	2.74 (2.71, 2.78)	2.51 (2.47, 2.55)	3.46 (3.41, 3.52)
Sleep duration	6.87 (6.85, 6.89)	6.84 (6.81, 6.86)	6.98 (6.94, 7.01)
Sex			
Female	50.37 (49.57, 51.17)	49.02 (48.04, 49.99)	54.57 (53.33, 55.82)
Male	49.63 (48.83, 50.43)	50.98 (50.01, 51.96)	45.43 (44.18, 46.67)
Income			
No response	4.93 (4.62, 5.25)	3.89 (3.53, 4.25)	8.19 (7.51, 8.86)
< $20,000	3.52 (3.26, 3.77)	2.89 (2.60, 3.18)	5.46 (4.92, 6.00)
$20,000 to < $50,000	16.45 (15.91, 16.99)	12.02 (11.44, 12.61)	30.29 (29.13, 31.46)
$50,000 to < $100,000	32.16 (31.43, 32.90)	30.60 (29.71, 31.48)	37.05 (35.84, 38.26)

$100,000 to < $150,000	21.08 (20.40, 21.76)	23.80 (22.95, 24.66)	12.58 (11.75, 13.41)
< $150,000 or more	21.85 (21.15, 22.56)	26.79 (25.90, 27.68)	6.42 (5.81, 7.03)
Residence			
Rural	7.40 (6.96, 7.84)	7.95 (7.41, 8.49)	5.68 (5.05, 6.32)
Urban	92.60 (92.16, 93.04)	92.05 (91.51, 92.59)	94.32 (93.68, 94.95)
Physical Activity			
No response	0.06 (0.02, 0.10)	0.05 (0.01, 0.10)	0.08 (0.02, 0.14)
Never	16.46 (15.87, 17.05)	15.02 (14.32, 15.72)	20.95 (19.91, 22.00)
Seldom (1-2 days)	18.70 (18.06, 19.33)	18.89 (18.12, 19.67)	18.09 (17.11, 19.06)
Sometimes (3-4 days)	17.99 (17.38, 18.60)	17.75 (17.01, 18.49)	18.75 (17.77, 19.73)
Often (5-7 days)	46.79 (46.00, 47.58)	48.28 (47.31, 49.25)	42.13 (40.90, 43.37)

4.9.2 Table 2: Multivariate multivariable regression of the analytic sample for path b (adiposity → cognition) and c (cognition → adiposity).

Age group	Outcome	Model 1		Model 2		Model 3	
		***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***
				Path b (WC → Cognition)			
Middle-aged	Stroop	**0.08 (0.06, 0.10)**	**<0.001**	**0.04 (0.03, 0.06)**	**<0.001**	**0.03 (0.01, 0.05)**	**0.001**
	AFT	**-0.05 (-0.07, -0.03)**	**<0.001**	-0.01 (-0.03, 0.00)	0.136	-0.01 (-0.03, 0.01)	0.230
	MRT	0.01 (0.00, 0.03)	0.099	0.02 (0.00, 0.04)	0.089	**0.02 (0.00, 0.04)**	**0.035**
Older adults	Stroop	**0.07 (0.04, 0.09)**	**<0.001**	**0.05 (0.03, 0.08)**	**<0.001**	**0.03 (0.01, 0.06)**	**0.011**
	AFT	0.02 (0.00, 0.05)	0.053	**0.03 (0.00, 0.05)**	**0.027**	**0.03 (0.00, 0.06)**	**0.023**
	MRT	0.00 (-0.03, 0.02)	0.792	0.02 (-0.01, 0.04)	0.225	0.01 (-0.02, 0.03)	0.661
				Path b ($BMI^{-0.7}$ → Cognition)			
Middle-aged	Stroop	**-0.08 (-0.10, -0.06)**	**<0.001**	**-0.05 (-0.06, -0.03)**	**<0.001**	**-0.04 (-0.05, -0.02)**	**<0.001**
	AFT	**0.05 (0.04, 0.07)**	**<0.001**	0.02 (0.00, 0.03)	0.072	0.01 (0.00, 0.03)	0.122
	MRT	-0.01 (-0.03, 0.01)	0.273	0.00 (-0.01, 0.02)	0.729	0.00 (-0.02, 0.02)	0.962
Older adults	Stroop	**-0.04 (-0.07, -0.02)**	**<0.001**	**-0.03 (-0.06, -0.01)**	**0.004**	-0.02 (-0.04, 0.01)	0.126
	AFT	-0.02 (-0.05, 0.00)	0.066	-0.03 (-0.05, 0.00)	0.019	**-0.03 (-0.05, -0.01)**	**0.017**
	MRT	0.02 (-0.01, 0.04)	0.149	0.00 (-0.02, 0.03)	0.750	0.01 (-0.01, 0.04)	0.271
				Path b (DXA → Cognition)			
Middle-aged	Stroop	**0.08 (0.06, 0.10)**	**<0.001**	**0.06 (0.04, 0.08)**	**<0.001**	**0.05 (0.03, 0.07)**	**<0.001**
	AFT	**-0.08 (-0.10, -0.06)**	**<0.001**	**-0.04 (-0.07, -0.02)**	**<0.001**	**-0.04 (-0.07, -0.02)**	**0.001**
	MRT	**0.07 (0.06, 0.09)**	**<0.001**	-0.02 (-0.04, 0.00)	0.105	-0.02 (-0.04, 0.01)	0.193
Older adults	Stroop	**0.05 (0.02, 0.07)**	**<0.001**	**0.07 (0.04, 0.10)**	**<0.001**	**0.05 (0.02, 0.09)**	**0.002**
	AFT	**-0.06 (-0.09, -0.04)**	**<0.001**	0.00 (-0.03, 0.04)	0.823	0.00 (-0.03, 0.04)	0.849
	MRT	**0.03 (0.01, 0.06)**	**0.008**	0.00 (-0.03, 0.04)	0.942	-0.01 (-0.04, 0.03)	0.657
				Path c (Stroop → Adiposity)			

Middle-aged	WC	**0.08 (0.06, 0.10)**	**<0.001**	**0.04 (0.02, 0.05)**	**<0.001**	**0.03 (0.02, 0.05)**	**<0.001**
	$BMI^{-0.7}$	**-0.06 (-0.08, -0.04)**	**<0.001**	**-0.04 (-0.05, -0.02)**	**<0.001**	**-0.03 (-0.05, -0.01)**	**<0.001**
Older adults	WC	**0.03 (0.01, 0.06)**	**0.003**	0.02 (-0.01, 0.04)	0.145	0.02 (-0.01, 0.04)	0.140
	$BMI^{-0.7}$	-0.02 (-0.04, 0.01)	0.189	-0.02 (-0.05, 0.00)	0.063	-0.02 (-0.04, 0.00)	0.077
				Path c (AFT → Adiposity)			
Middle-aged	WC	**-0.05 (-0.06, -0.03)**	**<0.001**	**-0.02 (-0.03, 0.00)**	**0.045**	-0.01 (-0.03, 0.00)	0.074
	$BMI^{-0.7}$	**0.06 (0.05, 0.08)**	**<0.001**	**0.03 (0.01, 0.05)**	**0.001**	**0.03 (0.01, 0.04)**	**0.001**
Older adults	WC	0.00 (-0.03, 0.02)	0.662	-0.01 (-0.03, 0.01)	0.254	-0.01 (-0.03, 0.01)	0.493
	$BMI^{-0.7}$	0.01 (-0.01, 0.03)	0.414	0.01 (-0.01, 0.03)	0.402	0.00 (-0.02, 0.03)	0.701
				Path c (MRT → Adiposity)			
Middle-aged	WC	**0.02 (0.01, 0.04)**	**0.010**	**0.03 (0.01, 0.04)**	**0.002**	**0.02 (0.01, 0.04)**	**0.003**
	$BMI^{-0.7}$	-0.01 (-0.02, 0.01)	0.555	0.00 (-0.01, 0.02)	0.786	0.00 (-0.01, 0.02)	0.567
Older adults	WC	0.00 (-0.03, 0.02)	0.678	0.02 (0.00, 0.04)	0.048	0.02 (0.00, 0.04)	0.103
	$BMI^{-0.7}$	**0.03 (0.01, 0.05)**	**0.015**	0.01 (-0.01, 0.03)	0.344	0.01 (-0.01, 0.04)	0.236

Note 1: AFT = Animal Fluency Task; MRT = Mean Reaction Time, WC = Waist Circumference; BMI = Body Mass Index; DXA = Dual-energy X-ray Absorptiometry (measure of total fat mass). Higher Stroop scores = worse executive function. Higher AFT scores = better semantic fluency. Higher MRT scores = worse processing speed. Cognition indicates cognitive function measured by Stroop task, AFT or CRT. Path b indicates the association between baseline adiposity (i.e., WC, $BMI^{-0.7}$, DXA) and follow-up cognitive function (i.e., Stroop, AFT, MRT). Path c indicates the association between baseline cognitive function and follow-up adiposity.

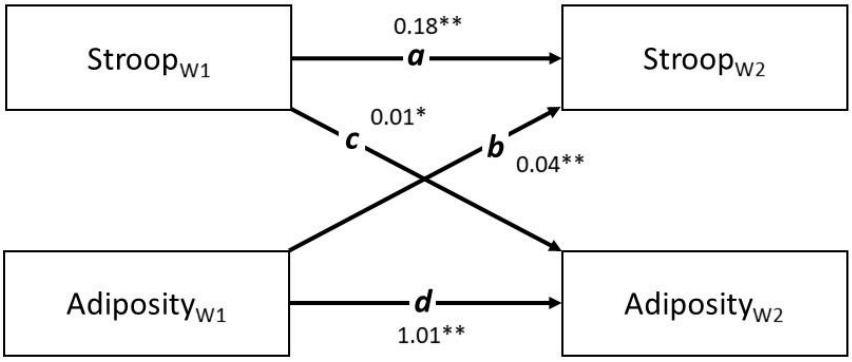
Note 2: Model 1 is the unadjusted model. Model 2 is the partially adjusted model controlled for age, sex, income and education. Model 3 is the fully adjusted model controlled for age, sex, ethnicity, income, education, residence, physical activity, comorbidity index and sleep duration. All estimates are standardized coefficients.

4.9.3 Table 3: Mediation analysis for the path b (Adiposity → BP/T2DM → Cognition) and path c Path c (Cognition → Activity/Diet → Adiposity) using waist circumference and Stroop interference.

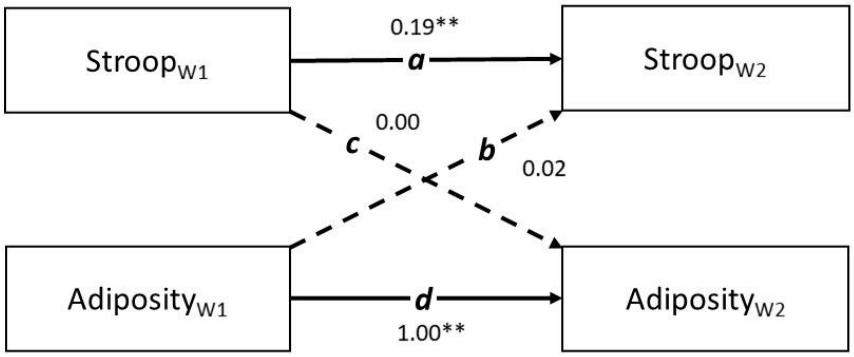
Mediators	Middle-aged		Older adults	
	Indirect effect (95% CI)	***p***	**Indirect effect (95% CI)**	***p***
	Path b (WC_{W1} → BP/T2DM → $Stroop_{W2}$)			
Blood pressure				
Total	0.0047 (-0.0018, 0.0111)	0.154	-0.0006 (-0.0049, 0.0037)	0.776
Systolic	**0.0195 (0.0094, 0.0297)**	**<0.001**	0.0016 (-0.0038, 0.0070)	0.568
Diastolic	**-0.0148 (-0.0231, -0.0066)**	**<0.001**	-0.0022 (-0.0065, 0.0021)	0.315
Type 2 diabetes	**0.0090 (0.0054, 0.0126)**	**<0.001**	**0.0066 (0.0021, 0.0110)**	**0.004**
	Path c ($Stroop_{W1}$ → Activity/Diet → WC_{W2})			
Physical activity	0.0000 (-0.0002, 0.0001)	0.609	0.0000 (-0.0001, 0.0001)	0.617
Diet				
Total	**-0.0006 (-0.0011, -0.0001)**	**0.018**	-0.0002 (-0.0013, 0.0009)	0.679
Legume	-0.0002 (-0.0005, 0.0000)	0.056	0.0002 (-0.0003, 0.0007)	0.393
Fruit	0.0000 (0.0000, 0.0000)	0.922	0.0001(-0.0001, 0.0002)	0.579
Salad	-0.0001 (-0.0003, 0.0001)	0.161	-0.0002 (-0.0006, 0.0002)	0.381
Carrot	0.0000 (-0.0001, 0.0001)	0.634	-0.0002 (-0.0006, 0.0002)	0.374
Fries	-0.0001 (-0.0002, 0.0001)	0.310	0.0001 (-0.0002, 0.0004)	0.407
Snack	0.0001(-0.0001, 0.0002)	0.272	0.0004 (0.0000, 0.0008)	0.058
Pastries	-0.0003 (-0.0006, 0.0000)	0.060	**-0.0006 (-0.0011, -0.0001)**	**0.013**
Chocolate	0.0000 (0.0000, 0.0001)	0.720	0.0000(-0.0001, 0.0002)	0.596

Note: Path b: the association between baseline adiposity and follow-up cognition; Path c: the association between baseline cognition and follow-up adiposity. Four decimal places were retained because of smaller values of the indirect effects and to clarify the direction of coefficient and CI. Total indicates the sum of individual indirect effects for the respective mediators. All estimates are standardized coefficients. Significant indirect effects indicate that the association between adiposity and cognition is, in part, mediated through that respective lifestyle behavior and chronic disease status.

4.9.4 Figure 1: Paths of the cross-lagged models using Stroop interference and latent adiposity.



Part a: Middle-aged adults

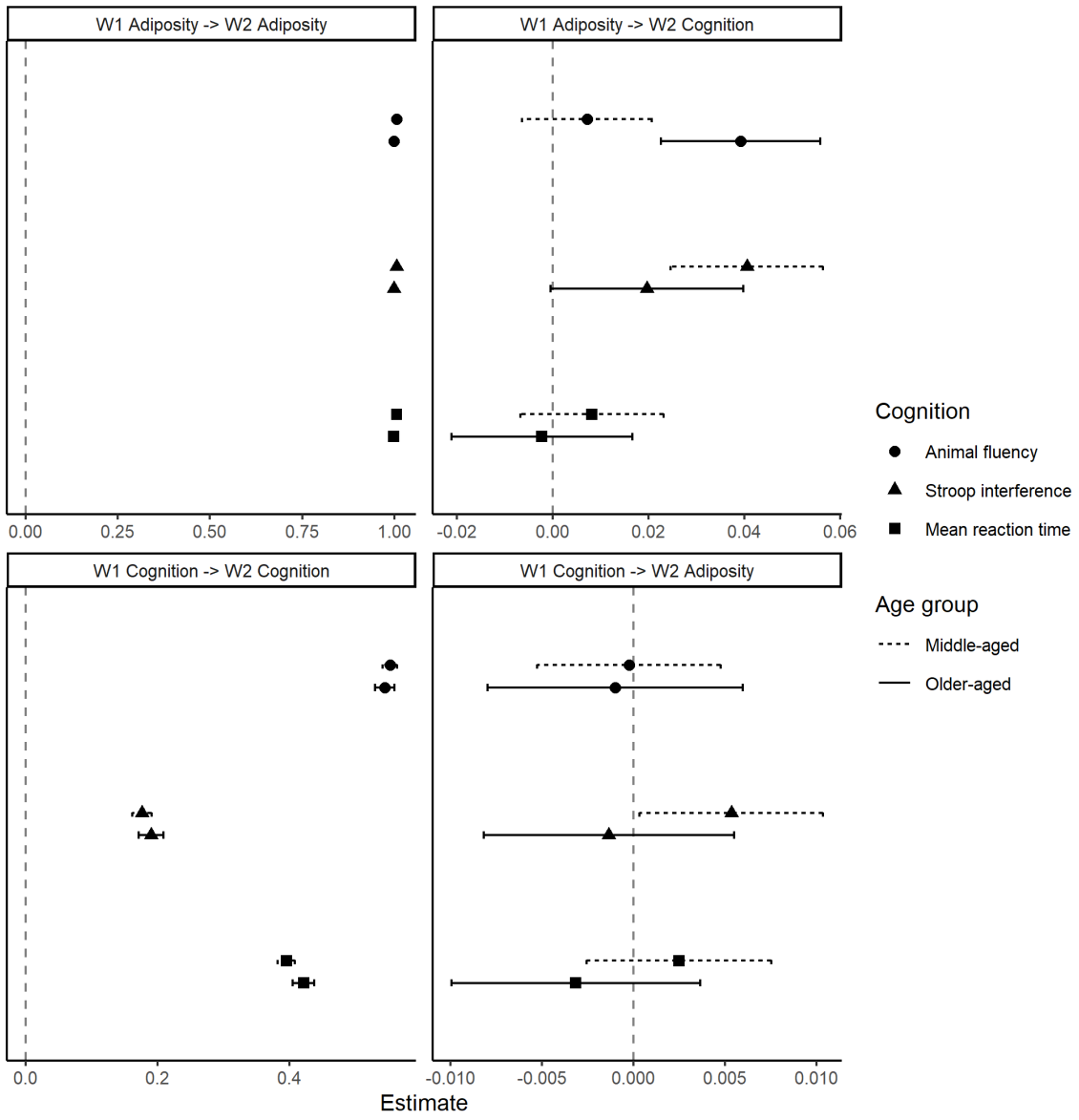


Part b: Older adults

Note 1: W1 and W2 indicate Wave 1 (baseline) and Wave 2 (3-year follow-up) measures, respectively. Adiposity indicates latent adiposity variable. Bolded arrows indicate statistically significant path coefficients; dotted arrows indicate non-significant path coefficients. BMI is power transformed by -0.7. All coefficients are standardized beta weights. *: $p < 0.05$. **: $p < 0.001$. Covariates include age, sex, ethnicity, household income, education, residence, physical activity, comorbidity and sleep duration.

Note 2: Description of the cross-lagged paths: (a) Path a: the association between baseline cognition and follow-up cognition, (b) Path b: the association between baseline adiposity and follow-up cognition, (c) Path c: the association between baseline cognition and follow-up adiposity, and (d) Path d: the association between baseline adiposity and follow-up adiposity.

4.9.5 Figure 2: Bidirectional associations between latent adiposity and cognitive function by age groups (45-65 years and > 65 years).



Note: W1 = Wave 1 or baseline measures; W2 = Wave 2 or 3-year follow-up measures; Adiposity = Latent adiposity variable.

5 Chapter 5: Manuscript 3

5.1 Cognitive function is bidirectionally associated with adiposity among adolescents: The evidence from the Adolescent Brain Cognitive Development (ABCD) Study

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5.2 Abstract

5.2.1 Objectives

Prior findings suggest that adiposity may adversely impact the executive functions and the cortical networks that underlie them. However, the prefrontal cortex also supports decision making and self-regulatory processes involved in eating behavior, and so a bidirectional association between adiposity and prefrontal function have been theorized. The current study aims to examine this possibility in adolescent populations wherein the prefrontal cortex is undergoing significant maturation.

5.2.2 Methods

Using data from the Adolescent Brain Cognitive Development (ABCD) (N = 11,878), we tested the bidirectionality hypotheses using five indicators of cognitive function (executive function, processing speed, episodic memory, receptive vocabulary and reading skills) and two indicators of adiposity (body mass index z scores [zBMI] and waist circumference [WC]). Multivariate multivariable regression and structural equation modeling (SEM) were employed to examine the hypothesized associations prospectively.

5.2.3 Results

Regression analyses suggested that higher baseline zBMI and WC were associated with worse follow-up picture sequence (standardized estimate, β = -0.04, 95% CI -0.07, -0.01) and better picture vocabulary (0.03, 95% CI 0.00, 0.06) task performance, respectively, in covariate adjusted models. Similarly, superior baseline performance on Flanker (zBMI: -0.03, 95% CI -0.06, -0.01; WC: -0.04, 95% CI -0.07, -0.01) and picture sequence (zBMI: -0.04, 95% CI -0.07, -0.02; WC: -0.03, 95% CI -0.06, 0.00) tasks were associated with better follow-up adiposity status in covariate adjusted models. Although a bidirectional association was observed, it was more

consistent between episodic memory and zBMI. Cross-lagged panel models with latent variable modeling revealed a bidirectional association with executive function (measured by Flanker task), but not with other cognitive domains.

5.2.4 Conclusion

Episodic memory and executive function were bidirectionally associated with adiposity indices among adolescents. However, these findings should be replicated and confirmed by future studies using more follow-up data with a longer follow-up interval.

5.3 Introduction

Childhood obesity continues to be a significant public health concern worldwide. The World Health Organization reported that over 18% of children and adolescents aged 5-19 years are either overweight or obese, representing approximately 340 million worldwide (2). Many developed nations in North America and Europe have observed several fold increases in obesity cases in the past few decades. In the United States and Canada, the estimated prevalence of obesity among children and adolescents is 19.3% and 13%, respectively (50-52). Overweight children tend to remain overweight throughout their adulthood (177), and adiposity substantially increases their risk of contracting non-communicable diseases, such as type 2 diabetes mellitus, heart diseases and other chronic conditions at an early age (50).

Obesity is negatively associated with several indicators of cognitive function in adult populations (8, 65, 72, 145, 147, 170, 178); however, this association is less well studied in children and adolescents. A number of studies reported that excess adiposity in childhood is negatively associated with performance on tests of neurocognitive function (146, 179, 180). For example, obese children tend to perform worse on tasks of executive function, including those measuring facets of inhibitory control, mental flexibility, set-shifting, and verbal fluency (146, 179, 180). In contrast, more mixed evidence has been found for impulsivity, planning, decision-making, reasoning, and sensitivity to reward (146, 179, 180). Furthermore, obesity is negatively associated with impaired attention, visuo-spatial performance, and motor skill among children and adolescents (146, 179, 180). Beyond cognitive performance, several structural MRI studies have identified reliable associations between obesity and cortical thickness and volume (155, 181-183).

Most studies in this area have adopted the brain-as-outcome perspective, wherein it is assumed that adiposity leads to cognitive outcomes. However, within the health neuroscience perspective of obesity, the brain may serve as both predictor and outcome in relation to adiposity (78). Prior theory and research findings have pointed to the possibility of such bidirectionality (77, 78, 82). For example, overweight children on average have more limited inhibitory control compared to normal-weight children, which may potentiate excess caloric intake (184). Experimental research using young adult samples reveals that using transcranial magnetic brain stimulation (TMS) to attenuate lateral prefrontal function leads to increased food consumption, particularly when foods are hedonically appealing and environmental cues are permissive (79, 82). Finally, a recent prospective analysis of the Canadian Longitudinal Study on Aging (CLSA) revealed evidence consistent with a bidirectional association between cognitive performance and adiposity, though only a unidirectional brain-as-outcome effect was observed for older adults individuals (178).

To date, very little is known about the hypothesized bidirectional associations between adiposity and cognition in children and adolescents despite having evidence of such bidirectionality in adult population. Therefore, we aim to investigate the hypothesized bidirectional associations in a large population-based sample of adolescents (N = 11,878). We hypothesized that better cognitive function at baseline will predict lower adiposity at follow-up and vice versa. We also hypothesize that such bidirectional association would be mediated throughout lifestyle and health characteristics (e.g., physical activity, diet, blood pressure), and morphological features of the lateral prefrontal cortex (PFC), given its connection to executive functions.

5.4 Method

5.4.1 Data source and study population

The current investigation made use of data from the Adolescent Brain and Cognitive Development (ABCD) Study (185), an ongoing longitudinal analysis of brain development in children in the United States. The ABCD Study was launched in 2015 and has recruited more than 11,000 children, aged 9-10 years at inception. The primary goal of the ABCD Study is to create a unique data resource to study the developing brain; therefore, it incorporates various forms of assessments, including structural and functional brain imaging, genetic testing, neuropsychological and behavioral measures. These assessments are conducted half-yearly (brief phone interview), annual (non-imaging) and biannual (imaging and bioassays) basis. The study will continue for 10 years until the participants are 19-20 years of age. This investigation used ABCD Data Release 4.0, which included baseline, first- and second-year follow-up data of 11,878 participants. Detailed information about the selection of participants and assessments has been published elsewhere (186-188). All parents and children provided written informed consent and assent to take part in the ABCD Study. The present study received ethics approval from the Office of Research Ethics, University of Waterloo.

5.4.2 Measures

5.4.2.1 Adiposity indicators

5.4.2.1.1 Body mass index (BMI)

In the ABCD protocol, participants' height and weight were measured three times and averaged together (189). BMI was calculated from average height and weight and converted to z-scores (zBMI) in accordance with the World Health Organization Child Growth Standards (190). The conversion was done in R using 'zscorer' package (191). To deal with the extreme values, winsorization was applied such that values below the 1st and above the 95th percentile were set to

those percentile values, respectively. Winsorization was applied asymmetrically because there were more extreme values at the positive end than the negative end. At wave 1, the 1st percentile corresponded to a BMI z-score of -2.99 and the 95th percentile was 5.83; at wave 3, these values were -2.35 and 7.33, respectively.

5.4.2.1.2 Waist circumference (WC)

WC was measured around the abdomen at the level of the iliac crest using a tape measure. This measurement was taken once and provided as in *cm* units (189).

5.4.2.2 Cognitive function

5.4.2.2.1 NIH Toolbox Cognitive Battery

The NIH Toolbox is a comprehensive set of neurobehavioral tests that assesses motor, emotional, sensory, and cognitive function (192). The cognition measures of NIH Toolbox, also known as NIH Toolbox Cognitive Battery, comprise seven tasks that measure executive function, working memory, processing speed, attention, episodic memory, and language abilities (188, 193-195). The advantage of the toolbox is that it is comprehensive, psychometrically sound, requires relatively short administration time, and is suitable for use in longitudinal studies. Furthermore, it can be used for a broad age group of people from 3 years onward, and requires only 35 minutes to complete via tablet device. Two of the seven tasks in Cognitive Battery (i.e., list sorting working memory and dimensional change card set) were not available at 2-year follow-up. Therefore, this study used five cognitive tasks for longitudinal assessments, as described below.

5.4.2.2.2 Flanker Task

The Flanker paradigm primarily measures executive function, particularly inhibitory control and attention (196, 197). It assesses participants' ability to suppress tempting, but

irrelevant responses to a given context. In the NIH Toolbox version of the task, participants are shown a row of five arrows on each trial (197). The outer 4 arrows are called distractors or "flankers", all of which are pointed in the same direction (right or left). Participants need to identify the direction of the middle arrow (the target), which either pointed towards the same direction as the flankers (congruent trial) or the opposite direction of the flankers (incongruent trial). Participants register their responses by pressing one of the two arrows displayed on the screen. The task is implemented using fish icons with arrows as stimuli in the case of younger children (3-6 years) (188). Given the older minimum age of 9-10 years in ABCD, the arrow version of the task was used. The variable of interest is flanker interference calculated by taking the difference between reaction time of correct incongruent and congruent trials. Higher flanker interference indicates poor ability to suppress the distracting stimuli, and accordingly, it suggests weaker control of executive function, particularly the inhibitory control domain. For the current analyses, Flanker scores were reversed coded such that higher scores indicate better executive control. The NIH toolbox version of the Flanker task showed excellent test-retest reliability (Intraclass Correlation Coefficients [ICC] = 0.95) and acceptable convergent (r = -0.48) and discriminant validity (r = 0.15) comparing the gold standard (192).

5.4.2.2.3 Pattern Comparison Processing Speed Test

This task is designed to measure the speed of visual processing (198-200). In this task, participants are shown two images side-by-side and asked to determine whether the images are identical or not. Nonidentical patterns are varied by one of three dimensions: color, adding/taking something away, or one versus many (200). Participants register their response by pressing a "yes" or "no" button on the screen. The test score calculated as the total number of correct answers in 90 seconds. In terms of psychometric properties, high test-retest reliability

(ICC = 0.82) and acceptable convergent and discriminant validity were shown in previous studies (192).

5.4.2.2.4 Picture Sequence Memory Test

This task assesses episodic memory and involves acquiring, storing and recalling new information (201, 202). It can be administered on participants aged between 3 and up. In this task, participants are presented with a sequence of pictures that depicts activities or events; an audio clip is played simultaneously to describe the contents briefly. Participants are asked to reproduce the sequence in the order it was shown. The sequence length is adjusted based on the age of the participants and can be varied between 6-18 images. One point is awarded for correctly placing each adjacent pair of the sequence. Therefore, the final score indicates the total number of adjacent pairs remembered accurately by each participant. This task also showed good test-retest reliability (ICC = 0.78) and acceptable convergent and discriminant validity (192).

5.4.2.2.5 Picture Vocabulary Task

This test is a modified version of the Peabody Picture Vocabulary Test (PPTV) and assesses receptive vocabulary and language comprehension of an individual (194, 203). In this test, children hear an audio clip of a word while observing four photographic images (of objects, actions and/or depictions of concepts) in a square on the screen. Children are instructed to press the image that closely matches the meaning of the word. Items are scored as correct or incorrect. This test implements computerized adaptive testing (CAT) in order to ensure appropriate item difficulty. The test-retest reliability (ICC = 0.94), convergent and discriminant validity reported for this task were acceptable (192).

5.4.2.2.6 Oral Reading Recognition Task

This task measures exposure to language materials and cognitive skills involved in reading (194, 203). In the task, participants are presented with a series of words on the screen and instructed to pronounce them as accurately as possible. This task uses CAT to ensure appropriate item difficulty. Good test-retest reliability (ICC = 0.99) and acceptable convergent and discriminant validity were also reported for this task in previous investigations (192).

5.4.2.3 Covariates and mediators:

The analyses are adjusted for the following demographic characteristics and potential confounders.

Demographic factors

Age. Participant's age in months at the time of the interview was recorded and rounded to the nearest chronological month (204).

Sex. Participant's sex at birth was recorded and coded as M = Male, F = Female, O = Other, NR = Not reported (204).

Race. The ABCD study participants were from various ethnic and racial backgrounds and reported to belong to one of the following groups: American Indian/Native American, Asian Indian, Black/African American, Chinese, Filipino, Guamanian, Japanese, Korean, Native Hawaiian, Other Asian, Other Pacific Islander, Samoan, Vietnamese, Caucasian and other race (204).

Child Hispanic ethnicity. Parents were asked "Do you consider the child Hispanic/Latino/Latina?" (205). This variable was coded as 1 = Yes and 2 = No.

Family income. Family income was defined as the combined income of all adults in home. Participants were asked "What is your total combined family income for the past 12

months?" with the options of the following categories provided: 1= Less than $5,000; 2=$5,000 through $11,999; 3=$12,000 through $15,999; 4=$16,000 through $24,999; 5=$25,000 through $34,999; 6=$35,000 through $49,999; 7=$50,000 through $74,999; 8= $75,000 through $99,999; 9=$100,000 through $199,999; 10=$200,000 and greater (205).

Primary parent education. The parent was asked, "What is the highest grade or level of school you have completed or the highest degree you have received?" The response to this question constitutes 21 categories with 1 being the "Never attended/Kindergarten only" to 21 being the "Doctoral degree", and the rest of the intermediate categories represented other education levels in between in the ascending order of the hierarchy (e.g., grade 1-12, high school graduate, GED or equivalent Diploma, Some college, Associate degree: Occupational, Associate degree: Academic Program, Bachelor's degree, Master's degree, and Professional School degree) (205).

Area deprivation index (ADI). The ADI is a multidimensional tool to assess socioeconomic disadvantage of neighborhoods constructed using income, education, employment, and housing status of the regions (206). Such index was previously found to have an association with health outcomes and obesity (207). The ADI score was provided in the dataset as a percentile, with higher values representing more deprivation (208). This score was used as a continuous variable in the covariate-adjusted models.

Health Status and Behavioral Factors

Pubertal status. Parents (209) and children (210) were asked several general and sex-specific questions (e.g., body hair, voice change, skin change, facial hair, menstrual history, etc.) to understand the pubertal status of the participants. The Pubertal Developmental Scale was created for boys and girls by using the responses to those questions with the following

categories: 1 – prepuberty, 2 – early puberty, 3 – mid puberty, 4 – late puberty, and 5 – post puberty (211).

Moderate-to-vigorous physical activity (MVPA). The data on physical activity were derived from the weekly physical activity summaries of a wrist-worn tri-axial accelerometer using a commercial Fitbit device (212). Average minutes spent in moderate activity (3-5.9 metabolic equivalent of task [METS]) and vigorous activity (6+ METS) during day were provided as two different measures. A sum of these measures was taken to create the MVPA variable.

Sleep duration. The sleep duration was also taken from the wrist-worn accelerometer device. Sleep periods were defined using the average of all minutes classified as being any kind of sleep (i.e., light + deep + REM) for all included days, based on (low) movement counts (212, 213).

Diet. Dietary behaviors were assessed in the "ABCD Child Nutrition Assessment" module (214). Intake of whole grains, green leafy vegetables, other vegetables, berries, beans and nuts were coded as "healthy" food choices. To query intake of healthy foods, parents of the participants were asked: "In a typical week, does your child eat (i) Whole grains 3 or more times per day, (ii) Green leafy vegetables 6 or more times per week, (iii) Other vegetables 1 or more time per day, (iv) Berries 2 or more times per week", (v) Beans 4 or more times per week, and (vi) Nuts 5 or more times per week? Responses for each of these probes were coded as 1 = Yes or 0 = No.

Intake of fast food and pastries were coded as "unhealthy" food choices. To query intake patterns of unhealthy foods, parents were asked: "In a typical week, does your child eat (i) fast

food or fried food less than 1 time per week, (ii) Pastries or sweets less than 5 times per week? These variables were also coded as 1 = Yes and 0 = No (214).

Blood pressure (BP). Systolic and diastolic BP was measured three times at wave 3 data collection (215). The average of systolic BP and the average of diastolic BP were provided separately in the dataset as continuous outcomes.

Brain Morphology

Lateral prefrontal cortex (LPFC) volume and thickness. The LPFC variables were derived from the structural magnetic resonance imaging (sMRI) module (216). The ABCD Study consortium conducted and preprocessed all the neuroimaging data. Morphological features (e.g., volume and thickness) of the LPFC and its subregions (e.g., lateral orbitofrontal cortex [LOFC], middle frontal gyrus [MFG] and inferior frontal gyrus [IFG]) were estimated using Freesurfer v5.3.0 (217). Freesurfer utilizes an automated, atlas-based, volumetric segmentation procedure for cortical surface reconstruction and subcortical segmentation. Images obtained from reconstruction were visually inspected, and only the images of sufficient quality were included in the study. Finally, morphological features were processed for the Deskian-Killiany atlas as part of the standard FreeSurfer pipeline (218). The details of the brain imaging protocol have been published elsewhere (219, 220).

5.4.2.4 Statistical analyses

Statistical analyses were performed using R statistical software (version 4.1.0) (134). We employed multivariate multivariable regression (MMR) and structural equation modeling (SEM) to assess the bidirectional associations between adiposity and cognitive function. In the first step, MMR analyses were undertaken as follows: Model 1 was the unadjusted model; Model 2 was the basic demographics-adjusted model (i.e., controlling for age, sex, parental education, and

parental income); Model 3 was the fully adjusted model (further control for ethnicity, ADI, pubertal status and sleep duration). The brain-as-outcome path (adiposity → cognition) was analyzed using individual Wave 1 adiposity variables as an independent variable (i.e., zBMI or WC) and all five Wave 3 cognitive tasks together as dependent variables. A similar approach was also undertaken for the brain-as-predictor path (cognition → adiposity), where individual Wave 1 cognitive variables were used as independent variables and two Wave 3 adiposity indicators together as a dependent variable.

Next, we constructed cross-lagged panel models with latent variable modeling (CLPM-L) for path analysis using "lavaan" R packages (165). The correlation matrix indicated that the correlation coefficients among cognitive measures both at baseline and follow-up were reliable but small-to-moderate in absolute magnitude (r = 0.09 – 0.49) (Supplementary Table C-1); however, the adiposity measures were strongly related (r = 0.78 – 0.87) at both data points (Supplementary Table C-2). It should also be noted that the different NIH toolbox tasks included in this investigation represent overlapping yet distinctive domains of cognitive function (i.e., executive function, episodic memory, processing speed, receptive vocabulary and reading comprehension); therefore, we used adiposity variables together (i.e., zBMI and WC) as a latent adiposity construct whereas the cognitive variables were each used as a sole indicator to represent their respective cognitive domain in the SEM analyses. The CLPMs are illustrated in Figure 1 and Supplementary Figure C-1. The diagonal lines in the diagram represent brain-as-outcome (path b) and brain-as-predictor (path c) paths, respectively. Path b examined the strength of association between latent adiposity at baseline and cognition at follow-up, controlling for the effects of baseline cognition and of the covariates. Similarly, path c examined the strength of association between cognition at baseline and latent adiposity at follow-up,

controlling for the effects of baseline adiposity and of the covariates. The primary set of models used full information maximum likelihood estimation, which means that all participants with at least baseline values on the variables of interest were included in the analysis regardless of whether those participants also had complete data at follow-up. This approach is suitable under the assumption that the data are missing at random (166).

Finally, we analyzed potential mediation paths using "lavaan" R package (165). Blood pressure and brain morphology (LPFC volume and thickness) were examined as mediators for path b (adiposity → cognition) whereas physical activity, diet, and LPFC volume and thickness were examined as mediators for path c (cognition → adiposity). Parallel mediation models were used where the mediator constitutes multiple variables (e.g., diet, blood pressure and LPFC). Mediation analyses were adjusted for all Model 3 covariates described above.

5.5 Results

Baseline and follow-up characteristics of the participants are presented in Table 1. Boys (52%) and girls (48%) were almost equally represented in the sample. Most participants were from a Caucasian (75%) ethnic background, and nearly a quarter of them identified themselves as of Hispanic ethnicity (21%). Participants showed an increase in zBMI (Mean = 1.0 [SD = 2.4] vs. 1.9 [SD = 2.4]) and waist circumference (26.5 [SD = 4.3] vs. 28.7 [SD = 4.8]) measures from Wave 1 to Wave 3 (Table 1). In terms of cognitive measures, children performed slightly better on some NIH toolbox tasks at Wave 3 compared to Wave 1 (e.g., pattern matching: 45.2 [SD = 14.4] vs. 54.5 [SD = 13.8]; and picture sequence: 49.5 [SD = 11] vs. 52.9 [SD = 11.6]).

Table 2 summarizes the finding of the MMR analyses. The analyses of path b (adiposity → cognition) with baseline zBMI as an independent variable and five follow-up cognitive tasks together as the dependant variable suggested that higher zBMI was associated with worse

performance on all cognitive tasks in the unadjusted models; however, this association was statistically significant in the fully adjusted model only for picture sequence task (standardized estimate, $\beta_{model\ 1}$ = -0.04, 95% CI -0.06, -0.02; $\beta_{model\ 2}$ = -0.04, 95% CI -0.07, -0.02; $\beta_{model\ 3}$ = -0.04, 95% CI -0.07, -0.01). This association was less consistent when baseline WC was used as a measure of adiposity, and only the association with follow-up picture vocabulary score emerged as statistically significant in the fully adjusted model ($\beta_{model\ 3}$ = 0.03, 95% CI 0.00, 0.06), but in the opposite direction (i.e., higher WC was associated with better scores on picture vocabulary task).

The analyses of path c (cognition → adiposity) with individual baseline cognitive tasks as an independent variable and both follow-up adiposity measures as dependent variables suggested that better baseline scores on Flanker (zBMI: $\beta_{model\ 3}$ = -0.03, 95% CI -0.06, -0.01; WC: $\beta_{model\ 3}$ = -0.04, 95% CI -0.07, -0.01) and picture sequence task (zBMI: $\beta_{model\ 3}$ = -0.04, 95% CI -0.07, -0.02; WC: $\beta_{model\ 3}$ = -0.03, 95% CI -0.06, 0.00) were associated with lower adiposity in fully adjusted models. Picture vocabulary and reading tasks showed statistically significant associations in unadjusted or partially adjusted models, whereas pattern matching was not significantly associated with adiposity in any models (Table 2). Therefore, the bidirectional hypothesis was more well supported across models when picture sequence task was considered as an indicator of cognitive function and zBMI was considered as an indicator of adiposity.

Table 3 summarizes the CLPM models testing prospective associations between individual cognitive function as a sole indicator and latent adiposity constructed from zBMI and WC. The brain-as-outcome path (path b; adiposity → cognition) revealed that lower baseline adiposity was associated better follow-up Flanker interference (standardized estimate, β = -0.02, 95% CI -0.05, 0.00) and pattern comparison (-0.03, 95% CI -0.05, 0.00) task performance

(Figure 1, 2; Table 3). On the other hand, the brain-as-predictor path (path c; cognition → adiposity) showed that better scores on Flanker (-0.01, 95% CI -0.02, 0.00), picture sequence (-0.02, 95% CI -0.03, 0.00), picture vocabulary (-0.02, 95% CI -0.03, 0.00) and oral reading (-0.02, 95% CI -0.03, -0.01) tasks were associated with significantly lower follow-up adiposity (Figure 1, 2; Table 3). Therefore, the bidirectional association emerged with Flanker task in the latent adiposity modeling.

Supplementary Table C-3 and C-4 summarize the findings of mediation analyses for path b and c cross-lagged effects. Path b mediation analyses suggested that the association between baseline adiposity and follow-up reading performance was mediated through systolic BP (zBMI: -0.0408, 95% CI -0.0768, -0.0048; WC: -0.0256, 95% CI -0.0470, -0.0042) and MFG volume (zBMI: -0.0073, 95% CI -0.0143, -0.0003; WC: -0.0051, 95% CI -0.0099, -0.0004). A statistically significant mediation effect was also observed through MFG (zBMI: -0.0183, 95% CI -0.0331, -0.0035; WC: -0.0061, 95% CI -0.0113, -0.0009) and IFG (zBMI: 0.0142, 95% CI 0.0012, 0.0272; WC: 0.0065, 95% CI 0.0007, 0.0123) for baseline adiposity and follow-up picture vocabulary task performance. MFG also emerged as a statistically significant mediator for the association between baseline adiposity and follow-up pattern recognition task (zBMI: 0.0373, 95% CI 0.0143, 0.0602; WC: 0.0117, 95% CI 0.0036, 0.0199). On the other hand, path c analyses showed that the association between baseline cognition and follow-up adiposity was mediated through physical activity for picture vocabulary task (zBMI: -0.0011, 95% CI -0.0015, -0.0007; WC: -0.0020, 95% CI -0.002, -0.0012) and the oral reading task (zBMI: -0.0007, 95% CI -0.0010, -0.0003; WC: -0.0013, 95% CI -0.0020, -0.0007). In addition, LPFC thickness was a significant mediator for the association between baseline pattern recognition task and follow-up

WC (0.0004, 95% CI 0.0001, 0.0006). No other significant mediation effect was observed for diet and LPFC volume/thickness for brain-as-predictor path (path c).

5.6 Discussion

The current investigation aimed to test the possibility of a bidirectional association between adiposity and cognitive function in adolescents using a large population sample. Our fully adjusted regression analyses revealed that higher baseline adiposity was associated with poor performance on an episodic memory task at follow-up. Although executive function was not found to be statistically significant in the fully-adjusted regression models, latent adiposity modeling showed a statistically significant inverse association between baseline adiposity and follow-up executive function, thereby supporting the brain-as-outcome hypothesis in relation to obesity and cognitive function. Similarly, better baseline executive function and visual processing speed were found to be associated with lower adiposity at follow-up in regression models; however, latent adiposity modeling showed statistically significant inverse associations for all cognitive variables except the pattern matching task. Overall, when considered using latent modeling of the adiposity variable, the brain-as-predictor perspective appears to be more well-supported in the adolescent age group than the brain-as-outcome perspective (although the latter received some limited support as well).

Our analyses also revealed a bidirectional association between adiposity and cognition; however, it was only evident with episodic memory in the case of regression modeling whereas with executive function in the case of latent adiposity modeling. The mediation analyses revealed significant indirect effects through blood pressure, physical activity and LPFC volume/thickness. Specifically, we observed that the association between baseline adiposity and follow-up cognition (i.e., picture vocabulary and oral reading) was mediated through blood pressure and

LPFC volume/thickness, whereas the association between baseline cognition (i.e., picture vocabulary, oral reading, pattern matching) and follow-up adiposity was mediated though physical activity and LPFC thickness. Although the mediation paths are not consistent across adiposity-cognition combinations, the pattern of findings illustrates that such "adiposity-to-brain" and "brain-to-adiposity" associations could be influenced by external factors.

The findings of this study are largely consistent with previous studies conducted on people of adult ages. In the medical literature, the "brain-as-outcome" view is predominant, and most of the studies that examined the association between adiposity and cognition were conducted with such a unidirectional approach. However, numerous cross-sectional and longitudinal analyses of those studies reported that excess adiposity is negatively associated with several domains of cognitive function in adults (e.g., short-term memory, psychomotor function, selective attention, decision making, planning and problem solving), with a more pronounced effect observed in the domain of executive function (8, 65). Similar to adult populations, excess adiposity was also reported to be associated with cognitive performance decrements in children and adolescents (146, 179). Consistent with our findings, previous studies reported that obese children/adolescents tend to have lower processing speed (221), weaker executive control (222) and suboptimal episodic memory (223) compared to their normal-weight counterparts.

Although the "brain-as-predictor" view was inadequately explored in previous studies, the results of several longitudinal investigations support our findings. For example, prior studies have shown that children/adolescents with relatively weaker executive control (e.g., poor self-control and cognitive flexibility), poorer planning and more impulsivity at baseline were more likely to have high BMI at follow-up (224-230). Consistent with previous findings, our analyses suggested that better performance on several measures of cognition function (e.g., executive

function, receptive vocabulary, episodic memory and reading comprehension) were associated with lower adiposity at follow-up. The hypothesized bidirectional association between adiposity and cognitive function has also been reported in previous studies using adult samples (178). A recent meta-analysis of longitudinal studies showed that the existing literature supports a bidirectional association between adiposity and executive function (180). However, it should be noted that meta-analyses included studies those assessed "adiposity → executive function" or "executive function → adiposity" associations primarily with a unidirectional assumption. Therefore, the bidirectional associations concluded in the meta-analysis were observed in different samples and over time windows. On the other hand, our investigation showed that the hypothesized bidirectional associations could happen in the same population and timeframe in parallel using CLPMs with latent variable modeling.

Our mediation analysis suggested that some of the path b (brain-as-outcome) and c (brain-as-predictor) associations were indirectly mediated through lifestyle factors and brain morphology parameters. Such findings are also consistent with prior works conducted on this topic. For example, high blood pressure is a well-known risk factor for cognitive decline in older adults (91-94); however, a similar negative association has also been reported in children and adolescents (231, 232). Similarly, physical activity emerged as a significant mediator for the association between baseline cognition and follow-up adiposity. It was previously reported that people with weaker performance on some cognitive tasks tend to engage in less physical activity (112) and such sedentary behavior can lead to adiposity at a temporal delay (233). Finally, we observed that MFG volume and thickness emerged as significant mediators, primarily for path b. Previous studies also reported a link between brain morphology and cognitive development in several domains. For example, using the same dataset, Ronan and colleagues (182) found that

higher BMI was associated with reduced PFC thickness in adolescents and such cortical thinness are partially accounted for subnormal executive control. Likewise, Hall and colleagues (155) reported that cortical thickness of PFC significantly predicted multiple indices of body composition (e.g., zBMI and WC). Additionally, excess adiposity can also adversely affect other brain structures as reported in previous studies, such as hippocampal volume (148) and amygdala (234).

With respect to mediational findings, not all effects were in the expected direction. For instance, although a significant indirect mediational effect involving MVPA was found, the direction of the effect suggested that higher vocabulary and reading scores predicted lower MVPA. This negative association might reflect time competition between academic pursuits and physical activity, such that more hours spend studying (a sedentary activity) might produce higher scores on tests of reading and vocabulary, and produce a negative correlation between cognitive task performance and MVPA (235). However, it should also be noted that the way in which hypertension and lifestyle mediators play out over time might be complex, particularly among adolescents when the brain is still undergoing maturation. Furthermore, socioeconomic/area deprivation could moderate these associations by adversely affecting structural and functional brain development (236-238).

The current study has several strengths. First, we made use of a large population-based dataset to explore the hypothesized bidirectional association. The large sample size ensured high statistical power to detect effects, even subtle cumulative effects that would be expected be barely discernable over a relatively brief developmental timeframe (i.e., <5 years). Second, given that the ABCD cohort was amassed from 21 research sites across the host country, it could be representative of the adolescent population of the United States to some extent. Third, the direct

measurement of anthropometric reduces the possibility of self-report biases (239). Fourth, the current analyses were adjusted for a number of sociodemographic variables that could potentially confound the hypothesized bidirectional association. Finally, we were able to examine the mediation paths using brain morphologic data assessed by structural brain imaging, a unique facet to this investigation.

The current study also has a number of limitations. First, although the participants were recruited from across the United States, survey weights were not constructed and implemented, and so the findings may not be truly representative of the larger population. Second, despite the fact that the ABCD dataset is rich in cognitive assessments, there are only two measures available for adiposity indicators. Therefore, it was not possible to test the bidirectionality hypothesis using other desirable measurements such as dual energy X-ray absorptiometry (DXA) and waist-hip ratio. Previous studies showed that such measures could also be associated with cognitive performance (139, 140, 170, 178). Third, we observed bidirectional associations between adiposity and episodic memory in fully adjusted models in regression analyses whereas CLPM analyses showed a bidirectional association between latent adiposity and executive function. However, it is worth mentioning that the CLPM approach depends on several assumptions, which are often violated or cannot be entirely met (175, 176). Fourth, at the time of this investigation, we only had three waves of data available, whereas adiposity and cognitive variables were measured only at Wave 1 (baseline) and Wave 3. Furthermore, the brief interval between Wave 1 and Wave 3 was barely sufficient for accumulation of changes in cognition or adiposity in this age group. More follow-up data with an extended period of follow-up are required to establish the hypothesized bidirectional association. Finally, morphological features of the LPFC were processed for the Deskian-Killiany atlas (218). The use of the default atlas

could have some influence on the mediation analyses; therefore, a stronger or weaker mediational effect could be observed using other atlases.

Despite the limitations mentioned above, this study provides some valuable insights on the bidirectional association that could be expected in the adolescent population. Further studies are needed to replicate the findings, particularly in the children, adolescents and youth populations. Future studies should also aim to include other adiposity measures and additional cognitive variables in the analyses to detect to what extent bidirectional associations exist beyond executive control and episodic memory.

5.7 Conclusion

In summary, the current investigation tested the possibility of bidirectional associations between cognition and adiposity in a large population-based sample of adolescents. The findings suggested that baseline adiposity was associated with later cognitive performance across a number of domains. Similarly, better baseline cognitive function predicted lower adiposity at follow-up, across a number of adiposity measures. Although the findings varied slightly based on the modeling approach, we observed bidirectional associations of adiposity with episodic memory and executive function. Findings of mediation analyses were less consistent; however, significant mediation paths were observed for blood pressure, physical activity, and MFG volume and thickness. Future studies should aim to replicate the finding of this study while incorporating additional adiposity and cognitive measures.

5.8 Acknowledgements

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sites and more than 11000 children (aged 9–10 years of age at baseline), who will be followed forward for 10 years. The ABCD Study is supported by the National Institutes of Health (NIH) and federal partners under the following awards: U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123 and U24DA041147. A complete list of funding support and partners can be found at the following link: https://abcdstudy.org/federal-partners.html. A complete list of participating sites and investigators can be found here: https://abcdstudy.org/consortium_members/. ABCD Study investigators did not participate in the analysis or writing of this report, and as such this paper reflects the view of the authors and may not reflect the views and opinions of the NIH or ABCD Study investigators.

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5.9 Tables and Figures

5.9.1 Table 1: Sample characteristics.

Variable	Mean (SD)/n (%)	Missing values
Total	N = 11,103	
Wave 1		
Age (in months)	118.9 (7.5)	-
Child sex		
Male	5,796 (52%)	-
Female	5,307 (48%)	
Child race		
American Indian/Native American	69 (0.6%)	
Asian Indian	55 (0.5%)	
Black/African American	1,828 (16%)	
Chinese	89 (0.8%)	
Filipino	47 (0.4%)	
Guamanian	1 (<0.1%)	
Japanese	13 (0.1%)	
Korean	20 (0.2%)	
Native Hawaiian	4 (<0.1%)	21
Other Asian	32 (0.3%)	
Other Pacific Islander	14 (0.1%)	
Other Race	477 (4.3%)	
Refuse	44 (0.4%)	
Samoan	4 (<0.1%)	
Vietnamese	21 (0.2%)	
Caucasian	8,293 (75%)	
Don’t Know	71 (0.6%)	
Child Hispanic ethnicity	2,264 (21%)	131
Puberty status	1.7 (0.8)	-
Family income level	7.2 (2.4)	946
Primary parent education	16.6 (2.8)	12
Second parent/partner education	16.4 (3.0)	2,284

Area deprivation index	40.0 (26.9)	796
Body mass index z-score	1.0 (2.4)	-
Waist circumference	26.5 (4.3)	8
Flanker task	46.0 (9.1)	9
Pattern matching	45.2 (14.4)	27
Picture sequence	49.5 (11.0)	17
Picture vocabulary	52.3 (11.0)	-
Reading	49.3 (11.6)	17
Wave 2		
Diet		
Whole grains	6,436 (64%)	1,067
Green, leafy vegetables	4,671 (45%)	832
Other vegetables	8,690 (84%)	749
Berries	6,719 (66%)	866
Beans	2,723 (27%)	837
Nuts	2,384 (23%)	874
Fast/fried food	6,875 (66%)	694
Pastries or sweets	6,093 (59%)	783
Wave 3		
Puberty status	2.5 (1.0)	1,377
Systolic blood pressure	102.3 (10.7)	6,894
Diastolic blood pressure	60.4 (8.7)	6,894
Physical activity	35.4 (32.1)	4,691
Sleep duration	480.6 (80.0)	4,860
Body mass index z-score	1.9 (2.4)	4,111
Waist circumference	28.7 (4.8)	4,138
Flanker task	46.7 (9.6)	3,804
Pattern matching	54.5 (13.8)	3,837
Picture sequence	52.9 (11.6)	1,999
Picture vocabulary	49.7 (10.3)	2,021
Reading	49.0 (10.7)	2,058

5.9.2 Table 2: Multivariate multivariable regression of the analytic sample for path b (adiposity → cognition) and c (cognition → adiposity).

Outcome	Model 1		Model 2		Model 3	
	β **(95% CI)**	***p***	***β*** **(95% CI)**	***p***	***β*** **(95% CI)**	***p***
			Path b (zBMI → Cognition)			
Flanker	**-0.04 (-0.06, -0.02)**	**<0.001**	**-0.04 (-0.06, -0.01)**	**0.004**	0.03 (-0.06, 0.00)	0.072
Pattern matching	**-0.03 (-0.05, -0.01)**	**0.010**	**-0.03 (-0.05, 0.00)**	**0.034**	-0.03 (-0.06, 0.00)	0.056
Picture sequence	**-0.04 (-0.06, -0.02)**	**0.001**	**-0.04 (-0.07, -0.02)**	**<0.001**	**-0.04 (-0.07, -0.01)**	**0.009**
Picture vocabulary	**-0.04 (-0.06, -0.01)**	**0.002**	0.01 (-0.01, 0.04)	0.320	0.02 (-0.01, 0.05)	0.217
Reading	**-0.05 (-0.08, -0.03)**	**<0.001**	-0.02 (-0.04, 0.00)	0.105	-0.02 (-0.05, 0.01)	0.204
			Path b (WC → Cognition)			
Flanker	**-0.04 (-0.06, -0.01)**	**0.002**	-0.02 (-0.05, 0.00)	0.063	-0.02 (-0.05, 0.01)	0.189
Pattern matching	-0.01 (-0.04, 0.01)	0.253	-0.01 (-0.04, 0.01)	0.301	-0.01 (-0.04, 0.02)	0.380
Picture sequence	-0.02 (-0.04, 0.00)	0.055	**-0.03 (-0.06, -0.01)**	**0.010**	-0.03 (-0.06, 0.00)	0.073
Picture vocabulary	-0.02 (-0.04, 0.01)	0.182	**0.03 (0.01, 0.06)**	**0.008**	**0.03 (0.00, 0.06)**	**0.038**
Reading	-0.02 (-0.05, 0.00)	0.051	0.01 (-0.02, 0.03)	0.637	0.00 (-0.03, 0.03)	0.901
			Path c (Flanker → Adiposity)			
zBMI	-0.02 (-0.04, 0.01)	0.191	-0.02 (-0.04, 0.00)	0.074	**-0.03 (-0.06, -0.01)**	**0.011**
WC	-0.02 (-0.04, 0.00)	0.089	**-0.03 (-0.05, -0.01)**	**0.016**	**-0.04 (-0.07, -0.01)**	**0.003**
			Path c (Pattern matching → Adiposity)			
zBMI	-0.02 (-0.04, 0.00)	0.094	-0.01 (-0.04, 0.01)	0.259	-0.01 (-0.03, 0.02)	0.598
WC	-0.01 (-0.03, 0.01)	0.477	-0.01 (-0.03, 0.02)	0.468	-0.01 (-0.03, 0.02)	0.556
			Path c (Picture sequence → Adiposity)			
zBMI	**-0.06 (-0.08, -0.03)**	**<0.001**	**-0.06 (-0.08, -0.03)**	**0.000**	**-0.04 (-0.07, -0.02)**	**0.001**
WC	**-0.05 (-0.08, -0.03)**	**<0.001**	**-0.05 (-0.07, -0.02)**	**0.000**	**-0.03 (-0.06, 0.00)**	**0.035**
			Path c (Picture vocabulary → Adiposity)			
zBMI	**-0.04 (-0.06, -0.02)**	**0.001**	-0.02 (-0.04, 0.01)	0.197	-0.02 (-0.04, 0.01)	0.260
WC	-0.02 (-0.05, 0.00)	0.070	0.00 (-0.03, 0.02)	0.874	0.00 (-0.03, 0.02)	0.727

			Path c (Reading → Adiposity)			
zBMI	**-0.06 (-0.08, -0.04)**	**<0.001**	**-0.03 (-0.05, 0.00)**	**0.035**	-0.02 (-0.05, 0.00)	0.066
WC	**-0.04 (-0.07, -0.02)**	**<0.001**	-0.02 (-0.04, 0.01)	0.158	-0.02 (-0.05, 0.01)	0.141

Note 1: zBMI = Body Mass Index z score; WC = Waist Circumference. Higher scores on cognitive tasks indicate better cognitive status whereas higher scores on adiposity measures indicate poor adiposity status.

Note 2: Model 1 is the unadjusted model. Model 2 is the partially adjusted model controlled for age, sex, family income and parent education. Model 3 is the fully adjusted model controlled for age, sex, ethnicity, family income, parent education, area deprivation index, pubertal status and sleep duration. All estimates are standardized coefficients.

5.9.3 Table 3: Assessment of bidirectional association between latent adiposity and cognitive function.

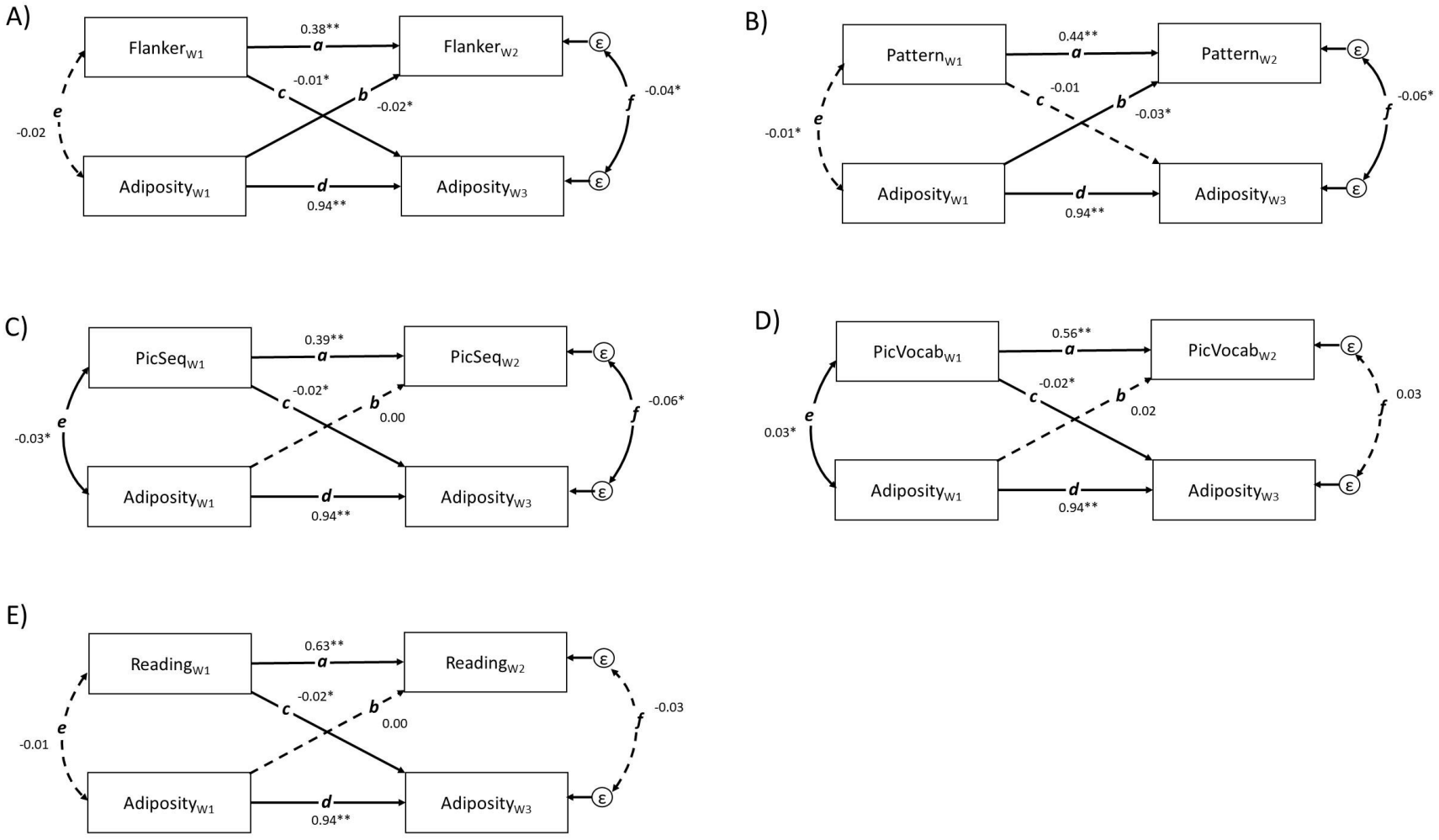
Path label	Path description	Estimate (95% CI)	*p* value
		Flanker Task	
a	$Cog_{W1} \rightarrow Cog_{W3}$	**0.38 (0.36, 0.40)**	**0.000**
b	$Adi_{W1} \rightarrow Cog_{W3}$	**-0.02 (-0.05, 0.00)**	**0.040**
c	$Cog_{W1} \rightarrow Adi_{W3}$	**-0.01 (-0.02, 0.00)**	**0.016**
d	$Adi_{W1} \rightarrow Adi_{W3}$	**0.94 (0.93, 0.95)**	**0.000**
e	$Adi_{W1} \leftrightarrow Cog_{W1}$	-0.02 (-0.04, 0.00)	0.077
f	$Adi_{W3} \leftrightarrow Cog_{W3}$	**-0.04 (-0.08, -0.01)**	**0.019**
		Pattern Comparison	
a	$Cog_{W1} \rightarrow Cog_{W3}$	**0.44 (0.42, 0.46)**	**0.000**
b	$Adi_{W1} \rightarrow Cog_{W3}$	**-0.03 (-0.05, 0.00)**	**0.028**
c	$Cog_{W1} \rightarrow Adi_{W3}$	-0.01 (-0.02, 0.00)	0.214
d	$Adi_{W1} \rightarrow Adi_{W3}$	**0.94 (0.93, 0.95)**	**0.000**
e	$Adi_{W1} \leftrightarrow Cog_{W1}$	-0.01 (-0.03, 0.01)	0.225
f	$Adi_{W3} \leftrightarrow Cog_{W3}$	**-0.06 (-0.09, -0.02)**	**0.002**
		Picture Sequence	
a	$Cog_{W1} \rightarrow Cog_{W3}$	**0.39 (0.37, 0.40)**	**0.000**
b	$Adi_{W1} \rightarrow Cog_{W3}$	0.00 (-0.02, 0.02)	0.829
c	$Cog_{W1} \rightarrow Adi_{W3}$	**-0.02 (-0.03, 0.00)**	**0.006**
d	$Adi_{W1} \rightarrow Adi_{W3}$	**0.94 (0.93, 0.95)**	**0.000**
e	$Adi_{W1} \leftrightarrow Cog_{W1}$	**-0.03 (-0.05, -0.01)**	**0.002**
f	$Adi_{W3} \leftrightarrow Cog_{W3}$	**-0.06 (-0.10, -0.02)**	**0.001**
		Picture Vocabulary	
a	$Cog_{W1} \rightarrow Cog_{W3}$	**0.56 (0.55, 0.57)**	**0.000**
b	$Adi_{W1} \rightarrow Cog_{W3}$	0.02 (0.00, 0.04)	0.061
c	$Cog_{W1} \rightarrow Adi_{W3}$	**-0.02 (-0.03, 0.00)**	**0.008**
d	$Adi_{W1} \rightarrow Adi_{W3}$	**0.94 (0.93, 0.95)**	**0.000**
e	$Adi_{W1} \leftrightarrow Cog_{W1}$	**0.03 (0.01, 0.05)**	**0.008**
f	$Adi_{W3} \leftrightarrow Cog_{W3}$	0.03 (-0.01, 0.07)	0.104

		Oral Reading Recognition	
a	Cog_{W1} → Cog_{W3}	**0.63 (0.62, 0.64)**	**0.000**
b	Adi_{W1} → Cog_{W3}	0.00 (-0.01, 0.02)	0.602
c	Cog_{W1} → Adi_{W3}	**-0.02 (-0.03, -0.01)**	**0.001**
d	Adi_{W1} → Adi_{W3}	**0.94 (0.93, 0.95)**	**0.000**
e	Adi_{W1} ↔ Cog_{W1}	-0.01 (-0.03, 0.01)	0.272
f	Adi_{W3} ↔ Cog_{W3}	-0.03 (-0.07, 0.01)	0.096

Note 1: Cog_{W1} and Cog_{W3} indicate cognition at baseline (Wave 1) and follow-up (Wave 3), respectively. Adi_{W1} and Adi_{W3} indicate latent adiposity variable at baseline (Wave 1) and follow-up (Wave 1), respectively. Higher scores on cognitive tasks indicate better cognitive status whereas higher scores on adiposity measure indicate worse adiposity status. The analyses were adjusted for age, sex, ethnicity, family income, parent education, area deprivation index, pubertal status and sleep duration. All estimates are standardized coefficients.

Note 2: Description of the cross-lagged paths: (a) Path a: the association between baseline cognition and follow-up cognition, (b) Path b: the association between baseline adiposity and follow-up cognition, (c) Path c: the association between baseline cognition and follow-up adiposity, and (d) Path d: the association between baseline adiposity and follow-up adiposity, (e) Path e: Covariance between baseline BMI and baseline cognition, and (f) Path f: Covariance between follow-up BMI and follow-up cognition.

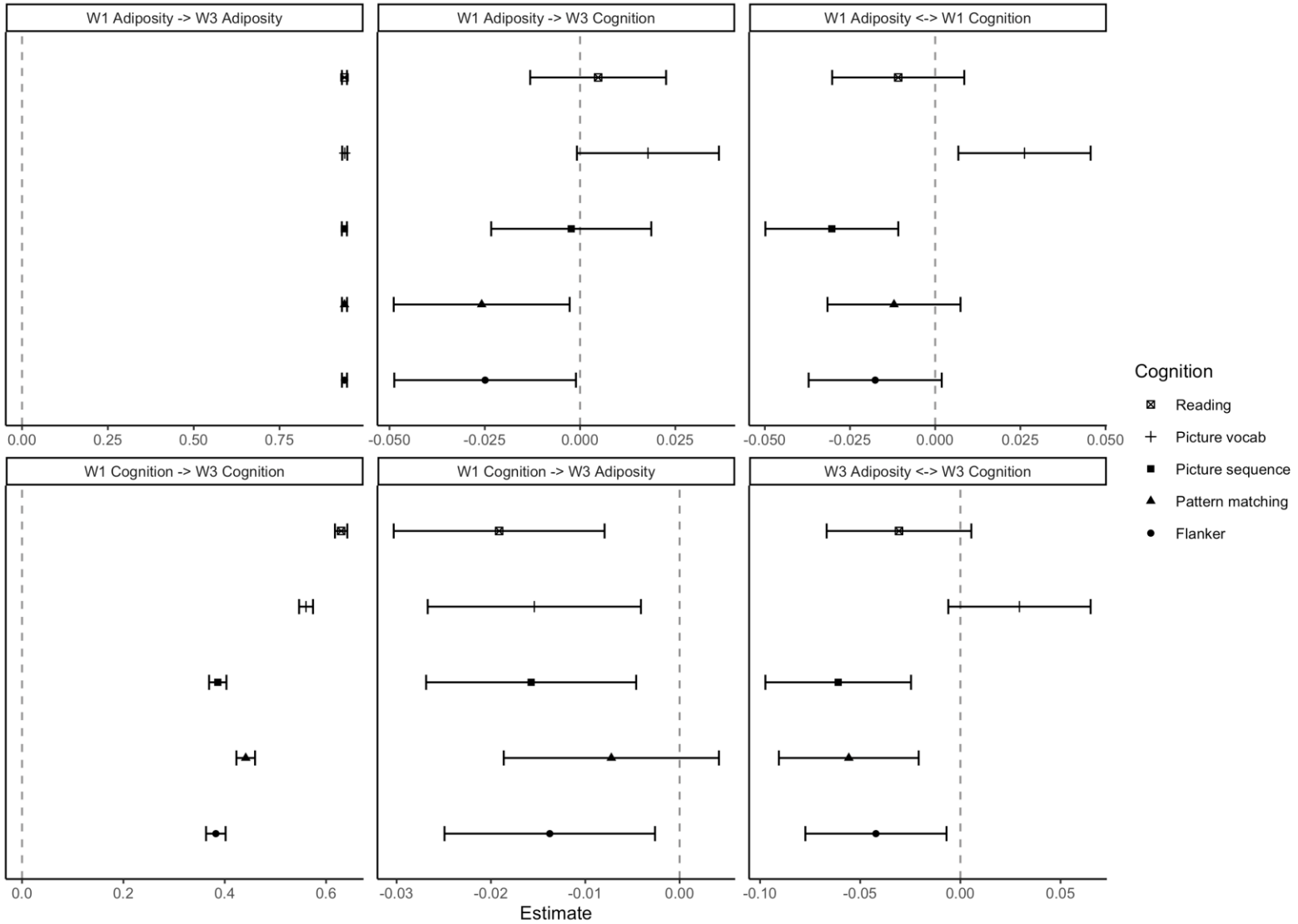
5.9.4 Figure 1: Cross-lagged model estimates for latent adiposity and cognitive function.



Note 1: Flanker = Flanker task; Pattern = Pattern comparison processing speed test; PicSeq = Picture sequence memory test; PicVocab = Picture vocabulary task; Reading = Oral reading Recognition Task; Adiposity = Latent adiposity variable. W1 and W3 indicate Wave 1 (baseline) and Wave 3 or follow-up measures, respectively. Bolded arrows indicate statistically significant path coefficients; dotted arrows indicate non-significant path coefficients. All coefficients are standardized beta weights. *: $p < .05$. **: $p < .001$. Covariates include age, sex, ethnicity, family income, parent education, area deprivation index, pubertal status and sleep duration.

Note 2: Description of the cross-lagged paths: (a) Path a: the association between baseline cognition and follow-up cognition, (b) Path b: the association between baseline adiposity and follow-up cognition, (c) Path c: the association between baseline cognition and follow-up adiposity, and (d) Path d: the association between baseline adiposity and follow-up adiposity, € Path e: Covariance between baseline adiposity and baseline cognition, and (f) Path f: Covariance between follow-up adiposity and follow-up cognition.

5.9.5 Figure 2: Bidirectional associations between latent adiposity and cognitive function.



Note: W1 = Wave 1 or baseline measures; W3 = Wave 3 or 2-year follow-up measures; Adiposity = Latent adiposity variable.

6 Chapter 6: General discussion

6.1 Overview

The overall purpose of this dissertation was to disentangle the bidirectional associations between adiposity and cognitive function. Using two large-scale population-based datasets spanning three major age groups, the bidirectionality hypothesis was examined using a variety of statistical techniques. Study 1 (Chapter 3) focused on examining the cross-sectional association between adiposity and cognition in the CLSA baseline dataset using four indicators of adiposity (e.g., BMI, WC, WHR, and DXA) and three indicators of cognitive function (e.g., Stroop, AFT, and MRT). In addition, mediation analyses for lifestyle variables (e.g., diet and physical activity) and medical conditions (e.g., hypertension and diabetes) were conducted to determine whether the mediators have any role in mediating the above-mentioned associations. This study provided important insights into the association between adiposity and cognitive function at the baseline level and helped us refine the hypotheses and analyses strategies for the longitudinal assessments.

Study 2 (Chapter 4) was a prospective analysis of the baseline and first follow-up datasets of the CLSA. Due to the prospective nature of the data and the wide age span of the study sample, this investigation was able to examine evidence in favor of both "brain-as-outcome" and "brain-as-predictor" paths separately for middle-aged and older adults. Individuals diagnosed with neurologic disorders (e.g., multiple sclerosis, dementia, stroke and Parkinson's disease) and who were unable to walk without assistance or for whom English or French was a second language were excluded from the analyses in order to remove the confounding effects of those measures from the analyses. The final analyses were conducted on N = 25,854 participants using three indicators of cognitive function (e.g., Stroop, AFT and MRT) and two indicators of

adiposity (e.g., BMI, and WC). Mediation analyses for lifestyle variables and medical conditions were also conducted.

Study 3 (Chapter 5) aimed to test whether the bidirectional associations between adiposity and cognitive function exist in younger age ranges when the brain is still undergoing significant maturation. We examined bidirectional associations in a large population-based sample of adolescents using the ABCD datasets (N = 11,878). This study examined the "brain-as-outcome" and "brain-as-predictor" paths using two indicators of adiposity (e.g., zBMI and WC) and five indicators of cognitive function (e.g., Flanker task, pattern matching, picture sequence, picture vocabulary, and oral reading). Mediation analyses were also conducted for lifestyle variables, blood pressure, and LPFC volume/thickness. Overall, these three studies together assessed the existence of bidirectional associations between adiposity and cognitive function across the lifespan, from adolescence to old age, using large-scale population-based datasets.

6.2 Discussion of Overall Findings

Study 1 showed that all measures of cognitive function were significantly associated with adiposity indices and in the expected directions. To illustrate, better scores on tests of executive function, verbal fluency, and reaction time were found to be associated with lower adiposity by most metrics. Next, using baseline and first follow-up data of the CLSA comprehensive cohort, Study 2 showed that baseline adiposity was associated with higher Stroop interference at follow-up for both middle-aged and older adults. Likewise, higher baseline Stroop interference was also associated with higher follow-up adiposity, but only in the middle-aged subsample. Therefore, a bidirectional association between adiposity and executive function was observed and appeared to be more prominent in mid-life.

Finally, Study 3 found that higher zBMI and WC at baseline were associated with worse picture sequence task performance at follow-up. Likewise, superior performance on Flanker and picture sequence tasks at baseline was associated with better adiposity status at follow-up. CLPM with latent variable modeling revealed a bidirectional association with executive function. Therefore, bidirectional associations emerged with only episodic memory and executive function among adolescents but not with other cognitive domains.

Altogether, this dissertation highlighted that attenuated performance on cognitive tasks (i.e., "brain-as predictor" view) could be a predictor and risk factor for excess adiposity although this directionality is often disregarded in clinical research. Both longitudinal analyses (Studies 2 and 3) revealed that the association between adiposity and cognitive function is somewhat bidirectional among adolescents and middle-aged. It should be noted that people of younger age groups (i.e., adolescents and middle-aged) are much less likely to be affected by the impact of chronic diseases, and some chronic conditions have a direct link with both adiposity and cognitive function (e.g., T2DM) (95, 96, 240). It is likely that in late life, much more variability in adiposity is absorbed by such chronic conditions; this could be a reason that bidirectionality becomes prominent in younger age groups but not in older adults. Furthermore, older adults are expected to face several lifestyle-related constraints, and some of those factors (e.g., lack of exercise opportunities, less access to healthy food options) could be more strongly associated with adiposity than cognitive function at this age. A similar pattern of associations (i.e., a weaker association between adiposity and cognitive function in old age) has also been reported in previous studies (241, 242). A systematic review and meta-analysis by Pedditizi and colleagues (72) reported a positive association between obesity and cognitive deficits in mid-life, but the association was reversed in late life. In agreement with these findings, our investigation revealed

a weaker “cognition-to-adiposity” association in old age, and a positive association was observed with semantic fluency in the same age group.

Although the bidirectionality was evident in mid-life, this was only true for executive function. In fact, executive function emerged as the common cognitive domain to be bidirectionality associated with adiposity in both adolescents and middle-aged. A stronger association between adiposity and executive function has also been reported in previous investigations (5, 8, 54-64). Our analysis also revealed several significant mediation paths through lifestyle variables (e.g., diet and physical activity) and medical conditions (e.g., hypertension and diabetes). The mediating role of lifestyle variables can also be explained by executive dysfunction. Executive function plays a critical role in maintaining lifestyle behaviors. Poor executive control has been reported to have an association with unhealthy food consumption, sedentary behavior, physical inactivity, and lower consumption of healthy foods (83, 87-89), in part because of the implementational challenges that such behaviors carry. Likewise, the impact of obesity on cognition could be mediated through obesity-related medical complications directly or indirectly, as reported in previous studies (91-96).

6.3 Implications for Research and Policy

This dissertation demonstrated the existence of bidirectionality between adiposity and cognitive function, particularly at a younger age and with reference to the executive function domain. These findings hold important policy and research implications.

As discussed previously, executive function deficits may lead to weight gain over time through obesogenic behaviors (e.g., less physical activity, poor dietary habits) (74, 90). Therefore, health-behavior interventions could potentially incorporate executive function training as a strategy for weight reduction. Repeated cognitive training using executive function

tasks was found to enhance executive function capacity (243, 244). Furthermore, several studies reported that weight loss interventions that adopted a strategy of augmenting executive function significantly reduced participants' BMI (245-247). Therefore, executive function training could be a significant addition to the existing weight reduction programs. It is also the case that environments that support lifestyle behaviors may be particularly important in adolescence and mid-life, in order to reduce excess demand on executive control resources. The existence of brain-as-predictor effects in these age ranges may signal the presence of ecologically mediated self-regulatory demand for obesity-mitigating behaviors (e.g., exercise, healthy food choice). If this is the case, policy recommendations around reducing implementational challenges for adolescents are very much needed.

Future research should also be directed to explore novel methods of enhancing executive function, such as using non-invasive brain stimulation technology. Previously, it was shown that high-frequency repetitive transcranial magnetic brain stimulation delivered to the left dlPFC effectively decreased food intake and facilitated weight reduction in obese individuals (248, 249). Such methods could be potentially useful for morbid obesity, as an alternative to bariatric surgery in the clinical environment (250, 251).

6.4 Overall Strengths

This dissertation has a number of strengths. First, the proposed bidirectionality hypotheses were examined using large-scale population-based datasets. The sample size of the CLSA comprehensive cohort and ABCD study were 30,097 and 11,878, respectively. High statistical power of the analyses enabled us to detect subtle effects that might not be possible using small-scale datasets. Many prior investigations that found no association between adiposity and cognition may have suffered from such limitations, in particular because the effects of any target

predictor would be expected to be weak over a limited time frame of several years, even if substantial if accumulated over a lifetime. Furthermore, the CLSA data analyses were conducted using survey weights to ensure representativeness to the larger Canadian population.

Studies 2 and 3 were longitudinal analyses. Because of the prospective nature of these investigations, we were able to preserve the temporality of the associations. As the previous research analyzed "brain-as-predictor" and "brain-as-outcome" paths in different samples, it cannot be concluded based on those findings whether bidirectionality can exist in the same sample. Also, in terms of timeframe, it was not entirely clear whether bidirectional influence can happen simultaneously. Unlike previous studies, we explored bidirectional association in the same sample, and based on our findings, we can expect that bidirectional influence can happen simultaneously in the same sample.

Another strength of the current analyses was to utilize multiple indices of adiposity and cognitive function to explore the bidirectionality. Accordingly, we were able to conclude that the bidirectional association was not limited to any specific measures of adiposity (e.g., general obesity vs. central obesity). Furthermore, adiposity measures were associated with less reporting bias as those measurements were taken in person at the data collection sites. Finally, the datasets used to test bidirectionality were rich in sociodemographic and lifestyle variables; this allowed us to control the analyses for a number of potential confounders that might distort the hypothesized bidirectional associations.

6.5 Overall Limitations

One major limitation of this dissertation is the availability of limited follow-up data at the time of this investigation. We were able to include only two waves of data (baseline and 3-year follow-up) for the CLSA analyses. Although three waves of data were available for the ABCD

study, focal variables (e.g., adiposity and cognitive function) were measured only at Wave 1 and Wave 3. Furthermore, the time interval between baseline and follow-up data collection for the focal variables was only 2-3 years. It should be noted that a detectable and clinically meaningful change in the cognitive status might require a substantially longer time to emerge than 2-3 years at the population level, as mentioned above. It is also expected that bidirectional influence accumulates over time. Therefore, multiple follow-up data collected over at least a decade or more would be necessary to observe a clearer picture of the absolute magnitude of any bidirectional effects. The current investigation only allowed us to examine the presence vs. absence of such effects, with relatively good power.

Although the analyses involving CLSA were conducted using survey weights, the representativeness of the sample itself is somewhat limited considering the fact that the CLSA comprehensive cohort was recruited from the vicinity of the major urban centers. Furthermore, a sizable number of participants were excluded from the CLSA prospective analysis, which further limits the representativeness to only functionally mobile and neurologically sound individuals. On the other hand, no survey weights were constructed or utilized for the ABCD data analyses.

6.6 Directions for Future Research

Future studies should aim to replicate the findings presented in this dissertation using other datasets and longer data collection periods. Because of the shorter follow-up intervals of the available datasets, the effect sizes observed here are subtle and may not have a large degree of clinical significance or policy relevance. It is expected that future studies will be able to overcome this issue by including more follow-up data collected over an extended period; for example, the ABCD Study will be continuing to collect annual data over the course of the next 15+ years, and the CLSA will continue for at least another decade. Likewise, it is also crucial to

know the extent of bidirectionality beyond the selected cognitive domains examined here. Future studies would be benefitted by including other tasks assessing different cognitive domains, such as complex decision-making, long-term and remote memory and other facets of cognition.

Similarly, a comprehensive set of adiposity measures should also be considered. We had a reasonably comprehensive but not exhaustive set of adiposity measures available for the longitudinal assessments in the two datasets. DXA is often regarded as the gold standard for fat mass assessments (12, 17, 45, 46); therefore, such measures should be incorporated to explore bidirectionality. Finally, future studies should also consider using brain imaging data to augment our understanding of brain-as-predictor and brain-as-outcome effects involving adiposity; these will be available in future iterations of the CLSA. Previous investigations reported that prefrontal cortex volume/thickness predicts body composition in adolescents (155), and therefore, it would be worth exploring whether such bidirectionality exists at the level of brain morphology.

6.7 Conclusions

In summary, this dissertation provides important evidence for the existence of bidirectional associations between adiposity and cognitive function in adolescents and middle-aged adults. Executive function and episodic memory emerged as the cognitive domains to be significantly associated with adiposity bidirectionally. Lifestyle factors and medical conditions appeared to influence the bidirectional associations. Further research should be conducted to replicate these findings using multiple waves of data collected over decades and assess to what extent such bidirectionality exists beyond executive function and episodic memory.

7 References

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8 Appendices

8.1 Appendix A: Supplementary materials for Manuscript 1 (Chapter 3)

8.1.1 Supplementary Table A-1: Baseline characteristics of full sample, included and excluded individuals.

Variables	Full sample (Weighted mean/percentage) (N = 30,097)	Included (Weighted mean/percentage) (N = 28,609)	Excluded (Weighted mean/percentage) (N = 1,488)
Stroop effect	9.95 (9.86, 10.05)	9.93 (9.84, 10.02)	10.74 (10.20, 11.28)
Mean reaction time	797.29 (794.89, 799.68)	795.42 (793.01, 797.82)	852.73 (835.48, 869.97)
Animal fluency	20.33 (20.25, 20.41)	20.35 (20.27, 20.44)	19.35 (18.81, 19.89)
BMI	27.80 (27.72, 27.88)	27.78 (27.71, 27.86)	28.20 (27.81, 28.59)
Total fat mass	33.48 (33.36, 33.60)	33.49 (33.37, 33.61)	33.23 (32.62, 33.83)
Waist circumference	92.85 (92.64, 93.05)	92.76 (92.55, 92.98)	94.84 (93.66, 96.01)
Waist-hip ratio	0.90 (0.90, 0.90)	0.90 (0.90, 0.90)	0.90 (0.90, 0.91)
Somatic comorbidity	2.48 (2.45, 2.50)	2.46 (2.43, 2.49)	2.77 (2.64, 2.91)
Age	59.49 (59.35, 59.63)	59.42 (59.28, 59.55)	61.02 (60.37, 61.68)
Sex			
Female	50.36 (49.65, 51.08)	50.44 (49.71, 51.18)	48.73 (45.50, 51.97)
Male	49.64 (48.92, 50.35)	49.56 (48.82, 50.29)	51.27 (48.03, 54.50)
Ethnicity			
Caucasian	5.30 (4.96, 5.65)	5.25 (4.90, 5.60)	6.30 (4.71, 7.88)
Non-Caucasian	94.70 (94.35, 95.04)	94.75 (94.40, 95.10)	93.70 (92.12, 95.29)
Income			
No response	5.60 (5.29, 5.91)	5.41 (5.09, 5.72)	9.56 (7.82, 11.31)
< $20,000	4.42 (4.17, 4.68)	4.27 (4.01, 4.53)	7.68 (6.14, 9.22)
$20,000 to < $50,000	17.69 (17.20, 18.19)	17.50 (16.99, 18.01)	21.62 (19.15, 24.08)
$50,000 to < $100,000	31.43 (30.77, 32.08)	31.61 (30.93, 32.28)	27.77 (24.98, 30.55)
$100,000 to < $150,000	20.94 (20.33, 21.55)	21.08 (20.45, 21.70)	18.05 (15.26, 20.83)
< $150,000 or more	19.92 (19.31, 20.53)	20.14 (19.52, 20.77)	15.33 (12.66, 18.00)
Education			
High school or less	13.85 (13.38, 14.32)	13.72 (13.24, 14.20)	16.43 (14.01, 18.84)
Below bachelor	39.73 (39.03, 40.43)	39.70 (38.98, 40.42)	40.28 (37.12, 43.43)

Bachelor or above	46.43 (45.72, 47.14)	46.58 (45.85, 47.31)	43.30 (40.07, 46.53)
Residence			
Urban	91.53 (91.14, 91.93)	91.37 (90.96, 91.78)	94.89 (93.53, 96.24)
Rural	8.47 (8.07, 8.86)	8.63 (8.22, 9.04)	5.11 (3.76, 6.47)
Neurologic comorbidity			
No	97.50 (97.30, 97.71)	97.69 (97.49, 97.89)	93.61 (92.17, 95.04)
Yes	2.50 (2.29, 2.70)	2.31 (2.11, 2.51)	6.39 (4.96, 7.83)

8.2 Appendix B: Supplementary materials for Manuscript 2 (Chapter 4)

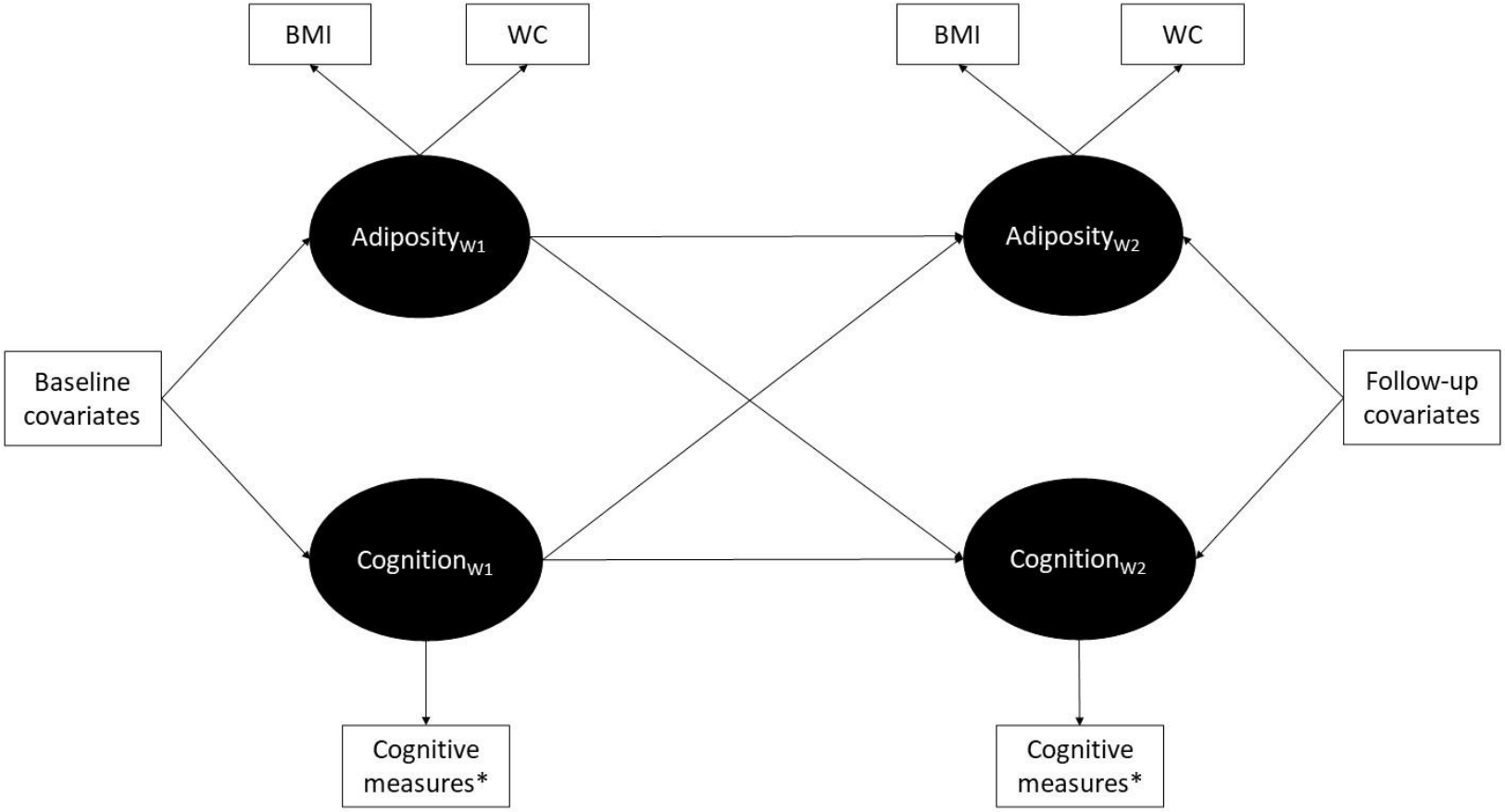
8.2.1 Comorbidity index

Each CLSA participant was inquired about the presence of chronic conditions. From the list of chronic diseases, the following 22 chronic conditions were selected to include in the comorbidity index. These variables were coded as 1 and 0 where 1 indicates the presence of specific chronic conditions. The comorbidity index was created by summing across all chronic conditions included in the index.

List of comorbidities in the comorbidity index:

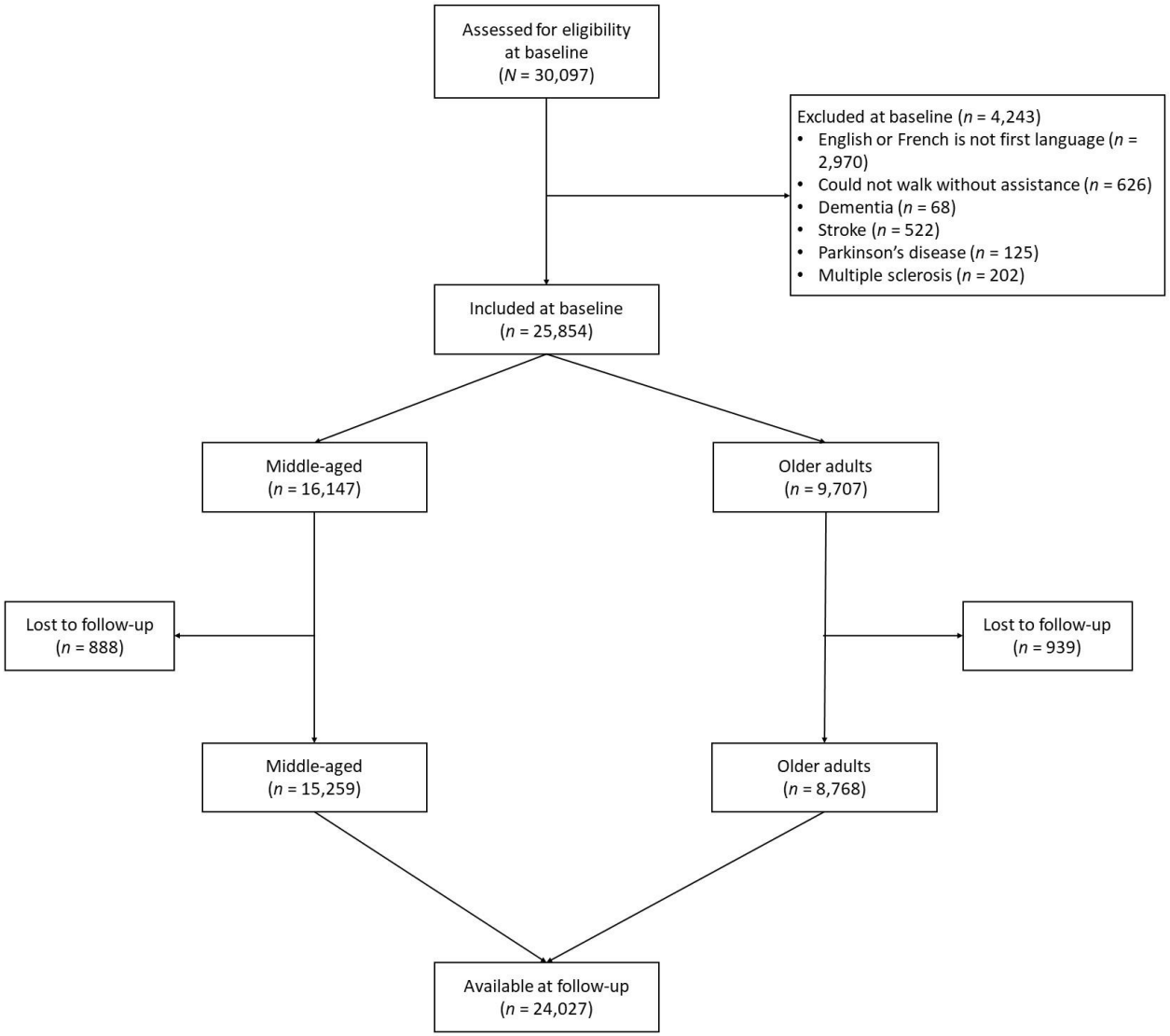
1. Diabetes
2. Chronic obstructive pulmonary disease
3. Asthma
4. Heart disease
5. Heart attack
6. Hypertension
7. Peripheral vascular disease
8. Epilepsy
9. Migraine
10. Rheumatoid arthritis
11. Osteoarthritis
12. Other arthritis
13. Back problems
14. Hyperthyroidism
15. Hypothyroidism
16. Depression
17. Mood disorder
18. Anxiety disorder
19. Cancer
20. Bowel disorder
21. Stomach ulcer
22. Kidney disease

8.2.2 Supplementary Figure B-1: Conceptual diagram of the bidirectional associations between adiposity and cognitive function.



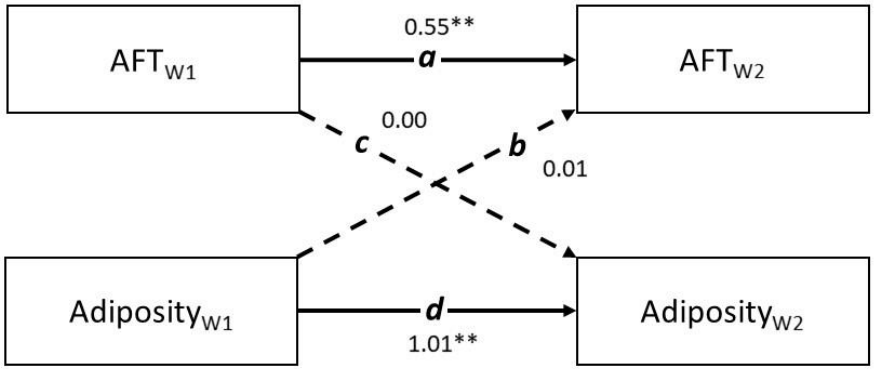
Note 1: WC = Waist Circumference, BMI = Body Mass Index, W1 = Wave 1 or baseline measures, W2 = Wave 2 or follow-up measures. *A separate cognitive measure was used in each model and included Stroop interference, animal fluency score and mean reaction time. The covariates considered for the bidirectional associations were age, sex ethnicity, household income, education, residence, physical activity, comorbidity and sleep duration. Each bidirectional association was tested for middle-aged and older adults separately.

8.2.3 Supplementary Figure B-2: Exclusion criteria and number of excluded participants from the study.

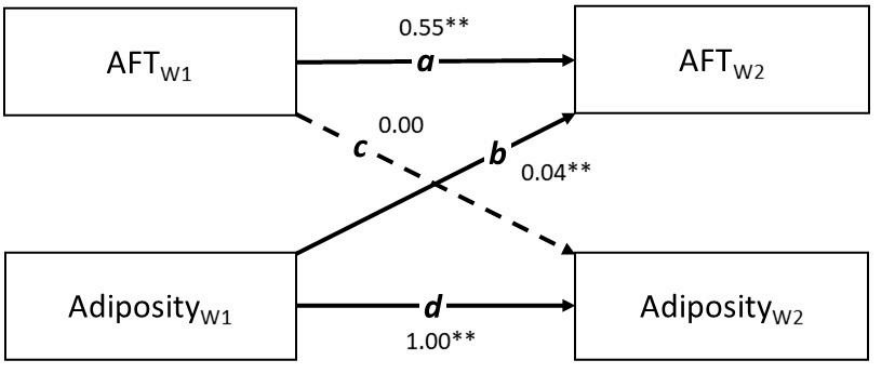


Note: Some participants possessed multiple exclusion criteria. Exclusion criteria were applied on the baseline measures.

8.2.4 Supplementary Figure B-3: Cross-lagged model estimates for latent adiposity and animal fluency.



Part a: Middle-aged adults

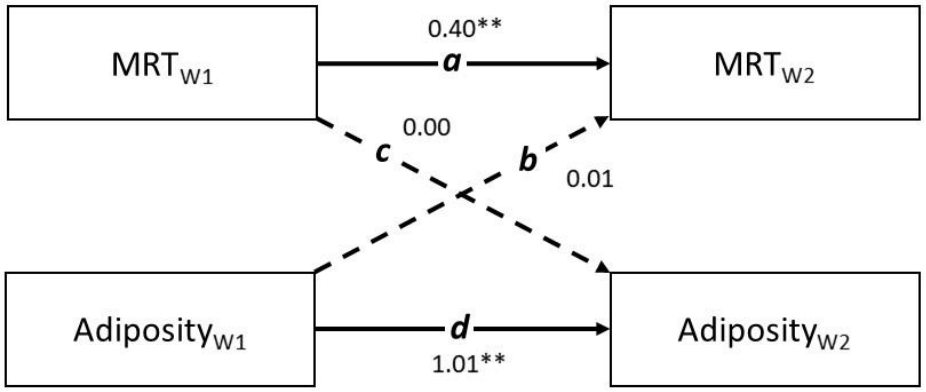


Part b: Older adults

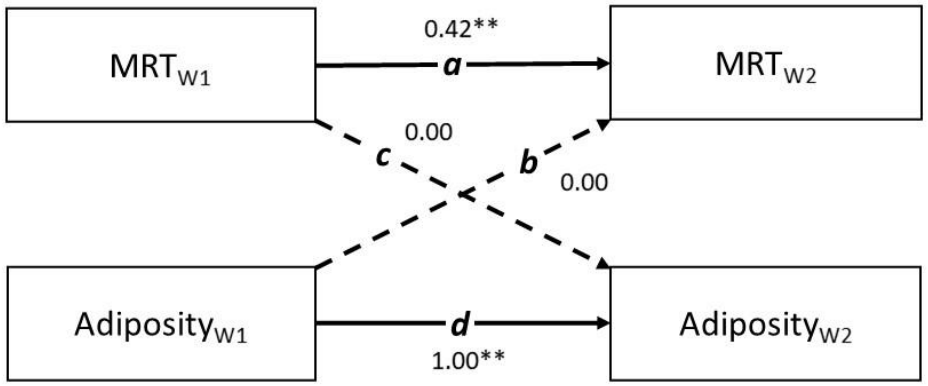
Note 1: AFT = Animal Fluency Task; Adiposity = Latent adiposity variable. W1 and W2 indicate Wave 1 (baseline) and Wave 2 (3-year follow-up) measures, respectively. Bolded arrows indicate statistically significant path coefficients; dotted arrows indicate non-significant path coefficients. BMI is power transformed by -0.7. All coefficients are standardized beta weights. *: $p < .05$. **: $p < .001$. Covariates include age, sex ethnicity, household income, education, residence, physical activity, comorbidity and sleep duration.

Note 2: Description of the cross-lagged paths: (a) Path a: the association between baseline cognition and follow-up cognition, (b) Path b: the association between baseline adiposity and follow-up cognition, (c) Path c: the association between baseline cognition and follow-up adiposity, and (d) Path d: the association between baseline adiposity and follow-up adiposity.

8.2.5 Supplementary Figure B-4: Cross-lagged model estimates for latent adiposity and mean reaction time.



Part a: Middle-aged adults



Part b: Older adults

Note 1: MRT = Mean reaction time; Adiposity = Latent adiposity variable. W1 and W2 indicate Wave 1 (baseline) and Wave 2 (3-year follow-up) measures, respectively. Bolded arrows indicate statistically significant path coefficients; dotted arrows indicate non-significant path coefficients. BMI is power transformed by -0.7. All coefficients are standardized beta weights. *: $p < .05$. **: $p < .001$. Covariates include age, sex ethnicity, household income, education, residence, physical activity, comorbidity and sleep duration.

Note 2: Description of the cross-lagged paths: (a) Path a: the association between baseline cognition and follow-up cognition, (b) Path b: the association between baseline adiposity and follow-up cognition, (c) Path c: the association between baseline cognition and follow-up adiposity, and (d) Path d: the association between baseline adiposity and follow-up adiposity.

8.2.6 Supplementary Table B-1: Comparison of baseline characteristics between those included in analytic sample versus excluded.

Variable	Included in analytic sample			
	Middle-aged adults		Older adults	
	No, N = 2,272[1]	**Yes**, N = 16,147[1]	**No**, N = 1,971[1]	**Yes**, N = 9,707[1]
Age	56.2 (5.8)	56.1 (5.6)	74.9 (5.4)	73.6 (5.4)
Sex (male)	1,079 (47%)	7,822 (48%)	1,043 (53%)	4,833 (50%)
Ethnicity	1,682 (74%)	15,812 (98%)	1,742 (88%)	9,535 (98%)
Income				
No response	135 (5.9%)	745 (4.6%)	225 (11%)	836 (8.6%)
< $20,000	187 (8.2%)	634 (3.9%)	179 (9.1%)	566 (5.8%)
$20,000 to < $50,000	437 (19%)	2,221 (14%)	681 (35%)	3,021 (31%)
$50,000 to < $100,000	704 (31%)	5,056 (31%)	626 (32%)	3,521 (36%)
$100,000 to < $150,000	441 (19%)	3,725 (23%)	161 (8.2%)	1,197 (12%)
< $150,000 or more	368 (16%)	3,766 (23%)	99 (5.0%)	566 (5.8%)
Education				
High school or less	251 (11%)	1,841 (11%)	409 (21%)	2,001 (21%)
Below bachelor	860 (38%)	6,571 (41%)	803 (41%)	3,789 (39%)
Bachelor or above	1,161 (51%)	7,735 (48%)	759 (39%)	3,917 (40%)
Residence (rural)	123 (5.4%)	1,532 (9.5%)	123 (6.2%)	646 (6.7%)
BMI	28.4 (5.9)	28.2 (5.7)	28.2 (5.4)	27.8 (4.9)
(Missing)	60	18	47	11
Waist circumference	94 (15)	93 (15)	97 (14)	95 (14)
(Missing)	62	71	57	45
Physical activity				
No response	134 (5.9%)	622 (3.9%)	151 (7.7%)	431 (4.4%)
Never	358 (16%)	1,968 (12%)	414 (21%)	1,566 (16%)
Seldom (1-2 days)	360 (16%)	2,411 (15%)	243 (12%)	1,292 (13%)
Sometimes (3-4 days)	367 (16%)	2,878 (18%)	290 (15%)	1,729 (18%)
Often (5-7 days)	1,053 (46%)	8,268 (51%)	873 (44%)	4,689 (48%)
Stroop interference	9.4 (6.0)	9.0 (5.1)	13 (8)	13 (7)
(Missing)	38	166	44	152
Mean reaction time	819 (167)	773 (152)	922 (188)	876 (174)

(Missing)	41	203	41	155
Animal fluency	19.0 (6.0)	21.3 (5.5)	16.1 (5.0)	17.7 (5.1)
(Missing)	78	329	84	241

[1] **Mean (SD); n (%)**

8.2.7 Supplementary Table B-2: Comparison of baseline characteristics between those lost to follow-up versus retained in the analytic sample.

Variable	Lost to follow-up			
	Middle-aged adults		Older adults	
	No, N = 15,259[1]	**Yes**, N = 888[1]	**No**, N = 8,768[1]	**Yes**, N = 939[1]
Age	56.1 (5.6)	56.1 (5.6)	73.4 (5.3)	75.1 (5.7)
Sex (male)	7,411 (49%)	411 (46%)	4,371 (50%)	462 (49%)
Ethnicity	14,959 (98%)	853 (96%)	8,613 (98%)	922 (98%)
Income				
No response	696 (4.6%)	49 (5.5%)	722 (8.2%)	114 (12%)
< $20,000	537 (3.5%)	97 (11%)	472 (5.4%)	94 (10%)
$20,000 to < $50,000	2,041 (13%)	180 (20%)	2,650 (30%)	371 (40%)
$50,000 to < $100,000	4,803 (31%)	253 (28%)	3,280 (37%)	241 (26%)
$100,000 to < $150,000	3,545 (23%)	180 (20%)	1,105 (13%)	92 (9.8%)
< $150,000 or more	3,637 (24%)	129 (15%)	539 (6.1%)	27 (2.9%)
Education				
High school or less	1,656 (11%)	185 (21%)	1,741 (20%)	260 (28%)
Below bachelor	6,155 (40%)	416 (47%)	3,372 (38%)	417 (44%)
Bachelor or above	7,448 (49%)	287 (32%)	3,655 (42%)	262 (28%)
Residence (rural)	1,448 (9.5%)	84 (9.5%)	583 (6.6%)	63 (6.7%)
BMI	28.1 (5.7)	28.7 (6.1)	27.8 (4.9)	28.0 (5.0)
(Missing)	14	4	9	2
Waist circumference	93 (15)	95 (15)	95 (14)	96 (14)
(Missing)	56	15	32	13
Physical activity				
No response	235 (1.5%)	387 (44%)	79 (0.9%)	352 (37%)
Never	1,899 (12%)	69 (7.8%)	1,437 (16%)	129 (14%)
Seldom (1-2 days)	2,334 (15%)	77 (8.7%)	1,212 (14%)	80 (8.5%)
Sometimes (3-4 days)	2,792 (18%)	86 (9.7%)	1,625 (19%)	104 (11%)
Often (5-7 days)	7,999 (52%)	269 (30%)	4,415 (50%)	274 (29%)
Stroop interference	8.9 (5.0)	9.7 (6.1)	13 (7)	15 (9)
(Missing)	139	27	121	31
Mean reaction time	771 (150)	801 (176)	872 (172)	913 (188)

(Missing)	178	25	123	32
Animal fluency	21.4 (5.5)	19.8 (5.6)	18.0 (5.1)	15.8 (5.1)
(Missing)	305	24	204	37

[1] **Mean (SD); n (%)**

8.2.8 Supplementary Table B-3: Pearson Product-Moment Correlations between adiposity and cognitive variables.

Measures	1	2	3	4	5	6	7	8	9	10
Baseline										
1. Animal fluency	1									
2. Stroop interference	-.259**	1								
3. Mean reaction time	-.244**	.220**	1							
4. BMI	-.027**	.040**	-0.004	1						
5. Waist circumference	-.058**	.081**	.042**	.821**	1					
Three-year										
6. Animal fluency	.646**	-.269**	-.256**	-0.009	-.043**	1				
7. Stroop interference	-.258**	.312**	.171**	.051**	.091**	-.280**	1			
8. Mean reaction time	-.235**	.230**	.505**	0.009	.045**	-.264**	.201**	1		
9. BMI	-.014*	.022**	-.018**	.940**	.769**	0.009	.037**	-0.006	1	
10. Waist circumference	-.038**	.071**	.030**	.779**	.901**	-.026**	.087**	.039**	.810**	1

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

8.2.9 Supplementary Table B-4: SEM analysis of the bidirectional association between latent adiposity and cognitive function using the analytic sample (standardized measures).

Path label	Path description	Middle-aged		Older adults	
		Estimate (95% CI)	***p* value**	**Estimate (95% CI)**	***p* value**
			Animal fluency		
a	Cog_{W1} → Cog_{W2}	**0.55 (0.54, 0.56)**	**<0.001**	**0.55 (0.53, 0.56)**	**<0.001**
b	Adi_{W1} → Cog_{W2}	0.01 (-0.01, 0.02)	0.297	**0.04 (0.02, 0.06)**	**<0.001**
c	Cog_{W1} → Adi_{W2}	0.00 (-0.01, 0.00)	0.925	0.00 (-0.01, 0.01)	0.779
d	Adi_{W1} → Adi_{W2}	**1.01 (1.00, 1.01)**	**<0.001**	**1.00 (1.00, 1.00)**	**<0.001**
			Stroop interference		
a	Cog_{W1} → Cog_{W2}	**0.18 (0.16, 0.19)**	**<0.001**	**0.19 (0.17, 0.21)**	**<0.001**
b	Adi_{W1} → Cog_{W2}	**0.04 (0.02, 0.06)**	**<0.001**	0.02 (0.00, 0.04)	0.055
c	Cog_{W1} → Adi_{W2}	**0.01 (0.00, 0.01)**	**0.036**	0.00 (-0.01, 0.01)	0.701
d	Adi_{W1} → Adi_{W2}	**1.01 (1.00, 1.01)**	**<0.001**	**1.00 (1.00, 1.00)**	**<0.001**
			Mean reaction time		
a	Cog_{W1} → Cog_{W2}	**0.40 (0.38, 0.41)**	**<0.001**	**0.42 (0.41, 0.44)**	**<0.001**
b	Adi_{W1} → Cog_{W2}	0.01 (-0.01, 0.02)	0.282	0.00 (-0.02, 0.02)	0.815
c	Cog_{W1} → Adi_{W2}	0.00 (0.00, 0.01)	0.335	0.00 (-0.01, 0.00)	0.363
d	Adi_{W1} → Adi_{W2}	**1.01 (1.00, 1.01)**	**<0.001**	**1.00 (1.00, 1.00)**	**<0.001**

Note 1: Cog_{W1} and Cog_{W2} indicate cognition at baseline and follow-up, respectively. Adi_{W1} and Adi_{W2} indicate latent adiposity variable at baseline and follow-up, respectively. Higher Stroop scores = worse executive function. Higher AFT scores = better semantic fluency. Higher MRT scores = worse processing speed. All estimates are standardized coefficients. Model fit statistic (RMSEA) for the cross-lagged panel models were 0.15.

Note 2: Description of the cross-lagged paths: (a) Path a: the association between baseline cognition and follow-up cognition, (b) Path b: the association between baseline adiposity and follow-up cognition, (c) Path c: the association between baseline cognition and follow-up adiposity, and (d) Path d: the association between baseline adiposity and follow-up adiposity.

8.2.10 Supplementary Table B-5: SEM analysis of the bidirectional association between latent adiposity and cognitive function using the analytic sample (unstandardized measures).

Path label	Path description	Middle-aged		Older adults	
		Estimate (95% CI)	*p* value	Estimate (95% CI)	*p* value
			Animal fluency		
a	Cog_{W1} → Cog_{W2}	**0.51 (0.50, 0.53)**	**<0.001**	**0.52 (0.50, 0.53)**	**<0.001**
b	Adi_{W1} → Cog_{W2}	0.00 (0.00, 0.01)	0.297	**0.02 (0.01, 0.02)**	**<0.001**
c	Cog_{W1} → Adi_{W2}	0.00 (-0.01, 0.01)	0.925	0.00 (-0.02, 0.01)	0.779
d	Adi_{W1} → Adi_{W2}	**1.01 (1.01, 1.02)**	**<0.001**	**1.01 (1.01, 1.02)**	**<0.001**
			Stroop interference		
a	Cog_{W1} → Cog_{W2}	**0.08 (0.07, 0.09)**	**<0.001**	**0.09 (0.08, 0.10)**	**<0.001**
b	Adi_{W1} → Cog_{W2}	**0.01 (0.00, 0.01)**	**<0.001**	0.01 (0.00, 0.01)	0.055
c	Cog_{W1} → Adi_{W2}	**0.01 (0.00, 0.03)**	**0.036**	0.00 (-0.01, 0.01)	0.701
d	Adi_{W1} → Adi_{W2}	**1.01 (1.01, 1.02)**	**<0.001**	**1.02 (1.01, 1.03)**	**<0.001**
			Mean reaction time		
a	Cog_{W1} → Cog_{W2}	**0.42 (0.41, 0.44)**	**<0.001**	**0.49 (0.47, 0.51)**	**<0.001**
b	Adi_{W1} → Cog_{W2}	0.00 (0.00, 0.01)	0.282	0.00 (-0.01, 0.01)	0.815
c	Cog_{W1} → Adi_{W2}	0.01 (-0.01, 0.03)	0.335	-0.01 (-0.03, 0.01)	0.363
d	Adi_{W1} → Adi_{W2}	**1.01 (1.01, 1.02)**	**<0.001**	**1.02 (1.01, 1.03)**	**<0.001**

Note 1: Cog_{W1} and Cog_{W2} indicate cognition at baseline and follow-up, respectively. Adi_{W1} and Adi_{W2} indicate latent adiposity variable at baseline and follow-up, respectively. Higher Stroop scores = worse executive function. Higher AFT scores = better semantic fluency. Higher MRT scores = worse processing speed. All estimates are unstandardized coefficients. Model fit statistic (RMSEA) for the cross-lagged panel models were 0.15.

Note 2: Description of the cross-lagged paths: (a) Path a: the association between baseline cognition and follow-up cognition, (b) Path b: the association between baseline adiposity and follow-up cognition, (c) Path c: the association between baseline cognition and follow-up adiposity, and (d) Path d: the association between baseline adiposity and follow-up adiposity.

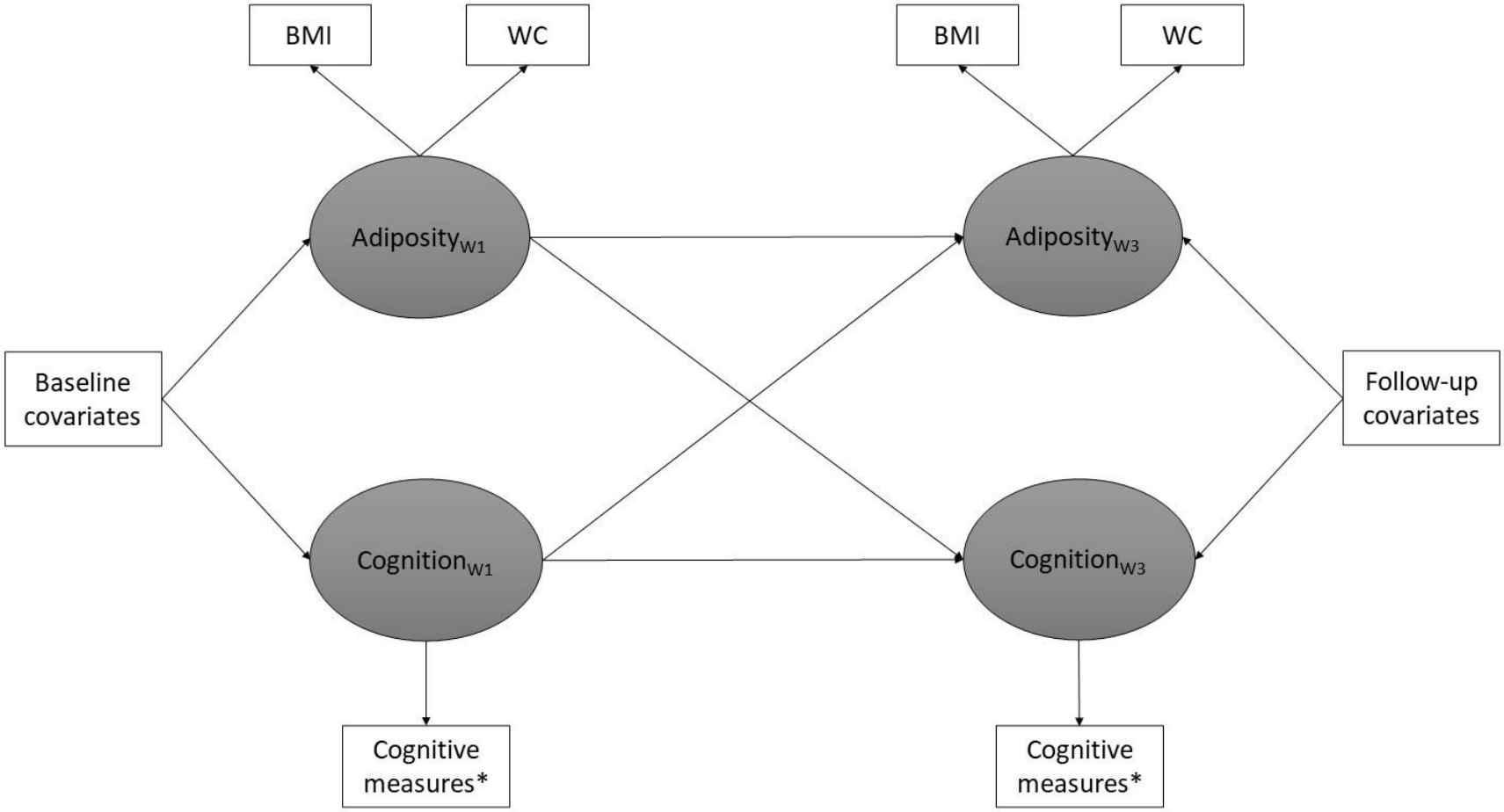
8.2.11 Supplementary Table B-6: Tests between two independent groups (middle-aged vs. older adults).

Path label	Path	z-score	*p* value
		Animal fluency	
b	Adi_{W1} → Cog_{W2}	**2.93**	**0.003**
c	Cog_{W1} → Adi_{W2}	-0.17	0.863
		Stroop interference	
b	Adi_{W1} → Cog_{W2}	-1.59	0.111
c	Cog_{W1} → Adi_{W2}	-1.55	0.122
		Mean reaction time	
b	Adi_{W1} → Cog_{W2}	-0.85	0.394
c	Cog_{W1} → Adi_{W2}	1.31	0.192

Note: Cog_{W1} and Cog_{W1} indicate cognition at baseline and follow-up, respectively. Adi_{W1} and Adi_{W2} indicate latent adiposity variable at baseline and follow-up, respectively.

8.3 Appendix C: Supplementary materials for Manuscript 3 (Chapter 5)

8.3.1 Supplementary Figure C-1: Conceptual diagram of the bidirectional associations between adiposity and cognitive function.



Note: WC = Waist Circumference, BMI = Body Mass Index, W1 = Wave 1 or baseline measures, W3 = Wave 3 or follow-up measures. *A separate cognitive measure was used in each model and included the following NIH Toolbox tasks: Flanker task, pattern matching, picture sequence, picture vocabulary and reading tasks. The covariates considered for the bidirectional associations were age, sex, ethnicity, family income, parent education, area deprivation index, pubertal status and sleep duration.

8.3.2 Supplementary Table C-1: Pearson Product-Moment Correlations among cognitive variables.

Measures	1	2	3	4	5	6	7	8	9	10
Baseline										
1. Flanker$_{W1}$	1.00									
2. Pattern$_{W1}$	0.32	1.00								
3. PicSeq$_{W1}$	0.17	0.14	1.00							
4. PicVocab$_{W1}$	0.17	0.09	0.16	1.00						
5. Reading$_{W1}$	0.18	0.12	0.16	0.41	1.00					
Follow-up										
6. Flanker$_{W3}$	0.38	0.19	0.12	0.16	0.18	1.00				
7. Pattern$_{W3}$	0.22	0.45	0.16	0.10	0.13	0.36	1.00			
8. PicSeq$_{W3}$	0.13	0.13	0.40	0.13	0.12	0.13	0.18	1.00		
9. PicVocab$_{W3}$	0.14	0.09	0.14	0.58	0.41	0.20	0.11	0.18	1.00	
10. Reading$_{W3}$	0.13	0.08	0.12	0.39	0.65	0.18	0.14	0.15	0.49	1.00

8.3.3 Supplementary Table C-2: Pearson Product-Moment Correlations among adiposity variables.

Measures	1	2	3	4
1. $zBMI_{W1}$	1.00			
2. WC_{W1}	0.85	1.00		
3. $zBMI_{W3}$	0.87	0.78	1.00	
4. WC_{W3}	0.79	0.79	0.86	1.00

8.3.4 Supplementary Table C-3: Mediation analysis for path b (Adiposity → Mediator → Cognition).

Mediators	Indirect effect (95% CI)	*p*	Indirect effect (95% CI)	*p*
	zBMI$_{W1}$ → Mediator → Flanker$_{W3}$		**WC$_{W1}$ → Mediator → Flanker$_{W3}$**	
Blood pressure				
Total	0.0305 (-0.0062, 0.0672)	0.103	0.0182 (-0.0031, 0.0396)	0.095
Systolic	0.0370 (-0.0045, 0.0785)	0.081	0.0226 (-0.0020, 0.0473)	0.072
Diastolic	-0.0065 (-0.0470, 0.0341)	0.755	-0.0044 (-0.0273, 0.0185)	0.705
LPFC volume				
Total	-0.0064 (-0.0132, 0.0004)	0.066	-0.0049 (-0.0093, -0.0005)	0.029
Lateral OFC	-0.0017 (-0.0048, 0.0014)	0.271	-0.0016 (-0.0042, 0.0010)	0.227
MFG	-0.0036 (-0.0112, 0.0039)	0.346	-0.0026 (-0.0077, 0.0026)	0.328
IFG	-0.0010 (-0.0050, 0.0030)	0.625	-0.0007 (-0.0037, 0.0023)	0.632
LPFC thickness				
Total	0.0017 (-0.0130, 0.0165)	0.817	0.0006 (-0.0046, 0.0058)	0.815
Lateral OFC	-0.0026 (-0.0203, 0.0152)	0.776	-0.0010 (-0.0074, 0.0054)	0.757
MFG	0.0018 (-0.0140, 0.0176)	0.823	0.0004 (-0.0046, 0.0054)	0.873
IFG	0.0025 (-0.0116, 0.0166)	0.726	0.0012 (-0.0048, 0.0072)	0.694
	zBMI$_{W1}$ → Mediator → Pattern$_{W3}$		**WC$_{W1}$ → Mediator → Pattern$_{W3}$**	
Blood pressure				
Total	-0.0109 (-0.0620, 0.0402)	0.677	-0.0044 (-0.0342, 0.0255)	0.774
Systolic	0.0553 (-0.0023, 0.1129)	0.060	0.0332 (-0.0012, 0.0676)	0.058
Diastolic	-0.0662 (-0.1229, -0.0094)	0.022	-0.0376 (-0.0697, -0.0055)	0.022
LPFC volume				
Total	0.0077 (-0.0013, 0.0166)	0.094	0.0051 (-0.0007, 0.0110)	0.086
Lateral OFC	-0.0006 (-0.0042, 0.0030)	0.745	-0.0006 (-0.0039, 0.0028)	0.748
MFG	0.0075 (-0.0032, 0.0181)	0.170	0.0051 (-0.0022, 0.0123)	0.169
IFG	0.0008 (-0.0047, 0.0063)	0.776	0.0006 (-0.0035, 0.0048)	0.763
LPFC thickness				
Total	0.0200 (-0.0021 0.0420)	0.076	0.0045 (-0.0042, 0.0131)	0.310
Lateral OFC	-0.0005 (-0.0253, 0.0243)	0.971	-0.0004 (-0.0093, 0.0085)	0.921
MFG	**0.0373 (0.0143, 0.0602)**	**0.001**	**0.0117 (0.0036, 0.0199)**	**0.005**
IFG	-0.0168 (-0.0370, 0.0034)	0.102	-0.0068 (-0.0156, 0.0020)	0.130

	$zBMI_{W1}$ → Mediator → $PicSeq_{W3}$		WC_{W1} → Mediator → $PicSeq_{W3}$	
Blood pressure				
Total	-0.0339 (-0.0743, 0.0065)	0.100	-0.0170 (-0.0405, 0.0064)	0.155
Systolic	0.0088 (-0.0364, 0.0541)	0.702	0.0064 (-0.0205, 0.0333)	0.642
Diastolic	-0.0428 (-0.0876, 0.0021)	0.062	-0.0234 (-0.0487, 0.0019)	0.070
LPFC volume				
Total	0.0004 (-0.0070, 0.0078)	0.915	0.0000 (-0.0048, 0.0049)	0.993
Lateral OFC	-0.0009 (-0.0040, 0.0022)	0.575	-0.0009 (-0.0037, 0.0020)	0.555
MFG	0.0019 (-0.0069, 0.0107)	0.669	0.0013 (-0.0046, 0.0073)	0.659
IFG	-0.0006 (-0.0053, 0.0041)	0.793	-0.0005 (-0.0040, 0.0031)	0.796
LPFC thickness				
Total	-0.0046 (-0.0224, 0.0132)	0.615	-0.0011 (-0.0075, 0.0053)	0.735
Lateral OFC	0.0129 (-0.0089, 0.0346)	0.246	0.0053 (-0.0026, 0.0132)	0.186
MFG	-0.0125 (-0.0326, 0.0075)	0.221	-0.0037 (-0.0102, 0.0029)	0.270
IFG	-0.0049 (-0.0230, 0.0131)	0.593	-0.0027 (-0.0105, 0.0051)	0.492
	$zBMI_{W1}$ → Mediator → $PicVocab_{W3}$		WC_{W1} → Mediator → $PicVocab_{W3}$	
Blood pressure				
Total	-0.0106 (-0.0424, 0.0213)	0.515	-0.0094 (-0.0279, 0.0091)	0.319
Systolic	-0.0081 (-0.0441, 0.0279)	0.659	-0.0075 (-0.0289, 0.0139)	0.490
Diastolic	-0.0025 (-0.0379, 0.0329)	0.891	-0.0019 (-0.0218, 0.0181)	0.854
LPFC volume				
Total	-0.0127 (-0.0204, -0.0050)	0.001	-0.0096 (-0.0144, -0.0049)	0.000
Lateral OFC	-0.0027 (-0.0063, 0.0008)	0.129	-0.0026 (-0.0053, 0.0001)	0.059
MFG	-0.0068 (-0.0139, 0.0004)	0.063	-0.0047 (-0.0095, 0.0001)	0.057
IFG	-0.0032 (-0.0073, 0.0010)	0.136	-0.0024 (-0.0053, 0.0006)	0.117
LPFC thickness				
Total	0.0096 (-0.0047, 0.0239)	0.189	0.0054 (-0.0003, 0.0111)	0.062
Lateral OFC	0.0137 (-0.0024, 0.0298)	0.096	0.0050 (-0.0008, 0.0109)	0.091
MFG	**-0.0183 (-0.0331, -0.0035)**	**0.015**	**-0.0061 (-0.0113, -0.0009)**	**0.021**
IFG	**0.0142 (0.0012, 0.0272)**	**0.033**	**0.0065 (0.0007, 0.0123)**	**0.029**
	$zBMI_{W1}$ → Mediator → $Reading_{W3}$		WC_{W1} → Mediator → $Reading_{W3}$	
Blood pressure				
Total	-0.0185 (-0.0504, 0.0133)	0.253	-0.0135 (-0.0319, 0.0050)	0.153

Systolic	**-0.0408 (-0.0768, -0.0048)**	**0.026**	**-0.0256 (-0.0470, -0.0042)**	**0.019**
Diastolic	0.0223 (-0.0130, 0.0575)	0.215	0.0121 (-0.0077, 0.0320)	0.231
LPFC volume				
Total	**-0.0109 (-0.0179, -0.0040)**	**0.002**	**-0.0082 (-0.0126, -0.0038)**	**<0.001**
Lateral OFC	-0.0020 (-0.0049, 0.0010)	0.196	-0.0018 (-0.0043, 0.0006)	0.131
MFG	**-0.0073 (-0.0143, -0.0003)**	**0.041**	**-0.0051 (-0.0099, -0.0004)**	**0.034**
IFG	-0.0016 (-0.0053, 0.0020)	0.374	-0.0013 (-0.0040, 0.0015)	0.364
LPFC thickness				
Total	-0.0052 (-0.0186, 0.0082)	0.450	-0.0024 (-0.0071, 0.0023)	0.317
Lateral OFC	-0.0029 (-0.0193, 0.0134)	0.726	-0.0012 (-0.0071, 0.0046)	0.677
MFG	0.0017 (-0.0130, 0.0165)	0.818	0.0006 (-0.0042, 0.0053)	0.816
IFG	-0.0040 (-0.0172, 0.0093)	0.556	-0.0017 (-0.0074, 0.0040)	0.555

Note: LPFC = lateral prefrontal cortex; LOFC = lateral orbitofrontal cortex; MFG = middle frontal gyrus; IFG = inferior frontal gyrus. Path b: the association between baseline adiposity and follow-up cognition. Four decimal places were retained because of smaller values of the indirect effects and to clarify the direction of coefficient and CI. Total indicates the sum of individual indirect effects for the respective mediators. All estimates are unstandardized coefficients. Significant indirect effects indicate that the association between adiposity and cognition is, in part, mediated through that respective variable.

8.3.5 Supplementary Table C-4: Mediation analysis for path c (Cognition → Mediator → Adiposity).

Mediators	Indirect effect (95% CI)	*p*	Indirect effect (95% CI)	*p*
	Flanker$_{W1}$ → Mediator → zBMI$_{W3}$		**Flanker$_{W1}$ → Mediator → WC$_{W3}$**	
Physical activity	0.0000 (-0.0004, 0.0004)	0.902	-0.0001 (-0.0008, 0.0007)	0.860
Diet				
Total	0.0001 (-0.0001, 0.0003)	0.175	0.0005 (0.0000, 0.0009)	0.043
Whole grains	0.0000 (0.0000, 0.0000)	0.765	0.0000 (-0.0001, 0.0001)	0.659
Green, leafy vegetables	0.0000 (0.0000, 0.0001)	0.399	0.0002 (-0.0001, 0.0004)	0.142
Other vegetables	0.0000 (-0.0001, 0.0001)	0.675	0.0000 (-0.0002, 0.0002)	0.851
Berries	0.0000 (0.0000, 0.0001)	0.335	0.0000 (-0.0001, 0.0001)	0.758
Beans	0.0000 (-0.0001, 0.0001)	0.473	0.0002 (-0.0001, 0.0004)	0.149
Nuts	0.0000 (-0.0001, 0.0000)	0.449	0.0000 (-0.0002, 0.0001)	0.461
Fast/fried food	0.0001 (0.0000, 0.0002)	0.145	0.0002 (-0.0001, 0.0005)	0.128
Pastries or sweets	0.0000 (-0.0001, 0.0000)	0.402	0.0000 (-0.0001, 0.0001)	0.569
LPFC volume				
Total	0.0000 (-0.0001, 0.0001)	0.693	0.0000 (-0.0002, 0.0001)	0.661
Lateral OFC	0.0000 (-0.0001, 0.0000)	0.703	0.0000 (-0.0001, 0.0001)	0.731
MFG	0.0000 (0.0000, 0.0000)	0.987	0.0000 (-0.0001, 0.0001)	0.985
IFG	0.0000 (0.0000, 0.0000)	0.819	0.0000 (-0.0001, 0.0001)	0.802
LPFC thickness				
Total	0.0000 (-0.0001, 0.0001)	0.909	-0.0002 (-0.0006, 0.0002)	0.390
Lateral OFC	0.0000 (0.0000, 0.0001)	0.374	0.0000 (-0.0001, 0.0002)	0.690
MFG	0.0000 (-0.0001, 0.0001)	0.533	-0.0002 (-0.0005, 0.0002)	0.269
IFG	0.0000 (-0.0001, 0.0001)	0.863	0.0000 (-0.0001, 0.0001)	0.825
	Pattern$_{W1}$ → Mediator → zBMI$_{W3}$		**Pattern$_{W1}$ → Mediator → WC$_{W3}$**	
Physical activity	0.0000 (-0.0003, 0.0003)	0.989	0.0000 (-0.0005, 0.0005)	0.928
Diet				
Total	0.0000 (-0.0002, 0.0001)	0.413	0.0000 (-0.0003, 0.0003)	0.902
Whole grains	0.0000 (0.0000, 0.0000)	0.752	0.0000 (0.0000, 0.0001)	0.599
Green, leafy vegetables	0.0000 (0.0000, 0.0001)	0.401	0.0001 (0.0000, 0.0003)	0.129
Other vegetables	0.0000 (0.0000, 0.0000)	0.712	0.0000 (-0.0001, 0.0001)	0.809
Berries	0.0000 (0.0000, 0.0000)	0.856	0.0000 (0.0000, 0.0000)	0.887

Beans	0.0000 (0.0000, 0.0000)	0.796	0.0000 (-0.0001, 0.0001)	0.786
Nuts	0.0000 (0.0000, 0.0000)	0.757	0.0000 (-0.0001, 0.0001)	0.755
Fast/fried food	0.0000 (-0.0001, 0.0000)	0.198	-0.0001 (-0.0003, 0.0000)	0.180
Pastries or sweets	0.0000 (-0.0001, 0.0000)	0.170	0.0000 (-0.0001, 0.0001)	0.464
LPFC volume				
Total	0.0000 (-0.0001, 0.0001)	0.740	0.0000 (-0.0002, 0.0002)	0.974
Lateral OFC	0.0000 (0.0000, 0.0000)	0.534	0.0000 (-0.0001, 0.0001)	0.555
MFG	0.0000 (0.0000, 0.0001)	0.268	0.0001 (-0.0001, 0.0002)	0.421
IFG	0.0000 (-0.0001, 0.0000)	0.479	0.0000 (-0.0002, 0.0001)	0.402
LPFC thickness				
Total	0.0000 (-0.0001, 0.0002)	0.561	**0.0004 (0.0001, 0.0006)**	**0.011**
Lateral OFC	0.0001 (0.0000, 0.0002)	0.196	0.0001 (-0.0001, 0.0003)	0.262
MFG	0.0001 (0.0000, 0.0002)	0.280	0.0002 (-0.0001, 0.0005)	0.117
IFG	-0.0001 (-0.0002, 0.0000)	0.196	0.0000 (-0.0002, 0.0002)	0.733
	$PicSeq_{W1}$ → Mediator → $zBMI_{W3}$		**$PicSeq_{W1}$ → Mediator → WC_{W3}**	
Physical activity	0.0000 (-0.0003, 0.0003)	0.893	-0.0002 (-0.0008, 0.0004)	0.621
Diet				
Total	0.0000 (-0.0002, 0.0001)	0.787	0.0001 (-0.0002, 0.0005)	0.482
Whole grains	0.0000 (0.0000, 0.0000)	0.918	0.0000 (0.0000, 0.0000)	0.947
Green, leafy vegetables	0.0000 (0.0000, 0.0001)	0.372	0.0001 (-0.0001, 0.0003)	0.156
Other vegetables	0.0000 (0.0000, 0.0000)	0.743	0.0000 (-0.0001, 0.0001)	0.794
Berries	0.0000 (0.0000, 0.0000)	0.769	0.0000 (0.0000, 0.0000)	0.842
Beans	0.0000 (0.0000, 0.0001)	0.509	0.0001 (-0.0001, 0.0003)	0.214
Nuts	0.0000 (-0.0001, 0.0000)	0.490	0.0000 (-0.0001, 0.0001)	0.498
Fast/fried food	0.0000 (-0.0001, 0.0000)	0.490	-0.0001 (-0.0003, 0.0001)	0.450
Pastries or sweets	0.0000 (-0.0001, 0.0000)	0.391	0.0000 (-0.0001, 0.0001)	0.558
LPFC volume				
Total	0.0000 (-0.0001, 0.0000)	0.396	-0.0001 (-0.0003, 0.0001)	0.327
Lateral OFC	0.0000 (-0.0001, 0.0000)	0.483	0.0000 (-0.0002, 0.0001)	0.508
MFG	0.0000 (0.0000, 0.0000)	0.883	0.0000 (-0.0001, 0.0001)	0.821
IFG	0.0000 (-0.0001, 0.0000)	0.565	0.0000 (-0.0002, 0.0001)	0.531
LPFC thickness				
Total	0.0000 (-0.0001, 0.0002)	0.589	0.0004 (0.0001, 0.0008)	0.023

Lateral OFC	0.0001 (0.0000, 0.0002)	0.206	0.0002 (-0.0001, 0.0004)	0.248
MFG	0.0000 (0.0000, 0.0001)	0.340	0.0002 (-0.0001, 0.0005)	0.168
IFG	-0.0001 (-0.0002, 0.0001)	0.225	0.0001 (-0.0003, 0.0004)	0.744
	PicVocab$_{W1}$ → Mediator → zBMI$_{W3}$		**PicVocab$_{W1}$ → Mediator → WC$_{W3}$**	
Physical activity	**-0.0011 (-0.0015, -0.0007)**	**<0.001**	**-0.0020 (-0.002, -0.0012)**	**<0.001**
Diet				
Total	0.0000 (-0.0002, 0.0001)	0.716	-0.0001 (-0.0005, 0.0003)	0.591
Whole grains	0.0000 (-0.0001, 0.0000)	0.799	0.0000 (-0.0002, 0.0001)	0.537
Green, leafy vegetables	0.0000 (0.0000, 0.0001)	0.442	0.0001 (-0.0001, 0.0003)	0.242
Other vegetables	0.0000 (0.0000, 0.0000)	0.761	0.0000 (0.0000, 0.0000)	0.804
Berries	0.0000 (0.0000, 0.0001)	0.505	0.0000 (0.0000, 0.0001)	0.782
Beans	0.0000 (0.0000, 0.0000)	0.655	0.0000 (-0.0001, 0.0001)	0.595
Nuts	0.0000 (0.0000, 0.0001)	0.544	0.0000 (-0.0001, 0.0001)	0.539
Fast/fried food	-0.0001 (-0.0002, 0.0000)	0.079	-0.0002 (-0.0005, 0.0000)	0.051
Pastries or sweets	0.0000 (0.0000, 0.0001)	0.619	0.0000 (0.0000, 0.0001)	0.664
LPFC volume				
Total	-0.0001 (-0.0002, 0.0000)	0.171	-0.0001 (-0.0004, 0.0001)	0.311
Lateral OFC	-0.0001 (-0.0002, 0.0001)	0.389	-0.0001 (-0.0005, 0.0002)	0.419
MFG	0.0000 (-0.0001, 0.0000)	0.309	-0.0001 (-0.0003, 0.0001)	0.445
IFG	0.0000 (0.0000, 0.0001)	0.468	0.0001 (-0.0001, 0.0002)	0.382
LPFC thickness				
Total	0.0000 (-0.0001, 0.0001)	0.736	-0.0001 (-0.0005, 0.0002)	0.445
Lateral OFC	0.0000 (-0.0001, 0.0001)	0.919	0.0000 (-0.0001, 0.0002)	0.714
MFG	0.0000 (-0.0001, 0.0000)	0.362	-0.0001 (-0.0004, 0.0002)	0.341
IFG	0.0000 (-0.0001, 0.0001)	0.563	0.0000 (-0.0002, 0.0001)	0.854
	Reading$_{W1}$ → Mediator → zBMI$_{W3}$		**Reading$_{W1}$ → Mediator → WC$_{W3}$**	
Physical activity	**-0.0007 (-0.0010, -0.0003)**	**<0.001**	**-0.0013 (-0.0020, -0.0007)**	**<0.001**
Diet				
Total	0.0000 (-0.0001, 0.0002)	0.798	0.0001 (-0.0002, 0.0005)	0.448
Whole grains	0.0000 (-0.0001, 0.0001)	0.788	-0.0001 (-0.0002, 0.0001)	0.536
Green, leafy vegetables	0.0000 (0.0000, 0.0001)	0.369	0.0002 (0.0000, 0.0004)	0.088
Other vegetables	0.0000 (0.0000, 0.0000)	0.806	0.0000 (0.0000, 0.0000)	0.814
Berries	0.0000 (0.0000, 0.0001)	0.298	0.0000 (-0.0001, 0.0001)	0.734

Beans	0.0000 (0.0000, 0.0001)	0.475	0.0001 (0.0000, 0.0003)	0.148
Nuts	0.0000 (-0.0001, 0.0000)	0.309	-0.0001 (-0.0002, 0.0001)	0.330
Fast/fried food	0.0000 (-0.0001, 0.0000)	0.372	-0.0001 (-0.0003, 0.0001)	0.328
Pastries or sweets	0.0000 (-0.0001, 0.0000)	0.784	0.0000 (-0.0001, 0.0000)	0.807
LPFC volume				
Total	-0.0001 (-0.0001, 0.0000)	0.201	-0.0001 (-0.0003, 0.0001)	0.478
Lateral OFC	0.0000 (-0.0001, 0.0001)	0.404	-0.0001 (-0.0003, 0.0001)	0.455
MFG	0.0000 (-0.0001, 0.0000)	0.329	-0.0001 (-0.0002, 0.0001)	0.489
IFG	0.0000 (0.0000, 0.0001)	0.436	0.0001 (-0.0001, 0.0002)	0.344
LPFC thickness				
Total	0.0000 (-0.0001, 0.0001)	0.974	0.0000 (-0.0003, 0.0003)	0.996
Lateral OFC	0.0000 (0.0000, 0.0001)	0.428	0.0001 (-0.0001, 0.0003)	0.345
MFG	0.0000 (-0.0001, 0.0000)	0.545	-0.0001 (-0.0003, 0.0002)	0.568
IFG	0.0000 (-0.0001, 0.0001)	0.845	0.0000 (-0.0001, 0.0001)	0.853

Note: LPFC = lateral prefrontal cortex; LOFC = lateral orbitofrontal cortex; MFG = middle frontal gyrus; IFG = inferior frontal gyrus. Path c: the association between baseline cognition and follow-up adiposity. Four decimal places were retained because of smaller values of the indirect effects and to clarify the direction of coefficient and CI. Total indicates the sum of individual indirect effects for the respective mediators. All estimates are unstandardized coefficients. Significant indirect effects indicate that the association between adiposity and cognition is, in part, mediated through that respective variable.