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Association between Type 2 Diabetes Mellitus and Brain Atrophy: A Meta-Analysis

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Background: Type 2 diabetes mellitus (T2DM) is known to be associated with cognitive decline and brain structural changes. This study systematically reviews and estimates human brain volumetric differences and atrophy associated with T2DM.
Methods: PubMed, PsycInfo and Cochrane Library were searched for brain imaging studies reporting on brain volume differences between individuals with T2DM and healthy controls. Data were examined using meta-analysis, and association between age, sex, diabetes characteristics and brain volumes were tested using meta-regression.
Results: A total of 14,605 entries were identified; after title, abstract and full-text screening applying inclusion and exclusion criteria, 64 studies were included and 42 studies with compatible data contributed to the meta-analysis (n=31,630; mean age 71.0 years; 44.4% male; 26,942 control; 4,688 diabetes). Individuals with T2DM had significantly smaller total brain volume, total grey matter volume, total white matter volume and hippocampal volume (approximately 1% to 4%); meta-analyses of smaller samples focusing on other brain regions and brain atrophy rate in longitudinal investigations also indicated smaller brain volumes and greater brain atrophy associated with T2DM. Meta-regression suggests that diabetes-related brain volume differences start occurring in early adulthood, decreases with age and increases with diabetes duration.
Conclusion: T2DM is associated with smaller total and regional brain volume and greater atrophy over time. These effects are substantial and highlight an urgent need to develop interventions to reduce the risk of T2DM for brain health.

Keywords: Atrophy; Brain; Diabetes mellitus, type 2; Neuroimaging

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common, chronic, and progressive metabolic disorder characterised by abnormally high blood glucose levels for a prolonged period, termed hyperglycaemia, due to insulin resistance and decreased production of insulin. Typical T2DM complications include retinopathy, kidney failure, and peripheral neuropathy [1]. Because of the high prevalence of T2DM among the elderly and the growing concern over cognitive health in older populations, there is a growing interest in how T2DM affects brain functions and related brain structures. T2DM is associated with an approximately 50% increased risk of developing dementia [2]; higher blood glucose levels in non-diabetics, which are known to be associated with increased risk of T2DM, are also associated with elevated risk of dementia [3]. Cognitive domains that may be affected by T2DM include memory, processing speed, and executive function [4]. Although the specific mechanisms that result in cognitive impairment in T2DM are not clear, hyperglycaemia, vascular disorders, hypoglycaemia, and insulin resistance are associated with increased risk; T2DM may also be involved in the pathogenesis of Alzheimer's disease [5]. Moreover, there is emerging evidence that brain changes that lead to functional deficits may start developing well before T2DM is clinically diagnosed [3].

Many studies have used human brain magnetic resonance imaging (MRI) to measure structural changes *in vivo* that may be associated with T2DM. Typically, they have used brain volu-

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metry to measure the extent of brain atrophy. Cross-sectional studies have consistently identified associations between T2DM and a decrease in mean total brain volume by 0.2 to 0.6 standard deviation units, which is comparable to 3 to 5 years of normal ageing [6-8]. More frequent brain lesions [8,9] and greater number of white matter hyperintensities [7,8] have also been identified in T2DM, likely due to the increased vascular pathology in this disease. These brain structural differences may also be associated with T2DM duration and blood glucose levels [8]. Studies focusing on specific brain regions have found negative associations between T2DM and volume of sub-regions including the hippocampus, basal ganglia, and many cortical regions among cognitively healthy individuals [6,8,10,11].

Longitudinal case-control and population-based studies have identified brain atrophy three times greater in T2DM than normal ageing [11-14]. Ventricular enlargement has also been observed [11,12,14,15], suggesting vulnerability of subcortical areas surrounding the ventricles. However, we lack robust estimates of atrophy rates attributable to T2DM as well as an understanding of which brain structures are most affected, as well as the timing of these changes across adulthood.

Therefore, the aim of this systematic review is to precisely quantify the volumetric differences and rates of brain atrophy associated with T2DM using a published methodology. We hypothesise that those with T2DM have smaller brain volumes and higher brain atrophy rate than those without T2DM.

METHODS

This systematic review and meta analysis was based on our previously published methodology [16], following predetermined search terms, inclusion and exclusion criteria, and quality assessment at the study level. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17] and was pre-registered in PROSPERO (No.: CRD42021230535).

Search strategy

PubMed, PsycInfo, and Cochrane Library (1950 to January 2020) was searched using the following terms: "(Diabetes or T2D) AND (brain or cerebrum or cerebral or cerebellum or cerebellar or hippocampus or hippocampal or subcortical or (cerebral ventricle) or ventricular or thalamus or thalamic or (basal ganglia) or striatum or (grey matter) or (white matter)) AND ((magnetic resonance imaging) or MRI or (computed tomography) or neuroimaging or morphometry or (diffusion tensor imaging) or volume or volumetric or thickness or atrophy or shrinkage)." Search included all text, all dates, full text papers in English (all article types for PubMed and PsycInfo; trials for Cochrane Library). Both literal and Medical Subject Heading searches were performed when possible. Titles and abstracts of the paper were screened by two reviewers (T.Z. and N.C./M.S.) for full text review. Full text and supplemental material of qualified studies were retrieved and examined by two reviewers against the inclusion and exclusion criteria. Disagreements between two reviewers were resolved by consensus or by a third reviewer. Citation maps of retrieved papers, previous reviews and previously identified journals were examined to identify additional journal articles that meet the criteria.

Inclusion and exclusion criteria

Studies were included if they had: (1) human adult participants; (2) at least a control group consisting of healthy participants without T2DM; (3) at least one comparison between participants diagnosed with T2DM and controls; (4) brain grey matter or white matter volume data from structural MRI or computed tomography (CT) scan data of T2DM and control participants; (5) data acquired using a validated automatic or manual segmentation method; (6) for longitudinal studies, longitudinal measurements at a minimum of two time points. Studies were excluded if they had: (1) participants with only type 1 diabetes mellitus (T1DM) or that did not differentiate T1DM and T2DM; (2) participants with only subclinical diabetes, including impaired fasting glucose, impaired glucose tolerance, insulin resistance, in the disease group or control group; (3) T2DM participants that all have major conditions other than diabetes, e.g., mental illness, behavioural problems, substance abuse, systemic illness or major brain structural abnormalities; (4) T2DM participants that are all under diabetes treatment (including placebo treatments) and being compared with those without such treatment; (5) only case studies and small samples with less than 10 participants in one group; (6) duplicate samples (for identified duplicates, the sample that best fits the study criteria will be included and the other samples will be excluded); (7) review articles, theses, unfinished studies, or entries with abstract only; (8) for longitudinal studies, samples where the total MRI follow-up period is less than 12 months.

Studies meeting the inclusion and exclusion criteria were assessed for quality using the Newcastle-Ottawa scale. Each

study was evaluated on eight items classified into three categories including the selection of the study groups, the comparability of the groups, and the ascertainment of outcome of interest. Each quality item was awarded by a star (except two for comparability) and for each study up to nine stars in total.

Data extraction

Two of the authors extracted data (T.Z. and N.C.) and discrepancies were resolved by consensus. Data extracted consisted of (1) study design and number of participants in each group; (2) participants' demographics including age, sex ratio, diagnostic criteria for T2DM, duration of T2DM, medication status, glycosylated hemoglobin (HbA1c) levels, fasting plasma glucose levels and body mass index; (3) measurement details including MRI parameters, structural measurements and segmentation method; and (4) study results including areas of interest (left and right) and effect sizes (left, right, and total). Data from studies reporting ratios relative to intracranial volume were included if a volumetric difference could be computed based on group statistics.

Multiple reports on the same cohort but on different brain structures were considered independent studies and included. Where a particular sample was reported in multiple studies on the same brain structure, the study that fit the selection criteria and provided data compatible for meta-analysis was included and other studies were excluded. Studies that reported effect sizes (or provided them after contact) were considered and from those the most recent study with the largest sample size was selected. If there was more than one study similar in sample size and time, the one with the highest quality rating was selected.

Statistical analysis

R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) [18] was used for statistical analysis. Meta-analyses were performed using the Metafor version 1.9-4 R package (https://www.metafor-project.org) [19]. Volumes of brain structures and annual percentage mean atrophy rate was considered as the effect size, and calculation of required standard error (SE) for meta-analysis was based on the standard deviation and number of participants in each group for each individual study. Availability of volume of a brain structure, either reported or computed based on other reported results, was the essential requirement for the meta-analysis. Atrophy rate was calculated using the formula: atrophy=[(volume_time1−volume_time2)/volume_time1]/(time1−time2) if not provided. Where insufficient data were available for inclusion in the meta-analysis, authors were contacted directly to seek additional information.

A random-effects model using a restricted maximum likelihood estimator was used for all meta-analyses. A random effects model was chosen based on the assumption that included studies are heterogeneous because they sample populations with different characteristics using a range of methodologies and therefore one cannot assume that there is a single effect size [20]. A random effects meta-analysis estimates the mean of a distribution of effects rather than estimating a unique effect [20]. We assessed heterogeneity across studies with the Q statistic (with $P<0.01$ being suggestive of significant heterogeneity) and the I^2 statistic (values of 25%, 50%, and 75% were indicative of low, medium, and high heterogeneity). Separate meta-analyses were performed for different brain structures.

Meta-regression was used to investigate the impact of demographic and diabetes characteristics on differences in brain volumes between metabolically healthy individuals and individuals with diabetes, if there were at least 10 studies providing information of a covariate, including age (centred at 60 years), sex, diabetes duration, ratio of diabetes patients taking medication, plasma insulin levels, HbA1c levels and fasting plasma glucose levels, using linear mixed-effects models.

Sensitivity analyses were conducted using the leave-one-out method to identify studies contributing excessively to heterogeneity. Visual evaluation of asymmetry of the funnel plots was used to assess the bias in the meta-analyses results toward publication of studies with significant outcomes. The trim-and-fill method was used to estimate the number of missing studies (representative of unreported effect sizes) in the meta-analysis to estimate adjusted effect sizes.

RESULTS

Literature search and study inclusion

The systematic search identified 10,360 entries from PubMed, 664 from PsycInfo, and 3,641 from Cochrane Library; 60 duplicate entries were identified and excluded. Of these 14,605 studies, 355 studies passed title screening, and 109 studies remained after abstract screening; 64 studies remained after applying inclusion criteria in full-text assessment (Fig. 1).

Of the included studies, 40 were cross-sectional case-control, 17 cross-sectional population-based, one longitudinal

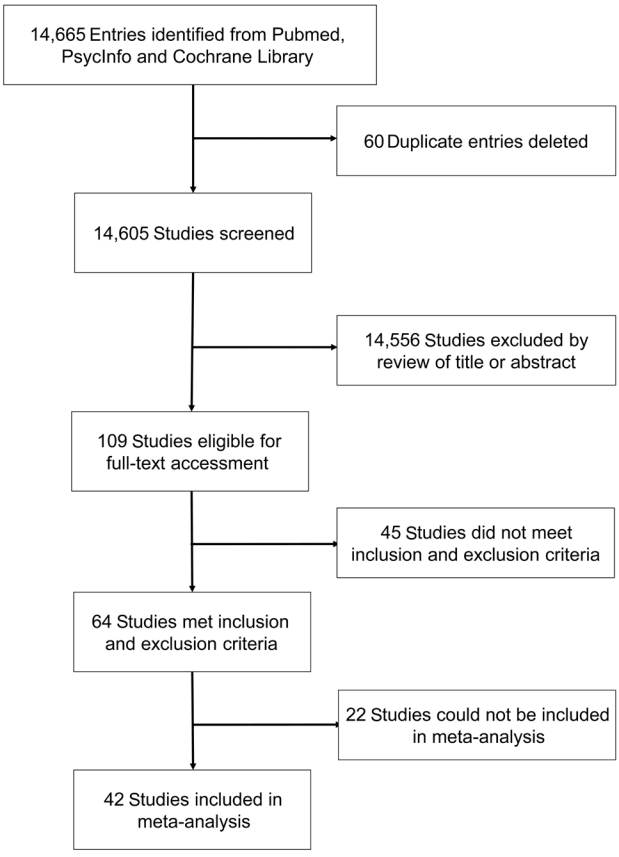

Fig. 1. Flowchart of the screening and inclusion of studies into the systematic review and meta-analysis.

case-control, and six longitudinal population-based studies. Forty-two studies (n=31,630; mean age 71.0 years; 44.4% male; 26,942 controls; 4,688 diabetes) with enough volumetric data could be considered for meta-analysis. Of these, 25 used automated segmentation, six used manual tracing, and 15 studies applied voxel-based morphometry (Tables 1 and 2) [11,21-84].

Twenty-eight studies reported disease duration, 17 medication status (number of patients taking medication, or specifically taking oral medication or insulin), five plasma insulin levels, 29 HbA1c levels, and 22 fasting plasma glucose levels (for specific demographic and T2DM-related information) (Table 2).

Meta-analysis

Of all the brain regions investigated, only total brain volume, total grey matter, total white matter, hippocampus, thalamus, caudate, putamen, globus pallidus, amygdala, nucleus accumbens, frontal lobe, superior temporal gyrus, total cerebrospinal fluid, and white matter hyperintensity were reported in a sufficient number of studies to be included in meta-analyses. Total brain volume annual atrophy rate was also reported in five longitudinal studies (see Table 1 for details).

Global brain volumes

Fifteen studies reported on total brain volume (15,937 normal; 2,277 diabetes), 24 studies on total grey matter volume (15,475 normal; 3,117 diabetes), and 22 studies on total white matter volume (14,091 normal; 2,965 diabetes). Participants with T2DM had significantly smaller total brain volume, with volumetric difference attributable to T2DM (T2DM-normal in Table 3) of 20.50 cm^3 (1.81% of normal volume). They also had significantly smaller grey matter volume (–17.43 cm^3; 2.88%) and white matter volume (–10.73 cm^3; 2.15%) (Table 3, Fig. 2).

Subcortical volumes

Fourteen studies reported on hippocampal volume (9,935 normal; 1,319 diabetes), four studies on thalamus (9,703 normal; 625 diabetes), and three studies on caudate, putamen, globus pallidus, amygdala, and nucleus accumbens (9,350 normal; 579 diabetes). Participants with T2DM had smaller hippocampus (–0.15 cm^3; 4.4%), thalamus (–0.33 cm^3; 4.2%), caudate (–0.09 cm^3; 2.6%), putamen (–0.14 cm^3; 2.9%), globus pallidus (–0.014 cm^3; 0.8%), amygdala (–0.003 cm^3; 0.2%), and nucleus accumbens volume (–0.035 cm^3; 7.8%); these associations were significant in hippocampus, thalamus, caudate, putamen, and nucleus accumbens (Table 3, Supplementary Fig. 1).

Local cortical volumes

Five studies reported on superior temporal gyrus volume (820 normal; 665 diabetes) and five studies on frontal lobe volume (1,617 normal; 282 diabetes). Participants with T2DM had smaller superior temporal gyrus (–0.18 cm^3; 0.88%) and smaller frontal lobe volume (–1.04 cm^3; 0.71%) but the association was not significant (Table 3, Supplementary Fig. 1).

Total cerebrospinal fluid volume

Ten studies reported on total cerebrospinal fluid volume (4,363 normal; 1,239 diabetes). Participants with T2DM had higher cerebrospinal fluid volume (7.15 cm^3; 1%) but the association was not significant (Table 3, Supplementary Fig. 1).

White matter hyperintensities volume

Twelve studies reported on white matter hyperintensities vol-

Table 1. Studies included in the review

No.	Study	Study design	Cohort	Newcastle-Ottawa quality assessment scale[a]							Compatibility with meta-analysis	
				Selection			Comparability		Outcome		In	
				Q1	Q2	Q3	Q4	Q5	Q6	Q7	Yes/No	Structures
1	Ajilore et al. (2010) [22][a]	CCC		*			*	**		*	Yes	Total brain volume
2	Ajilore et al. (2015) [23]	CCC		*		*	*	*	*	*	Yes	Hippocampus
3	Armstrong et al. (2019) [24]	LP	BLSA	*	*	*	**	**	*	*	No	
4	van Bloemendaal et al. (2016) [25]	CCC		*			*		*	*	No	
5	Bruehl et al. (2009I) [26]	CCC		*			*		*	*	Yes	Hippocampus, superior temporal gyrus
6	Bruehl et al. (2009II) [27]	CCC		*	*	*	*	**	*	*	Yes	Superior temporal gyrus, frontal lobe, cerebrospinal fluid
7	Brundel et al. (2010) [28]	CCC	UDES	*	*	*	*	**	*	*	Yes	Grey matter, hippocampus
8	Brundel et al. (2014) [29]	CCC	UDES	*	*	*	*	**	*	*	Yes	White matter hyperintensity
9	Callisaya et al. (2019) [30]	LP	CDOT	*	*	*	*	**	*	*	Yes	Total brain volume, white matter hyperintensity
10	Chen et al. (2006) [31]	CP	PATH	*	*	*	*	**	*	*	No	
11	Chen et al. (2012) [32]	CCC		*	*		**	**	*	*	Yes	Grey matter, white matter
12	Chen et al. (2014) [33]	CCC		*	*		**		*	*	Yes	Grey matter, white matter
13	Chen et al. (2017) [34]	CCC		*				**	*	*	Yes	Grey matter, white matter, hippocampus, thalamus, caudate, putamen, globus pallidus, amygdala, nucleus accumbens
14	Climie et al. (2014) [35]	CCC			*	*	**	**	*	*	Yes	Grey matter, white matter, hippocampus, white matter hyperintensity
15	Cox et al. (2019) [36]	CP	UK Biobank		*	*	*	**	*	*	Yes	Total brain volume, grey matter, hippocampus, thalamus, caudate, putamen, globus pallidus, amygdala, nucleus accumbens
16	Cui et al. (2014) [37]	CCC		*	*	*	*	**	*	*	Yes	Grey matter, white matter, cerebrospinal fluid
15	Cui et al. (2017) [38]	CCC		*		*	**	**	*	*	Yes	Grey matter, white matter, cerebrospinal fluid
16	Cui et al. (2020) [39]	CCC		*		*	*	**	*	*	No	
17	de Bresser et al. (2010) [12]	LCC		*	*	*	**	*	*	*	Yes	Total brain atrophy rate
18	de Bresser et al. (2018) [40]	LP	BLSA	*	*	*	*	*	*	*	No	
19	den Heijer et al. (2003) [41]	CP	Rotterdam Study	*	*	*	**	**	*	*	No	
20	Espeland et al. (2013) [11]	LP	WHIMS-MRI	*	*	*		**	*	*	Yes	Total brain volume, grey matter, white matter, cerebrospinal fluid, total brain atrophy rate
21	Fang et al. (2018) [42]	CCC					*		*	*	No	
22	Fang et al. (2019) [43]	CCC		*	*		*	**	*	*	Yes	Grey matter, white matter

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Table 1. Continued

No.	Study	Study design	Cohort	Newcastle-Ottawa quality assessment scale[a]							Compatibility with meta-analysis	
				Selection			Comparability		Outcome		In	
				Q1	Q2	Q3	Q4	Q5	Q6	Q7	Yes/No	Structures
23	Ferreira et al. (2017I) [44]	CCC		*	*	*	*	*	*	*	No	
24	Ferreira et al. (2017II) [45]	CCC		*	*	*	*	*	*	*	No	
25	Gold et al. (2007) [46]	CCC		*	*	*	*	*	*	*	Yes	Hippocampus, superior temporal gyrus, frontal lobe
26	Hempel et al. (2012) [47]	CCC		*	*	*	*		*	*	Yes	Hippocampus, superior temporal gyrus, frontal lobe
27	Hirabayashi et al. (2016) [48]	CP	Hisayama Study	*	*	*	*	**	*	*	No	
28	Hoogendam et al. (2012) [49]	CP	Rotterdam Study	*	*	*	*	*	*	*	No	
29	Hsu et al. (2012) [50]	CCC		*	*	*	**		*	*	Yes	Grey matter, white matter, cerebrospinal fluid
30	Jongen et al. (2007) [51]	CCC	UDES	*	*	*	*	**	*	*	Yes	Total brain volume, grey matter, white matter, white matter hyperintensity, cerebrospinal fluid
31	Kumar et al. (2008I) [52]	CP	PATH	*	*	*			*	*	Yes	Total brain volume, grey matter, white matter, hippocampus, cerebrospinal fluid
32	Kumar et al. (2008II) [53]	CCC		*	*	*			*	*	Yes	Grey matter, white matter
33	Last et al. (2007) [54]	CCC		*	*		**	**	*	*	Yes	Total brain volume
34	Launer et al. (2015) [55]	CP	CARDIA		*	*	*	**	*	*	No	
35	Lee et al. (2013) [56]	CCC					**	*	*	*	No	
36	Li et al. (2016) [57]	CP	ADNI	*	*	*	*	**	*	*	Yes	Total brain volume
37	Li et al. (2018) [58]	CCC			*			*	*	*	No	
38	Liu et al. (2018) [59]	CCC			*	*	*	**	*	*	No	
39	Lucatelli et al. (2016) [60]	CCC		*	*	*	*	**	*	*	No	
40	Luchsinger et al. (2020) [61]	CCC		*			*	**	*	*	Yes	Total brain volume, white matter hyperintensity
41	Maldijan et al. (2013) [62]	CP	Diabetes Heart Study-Mind	*	*	*	*		*	*	Yes	White matter hyperintensity
42	Manor et al. (2012) [63]	CCC		*	*	*	*	*	*	*	No	
43	Moran et al. (2015) [64]	CP	ADNI	*	*	*	*	**	*	*	No	
44	Moran et al. (2016) [65]	CCC		*	*	*	*	**	*	*	Yes	Grey matter, white matter, white matter hyperintensity
45	Musen et al. (2012) [66]	CCC					**		*	*	Yes	Hippocampus
46	Novak et al. (2011) [67]	CCC			*	*	*	**	*	*	No	
47	Peng et al. (2015) [68]	CCC		*			**		*	*	No	
48	Qiu et al. (2014) [69]	CP	AGES-Reykjavik Study	*	*	*	*	**	*	*	Yes	Total brain volume, grey matter, white matter, white matter hyperintensity, cerebrospinal fluid

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Table 1. Continued

No.	Study	Study design	Cohort	Newcastle-Ottawa quality assessment scale[a]							Compatibility with meta-analysis	
				Selection			Comparability		Outcome		In	
				Q1	Q2	Q3	Q4	Q5	Q6	Q7	Yes/No	Structures
49	Raffield et al. (2016) [70]	CP	Diabetes Heart Study-Mind	*	*	*	*	**	*	*	Yes	Grey matter, white matter
50	Redel et al. (2018) [71]	CCC		*			**		*	*	Yes	Total brain volume, grey matter
51	Reinhard et al. (2012) [72]	CCC		*	*	*	*	*	*	*	Yes	Total brain volume, grey matter, white matter, white matter hyperintensity
52	Rensma et al. (2020) [73]	LP	AGES-Reykjavik Study		*	*	*	**	*	*	Yes	Total brain atrophy rate
53	Roberts et al. (2014) [74]	CP	MCSA	*	*	*	*	**	*	*	No	
54	Roy et al. (2020) [75]	CCC		*		*	*	*	*	*	No	
55	Saczynski et al. (2009) [76]	CP	AGES-Reykjavik Study	*	*	*	*	**	*	*	No	
56	Samaras et al. (2014) [21]	LP	Sydney Memory and Aging Study	*	*	*	**	**	*	*	Yes	Total brain volume, hippocampus, frontal lobe, cerebrospinal fluid, total brain atrophy rate
57	Shibata et al. (2019) [77]	CP	Strong Heart Study (CD-CAI)	*	*	*	*	**	*	*	No	
58	Sun et al. (2018) [78]	CCC		*			*	**	*	*	Yes	Total brain volume, grey matter, white matter
59	Suzuki et al. (2019) [79]	CP	UK Biobank		*	*	*	**	*	*	Yes	White matter volume
60	Walsh et al. (2019) [80]	CP	PATH	*	*	*	**	**	*	*	Yes	Total brain volume, grey matter, white matter, thalamus
61	Wood et al. (2016) [81]	CCC		*	*	*	*	*	*		Yes	Grey matter, white matter, hippocampus, white matter hyperintensity
62	Yau et al. (2014) [82]	CCC		*	*	*	**	*	*	*	Yes	Hippocampus, superior temporal gyrus
63	Zhang et al. (2014) [83]	CCC		*				**	*	*	Yes	Grey matter, white matter
64	Zhang et al. (2015) [84]	CCC		*	*	*	*	**	*	*	Yes	Grey matter, white matter, hippocampus, white matter hyperintensity, thalamus, caudate, putamen, globus pallidus, amygdala, nucleus accumbens

CCC, cross-sectional case-control studies; CP, cross-sectional population-based studies; LCC, longitudinal case-control studies; LP, longitudinal population-based studies; abbreviations of cohort studies, in order of appearance: BLSA, Baltimore Longitudinal Study of Aging; UDES, Utrecht Diabetic Encephalopathy Study; CDOT, Cognition and Diabetes in Older Tasmanians Study; PATH, Personality and Total Health Through Life Study; WHIMS-MRI, Women's Health Initiative Memory Study; CARDIA, Coronary Artery Risk Development in Young Adults; ADNI, Alzheimer's Disease Neuroimaging Initiative; MCSA, The Mayo Clinic Study of Aging; CDCAI, Cerebrovascular Disease and its Consequences in American Indians Study.

[a]A 'star system' for a quick visual assessment. Stars awarded for each quality item. Questions: (1) Is the case definition adequate; (2) Representativeness of the cases (cross-sectional)/exposed cohort (longitudinal); (3) Selection of controls (cross-sectional)/non-exposed cohort (longitudinal); (4) Definition of controls (cross-sectional)/adequacy of follow-up of cohorts (longitudinal); (5) The participants in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled for; (6) Measurement of the outcome (brain volume); (7) Statistical test is clearly described and appropriate.

Table 2. Demographic and type 2 diabetes mellitus characteristics for studies included in meta-analysis

No.	Study	Total No.	Age, yr	Male, %	T2DM duration, yr	Oral No.	Insulin No.	Medication, %	Serum insulin, μU/mL	HbA1c, %	Fasting glucose, mmol/L	MRI strength	Measurement
1	Ajilore et al. (2010) [22]	46	56.6±8.4	28.3								1.5	Volumetry (automated)
	Normal	20	55.2±8.2	25.0						5.6±1.1			
	T2DM	26	57.8±8.5	30.8	9.8±8.2					7.1±1.1			
2	Ajilore et al. (2015) [23]	56	55.7±9.8	32.1								1.5	Volumetry (automated)
	Normal	32	53.5±10.3	28.1						5.5±0.4			
	T2DM	24	58.9±8.3	37.5	9.7±7.8					7±1.1			
3	Bruehl et al. (2009I) [26]	30	59.8±8	60.0								1.5	Volumetry (manual)
	Normal	12	63.0±6.8	66.7					6.9±3.3	5.3±0.5	4.5±0.5		
	T2DM	18	57.7±8.2	55.6	5.9±3.7	17		94.4	19.6±13.1	8±2	7.5±3		
4	Bruehl et al. (2009II) [27]	88	59.5±8.1	52.3								1.5	Volumetry (manual)
	Normal	47	60.0±8.0	51.1					5.6±1.7	5.2±0.4	4.5±0.5		
	T2DM	41	59.0±8.4	53.7	7±6.4				14.1±10.4	7.9±1.8	7.8±2.9		
5	Brundel et al. (2010) [28]	86	69.3±4.9	46.5								1.5	Volumetry (automated)
	Normal	30	68.1±4.3	43.3						5.7±0.5	5.6±0.8		
	T2DM	56	70.0±5.2	48.2	13.6±6.8		27	48.2	8.1±6.8	7.1±1	8.3±3		
6	Brundel et al. (2014) [29]	97	70.7±4.3	57.7								3.0	Volumetry (manual; automated)
	Normal	49	71.1±4.5	61.2						5.7±0.4	5.6±0.7		
	T2DM	48	70.3±4.1	54.2	11±9.3					6.8±0.8	8±2		
7	Callisaya et al. (2019) [30]	705	70.4±7.4	57.1								1.5	Volumetry (automated)
	Normal	357	72.5±7.1	53.2						5.6±0.3	5.3±0.5		
	T2DM	348	68.2±7.0	60.1	9.5±9.4	234	71	67.2		7.2±1.2	7.7±2.3		
8	Chen et al. (2012) [32]	32	60.4±7	75.0								1.5	VBM
	Normal	16	59.6±6.1	75.0									
	T2DM	16	61.2±7.8	75.0	13.2±5.6								
9	Chen et al. (2014) [33]	22	58.7±2.5	27.3								3.0	VBM
	Normal	11	56.2	27.3									
	T2DM	11	61.2	27.3	13.9					8.3±1.9	9.9±2.4		
10	Chen et al. (2017) [34]	47	58.8±8.1	51.1								3.0	Volumetry (automated)
	Normal	24	57.0±7.5	50.0					8.8±4.5	5.8±0.2	5.3±0.3		
	T2DM	23	60.8±8.3	52.2	8.9±4.8	23	12	100.0	12.3±5.8	8.6±2.2	9±2.7		
11	Climie et al. (2014) [35]	80	57.5±10.1	45.0								1.5	Volumetry (manual; semi-auto; automated)
	Normal	40	52.0±8.0	47.5					2.4±4.7	5.5±0.3	4.7±0.4		
	T2DM	40	63.0±9.0	42.5	6±6				10.2±8.6	7.2±0.8	7.5±1.8		

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Table 2. Continued

No.	Study	Total No.	Age, yr	Male, %	T2DM duration, yr	Oral No.	Insulin No.	Medication, %	Serum insulin, μU/mL	HbA1c, %	Fasting glucose, mmol/L	MRI strength	Measurement
12	Cox et al. (2019) [36]	9,722	62.0±7.5	47.5								3.0	Volumetry (automated)
	Normal	9,246	61.8±7.5	46.6									
	T2DM	476	64.5±6.9	65.1									
13	Cui et al. (2014) [37]	69	65.4±9.3	49.3								3.0	VBM
	Normal	26	65.2±10.2	53.8						5.7±0.3	5.0±0.6		
	T2DM	43	65.5±8.7	42.5	13.3±6.8	34	11	79.1		7.1±1.1	6.9±2.6		
14	Cui et al. (2017) [38]	81	59.2±6.8	42.0								3.0	VBM
	Normal	41	57.9±6.5	31.7						5.6±0.3	5.4±0.3		
	T2DM	40	60.5±6.9	52.5	8.9±5		8	20.0		7.7±1.6	7.8±2.1		
15	de Bresser et al. (2018) [40]	83	65.3±5.1	45.8								1.5	Volumetry (automated)
	Normal	28	64.2±4.3	42.9									
	T2DM	55	65.9±5.4	47.3	9.5±6.6		31	56.4		7.0±1.1	5.6±0.6		
16	Espeland et al. (2013) [11]	1,366	78.5±0.2	0.0								1.5	Volumetry (automated)
	Normal	1,221	78.6±0.1	0.0									
	T2DM	145	78.1±0.3	0.0									
17	Fang et al. (2019) [43]	67	33.1±5.2	64.2								3.0	VBM
	Normal	32	34.1±4.8	59.4						5.5±0.3	4.8±0.5		
	T2DM	35	32.1±5.3	68.6	1	33	25	94.2		10.4±2.4	8.5±3.8		
18	Gold et al. (2007) [46]	46	59.5±8.5	47.8								1.5	Volumetry (automated); VBM
	Normal	23	59.9±8.6	47.8						5.1±0.4	4.5±0.5		
	T2DM	23	59.2±8.4	47.8	6±6.3					6.9±0.8	6.7±1.8		
19	Hempel et al. (2012) [47]	87	59.4±11.7	52.9								1.5	Volumetry (manual)
	Normal	47	60.0±11.3	51.1					5.6±2.5	5.2±0.5	4.5±0.7		
	T2DM	40	58.9±12.2	55.0					14.6±14.9	7.7±2.3	7.7±3.9		
20	Hsu et al. (2012) [50]	137	56.3±4.9	57.7								1.5	VBM
	Normal	97	56.2±4.7	55.7						5.5±0.3	5.0±0.6		
	T2DM	40	56.8±5.5	62.5	5.1±4.7		29	72.5		7.7±1.7	7.8±2.4		
21	Jongen et al. (2007) [51]	145	65.5±5.6	47.6								1.5	Volumetry (automated)
	Normal	46	64.9±5.6	43.5						5.5±0.3			
	T2DM	99	65.9±5.6	49.5	8.7±6.1		29	29.3		6.8±1.2			
22	Kumar et al. (2008I) [52]	467	62.6±1.1	51.8								1.5	VBM; Volumetry (manual)
	Normal	428	62.6±1.5	51.2									
	T2DM	39	62.6±1.2	59.0		19	7	49					

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Table 2. Continued

No.	Study	Total No.	Age, yr	Male, %	T2DM duration, yr	Oral No.	Insulin No.	Medication, %	Serum insulin, μU/mL	HbA1c, %	Fasting glucose, mmol/L	MRI strength	Measurement
23	Kumar et al. (2008II) [53]	51	55.5±9.1	23.5	9.8±8.2							1.5	Volumetry (automated)
	Normal	25	53.2±9.1	20.0						5.3±0.4			
	T2DM	26	57.9±8.5	26.9		16	9	96.2		7.1±1.1			
24	Last et al. (2007) [54]	51	61±7.6	51.0								1.5	Volumetry (automated)
	Normal	25	60.4±8.6	52.0						5.5±0.4	4.4±0.9		
	T2DM	26	61.6±6.6	50.0	12.9±11.3					7.1±0.1	7.4±4.3		
25	Li et al. (2016) [57]	429	74.3±0.5	49.7								1.5, 3.0	Volumetry (automated)
	Normal	398	74.3±0.4	48.0									
	T2DM	31	74.8±1.3	71.0									
26	Luchsinger et al. (2020) [61]	250	64.1±3.5	28.0				73.0		7.6±1.7		3.0	Volumetry (automated)
	Normal	139	63.7±3.4	24.6						5.4±0.2			
	T2DM	111	64.7±3.5	33.3						7.6±1.7			
27	Maldijan et al. (2013) [62]	200	67.6±9.3	19.0								1.5	Volumetry (manual; automated)
	Normal	100	67.5±9.4	15.0						5.9±0.3			
	T2DM	100	67.7±9.2	23.0						7.6±1.4			
28	Moran et al. (2016) [65]	451	69.5±7.2	56.8								1.5	VBM
	Normal	181	72.9±6.7	53.6						5.6±0.3	5.3±0.6		
	T2DM	270	67.3±6.7	58.9			53	19.6		7.1±1.2	7.7±2.1		
29	Musen et al. (2012) [66]	21	54.9±2.2	66.7								1.5	Volumetry (automated)
	Normal	11	54.0±1.8	63.6					11.9±2.1	5.6±0.1	4.8±0.2		
	T2DM	10	56.0±2.2	70.0	6.1±0.9				19.7±3.6	7.5±0.5	8.4±1.3		
30	Qiu et al. (2014) [69]	4,206	76.1±5.3	41.6								1.5	Volumetry (automated)
	Normal	3,744	76.2±5.4	39.9									
	T2DM	462	76.0±5.1	55.2									
31	Raffield et al. (2016) [70]	784	65.8±9.8	45.9								1.5, 3.0	VBM
	Normal	102	66.7±10.0	34.3		3		2.9		5.9±0.3	5.4±0.6		
	T2DM	682	65.8±9.8	47.7	15.2±7.7	445	227	65.3		7.5±1.4	8.2±3.0		
32	Redel et al. (2018) [71]	40	16.7±2.3	25.0								3.0	VBM
	Normal	20	16.7±2.6	25.0									
	T2DM	20	16.7±2.0	25.0									
33	Reinhard et al. (2012) [72]	46	54.1±13.2	82.6								3.0	Volumetry (automated)
	Normal	26	52.0±15.0	80.8									
	T2DM	20	57.0±10.0	85.0	12.0±6.0	18	14	90.0		7.9			

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Table 2. Continued

No.	Study	Total No.	Age, yr	Male, %	T2DM duration, yr	Oral No.	Insulin No.	Medication, %	Serum insulin, μU/mL	HbA1c, %	Fasting glucose, mmol/L	MRI strength	Measurement
34	Rensma et al. (2020) [73]	2135	74.5±4.6	41.7								1.5	Volumetry (automated)
	Normal	1,938	74.5±4.6	41.4						5.6±0.3			
	T2DM	197	74.6±4.3	52.3						6.5±0.9			
35	Samaras et al. (2014) [21]	312	78.4±4.7	51.6								3.0	Volumetry (automated); VBM
	Normal	279	78.4±4.8	53.0									
	T2DM	33	78.4±4.7	39.4									
36	Sun et al. (2018) [78]	36	66.9±5.2	33.3								3.0	VBM
	Normal	24	66.7±5.4	16.7									
	T2DM	12	67.3±4.7	66.7	7.9±5.3								
37	Suzuki et al. (2019) [79]	8,312	62.3±7.4	47.6								3.0	Volumetry (automated)
	Normal	7,912	62.2±7.4	46.8									
	T2DM	400	64.8±7.0	63.5									
38	Walsh et al. (2019) [80]	399	64.4±9.7	46.9								1.5	Volumetry (automated)
	Normal	353	63.7±9.6	45.0							5.4±0.2		
	T2DM	46	70.0±8.7	60.9							7.5±2.7		
39	Wood et al. (2016) [81]	44	59.5±5.3	45.5								3.0	VBM
	Normal	22	59.5±5.3	36.4							5.7±0.8		
	T2DM	22	59.5±5.3	54.5	10.1±9.7	20	4	90.9			7.0±1.5		
40	Yau et al. (2014) [82]	96	58.7±8	44.8								1.5	Volumetry (manual)
	Normal	50	58.8±7.9	44.0						5.3±0.4	4.3±0.5		
	T2DM	46	58.8±8.2		7.5±6.7					7.8±1.8	7.9±3		
41	Zhang et al. (2014) [83]	54	53.9±9.3	48.1								3.0	VBM
	Normal	29	55.5±9.1	41.4									
	T2DM	25	52.2±9.2	56.0	6.4±5.3					7.3±1.3			
42	Zhang et al. (2015) [84]	160	57.6±9.6	40.0								3.0	Volumetry (automated)
	Normal	80	57.8±10.3	36.3						5.6±0.4			
	T2DM	80	57.5±9.0	43.8	7.0±6.7					7.5±1.5			

Values are presented as mean±standard deviation.
T2DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin; MRI, magnetic resonance imaging; VBM, voxel-based morphometry.

ume (14,030 normal; 2,070 diabetes). Participants with T2DM had smaller white matter hyperintensities volume (–0.006 cm^3; 0.001%) but the association was not significant (Table 3, Supplementary Fig. 1).

Total brain atrophy rate

Five longitudinal studies reported on total brain atrophy rate (3,823 normal; 778 diabetes). An initial analysis produced a paradoxical non-significant result given all studies reported a greater atrophy in T2DM, with four being highly significant

Table 3. Random-effect models of brain volumes and atrophy rates in normal controls and type 2 diabetes mellitus patients, including total volumes and differences between groups

Brain areas	Group	k	No.	Male, %	Age, yr	Volume, cm^3	SE	95% CI	Sig	tau^2	tau	I^2	QE
Total brain volume	All	30	18,214	42.863	67.392	1120.675	30.243	1,061.400 to 1,179.950	[a]	27,198.99	164.9212	99.98716	76,018.724
	Normal	15	15,937	42.731	67.328	1132.803	44.902	1,044.797 to 1,220.808	[a]	30,041.44	173.3247	99.99302	66,446.501
	T2DM	15	2,277	43.786	67.846	1108.552	41.846	1,026.535 to 1,190.569	[a]	25,986.99	161.2048	99.91959	8,472.641
	T2DM-normal	15	18,214	42.863	67.392	−20.502	5.851	−31.970 to −9.034	[a]	439.6137	20.96697	99.57289	487.3966
Grey matter volume	All	48	18,592	42.938	66.513	596.956	12.889	571.694 to 622.218	[a]	7,886.426	88.80555	99.91265	121,045.52
	Normal	24	15,475	42.488	66.608	605.984	18.299	570.119 to 641.849	[a]	7,947.538	89.14896	99.94295	101,310.41
	T2DM	24	3,117	45.172	66.039	587.935	18.363	551.944 to 623.925	[a]	8,005.686	89.4745	99.77253	19,310.03
	T2DM-normal	24	18,592	42.938	66.513	−17.433	4.296	−25.853 to −9.013	[a]	405.1253	20.12772	99.13594	808.9859
White matter volume	All	44	17,056	42.642	67.164	493.281	10.613	472.481 to 514.081	[a]	4,874.427	69.8171	99.89194	25,351.214
	Normal	22	14,091	42.247	67.330	499.042	14.641	470.346 to 527.739	[a]	4,645.458	68.1576	99.92809	16,527.384
	T2DM	22	2,965	44.519	66.376	487.500	15.610	456.904 to 518.095	[a]	5,269.203	72.58927	99.66385	7,907.034
	T2DM-normal	22	17,056	42.642	67.164	−10.733	2.864	−16.347 to −5.119	[a]	148.5759	12.18917	98.16723	251.0688
Hippocampal volume	All	28	11,254	47.672	62.288	3.318	0.113	3.097 to 3.540	[a]	0.3543962	0.5953118	99.72612	7,037.232
	Normal	14	9,935	48.676	62.175	3.394	0.161	3.078 to 3.710	[a]	0.3602119	0.6001765	99.69904	2,707.878
	T2DM	14	1,319	40.106	63.134	3.243	0.162	2.926 to 3.561	[a]	0.3639983	0.6033227	99.54532	2,151.285
	T2DM-normal	14	11,254	47.672	62.288	−0.151	0.045	−0.239 to −0.063	[a]	0.02663409	0.1631996	97.89546	401.8367
Thalamus volume	All	8	10,328	47.366	61.983	7.562	0.089	7.388 to 7.736	[a]	0.05621649	0.2371002	96.45107	123.66
	Normal	4	9,703	46.450	61.861	7.723	0.112	7.503 to 7.942	[a]	0.04570418	0.2137854	94.21684	25.00385
	T2DM	4	625	61.600	63.878	7.387	0.074	7.242 to 7.532	[a]	0.01404856	0.1185266	70.47676	10.83599
	T2DM-normal	4	10,328	47.366	61.983	−0.325	0.062	−0.447 to −0.203	[a]	0.01298164	0.113937	88.01778	20.0754
Caudate volume	All	6	9,929	47.386	61.886	3.353	0.042	3.270 to 3.436	[a]	0.009062094	0.09519503	93.94834	74.60724
	Normal	3	9,350	46.503	61.793	3.408	0.049	3.312 to 3.504	[a]	0.005463963	0.07391862	79.6928	12.1904
	T2DM	3	579	61.658	63.392	3.302	0.065	3.174 to 3.430	[a]	0.011110639	0.10540702	89.75669	20.24112
	T2DM-normal	3	9,929	47.386	61.886	−0.090	0.025	−0.139 to −0.041	[a]	0.001316991	0.03629038	73.38077	5.694014
Putamen volume	All	6	9,929	47.386	61.886	4.745	0.050	4.647 to 4.843	[a]	1.21E-02	0.110161803	92.06085	56.336064
	Normal	3	9,350	46.503	61.793	4.814	0.081	4.656 to 4.973	[a]	1.71E-02	0.13082691	89.303203	11.837765
	T2DM	3	579	61.658	63.392	4.689	0.023	4.644 to 4.735	[a]	8.96E-05	0.009463786	3.049979	1.536428
	T2DM-normal	3	9,929	47.386	61.886	−0.139	0.062	−0.260 to −0.017	[c]	0.009963195	0.09981581	88.87643	10.80907
Globus pallidus volume	All	6	9,929	47.386	61.886	1.762	0.016	1.731 to 1.793	[a]	0.000838993	0.02896537	79.07953	37.0150961
	Normal	3	9,350	46.503	61.793	1.782	0.002	1.778 to 1.786	[a]	0	0	0	0.5905017
	T2DM	3	579	61.658	63.392	1.766	0.043	1.681 to 1.851	[a]	0.004061401	0.06372913	81.56729	6.5953594
	T2DM-normal	3	9,929	47.386	61.886	−0.014	0.038	−0.089 to 0.060		0.003180063	0.05639205	91.2341	14.47432

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Table 3. Continued

Brain areas	Group	k	No.	Male, %	Age, yr	Volume, cm^3	SE	95% CI	Sig	tau^2	tau	I^2	QE
Amygdala volume	All	6	9,929	47.386	61.886	1.299	0.037	1.226 to 1.372	[a]	0.007582182	0.08707572	97.63179	39.40874
	Normal	3	9,350	46.503	61.793	1.298	0.055	1.190 to 1.405	[a]	0.008433407	0.09183358	95.38069	21.78316
	T2DM	3	579	61.658	63.392	1.303	0.065	1.175 to 1.431	[a]	0.011780498	0.108538	95.01308	17.51575
	T2DM-normal	3	9,929	47.386	61.886	–0.003	0.002	–0.007 to 0.002		0	0	0	0.872544
Nucleus accumbens volume	All	6	9,929	47.386	61.886	0.429	0.010	0.409 to 0.448	[a]	0.000398667	0.01996666	90.67598	107.1207294
	Normal	3	9,350	46.503	61.793	0.446	0.011	0.424 to 0.468	[a]	0.000247974	0.01574719	68.49809	7.0336341
	T2DM	3	579	61.658	63.392	0.415	0.004	0.406 to 0.423	[a]	0	0	0	0.7617099
	T2DM-normal	3	9,929	47.386	61.886	–0.035	0.012	–0.059 to –0.012	[b]	0.000331685	0.01821223	83.76001	12.15621
Nucleus accumbens volume	All	6	9,929	47.386	61.886	0.429	0.010	0.409 to 0.448	[a]	0.000398667	0.01996666	90.67598	107.1207294
	Normal	3	9,350	46.503	61.793	0.446	0.011	0.424 to 0.468	[a]	0.000247974	0.01574719	68.49809	7.0336341
	T2DM	3	579	61.658	63.392	0.415	0.004	0.406 to 0.423	[a]	0	0	0	0.7617099
	T2DM-normal	3	9,929	47.386	61.886	–0.035	0.012	–0.059 to –0.012	[b]	0.000331685	0.01821223	83.76001	12.15621
Superior temporal gyrus volume	All	10	347	50.432	59.351	20.376	2.597	15.286 to 25.465	[a]	66.93965	8.181666	99.64734	1,633.6882
	Normal	5	179	49.721	59.856	20.570	3.961	12.807 to 28.333	[a]	77.96256	8.829641	99.66233	841.5952
	T2DM	5	168	51.190	58.812	20.189	3.827	12.689 to 27.690	[a]	72.71978	8.527589	99.64757	777.338
	T2DM-normal	5	347	50.432	59.351	–0.183	0.153	–0.482 to 0.116		0	0	0	3.195813
CSF volume	All	20	5,602	44.199	73.170	355.538	42.541	272.159 to 438.917	[a]	35,986.88	189.7021	99.93566	10,942.665
	Normal	10	4,363	46.161	74.898	353.829	62.682	230.975 to 476.682	[a]	39,060.57	197.6375	99.91702	5,588.27
	T2DM	10	1,239	37.288	67.084	357.362	60.961	237.881 to 476.844	[a]	36,975.35	192.2898	99.90901	4,253.568
	T2DM-normal	10	5,602	44.199	73.170	7.145	5.092	–2.835 to 17.126		210.2279	14.49924	93.53862	101.4667
WMH volume	All	24	16,100	46.043	66.355	6.040	1.101	3.882 to 8.198	[a]	27.38855	5.233407	99.72127	3,723.2096
	Normal	12	14,030	44.647	66.114	6.282	1.509	3.324 to 9.241	[a]	24.58371	4.958196	99.71089	2,849.344
	T2DM	12	2,070	55.507	67.986	5.824	1.659	2.571 to 9.076	[a]	32.50942	5.701703	99.54469	873.7837
Atrophy rate (%/year)	All	8	4,283	30.983	74.948	–0.00565	0.00080	–0.00722 to –0.00408	[a]	4.78E-06	0.00218744	99.34591	256.421
	Normal	4	3,544	27.906	75.651	–0.00537	0.00129	–0.00790 to –0.00285	[a]	6.32E-06	0.002513821	99.53845	189.94315
	T2DM	4	739	45.737	71.774	–0.00598	0.00116	–0.00825 to –0.00370	[a]	4.97E-06	0.002228805	98.69538	63.01815
	T2DM-normal	4	4,283	30.983	74.948	–0.00072	0.00006	–0.00083 to –0.00062	[a]	0.00E+00	0	0	0.8717236

k, number of studies; SE, standard error; CI, confidence interval; Sig, statistical significance; QE, test statistic of Cochran's test of heterogeneity; T2DM, type 2 diabetes mellitus; CSF, cerebrospinal fluid; WMH, white matter hyperintensity.
[a]$P<0.001$, [b]$P<0.01$, [c]$P<0.05$.

(Supplementary Fig. 2). A leave-one-out analysis indicated that this perplexing finding was attributable to a single study [21], likely due to it being an outlier in the size of its estimate and having a very large confidence interval, which would unduly inflate the error variance estimate of the analysis. Consequently, a follow-up analysis excluding this study is reported. Participants with T2DM had significantly larger atrophy rate (0.072%; 13.4% larger than normal) (Table 3, Fig. 2).

Inhomogeneity and publication bias

Significant inhomogeneity was observed in Q tests of the meta-analysis, except in thalamus, caudate, putamen, globus pallidus, amygdala, nucleus accumbens, and in T2DM-normal difference in superior temporal gyrus and frontal lobe (Table 3).

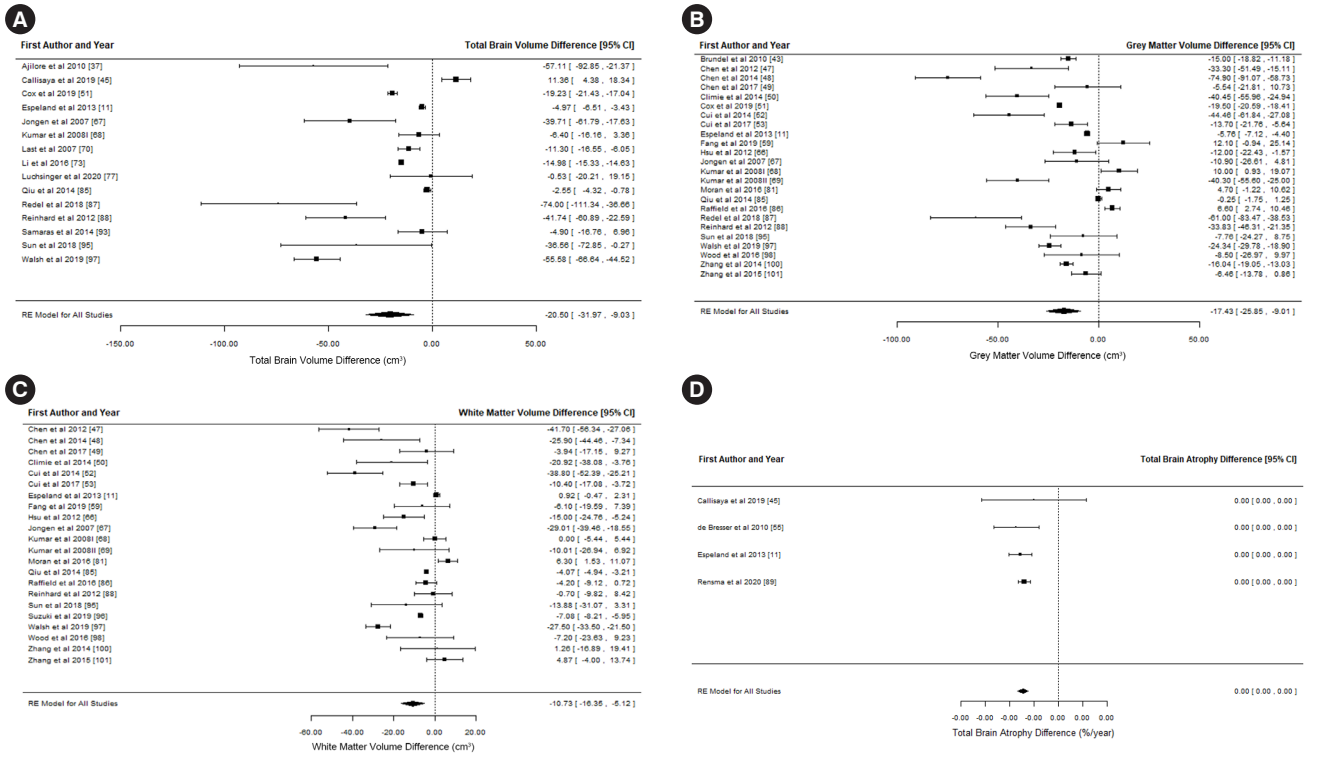

Fig. 2. Forest plots of differences in global brain volumes and total brain atrophy rate between participants with and without type 2 diabetes mellitus. (A) Total brain volume difference, (B) grey matter volume difference, (C) white matter volume difference, (D) total brain atrophy difference. CI, confidence interval.

Evidence of some publication bias was also detected for most brain regions investigated. Visual inspection of funnel plots revealed that studies were likely missing for total brain volume (13.3% of total), globus pallidus (40%), superior temporal gyrus (16.7%), frontal lobe (28.6%), cerebrospinal fluid (20%), and white matter hyperintensity (20%). Although asymmetry and presence of missing studies suggested some publication bias toward studies reporting higher atrophy rates, trim and fill test indicated that the differences between corrected and reported volumetric differences were generally small and therefore publication bias is unlikely to have significantly influenced the present results (Fig. 3).

Meta-regression analyses

The effect of age, sex ratio, diabetes duration, medication, fasting glucose and HbA1c on the association between T2DM and volume of total brain, grey matter, white matter and hippocampus was investigated by meta-regression analysis. A significant negative association between decreasing total brain volume difference and increasing age was detected such that every additional year in age above 60 was associated with a 4.4% smaller volumetric dif ference between individuals with and without diabetes (individuals with diabetes at age 60 years are 28.45cm^3 smaller; this difference decreases by 1.24 cm^3 per year) (Supplementary Table 1). A significant positive association between decreasing grey matter volume difference and increasing diabetes duration was also detected such that every additional year above mean diabetes duration (10.5 years) in age above 60 was associated with an 8.8% larger volumetric difference between individuals with and without diabetes. No significant effects were observed in other analyses (Supplementary Table 1, Supplementary Fig. 3).

DISCUSSION

The aim of this study was to synthesise the evidence on quantitative differences in brain volumes and rates of brain atrophy associated with T2DM via systematic review and meta-analysis of the published literature. In total, 42 studies including 31,630 participants were included. The main findings indicated that individuals with T2DM had significantly smaller brain volumes compared to those without T2DM, as well as larger

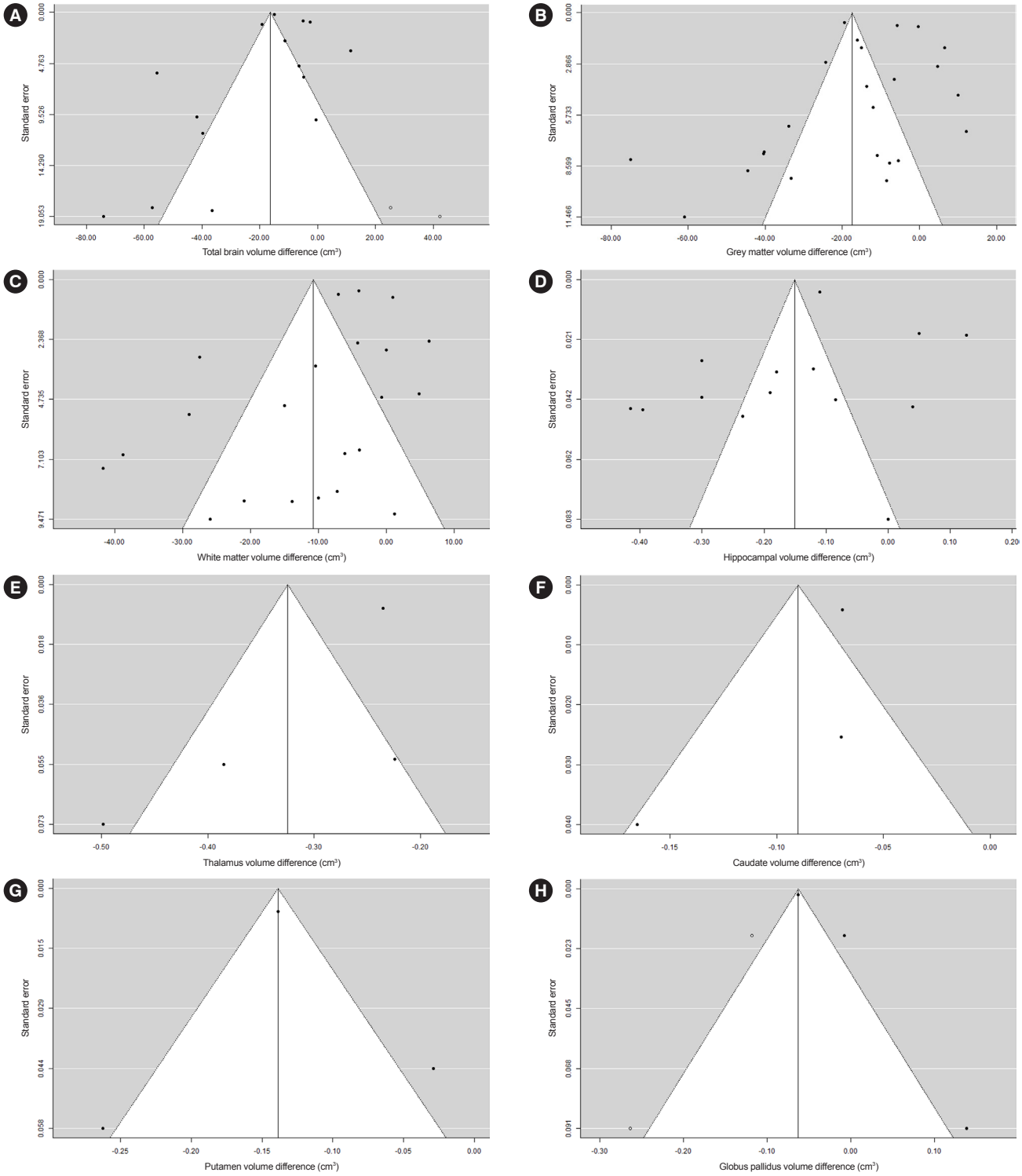

Fig. 3. Funnel plots of brain volumes and atrophy rate assessing possible publication bias using the trim and fill method. Filled circles represent studies included in the meta-analysis. Open circles represent possible missing studies. Brain volumes: (A) total brain volume, (B) grey matter, (C) white matter, (D) hippocampus, (E) thalamus, (F) caudate, (G) putamen, (H) globus pallidus, (I) amygdala, (J) nucleus accumbens, (K) superior temporal gyrus, (L) frontal lobe, (M) cerebrospinal fluid, (N) white matter hyperintensity, and (O) total brain atrophy rate.
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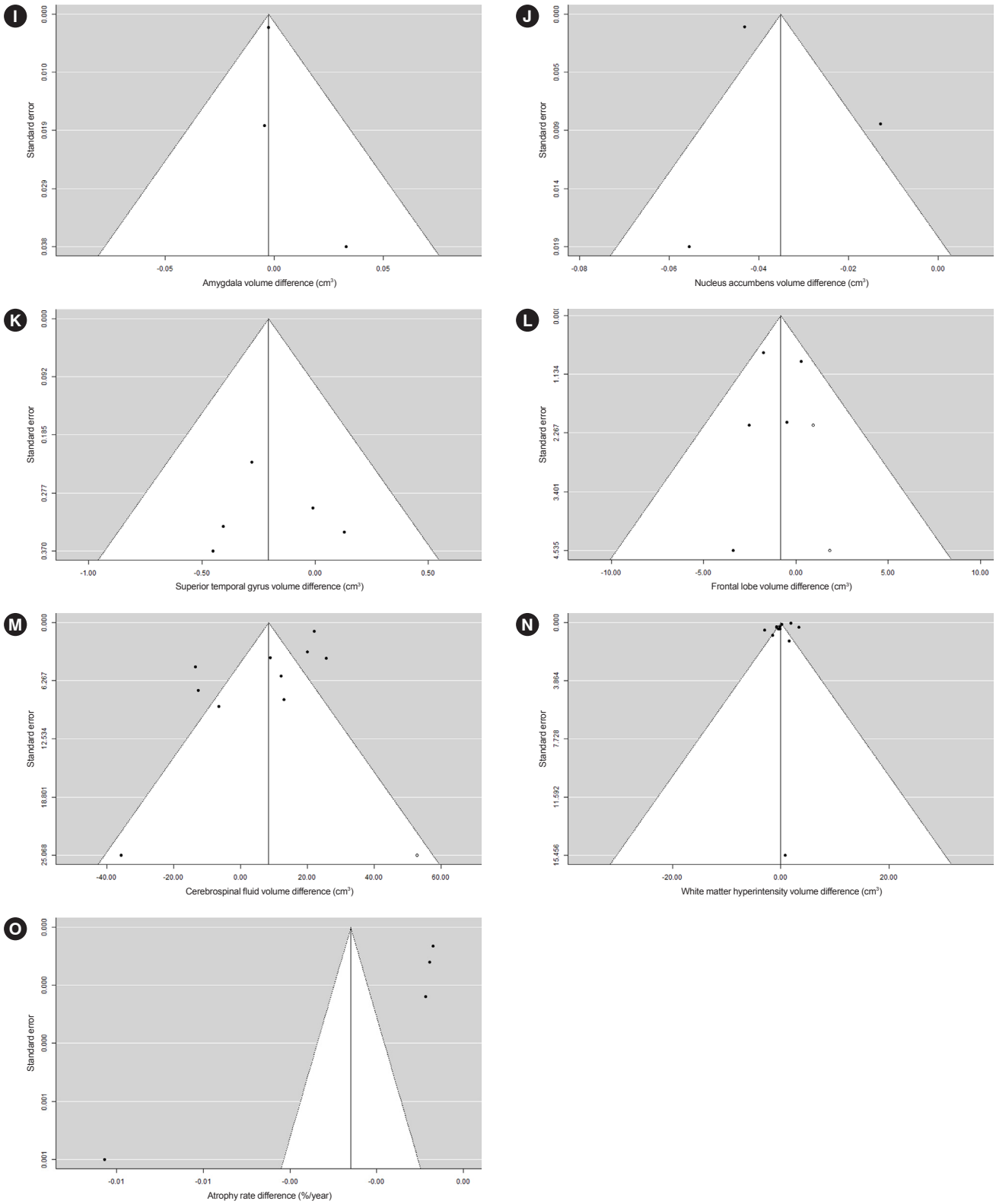

Fig. 3. Continued.

atrophy rates. Moreover, T2DM-related volumetric differences appeared to decrease with age and increase with diabetes duration but did not differ between men and women.

Global and local brain volumes

This study's results are consistent with the findings of previous reviews reporting that brain volumes are smaller in those who live with T2DM, but it also substantially extends our understanding of the scope of this effect. The present study was able to convincingly demonstrate volumetric differences in four brain structures while also precisely summarising their magnitude. It demonstrated that diabetes-related volumetric brain differences were substantial (total brain: 1.88%; grey matter: 2.81%; white matter: 2.15%; hippocampus: 4.4%). Indeed, in normal ageing, total brain volume shrinks by about 0.5% every year from the 40s onwards with further acceleration after age 70 [21]. Similarly, the hippocampus shrinks by about 0.3%/year before 55, 0.85%/year between 55 and 70, and 1.1%/year thereafter in those cognitively intact [16]. Thus, the differences observed in T2DM correspond to about 4 to 5 years of normal ageing, and possibly more. It is also worth noting that while these effects were relatively large across these brain regions, they were particularly strong in the hippocampus. This is noteworthy because subcortical atrophy in the hippocampus is a hallmark of Alzheimer's disease and is one of the strongest predictors of conversion from mild cognitive impairment to Alzheimer's disease [85,86]. Importantly, the rate of hippocampal atrophy in mild cognitive impairment has been estimated in a recent meta-analysis to be approximately 2.5%/year [87]. This may suggest that the hippocampal volumetric difference observed in T2DM might lead to an earlier conversion to Alzheimer's disease by almost 2 years.

Furthermore, the rate of total brain atrophy in T2DM was significantly higher than in metabolically healthy individuals by 13.4%. This is consistent with cross-sectional results, and that cross-sectional volumetric differences may increase with diabetes duration according to meta-regression analysis. However, meta-regression results also revealed that the difference in total brain volume between those with T2DM and metabolically healthy individuals decreased with age (4.4% for every year above 60). This implies that a disease onset before age 60 years may have a greater impact on brain volumes. Moreover, similar consistent trends were observed for grey matter, white matter, and hippocampal volumes. Together, these may suggest that diabetes-related neurodegeneration occurs before onset of diabetes and slows down with increasing age. Hyperglycaemia is the main characteristic of T2DM pathology, and studies on metabolically healthy individuals and individuals with prediabetes have found association between higher blood glucose levels, smaller brain volumes and poorer cognitive functions [21,88,89]. Known mechanisms that may contribute to T2DM-related brain changes, such as hyperglycaemia, vascular disorders and insulin resistance, were likely present before clinical diagnosis [5]. An implication of these findings is that it will be important for future research to investigate brain changes leading to T2DM diagnosis, and to conduct more longitudinal studies following individuals with T2DM over longer periods of time to clarify these issues. From a health policy perspective, it may also suggest that more resources should be directed towards risk reduction interventions in those at risk before the disease develops, rather than mitigate the effects of T2DM when much of the damage has already taken place.

Clinical implications and moderators of T2DM-related brain atrophy

T2DM is a known risk factor of dementia, with increased risk of dementia by two-to-three fold [90]. The current study not only shows substantial brain volume differences that might result in earlier conversion to mild cognitive impairment and Alzheimer's disease, but also indicates potential predictors and structural basis of cognitive deficit among individuals with T2DM. Previous studies showed evidence of cognitive decline in important functions that may affect self-caring ability of diabetes patients, such as executive function [91] and processing speed [89]. Our study has also found significant associations between brain volume of some subcortical structures and diabetes, even though studies on local volumes were fewer. Indeed, studies on specific cognitive deficits in T2DM are relatively few with inconsistent results, and even fewer studies on both brain volumes and cognition. Further studies with larger sample size are needed to understand how changes at local brain structures are related to cognitive functions of diabetes patients.

We conducted meta-regression analyses to investigate moderators of volumetric differences between metabolically healthy individuals and individuals with T2DM. In this study, meta-regression analyses to examine the moderating effects of age, sex ratio, diabetes duration, ratio of medication, fasting glucose and HbA1c were only possible for some brain structures. These showed that volumetric differences decreased with

age, which suggests early pre-clinical occurrence of diabetes-related brain changes. However, an increase in volumetric differences was also observed with diabetes duration in grey matter, and a similar trend in white matter. A likely explanation may be that effects related to T2DM are attributable to pathogenic mechanisms but that they become obscured by the increasingly prevalent, and often related, effects of other risk factors for neurodegeneration including cardiovascular diseases, hyperlipidemia, obesity, and others. The cause of the brain differences reported in the present study may be a combination and interaction of pathogenic mechanisms of T2DM and genetic factors, environmental exposures, age, sex, comorbidities, and medication. Some anti-diabetes oral medications, such as dipeptidyl peptidase 4 inhibitors, metformin, thiazolidinediones and sulfonylurea have potential neuroprotective effects for individuals with diabetes, whereas insulin may be associated with increased risk of dementia [92]. Although lifestyle factors such as high cholesterol diet, smoking, etc. are known risk factors for cognitive decline common among people with T2DM, no conclusive evidence is available on whether cardiovascular risk factor management via lifestyle change, controlling blood pressure and cholesterol levels may reduce the risk of cognitive dysfunction in people with diabetes compared with those without diabetes [93]. While these factors are sometimes reported by studies included in our meta-analysis, usually only some of these factors were reported in one study; reports on medication were often unspecific. This limited the covariates we could control for in our meta-analysis, the types of meta-regression we could conduct and the number of studies that could be included.

Strengths and limitations

The main strengths of this review were an extensive search of the literature using a wide range of search terms across multiple databases, and inclusion of both cross-sectional and longitudinal studies across many brain structures. The main limitation was the relatively small number of studies which could be included in meta-analyses of regional volumes and particularly longitudinal atrophy. This also limited the number of moderators that could be tested in meta-regressions.

In conclusion, to our knowledge, this is the first meta-analysis that synthesises and precisely quantifies findings from both cross-sectional and longitudinal studies on the association between T2DM and brain atrophy. Results showed that T2DM is associated with smaller total and regional brain volumes with this difference decreasing at older ages. These effects are important and highlight an urgent need for the development of interventions to prevent them. How T2DM-related brain atrophy changes over time, and in the pre-clinical stages of the disease is unclear based on the available evidence and requires further investigation.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2021.0189.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: T.Z., N.C.
Acquisition, analysis, or interpretation of data: T.Z., M.S., N.C.
Drafting the work or revising: M.S., N.C.
Final approval of the manuscript: M.S., N.C.

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