Research Paper

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

Maya Selitser, BSc; Lorielle M.F. Dietze, MSc; Sean R. McWhinney, PhD; Tomas Hajek, MD, PhD

Background: Cardiometabolic risk factors — including diabetes, hypertension, and obesity — have long been linked with adverse health outcomes such as strokes, but more subtle brain changes in regional brain volumes and cortical thickness associated with these risk factors are less understood. Computer models can now be used to estimate brain age based on structural magnetic resonance imaging data, and subtle brain changes related to cardiometabolic risk factors may manifest as an older-appearing brain in prediction models; thus, we sought to investigate the relationship between cardiometabolic risk factors and machine learning–predicted brain age. **Methods:** We performed a systematic search of PubMed and Scopus. We used the brain age gap, which represents the difference between one's predicted and chronological age, as an index of brain structural integrity. We calculated the Cohen *d* statistic for mean differences in the brain age gap of people with and without diabetes, hypertension, or obesity and performed random effects meta-analyses. **Results:** We identified 185 studies, of which 14 met inclusion criteria. Among the 3 cardiometabolic risk factors, diabetes had the highest effect size (12 study samples; $d = 0.275$, 95% confidence interval [CI] 0.198–0.352; $n = 47\,436$), followed by hypertension (10 study samples; $d = 0.113$, 95% CI 0.063–0.162; $n = 45\,102$) and obesity (5 study samples; $d = 0.112$, 95% CI 0.037–0.187; $n = 15\,678$). These effects remained significant in sensitivity analyses that included only studies that controlled for confounding effects of the other cardiometabolic risk factors. **Limitations:** Our study tested effect sizes of only categorically defined cardiometabolic risk factors and is limited by inconsistencies in diabetes classification, a smaller pooled sample in the obesity analysis, and limited age range reporting. **Conclusion:** Our findings show that each of the cardiometabolic risk factors uniquely contributes to brain structure, as captured by brain age. The effect size for diabetes was more than 2 times greater than the independent effects of hypertension and obesity. We therefore highlight diabetes as a primary target for the prevention of brain structural changes that may lead to cognitive decline and dementia.

Introduction

Obesity is a growing global health concern, affecting 1 in 8 people worldwide.[1] With a rise in prevalence comes a rise in economic burden, which is projected to reach US$3 trillion per year by 2030.[2] Ischemic heart disease and stroke rank as the first and second leading causes of death globally,[3] and both of these conditions have been shown to be independently predicted by excess body weight.[4–6] Obesity targets many organ systems and leads to a host of issues, including type 2 diabetes, hypertension, coronary artery disease, infertility, osteoarthritis, and the development of certain cancers.[7] Although most of the conversation regarding the impact of obesity and other cardiometabolic risk factors on the brain is centred around grave neurologic outcomes like stroke and vascular dementia,[8] the more insidious and gradual alterations in brain structure that accompany cardiometabolic risk factors, such as changes in regional brain volumes and cortical thickness, have only recently become apparent and are much less understood.

Obesity, diabetes, and hypertension are highly comorbid,[9] posing a challenge in discerning their individual contributions to adverse health outcomes. All 3 cardiometabolic risk factors are frequently linked with impairments in brain structure and function, ultimately resulting in an increased risk of dementia.[10–14] Both diabetes and hypertension are damaging to cerebral vasculature,[15,16] but diabetes also causes many biochemical and 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

Correspondence to: T. Hajek, Department of Psychiatry, Dalhousie University, QEII HSC, A.J. Lane Building., Room 3095, 5909 Veteran's Memorial Lane, Halifax, N.S., B3H 2E2; tomas.hajek@dal.ca

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sequalae of cardiometabolic risk factors. Therefore, we need a better quantification of the effects of these individual cardiometabolic risk factors on brain structure derived from all available studies.

Classic measures of neurodegeneration are based on regional brain atrophy, such as the use of hippocampal volume to assess severity of Alzheimer dementia and age-related cognitive decline.[17] However, in Aristotle's words, "the whole is something beside the parts,"[18] 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 are 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, 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 people to estimate brain age from structural magnetic resonance imaging (MRI). The difference between the predicted brain age and the person's chronological age is termed the brain age gap estimate (brainAGE), which is used as an index of brain structural integrity. In this way, chronological age is used as a reference point by which subtle alterations in brain structure that are deemed abnormal for an individual at their given age can be assessed. A higher positive brainAGE suggests a greater degree of structural alterations, which has been shown to correlate with functional and health outcomes such as progression to dementia, poor cognitive performance, early death, and other measures of biological aging, including weaker grip strength, slower walking speed, and decreased lung capacity.[19–23] This measure captures not only aging, but many external factors that result in atrophy. Subtle brain changes related to cardiometabolic risk factors may therefore 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 a single, easily interpretable numerical value, albeit at the cost of regional specificity.

Higher body mass index (BMI), diabetes, and hypertension have previously been associated with higher brainAGEs;[22,24,25] however, the effect sizes in individual studies vary widely, and the relative magnitude of their independent contributions to brain age remains unclear. Therefore, we wanted to maximize sample size to get a more precise and generalizable estimate of the strength of the associations between these 3 cardiometabolic risk factors and brainAGE. To this goal, we conducted a meta-analysis of all available studies investigating associations between brainAGE and obesity, diabetes, and hypertension. To quantify the unique contribution of each of the factors, we separately calculated pooled estimates from studies that controlled for the other cardiometabolic risk factors.

Methods

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix 1, available at www.jpn.ca/lookup/doi/10.1503/jpn.240105/tab-related-content).[26] We performed a systematic search of articles in PubMed, MEDLINE, and Scopus from inception until July 11, 2024, using a combination of the search terms "brain age," with "obesity," "diabetes," "HDL" (high-density lipoprotein), "triglycerides," "blood pressure," and "hypertension." Two raters independently screened articles following removal of duplicates identified by Covidence (Covidence.org) and by screeners.

Eligibility criteria

At the project's conception, we hoped to be able to analyze both categorical (diabetes, hypertension, obesity) and dimensional (glycated hemoglobin [HbA_{1c}], blood pressure, BMI, lipid levels) cardiometabolic risk factor data. Statistically, we cannot combine categorical and dimensional effects into the same meta-analysis and therefore required a sufficient number of studies for each type of predictor. For continuous measures, our search identified only 3 studies for HbA_{1c}, 2 for lipid levels, and 3 for triglycerides, which was too few for a separate meta-analysis. Therefore, we decided to proceed with only 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, or intra-abdominal fat percentage. 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 electroencephalography. Of the studies that included participants from the same database, such as from the UK Biobank,[22,25,27–32] we selected only the study with the largest number of participants to ensure there was no overlap between study samples.[30]

Our studies included those describing clinical populations, such as those with sleep apnea[33] or first-episode psychosis,[34] so long as they reported separate data from control participants or controlled for the effect of diagnosis in their statistical models. We included studies that defined diabetes, hypertension, or obesity categorically (yes v. 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 Appendix 1, Tables S2, S3, and S4, respectively.

Quality and risk of bias assessment

We used the Newcastle–Ottawa Scale for assessing the quality and potential risk of bias in nonrandomized studies, adapted for use in cross-sectional studies[35] following the original

scale developed by Wells and colleagues (Appendix 1).[36] According to prespecified criteria for risk of bias in sample selection, comparability of participants, and assessment of outcomes, studies were considered to have a low (scores > 7), medium (scores from 5–7), or high risk of bias (scores < 5). Two raters (M.S. and S.M.) assessed each study independently. We ran a jack-knife analysis using Comprehensive Meta-Analysis (CMA) software[37] to assess the robustness of the results after removing individual studies from each meta-analysis.

Calculation of effect sizes and meta-analysis

The CMA software converts study results into standardized effect size (Cohen *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 *d* for mean differences in brain age gap of people with and without diabetes, hypertension, or obesity. We then conducted a meta-analysis of Cohen *d* estimates for each study using random effects models. We computed Cohen *d* and 95% confidence intervals (CIs) either from the independent group means and standard deviations, from *t* values and sample sizes, or from β coefficients and standard errors extracted from each study. When the data were not available in the paper, we contacted the authors for more details.[30,38] To quantify the independent association between each cardiometabolic risk factor and brainAGE, we ran a secondary analysis to include only studies that controlled for the other cardiometabolic risk factors within their models.

Ethics approval

The present study was not granted approval by an ethics approval committee or an institutional review board, as it did not involve human or animal experimentation. We did not obtain participant consent forms, as we worked solely with sample statistics extracted from published peer-reviewed studies, and not with individual or identifiable participant data. All studies included in this meta-analysis had been granted ethics approval by their respective institutional review boards.

Results

Our initial search identified 185 studies. Figure 1 provides an overview of the selection process. A total of 14 studies met all inclusion criteria. Table 1 and Table 2 provide a description of the study samples and the brain age models employed, respectively. Because the study by Kang and colleagues[25] reported data from 4 nonoverlapping samples (females and males from Korea or the United Kingdom), the data from each sample were entered separately.

The samples described in the studies ranged in size from 92 to 32 175 participants, with an average age range of 26.4–76.0 years. The brain age models employed were most commonly based on T_1-weighted structural grey and white matter MRI data, with the exception of 2 studies that used data from T_1-weighted grey matter only,[25,38] 2 studies that used T_2-weighted scans,[39,40] and 1 study that used a composite of white matter diffusion metrics.[30] Most studies reported using scanners with 3.0 T magnets, with the exception of 2 studies using a 1.5 T scanner[33,39] and 1 study that used both types on an even number of their participants.[40] Brain age model performance was most often reported as the mean absolute error (MAE) of prediction, which ranged from 3.1 to 6.9. Of the studies that investigated diabetes as a predictor of brain age, 1 study defined diabetes as both type 1 and type 2 diabetes,[30] 2 studies defined it as only type 2 diabetes,[24,25] 3 defined it as diabetes mellitus,[39–41] and 5 did not specify the type (Appendix 1, Table S1).[33,38,42–44] Although most studies looked at more than 1 of the risk factors, only 2 included all 3 risk factors of interest (Appendix 1, Table S5).

Quality and risk of bias assessment

There was a high degree of agreement between the 2 independent raters (r = 0.880, intraclass correlation coefficient = 0.882). Six studies were deemed to have a low risk of bias, 7 had a medium risk of bias, and 1 had a high risk of bias. Figure 2 shows each study's risk of bias score, as assessed by each of the 2 raters.

Cardiometabolic risk factors and brain age

Among the 12 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 diabetes (Figure 3A). The effect of diabetes on brainAGE remained significant among the 6 study samples that controlled for hypertension (d = 0.232, 95% CI 0.132–0.332; n = 42 842; I^2 = 75.035) (Figure 3B) and 5 that controlled for BMI (d = 0.247, 95% CI 0.126–0.367; n = 39 875; I^2 = 77.644) (Figure 3C). Results of the jack-knife analysis showed that no particular study changed the significance of the effect when left out of the analysis.

Between the 10 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 4A). The effect of hypertension on brainAGE remained significant among the 6 study samples that controlled for diabetes (d = 0.101, 95% CI 0.064–0.137; n = 42 849; I^2 = 33.824) (Figure 4B) and 4 that controlled for BMI (d = 0.109, 95% CI 0.054–0.165; n = 37 933; I^2 = 55.242) (Figure 4C). Results of the jack-knife analysis showed no particular study changed the significance of the effect when left out of the analysis.

Among the 6 samples from 3 studies that investigated the effect of categorically defined obesity on brainAGE, 1 study was deemed to have a high risk of bias and reported an unrealistically large effect size (d = 1.476, z = 6.276); we therefore

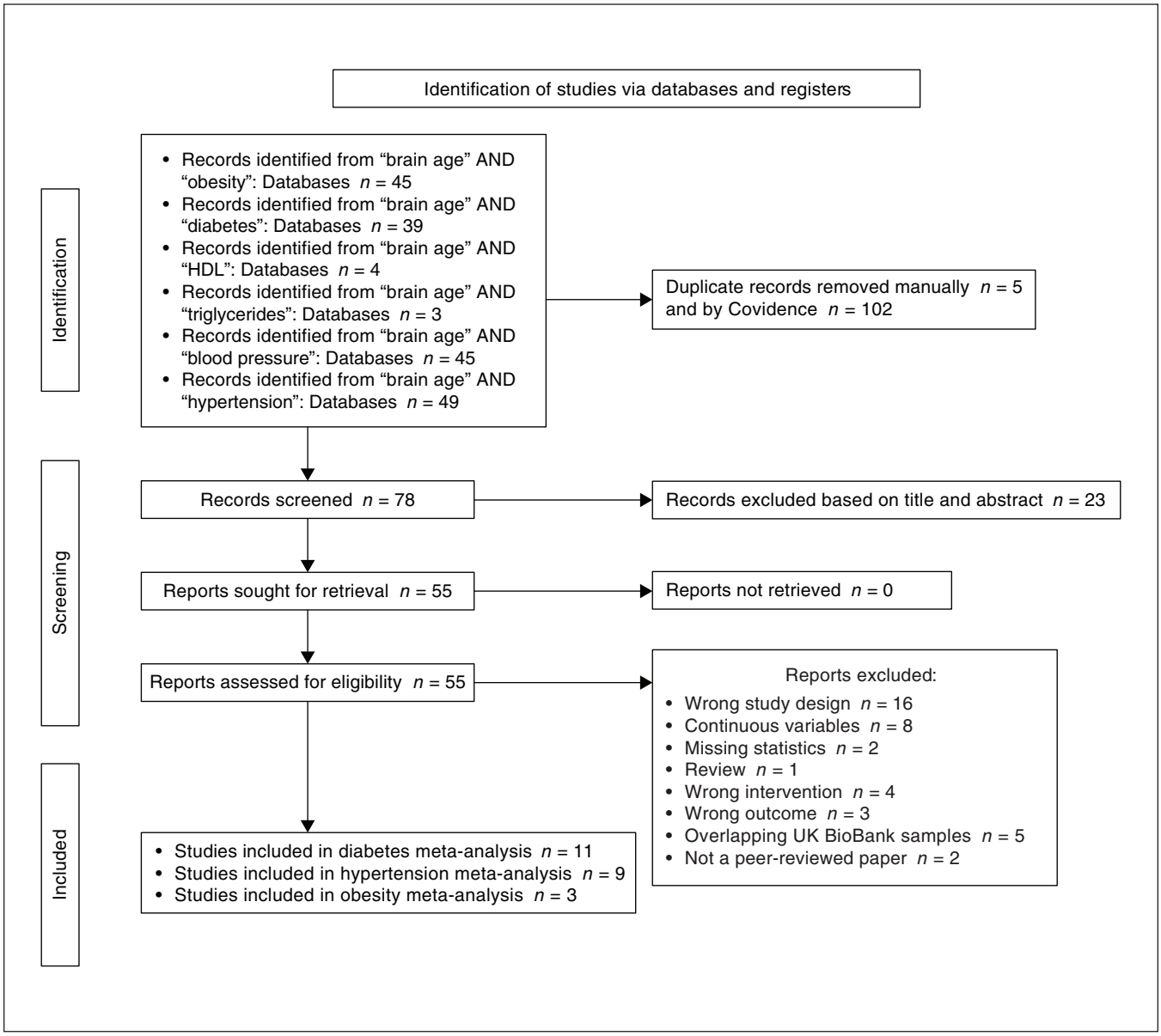

Figure 1: Flowchart describing the search strategy and study selection process. A total of 14 studies were included in this study, 11 of which were used in the diabetes meta-analysis, 9 in the hypertension meta-analysis, and 3 in the obesity meta-analysis. HDL = high-density lipoprotein. See Related Content for accessible version.

excluded this sample as an outlier. Among the 5 included 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 = 15678; I^2 = 40.577) such that those with obesity had a higher brainAGE than those without obesity (Figure 5A). The effect of obesity on brainAGE remained significant among the 4 study samples that controlled for hypertension and diabetes (d = 0.096, 95% CI 0.040–0.152; n = 15444; I^2 < 0.01) (Figure 5B). Results of the jack-knife analysis showed that no particular study changed the significance of the effect when left out of the analysis.

Discussion

Diabetes, hypertension, and obesity were all significantly associated with subtle brain changes as measured by brainAGE. Among the 3 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 3 effect sizes remained significant and comparable among studies that controlled for the other cardiometabolic risk factors, suggesting each has a unique effect on the brain. Consequently, people with all 3 conditions will likely show more pronounced brain changes than those with only 1 or 2.

Table 1: Sample descriptives

Study	Sample	Sample size	Age, yr, mean ± SD (range)	No. (%) female	No. (%) with diabetes	No. (%) with hypertension	BMI, mean ± SD	Clinical populations
Bretzner et al., 2023[39]	MRI-GENIE	4163	62.8 ± 15.0	1748 (42)	687 (16.5)	2825 (67.9)	NA	Prior stroke (12.9%) CAD (18.5%) Afib (14.3%)
Busby et al., 2023[42]	ABC USC	217	47.4 ± 18.3 (20–79)	167 (77.0)	14 (6.5)	50 (23.1)	27.53	None
Casanova et al., 2024[38]	ARIC	1172	76.0 ± 5.3	747 (63.7)	359 (30.6)	871 (74.3)	28.5 ± 5.7	Dementia (4.76%) MCI (31.85%)
Franke et al., 2013[24]	SAFE	185	64.9 ± 8.3	91 (49)	98 (53.0)	78 (42.2)	27.3 ± 4.3	Syncope
Guan et al., 2022[60]	BPRHS	121	66.6 ± 6.4	96 (79.3)	0 (0)	67 (55.4)	32.3 ± 6.6	None
Hwang et al., 2021[40]	SNUH	270	64.7 ± 9.3	127 (47)	52 (19)	137 (51)	NA	None
Jawinski et al., 2022[41]	BASE-II	335	70.5 ± 3.8 (61–82)	127 (38)	34 (10.4)	NA	26.7 ± 3.5	None
Jha et al., 2022[43]	DHS-2	1949	49.9 ± 10.6	1150 (59)	246 (14.4)	NA	29.7 ± 5.3	None
Kang et al., 2023a[25]	SHPC-F	2599	63.2 ± 6.9	2599 (100)	273 (10.5)	965 (37.1)	23.5 ± 2.9	None
Kang et al., 2023b[25]	SHPC-M	2942	64.7 ± 6.5	0 (0)	683 (23.2)	1402 (47.7)	24.5 ± 2.6	None
Kang et al., 2023c[25]	UKBB-F	5167	63.4 ± 7.1	5167 (100)	365 (7.1)	1813 (35.1)	26.8 ± 5.2	None
Kang et al., 2023d[25]	UKBB-M	4736	63.8 ± 7.4	0 (0)	602 (12.7)	2208 (46.6)	27.7 ± 4.4	None
Kolenic et al., 2018[34]	Prague	234	26.4 ± 4.5	107 (45.7)	NA	13 (5.6)	23.0 ± 3.5	First-episode psychosis
Korbmacher et al., 2023[30]	UKBB	32 175	64.5 ± 7.6	15161 (52.9)	543 (1.7)	6332 (19.8)	26.3 ± 4.3	
Sone et al., 2022[44]	JPSC-AD	773	71.7 (7.2)*	453 (58.6)	111 (14.4)	371 (48.0)	NA	
Weihs et al., 2021[33]	SHIP	690	52.5 ± 13.4	337 (48.8)	66 (9.6)	308 (44.6)	NA	Sleep apnea
Zeighami et al., 2022[61]	HCP	92	NA	NA	NA	NA	NA	

ABC USC = Aging Brain Cohort at the University of South Carolina; Afib = atrial fibrillation; ARIC = Atherosclerosis Risk in Communities; BASE-II = Berlin Aging Study II; UBMI = body mass index; BPHRS = Boston Puerto Rican Health Study; CAD = coronary artery disease; DHS-2 = Dallas Heart Study, second 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; NA = not available; SAFE = Syncope and Falls in the Elderly; SD = standard deviation; SHIP = Study of Health in Pomerania; SHPC-F = Health Promotion Center of Samsung Medical Center (Females); SHPC-M = Health Promotion Center of Samsung Medical Center (Males); SNUH = Seoul National University Hospital; UKBB = UK BioBank sample that did not appear in the same analyses as UKBB-F or UKBB-M; UKBB-F = UK BioBank (Females); UKBB-M = UK BioBank (Males).
*Refers to median and interquartile range.

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 among people who went on to develop Alzheimer or vascular dementia 14 years later.[45] Those who developed vascular dementia had higher glucose levels than those who developed Alzheimer dementia, suggesting that while extreme perturbations may primarily translate into vascular pathology, milder changes in glucose may contribute to Alzheimer disease. This is in keeping with an obesity dose–response relationship observed in a meta-analysis by Qu and colleagues,[46] which found a higher risk for Alzheimer dementia among those with an overweight BMI of up to 30, and a higher risk of vascular dementia when this BMI cut-off was exceeded. Another study that investigated the impact of cardiovascular risk factors and all-cause dementia also showed diabetes to have a much larger effect on dementia risk than hypertension, smoking, alcohol, and low physical activity, even when adjusting for age and genetic risk.[47] Although both diabetes and hypertension are mentioned in current guidelines on dementia prevention,[48] our findings add to the urgency by documenting that these cardiometabolic risk factors contribute to brain structural alterations even among people without dementia.

The multidimensional nature of diabetes pathology may explain the larger pooled effect of diabetes on brainAGE. Hypertension is characterized by higher-than-normal blood pressure, which puts stress on arterial walls and can lead to cerebral small vessel disease.[49] The damaged microvessels do not sufficiently supply blood to the deeper structures of the brain, leading to neuronal atrophy and cognitive decline.[15,50] Diabetes also causes damage to microvascular structures via several mechanisms, including chronic oxidative stress and hyperglycemia, among others.[16] However, the damage caused by diabetes extends beyond cardiovascular injury because diabetic insulin resistance impairs the function of insulin-like growth factor 1, which functions as a neurotrophic factor and stimulates neuronal plasticity, angiogenesis, metabolic function, and protein clearance.[51,52] As such, although both hypertension and diabetes impair cerebral microcirculation, the burden of diabetes also leads to impairments in endocrine function, specifically by hindering the signalling 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 neurologic outcomes,

Table 2: Brain age models

Study	Machine learning model	Tissue type	Scanner type	Model performance	External training set	Model covariates
Bretzner et al., 2023[39]	ElasticNet linear regression	T_2-FLAIR MRI radiomics	1.5 T	MAE = 6.9	Yes	HTN, DM, Afib, CAD, history of smoking, prior stroke
Busby et al., 2023[42]	Gaussian regression	T_1-weighted GM + WM	3.0 T	r = 0.936	Yes	Age, sex, SES, BMI, HTN, diabetes, years of education, race
Casanova et al., 2024[38]	ElasticNet linear regression	T_1-weighted GM	3.0 T	MAE = 2.35	Yes	Age, sex, centre-race
Franke et al., 2013[24]	RVR	T_1-weighted GM + WM	3.0 T	MAE = 4.98	Yes	None
Guan et al., 2022[60]	XGBoost	T_1-weighted GM + WM	3.0 T	–	Yes	Age, sex, ICV, education
Hwang et al., 2021[40]	DCNN	T_2-weighted images	1.5 T n = 894 3.0 T n = 906	MAE = 4.22	Yes	None
Jawinski et al., 2022[41]	RVR	T_1-weighted GM + WM	3.0 T	MAE = 3.09	Yes	Sex, age, age,^{2} ICV
Jha et al., 2022[43]	BrainageR (Gaussian process regression)	T_1-weighted GM + WM	3.0 T	MAE = 3.93	Yes	Framingham 10-year risk, race or ethnicity, income, BMI, history of myocardial infarction
Kang et al., 2023[25]	GCN	T_1-weighted GM	3.0 T	–	Unknown	Type 2 DM, HTN, obesity, underweight
Kolenic et al., 2018[34]	RVR	T_1-weighted GM + WM	3.0 T	MAPE = 16.29%	Yes	Age, BMI category, FEP
Korbmacher et al., 2023[30]	XGBoost	WM: DTI, DKI, WMTI, SMT, mcSMT	3.0 T	–	Yes	BMI, pulse pressure, WHR, smoking status, type 1 DM, type 2 DM, binary high cholesterol, binary diagnosed vascular problem, birth weight, sleeping hours, daily coffee intake
Sone et al., 2022[44]	SVR	T_1-weighted GM + WM	3.0 T	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
Weihs et al., 2021[33]	OLS	T_1-weighted GM + WM	1.5 T	–	Unknown	Diabetes (AHI + diabetes + HbA_{1c} + age + sex + age × sex + ICV) HTN (AHI + HTN + diastolic BP + age + sex + age × sex + ICV)
Zeighami et al., 2022[61]	Linear regression with PCA	T_1-weighted GM + WM	3.0 T	RMSE = 8.8, r = 0.90	Yes	None

Afib = atrial fibrillation; AHI = apnea–hypopnea index; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; DCNN = deep convolutional neural network; DKI = diffusion kurtosis imaging; DM = diabetes mellitus; DTI = diffusion tensor imaging; FEP = first-episode psychosis; FLAIR = fluid-attenuated inversion recovery; GCN = graph convolutional network; GDS = Geriatric Depression Scale; GM = grey matter; HbA_{1c} = glycated hemoglobin; HTN = hypertension; ICV = intracranial volume; MAE = mean absolute error; MAPE = mean absolute percent error; mcSMT = multicompartment spherical mean technique; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; OLS = ordinary least squares; PCA = principle component analysis; RMSE = root mean squared error; RVR = relevance vector regression; SES = socioeconomic status; SMT = spherical mean technique; SVR = support vector regression; SWLS = Satisfaction with Life Scale; XGBoost = extreme gradient boosting; WHR = waist-to-hip ratio; WM = white matter; WMTI = white matter tract integrity.

yet our findings add to existing evidence suggesting that biochemical dysfunctions, as seen in diabetes, may play a substantial and possibly even greater role.

Seeing as the data included in this study were cross-sectional, we cannot infer the direction of changes and causality. Although 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 brain,[53] which parallel the patterns of age-related neurodegeneration[54] and are in keeping with the fact that brain age reflects a diffuse pattern of brain alterations.[55] 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 3 cardiometabolic risk factors and brain structure.[56–59]

Heterogeneity was generally high in the included studies with I^2 estimates ranging from 40.58 to 66.77. Subgroup analyses of studies that 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 among people with the specific cardiometabolic risk factor). However, the effect sizes differed among the studies. This could possibly reflect differences in duration of illness or treatment, which were

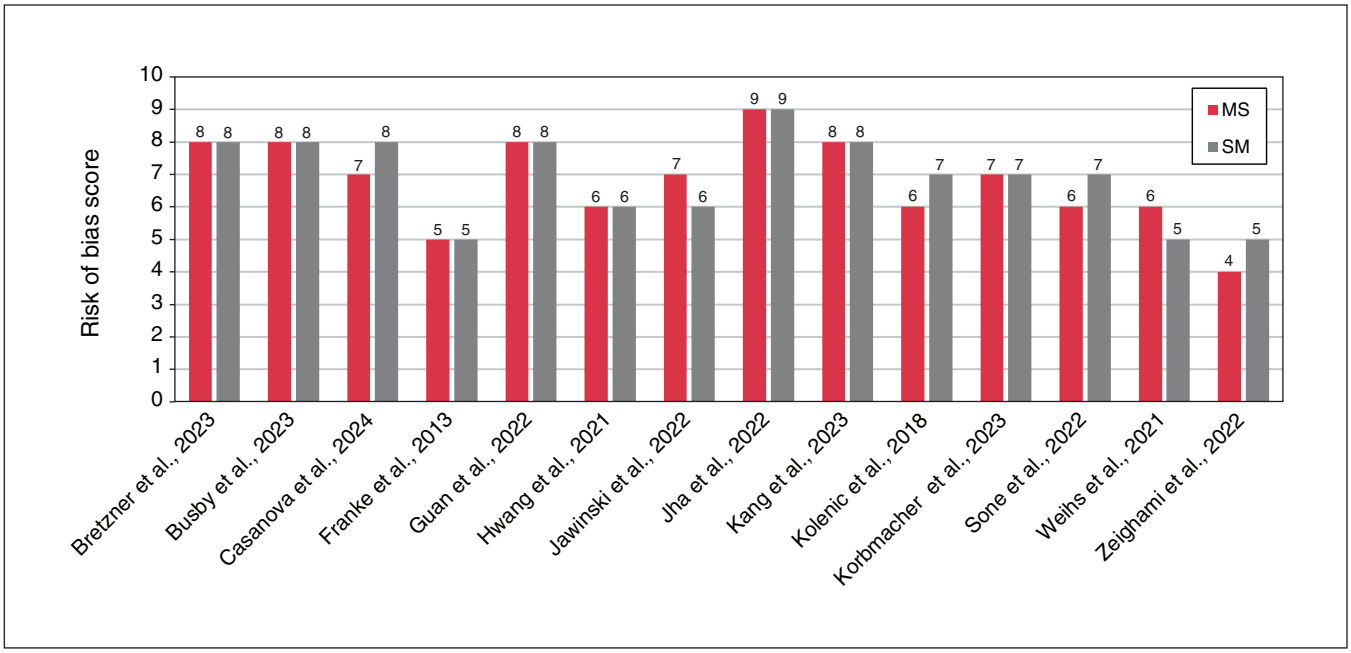

Figure 2: Each included study's risk of bias score per independent rater (M.S. or S.M.) using the adapted Newcastle–Ottawa Scale. Of the 14 included studies, 6 were deemed to have a low risk of bias (score > 7), 7 were deemed to have a medium risk of bias (score of 5–7), and 1 was deemed to have a high risk of bias (score < 5) by at least 1 rater. There was a high degree of agreement between the 2 independent raters (r = 0.880, intraclass correlation coefficient = 0.882).

not well quantified in individual studies. Someone who received a recent diagnosis of type 2 diabetes or hypertension may demonstrate smaller brain changes than someone who has been affected by the condition for several years. At the same time, shorter treatment is likely less protective of brain structure than longer treatment, but none of the included studies quantified treatment of cardiometabolic risk factors. Most studies relied on either self-reported diagnosis of cardiometabolic risk factors or the use of antihypertensive or antidiabetic medications as inclusion criteria. Consequently, it is likely that most 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 even though most participants were likely receiving treatment.

Limitations

Of the 11 studies that provided data for diabetes, only 2 studies specified that they included only participants with type 2 diabetes,[24,25] whereas many did not specify the type. The cumulative sample size in the obesity meta-analysis (n = 15 678) was much smaller than that in the diabetes (n = 47 436) or 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 reported only a mean age of participants, rather than 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. Finally, as diabetes, hypertension, and obesity are highly comorbid, we would ideally want to always control for the effects of the other cardiometabolic risk factors. However, that was not always done in the available studies. To maximize sample size, we first looked at all available studies in the same analysis, and then ran a secondary sensitivity analysis that included only 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 remained significant.

Conclusion

Our findings identified diabetes as having the highest effect size on brainAGE, followed by hypertension and obesity, with all 3 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 vascular disturbances alone, as seen in hypertension. We propose that diabetes

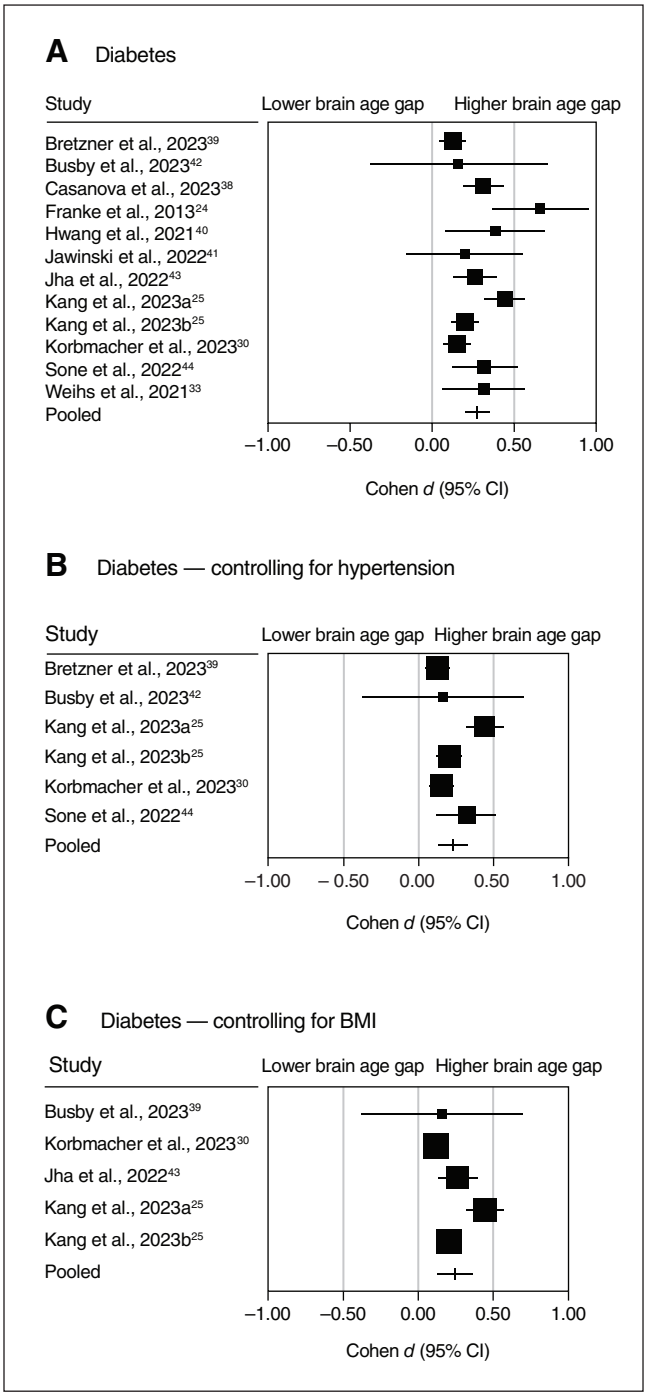

Figure 3: Results of the diabetes random effects meta-analyses. (A) A comparison of 12 study samples showed a significant effect of diabetes on brain age gap estimates (brainAGE) (d = 0.275, 95% confidence interval [CI] 0.198–0.352; n = 47 436; I^2 = 66.765). (B) Among the studies that controlled for 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 body mass index (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). See Related Content for accessible version.

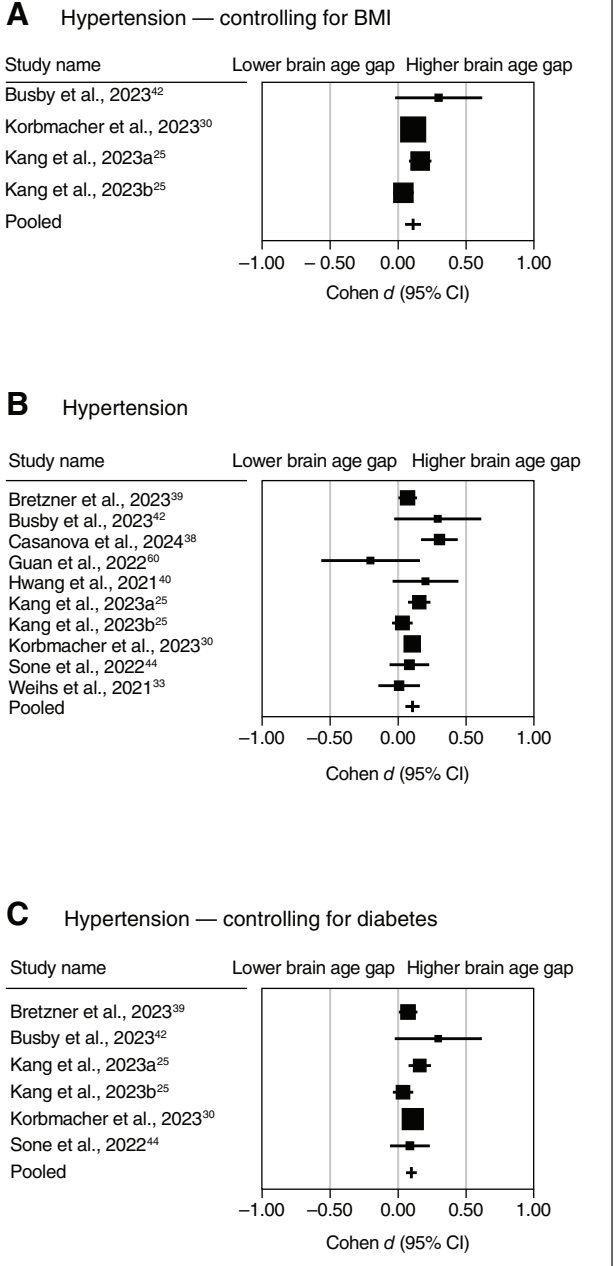

Figure 4: Results of the hypertension random effects meta-analyses. (A) A comparison of 10 study samples showed a significant effect of hypertension on brain age gap estimates (brainAGE) (d = 0.113, 95% confidence interval [CI] 0.063–0.162; n = 45 102; I^2 = 58.540). (B) Among the studies that controlled 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 body mass index (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). See Related Content for accessible version.

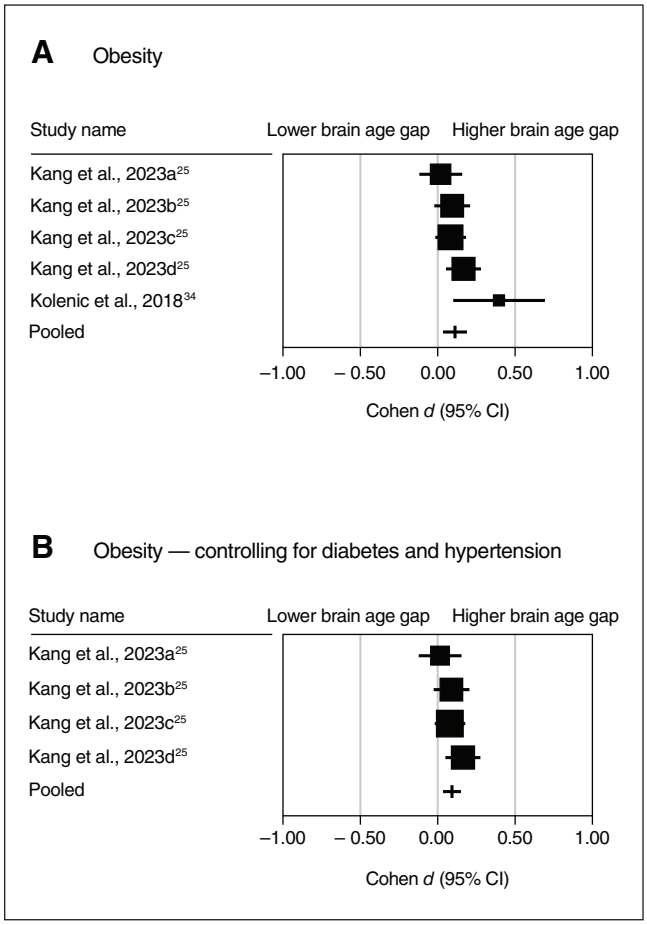

Figure 5: Results of the obesity random effects meta-analysis. (A) A comparison of 5 study samples showed a significant effect of obesity on brain age gap estimates (brainAGE) (d = 0.112, 95% confidence interval [CI] 0.037–0.187; n = 15 678; I^2 = 40.577). (B) Only 1 study[25] controlled for the effects of diabetes and hypertension within their model, and so its 4 independent samples were meta-analyzed separately, revealing a significant independent effect of obesity on brain age (d = 0.096, 95% CI 0.040–0.152; n = 15 444; I^2 < 0.01). See Related Content for accessible version.

should serve as the primary target of clinical interventions aimed at preventing brain structural changes that may lead to cognitive decline and development of Alzheimer dementia.

Affiliations: From the Department of Psychiatry, Dalhousie University, Halifax, N.S. (Selitser, Dietze, McWhinney, Hajek) and the Charles University, Third Faculty of Medicine, Prague, Czech Republic (Hajek).

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