

**The Interplay Between Metabolic Health, Brain Structure, and Cognition in Severe Mental
Illness**

by

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Dalhousie University is located in Mi'kma'ki, the
ancestral and unceded territory of the Mi'kmaq.
We are all Treaty people.

DEDICATION PAGE

I dedicate this work to my identical twin sister Lena, who is quite literally my second half.

And to Anaïs, whose light continues to shine on us every day.

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ABSTRACT

Across three studies, this thesis explores associations between metabolic dysfunction, brain structural, and cognitive alterations in severe mental illnesses (SMI). In a meta-analysis, diabetes emerged as the strongest predictor of brain structural alterations as captured by a machine-learning predicted brain age, highlighting it as a key biological target for intervention. In a sample of first-episode psychosis patients, central obesity was the strongest predictor of brain age, which partially mediated cognitive deficits. In a heterogeneous BD sample, the metabolic syndrome cluster accounted for the most variance in metabolic health, which mediated both structural and cognitive outcomes. These findings suggest that diabetes may pose the greatest biological risk, while obesity, given its early onset and high prevalence, may be the most practical public health target aimed at preventing structural and cognitive alterations in SMI. Longitudinal studies are needed to establish causality and evaluate the therapeutic potential of metabolic interventions in SMI.

STATEMENT

This thesis summarizes research I carried out during my master's studies at Dalhousie University Department of Medical Neuroscience from September 2023 – June 2025, under the supervision of Dr. Tomas Hajek.

I tested my hypotheses using data from: (1) the Early-Stage Schizophrenia Outcome (ESO) project, at the National Institute of Mental Health, Czech Republic and (2): patients followed up at a specialized Mood Disorders Program at Dalhousie University, Halifax, NS, a prospective clinical and research program for people receiving treatment for bipolar disorders, which was initiated by Dr. Tomas Hajek in 2005. The procedures described for both cohorts were approved by their respective ethics research boards.

I have collaborated on a number of manuscripts based on the data and conclusions presented here. For the first manuscript, I conceptualized the research project together with Dr. Hajek and designed the research approach, conducted the statistical analysis, wrote the first draft of the paper, and revised the paper based on my co-authors' comments. For the second manuscript, I assisted in conceptualization of the project, interpretation of statistical results, wrote the abstract, introduction, and parts of the discussion of the first draft, and revised the second draft based on my co-authors' comments.

LIST OF ABBREVIATIONS USED

ABC@UofSC Aging Brain Cohort at the University of South Carolina

ACME	Average causal mediated effects
ADE	Average direct effects
Afib	Atrial fibrillation
AHI	Apnea-hypopnea index
ARIC	Atherosclerosis Risk in Communities
BASE-II	Berlin Aging Study II
BD	Bipolar Disorders
BMI	Body Mass Index
BPHRS	Boston Puerto Rican Health Study
BrainAGE	Brain Age Gap Estimate
CAD	Coronary artery disease
CI	Confidence Interval
CMA	Comprehensive Meta-Analysis Software
CNN	Deep Convolutional Neural Network
CRF	Cardiometabolic Risk Factor
CVLT-II	California Verbal Learning Test, Version II
D	Diabetes
DHS-2	Dallas Heart Study 2nd wave
DM	Diabetes Mellitus
EEG	Electroencephalogram
FEP	First Episode of Psychosis
GCN	Graph Convolutional Networks
GDP	Gross Domestic Product
GM	Gray matter
HAM-D	Hamilton Depression Scale
HbA1c	Glycated hemoglobin A1C

HbA1c	Glycosylated hemoglobin
HCP	Human Connectome Project
HDL	High-density lipoprotein
HOMA-IR	Homeostatic model assessment of insulin resistance
Hs-CRP	High sensitivity C-Reactive protein
HTN	Hypertension
ICV	Intracranial volume
IQR	Interquartile Range
JPSC-AD	Japan Prospective Studies Collaboration for Aging and Dementia
LDL	Low-density lipoprotein
MAE	Mean Absolute Error
MAPE	Mean Absolute Percent Error
MCI	Mild cognitive impairment
MetSy	Metabolic Syndrome
MRI	Magnetic Resonance Imaging
MRI-GENIE	MRI-GENetics Interface Exploration
NOS	The Newcastle-Ottawa Scale
OLS	Ordinary Least Squares
PCA	Principal Component Analysis
PI	Proactive Interference
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RI	Retroactive Interference
RMSE	Root Mean Squared Error
RVR	Relevance Vector Regression
SADS-L	Schedule for Affective Disorders and Schizophrenia, Lifetime version
SAFE	Syncopal and Falls in the Elderly
SHIP	Study of Health in Pomerania
SMI	Severe Mental Illness
SVR	Support Vector Regression

T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TGC	Triglycerides
UK	United Kingdom
UKBB	UK BioBank
VIF	Variance inflation factor
WHR	Waist-to-Hip Ratio
WM	White matter
YMRS	Young Mania Ratings Scale

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I would additionally like to thank all past and present members of the Hajek BD lab. Their contributions to data collection, statistical analyses, and manuscript revisions have enhanced the rigor, clarity, and impact of my work. I am especially thankful for their mentorship, collaboration, and support throughout this journey.

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CHAPTER 1 INTRODUCTION

“*Anima sana in corpore sano*”, a healthy mind in a healthy body¹. This phrase dates back to early 2nd century Rome, reflecting a long-standing recognition of the interconnectedness between mental and physical health. However, in modern medicine, these domains have often been treated as separate entities, with mental illnesses studied in psychiatry and physical illnesses in other medical specialties. This divide is now narrowing as growing evidence has emerged linking mental and physical health through shared genetic, biological, and environmental factors. This understanding has begun to reshape clinical practice, encouraging a more integrated approach to treatment where both mental and physical health are addressed simultaneously. By recognizing their interplay, physicians and mental health specialists can develop more effective interventions that improve overall patient outcomes. This thesis builds on this growing understanding by examining the role of metabolic health in brain structure and cognition among individuals with severe mental illnesses (SMIs) with the goal of identifying potential strategies to improve clinical outcomes.

1.1 THE BURDEN OF SEVERE MENTAL ILLNESS

People suffering from a severe mental illness (SMI) are affected by psychiatric conditions, such as schizophrenia and bipolar disorders (BD), that are so debilitating that their ability to engage in daily functional, social, and occupational activities is severely impaired². Schizophrenia is primarily characterized by psychotic symptoms such as hallucinations, delusions, and disordered thinking³, while BD is characterized by recurrent mood episodes, with periods of extreme highs (manic episodes) and lows (depressive episodes) that can persist for weeks or even months⁴. Both disorders typically emerge in the late teens to early thirties^{3,5}, during a critical period for neurological and psychosocial development as individuals transition into adulthood, establish independence, and navigate key milestones in education, career development, and social relationships. Consequently, people with SMIs

are significantly more likely to experience unemployment, incarceration, suicidality, and homelessness^{6–12}. With an estimated combined prevalence of 3.1 to 4.4% in the US population^{3,4,13}, schizophrenia and BD impose a substantial economic burden, costing approximately \$550 billion annually, or 2.04% of the US gross domestic product (GDP)^{14,15}.

1.2 BRAIN STRUCTURAL AND COGNITIVE CORRELATES OF SMI

Despite their classification as discrete clinical disorders, many studies report substantial overlap in the brain structural and cognitive correlates of the two disorders, with schizophrenia typically being linked to more pronounced alterations. Both disorders show cortical thinning, particularly in the frontal and temporal lobes, with similar but more pronounced grey matter deficits in fronto-temporo-occipital regions in schizophrenia¹⁶. Both patient groups show substantial reductions in subcortical volumes in the hippocampus, the thalamus, the nucleus accumbens, the left cerebellar cortex, and the brainstem, along with substantial ventricular enlargements¹⁷. Cognitive impairment is a hallmark feature of SMI, with cognitive alterations in BD being qualitatively similar to those reported in schizophrenia, although less severe¹⁸. The most commonly described alterations are in the domains of working memory, verbal learning and memory, attention, and executive function^{19–27}.

1.3 OBESITY AND METABOLIC HEALTH IN SMI

The obesity pandemic is a growing global health concern, affecting 1 in 8 people worldwide²⁸. Ischemic heart disease and stroke rank as the first and second leading causes of death globally²⁹, both of which have been shown to be independently predicted by excess body weight^{30–32}. Obesity targets many organ systems and leads to a host of issues including type 2 diabetes (T2DM), hypertension, coronary heart disease, and metabolic syndrome (MetSy)^{33,34}.

Individuals with SMIs have a life expectancy 15–30 years shorter than the general population

³⁵, with metabolic comorbidities among the leading causes of death³⁶. Cardiovascular disease alone accounts for up to 30 years of life lost³⁶. The high cardiovascular-related mortality rate is widely attributable to the 3.0 fold relative risk of obesity³⁷, and a 1.5-5.0 fold relative risk of MetSy, diabetes, hypertension, and dyslipidemia^{38,39}, compared to the general population. Given the high prevalence of metabolic disorders in SMI, it is crucial to explore how these conditions impact brain structure and cognitive function, which may in turn influence clinical outcomes.

1.4 ASSOCIATIONS BETWEEN METABOLIC HEALTH, BRAIN STRUCTURE, AND COGNITION IN SMI

Body mass index (BMI) has been linked to the same neurostructural alterations observed in schizophrenia and BD, including ventricular enlargement and cortical thinning⁴⁰⁻⁴³. In fact, some of the most replicated alterations in BD, including larger ventricles, were to a large extent (up to 47%) mediated by obesity⁴¹. Of the cortical regions related to schizophrenia, 42% are additively associated with BMI⁴⁰. Diabetes and insulin resistance have also been linked with smaller hippocampal volumes and reduced medial cortical thickness in individuals with BD⁴⁴. Beyond structural alterations, comorbid SMI and insulin resistance, T2DM, Metabolic syndrome (MetSy), greater BMI and triglycerides (TGC) are all negatively associated with global cognition⁴⁵, attention, working memory, executive function, verbal and visual memory⁴⁵⁻⁵¹.

Considering individuals with SMI who are overweight or obese tend to experience more severe depressive episodes, more positive and negative psychotic symptoms, and worse response to treatment⁵²⁻⁵⁶, addressing metabolic health could be a crucial strategy in mitigating adverse neurological, cognitive, and clinical outcomes. However, current literature mostly examines metabolic factors as discrete and isolated components, ignoring the multifactorial and multidimensional nature of metabolic dysfunction. Additionally, there exists a significant gap in understanding which aspect of metabolic dysfunction is most strongly associated with brain and cognitive health, both on an

individual (biological) and population (epidemiological) scale. This understanding is crucial as it may inform clinical treatment plans, as well as research initiatives and public health efforts aimed at preventing metabolic health-related brain and cognitive alterations in SMI.

1.5 THESIS OVERVIEW

This thesis summarizes and synthesizes the results of three investigations aimed at addressing the central question: *How does poor metabolic health contribute to structural and cognitive outcomes in SMI?* To address this overarching question, this thesis breaks it down into smaller, targeted questions.

- 1) *Which metabolic factor (e.g., diabetes, hypertension, obesity) has the strongest association with neurostructural alterations?*

This question is addressed in [Chapter 2](#) through a meta-analysis of available data to investigate the independent effects of diabetes, hypertension, and obesity on machine learning-predicted brain age. The goal of this chapter is to identify the metabolic factor that is the most biologically relevant and poses the greatest risk to neurostructural alterations.

- 2) *How do these metabolic factors interact with different SMIs such as Schizophrenia or BD?*
- 3) *Do metabolic health-related neurostructural changes have measurable consequences to cognitive function? i.e. are there structure-function links between obesity, brain and cognition?*

Chapters 3 and 4 explore these questions using two distinct clinical samples. In [Chapter 3](#), we investigate a sample of young patients at their first episode of psychosis. Not only is this a critical period when most weight gain typically occurs⁵⁷, this phase of illness is also characterized by shorter durations of medication exposure and fewer chronic illness-related complications. It therefore presents a unique opportunity to examine associations with metabolic health with fewer confounding influences.

In [Chapter 4](#), we investigate a heterogenous sample of BD patients at various ages, illness

stages and trajectories, medication histories, number of prior episodes, history of hospitalizations, and prevalences of metabolic conditions that reflect population-level trends. Investigating metabolic associations in this sample therefore offers greater generalizability.

In both samples, we examine whether observed obesity-related alterations in brain structure are associated with functional cognitive deficits. If obesity-related structural alterations do not have functional consequences, their clinical relevance may be limited. Additionally, if alterations in cognition do in fact arise from alterations in brain structure, then the brain may serve as a clearer, more effective target for interventions aimed at preventing cognitive changes.

4) How does the combined effect of multiple metabolic factors contribute to structural and cognitive changes in SMI?

Also addressed in [Chapter 4](#), this question considers the multifactorial and multidimensional nature of metabolic dysfunction. By using principal component analysis (PCA) in this broad, heterogeneous sample, we assess the combined effect of multiple metabolic indices on brain structural and cognitive outcomes. This multivariate analysis offers an objective assessment of the associations of metabolic health in a way that reflects the real-world epidemiology of these conditions.

Finally, [Chapter 5](#) synthesizes these findings and discusses them in the context of existing literature, highlighting the clinical significance and unique contribution of each chapter to the global understanding of the interplay between metabolic health, brain structure, and cognition in SMI. Suggested future directions are also discussed in this chapter.

CHAPTER 2 CARDIOMETABOLIC RISK FACTORS AND BRAIN AGE: QUANTIFYING BRAIN STRUCTURAL DIFFERENCES LINKED TO DIABETES, HYPERTENSION, AND OBESITY THROUGH META-ANALYSIS

2.1 INTRODUCTION

Most of the conversation regarding the impact of obesity and other cardiometabolic risk factors on the brain is centered around grave neurological outcomes like stroke and vascular dementia⁵⁸. However, the more insidious and gradual alterations in brain structure that accompany these cardiometabolic risk factors, such as changes in regional brain volumes and cortical thickness, have only recently become apparent and are much less understood.

All three cardiometabolic risk factors are frequently linked with impairments in brain structure and function, ultimately resulting in an increased risk of dementia⁵⁹⁻⁶³. Both diabetes and hypertension are damaging to cerebral vasculature^{64,65}, but diabetes also causes many biochemical and/or endocrine perturbations. Quantifying the independent effects of diabetes, hypertension, and obesity could give some insights into the vascular versus biochemical contributions to brain changes. From a clinical, public health perspective, identifying the strongest predictor would also identify the best targets for intervention and prevention of these more subtle neurodegenerative sequelae of cardiometabolic risk factors. Yet, we do not currently have a quantification of the effects of these individual cardiometabolic risk factors on brain structure derived from all available studies in a meta-analytical way.

Classical measures of neurodegeneration are based on regional brain atrophy, such as the use of hippocampal volume to assess severity of Alzheimer's dementia and age-related cognitive decline⁶⁶. However, in Aristotle's words, "*the whole is something beside the parts*"⁶⁷, and this is especially true

in the context of the brain. Traditional mass univariate methods of analysis treat each region as independent from all others, which ignores the network architecture of the brain and is subject to many statistical and interpretational issues. These techniques are sensitive to large but highly localized changes, which may not reflect the diffuse damage typically seen with complex pathologies such as cardiometabolic risk factors. As such, focusing solely on volumes of specific regions may not capture the whole picture. Machine-learning techniques may be better suited to capture such diffuse but subtle changes.

One such technique is the brain age estimation framework. This approach trains a machine-learning model using hundreds to thousands of brain scans from healthy individuals to estimate brain age from structural magnetic resonance imaging (MRI) scans. The difference between the predicted brain age and the individual's chronological age is termed the brain age gap estimate (BrainAGE), which is then used as an index of brain structural integrity. In this way, chronological age is used as a reference point by which we can assess subtle alterations in brain structure that are deemed abnormal for an individual at their given age. A higher positive BrainAGE would thereby suggest a greater degree of structural alterations, which has been shown to correlate with functional and health outcomes such as progression to dementia, poorer cognitive performance, mortality, and other measures of biological aging including weaker grip strength, slower walking speed, and decreased lung capacity⁶⁸⁻⁷². This measure captures not only aging, but many external factors that result in atrophy. cardiometabolic risk factor-related subtle brain changes may therefore also manifest as an older-appearing brain. A major advantage of the brain age model is the aggregation of all region-specific patterns in structural alterations into one easily interpretable numerical value, albeit at the cost of regional specificity.

Previously, cardiometabolic risk factors including higher body mass index (BMI), diabetes, and hypertension have been associated with higher BrainAGE scores^{71,73,74}, however the effect sizes in

individual studies vary widely and the relative magnitude of their independent contributions to brain age remains unclear. Obesity, diabetes, and hypertension are unequally prevalent in the general population, with obesity being roughly 4 times more common than diabetes⁷⁵⁻⁷⁷. The three conditions are also highly comorbid⁷⁸, and so discerning their independent contributions to adverse health outcomes is challenging owing to unequal or insufficient representation of each condition in smaller study samples. Therefore, we wanted to maximize sample size in order to get a more precise and generalizable estimate of the strength of the associations between the three cardiometabolic risk factors and brain age. To this goal, we meta-analyzed all available studies investigating associations between obesity, diabetes, hypertension and brain age. To quantify the unique contribution of each of the factors, we separately calculated pooled estimates from studies which controlled for the other cardiometabolic risk factors.

2.2 METHODS

2.2.1. Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement⁷⁹ and performed a systematic search of articles in PubMed, MEDLINE, and Scopus databases from inception until July 11th, 2024, using the following search terms: (1) “brain age” AND “obesity”, (2) “brain age” AND “diabetes”, (3) “brain age” AND “HDL”, (4) “brain age” AND “triglycerides”, (5) “brain age” AND “blood pressure”, and (6) “brain age” AND “hypertension”. Two raters independently screened articles following removal of duplicates identified by Covidence ([Covidence.org](https://www.covidence.org)) and by screeners.

2.2.2. Eligibility Criteria

At the project’s conception, we hoped to be able to analyze both categorical (diabetes, hypertension, obesity) and dimensional (HbA1c, blood pressure, BMI, lipid levels) cardiometabolic

risk factor data. Statistically, we cannot combine categorical and dimensional effects into the same meta-analysis and so there needs to be a sufficient number of studies for each type of predictor. For continuous measures, our search identified only 3 studies for HbA1c, 2 for high-density lipoprotein (HDL) and low-density lipoprotein (LDL), and 3 for triglycerides (TGC), which is too few for a separate meta-analysis. Therefore, we decided to proceed only with categorical data, which had enough studies for all predictors of interest. For those predictors, we did not want to limit our search to specific measures of obesity such as BMI, waist-to-hip ratio, intraabdominal fat percentage, etc. We wanted to keep our search as broad as possible to include all studies that investigated obesity.

We excluded studies that computed brain age from imaging modalities other than structural MRI, such as from electroencephalogram (EEG). Of the studies that included participants from the same database, such as from UK BioBank (UKBB)^{71,74,80–85}, we selected only the one with the largest number of participants⁸³ to ensure there was no overlap between study samples.

Our studies included those describing clinical populations, such as those with sleep apnea⁸⁶ or first-episode psychosis⁸⁷, so long as they reported separate data from control participants and/or controlled for the effect of diagnosis in their statistical models. We included studies that defined diabetes, hypertension, and/or obesity, categorically (yes/no) and excluded those that used continuous predictors of blood pressure and BMI. The definitions of diabetes, hypertension, and obesity within each study are described in supplementary [Tables A2, A3](#), and [A4](#), respectively.

2.2.3 Quality and Risk of Bias Assessment

The Newcastle-Ottawa Scale (NOS) for assessing the quality and potential risk of bias in nonrandomized studies was adapted for use in cross-sectional studies⁸⁸, following the original scale developed by Wells et al. (2000)⁸⁹, see [Appendix D](#). According to prespecified criteria for risk of bias in sample selection, comparability of subjects, and assessment of outcomes, studies were considered to

have a low (scores above 7), medium (scores from 5-7) or high risk of bias (scores below 5). Two raters, M.S. and S.M. rated each study independently. Potential for publication bias was further assessed by running a jack-knife analysis in CMA software, where the robustness of the results was determined after removing individual studies from each meta-analysis.

2.2.4 Calculation of Effect Sizes and Meta-Analysis

The CMA software⁹⁰ converts study results into standardized effect size (Cohen's d), which can be aggregated across multiple studies using random effects. Brain age is calculated for each individual participant within each study, which then reports group summary statistics for brain age gaps. We used CMA version 4 to calculate Cohen's d for mean differences in BrainAGE of individuals with and without diabetes, hypertension, or obesity. The Cohen's d estimates per each study were then meta-analyzed using random effects models. We computed Cohen's d and 95% confidence intervals (CIs) either from the independent group means and standard deviations, t -values and sample sizes, or from β coefficients and standard errors extracted from each study. When the data was not available in the paper, we contacted the authors, who then provided more details^{83,91}. To quantify the independent association between each cardiometabolic risk factor and brain age, we ran a secondary analysis to only include studies that controlled for the other cardiometabolic risk factors within their models.

2.3 RESULTS

2.3.1 Study Samples

Our initial search identified 185 studies. Figure 2.1 provides an overview of the selection process. A total of 14 studies met all inclusion criteria. Table 2.1 and Table 2.2 provide a description of the study samples and the brain age models employed, respectively. Because the study by Kang et al. (2023)⁷⁴ reported data from 4 non-overlapping samples (Korean females, Korean males, UK females, UK males), the data from each sample was entered separately.

The samples described in the studies ranged in size from 92 to 32,175 participants, with an average

age range of 26.4 to 76.0 years. The brain age models employed were most commonly based on T1-weighted structural gray and white matter MRI data, with the exception of two studies that used data from T1-weighted gray matter only ^{74,91}, two studies that used T2-weighted scans ^{92,93} and one study that used a composite of white matter diffusion metrics ⁸³. Most studies reported using scanners with 3.0 Tesla magnets, with the exception of two studies using a 1.5 Tesla scanner ^{86,92}, and one study that used both types on an even number of their participants ⁹³. Brain age model performance was most often reported as mean absolute error (MAE) of prediction, which ranged from 3.09 to 6.9. Of the studies that investigated diabetes as a predictor of brain age, one study defined diabetes as both type 1 (T1DM) and T2DM ⁸³, two studies defined it as only T2DM ^{73,74}, three defined it as diabetes mellitus (DM)⁹²⁻⁹⁴, and five did not specify the type (D)^{86,91,95-97} ([Table A2](#)). While most study samples looked at more than one of the risk factors, only two included all three ([Table A5](#)).

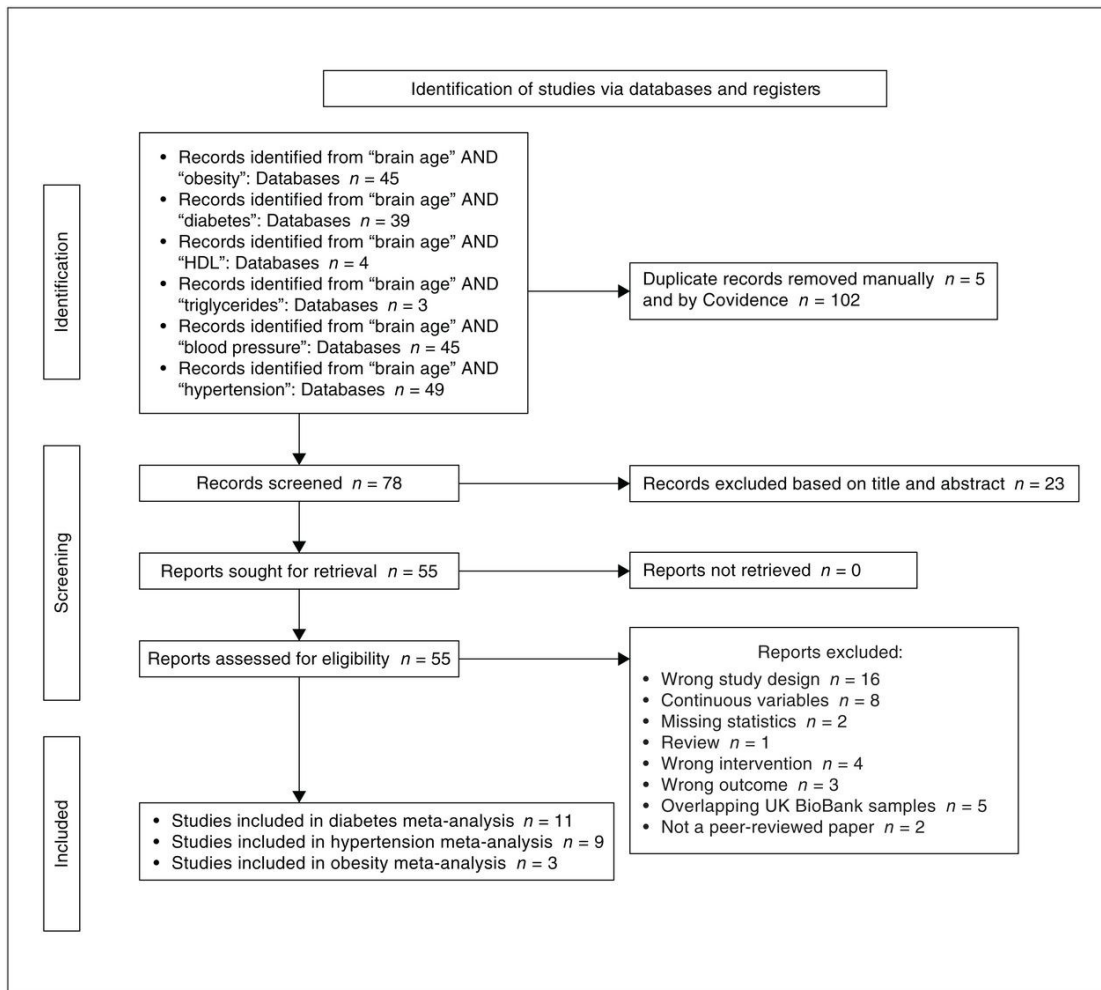


Figure 2.1 Flowchart describing the search strategy and study selection process. A total of 14 studies were included in this study, 11 of which were used in the diabetes meta-analysis, 9 in the hypertension meta-analysis, and 3 in the obesity meta-analysis.

Table 2.1 Sample descriptives

Study Sample	Sample	Sample Size	Sample Age, mean \pm SD (age range)	N (%) Female	N (%) Diabetic	N (%) Hypertensive	Mean BMI	Clinical Populations Included
Bretzner et al., 2023 92	MRI-GENIE	4163	62.8 \pm 15.0	1748 (42%)	687 (16.5%)	2,825 (67.9%)	-	Prior stroke (12.9%) CAD (18.5%) Afib (14.3%)
Busby et al., 2023 95	ABC@UofSC	217	47.44 \pm 18.33 (20-79)	167 (76.96%)	14 (6.48%)	50 (23.14%)	27.53	None
Casanova et al., 2024 91	ARIC	1172	76.0 \pm 5.3	747 (63.7%)	359 (30.63%)	871 (74.32%)	28.5 \pm 5.7	Dementia (4.76%), MCI (31.85%)
Franke et al., 2013 73	SAFE	185	64.92 \pm 8.29	91 (49%)	98 (52.97%)	78 (42.16%)	27.26 \pm 4.32	Syncope
Guan et al., 2022 98	BPHRS	121	66.58 \pm 6.43	96 (79.34%)	0 (0%)	67 (55.37%)	32.31 \pm 6.59	None
Hwang et al., 2021 93	Seoul ^a	270	64.7 \pm 9.3	127 (47%)	52 (19%)	137 (51%)	-	None
Jawinski et al., 2022 94	BASE-II	335	70.5 \pm 3.8 (61-82)	127 (38%)	34 (10.4%)	-	26.69 \pm 3.46	None
Jha et al., 2022 96	DHS-2	1949	49.9 \pm 10.6	1150 (59%)	246 (14.45%)	-	29.7 \pm 5.3	None
Kang et al., 2023a 74	Seoul ^b	2599	63.2 \pm 6.9	2599 (100%)	273 (10.5%)	965 (37.1%)	23.5 \pm 2.9	None
Kang et al., 2023b 74	Seoul ^c	2942	64.7 \pm 6.5	0 (0%)	683 (23.2%)	1402 (47.7%)	24.5 \pm 2.6	None
Kang et al., 2023c 74	UKBB ^a	5167	63.4 \pm 7.1	5167 (100%)	365 (7.1%)	1813 (35.1%)	26.8 \pm 5.2	None
Kang et al., 2023d 74	UKBB ^b	4736	63.8 \pm 7.4	0 (0%)	602 (12.7%)	2208 (46.6%)	27.7 \pm 4.4	None
Kolenic et al., 2018 87	Prague	234	26.37 \pm 4.51	107 (45.73%)	-	13 (5.56%)	22.97 \pm 3.52	First-episode psychosis
Korbmacher et al., 2023 83	UKBB ^c	32,175	64.47 \pm 7.61	15161 (52.88%)	543 (1.69%)	6332 (19.80%)	26.32 \pm 4.27	
Sone et al., 2022 97	JPSC-AD	773	71.68 (7.20)*	453 (58.6%)	111 (14.36%)	371 (47.99%)	-	
Weihls et al., 2021 86	SHIP	690	52.5 \pm 13.4	337 (48.8%)	66 (9.57%)	308 (44.60%)	-	Sleep apnea
Zeighami et al., 2022 99	HCP	92	-	-	-	-	-	

Notes: ABC@UofSC, Aging Brain Cohort at the University of South Carolina; Afib, Atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BASE-II, Berlin Aging Study II; BPHRS, Boston Puerto Rican Health Study; CAD, coronary artery disease; DHS-2, Dallas Heart Study 2nd wave; HCP: Human Connectome Project; JPSC-AD, Japan Prospective Studies Collaboration for Aging and Dementia; MCI, mild cognitive impairment; MRI-GENIE, MRI-GENetics Interface Exploration; SAFE, Syncope and Falls in the Elderly; Seoul^a, Seoul National University Hospital; Seoul^b, Health Promotion Center of Samsung Medical Center (Females); Seoul^c, Health Promotion Center of Samsung Medical Center (Males); SHIP, Study of Health in Pomerania; UKBB^a, UK BioBank (Females); UKBB^b, UK BioBank (Males); UKBB^c, UK BioBank sample that did not appear in the same analyses as UKBB^a or UKBB^b

* refers to median (IQR)
- means data not available

Table 2.2 Brain Age Models

Study Name	Machine Learning Model	Tissue Type	Scanner Type	Model Performance	External Training Set	Model Covariates
Bretzner et al., 2023 ⁹²	ElasticNet linear regression	T2-FLAIR MRI radiomics	1.5 Tesla	MAE = 6.9	Yes	HTN, DM , Afib, CAD, History of smoking, prior stroke
Busby et al., 2023 ⁹⁵	Gaussian Regression	T1-weighted GM + WM	3.0 Tesla	r = 0.936	Yes	Age, Sex, SES, BMI, HTN, Diabetes , Years of education, Race
Casanova et al., 2024 ⁹¹	ElasticNet linear regression	T1-weighted GM	3.0 Tesla	MAE = 2.35	Yes	Age, sex, center-race
Franke et al., 2013 ⁷³	RVR	T1-weighted GM + WM	3.0 Tesla	MAE = 4.98	Yes	None
Guan et al., 2022 ⁹⁸	XGBoost	T1-weighted GM + WM	3.0 Tesla	-	Yes	Age, sex, ICV, education
Hwang et al., 2021 ⁹³	CNN	T2-weighted images	1.5 Tesla (n = 894) 3.0 Tesla (n = 906)	MAE = 4.22	Yes	None
Jawinski et al., 2022 ⁹⁴	RVR	T1-weighted GM + WM	3.0 Tesla	MAE = 3.09	Yes	sex, age, age ² , ICV
Jha et al., 2022 ⁹⁶	BrainageR (Gaussian Process Regression)	T1-weighted GM + WM	3.0 Tesla	MAE = 3.93	Yes	Framingham 10-year risk, race/ethnicity, income, BMI , history of myocardial infarction
Kang et al., 2023a-d ⁷⁴	GCN	T1-weighted GM	3.0 Tesla	-	Unknown	T2DM, HTN, obesity , underweight
Kolenic et al., 2018 ⁸⁷	RVR	T1-weighted GM + WM	3.0 Tesla	MAPE = 16.29%	Yes	age, BMI category , FEP diagnosis
Korbmacher et al., 2023 ⁸³	XGBoost	WM: DTI, DKI, WMTI, SMT, mcSMT	3.0 Tesla	-	Yes	BMI , Pulse pressure, WHR , smoking status, diabetes (T1 and T2), binary high cholesterol, binary diagnosed vascular problem, birth weight, sleeping hours, daily coffee intake
Sone et al., 2022 ⁹⁷	SVR	T1-weighted GM + WM	3.0 Tesla	MAE = 5.49	Unknown	Age, sex, education level, total ICV, MMSE score, SWLS score, resilience score, GDS score, alcohol use, current smoking, diabetes, HTN , dyslipidemia
Weihls et al., 2021 ⁸⁶	OLS	T1-weighted GM + WM	1.5 Tesla	-	Unknown	Diabetes : AHI + Diabetes + HbA1c + age + sex + age*sex + ICV. HTN : AHI + HTN + DiasBP + Age + Sex + Age*Sex + ICV
Zeighami et al., 2022 ⁹⁹	Linear Regression with PCA	T1-weighted GM + WM	3.0 Tesla	RMSE = 8.8, r = 0.90	Yes	None

Notes. AHI, apnea-hypopnea index; BMI, body mass index; CNN, Deep Convolutional Neural Network; DM, diabetes mellitus; GCN, Graph Convolutional Networks; GM, Gray matter; HTN, hypertension; ICV, intracranial volume; MAE, mean absolute error; MAPE, mean absolute percent error; OLS, Ordinary Least Squares; PCA, principle component analysis; RMSE, root mean squared error; RVR, Relevance Vector Regression; SVR, Support Vector Regression; T2DM, type 2 diabetes mellitus; WHR, waist-to-hip ratio; WM, White matter

2.3.2 Quality and Risk of Bias Assessment

There was a high degree of agreement between the two independent raters ($r = 0.880$, $ICC = 0.882$). Six studies were deemed to have a low risk of bias, seven were deemed to have a medium risk of bias, and one was deemed to have a high risk of bias. Figure 2.2 shows each study's risk of bias score, as assessed by each of the two raters.

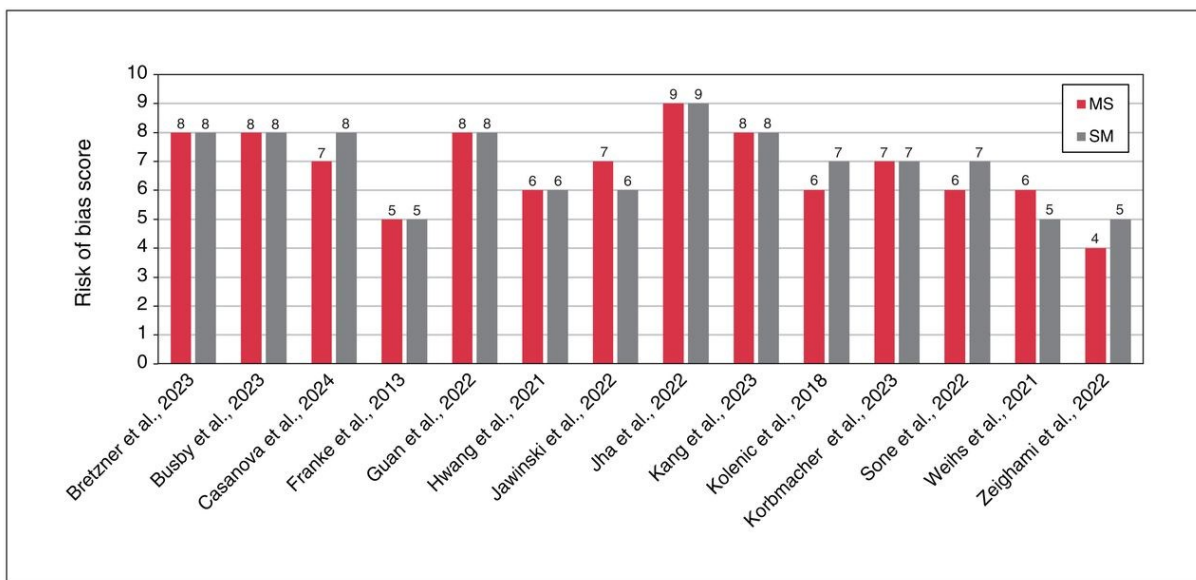


Figure 2.2 Each included study's risk of bias score per independent rater using the adapted Newcastle-Ottawa Scale. Of the 14 included studies, six were deemed to have a low risk of bias (score > 7), seven were deemed to have a medium risk of bias (score of 5-7), and one was deemed to have a high risk of bias (score < 5) by at least one rater. There was a high degree of agreement between the two independent raters ($r = 0.880$, $ICC = 0.882$).

2.3.3 Cardiometabolic Risk Factors and Brain Age

Between the 12 study samples from 11 studies that investigated the effect of diabetes on brain age, we found a significant pooled effect ($d = 0.275$, 95%CI: 0.198, 0.352, $N = 47,436$, $I^2 = 66.765$) such that those with diabetes had a higher BrainAGE than those without (Figure 2.3A). The effect of diabetes on BrainAGE remained significant among the six study samples that controlled for hypertension ($d = 0.232$, 95%CI: 0.132, 0.332, $N = 42,842$, $I^2 = 75.035$, Figure 2.3B) and five that controlled for BMI ($d = 0.247$, 95%CI = 0.126, 0.367, $N = 39,875$, $I^2 = 77.644$, Figure 2.3C). Results of the jack-knife analysis showed no particular study to change the significance of the effect when left out of the analysis.

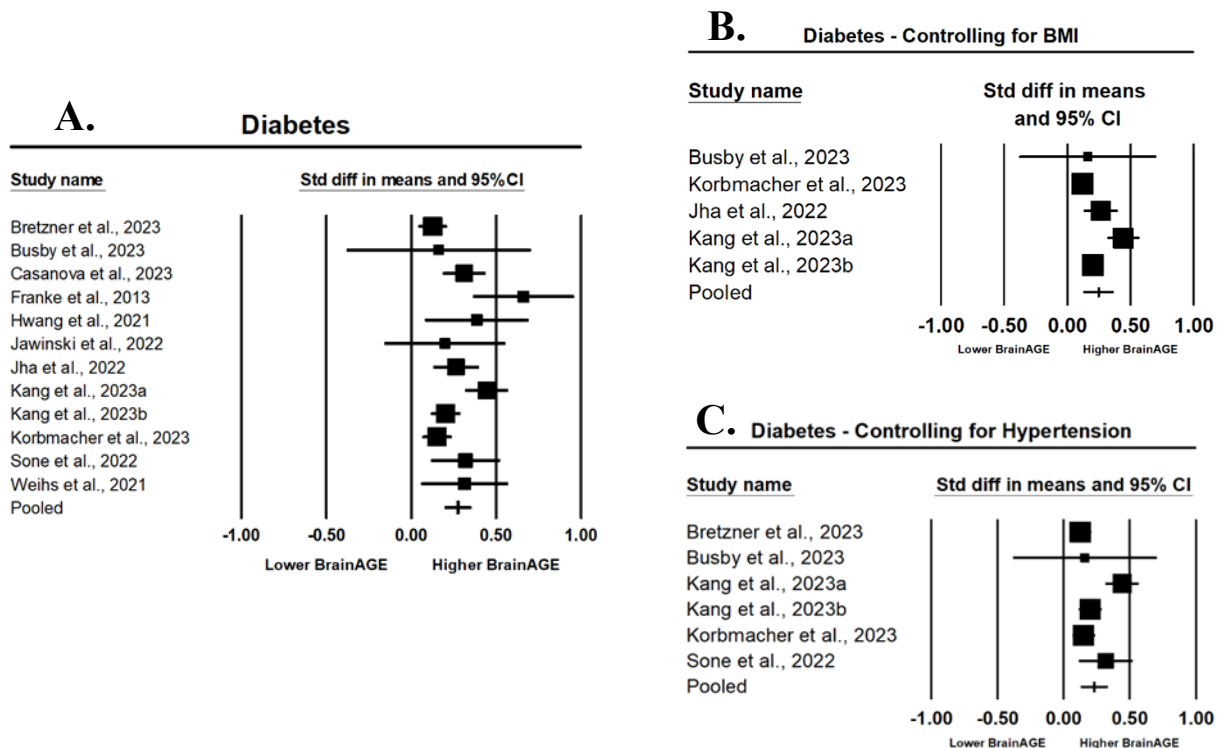


Figure 2.3 Results of the diabetes random effects meta-analyses. **A.** A comparison of 12 study samples showed a significant effect of diabetes on BrainAGE ($d = 0.275$, 95%CI: 0.198, 0.352, $N = 47,434$, $I^2 = 66.765$). **B.** Among the studies that controlled for

hypertension in their model, the effect of diabetes remained significant ($d = 0.232$, $95\%CI: 0.132, 0.332$, $N = 42,842$, $I^2 = 75.035$). **C.** Among the studies that controlled for BMI in their model, the effect of diabetes remained significant ($d = 0.247$, $95\%CI: 0.126, 0.367$, $N = 39,875$, $I^2 = 77.644$).

Between the 10 study samples from 9 studies that investigated the effect of hypertension on BrainAGE, we found a significant pooled effect ($d = 0.113$, $95\%CI: 0.063, 0.162$, $N = 45,102$, $I^2 = 58.540$) such that those with hypertension had a higher BrainAGE than those without (Figure 2.4A). The effect of hypertension on BrainAGE remained significant among the six study samples that controlled for diabetes ($d = 0.101$, $95\%CI: 0.064, 0.137$, $N = 42,849$, $I^2 = 33.824$, Figure 2.4B) and four that controlled for BMI ($d = 0.109$, $95\%CI = 0.054, 0.165$, $N = 37,933$, $I^2 = 55.242$, Figure 2.4C). Results of the jack-knife analysis showed no particular study to change the significance of the effect when left out of the analysis.

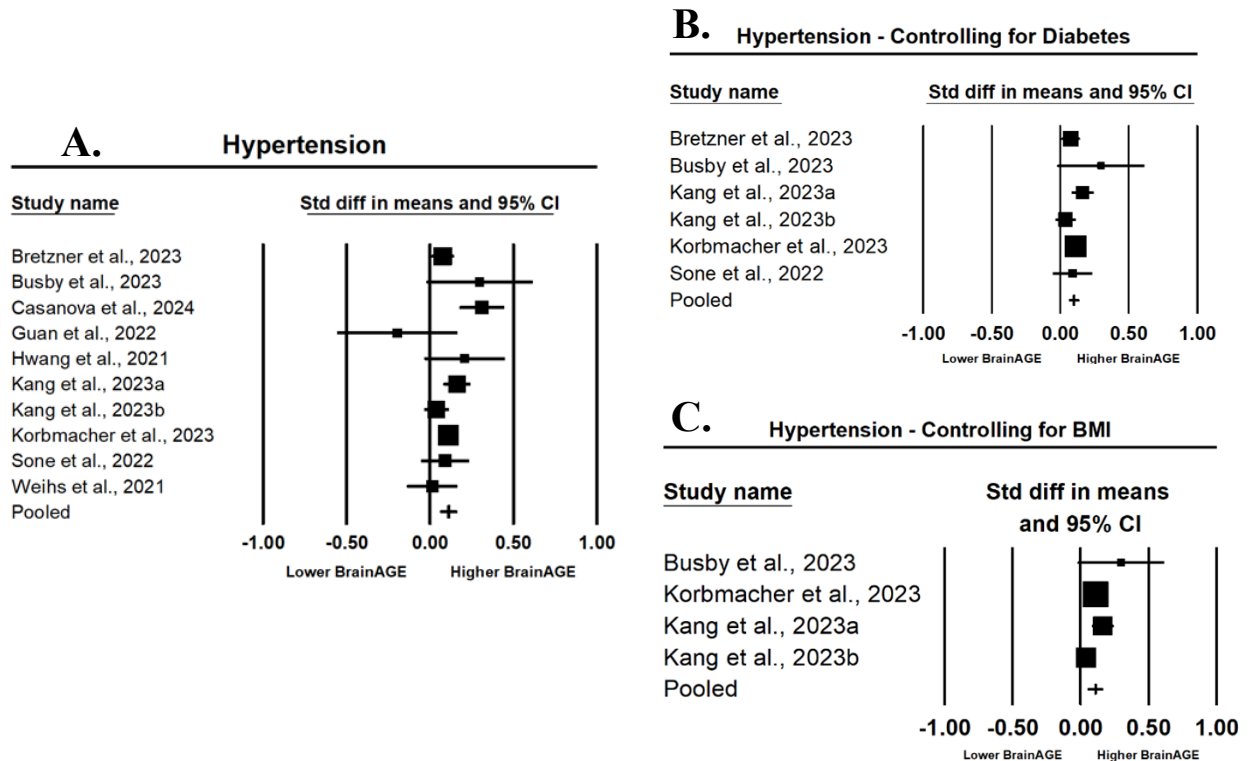


Figure 2.4 Results of the hypertension random effects meta-analyses. **A.** A comparison of 10 study samples showed a significant effect of hypertension on BrainAGE ($d = 0.113$, 95%CI: 0.063, 0.162, $N = 45,102$, $I^2 = 58.540$). **B.** Among the studies that controlled for diabetes in their model, the effect of hypertension remained significant ($d = 0.101$, 95%CI: 0.064, 0.137, $N = 42,849$, $I^2 = 33.824$). **C.** Among the studies that controlled for BMI in their model, the effect of hypertension remained significant ($d = 0.109$, 95%CI = 0.054, 0.165, $N = 37,933$, $I^2 = 55.242$).

Among the 6 study samples from 3 studies that investigated the effect of categorically defined obesity on BrainAGE, one study was deemed to have a high risk of bias and reported an unrealistically large effect size ($d = 1.476$, $z = 6.276$), and was therefore excluded as an outlier. Between the 5 included study samples from 2 studies that investigated the effect of categorically defined obesity on BrainAGE, we found a significant pooled effect ($d = 0.112$, 95%CI: 0.037,

0.187, $N = 15,678$, $I^2 = 40.577$) such that those with obesity had a higher BrainAGE than those without (Figure 2.5A). The effect of obesity on BrainAGE remained significant among the four study samples that controlled for hypertension and diabetes ($d = 0.096$, 95%CI: 0.040, 0.152, $N = 15,444$, $I^2 < 0.01$, Figure 2.5B). Results of the jack-knife analysis showed no particular study to change the significance of the effect when left out of the analysis.

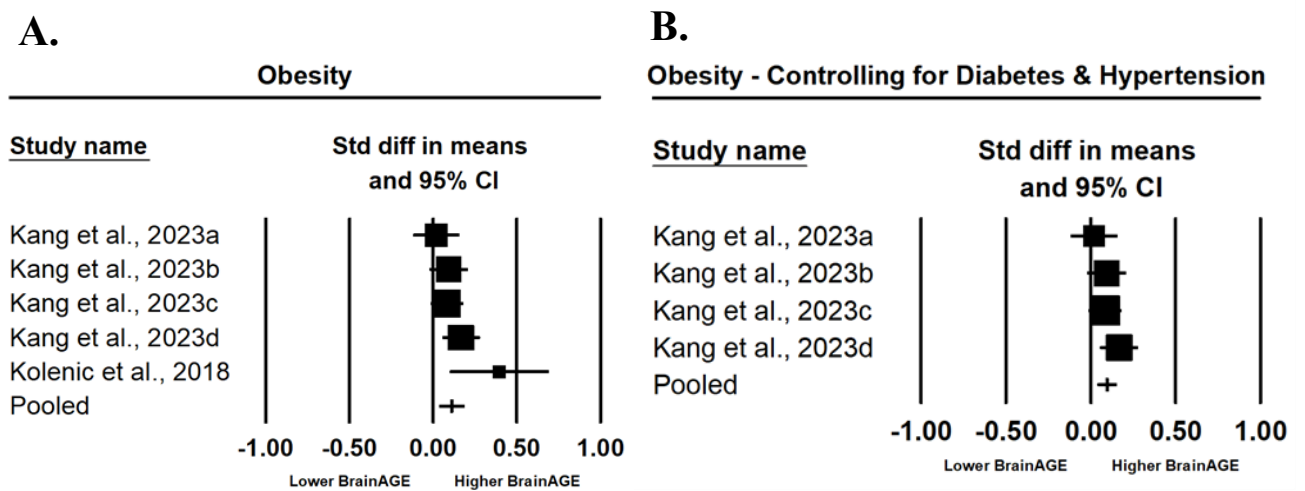


Figure 2.5. Results of the obesity random effects meta-analysis. **A.** A comparison of 5 study samples showed a significant effect of obesity on BrainAGE ($d = 0.112$, 95%CI: 0.037, 0.187, $N = 15,678$, $I^2 = 40.577$). **B.** The Kang et al. (2023) study was the only study that controlled for the effects of diabetes and hypertension within their model, and so their four independent samples were meta-analyzed separately, revealing a significant independent effect of obesity on BrainAGE ($d = 0.096$, 95%CI: 0.040, 0.152, $N = 15,444$, $I^2 < 0.01$).

2.4 DISCUSSION

All of diabetes, hypertension, and obesity were significantly associated with subtle brain changes as measured by BrainAGE. Among the three cardiometabolic risk factors, diabetes was associated with the largest BrainAGE ($d = 0.275$), followed by hypertension ($d = 0.113$), and obesity ($d = 0.112$). All three effect sizes remained significant and comparable among studies that controlled for the other cardiometabolic risk factors, suggesting that each condition has a unique effect on the brain. Consequently, people with all three conditions will likely show more pronounced brain changes than those with only one or two. Diabetes may be particularly problematic, as it showed the largest unique effect on the brain.

These findings are in keeping with previous work that has shown diabetes to be the strongest predictor of neurodegenerative conditions. Among measures of BMI, systolic and diastolic blood pressure, and blood glucose, only blood glucose levels have been found to be consistently elevated in people who went on to develop Alzheimer's or vascular dementia 14 years later¹⁰⁰. Those who developed vascular dementia had higher glucose levels than those who developed Alzheimer's dementia, suggesting that while extreme perturbations may primarily translate into vascular pathology, milder changes in glucose may rather contribute to Alzheimer's disease. This is in keeping with an obesity dose-response meta-analysis by Qu et al. (2020)¹⁰¹, which found a higher risk for Alzheimer's dementia among those with an overweight BMI of up to 30 kg/m², and a higher risk of vascular dementia when this BMI cutoff was exceeded. Another study investigating the impact of cardiovascular risk factors and all-cause dementia also showed diabetes to have a much larger impact on dementia risk than hypertension, smoking, alcohol, and low physical activity, even when adjusting for age and genetic risk¹⁰². While both diabetes and hypertension are mentioned in current dementia prevention guidelines

¹⁰³, our findings add to the urgency by documenting that these cardiometabolic risk factors contribute to brain structural alterations even in people without dementia.

The multidimensional nature of diabetes pathology may explain the larger pooled effect of diabetes on brain age. Hypertension is characterized by higher-than-normal blood pressure, which puts stress on arterial walls and can lead to cerebral small vessel disease¹⁰⁴. The damaged microvessels insufficiently supply blood to the deeper structures of the brain, leading to neuronal atrophy and cognitive decline^{64,105}. Diabetes also causes damage to microvascular structures via several mechanisms including chronic oxidative stress and hyperglycemia, among others⁶⁵. However, the damage caused by diabetes extends beyond cardiovascular injury as diabetic insulin resistance impairs the function of insulin-like growth factor 1 (IGF-1), which functions as a neurotrophic factor and stimulates neuronal plasticity, angiogenesis, metabolic function, and protein clearance^{106,107}. As such, while both hypertension and diabetes impair cerebral microcirculation, the burden of diabetes also carries impairments in endocrine function, specifically by hindering the signaling of important neuroprotective factors that may slow the progression of neurodegeneration. The multidimensionality of diabetes pathology could explain why the largest observed statistical effect size was that of diabetes. The status quo among clinicians tends to be that cardiovascular dysfunction is primarily to blame for the development of adverse neurological outcomes, yet our findings add to existing evidence suggesting that biochemical dysfunctions, as seen in diabetes, may play a significant and even greater role.

Seeing as the data included in this study is cross-sectional, we cannot infer the direction of changes and causality. While it is possible that cardiometabolic risk factors cause these brain changes, it may also be that certain brain alterations predispose one to developing cardiometabolic risk factors. People born with high impulsivity and impaired reward or satiety

signalling may later develop obesity, and consequently diabetes and hypertension. If this was the case, we would expect to find highly localized brain changes in regions subserving these functions. However, studies investigating regional structural changes associated with cardiometabolic dysfunctions report diffuse changes across many regions of the brain¹⁰⁸, which parallel the patterns of age-related neurodegeneration¹⁰⁹, and are in keeping with the fact that brain age reflects a diffuse pattern of brain alterations¹¹⁰. These findings support the idea that cardiometabolic factors cause global damage to the brain, as opposed to being a consequence of a region-specific structural impairment. Several recent mendelian randomization studies have further supported a causal link between each of the three cardiometabolic risk factors and brain structure^{111–114}.

Heterogeneity was generally high in the included studies with I^2 estimates ranging from 40.58 to 66.77. Subgroup analyses in studies which controlled for other relevant factors did not substantially lower the heterogeneity in most instances. The studies were mostly consistent in the direction of association, i.e. greater BrainAGE in people with each specific cardiometabolic risk factor. However, the effect sizes differed between the studies. This could possibly reflect differences in duration of illness or treatment, which were not well quantified in individual studies. Someone who was diagnosed with T2DM or hypertension several weeks ago may demonstrate smaller brain changes than someone who has been diabetic or hypertensive for several years. At the same time, shorter treatment is likely less protective of brain structure than longer treatment. Yet, none of the included studies quantified treatment of cardiometabolic conditions. Most studies relied on either self-reported diagnoses of the three conditions or the use of antihypertensive or antidiabetic medications as inclusion criteria. Consequently, it is likely that the majority of participants with diabetes or hypertension were undergoing treatment

in accordance with current guidelines. This makes our findings all the more concerning, as the observed structural brain changes persist despite most participants likely receiving treatment.

Our study is not without limitations. Out of the 11 studies that provided data for diabetes, only two studies specified that they only included those with T2DM^{73,74} whereas many did not specify the type. The cumulative sample size in the obesity meta-analysis with a pooled N of 15,770 was much smaller than that in the diabetes ($N = 47,436$) and hypertension ($N = 45,102$) meta-analyses. As such, more studies investigating the effect of categorically-defined obesity are needed to make more meaningful comparisons with the effects of diabetes and hypertension. Most studies only reported a mean age of participants, not the exact age range. However, age did not seem to factor into the size of the effect, seeing as both the largest and smallest effect sizes came from studies with similar age ranges. Likewise, the studies that included the highest and lowest age ranges showed effect sizes that were in the middle of the effect size range. Last but not least, as diabetes, hypertension, and obesity are highly comorbid, ideally, we would want to always control for the effects of the other cardiometabolic risk factors. However, that was not always what the available studies did. In order to maximize sample size, we first looked at all available studies in one analysis, and then ran a secondary sensitivity analysis that only included a subset of studies that were able to control for confounding effects of the other cardiometabolic risk factors. Even in these sensitivity analyses, the effect sizes still remained significant.

Because diabetes and hypertension are less prevalent than obesity in the general population and often comorbid, obtaining an unbiased estimate of their individual contributions to BrainAGE can be challenging owing to small or unequal sampling of each condition. Through this meta-analysis, we were able to leverage available data that included a substantial number of participants with each of the three conditions. This allowed us to assess the unique associations

between each cardiometabolic risk factors and BrainAGE when controlling for the other factors, and determine which metabolic factor has the greatest biological relevance on an individual level.

2.5 CONCLUSIONS

Our findings identify diabetes as having the highest effect size on brain age, followed by hypertension and obesity, with all three cardiometabolic risk factors showing significant independent links with brain structure. This confirms the intuitive understanding that having multiple risk factors will exert a greater effect on the brain than having a single one. Our findings align with previous research that shows diabetes to be the strongest predictor of neurodegenerative diseases. Future studies should test whether biochemical disturbances associated with diabetes, such as insulin resistance and high circulating glucose, play a greater role in progression of neurodegenerative conditions than do vascular disturbances alone, as seen in hypertension. These findings underscore the importance of considering the independent effects of all three metabolic conditions when assessing brain structural alterations as seen in people with SMIs. We propose that diabetes should serve as the primary target of clinical interventions aimed at preventing brain structural changes in patients with comorbid metabolic conditions.

CHAPTER 3 CENTRAL OBESITY-RELATED BRAIN ALTERATIONS PREDICT COGNITIVE IMPAIRMENTS IN FIRST EPISODE OF PSYCHOSIS

3.1 INTRODUCTION

Schizophrenia is a severe and often disabling mental disorder¹¹⁵. Cognitive impairments, which contribute to unemployment, social isolation and inability to live independently, are among the most challenging aspects of schizophrenia^{116–118}. Available treatments do not specifically target cognitive impairment and may even contribute to its progression^{119–122}. Therefore, it is of utmost importance to investigate risk factors for cognitive alterations, especially those that are preventable or treatable.

Obesity is disproportionately frequent in psychotic disorders. It is linked with worse cognitive outcomes in the same domains that are impaired in schizophrenia, including working memory, verbal learning and memory, attention, and executive function^{19–22}. At the same time, cognitive functioning varies significantly among people with schizophrenia, including those in their first episode^{123–125}. Variations in obesity could thus help explain variations in cognitive deficits in schizophrenia. Indeed, obesity is one of the strongest predictors of cognitive impairment and functional decline in psychotic disorders^{126–129}. The link between a peripheral disorder, i.e. obesity, and cognitive alterations could be related to the impact of obesity on the brain.

Brain alterations in obesity and psychosis partially overlap^{130–132}. Obesity has been additively associated with brain alterations in schizophrenia¹³³ and with higher brain age both in the general population^{134,135} and in individuals with FEP¹³⁶. Furthermore, in people with FEP, greater baseline body mass index (BMI) predicts faster brain aging in the future¹³⁷. Quantifying which metabolic markers are the strongest predictors of such structural and cognitive changes

would allow us to better prognosticate and monitor neuroprogression/cognitive impairment in FEP. Additionally, it is of clinical importance to understand whether these obesity-related alterations in brain structure are in fact linked with impairments in cognition. However, studies of such structure-function links are missing.

It is key to study these structure-function links early in the course of illness, as this is a critical period for weight gain and development of other metabolic alterations¹³⁸. Indeed, more than half of the weight gain in people with psychosis occurs in the first 12 weeks of treatment^{139–144}. This is also the phase of illness when chronicity, long-term use of medications, and the impact of social factors are relatively limited, thereby providing a clearer interpretation of findings. During this period, therapeutic interventions aimed at preventing or targeting obesity may be the most effective and their impact on future progression of brain and cognitive alterations may be the most pronounced.

To fill in these knowledge gaps, we sought to establish a structure-function link between obesity-related brain and cognitive alterations in individuals with FEP. We considered different measures of obesity and a range of obesity-related metabolic alterations to determine whether and which obesity/metabolic disturbances predicted neurostructural alterations and whether these neurostructural alterations were associated with worse cognitive outcomes in FEP.

3.2 METHODS

3.2.1 Patient Recruitment

The present study is a part of the Early-Stage Schizophrenia Outcome (ESO) project, at the National Institute of Mental Health, Czech Republic (NIMH-CZ)^{132,136,137,145}. Individuals with FEP met the following inclusion criteria: (1) were undergoing their first psychiatric

hospitalization; (2) had the ICD-10 diagnosis of schizophrenia (F20), acute and transient psychotic disorders (F23), or schizoaffective disorders (F25) based on MiniInternational Neuropsychiatric Interview¹⁴⁶; (3) had fewer than 24 months of untreated psychosis; and (4) were at least 18 years old. We focused on early stages of illness, to minimize the effects of illness burden and medications on brain structure. Thus, individuals who were hospitalized before meeting the diagnostic criteria for schizophrenia are a particularly interesting group. These participants were included in the study and received the working diagnosis of acute and transient psychotic disorders, congruent with the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) brief psychotic disorder. Healthy controls, at least 18 years old, were recruited via advertisement, using the following exclusion criteria: (1) lifetime history of any psychiatric disorders and (2) psychotic disorders in first- or second-degree relatives. Additional exclusion criteria for both groups included history of neurological or cerebrovascular disorders and any MRI contraindications.

3.2.2 *MRI Acquisition*

Structural MRI data were collected at 2 sites, the NIMHCZ, N=378, and Institute of Clinical Experimental Medicine in Prague (IKEM), N=319. We acquired T1-weighted 3D MPRAGE scans (TE=4.63 ms, TR=2300 ms, bandwidth 130 Hz/pixel, FOV=256×256 mm, matrix 256×256, voxel size 1×1×1 mm³) on 3T Siemens Trio MRI scanner (IKEM) or 3T Siemens Prisma MAGNETOM (NIMHCZ) MRI equipped with standard head coil.

3.2.3 *Brain Age Estimation*

We estimated the brain age of each participant using a machine learning method which was developed by us (K.F.), extensively validated^{147,148}, shown to be sensitive to metabolic or psychiatric disorders^{136,145,149,150}, and robust to inter-scanner differences^{147,148}. Briefly, this

included (1) standard voxel-based morphometry preprocessing of structural MRI data, (2) feature reduction via smoothing and principal component analysis, and (3) age estimation using relevance vector regression (RVR). This RVR model was trained using an independent sample of 504 healthy individuals from the IXI database (<http://www.brain-development.org>). For more details, see Franke et al¹⁴⁸⁻¹⁵⁰ and [Appendix E](#).

3.3.3 Cognitive Data

Cognitive measures included verbal and working memory tests. Verbal memory performance was assessed using validated Czech versions of the Rey Auditory Verbal Memory test (AVLT)¹⁵¹. Two AVLT scores were used for analysis: total immediate recall score (i.e. the sum of recalled words in Trials I-V), and delayed recall after 30 minutes. Working memory was assessed using digit span (forward, backward span), which is a part of Wechsler Adult Intelligence Scale III (WAIS-III)¹⁵². These measures may be more sensitive than other cognitive tests to metabolic alterations or schizophrenia^{153,154 155,156}.

3.3.4 Other Variables

Within one week before scanning, we acquired information about personal history of hypertension, diabetes mellitus, myocardial infarction, duration of untreated/treated psychiatric illness and current medications (name, dosage). On the day of scanning, we obtained symptom ratings, weight, height, hip and waist circumference as well as fasting blood samples. Body mass index (BMI) was calculated using the formula: $BMI = \text{weight (kg)}/\text{height (meters)}^{157}$. Waist-Hip Ratio (WHR) was measured by first determining the waist circumference at the narrowest part of the waist, and the hip circumference at the widest part of the hips or buttocks¹⁵⁸. The assessment of blood metabolite levels was performed in a single clinical laboratory using standard methods. We measured LDL-cholesterol, HDL-cholesterol and triglycerides (TGC), fasting glucose and

insulin and high sensitivity C-reactive protein. We calculated HOMA-IR to quantify insulin resistance, using the equation:

$$\text{HOMA-IR} = \frac{[\text{fasting plasma insulin (mU/L)} \times \text{fasting plasma glucose (mmol/L)}]}{22.5}.$$

We collected information about clinical and treatment variables via personal interview together with all available collateral data from medical records, treatment providers, and family members. All diagnostic assessments and symptom ratings were performed by a psychiatrist using the Mini-International Neuropsychiatric Interview¹⁴⁶ and the Positive and Negative Syndrome Scale¹⁵⁹. We expressed antipsychotic doses in chlorpromazine equivalents.

3.3.5 Statistical Analysis

We compared FEP and controls using linear or logistic regression modeling, based on the outcome (continuous vs. categorical), while adjusting for age and sex. For HDL, LDL, hs-CRP, BMI and WHR, all measurements were within an expected physiological range. For TGC and HOMA-IR, values beyond four standard deviations of the mean were excluded as they were biologically implausible. Measures that were not normally distributed were transformed using either a logarithmic function (HDL, LDL) or Box-Cox transformation (hs-CRP, HOMA-IR, TGC, BMI), whichever achieved better normalization.

In the first part of the analyses, we attempted to identify whether obesity/metabolic marker-related brain alterations were associated with cognitive changes. To this goal, we used linear regression to test in a single model whether BrainAGE was significantly predicted by WHR, BMI, and/or HDL, LDL, TGC, HOMA-IR, hs-CRP. Next, we tested whether the strongest predictors of brain structure also predicted cognitive performance (one model per cognitive

measure, including verbal and working memory). Lastly, we tested whether obesity-related cognitive alterations were predicted by BrainAGE. All models adjusted for age, sex, and diagnosis.

In the second part of the analyses, we tested whether BrainAGE mediated the differences between FEP and controls in obesity-related cognitive alterations. Further, we tested whether differences in BrainAGE between FEP and controls were mediated by obesity. The mediation analyses included average direct effects (ADE) and average causal mediated effects (ACME) using a quasi-Bayesian approximation of the 95% confidence interval (95% CI) with the R package *mediation*¹⁶⁰.

To test for possible confounding by clinical variables, we used linear regression in people with FEP to test whether obesity, BrainAGE or cognitive scores were associated with medication dosage, duration of treatment, illness duration, specific diagnosis (F20, F23, F25), arterial hypertension and whether the associations between obesity versus brain or cognitive alterations remained significant when controlling for these clinical variables. As BMI alone was used in many previous studies, we also tested for associations between BMI and BrainAGE or cognition.

All regression and mediation models controlled for age, sex, and diagnosis. We also controlled for scanner as a random effect, when appropriate. We report FDR-adjusted *p*-values to control for multiple comparisons across cognitive measures. Model residuals were confirmed as normally distributed using QQ plots, and the Kolmogorov-Smirnov test for normality. We assessed multicollinearity using the variance inflation factor (VIF), and used the *stats* package in R version 4.1.1 for regression modeling (R Core Team, 2023, DOI: 10.18637/jss.v059.i05).

3.3 RESULTS

3.3.1 Sample

The study consisted of 440 participants with FEP and 257 controls. Relative to controls, participants with FEP had a higher BrainAGE, higher WHR, more abnormal biochemical markers (HDL, LDL, TGC), lower performance in all cognitive tasks, and were more likely to be male, see Table 3.1 and supplementary [Figure C1](#).

Table 3.1. Participant demographic and clinical characteristics by group, with significant group differences marked using asterisks (*, $p < 0.05$), adjusting for age and sex. For BMI, hs-CRP, HDL, LDL, TGC and HOMA-IR, raw values are reported but statistical testing uses normalized values.

	Control N=257	FEP N=440	Group difference
Age – Mean (SD)	28.58 (7.27)	28.87 (7.57)	$t(695) = 0.50, p = 0.618$
Sex, M – n (%)	109 (42.4)	260 (59.1)	$\chi^2=17.45, p < 0.001 *$
BrainAGE - Mean (SD)	1.44 (5.39)	4.16 (6.32)	$t(693) = 6.59, p < 0.001 *$
Waist Hip Ratio (WHR) - Mean (SD)	0.82 (0.07)	0.87 (0.08)	$t(307) = 4.16, p < 0.001 *$
BMI - Mean (SD)	23.22 (3.50)	24.18 (4.29)	$t(692) = 1.42, p = 0.155$
hs-CRP - Mean (SD)	1.82 (2.82)	2.14 (3.91)	$t(553) = 0.61, p = 0.545$
HDL - Mean (SD)	1.57 (0.40)	1.33 (0.37)	$t(551) = -5.88, p < 0.001 *$
LDL - Mean (SD)	2.49 (0.70)	2.68 (0.78)	$t(542) = 2.37, p = 0.018 *$
TGC - Mean (SD)	1.11 (0.53)	1.31 (0.67)	$t(543) = 2.72, p = 0.007 *$
HOMA-IR - Mean (SD)	1.49 (1.02)	1.96 (1.61)	$t(412) = 1.9, p = 0.058$
Arterial hypertension – n (%)	5 (1.0)	16 (2.0)	$Z = 1.19, p = 0.234$
Myocardial infarction – n (%)	0 (0.0)	1 (0.0)	NA
T1DM – n (%)	0 (0.0)	1 (0.0)	NA
T2DM – n (%)	0 (0.0)	1 (0.0)	NA
AVLT Trials I-V - Mean (SD)	59.92 (8.23)	46.59 (11.61)	$t(396) = -11.12, p < 0.001 *$
AVLT Trial VI - Mean (SD)	12.59 (2.19)	9.24 (3.08)	$t(398) = -10.57, p < 0.001 *$
AVLT After 30 Min - Mean (SD)	12.59 (2.29)	8.49 (3.40)	$t(398) = -12, p < 0.001 *$
Digit Span Forward - Mean (SD)	9.98 (2.11)	8.68 (1.89)	$t(396) = -6.42, p < 0.001 *$
Digit Span Backward - Mean (SD)	8.15 (2.22)	5.85 (2.04)	$t(396) = -10.66, p < 0.001 *$
Digit Span Total - Mean (SD)	18.10 (3.76)	14.47 (3.64)	$t(397) = -9.5, p < 0.001 *$
PANSS Positive score – Mean (SD)	N/A	11.86 (4.11)	N/A
PANSS Negative score – Mean (SD)	N/A	15.57 (5.78)	N/A
PANSS Global score – Mean (SD)	N/A	29.34 (8.08)	N/A

Antipsychotic dose (chlorpromazine equivalent, mg) – Mean (SD)	N/A	544 (345)	N/A
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3.3.2 *BrainAGE Model Performance*

Among healthy subjects (testing sample), the mean absolute error (MAE) of prediction was 5.38 years with an acceptable agreement between chronological and predicted brain age (intraclass correlation coefficient [ICC] = 0.70; 95% confidence interval [CI]: 0.64–0.76).

Although the model performance is somewhat lower than in our previous validation (MAE = 5.08, $R^2 = 0.83$)¹⁴⁸ and other models (e.g., MAE = 4.6, $R^2 = 0.83$ ¹⁶¹; MAE = 4.31, $R^2 = 0.79$ ¹⁶²), it is to be expected given the relatively young age of included subjects and a known model tendency to overestimate the brain age of younger individuals¹⁶³.

3.3.3 *Obesity-Related Brain and Cognitive Alterations*

We first tested which predictors among BMI, WHR, or the metabolic/inflammatory markers were most strongly associated with BrainAGE. With all measures in a single model while adjusting for age, sex, and diagnosis, only WHR significantly predicted BrainAGE ($F(1, 281)=6.38$, $p=0.012$, Figure 3.1). We therefore took WHR as our indicator of obesity for subsequent analyses.

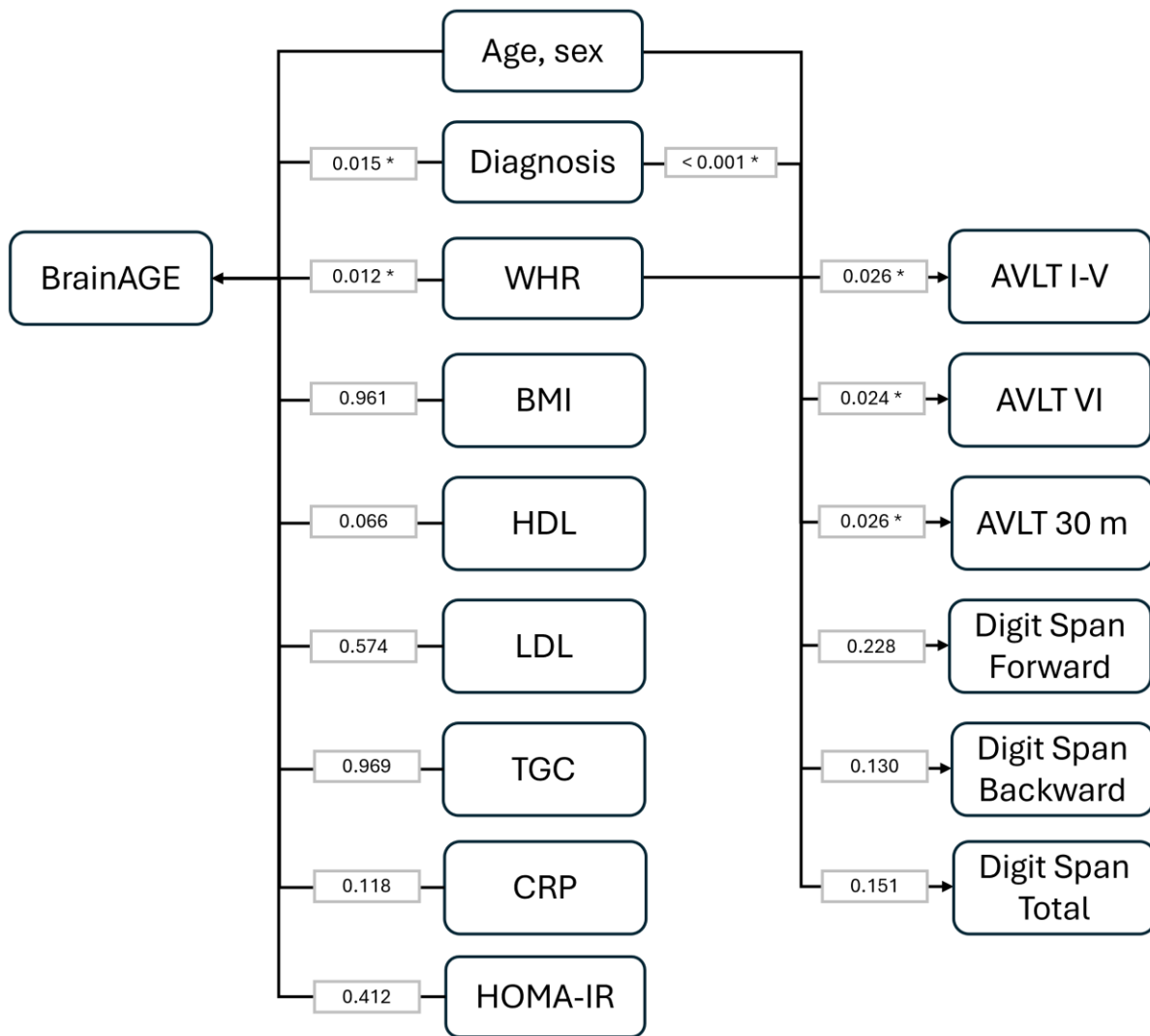


Figure 3.1. Significance (p) for associations between metabolites, measures of obesity, BrainAGE, and cognition, when adjusting for age, sex, and diagnosis. Significance is marked using asterisks (*, $p < 0.05$).

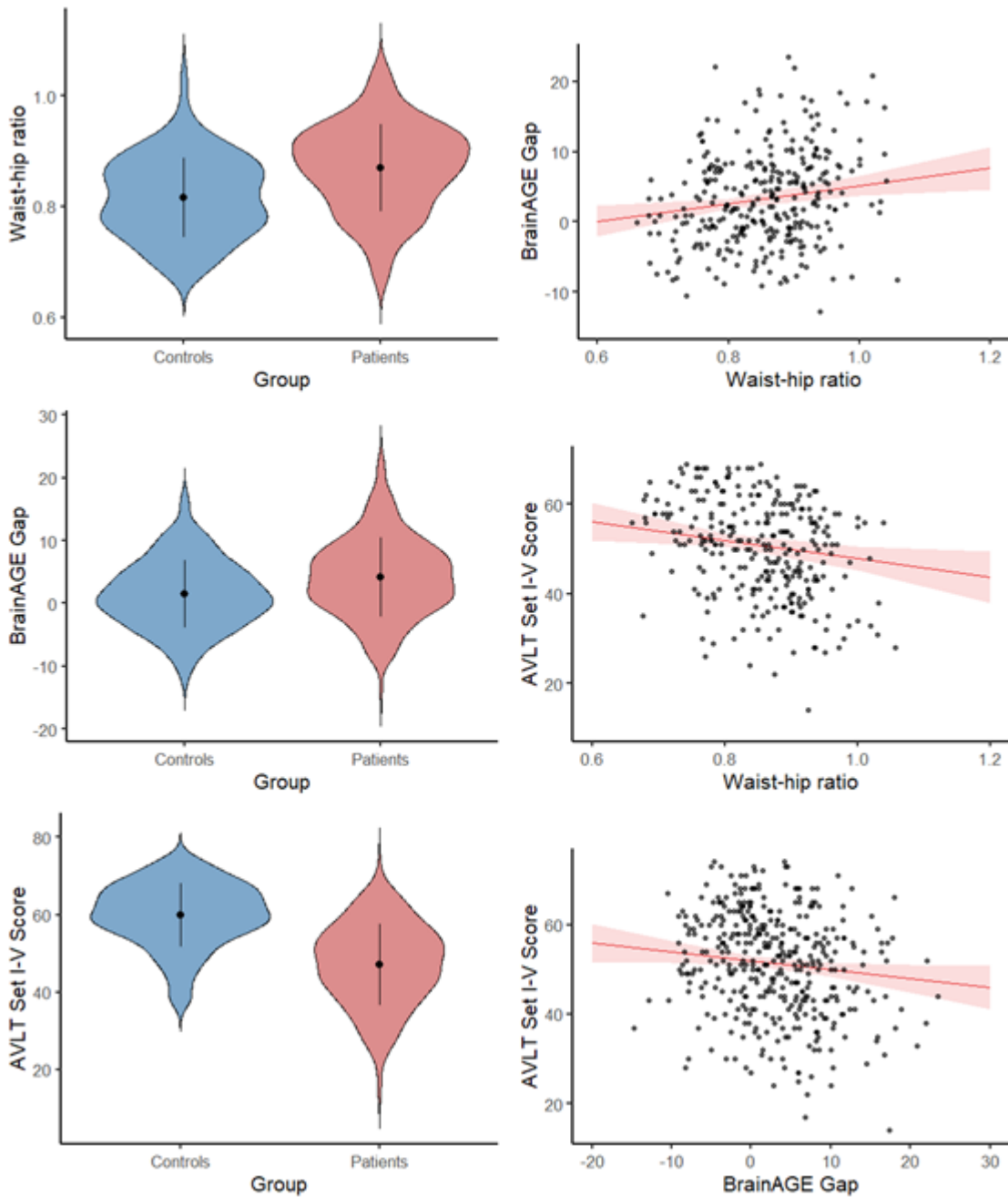


Figure 3.2 Differences between FEP and control participants and associations between relevant variables. Raw data distributions are shown, with error bars showing one standard deviation.

Next, we aimed to identify cognitive correlates of obesity. Higher WHR was significantly associated with worse AVLT performance when adjusting for age, sex, and diagnosis (Figure 3.2, Table 3.2). However, it was not significantly associated with digit span (Figure 3.1, Table 3.2). We therefore took AVLT as our obesity-related cognitive performance indicator for subsequent analyses.

Table 3.2 Partial effects of WHR and diagnosis on cognitive tests while adjusting for one another, age, and sex, with significance marked using asterisks (*, $p < 0.01$).

Outcome	Effect	Estimate (SE)	Significance
AVLT Trials I-V	WHR	-0.14 (0.05)	$t(290) = -2.51, p = 0.026 *$
	Diagnosis	-0.90 (0.10)	$t(290) = -8.65, p < 0.001 *$
AVLT Trial VI	WHR	-0.17 (0.06)	$t(290) = -2.88, p = 0.024 *$
	Diagnosis	-0.92 (0.11)	$t(290) = -8.10, p < 0.001 *$
AVLT After 30 Min	WHR	-0.15 (0.06)	$t(290) = -2.60, p = 0.026 *$
	Diagnosis	-1.00 (0.11)	$t(290) = -8.97, p < 0.001 *$
Digit Span Forward	WHR	-0.08 (0.07)	$t(288) = -1.21, p = 0.228$
	Diagnosis	-0.65 (0.13)	$t(288) = -4.98, p < 0.001 *$
Digit Span Backward	WHR	-0.11 (0.07)	$t(288) = -1.72, p = 0.131$
	Diagnosis	-0.98 (0.13)	$t(288) = -7.86, p < 0.001 *$
Digit Span Total	WHR	-0.10 (0.07)	$t(289) = -1.53, p = 0.151$
	Diagnosis	-0.90 (0.13)	$t(289) = -7.04, p < 0.001 *$
Age and sex were included as covariates in each model, but were not significant predictors of any cognitive measure.			

Lastly, we tested whether BrainAGE predicted these cognitive alterations. Higher BrainAGE was significantly associated with worse AVLT scores (Trials I-V: $t(394) = -2.42, p = 0.028$; Figure 3.2, 30-minute recall: $t(397) = -2.35, p = 0.028$), when adjusting for age, sex, and diagnosis.

3.3.4 Mediation Analyses

As shown in Table 3.1 and Figure 3.2, participants with FEP had significantly higher BrainAGE, WHR and significantly worse AVLT performance. The association between FEP and AVLT scores (Trials I-V) was partially mediated by BrainAGE (ACME=-0.04 [-0.10,-0.01], $p=0.022$, 4.1% mediation) and the higher BrainAGE in FEP was partially mediated by higher WHR (ACME=-0.08 [0.02, 0.15], $p=0.006$, 15.4% mediation, see Figure 3.3). The results were similar using AVLT 30-minute recall scores (Supplementary Figure C2).

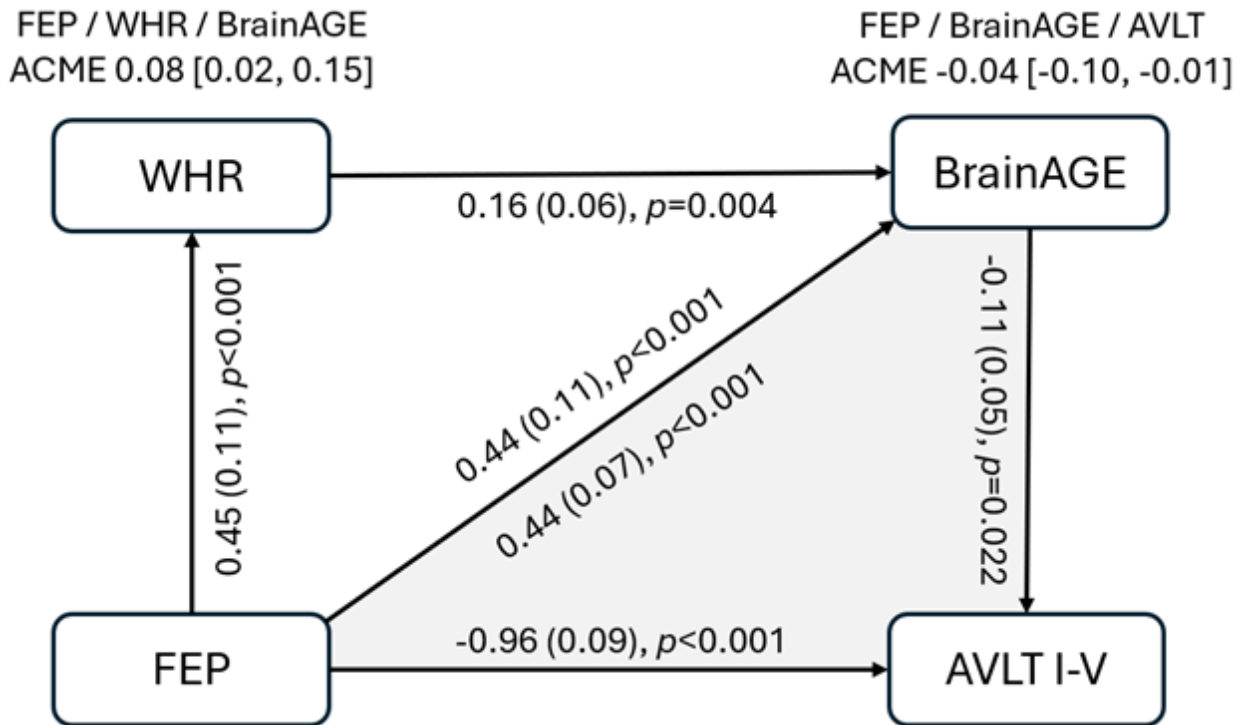


Figure 3.3 Standardized coefficients and their standard error for associations between FEP, WHR, BrainAGE, and AVLT scores (Trials I-V), while controlling for participant age and sex. Average causal mediated effect (ACME) is shown with its 95% confidence interval.

3.3.5 *Potential Confounding by Psychotic Symptoms, Antipsychotic Medication*

Medication dose was associated with BrainAGE but not with WHR or AVLT. Duration of illness, duration of treatment, specific diagnosis (F20, F23, F25), and arterial hypertension were not significantly associated with either of WHR, AVLT scores or BrainAGE. Furthermore, even when we controlled for these clinical variables, the effect of WHR on BrainAGE or AVLT scores remained significant, see supplementary [Table A9](#) for details.

3.3.6 *Exploratory Analyses*

BMI was significantly associated with BrainAGE ($t(690)=3.06, p=0.003$), but not AVLT or digit span scores, see supplementary [Tables A10, A11](#).

3.4 DISCUSSION

In this study, we showed that central obesity, as measured by WHR, was a stronger predictor of brain alterations than BMI or serum concentrations of HDL, LDL, TGC, HOMA-IR or hs-CRP. An increase in WHR by 0.08 (one quartile of the range in this sample) was associated with a 1-year increase in BrainAGE. Central obesity as captured by WHR was also associated with verbal, but not working memory. Most importantly, brain and cognitive alterations in FEP were in part related to central obesity. Specifically, cognitive impairment in FEP was mediated by neurostructural alterations, which were in turn mediated by central obesity.

This is, to our knowledge, the first study showing that obesity-related brain alterations are associated with worse verbal memory in individuals with FEP. In the general population, regional alterations related to obesity were also associated with poor executive functioning (orbital frontal lobe) or spatial memory (posterior cingulate)^{164,165}. Our findings also broadly match other studies,

showing more pronounced brain changes¹³³ or cognitive impairments^{166,167} in obese individuals with SMI. In our study, BrainAGE explained part of the association between psychosis and verbal memory and obesity explained part of the association between psychosis and BrainAGE. The proportions mediated may seem small, i.e. 4.1% and 15.4%, respectively. However, considering the many competing factors which can contribute to cognitive impairment in psychosis, it is striking that a measure as broad as BrainAGE claimed part of this association. Additionally, these are individuals in the early stages of illness with relatively preserved cognition and yet, we are already detecting the effects of obesity via changes in brain structure. As these are young individuals (average age ~29 years), these changes are likely to compound over time. These obesity-related brain structure-function links could help partially explain why obese, relative to lean, individuals with severe mental illnesses have worse psychiatric outcomes or show worse psychosocial functioning^{52,137,168-171}.

In our study, central obesity was a stronger predictor of brain and cognitive alterations compared to BMI or individual metabolic markers. This replicates results from other studies in which WHR relative to BMI showed stronger and more widespread associations with brain structure¹⁷²⁻¹⁷⁷, cognitive alterations¹⁷⁸ or dementia¹⁷⁹. Other studies have also shown that obesity is a stronger predictor of brain changes than individual biochemical markers^{137,175,176,180-182}. Furthermore, improvements in brain structure following bariatric surgery are more strongly associated with weight loss than with improvements in metabolic or inflammatory markers¹⁸³⁻¹⁸⁶. In younger populations, overweight/obesity may be the dominant predictor of brain and cognitive changes, as it is generally more prevalent and usually manifests much earlier than the other metabolic alterations. The broader range of cognitive impairments associated with obesity in other studies^{167,187-190} could be related to older participant age, greater extent of obesity, or the fact that

digit span was perhaps not challenging enough in this young population early in the course of illness¹⁹¹.

The directionality and underlying mechanisms linking obesity to brain alterations remain unclear. Obesity could impair the brain through pathways such as excessive glycation via hyperglycemia, impaired insulin signaling, and systemic inflammation. Interestingly, in our multiple regression model (Figure 3.1), neither hyperglycemia, insulin resistance (as measured by HOMA-IR) nor inflammation (as measured by hs-CRP) were associated with BrainAGE. Given the relatively young age of this population, contributions from vascular pathologies including hypertension or angiopathy are not particularly likely. Other potential mechanisms which we did not measure could include oxidative stress¹⁹², mitochondrial dysfunction¹⁹³, hypercortisolemia¹⁹⁴ or leptin modulation of microglia¹⁹⁵. It is also possible that certain brain alterations, perhaps those involving regions related to reward processing, appetite regulation, or impulse control, may predispose one to become obese. However, the diffuse nature of the changes as captured by BrainAGE make this less likely^{137,145} and findings from several Mendelian randomization studies further suggest that obesity causes brain alterations, not the other way around^{137,171,196–200}. Importantly, several longitudinal studies have identified obesity as a prognostic factor for future worsening of cognitive and brain changes¹³⁷ and successful weight loss following bariatric surgery has been shown to improve brain and cognitive indices^{183,201,185,202,186}.

Regardless of what came first, monitoring of obesity is relevant not only for cardiovascular, but also for brain and cognitive health. A clinician could expect more pronounced brain and cognitive alterations in people with central obesity. However, current guidelines do not specifically recommend using WHR to monitor for obesity, which we have shown to be a stronger

predictor of brain and cognitive outcomes than BMI. While we cannot confirm causality, our findings raise the possibility that preventing or treating obesity could help prevent or mitigate brain/cognitive alterations in FEP, which are currently mostly intractable. This is particularly interesting as we now have very effective weight loss medications and GLP1 agonists are now being tested for treatment of antipsychotic-induced weight gain²⁰³. These findings also raise important questions about whether weight gain itself may contribute to the adverse cognitive^{119–121} and neurostructural^{204,205} effects associated with certain obesogenic psychiatric medications. There is enough evidence to emphasize preferentially using medication with lower propensity for weight gain especially in lean individuals, who are most likely to gain weight¹³⁸. These findings could also create additional impetus for clients to focus on weight management and help promote healthy lifestyle choices.

Our study has several limitations. First, due to its cross-sectional design, we cannot establish the direction of these associations, i.e. obesity first or brain changes first. Second, we were unable to account for the influence of socioeconomic status, life events, chronic stress, dietary habits, or physical activity levels, all of which are complex to measure and often subject to reporting bias. Nevertheless, even if obesity is only a proxy for broader lifestyle factors, it remains a more quantifiable and clinically actionable target than any single behavioral or environmental measure. While we did exclude participants with large vessel disease, we cannot rule out microangiopathy. Due to complexity of recruitment, cognitive or biochemical measures were missing in some individuals. Lastly, we used chlorpromazine equivalents at the time of the MRI scan as a proxy for antipsychotic exposure, which may not fully capture the cumulative or differential effects of medication over time.

Our study has the following strengths. This is, to our knowledge, the first dedicated study focusing on the structure-function links between obesity, brain, and cognition in FEP or any SMI. The large sample size allowed us to model the effects of multiple predictors. We focused on people in the early stages of illness, which is a particularly dynamic period where small changes can have lasting consequences. We replicated many previous observations, which increases the chance that even the new links we observed are true positive findings. We included a cumulative measure of diffuse brain structural alterations (BrainAGE), which is easier to interpret than focusing on many individual brain regions of interest.

In conclusion, we showed that central obesity was associated with both brain structural and cognitive alterations already early in the course of psychosis. The fact that obesity-related brain alterations are linked with impairment in verbal learning could explain the poorer cognitive and psychiatric outcomes in obese individuals with SMI. The links between central obesity and brain as well as cognitive changes put a greater emphasis on monitoring of WHR not only for cardiovascular, but also brain health and already early in the course of psychosis. Future studies should investigate whether treatment of obesity with GLP1 agonists could help reverse the brain and cognitive changes and improve psychiatric outcomes.

CHAPTER 4 THE ROLE OF METABOLIC HEALTH IN NEUROSTRUCTURAL AND COGNITIVE ALTERATIONS IN BIPOLAR DISORDERS

4.1 INTRODUCTION

Bipolar disorder (BD) is a chronic psychiatric condition affecting approximately 20,000 Nova Scotians²⁰⁶, and is characterized by recurrent episodes of mania and depression.

Individuals with BD suffer significant functional impairments such as difficulty living independently, employment instability, and housing insecurity^{6,9,11,129}. In fact, approximately 79% of the economic burden of bipolar disorder is due to indirect costs such as occupational impairment, as opposed to direct treatment costs such as hospitalization²⁰⁷.

Cognitive deficits, specifically in verbal learning and memory, attention, working memory, and executive function²³⁻²⁷, persist well into remission and are among the strongest predictors of psychosocial and occupational impairment in BD, even more so than clinical factors²⁰⁸⁻²¹⁰. Moreover, individuals with BD exhibit widespread brain structural alterations, including reduced hippocampal, amygdala, and thalamic volumes, ventricular enlargement, and cortical thinning^{211,212}. The underlying cause of these brain structural and cognitive alterations is difficult to pinpoint, as they could be attributable to shared genetic susceptibility, inherent pathophysiological mechanisms, illness burden and chronicity, socioeconomic factors, or medications. From a clinical perspective, these factors are difficult to address, and current first-line treatments such as antipsychotics or anticonvulsants may even themselves contribute to poorer structural and cognitive outcomes^{211,213-215}. For this reason, identifying risk factors of these alterations that are modifiable and treatable is crucial for improving treatment strategies and functional outcomes.

One such risk factor that is modifiable and overrepresented in BD is obesity, which has

been independently associated with both brain and cognitive outcomes. People with BD are at a significantly higher risk of developing metabolic disorders, including a fivefold greater risk of cardiovascular disease²¹⁶, 3.5-fold greater risk of metabolic syndrome (MetSy), and 1.2-fold greater risk of insulin resistance²¹⁷, compared to the general population. Specifically, studies of metabolic health in BD report greater adiposity, blood pressure, impaired fasting glucose, low HDL cholesterol, hypertriglyceridemia, and insulin resistance^{217,218}. Previous findings suggest that obesity and related metabolic disturbances may actively contribute to the severity and progression of the illness, as obese individuals with BD tend to have more severe mood symptoms, rapid cycling, and worse treatment response⁵²⁻⁵⁵. Moreover, individuals with comorbid BD and metabolic disturbances show more pronounced brain structural alterations^{41,43,46,219}, with several large-scale studies linking BMI to the same neurostructural alterations observed in BD, including ventricular enlargement and cortical thinning⁴¹⁻⁴³.

Beyond structural alterations, comorbid BD and insulin resistance, T2DM, MetSy, greater BMI and TGC are all negatively associated with global cognition⁴⁵, attention, executive function, verbal and visual memory⁴⁵⁻⁴⁷. These cognitive alterations are particularly concerning as they have been closely linked to social and occupational functional outcomes²²⁰. Ideally, interventions would aim to reduce both brain and cognitive impairments. However, if cognitive deficits are mediated by underlying structural brain changes, then preventing these neurostructural alterations could mitigate the progression of cognitive and functional decline, providing a more precise and effective therapeutic target.

Most prior studies have examined metabolic dysfunction as isolated factors (e.g., BMI alone). However, metabolic dysfunction rarely occurs in isolation; Many of these risk factors are interrelated, sharing common pathophysiological mechanisms such as microvascular damage,

systemic inflammation, and hormonal dysregulation. Assessing each factor independently overlooks the cumulative, multifactorial nature of metabolic health. Additionally, testing each factor separately reduces statistical power when included in the same model, or runs the risk of Type I errors associated with running multiple tests. The common use of categorical definitions of metabolic markers and metabolic syndrome is also suboptimal, as it disregards the dimensional nature of these conditions and further diminishes statistical power.

To address these challenges, our study employs a fully multivariate, data-driven approach to examine the complex interplay between metabolic health, brain structure, and cognition in BD. Using principal component analysis (PCA), we derive a composite metabolic health variable that captures the cumulative and interactive effects of multiple metabolic factors in a way that reflects real-world epidemiological trends. Additionally, we generate a PCA-derived composite cognitive measure that includes measures of executive function, working memory, and verbal learning and memory – domains which have been implicated in BD. We employ a machine-learning-predicted BrainAGE to assess whole-brain neurostructural alterations, making this the first study to integrate these two multivariate approaches.

We hypothesize that BD will be associated with accelerated BrainAGE, lower cognitive performance, and poorer metabolic health, with the latter partially mediating the effects of BD on brain structure and cognition. By leveraging these advanced multivariate methods, our study offers a more objective and comprehensive framework for understanding the impact of metabolic health on neurostructural and cognitive alterations in BD, in a way that reflects the real-world epidemiology of these conditions.

4.2 METHODS

4.2.1 Patient Recruitment

We recruited 75 BD patients through follow up at a specialized Mood Disorders Program at the Abbie J Lane hospital in Halifax, NS and 88 community-dwelling healthy controls. The Mood Disorders Program is a tertiary care clinic providing consultation services to family physicians and community psychiatrists and following up patients with BD. The diagnostic interviews were performed by pairs of clinicians, according to the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L) and diagnoses were made according to DSM-IV criteria. Included patients were required to 1) have the diagnosis of bipolar I or II disorder made by a psychiatrist; and 2) be at least 18 years of age. Patients were excluded if they had 1) the diagnosis of organic mood disorder; 2) mood disorder not otherwise specified; or 3) more than one lifetime course of electroconvulsive therapy or electroconvulsive therapy within the last 6 months. Controls were excluded if they had 1) a personal history of psychiatric disorders; or 2) T2DM. Additional exclusion criteria for both groups included history of 1) substance use disorder in the last 12 months; 2) neurological or cerebrovascular disorders, and any MRI contraindications.

4.2.2 MRI Acquisition

All magnetic resonance acquisitions were performed with a 1.5 Tesla General Electric Signa scanner (General Electric Medical Systems, Fairfield, Connecticut) and a standard quadrature head coil. After a localizer scan, a T1-weighted spoiled gradient recalled scan was performed (flip angle=40°, echo time=5 ms, repetition time=25 ms, field of view=24 cm x 18cm, matrix=256 x 160 pixels, number of excitations=1, no interslice gap, 124 slices, 1.5mm thick).

4.2.3 *BrainAGE Estimation*

BrainAGE was estimated using the same methods described in [section 3.2.3](#). For more details, see Franke et al¹⁴⁸⁻¹⁵⁰ and [Appendix E](#).

4.2.4 *Cognitive Data*

Based on evidence that cognitive deficits in BD are similar in pattern but less severe than in schizophrenia^{18,221}, we selected cognitive assessments that are analogous to those described in [Chapter 3](#). Verbal learning and memory was assessed using the second edition of the California Verbal Learning Test (CVLT-II)²²². The test involves remembering a list of 16 words (List A) over five learning trials, followed by interference (List B) and delayed recall trials. Scores evaluate aptitude for verbal learning, as well as the impact of interference on retention and retrieval. We included the following measures from the CVLT-II: 1) the total immediate recall score (i.e. the sum of recalled words across Trials I-V); 2) the learning slope (i.e. the difference between each participant's Trial V and Trial I scores), 3) Short-Delay (5 min) free recall scores, 4) Long-Delay (20 min) free recall scores, Total 5) intrusion and 6) repetition errors (across all recall trials).

We further assessed executive function and cognitive flexibility by deriving two performance contrast measures, as per the CVLT-II scoring manual: 1) Proactive Interference (PI), and 2) Retroactive Interference (RI) scores. PI is defined as the decremental effect of prior learning on the retention of subsequently learned material²²³ and was calculated by subtracting each participant's Trial I immediate recall score from their score on the List B Trial²²⁴. Negative scores therefore represent greater PI, such that prior learning of List A words interferes with the ability to retain novel List B words. RI is defined as the decremental effect of learning new information on the recall of previously learned information²²³ and was calculated by subtracting each participant's Trial V score from their Short-Delay free recall score²²⁴. Negative scores

represent greater RI, such that learning of new List B words interferes with the recall of previously learned List A words. There exists some debate regarding which specific cognitive processes govern susceptibility to interference effects²²⁵, yet patients with BD exhibit demonstrated deficits in many of the proposed executive components necessary for suppression of interference effects, including memory for temporal order²²⁶, response inhibition²²⁷, verbal fluency²²⁸, and cognitive flexibility/set shifting^{229,230}. It has previously been shown that Schizophrenia patients are more susceptible to RI but comparable in PI to controls²²⁵, however, the present study is the first to our knowledge to examine these cognitive processes in BD.

Auditory attention was assessed using the forward digit span test and working memory was assessed using the backward digit span test of the Wechsler Adult Intelligence Scale III (WAIS-III)¹⁵².

4.2.5 *Other Variables*

Prior to scanning, we collected participants' responses to detailed personal history questionnaires regarding history of hypertension, diabetes mellitus, myocardial infarction, and other somatic comorbidities as well as medications history. Full psychiatric evaluations were performed by a registered psychiatrist and included information regarding BD type, age of onset, number of prior hospitalizations, number of manic and/or depressive episodes, duration of illness and current medications (name, dosage).

On the day of scanning, we obtained symptoms ratings using the Young Mania Ratings Scale (YMRS)²³¹ and Hamilton Depression (HAM-D) scale²³². We collected anthropometric measures, including weight, height, hip and waist circumferences. Body-mass index (BMI) was calculated using the formula: $BMI = \text{weight (kg)}/\text{height (meters)}$. Waist-to-hip ratio (WHR) was calculated by dividing waist circumference by hip circumference. We collected fasting blood

samples, and assessment of blood metabolite levels was performed in a single clinical laboratory using standard methods. We measured LDL-cholesterol, HDL-cholesterol, fasting triglycerides (TGC), fasting glucose, glycosylated hemoglobin (HbA1c), and fasting insulin. We calculated the homeostatic model assessment of insulin resistance (HOMA-IR) using the equation,

$$\text{HOMA-IR} = [\text{fasting plasma insulin (mU/L)} \times \text{fasting plasma glucose (mmol/L)}] / 22.5.$$

4.2.6 Principal Component Analysis

We used Principal Component Analysis (PCA) to derive a composite measure of metabolic health from a set of metabolic indicators: 1) WHR, 2) BMI, 3) HOMA-IR, 4) HbA1c, 5) TGC, 6) HDL, 7) LDL, 8) Systolic BP, 9) Diastolic BP. Due to a high degree of multicollinearity as measured by the variance inflation factor (VIF = 13.03), waist circumference was not included in the PCA model. Missing values (a maximum of 12.27% in WHR]) were imputed using the *missForest* algorithm, using the R package *missForest*²³³. The PC1 scores for each individual were extracted and used as a continuous variable (Metabolic PC1) in subsequent analyses.

Similarly, we used PCA to derive a composite measure of cognitive function from the following cognitive test scores: 1) Sum of Trials I-V, 2) Learning Slope, 3) Short-Delay free recall, 4) Long-Delay free recall, 5) Total Intrusions, 6) Total Repetitions, 7) Retroactive Interference, 8) Proactive Interference, 9) Forward digit span, 10) Backward digit span. Missing values (20.25% for Learning Slope, Retroactive Interference, and Proactive Interference) were imputed using *missForest*²³³. The PC1 scores for each individual were extracted and used as a continuous variable (Cognitive PC1) in subsequent analyses. All variables were standardized (z-scored) prior to PCA to ensure comparability across different scales. PCA was performed using the *prcomp* function in R.

4.2.6 Statistical Analyses

We compared demographic and clinical characteristics, as well as BrainAGE and cognitive test scores between BD and controls using multiple linear regression for continuous variables and logistic regression for categorical variables, with age and sex as covariates. Lithium treatment was additionally included as a covariate in all models where BrainAGE served as the outcome, to account for its well-established neuroprotective effects^{234,235}. CVLT Trial I score was included as an additional covariate in models with Learning Slope as the outcome. Measures that were not normally distributed were transformed using a Box-Cox transformation, which included triglycerides, HDL, fasting glucose, HbA1c, HOMA-IR. Total repetitions and total intrusions were transformed using the Yeo-Johnson transformation²³⁶, as this best improved normality, using the R package *bestNormalize*.

We first tested associations between metabolic health, BrainAGE, and cognitive performance. We created linear regression models to test Metabolic PC1 as a predictor of either BrainAGE or Cognitive PC1. To test whether brain structural changes were associated with cognitive alterations, we tested whether BrainAGE significantly predicted Cognitive PC1. All models controlled for age, sex, and diagnosis.

We next tested whether metabolic health contributed to brain structural changes in BD. To this goal, we ran a mediation model with diagnosis as the independent variable, BrainAGE as the dependent variable, and Metabolic PC1 as the mediator.

Last, we tested whether metabolic health contributed to cognitive alterations in BD. To this goal, we performed a mediation analysis with diagnosis as the independent variable, Cognitive PC1 as the dependent variable, and Metabolic PC1 as the mediator. All mediation analyses controlled for age and sex, and included average direct effects (ADE) and average causal

mediated effects (ACME) using a quasi-Bayesian approximation of the 95% confidence interval (95% CI) using the R package *mediation*¹⁶⁰.

To test for possible contributing effects of symptoms and medications, we used linear regression in the subset of participants with BD to test whether Metabolic PC1 was predicted by YMRS and HAM-D scores, number of prior episodes, number of prior hospitalizations, duration of illness, use of antipsychotics, antidepressants, anticonvulsants, or benzodiazepines, adjusting for age and sex. Factors that were associated with Metabolic PC1 were then tested as predictors of BrainAGE and/or Cognitive PC1.

4.3 RESULTS

4.3.1 Sample Descriptives

The sample consisted of 76 participants with BD and 87 controls. The mean age of participants was 43.14 (SD = 15.26), with a range of 18.89 to 74.25 years. Relative to controls, participants with BD were older, had lower levels of HDL, higher levels of TGC, greater BMI, waist circumference, and WHR. They were comparable to controls on digit span scores but performed worse on all measures of verbal learning and memory (see Tables 4.1 and 4.3).

Table 4.1 Participant demographic characteristics are presented by group, with significance indicated as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. All comparisons are adjusted for age and sex.

	Control	Patient	Significance
n	87	76	
Age (mean (SD))	39.88 (14.68)	46.82 (15.15)	$F(1,159)=8.76, p=0.004^{**}$
Sex (% Male)	34 (39.1)	34 (44.7)	$F(1,159)=0.5, p=0.479$
Diabetes (% Yes)	8 (9.8)	13 (21.0)	$F(1,139)=1.41, p=0.238$
Hypertension (% Yes)	13 (14.9)	22 (28.9)	$F(1,158)=1.49, p=0.225$
Overweight/Obese, BMI > 25 kg/m² (% Yes)	48 (55.2)	59 (77.6)	$F(1,158)=5.78, p=0.017^*$
TGC, mmol/L (mean (SD))	1.11 (0.66)	1.61 (1.57)	$F(1,150)=8.05, p=0.005^{**}$

LDL, mmol/L (mean (SD))	2.72 (0.78)	2.82 (0.81)	<i>F (1,150)=0.04,p=0.836</i>
HDL, mmol/L (mean (SD))	1.50 (0.46)	1.26 (0.34)	<i>F (1,150)=16.05,p<0.001***</i>
Fasting glucose, mmol/L (mean (SD))	5.13 (1.44)	5.18 (1.10)	<i>F (1,149)=0,p=0.955</i>
HbA1c (mean (SD))	5.31 (0.80)	5.58 (2.65)	<i>F (1,134)=1.83,p=0.179</i>
HOMA-IR (mean (SD))	2.06 (1.45)	2.50 (2.15)	<i>F (1,146)=0.82,p=0.367</i>
Systolic Blood Pressure (mean (SD))	115.15 (12.84)	120.54 (13.42)	<i>F (1,151)=2.25,p=0.136</i>
Diastolic Blood Pressure (mean (SD))	75.08 (10.21)	77.90 (12.46)	<i>F (1,151)=1.72,p=0.192</i>
BMI (mean (SD))	26.12 (4.88)	30.26 (6.21)	<i>F (1,158)=18.25,p<0.001***</i>
Waist circumference, cm (mean (SD))	88.32 (14.92)	101.57 (15.57)	<i>F (1,154)=20.8,p<0.001***</i>
Waist-to-Hip Ratio (mean (SD))	0.86 (0.09)	0.92 (0.08)	<i>F (1,137)=14.7,p<0.001***</i>

Table 4.2 Participant clinical characteristics are presented by group.

	Controls	Patients
n	87	76
Age of Onset (mean (SD))	NA	23.99 (9.30)
BD Type (Type 2 (%))	NA	21 (27.6)
Number of Prior Episodes (mean (SD))	NA	10.35 (11.28)
Number of Prior Hospitalizations (mean (SD))	NA	2.22 (4.94)
Duration of Illness, years (mean (SD))	NA	20.74 (12.00)
ADHD (Yes (%))	1 (1.1)	2 (2.6)
Anxiety Disorders (Yes (%))	6 (6.9)	24 (31.6)
Eating Disorders (Yes (%))	0 (0.0)	1 (1.3)
Substance Use Disorder (Yes (%))	1 (1.1)	12 (15.8)
Other Psychiatric Disorder (Yes (%))	1 (1.1)	9 (11.8)
Antipsychotics (Yes (%))	0 (0.0)	38 (50.0)
Anticonvulsants (Yes (%))	2 (2.3)	36 (47.4)
Antidepressants (Yes (%))	2 (2.3)	30 (39.5)
Benzodiazepine (Yes (%))	0 (0.0)	15 (19.7)
Lithium (Yes (%))	0 (0.0)	42 (55.3)
HAM-D Score (mean (SD))	1.25 (1.97)	5.41 (5.44)
YMRS Score (mean (SD))	0.60 (1.25)	1.92 (3.04)

Table 4.3 Participant cognitive performance presented by group, with significance indicated as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. All comparisons are adjusted for age and sex, with additional control for CVLT Trial I score in Learning Slope analyses.

	Control	Patient	Significance
n	87	76	
CVLT Trial I (mean (SD))	7.24 (2.10)	6.61 (2.21)	$F(1,120)=1.04, p=0.309$
CVLT Trial V (mean (SD))	13.52 (2.10)	12.07 (2.72)	$F(1,120)=6.13, p=0.015^*$
Sum Trials I-V (mean (SD))	54.77 (10.76)	48.58 (11.43)	$F(1,158)=7.64, p=0.006^{**}$
List B (mean (SD))	6.32 (2.08)	5.14 (1.96)	$F(1,158)=8.36, p=0.004^{**}$
Short Delay Free Recall (mean (SD))	11.90 (3.00)	9.97 (3.47)	$F(1,158)=8.34, p=0.004^{**}$
Long Delay Free Recall (mean (SD))	12.24 (3.13)	10.51 (3.63)	$F(1,156)=6.44, p=0.012^*$
Total Intrusions (mean (SD))	2.06 (2.59)	2.76 (3.50)	$F(1,158)=0.11, p=0.739$
Total Repetitions (mean (SD))	3.36 (3.26)	2.38 (2.50)	$F(1,158)=2.75, p=0.099$
Learning Slope (mean (SD))	6.27 (1.96)	5.46 (2.42)	$F(1,119)=5.09, p=0.026^*$
Retroactive Interference (mean (SD))	-1.76 (1.87)	-1.80 (2.06)	$F(1,120)=0.12, p=0.725$
Proactive Interference (mean (SD))	-0.65 (2.12)	-1.15 (2.22)	$F(1,120)=1.5, p=0.223$
Forward Digit Span (mean (SD))	11.01 (2.27)	11.10 (2.45)	$F(1,145)=0, p=0.960$
Backward Digit Span (mean (SD))	9.25 (2.46)	8.75 (2.36)	$F(1,145)=1.33, p=0.252$

4.3.2 BrainAGE Model Performance

The brain age model explained 76% of the variance in age ($R^2=0.76$) in healthy control subjects in this study (testing sample), with mean absolute error (MAE) of 6.34 years and an excellent agreement between chronological age and brain age (intraclass correlation [ICC]=0.85, 95% confidence interval [CI]=[0.78, 0.90]). This is comparable to our previous validation of the method (MAE=5.08, $R^2=0.83$)¹⁴⁸ and to other models, i.e., MAE=4.6 years, $R^2=0.83$ ¹⁶¹, and MAE=4.31, $R^2=0.79$ ¹⁶². When adjusting for age, sex, and lithium treatment, patients had a significantly higher BrainAGE than controls (Figure 4.1).

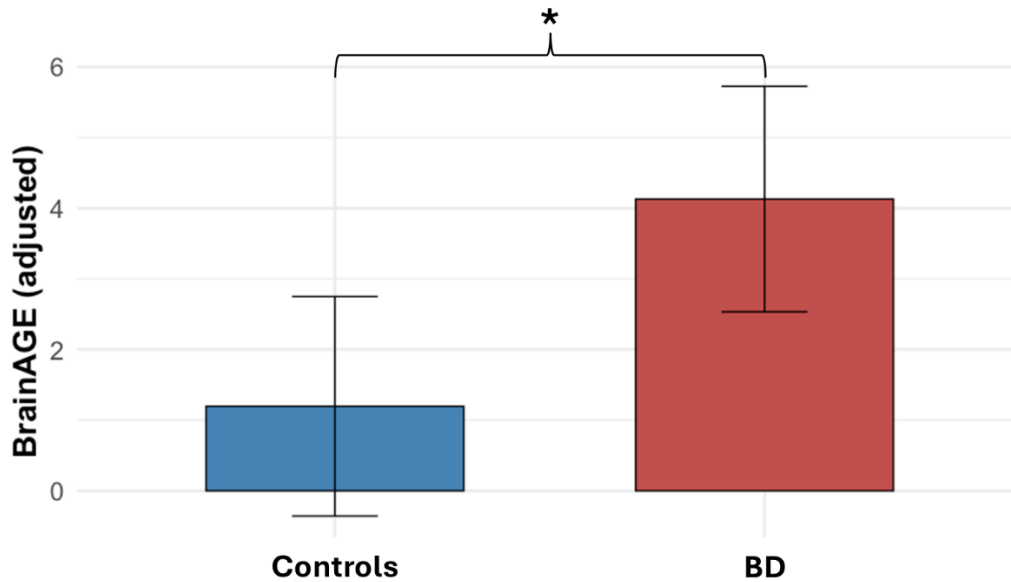


Figure 4.1 BrainAGE was significantly greater in patients than in controls ($F(1,157) = 6.76, p=0.010^*$), when adjusting for age, sex, and lithium treatment.

4.3.3 Metabolic and Cognitive Principal Components

The first metabolic principal component (Metabolic PC1) accounted for 34.7% of variance in metabolism. Metabolic PC1 captured the metabolic syndrome constellation and showed the highest loadings for BMI (0.43) and WHR (0.41), followed by systolic BP (0.40) and HOMA-IR (0.38). Therefore, a higher metabolic PC1 indicated higher (worse) metabolic scores, in these proportions. For more detailed results of the metabolic PCA, see [Table A12](#) and [Figure C3](#) in the supplement.

The first cognitive principal component (Cognitive PC1) accounted for 34.4% of the variance in cognition. Cognitive PC1 showed the highest loadings for Short-Delay free recall (0.51), Long-Delay free recall (0.49) and Sum of Trials I-V (0.46), suggesting that it primarily represents verbal learning and memory. Higher cognitive PC1 scores therefore indicated better performance. For more detailed results of the cognitive PCA, see supplementary [Table A13](#).

Relative to controls, patients had significant higher Metabolic PC1 scores and lower Cognitive PC1 scores, when adjusting for age and sex.

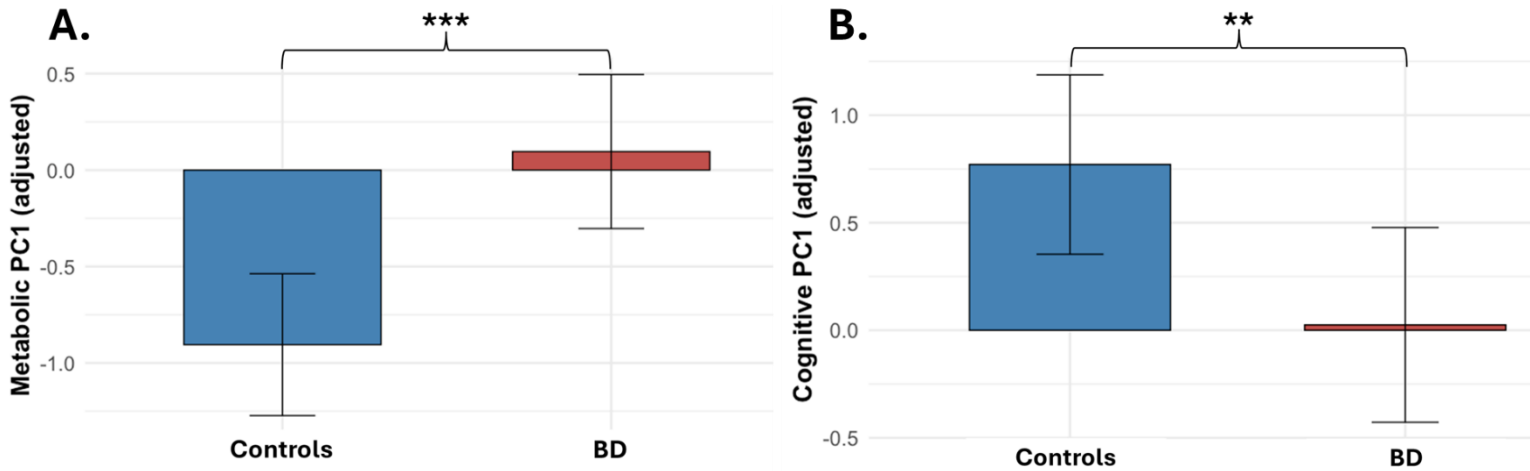


Figure 4.2 Compared to controls, patients had **A.** significantly higher (worse) Metabolic PC1 scores ($F(1, 158)=18.08, p<0.001^{***}$) and **B.** significantly lower (worse) Cognitive PC1 scores ($F(1, 158)=7.65, p=0.006^{**}$), when adjusting for age and sex.

4.3.4 Associations Between Metabolic Health, BrainAGE, and Cognitive Performance

In the overall sample, greater Metabolic PC1 scores significantly predicted higher BrainAGE ($\beta = 0.75 (SE = 0.29), t(157) = 2.58, p = 0.011$, Fig. 4.3). Greater Metabolic PC1 scores were also significantly associated with lower Cognitive PC1 scores ($\beta = -0.19 (SE = 0.09), t(157) = -2.11, p = 0.037$, Fig. 4.4). BrainAGE did not predict Cognitive PC1 scores ($\beta = -0.01 (SE = 0.02), t(157) = -0.46, p = 0.645$, Fig 4.5).

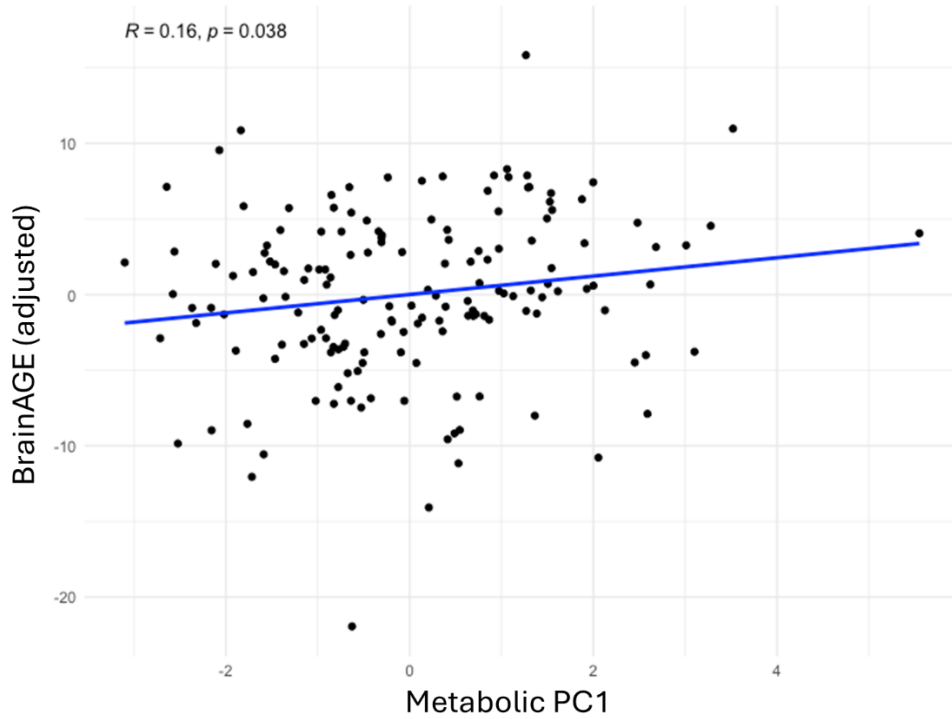


Figure 4.3 Metabolic PC1 was significantly associated with BrainAGE ($r = 0.16, p = 0.038$).

We adjusted for age, sex, and diagnosis by first regressing those effects out of both Metabolic PC1 and BrainAGE and running a Pearson correlation on their residuals.

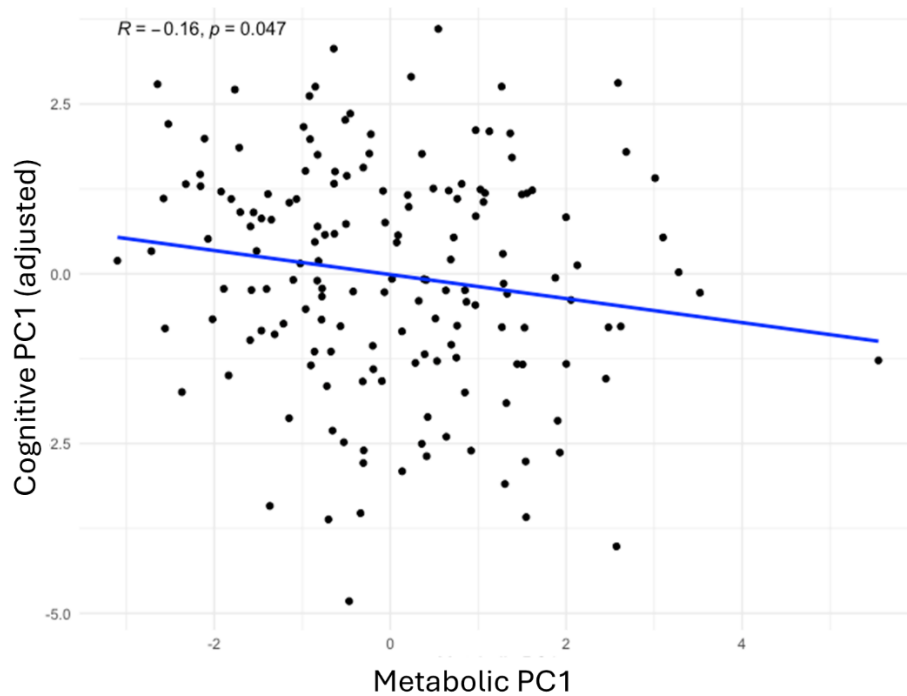


Figure 4.4 Metabolic PC1 was significantly associated with Cognitive PC1 ($r = -0.16, p = 0.047$). We adjusted for age, sex, and diagnosis by first regressing those effects out of the two principal components and running a Pearson correlation on their residuals.

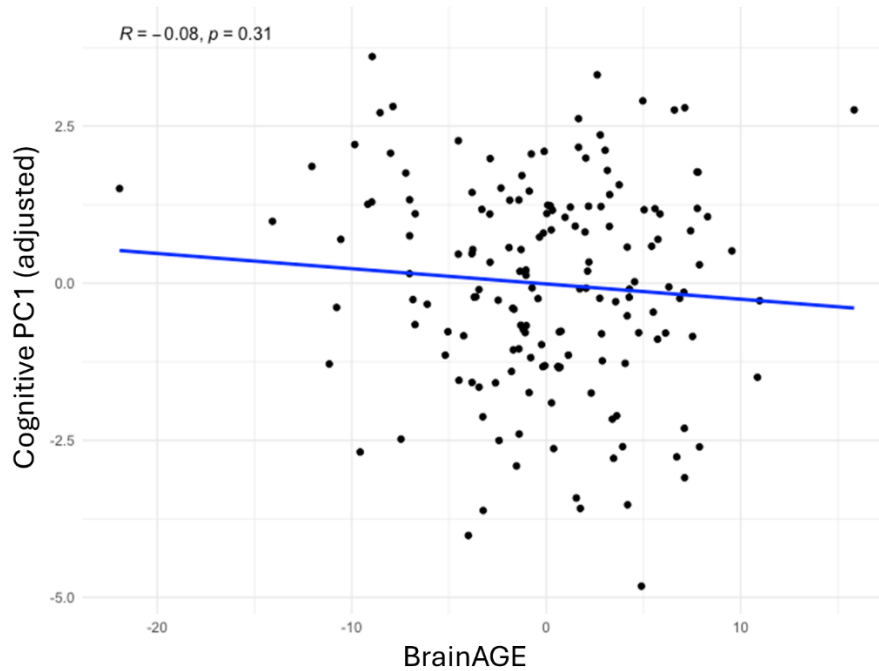


Figure 4.5 BrainAGE was not associated with Cognitive PC1 ($r = -0.08, p = 0.310$). We adjusted for age, sex, and diagnosis by first regressing those effects out of both BrainAGE and Cognitive PC1 and running a Pearson correlation on their residuals.

4.3.4 Mediation Analyses

Metabolic PC1 scores significantly mediated 26% of the association between BD and BrainAGE (ACME = 0.71, 95% CI [0.10, 1.44], $p = 0.016$; Figure 4.6), while controlling for age, sex, and lithium treatment. Metabolic PC1 scores also significantly mediated 25% of the association between BD and Cognitive PC1 scores (ACME = -0.19, 95% CI [-0.39, -0.03], $p = 0.012$; Figure 4.7), while controlling for age and sex.

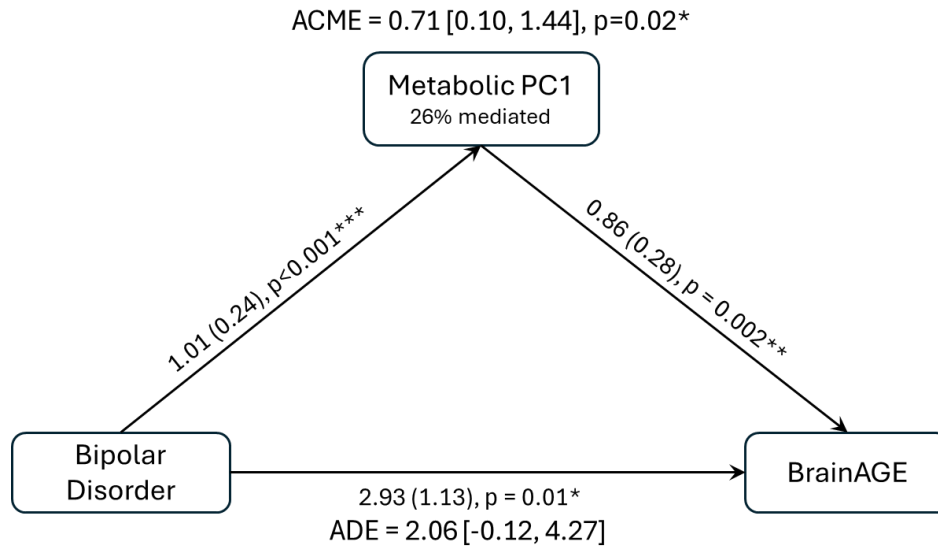


Figure 4.6 Results of the first mediation analysis, showing coefficients and their standard errors for associations between BD, Metabolic PC1, and BrainAGE while controlling for participant age, sex, and lithium treatment (where applicable), as well as the average causal mediated effect (ACME), and average direct effect (ADE).

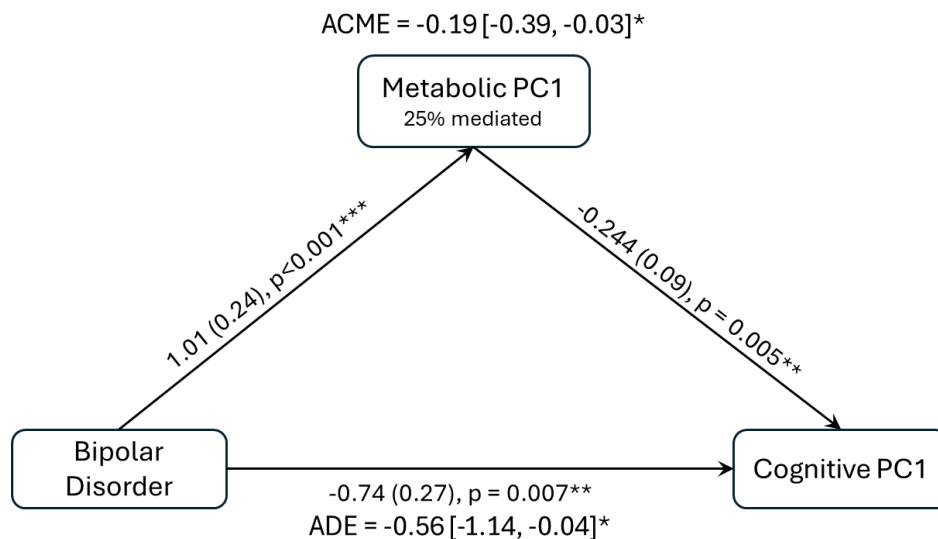


Figure 4.7 Results of the second mediation analysis, showing coefficients and their standard errors for associations between BD, Metabolic PC1, and Cognitive PC1 while

controlling for participant age and sex, as well as the average causal mediated effect (ACME), and average direct effect (ADE).

4.3.5 Potential Contribution of Symptoms and Medications

We investigated how illness-associated factors contribute to metabolic health, BrainAGE, and cognition in BD by testing their effects within the patient group. Out of all clinical factors, only benzodiazepine use was associated with Metabolic PC1. However, it was not significantly associated with either BrainAGE or Cognitive PC1 and therefore cannot confound the associations between Metabolic PC1 and either outcome measure.

Additionally, higher BrainAGE was predicted by use of antipsychotics and anticonvulsants, while lower Cognitive PC1 scores were predicted by antipsychotics and duration of illness. It is possible that these factors also contribute to brain and cognitive alterations in BD, however as neither factor was associated with Metabolic PC1, these associations most likely exist independently from those related to metabolic dysfunction.

4.4 DISCUSSION

In this study, we showed that the brain and cognitive alterations associated with BD were in part explained by poorer metabolic health. Notably, the metabolic syndrome cluster, as captured by Metabolic PC1, accounted for the greatest variance in metabolic health.

The loadings of Metabolic PC1 suggest that obesity, hypertension, insulin resistance, and dyslipidemia are the strongest contributors to variance in metabolic health. This specific cluster of metabolic markers clearly aligns with the definition of MetSy²³⁷. The combined effect of multiple MetSy-related markers could explain why such a large proportion (26%) of the brain changes in BD were mediated by Metabolic PC1. This is considerably larger than the proportion

of the association mediated by WHR (15%) in the young sample of individuals with FEP described in [Chapter 3](#), which tested only the independent effect of central obesity. While the findings of [Chapter 3](#) suggest that obesity in itself may be harmful, the present findings underscore the importance of considering the additive effects of multiple metabolic factors, especially considering their high rate of comorbidity.

Our findings align with previous literature that shows metabolic disturbances including obesity, diabetes, and hypertension to have a negative impact on BrainAGE^{73,74,82,83,96,98,112,219} and cognition^{238–242}. Interestingly, we did not detect an association between obesity-related brain changes and cognition, which contrasts the findings from [Chapter 3](#). However, the sample size in [Chapter 3](#) was more than three times that of the present study, and power analysis revealed that the effect in our study was small ($f^2 = 0.005$) and would require a sample size of approximately 1345 to reliably detect significance. Moreover, the sample described in [Chapter 3](#) included people at their first episode, with minimal confounding from chronic illness-related factors, and therefore involves considerably less noise in detecting these associations. In the broader literature, there exists a considerable knowledge gap regarding the effects of higher BrainAGE on cognition. Several studies have found significant associations between BrainAGE and traditional neurocognitive assessments for Alzheimer’s dementia, such as the Mini-Mental State Examination (MMSE) and the global Clinical Dementia Rating Scale (CDR)^{243,244}, or tests of general cognitive status, semantic verbal fluency, processing speed, cognitive flexibility, and visual attention²⁴⁵. However, others failed to demonstrate an association between BrainAGE and verbal learning and memory²⁴⁶, the cognitive domains that were most dominant in our study. One study in particular found that regional BrainAGE, but not global BrainAGE, was associated with CVLT scores²⁴⁷. It is possible that verbal learning and memory involve more localized alterations in brain structure that are not captured by a measure as broad as BrainAGE. It is also

possible that BrainAGE lacks the sensitivity to capture the more subtle cognitive impairments observed in BD or metabolic syndrome, as opposed to people with psychosis or dementia. We therefore cannot conclude that the neurostructural alterations captured by BrainAGE explain the cognitive impairments in this sample.

This study is the first to our knowledge to show that a cumulative and epidemiologically valid measure of poor metabolic health mediates the effect of BD on both brain structure and cognition in the same sample. These findings are in line with those that have shown associations between individual metabolic factors and alterations in either brain structure^{41,43,46,248–252} or cognition^{46,253–259} in BD. Notably, over a quarter of the total effect of BD on either BrainAGE or Cognitive PC1 was accounted for by the indirect effect through Metabolic PC1, suggesting that poor metabolic health may be a substantial contributor to neurostructural and cognitive alterations associated with BD.

By testing the potential contributions of illness-related factors such as symptoms, medications, and course of illness in the patient group, we further show that the effects of metabolic health are not confounded by these factors. Among patients, antipsychotic and anticonvulsant use was significantly associated with BrainAGE. Duration of illness was a significant predictor of Cognitive PC1, even after controlling for age, suggesting that the cumulative burden of BD over time may contribute to cognitive decline beyond the effects of normal aging. Neither of these factors was significantly associated with Metabolic PC1, indicating that although these illness-related factors may influence brain and cognitive outcomes in BD, their effects are independent of those exerted by poor metabolic health.

A major strength of our study is the use of two data-driven approaches, BrainAGE and PCA, to assess all three domains associated with BD including metabolic health, brain structure,

and cognition. BrainAGE provides an individualized marker that captures whole brain neurostructural alterations that deviate from a healthy pattern of aging, while PCA allows for an unbiased assessment of shared variance among multiple interrelated factors. This is especially important as cardiometabolic risk factors are highly comorbid and share common pathologies such as vascular damage, systemic inflammation, and hormonal dysregulation. Unlike previous studies that examined metabolic factors in isolation, our use of a composite metabolic variable accounts for the cumulative and interactive effects of multiple metabolic disturbances. Because the prevalences of each metabolic condition in our sample mirror those seen in the broader North American population, which is estimated as 73.6% for overweight/obesity⁷⁵, 11.6% for diabetes⁷⁶, and 48.1% for hypertension⁷⁷, using a PCA-derived composite measure of metabolic health improves the epidemiological validity and generalizability of our findings. Cognitive function is also multifactorial, wherein a multitude of different scores from the CVLT and digit span reflect overlapping cognitive functions including attention, working memory, verbal learning and memory, and cognitive control. Considering the large number of individual measures, a multivariate approach is also more robust to statistical issues associated with testing each measure against one another in a univariate way²⁶⁰. The combination of these methods offers a statistically robust and objective framework to evaluate the complex interplay between metabolism, brain structure, and cognition in BD, reducing the reliance on arbitrarily selected metabolic markers and avoiding collinearity issues inherent in traditional regression models.

Our study has several limitations. PCA is a data-driven method that captures shared variance among multiple interrelated metabolic factors and organizes them into orthogonal components. However, this does not consider the biological relevance of individual factors to cardiometabolic burden or BrainAGE, as components are derived purely from statistical variance within metabolism, independently of their association with any given outcome. As

such, metabolic disturbances which are less prevalent, such as abnormally high HbA1c, and potentially contribute less to the covariance with other factors ([Figure C3](#)) may have weaker loadings despite showing strong associations with BrainAGE in the literature⁹⁶. The consequence of this is a weaker signal from these factors. A related limitation is poor interpretability. In contrast to our approach, Van Rheenan et al. (2021)²⁵⁴ used a cumulative cardiovascular risk score, calculated based on the Framingham Heart Study method²⁶¹, to investigate cognition in BD. This method, while similar in that it aggregates multiple risk factors into a single score, differs in its biological validity; It assigns predetermined weights to each factor based on preestablished cardiovascular risk. This is more reflective of real-world cardiometabolic burden, particularly for outcomes like stroke or heart disease. However, a limitation of such predefined scores is that they may not be generalizable across different populations or lack applicability to non-biological outcomes such as cognition. Future studies could improve upon our findings by incorporating both a PCA-derived metabolic score and a biologically weighted risk score, such as the Framingham Risk Score, to compare their respective predictive value for BrainAGE and cognition in BD.

Our study contributes to a growing body of literature emphasizing the importance of prioritizing metabolic health in BD. We identify metabolic syndrome as an especially concerning target, as it is most predictive of overall poor metabolic health. Given the high burden of cardiometabolic comorbidities in BD, our findings support the need for metabolic monitoring and interventions in psychiatric care. Future studies should aim to build on the validity of our findings by testing the direction of these associations longitudinally, as well as by comparing the effects of Metabolic PC1 to those of biologically relevant metabolic scores, and against a broader composite measure of cognitive domains implicated in BD that includes psychomotor speed, impulsivity, visuospatial function, and semantic fluency.

CHAPTER 5 CONCLUSION

Each of the three studies described in this work contribute unique insights to understanding the interplay between poor metabolic health, brain structural and cognitive alterations in SMI.

The focus of [Chapter 2](#) was to identify which of the three cardiometabolic risk factors - diabetes, hypertension, and obesity - has the greatest biological relevance to BrainAGE. Because the three conditions are not equally prevalent in the general population and are often comorbid, obtaining an unbiased estimate of their individual contributions can be challenging owing to small or unequal sampling of each condition. Through a meta-analysis, we were able to leverage available data that included a substantial number of participants with each of the three conditions. This allowed us to assess the unique association between each cardiometabolic risk factor and BrainAGE, when controlling for the other factors. We found that each of the three metabolic conditions exerts unique, independent effects on brain structure, highlighting the importance of considering all three in people with SMIs. Diabetes had the largest effect on BrainAGE, suggesting that diabetes management could serve as the primary target in clinical and research efforts aimed at preventing neurostructural alterations in patients with multiple comorbid metabolic conditions.

The focus of [Chapter 3](#) was to determine whether metabolic health is associated with neurostructural and cognitive alterations already early in the course of illness, as this is a critical time when weight gain most commonly occurs. Since this phase of illness is characterized by shorter durations of medication exposure and fewer chronic illness-related complications, it presents a unique opportunity to examine the effects of metabolic health with fewer confounding influences. In this sample of first-episode patients, central obesity emerged as the most biologically relevant factor associated with BrainAGE. This finding is consistent with the

progressive nature of metabolic dysfunction, where obesity typically precedes the onset of other metabolic conditions and, as these were young patients, their weight gain was likely recent. In fact, the sample contained only 2 participants with diabetes (0.29%) and 21 participants with hypertension (3%). In a sample where the prevalence of these conditions is so much lower than observed in the general population, it is most logical to select the strongest predictor of BrainAGE in order to maximize statistical power in detecting effects on cognition. While doing so ignores the independent contributions from other metabolic factors, their effects may be too difficult to reliably detect under these conditions. Our results showed that central obesity independently explained some of the brain structural alterations observed already in the early stages of the illness. These structural alterations in turn partially mediated the poorer cognitive outcomes in this group, highlighting the clinical importance of preventing brain structural changes in order to mitigate adverse cognitive outcomes. While these associations are cross-sectional, our findings suggest that early intervention for obesity may be a valuable strategy in preserving cognitive function in SMI.

In [Chapter 4](#), we examined a sample of euthymic individuals with bipolar disorder who varied in age, illness stage and trajectory, medication use, number of prior episodes, and history of hospitalizations. In this diverse sample, the MetSy cluster accounted for the greatest proportion of variance in metabolic health, with BMI and WHR among the strongest contributors. This is consistent with the definition of MetSy, where central obesity is not only the most commonly observed component but has also been identified in numerous longitudinal studies as the precursor to MetSy itself, as well as to individual metabolic disturbances such as insulin resistance, type 2 diabetes, and hypertension^{34,237,262,263}. By using PCA to derive a composite measure of metabolic health that incorporates the cumulative and interactive influence of multiple metabolic factors, we showed that poor metabolic health/MetSy partially

mediated both structural and cognitive alterations in people with BD, and these effects were not confounded by illness-related factors such as symptoms or medications. Given its widespread prevalence and strong association with MetSy-related markers, obesity should be prioritized in public health strategies for SMI management.

Taken together, our findings have important biological and epidemiological implications. From a biological perspective, diabetes was the strongest predictor of brain structural alterations. Clinicians treating patients with comorbid diabetes should therefore prioritise diabetes management, as it may present the greatest risk of neurostructural alterations that may ultimately predict cognitive function. From an epidemiological perspective, obesity should serve as the primary target for preventing structural and cognitive alterations in SMI because its effects emerge early in the course of illness, and it remains the most predictive factor of overall metabolic health in a broad sample. Clinicians treating young patients at illness onset should therefore consider selecting interventions that minimize the risk of weight gain. Early intervention for obesity could be a crucial strategy in preventing downstream metabolic dysfunctions like diabetes and insulin resistance, as well as associated neurostructural and cognitive alterations in SMI.

Our findings contribute to a robust understanding of the complex interplay between metabolic health, brain structure, and cognition in SMI, both on an individual (biological) and population (epidemiological) level. Specifically, we highlight the biological relevance of individual metabolic factors, demonstrate the cumulative impact of poor metabolic health in a way that reflects real-world epidemiology, and account for key confounders to strengthen the validity of our conclusions. However, given the cross-sectional nature of our analyses, we cannot infer the causal direction of these associations. Future studies should therefore employ longitudinal designs to establish direction of causality and determine whether targeted

interventions, such as GLP-1 agonists for weight loss and diabetes management, can rescue structural and cognitive alterations in SMI.

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APPENDIX A Supplementary Tables

Table A1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction, Paragraphs 2, 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction, Paragraph 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods, Paragraphs 2,3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods, Paragraph 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods, Paragraph 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods, Paragraph 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods, Paragraph 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods, Paragraph 1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods, Paragraph 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods, Paragraph 4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods, Paragraph 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods, Paragraphs 2,3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods,

Section and Topic	Item #	Checklist item	Location where item is reported
			Paragraph 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods, Paragraph 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods, Paragraph 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods, Paragraphs 4, 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods, Paragraph 4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods, Paragraph 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods, Paragraph 4
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Methods, Paragraph 2
Study characteristics	17	Cite each included study and present its characteristics.	Results, Tables 1, 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results, Paragraph 2, Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplementary Tables S6, S7, S8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results, Paragraph 2, Tables 1, 2, Figure 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results Paragraphs 3, 4, 5, Figures 3, 4, 5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results, Paragraphs 3, 4, 5, Discussion, Paragraph 4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results Paragraphs 3, 4, 5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results Paragraphs 3, 4, 5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion Paragraphs 1, 2
	23b	Discuss any limitations of the evidence included in the review.	Discussion Paragraphs 3, 5
	23c	Discuss any limitations of the review processes used.	Discussion Paragraph 7
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion Paragraph 5, Conclusion Paragraph 1
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Review was not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Protocol was not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding
Competing interests	26	Declare any competing interests of review authors.	Competing Interests Statement
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data Availability Statement

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

Table A2 Definition of Diabetes by Included Studies

Diabetes Studies	Type Specified
Bretzner et al., 2023	DM
Busby et al., 2023	D
Casanova et al., 2024	D
Franke et al., 2013	T2DM
Hwang et al., 2021	DM
Jawinski et al., 2022	DM
Jha et al., 2022	D
Kang et al., 2023	T2DM
Korbmacher et al., 2023	T1DM, T2DM
Sone et al., 2022	D
Weihs et al., 2021	D

Note: DM, Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; T1DM, Type 1 Diabetes Mellitus; D, Diabetes (not specified).

Table A3 Definition of Hypertension by Included Studies

Studies	Definition of Hypertension
Bretzner et al., 2023	-
Busby et al., 2023	Hypertension was defined based on participants' responses to a medical history questionnaire, corroborated by medical records where available.
Casanova et al., 2024	-
Guan et al., 2022	systolic BP \geq 140 mmHg or diastolic BP \geq 90 mmHg or use of antihypertensive medication.
Hwang et al., 2021	Hypertension was diagnosed according to the Seventh Report of the Joint National Committee and 2018 Korean Society of Hypertension Guidelines.
Kang et al., 2023	Hypertension was defined as a diagnostic history of hypertension or current use of any antihypertensive medication.
Korbmacher et al., 2023	-
Sone et al., 2022	Diagnosis of hypertension described by participants in their responses to a questionnaire
Weihs et al., 2021	Systolic BP > 140 mmHg, Diastolic BP > 90 mmHg, or use of anti-hypertensive medication

Table A4 Definition of Obesity by Included Studies

Studies	Definition of Obesity
	Obesity was defined as BMI ≥ 27.5 kg/m ² .
Kang 2023	The non-obese group excluded those that were underweight (BMI < 18 kg/m ²).
Kolenic 2018	BMI > 25 kg/ m ²
Zeighami 2022	BMI > 35 kg/m ²

Table A5 Summary of Study Samples which Included Data for Hypertension, Diabetes, Obesity

STUDY SAMPLE	HYPERTENSION	DIABETES	OBESITY
Bretzner et al., 2023	Bretzner et al., 2023	Bretzner et al., 2023	
Busby et al., 2023	Busby et al., 2023	Busby et al., 2023	
Casanova et al., 2024	Casanova et al., 2024	Casanova et al., 2024	
Franke et al., 2013		Franke et al., 2013	
Guan et al., 2022	Guan et al., 2022		
Hwang et al., 2021	Hwang et al., 2021	Hwang et al., 2021	
Jawinski et al., 2022		Jawinski et al., 2022	
Jha et al., 2022		Jha et al., 2022	
Kang et al., 2023a	Kang et al., 2023a	Kang et al., 2023a	Kang et al., 2023a
Kang et al., 2023b	Kang et al., 2023b	Kang et al., 2023b	Kang et al., 2023b
Kang et al., 2023c			Kang et al., 2023c
Kang et al., 2023d			Kang et al., 2023d
Kolenic et al., 2018			Kolenic et al., 2018
Korbmacher et al., 2023	Korbmacher et al., 2023	Korbmacher et al., 2023	
Sone et al., 2022	Sone et al., 2022	Sone et al., 2022	
Weihs et al., 2021	Weihs et al., 2021	Weihs et al., 2021	
Zeighami et al., 2022			Zeighami et al., 2022

Note. The data from the Kang 2023c and Kang 2023d samples were not used in the diabetes or hypertension analyses as they were sampled from the UK BioBank, which potentially overlaps with the Korbmacher 2023 sample.

Table A6 Results of Diabetes Meta-Analysis

Study Sample	Cohen's d	St Error	Variance	Lower Limit	Upper Limit	Z-value	p-value	D ⁺ n	D ⁻ n	Total N	I ²
Bretzner et al., 2023	0.126	0.042	0.002	0.044	0.208	3.011	0.003	687	3476	4163	
Busby et al., 2023	0.161	0.276	0.076	-0.381	0.703	0.582	0.560	14	203	217	
Casanova et al., 2023	0.311	0.064	0.004	0.187	0.436	4.889	0.000	359	813	1172	
Franke et al., 2013	0.660	0.151	0.023	0.364	0.956	4.364	0.000	98	87	185	
Hwang et al., 2021	0.386	0.155	0.024	0.082	0.690	2.486	0.013	52	218	270	
Jawinski et al., 2022	0.198	0.181	0.033	-0.157	0.554	1.094	0.274	34	294	328	
Jha et al., 2022	0.264	0.068	0.005	0.130	0.398	3.862	0.000	246	1703	1949	
Kang et al., 2023a	0.443	0.064	0.004	0.317	0.569	6.888	0.000	273	2326	2599	
Kang et al., 2023b	0.202	0.044	0.002	0.117	0.288	4.623	0.000	683	2259	2942	
Korbmacher et al., 2023	0.151	0.043	0.002	0.067	0.236	3.499	0.000	543	31625	32168	
Sone et al., 2022	0.319	0.103	0.011	0.117	0.521	3.093	0.002	111	642	753	
Weihs et al., 2021	0.314	0.130	0.017	0.059	0.568	2.417	0.016	66	624	690	
Pooled	0.275	0.039	0.002	0.198	0.352	6.970	0.000	3166	44270	47436	66.770

Table A7 Results of Hypertension Meta-Analysis

Study Sample	Cohen's d	St Error	Variance	Lower Limit	Upper Limit	Z-value	p-value	HTN+ N	HTN- N	Total N	I ²
Bretzner et al., 2023	0.077	0.033	0.001	0.012	0.142	2.309	0.021	2825	1338	4163	
Busby et al., 2023	0.298	0.162	0.026	-0.019	0.615	1.841	0.066	50	167	217	
Casanova et al., 2024	0.311	0.067	0.005	0.179	0.443	4.630	0.000	871	301	1172	
Guan et al., 2022	-0.196	0.183	0.034	-0.555	0.164	-1.067	0.286	67	54	121	
Hwang et al., 2021	0.208	0.122	0.015	-0.031	0.447	1.705	0.088	137	133	270	
Kang et al., 2023a	0.162	0.041	0.002	0.083	0.242	3.994	0.000	965	1634	2599	
Kang et al., 2023b	0.039	0.037	0.001	-0.033	0.111	1.055	0.291	1402	1540	2942	
Korbmacher et al., 2023	0.111	0.014	0.000	0.083	0.138	7.902	0.000	6332	25843	32175	
Sone et al., 2022	0.090	0.073	0.005	-0.053	0.233	1.234	0.217	371	382	753	
Weihs et al., 2021	0.014	0.077	0.006	-0.136	0.164	0.187	0.852	308	382	690	
Pooled	0.113	0.025	0.001	0.063	0.162	4.449	0.000	13328	31774	45102	58.540

Table A8 Results of Obesity Meta-Analysis

Study Sample	Cohen's d	St Error	Variance	Lower Limit	Upper Limit	Z-value	p-value	Obese N	Non-Obese N	Total N	I-Squared
Kang et al., 2023a	0.019	0.069	0.005	-0.117	0.155	0.277	0.782	227	2372	2599	
Kang et al., 2023b	0.093	0.058	0.003	-0.020	0.207	1.608	0.108	336	2606	2942	
Kang et al., 2023c	0.083	0.049	0.002	-0.014	0.180	1.684	0.092	450	4717	5167	
Kang et al., 2023d	0.167	0.057	0.003	0.056	0.278	2.953	0.003	336	4400	4736	
Kolenic et al., 2018	0.396	0.150	0.023	0.102	0.690	2.640	0.008	61	173	234	
Pooled	0.112	0.038	0.001	0.037	0.187	2.921	0.003	1410	14268	15678	40.580

Table A9 Effects of clinical variables on waist-to-hip ratio (WHR), as well as the partial effects of clinical variables and WHR on BrainAGE and AVLT scores. Effects of WHR remained significant when adjusting for clinical variables in all cases.

Effect on WHR		
Treatment duration	F(1,217)=0.82, p=0.365	
Arterial hypertension	F(1,213)=3.58, p=0.060	
Illness duration	F(1,214)=0.01, p=0.936	
Diagnosis	F(2,214)=1.51, p=0.225	
AP Dose (Chlpz, mg)	F(1,217)=1.16, p=0.283	
	Effect on BrainAGE	WHR Effect on BrainAGE
Treatment duration	F(1,216)=0.21, p=0.644	F(1,216)=7.22, p=0.008 *
Arterial hypertension	F(1,212)=0.29, p=0.591	F(1,212)=5.03, p=0.026 *
Illness duration	F(1,213)=0.39, p=0.533	F(1,213)=7.70, p=0.006 *
Diagnosis	F(2,213)=0.90, p=0.407	F(1,213)=8.63, p=0.004 *
AP Dose (Chlpz, mg)	F(1,216)=6.73, p=0.010 *	F(1,216)=6.58, p=0.011 *
	Effect on AVLT	WHR Effect on AVLT
Treatment duration	F(1,205)=0.50, p=0.479	F(1,205)=4.76, p=0.030 *
Arterial hypertension	F(1,201)=0.05, p=0.817	F(1,201)=4.14, p=0.043 *
Illness duration	F(1,202)=1.32, p=0.251	F(1,202)=4.91, p=0.028 *
Diagnosis	F(2,202)=1.09, p=0.339	F(1,202)=4.93, p=0.028 *
AP Dose (Chlpz, mg)	F(1,205)=0.31, p=0.575	F(1,205)=4.41, p=0.037 *

Table A10 Associations between BMI, diagnosis, age and sex with BrainAGE. Standardized coefficients with their standard error and FDR-adjusted significance are shown, with significance denoted using asterisks (*, $p < 0.05$).

Model	Effect	Estimate (SE)	Significance
BrainAGE vs BMI	BMI	0.10 (0.03)	t(690)=3.06, p=0.003 *
	Age	-0.07 (0.00)	t(691)=-15.96, p<0.001 *
	Sex	0.09 (0.07)	t(690)=1.40, p=0.486
	Diagnosis	0.43 (0.07)	t(691)=6.44, p<0.001 *

Table A11 Partial effects of BMI, age, sex, and diagnosis on cognitive measures.

Outcome	Effect	Estimate	Standard Error	<i>t</i>	<i>df</i>	<i>p</i>	Significant
AVLT Trials I-V	BMI	-0.01	0.04	-0.22	393	0.824	
	Age	0.00	0.01	-0.59	393	0.554	
	Sex	-0.47	0.09	-5.20	394	0.000	*
	Diagnosis	-1.00	0.09	-11.01	393	0.000	*
AVLT Trial VI	BMI	-0.07	0.04	-1.48	396	0.209	
	Age	-0.01	0.01	-1.30	395	0.305	
	Sex	-0.42	0.09	-4.62	396	0.000	*
	Diagnosis	-0.96	0.09	-10.44	396	0.000	*
AVLT After 30 Min	BMI	-0.02	0.04	-0.57	396	0.680	
	Age	-0.01	0.01	-2.17	396	0.186	
	Sex	-0.46	0.09	-5.23	396	0.000	*
	Diagnosis	-1.06	0.09	-11.94	396	0.000	*
Digit Span Forward	BMI	-0.08	0.05	-1.55	394	0.209	
	Age	-0.01	0.01	-0.94	394	0.418	
	Sex	0.14	0.10	1.31	394	0.192	
	Diagnosis	-0.65	0.10	-6.25	394	0.000	*
Digit Span Backward	BMI	-0.08	0.05	-1.82	394	0.209	
	Age	-0.01	0.01	-1.86	393	0.189	
	Sex	0.19	0.10	2.02	394	0.066	
	Diagnosis	-1.01	0.10	-10.53	394	0.000	*
Digit Span Total	BMI	-0.08	0.05	-1.72	395	0.209	
	Age	-0.01	0.01	-1.27	395	0.305	
	Sex	0.17	0.10	1.71	395	0.106	
	Diagnosis	-0.92	0.10	-9.36	395	0.000	*

Table A12 Loadings from the metabolic principal component analysis

	PC1	PC2	PC3
Fasting HDL	-0.266510	-0.234910	-0.637150
Fasting LDL	0.148155	-0.518450	0.015348
HOMA-IR	0.379274	0.330194	-0.169250
BMI	0.425079	0.043511	-0.063870
WHR	0.408106	0.084410	0.005373
Systolic BP	0.403137	-0.296390	-0.180090
Diastolic BP	0.338546	-0.378600	-0.317180
HbA1c	0.112111	0.568906	-0.493930
Fasting TGC	0.355285	0.056023	0.429012

Table A13 Loadings from the cognitive principal component analysis

	PC1	PC2	PC3
Sum Trials I-V	0.454930	-0.033100	-0.004490
Short Delay Free Recall	0.508066	-0.114720	0.153538
Long Delay Free Recall	0.491053	-0.042620	0.131007
Total Intrusions	-0.234370	-0.068550	-0.182530
Total Repetitions	0.082529	0.102876	-0.286630
Learning Slope	0.200344	0.613793	0.286954
Retroactive Interference	0.291079	-0.461210	0.150735
Proactive Interference	-0.045850	0.517687	0.370803
Forward Digit Span	0.184702	0.251878	-0.583510
Backward Digit Span	0.266372	0.218509	-0.510610

APPENDIX C Supplementary Figures

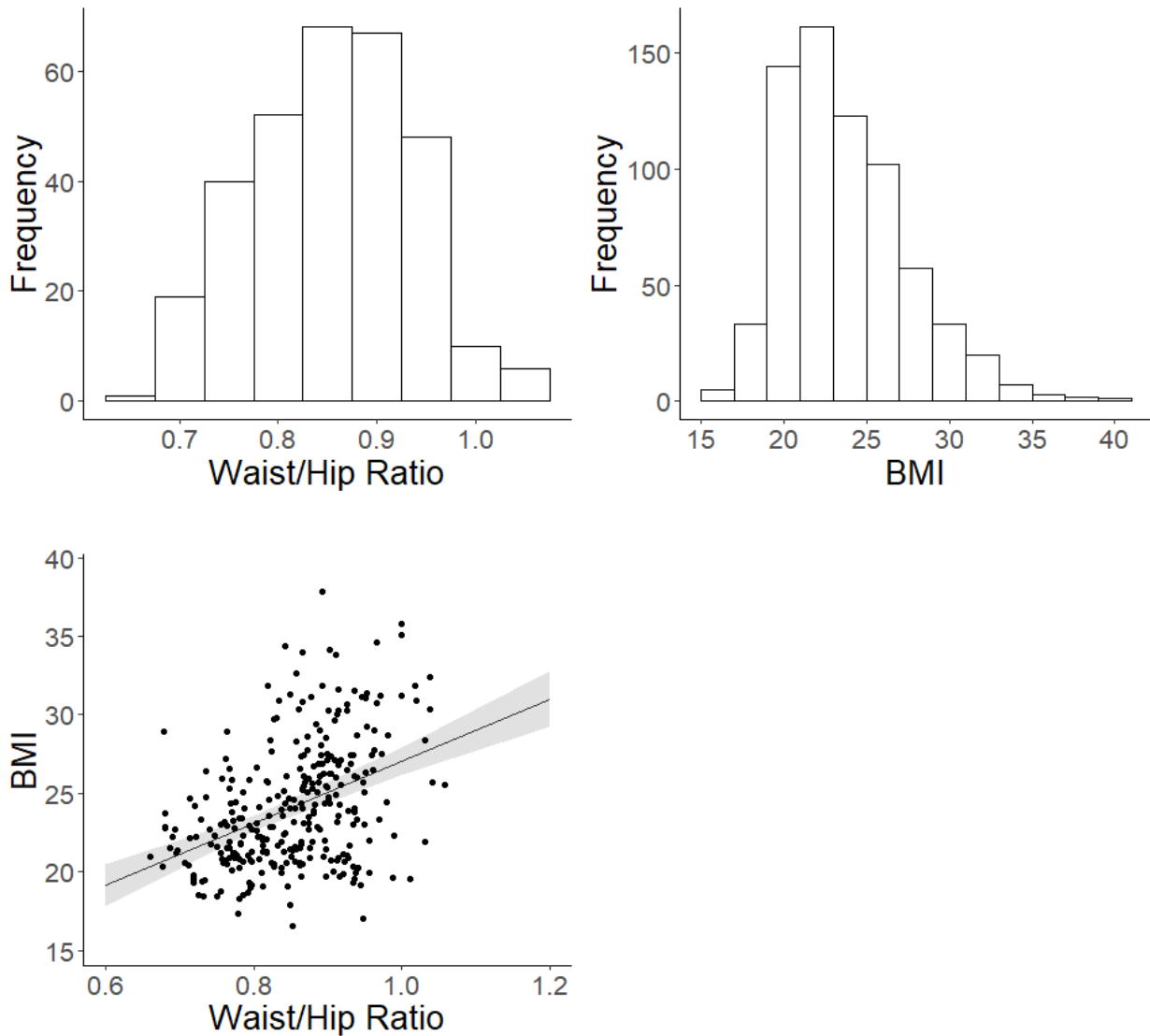


Figure C1. Distributions of waist/hip ratio (WHR), BMI, and their significant associations with one another. Untransformed BMI is shown for interpretability. BMI was significantly associated with WHR ($t(308)=7.59, p<0.001$).

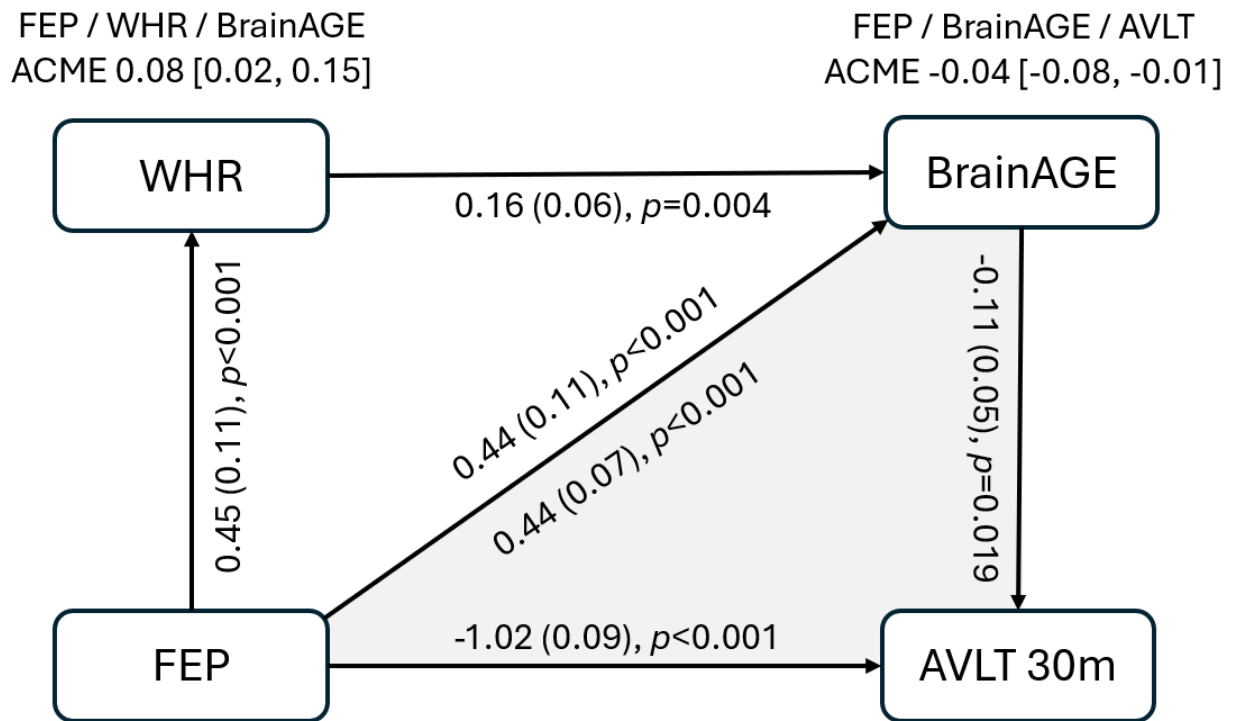


Figure C2. Standardized coefficients and their standard error for associations between FEP, WHR, BrainAGE, and AVLT scores (30-minute recall), while controlling for participant age and sex. Average causal mediated effect (ACME) is shown with its 95% confidence interval.

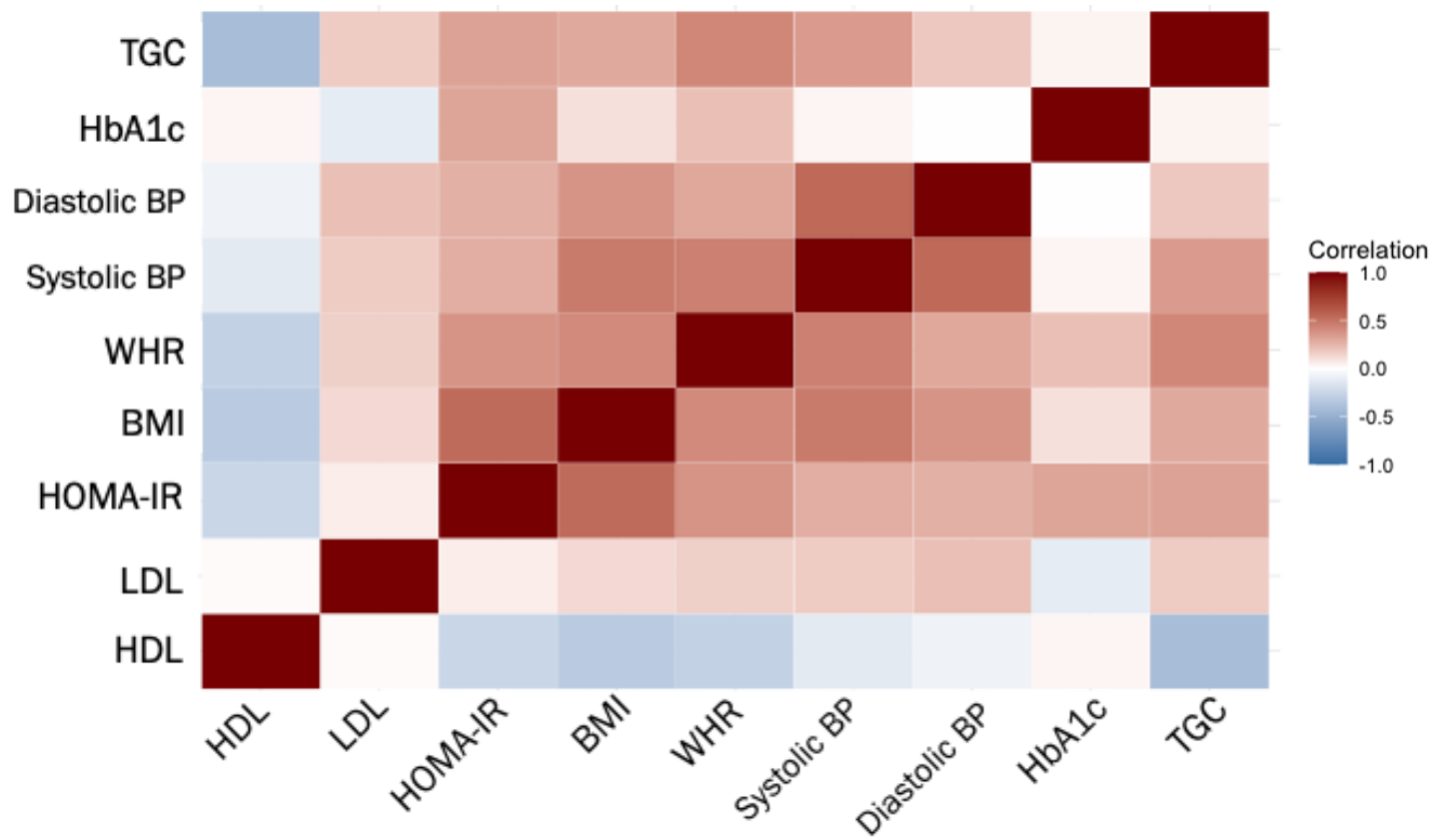


Figure C3. Correlation matrix showing relationships among the nine metabolic variables used in the metabolic principal component analysis.

APPENDIX D Adapted Newcastle-Ottawa Scale

NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE (adapted for cross-sectional studies)

This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to provide a quality assessment of cross-sectional studies.

Selection (maximum 5 pts)

1. Representativeness of the sample

- a. Truly representative of the average in the general population (all subjects or random sampling) or somewhat representative of the average in the general group (non-random sampling) *
- b. Selected group/convenience sample
- c. No description of the derivation of the included subjects

2. Sample size

- a. Large ($n \geq 1000$ participants) **
- b. Satisfactory ($n = 100-999$ participants) *
- c. Not justified

3. Non-respondents

- a. The response rate is satisfactory and any reasons for excluding participant data is clearly stated *
- b. The response rate is unsatisfactory
- c. No justification is given for the exclusion of participant data

4. Ascertainment of the exposure (cardiometabolic risk factor)

- a. Presence of cardiometabolic risk factor is clearly defined based on pre-established criteria *
- b. Presence of cardiometabolic risk factor is defined based on self-report
- c. No clear definition of cardiometabolic risk factor

Comparability (maximum 2 pts)

1. Comparability of subjects in different outcome groups on the bases of the design or analysis

- a. Age and sex were comparable between groups, or their effects were controlled for in multiple regression models *
- b. Study controls for any additional factor (ex. race/ethnicity, smoking status, education level, income, physical activity) *
- c. Information was not provided or groups were not comparable

Outcome (maximum 3 pts)

1. Assessment of outcome:

- a. Brain age prediction model is based on an independent training set *
- b. Brain age prediction model is adjusted for age-bias *
- c. Information not provided

2. Statistical test

- a. Statistical test used to analyze the data is clearly described, appropriate, and measures of association presented include confidence intervals or standard error *
- b. Statistical test is not appropriate, not described, or incomplete
- c. Authors failed to report the confidence intervals or standard error of associations

APPENDIX E MRI Preprocessing and BrainAGE Model Framework

The BrainAGE analyses in Chapters 3 and 4 included (1) preprocessing of the raw T1-weighted image data using standard voxel-based morphometry pipelines in SPM (www.fil.ion.ucl.ac.uk/spm/), running under MATLAB (www.mathworks.com)¹⁴⁸. Prior to processing, we performed detailed visual and statistical quality controls. T1-weighted images were corrected for bias-field inhomogeneity, then spatially normalized and segmented into GM, white matter (WM) and cerebrospinal fluid within the same generative model, while accounting for partial volume effects, applying adaptive maximum a posteriori estimations, and using a hidden Markov Random Field model. Subsequently, we applied (2) data reduction using smoothing and principal component analysis (MATLAB Toolbox for Dimensionality Reduction, <http://ict.ewi.tudelft.nl/~lvandermaaten/Home.html>), in order to reduce computational costs, avoid severe over-fitting and produce a robust and widely applicable age-estimation model. Lastly, we performed (3) estimation of brain age using relevance vector regression (RVR). We utilized RVR, which was introduced as a Bayesian alternative to support vector machines (SVM) for obtaining sparse solutions to pattern recognition tasks. In contrast to SVM, it does not require additional parameter optimization during the training phase. We utilized a linear kernel, since age estimation accuracy is not improved when using non-linear kernels, which may also increase the risk of overfitting. We trained the RVR model using an independent sample of 504 healthy individuals (230 males) from the IXI database, aged 19–86 years (www.brain-development.org). We applied a cross-validation approach, which produced an unbiased estimate of performance in new individuals. We used the resulting age prediction model to individually estimate brain age in our study participants, thus completely separating the training and testing phase. We used ‘The Spider’ (<http://people.kyb.tuebingen.mpg.de/spider/>) toolbox,

running under MATLAB, to train the model and predict individual brain ages. Our outcome measure was BrainAGE, which was calculated as the difference between estimated brain age and chronological age¹⁴⁸.

APPENDIX F Copyright Permission Letters

These manuscripts have been published in or submitted to peer-reviewed journals, including:

A version of Chapter 2 is accepted as:

Selitsner, M., Dietze, L.M.F., McWhinney, S.R., Hajek, T. "Cardiometabolic Risk Factors and Brain Age: quantifying brain structural differences linked to diabetes, hypertension, and obesity through meta-analysis". *J Psychiatry Neurosci*, 2025, 50 (2): E102-E111. doi: 10.1503/jpn.240105.

The copyright permission forms for this manuscript are appended below.

A version of Chapter 3 is submitted as:

Kolenič, M., McWhinney, S.R., **Selitsner, M.**, Šafářová, N., Franke, K., Vochoskova, K., Burdick, K., Španiel, F., Hajek, T. "Central Obesity-Related Brain Alterations Predict Cognitive Impairments in First Episode of Psychosis". *SchBull* 2025.

A version of Chapter 4 is in preparation as:

Selitsner, M., McWhinney, S.R., Wu, L., Dietze, M.F., Fraiha Pegado, J., Corkum, E., Franke, K., Hajek, T. "The role of metabolic health in neurostructural and cognitive alterations in bipolar disorders". *In preparation*.

April 22, 2025

Cardiometabolic risk factors and brain age: a meta-analysis to quantify brain structural differences related to diabetes, hypertension, and obesity

Journal of Psychiatry & Neuroscience

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