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Brain Imaging Changes Associated With Risk Factors for Cardiovascular and Cerebrovascular Disease in Asymptomatic Patients

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CME Objective for This Article: At the end of this activity the reader should be able to: 1) review brain structural and functional imaging changes in persons harboring risk factors for cardiovascular and cerebrovascular disease, but with no clinical manifestations of either cardiovascular or cerebrovascular disease; 2) understand that cognitive impairment is an important clinical manifestation of these vascular risk factor-related structural and functional brain imaging changes in these asymptomatic persons; and 3) review the evidence demonstrating that effective management of these modifiable vascular risk factors reduces the severity of associated brain imaging abnormalities and related cognitive impairments; suggesting that adequate treatment of vascular risk factors may have beneficial effects on brain function.

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Brain Imaging Changes Associated With Risk Factors for Cardiovascular and Cerebrovascular Disease in Asymptomatic Patients

ABSTRACT

Reviews of imaging studies assessing the brain effects of vascular risk factors typically include a substantial number of studies with subjects with a history of symptomatic cardiovascular or cerebrovascular disease and/or events, limiting our ability to disentangle the primary brain effects of vascular risk factors from those of resulting brain and cardiac damage. The objective of this study was to perform a systematic review of brain changes from imaging studies in patients with vascular risk factors but without clinically manifest cardiovascular or cerebrovascular disease or events. The 77 studies included in this review demonstrate that in persons without symptomatic cardiovascular, cerebrovascular, or peripheral vascular disease, the vascular risk factors of hypertension, diabetes mellitus, obesity, hyperlipidemia, and smoking are all independently associated with brain imaging changes before the clinical manifestation of cardiovascular or cerebrovascular disease. We conclude that the identification of brain changes associated with vascular risk factors, before the manifestation of clinically significant cerebrovascular damage, presents a window of opportunity wherein adequate treatment of these modifiable vascular risk factors may prevent the development of irreversible deleterious brain changes and potentially alter patients' clinical course. (J Am Coll Cardiol Img 2014;7:1039–53) © 2014 by the American College of Cardiology Foundation.

Risk factors for cardiovascular and cerebrovascular disease, whether they result in clinically significant vascular events or not, have been associated with pathological brain changes related to cognitive dysfunction such as vascular dementia (VaD) and Alzheimer's disease (1–3). These same vascular risk factors (VRFs) have also been associated with more subtle forms of cognitive impairment than those associated with these brain pathologies (4). For example, the concept of vascular cognitive impairment has been invoked to describe those patients with cognitive impairment and risk of VaD but not meeting criteria for VaD (5).

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There have been several published reviews cataloguing brain imaging changes in association with risk factors for cardiovascular and cerebrovascular disease. However, these reviews typically include a substantial number of studies with subjects with a history of symptomatic cardiovascular and/or cerebrovascular disease and/or events. Indeed, decline in cognitive abilities has been related directly to strokes (6) and severe cardiovascular disease in the absence of clinically identified stroke (7,8), particularly in cases of heart failure (9). By extrapolation, these same subjects harbor significant brain dysfunction directly related to strokes and cardiovascular disease. Therefore, a major limitation of reviews of brain changes associated with VRFs published to date is the inability to disentangle the primary brain effects of VRFs from the brain effects of symptomatic cardiovascular and cerebrovascular end-organ damage. To characterize the nature of brain imaging changes associated primarily with VRFs, we conducted a systematic review of brain imaging studies carried out in patients with risk factors for cardiovascular and cerebrovascular disease but without a diagnosis of cardiovascular, cerebrovascular, or peripheral vascular disease or events.

METHODS

This systematic review was conducted following the guidelines of the PRISMA statement (10).

STUDY SELECTION. Studies included in this review report the results of brain imaging investigations of persons with any of the following risk factors for cardiovascular or cerebrovascular disease: hypertension (HTN), diabetes mellitus (DM), increased adiposity, hyperlipidemia, smoking, and metabolic syndrome (MetS). Included studies assessed the association between these VRFs and findings with all brain structural and functional imaging modalities available. This review is limited to English-language publications from 1980 to August 31, 2013. Published studies were excluded if: 1) subjects were younger

than 18 years of age; 2) subjects carried a diagnosis of dementia (i.e., Alzheimer's disease, VaD) or other primary neurological condition associated with brain dysfunction; 3) subjects had a diagnosis of a psychiatric disorder except depression; 4) subjects had a history of cerebrovascular accident, transient ischemic attack, symptomatic infarcts on magnetic resonance imaging (MRI), or the methodology made no mention of the exclusion of such subjects; 5) ≥5% of the study cohort had a diagnosis of coronary artery disease, myocardial infarction, congestive heart failure, and peripheral vascular disease and if a <5% prevalence rate was present in the sample, no subanalyses were carried out excluding subjects with those diagnoses or no statistical adjustment was performed to control for the effects of these diagnoses; and 6) no statistical correction for the effects of age, sex, and the effects of other VRFs not the primary focus of investigation.

SEARCH STRATEGY. Studies were identified by searching the following electronic databases: MEDLINE, CINAHL, and Cochrane Database of Systematic Review using the following search terms: "vascular risk factor," "hypertension," "diabetes," "obesity," "hyperlipidemia," "smoking," "metabolic syndrome," "brain," "imaging," "magnetic resonance imaging (MRI)," "fMRI," "DTI", "PET," and "computed tomography (CT)." References of review papers were searched to identify studies that might have been overlooked in the initial search. Six of the authors (J.F., C.T., G.G., H.D., L.C., and P.D.) reviewed abstracts of all citations from the search and the full papers for inclusion. The final decision to include studies was on the basis of the inclusion and exclusion criteria and a review of the full text papers by the primary author (J.I.F.).

DATA EXTRACTION. We developed a data extraction sheet and had 6 review authors (J.F., C.T., G.G., H.D., L.C., P.D.) extract the following data from included studies with the primary author (J.I.F.), checking the extracted data for its integrity and accuracy: 1) number of study subjects in each group; 2) demographic characteristics of subjects (i.e., age, sex, ethnicity); 3) VRF being assessed; 4) presence of symptomatic cardiovascular, cerebrovascular, or peripheral vascular disease; 5) whether prevalence of vascular disease ≥5%, was a subanalysis performed excluding those subjects with disease or were statistical analyses performed to control for the effects of vascular disease; 6) the presence of other VRFs and, if present, was a subanalysis performed excluding those subjects with multiple risk factors or were statistical analyses performed to control for the effects of the other VRFs; 8) onset (i.e., mid-life, late life) and length of exposure to risk factor; 9) treatment of VRFs, analyses of effects of treatment; 9) imaging modality; 10) all structural and functional imaging outcomes; and 11) correlations between imaging variables and neuropsychological test performance.

RESULTS

To better understand the data presented in this review, a summary of neuroimaging acronyms referenced herein is provided in Table 1. A total of 77 published studies of the effects of HTN, DM, increased adiposity, hyperlipidemia, smoking, and MetS on brain structural and functional imaging findings are included in this review. A concise summary of the more salient findings of the effects of these VRFs and their treatment on brain structure and function is presented in Table 2.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index
BP = blood pressure
DBP = diastolic blood pressure
DM = diabetes mellitus
fMRI = functional magnetic resonance imaging
GM = gray matter
HbA_{1c} = glycosylated hemoglobin
HDL = high-density lipoprotein
HTN = hypertension
LDL = low-density lipoprotein
MRI = magnetic resonance imaging
MetS = metabolic syndrome
SBI = silent brain infarct
SBP = systolic blood pressure
VaD = vascular dementia
VRF = vascular risk factor
WM = white matter
WMH = white matter hyperintensity

I. HYPERTENSION. A total of 22 published brain imaging studies of HTN effects are included in this review (Online Table 1).

Structural brain changes. *Global changes.* Whole-brain volume reduction has been associated with a diagnosis of HTN (11). Other global changes associated with HTN include brain cerebrospinal fluid space enlargement (12,13).

Gray matter changes. HTN has been associated with brain gray matter (GM) volume reductions in cross-sectional studies, with a heterogeneous pattern of these volume reductions between studies (12–14). It is possible that the confounding effects of aging may partially contribute to the discrepancies in location of HTN-related GM reductions between studies. In support of this supposition is the finding of Strassburger et al. (13), who, when considering the interaction of aging and a diagnosis of HTN, extended their findings from the thalamus to include atrophy of the frontal cortices of the brain. However, when a more continuous variable such as blood pressure (BP) was used, a more complex U-shaped association of brain cortical atrophy with concurrent diastolic blood pressure (DBP) emerges (15). DBP outside an ideal range of 65 to 74 mm Hg has been associated with brain cortical atrophy, including both elevated (>85 mm Hg) and reduced (<65 mm Hg) DBP (15).

Longitudinal relationships between BP and brain GM volume have been more inconsistent. These inconsistencies include some reports of HTN-associated brain GM volume loss over time (16), whereas some

TABLE 1 Summary of Referenced Neuroimaging Acronyms

Imaging Acronym	Acronym Expansion	Imaging Modality	Explanation of Imaging Outcome
$[O^{15}]H_2O$ PET	Positron emission tomography using oxygen 15-labeled water	PET	A form of PET using a freely diffusible tissue tracer $[O^{15}]H_2O$ to calculate regional cerebral blood flow
AD	Axial diffusivity	MRI (DTI)	The measure of restriction along the axis of the axons (perpendicular to the direction of radial diffusivity). AD is a more specific index of axonal degeneration.
BOLD	Blood oxygen level dependent	MRI	The principal mechanism of signal contrast in fMRI produced by a combination of brain neuronal oxygen consumption (oxygenation state of hemoglobin is measured) and blood flow. The BOLD signal is associated with brain neuronal activation, more activation = increased BOLD.
Cho	Choline	MRS	A metabolite quantified in the brain by MRS. Cho is a marker of cellular membrane turnover reflecting cellular proliferation. Increased Cho can be seen in malignancy, infarction, and inflammation.
Cr	Creatine	MRS	A metabolite quantified in the brain by MRS. Cr is considered a marker of intracellular metabolism. It is considered a stable brain metabolite.
DA D_2 receptor binding potential	Dopamine D_2 receptor subtype occupancy	PET ($[^{11}C]$raclopride PET)	$[^{11}C]$Raclopride ligand PET scanning is used to determine changes in brain DA D_2 receptor binding potential, which indexes changes in DA release in the brain.
DMN	Default mode network	MRI (fMRI)	A brain functional network, the activity of which is measured during resting state fMRI. This network of brain regions is normally engaged when patients are left to think to themselves undisturbed; composed of medial temporal lobe, prefrontal cortex, posterior cingulate, and parietal cortex.
DTI	Diffusion tensor imaging	MRI	DTI produces MRI indexes of white matter integrity and axonal bundle formation and geometries.
FA	Fractional anisotropy	MRI (DTI)	An index of myelination or white matter integrity and/or organization. FA is expressed as a number on a scale between 0 and 1, without any unit of measure. The greater the FA, the greater the integrity/organization of the white matter tract.
FC	Functional connectivity	MRI or PET	Time synchronous activation between multiple distant brain regions.
FDG-PET	Fluorodeoxyglucose positron emission tomography	PET	Scanning technique measuring glucose metabolism in the brain using a radiolabeled glucose analogue.
fMRI	Functional magnetic resonance imaging	MRI	Stimulus-driven brain activation measured from the changes in oxygenation states of hemoglobin.
GM volume	Gray matter volume	MRI	The volume of the brain GM can be expressed as a global or region-specific measure. GM in the brain contains the cell bodies, dendrites, and axon terminals of neurons.
MAO-A	Monoamine oxidase A	PET ($[^{11}C]$clorgyline PET)	MAO-A metabolizes serotonin, norepinephrine, and dopamine. PET using $[^{11}C]$clorgyline measures brain MAO-A.
MAO-B	Monoamine oxidase B	PET (deuterium substituted $[^{11}C]$-L-deprenyl PET)	MAO-B primarily metabolizes dopamine. PET using deuterium substituted $[^{11}C]$-L-deprenyl measures brain MAO-B.
MD	Mean diffusivity	MRI (DTI)	Also referred to as the apparent diffusion coefficient (ADC). It is a measure of diffusion (Brownian motion) of water molecules in tissue measured in mm^2/s. MD is affected by restricted spaces, barriers such as cell membranes, tubules, and macromolecules. ADC maps of the brain can be generated, and good diffusion is bright on these maps.
MRS	Magnetic resonance spectroscopy	MRS	An imaging technique based on MRI that allows one to visualize certain metabolite concentrations in brain tissue; either single-voxel spectra or metabolite images can be produced (MRS imaging). The major peaks of the ^{1}H-MRS spectrum (each peak represent a metabolite) reported in this review include *N*-acetylaspartate (NAA), creatine (Cr), and choline (Cho) containing phospholipids.
NAA	*N*-Acetylaspartate	MRS	A metabolite quantified in the brain by MRS. NAA is considered a metabolic marker reflecting the functional status of neurons and axons in the brain, with a decrease indicating neuronal or axonal loss or dysfunction.
NAA/Cr, NAA/Cho	*N*-Acetylaspartate ratios with Cr/Cho	MRS	The concentration of Cr is relatively constant and is considered a stable brain metabolite; therefore, it is used as an internal reference for calculating metabolite ratios such as NAA. Cho is also used as an internal reference for calculating NAA ratios.
$[O^{15}]H_2O$ PET	Positron emission tomography using oxygen 15-labeled water	PET	A form of PET using a freely diffusible tissue tracer, $[O^{15}]H_2O$, to calculate regional cerebral blood flow.

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TABLE 1 Continued

Imaging Acronym	Acronym Expansion	Imaging Modality	Explanation of Imaging Outcome
rCBF	Regional cerebral blood flow	^{99}Tc-HMPAO SPECT ^{133}Xe SPECT [O^{15}] water PETdynamic susceptibility contrast MRI	The volume of blood traversing a brain region per unit of time (ml/100 g/min). rCBF is measured using SPECT (single-photon emission tomography) with ^{99}Tc-HMPAO, ^{133}Xe SPECT, [O^{15}]H_2O PET, or dynamic susceptibility contrast MRI.
rCBV	Regional cerebral blood volume	MRI	Total volume of blood traversing a brain region measured in ml/100 g of brain tissue, commonly obtained using contrast-enhanced MRI.
rCMRglu	Regional cerebral glucose metabolic rate	PET (fluorodeoxyglucose-PET)	Metabolic rate of glucose in the brain.
RD	Radial diffusivity	MRI (DTI)	Measures the degree of restriction due to the presence of the myelin sheath (i.e., perpendicular to the axonal fibers). Radial diffusivity is modulated by myelin in white matter and therefore is a more specific index of myelin pathology.
rsFDG-PET	Resting state fluorodeoxyglucose positron emission tomography	PET	Glucose metabolic activity measured during resting state.
rsfMRI	Resting state functional MRI	MRI	Functional connectivity measured using MRI with a subject at wakeful rest and not performing any goal-oriented task.
V_T/f_P	Total volume of the radioligand 2FA corrected for fraction in free plasma	PET (2FA-PET)	The 2FA radioligand PET imaging procedure is used to quantify the α-4β-2 nicotinic acetylcholine receptor in the brain.
WM volume	White matter volume	MRI	Volume of the brain white matter can be expressed as a global or region-specific measure. White matter is composed of axons connecting different regions of gray matter in the brain to each other.
WMH Note: The commonly accepted categorization of WMH is as follows: 1. PVWMH 2. DWMH	White matter hyperintensity 1. Periventricular white matter hyperintensity 2. Deep white matter hyperintensity	MRI	These are hyperintense areas seen on T2-fluid attenuated inversion recovery magnetic resonance images. WMHs are seen in normal aging and are also correlated with enlarged perivascular spaces, demyelination, or gliosis; localized pathological changes in the white matter of the brain due to chronic hypoperfusion by arteriolosclerotic changes to the brain microvasculature. 1. WMH lining the lateral ventricles. 2. WMH located in the remaining WM, not adjacent to the lateral ventricles.

^{99}Tc-HMPAO = technetium 99 hexamethyl-propyl creatinine oxime.

report no volume loss (17,18). In addition, some studies report higher DBP associated with greater brain GM volume loss over time (15), whereas others report higher SBP associated with greater volume loss (19).

When considering the effects of pharmacological treatment of HTN on brain GM volumetric changes, 2 outcomes emerge: 1) pharmacological treatment of HTN fails to prevent increased brain GM loss over time (14,16,19); and 2) pharmacological treatment of HTN results in either a reduction or acceleration of brain GM volume loss over time, the direction dependent on the timing of treatment initiation and the magnitude of BP reduction. For example, investigators have shown that higher DBP in midlife predicts more brain GM volume loss late in life when antihypertensive medication is not used, whereas this relationship is lost when antihypertensive medication is used (15). However, when antihypertensive use is initiated late in life instead of midlife, it is associated with more pronounced brain GM loss, particularly when there is a steeper decrease in DBP (15).

White matter changes. Cross-sectional investigations have shown a diagnosis of HTN to be associated with loss of prefrontal brain white matter (WM) volume (14) and a variable pattern of MRI-identified WM hyperintensity (WMH) increases with respect to overall burden and location in the brain (11,13,14,19). WMHs are localized pathological changes in the WM of the brain caused by chronic hypoperfusion of the WM by arteriolosclerotic changes to the brain microvasculature, and thus WMHs can be considered an MRI index of brain microvascular pathology. Indeed, the relationship between HTN and the MRI index of brain microvascular disease assumes a J-shaped function when nocturnal BP changes are considered, wherein hypertensive patients with extreme nocturnal BP dips (>20% decrease from awake systolic blood pressure [SBP]) and those with no significant nocturnal dips (<10% decrease from awake SBP) show an increased MRI index of brain microvascular

TABLE 2 Summary of the Effects of VRFs and Their Treatment on Structural and Functional Brain Imaging

VRF	Structural Imaging Findings	Treatment Effects on VRF-Related Structural Imaging Findings	Functional Imaging Findings	Treatment Effects on VRF-Related Functional Imaging Findings
HTN	1. HTN is associated with whole-brain volumetric reductions. 2. HTN is associated with a variable pattern of gray matter volumetric reductions across studies. 3. HTN is associated with a variable pattern of increased WMH burden across studies. 4. Hypertensive patients with extreme or no nocturnal dips in SBP have greater WMH burden compared with hypertensive patients with moderate nocturnal dips in BP.	1. Higher DBP is associated with more cortical atrophy over 20 years in untreated hypertensive patients, but not in treated hypertensive patients. 2. Reduction in BP to normotensive levels in hypertensive patients with treatment fails to prevent gray matter loss over 1 year. 3. Antihypertensive use in hypertensive patients in late life, but not midlife is associated with more cortical atrophy.	1. HTN is associated with reduced resting state gCBF and rCBF. 2. A greater duration of HTN is associated with a greater reduction in resting state CBF. 3. HTN is associated with an altered pattern of cognitive activation rCBF responses. 4. HTN is associated with reduced correlations of rCMRglu between synchronized brain regions (i.e., reduction of functional network connectivity).	1. Antihypertensive treatment reverses/mutes HTN-related decreases in resting state and cognitive task activated gCBF and rCBF. 2. The quality of BP control in hypertensive patients is positively correlated with resting state gCBF and rCBF. 3. Antihypertensive treatment increases correlations in cognitive task-related rCBF between regions associated with task performance (limited evidence). 4. After 36 months of antihypertensive treatment, there is a return to pre-treatment reduced levels of CBF in hypertensive patients (limited evidence).
DM	1. No consensus on the association of DM with global GM volumetric reductions. 2. No consensus on the association of DM with WMH burden. 3. Type 1 DM is associated with a variable pattern of WM FA reductions across studies.	1. The quality of glycemic control (HbA_{1c}) is associated with the magnitude of WMH burden (limited evidence). 2. The quality of glycemic control (HbA_{1c}) is associated with FA in the corona radiata and optic radiations (limited evidence).	1. DM is associated with lower resting state rCBF (limited evidence). 2. DM is associated with a redistributed pattern of cognitive task-related rCMRglu (limited evidence). 3. Types 1 and 2 DM are associated with reduced functional connectivity in default mode network and other various cognitive networks on fMRI.	No treatment data available.
Adiposity	1. Increased adiposity is associated with decreased total cerebral volume. 2. Increased BMI is associated with a variable pattern of GM volumetric reductions across studies. 3. No consensus on the association of BMI with WM volumetric changes. 4. No association between indexes of adiposity and burden of WMHs (limited data).	1. Greater aerobic fitness is associated with greater FA in the cingulum (limited data).	1. Increased BMI is associated with decreased resting state rCBF (limited data). 2. Increased BMI is associated with reduced rCMRglu in bilateral prefrontal and anterior cingulate regions (limited data).	No treatment data available.
Hyperlipidemia	1. Higher total cholesterol and LDL are associated with lower GM volume (limited evidence). 2. Higher total cholesterol and LDL are associated with lower FA in WM of the right hemisphere (limited evidence). 3. No association between familial hypercholesterolemia and burden of WMHs.	1. No effects of lipid-lowering medications on the LDL- or cholesterol-related FA decreases observed in the right hemisphere (limited evidence).	1. Hypertriglyceridemia is associated with temporal lobe hypoperfusion. 2. Higher serum total cholesterol is associated with lower rCMRglu in the precuneus, prefrontal, parietotemporal, and frontal regions (limited evidence). 3. Higher cholesterol-related genetic scores (CREGG) are associated with lower rCMRglu in the posterior cingulate, precuneus, parietotemporal, and frontal regions (limited evidence).	The association between higher total cholesterol with lower rCMRglu in the precuneus, prefrontal, parietotemporal, and frontal regions remain significant after controlling for statin use (limited data).

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pathology, whereas those with less extreme nocturnal BP dips (10% to 20% decrease from awake SBP) show no increases in the MRI index of brain microvascular pathology (20). Over time, the burden of the MRI index of brain microvascular pathology increases in hypertensive patients (19), with some reports showing SBP increases to be more important in this process (17,21), and others DBP increases (22,23). Finally, the impaired cognitive function of hypertensive patients has been attributed to this increased MRI index of brain microvascular pathology (22). The pharmacological treatment of HTN has been reported to increase the MRI index of brain microvascular pathology compared with untreated hypertensive patients (24). The same study also reported greater disorganization of the brain white matter fiber tracts that connect brain regions (indexed on MRI as lower fractional anisotropy values) in treated compared with untreated hypertensive patients (24). However, these results are confounded by the

TABLE 2 Continued

VRF	Structural Imaging Findings	Treatment Effects on VRF-Related Structural Imaging Findings	Functional Imaging Findings	Treatment Effects on VRF-Related Functional Imaging Findings
Smoking	1. Smoking is associated with smaller total brain volume (limited evidence). 2. Greater lifetime exposure to tobacco associated with smaller total brain volume (limited evidence). 3. Smoking is associated with a variable pattern of GM volumetric reductions across studies. 4. Greater lifetime exposure to tobacco is associated with greater GM volume reductions. 5. No association between smoking and WM volume or WMH burden (limited evidence). 6. Smoking is associated with elevated FA in the body of corpus callosum (limited evidence).	No treatment data available.	1. Smoking is not associated with reduced resting state rCBF (limited evidence). 2. Acute administration of nicotine to smokers is associated with a bidirectional pattern of rCBF changes in several regions. 3. Smoking is associated with reduced brain levels of MAO A and MAO B.	1. Smoking cessation is associated with an increase in MAO B levels comparable to those of nonsmokers.
Metabolic syndrome	1. Higher prevalence of MetS in persons with SBIs. 2. A greater number of individual components of MetS is associated with a greater burden of SBIs. 3. No consensus on the association of MetS with WMH burden. 4. MetS is associated with lower FA and higher ADC in the anterior corpus callosum (limited data).	No treatment data available.	1. MetS is associated with reduced working memory task-related activation of multiple brain regions on fMRI (limited evidence).	1. The use of medications to treat multiple components of MetS has no influence on MetS-associated reduced brain activation during a working memory task (limited data).

ADC = apparent diffusion coefficient; BMI = body mass index; BP = blood pressure; CBF = cerebral blood flow; DM = diabetes mellitus; FA = fractional anisotropy; fMRI = functional magnetic resonance imaging; gCBF = global cerebral blood flow; GM = gray matter; HbA_{1c} = glycosylated hemoglobin; HTN = hypertension; LDL = low-density lipoprotein; MAO = monoamine oxidase; MetS = metabolic syndrome; rCBF = regional cerebral blood flow; rCMRglu = regional cerebral glucose metabolic rate; SBIs = silent brain infarcts; SBP = systolic blood pressure; VRF = vascular risk factor; WM = white matter; WMHs = white matter hyperintensities.

significantly younger mean age of the untreated hypertensive patient subgroup compared with the treated group (57.6 vs. 68.2).

Functional brain changes. *Cerebral blood flow changes.* There is consensus among reports that a diagnosis of HTN is associated with abnormally reduced blood flow during rest throughout the whole brain (global cerebral blood flow) and in discrete brain areas (regional cerebral blood flow), and is associated with bidirectional alterations in cognitive test performance-related activation of regional brain blood flow, with some brain regions showing abnormally reduced blood flow and some abnormally increased blood flow (25-30). The quality of BP control in hypertensive patients has been positively correlated with brain blood flow in specific regions observed during rest in both cross-sectional (29,30) and longitudinal (25) studies. These data would suggest a potential for antihypertensive treatment to reverse the HTN-associated abnormally decreased brain regional blood flow observed during rest. Indeed, both global and regional brain blood flow observed during rest is lower in persons with untreated HTN compared with normotensive persons, whereas treatment with antihypertensive medication nearly normalizes regional brain blood flow at rest in hypertensive persons (26,29,30), with a treatment period as short as 6 months to produce these effects (26,31). However, there is evidence, although limited, that these antihypertensive treatment-related improvements in brain blood flow observed at rest in hypertensive patients may be transient, wherein such improvements have been observed at 6, 12, and 24 months after initiation of antihypertensive treatment, but returned to pretreatment abnormally low levels after 36 months of treatment (31).

The bidirectional nature of regional brain blood flow changes observed during cognitive task performance in persons with HTN may reflect compensatory mechanisms. For example, hypertensive patients show greater left brain hemispheric blood flow increases while performing tests of attention and memory, whereas normotensive patients show greater right hemispheric brain blood flow increases while performing the same tests (27). These data suggest that regional blood flow changes in the brains of hypertensive patients performing cognitive tests redistribute to alternate brain regions to maintain successful performance of these cognitive tests. This

assertion is supported by observations that hypertensive patients with better memory performance show less HTN-related abnormal increases in blood flow in the prefrontal region and less HTN-related abnormal muting of blood flow increases in right hippocampal region (28), 2 important brain blood flow changes necessary for normal memory performance. Also, there appears to be a secondary brain blood flow compensatory mechanism manifested as an increase in the correlation of blood flow rates between brain regions in hypertensive persons performing cognitive tests. Specifically, hypertensive patients have shown increased linkage of brain blood flow increases in the hippocampal and prefrontal regions compared with normotensive persons while performing memory tests (28). Antihypertensive treatment appears to facilitate this secondary brain blood flow compensatory mechanism observed in hypertensive patients. For example, 1 year of treatment with either lisinopril or atenolol results in greater linkage of blood flow increases between prefrontal, parietal, prefrontal, and hippocampal brain regions, regions involved in specific memory processes (32). Additionally, diuretic treatment over a period of 6 months has been shown to improve performance on tests of several different cognitive abilities; these improvements correlate with the magnitude of blood flow increases in several brain regions (26) (Online Table 1).

Cerebral glucose metabolic changes. Using positron emission tomography, patients with HTN at rest have been shown to have reduced rates of brain glucose metabolism in regions supplied by the perforator arteries of the circle of Willis (33) and reduced correlations between brain glucose metabolic rates in these regions (33), suggestive of a reduction in connectivity between the functioning of neurons in these brain regions (33).

II. DIABETES MELLITUS. A total of 13 published imaging studies of the brain in association with DM are included in this review (Online Table 2).

Structural brain changes. *GM changes.* Reports of volumetric changes in brain GM of patients with type 2 DM have been inconsistent across studies, with some reports demonstrating an association between a diagnosis of type 2 DM and GM volume loss across the whole brain (34,35), whereas others show no GM volume loss globally in the brain of patients diagnosed with type 2 DM (36–38). However, when assessing specific brain regions, a number of reports show the diagnosis of type 2 DM to be associated with GM volume loss in discrete brain regions (34,37,39,40), although no consensus exists on the location of this GM volume loss (Online Table 2). Additionally, inconsistent associations between the effectiveness of glycemic control over time (glycosylated hemoglobin [HbA_{1c}] levels) and brain GM volume have been observed: some reports show an inverse relationship between HbA_{1c} levels and volume of the hippocampus (37), whereas others show no relationship between HbA_{1c} levels and volume of specific GM brain regions (36).

WM changes. Some reports show type 2 DM to be associated with reduced global brain WM volume (34), whereas some show regionally specific WM volume reductions (34,36). The associations between

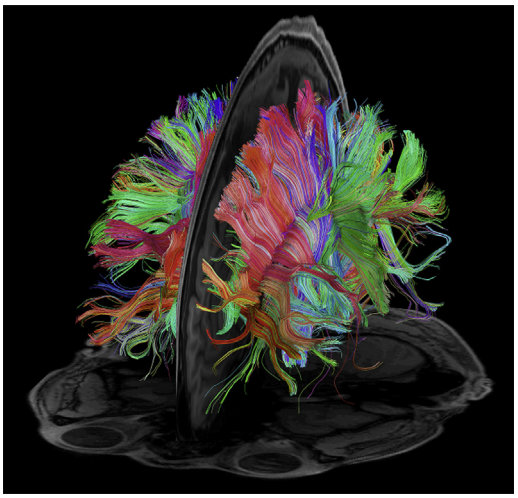

FIGURE 1 How Can Brain Circuit Connectivity Inform Us About Cardiovascular Health?

A 3-dimensional visualization of normal brain white matter tracts generated by tractography analysis of data collected by diffusion tensor imaging (DTI). This analysis uses special techniques of magnetic resonance imaging and computer-based image analysis to provide insight into the complex white matter connections between neural networks formed by short connections among different cortical and subcortical brain regions. DTI can be used to evaluate the integrity of these white matter connections. Data from this review demonstrate that the same risk factors for cardiovascular disease also compromise the integrity of these white matter connections and thus the normal physiological pattern of synchronized activation/deactivation of these interconnected brain regions (also presented in this review). These disruptions result in subtle cognitive impairments. Although not easily recognizable, we hypothesize that they are sufficient to adversely affect the adoption of primary prevention measures for cardiovascular events. The use of sophisticated neuroimaging techniques such as DTI to assess changes in structure of brain connectivity and related neuroimaging techniques to assess functional changes in brain connectivity in persons at risk of cardiovascular disease and events will enhance our understanding of the role of the brain in the progression from cardiovascular risk factor to symptomatic disease.

type 2 DM and MRI indexes of brain microvascular disease have been more inconsistent. Some studies show significant associations between a diagnosis of type 2 DM and an increased presence of MRI indexes of brain microvascular disease (34–36,39), whereas others show no such association with type 2 DM (37,38,41). However, even in the studies that report significant associations between type 2 DM and brain microvascular disease, the type and location of the MRI indexes of brain microvascular disease differ between studies (34–36,39) (Online Table 2). Moreover, limited data suggest the quality of glycemic control affects the amount of observed brain microvascular disease, as demonstrated by a positive correlation between HbA_{1c} level and the quantity of observed MRI indexes of brain microvascular disease (35).

MRI indexes of the structure (i.e., diffusivity) and organization (i.e., fractional anisotropy) of brain WM connecting tracts have also been reported to be affected by a diagnosis of DM. For example, type 1 DM has been associated with more disorganized WM tracts in several brain regions (42,43), with better long-term glycemic control associated with a greater degree of preservation of the organization of the brain WM tracts in some of these regions (42). In addition, a diagnosis of DM has also been associated with increased myelin degeneration in a number of the same brain regions in which increased WM tract disorganization has been observed (43). Finally, increased brain WM tract disorganization in several regions affected by DM has been associated with poorer cognitive performance (42).

Functional brain changes. *Cerebral blood flow changes.* Over all brain regions investigated, regional blood flow observed at rest is lower in patients with type 2 DM (34), and the normal increase in blood flow associated with hypercapnea is also lower in patients with type 2 DM (34).

Cerebral glucose metabolic changes. Similar to the brain blood flow changes observed in patients with HTN, both type 2 DM and pre-diabetes are associated with a bidirectional alteration and a redistributed pattern of brain glucose metabolism in patients performing tests of memory function (2 proposed compensatory mechanisms for the brain metabolism dysfunction that accompanies DM). Specifically, patients with type 2 DM and pre-diabetes show a more widespread pattern of brain glucose metabolism, extending to brain regions adjacent to those activated in nondiabetic patients while performing tests of memory function (44) (Online Table 2). Moreover, better performance of pre-diabetic and diabetic patients on memory tests has been associated with a greater ability to increase brain glucose metabolism during performance of these memory tests in regions normally activated (44). Furthermore, a greater decrease in the ability of body's cells to respond to the actions of the insulin has been associated with reduced brain glucose metabolism during rest in a number of brain regions (44) (Online Table 2).

Brain regional activation (fMRI) changes. Patients with type 2 DM have demonstrated reduced synchronized activity between several specific brain regions, observed by functional magnetic resonance imaging (fMRI) (reduced functional connectivity), regions normally engaged when patients are left to think to themselves undisturbed (referred to as the default mode network) (40,45) (Online Table 2). Moreover, the reduction in functional connectivity of this free-thinking brain network is accompanied by impaired cognitive performance (45). When parsing patients with type 1 DM on the basis of the presence or absence of microangiopathy (a group of microvascular abnormalities including vessel wall remodeling, media hypertrophy, and increased vascular wall stiffness), a mixed pattern of functional connectivity changes compared with nondiabetic patients emerges. Patients with type 1 DM and microangiopathy have demonstrated decreased functional connectivity compared with nondiabetic patients in 5 different brain networks: 1) the network of brain regions that subserves motor and sensory tasks (sensorimotor network); 2) the network of brain regions that subserves visual processing (secondary visual network); 3) the network of brain regions that subserves attention (ventral attention network); 4) the network of brain regions that subserves the processing of auditory and language information (language-processing network); and 5) the network of brain regions that subserves working memory (a form of short-term memory in which information is stored and manipulated) (left frontoparietal network) (46). In contrast, type 1 DM patients without microangiopathy have demonstrated increased connectivity in 2 of these brain networks compared with nondiabetic patients: the sensorimotor and secondary visual networks compared with nondiabetic patients: the network of brain regions that subserves motor and sensory tasks and the network of brain regions that subserves visual processing. Type 1 DM patients without microangiopathy have demonstrated decreased connectivity in the other 3 brain networks compared with nondiabetic patients: 1) the network of brain regions that subserves attention; 2) the network of brain regions that subserves the processing of auditory and language information; and 3) the network of brain regions that subserves working memory (46)

(Online Table 2). The increased connectivity in 2 of the networks of diabetic patients without microangiopathy (which we may consider an earlier stage in the course of diabetes compared with diabetic patients with microangiopathy) has also been observed early in the process of other pathological brain states such as multiple sclerosis and mild cognitive impairment (47,48). One explanation for this early-stage increased connectivity is that it is a compensatory reaction characterized by functional reorganization in attempts to maintain cognitive functions, occurring in response to early subtle brain damage. Indeed, as the severity of multiple sclerosis increases, brain network connectivity decreases (48).

III. ADIPOSITY. A total of 15 published imaging studies of the brain in association with measures of adiposity are included in this review (Online Table 3).

Structural brain changes. *Global changes.* Various indexes of increased adiposity such as increased body mass index (BMI), increased waist circumference, increased subcutaneous adipose tissue, and increased visceral adipose tissue have all been associated with total brain volume decreases (49–51).

Gray matter changes. Indexes of increased adiposity (most frequently BMI), have been consistently associated with regional brain GM volume decreases, although the location of these volume decreases has been inconsistent (52–55) (Online Table 3). Interestingly, some investigations report significant brain GM volume reductions in those considered obese (BMI ≧30) (51), whereas others report significant brain GM volume reductions in those considered simply overweight (BMI >25) (52,55). Indeed, the magnitude of cognitive impairment is associated with the magnitude of brain GM volume loss volume in those regions significantly affected by increased adiposity (53). Finally, a higher BMI has been associated with decreased MRI neurochemical markers of neuronal integrity (*N*-acetylaspartate) in several brain GM regions (56,57) (Online Table 3).

WM changes. Reported brain WM volumetric changes associated with indexes of adiposity have been more inconsistent. Some have reported increased adiposity to be associated with brain WM volume increases (53), some have reported brain WM volume reductions (52), and yet others have reported no brain WM volumetric changes (51). We identified only 1 study for inclusion that evaluated the extent of MRI markers of brain microvascular disease in association with measures of adiposity that reported no association between several different indexes of adiposity and brain microvascular disease (50) (Online Table 3). Brain WM neurochemical changes indicate greater adiposity to be associated with MRI indexes of decreased neuronal integrity in several brain WM regions (56). Moreover, MRI indexes of brain WM microstructural changes indicate that greater adiposity is associated with reduced brain WM connecting tract coherence in several regions, most consistently in the corpus callosum (largest WM structure in the brain, connecting the left and right cerebral hemispheres) (58–61), increased axonal damage in brain WM (59), and increased myelin damage in brain WM (61) (Online Table 3). Interestingly, greater aerobic fitness has been associated with greater coherence of brain WM in the same persons demonstrating a deleterious effect of increased adiposity on brain WM coherence (58).

Functional brain changes. *Cerebral blood flow changes.* Only a single study was identified for inclusion evaluating the effects of adiposity of brain blood flow that demonstrated a global decrease in brain blood flow in persons with increased adiposity (62).

Cerebral glucose metabolic changes. Negative correlations between adiposity and glucose metabolic rate in anterior regions of the brain have been identified (63), with a lower glucose metabolic rate in these regions associated with poorer cognitive performance (63).

IV. HYPERLIPIDEMIA. A total of 8 published imaging studies of the brain in association with hyperlipidemia are included in this review (Online Table 4).

Structural brain changes. *GM changes.* Higher total cholesterol and low-density lipoprotein (LDL) levels have been associated with lower total brain GM volume (64). Moreover, lower levels of high-density lipoprotein (HDL) cholesterol and higher levels of total cholesterol and non-HDL cholesterol have been associated with MRI indexes of reduced neuronal integrity in posterior brain regions (65).

WM changes. Structural MRI has not revealed any significant associations between lipid levels and WM volume (64) nor with MRI indexes of brain microvascular disease (66–68). MRI indexes of brain WM tract organization have been more revealing. For example, higher LDL, total cholesterol, and HDL have all been associated with widespread decreases in the coherence of brain WM tracts lateralized to the right hemisphere (69), with LDL levels showing the strongest associations and additional associations with imaging indexes of myelin integrity (69). Although higher triglyceride levels have been associated with decreased brain WM tract coherence, this association is weaker and less widespread compared with other lipid measures (69). Finally, treatment with lipid-lowering medication seems to have no effect on reversing the changes in brain WM associated with increased lipid measures (69).

Functional brain changes. *Cerebral blood flow changes.* Patients with hypertriglyceridemia have demonstrated decreased blood flow in select regions of the brain (65) (Online Table 4).

Cerebral glucose metabolic changes. Higher total cholesterol has been associated with decreased glucose metabolism in several brain regions (70) (Online Table 4). Use of lipid-lowering drugs had no effect on these findings (70). Moreover, a higher genetic risk of abnormal cholesterol has been associated with lower glucose metabolism in the same brain regions affected by high total cholesterol (71).

V. SMOKING. A total of 12 published imaging studies of the brain in association with smoking are included in this review (Online Table 5).

Structural brain changes. *Global changes.* Smokers have demonstrated significantly smaller total brain volume compared with nonsmokers (72). Moreover, greater lifetime exposure to tobacco has been associated with smaller total brain volume (72).

GM changes. Smokers have shown significantly smaller GM volume and lower GM density in multiple brain regions compared with never smokers (73,74) (Online Table 5). Among those who smoke, a greater lifetime exposure tobacco has been associated with smaller GM volume in several brain regions (73,74). Smoking has also been associated with MRI indexes of reduced neuronal integrity in the hippocampus (75), and increased cellular turnover in anterior cingulate cortex (75).

White matter changes. Structural MRI has revealed no significant effects of smoking on WM volume (76), nor MRI indexes of brain microvascular disease (77). However, smoking has been associated with increased coherence of brain WM tracts in the body of the corpus callosum (76).

Functional brain changes. *Cerebral blood flow changes.* Global brain blood flow during rest has not been show to differ between smokers and nonsmokers (77). However, among smokers, acute administration of nicotine has been reported to induce a reduction in global brain blood flow during rest, more in the right than left hemisphere (78). Moreover, when considering individual brain regions, a bidirectional pattern of brain regional blood flow changes during rest has been seen in smokers acutely administered tobacco products, with some regions showing reductions and some increases (79) (Online Table 5).

Neurochemical and receptor changes. Monoamine oxidase B levels have been shown to be reduced in the brains of smokers compared with nonsmokers (80,81). In addition, nicotinic acetylcholine receptor density has been shown to be greater in several brain regions in smokers compared with nonsmokers (82) (Online Table 5). Smokers acutely exposed to cigarettes show greater post-smoking imaging indexes of increased dopamine release in several brain regions compared with smokers with no acute exposure (83).

VI. METABOLIC SYNDROME. A total of 7 published imaging studies of the brain in association with MetS are included in this review (Online Table 6).

Structural brain changes. *GM changes.* None of the selected studies for inclusion in this review assessed for brain GM changes in association with MetS.

WM changes. The prevalence of MetS has been reported to be higher in patients with silent brain infarcts (SBIs), an MRI-based indication of subclinical cerebrovascular disease (84,85). Moreover, among those persons with SBIs, those with a greater number of individual components of MetS demonstrated a greater burden of SBIs (84,85). The data on MRI indexes of brain microvascular disease are more mixed, with some showing no increase in MRI indexes of brain microvascular disease in persons with MetS (86,87), whereas others found increased MRI indexes of brain microvascular disease in persons with MetS (88). Limited data have demonstrated decreased organization and cellularity of the anterior portion of the largest WM connecting structure in the brain (corpus callosum) of patients with MetS (89). Among those with a diagnosis of MetS, MRI indexes of the organization of this WM connecting structure correlate with performance on various cognitive tasks (86) (Online Table 6).

Functional brain changes. *Brain regional activation (fMRI) changes.* MetS has been associated with reduced activation of several brain regions in patients performing cognitive tasks, detected by fMRI (90). Moreover, lower activation of these brain regions was associated with poorer performance on these cognitive tasks (90) (Online Table 6). Finally, these findings remained significant after controlling for the use of all medications used to treat components of MetS (90).

DISCUSSION

The results of this systematic review demonstrate that patients without symptomatic cardiovascular, cerebrovascular, or peripheral vascular disease but harboring risk factors for these diseases show significant structural and functional brain imaging changes (**Table 1**). Specifically, the risk factors of HTN, DM, increased adiposity, hyperlipidemia, and smoking are all independently associated with brain imaging changes. Moreover, the presence of an increasing number of individual VRF appears to increase the magnitude of these brain imaging changes as implied

by the MetS imaging data (Online Table 6). An important clinical manifestation of these VRF-related structural and functional brain imaging changes in these otherwise healthy persons is cognitive impairment.

The greater consistency of VRF-related functional brain imaging changes compared with structural changes in these asymptomatic at-risk persons, specifically, reductions in brain blood flow and glucose metabolism during rest, suggest early pathological changes in brain microcirculation affecting cerebral hemodynamics before the occurrence of detectable structural changes caused by atherosclerosis. Some potential changes include damage to mechanisms regulating vasomotor tone leading to enhanced vasoconstriction or reduced vasodilator responses (91), hypertrophy of the smooth muscles of precapillary resistance vessels, or perhaps reductions in the density of arterioles or capillaries in specific vascular beds (92,93).

Moreover, the redistribution of the normal pattern of hemodynamic and metabolic brain activation during a cognitive challenge observed in these asymptomatic patients harboring VRFs may indicate a compensatory mechanism invoked in response to early-stage dysfunction of the neuroarchitectural network that typically would support these cognitive tasks. These points are best illustrated in the observations of van Duinkerken et al. (46) wherein patients with DM with cerebral microangiopathy show decreased connectivity in 5 functional brain networks, whereas patients with DM without cerebral microangiopathy show decreased connectivity in 3 of these functional networks and increased connectivity in the remaining 2. This supports the notion of functional reorganization occurring in response to early subtle brain damage (effect of diabetes without microangiopathy), followed by a failing of this functional reorganization as disease severity increases (diabetes with microangiopathy). To investigate the possible structural substrates of the observed redistribution of the normal pattern of hemodynamic and metabolic brain activation during a cognitive challenge in asymptomatic persons harboring VRFs, correlations between metrics of WM tract connectivity demonstrated by MRI within and between coordinated brain regions would be revealing. Such techniques for visualizing brain complex white matter connections between neural networks formed by short connections among different cortical and subcortical brain regions currently exist and can be generated by tractography analysis of data collected by diffusion tensor imaging as depicted in **Figure 1**. Unfortunately, nearly all of the studies included in this review failed to acquire such data in conjunction with hemodynamic and metabolic brain data. Clearly, such investigations are warranted in the future.

Given that a greater number of patients in our aging population are projected to experience the development of mild forms of vascular cognitive impairment, this trend necessitates a better understanding of the mechanisms underlying their development and potential interventions to reverse or halt their progression. Indeed, cognition is the most important determinant of health status, quality of life, and functional ability in older age (94). Diminished cognitive capacity adversely affects a person's ability to benefit from treatment for other medical problems (95). Given that the VRFs associated with the brain changes and cognitive impairments reviewed here are potentially modifiable, management of these modifiable factors could be a primary line of treatment. Indeed, the relationships between indexes of how effectively these VRFs are controlled (i.e., BP, HbA_{1c}, BMI, total cholesterol, and LDL) and the severity of imaging abnormalities and related cognitive impairments reviewed here suggest that adequate treatment of these risk factors may have beneficial effects on brain function. Unfortunately, among the publications included in this review, analyses of medication effects on VRF-related brain imaging changes were scarce, but the limited evidence is compelling nonetheless. For example, antihypertensive treatment consistently blunted and/or reversed the decrease in global and regional brain blood flow and associated cognitive dysfunction in hypertensive patients. Therefore, future investigations of the treatment effects of VRFs on brain function and related cognitive abilities are sorely needed.

A precise summary of the somewhat disparate findings of brain imaging studies of VRFs was challenging due to a number of factors influencing outcomes. Although the selection of studies for inclusion in this review was based, in part, on the conduct of a minimal number of statistical corrections for confounds such as age, sex, and the presence of other VRFs, these variables did differ between studies. Other disparate factors that could have influenced the outcome of this review include age at onset of disease, duration of disease, and treatment status of the groups for these particular VRFs. Such confounds were inconsistently accounted for or data not provided at all. Moreover, studies differed in how the particular risk factor was defined (i.e., some studies used a dichotomous designation for HTN, whereas others used SBP and DBP as continuous variables in their analyses). Additionally, structural imaging methodology varied significantly between studies

including the method to quantify the volume of the brain region of interest or the methodology of brain tissue type segmentation (i.e., GM, WM, cerebrospinal fluid), grading of WMH burden, or even the type of subclinical cerebrovascular pathology assessed. Moreover, comparing the findings of functional brain imaging studies that used varying techniques for quantifying hemodynamic and metabolic changes was challenging.

Despite these limitations, this review represents an important endeavor given that the early identification and initiation of adequate treatment of these modifiable risk factors before the development of irreversible end-organ damage in the brain is an important clinical challenge that we must continue to address.

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REFERENCES

1. Wiesmann M, Kiliaan AJ, Claassen JA. Vascular aspects of cognitive impairment and dementia. J Cereb Blood Flow Metab 2013;33:1696–706.

2. Akinyemi RO, Mukaetova-Ladinska EB, Attems J, Ihara M, Kalaria RN. Vascular risk factors and neurodegeneration in ageing related dementias: Alzheimer's disease and vascular dementia. Curr Alzheimer Res 2013;10:642–53.

3. Carotenuto A, Rea R, Colucci L, et al. Late and early onset dementia: what is the role of vascular factors? A retrospective study. J Neurol Sci 2012; 322:170–5.

4. van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, HTN, dyslipidemia and obesity: A systematic comparison of their impact on cognition. Biochim Biophys Acta 2009;1792:470–81.

5. Bowler JV, Steenhuis R, Hachinski V. Conceptual background to vascular cognitive impairment. Alzheimer Dis Assoc Disord 1999;13 Suppl 3:S30–7.

6. Makin SD, Turpin S, Dennis MS, Wardlaw JM. Cognitive impairment after lacunar stroke: systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. J Neurol Neurosurg Psychiatry 2013;84: 893–900.

7. Moser DJ, Cohen RA, Clark MM, et al. Neuropsychological functioning among cardiac rehabilitation patients. J Cardiopulm Rehabil 1999;19: 91–7.

8. Paul RH, Gunstad J, Poppas A, et al. Neuroimaging and cardiac correlates of cognitive function among patients with cardiac disease. Cerebrovasc Dis 2005;20:129–33.

9. Bennett SJ, Sauve MJ. Cognitive deficits in patients with heart failure: a review of the literature. J Cardiovasc Nurs 2003;18:219–42.

10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;21:339.

11. Wiseman RM, Saxby BK, Burton EJ, Barber R, Ford GA, O'Brien JT. Hippocampal atrophy, whole brain volume, and white matter lesions in older hypertensive subjects. Neurology 2004;63: 1892–7.

12. Salerno JA, Murphy DGM, Honvitz B, et al. Brain atrophy in older hypertensive men: a volumetric magnetic resonance study. Hypertension 1992;20:340–8.

13. Strassburger TL, Lee HC, Daly EM, et al. Interactive effects of age and hypertension on volumes of brain structures. Stroke 1997;28:1410–7.

14. Raz N, Rodrigue KM, Acker JD. Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. Behav Neurosci 2003;117:1169–80.

15. den Heijer T, Skoog I, Oudkerk M, et al. Association between blood pressure levels over time and brain atrophy in the elderly. Neurobiol Aging 2003;24:307–13.

16. Jennings JR, Mendelson DN, Muldoon MF, et al. Regional gray matter shrinks in hypertensive individuals despite successful lowering of blood pressure. J Hum Hypertens 2012;26: 295–305.

17. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 2011; 77:461–8.

18. DeCarli C, Miller BL, Swan GE, et al. Predictors of brain morphology for the men of the NHLBI Twin Study. Stroke 1999;30:529–36.

19. Firbank MJ, Wiseman RM, Burton EJ, Saxby BK, O'Brien JT, Ford GA. Brain atrophy and white matter hyper-intensity change in older adults and relationship to blood pressure. Brain atrophy, WMH change and blood pressure. J Neurol 2007; 254:713–21.

20. Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients: advanced silent cerebrovascular damage in extreme dippers. Hypertension 1996;27:130–5.

21. White WB, Wolfson L, Wakefield DB, et al. Average daily blood pressure, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people. Circulation 2011;124:2312–9.

22. Söderlund H, Nyberg L, Adolfsson R, Nilsson LG, Launer LJ. High prevalence of white matter hyperintensities in normal aging: relation to blood pressure and cognition. Cortex 2003;39: 1093–105.

23. Guo X, Pantoni L, Simoni M, et al. Blood pressure components and changes in relation to white matter lesions: a 32-year prospective population study. Hypertension 2009;54:57–62.

24. Hannesdottir K, Nitkunan A, Charlton RA, Barrick TR, MacGregor GA, Markus HS. Cognitive impairment and white matter damage in hypertension: a pilot study. Acta Neurol Scand 2009; 119:261–8.

25. Beason-Held LL, Moghekar A, Zonderman AB, Kraut MA, Resnick SM. Longitudinal changes in cerebral blood flow in the older hypertensive brain. Stroke 2007;38:1766–73.

26. Efimova IY, Efimova NY, Triss SV, Lishmanov YB. Brain perfusion and cognitive function changes in hypertensive patients. Hypertens Res 2008;31:673–8.

27. Jennings JR, Muldoon MF, Ryan CM, et al. Cerebral blood flow in hypertensive patients: an initial report of reduced and compensatory blood flow responses during performance of two cognitive tasks. Hypertension 1998;31:1216–22.

28. Jennings JR, Muldoon MF, Ryan C, et al. Reduced cerebral blood flow response and compensation among patients with untreated hypertension. Neurology 2005;64:1358–65.

29. Nobili F, Rodriguez G, Marenco S, et al. Regional cerebral blood flow in chronic hypertension. A correlative study. Stroke 1993;24:1148–53.

30. Rodriguez G, Arvigo F, Marenco S, et al. Regional cerebral blood flow in essential hypertension: data evaluation by a mapping system. Stroke 1987;18:13–20.

31. Meyer JS, Rogers RL, Mortel KF. Prospective analysis of long term control of mild hypertension on cerebral blood flow. Stroke 1985;16: 985–90.

32. Jennings JR, Muldoon MF, Price J, Christie IC, Meltzer CC. Cerebrovascular support for cognitive processing in hypertensive patients is altered by blood pressure treatment. Hypertension 2008;52: 65–71.

33. Mentis MJ, Salerno J, Horwitz B, et al. Reduction of functional neuronal connectivity in long-term treated hypertension. Stroke 1994;25: 601–7.

34. Last D, Alsop DC, Abduljalil AM, et al. Global and regional effects of type 2 diabetes on brain

tissue volumes and cerebral vasoreactivity. Diabetes Care 2007;30:1193–9.

35. van Harten B, Oosterman J, Muslimovic D, van Loon BJ, Scheltens P, Weinstein HC. Cognitive impairment and MRI correlates in the elderly patients with type 2 diabetes mellitus. Age Ageing 2007;36:164–70.

36. Chen Z, Li L, Sun J, Ma L. Mapping the brain in type II diabetes: voxel-based morphometry using DARTEL. Eur J Radiol 2012;81:1870–6.

37. Gold SM, Dziobek I, Sweat V, et al. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. Diabetologia 2007;50:711–9.

38. Schmidt R, Launer LJ, Nilsson LG, et al. Magnetic resonance imaging of the brain in diabetes: the Cardiovascular Determinants of Dementia (CASCADE) Study. Diabetes 2004;53:687–92.

39. Novak V, Zhao P, Manor B, et al. Adhesion molecules, altered vasoreactivity, and brain atrophy in type 2 diabetes. Diabetes Care 2011;34:2438–41.

40. Musen G, Jacobson AM, Bolo NR, et al. Resting-state brain functional connectivity is altered in type 2 diabetes. Diabetes 2012;61:2375–9.

41. Weinger K, Jacobson AM, Musen G, et al. The effects of type 1 diabetes on cerebral white matter. Diabetologia 2008;51:417–25.

42. Kodl CT, Franc DT, Rao JP, et al. Diffusion tensor imaging identifies deficits in white matter microstructure in subjects with type 1 diabetes that correlate with reduced neurocognitive function. Diabetes 2008;57:3083–9.

43. van Duinkerken E, Schoonheim MM, Ijzerman RG, et al. Diffusion tensor imaging in type 1 diabetes: decreased white matter integrity relates to cognitive functions. Diabetologia 2012;55:1218–20.

44. Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol 2011;68:51–7.

45. Zhou H, Lu W, Shi Y, et al. Impairments in cognition and resting-state connectivity of the hippocampus in elderly subjects with type 2 diabetes. Neurosci Lett 2010;473:5–10.

46. van Duinkerken E, Schoonheim MM, Sanz-Arigita EJ, et al. Resting-state brain networks in type 1 diabetic patients with and without microangiopathy and their relation to cognitive functions and disease variables. Diabetes 2012;61:1814–21.

47. Celone KA, Calhoun VD, Dickerson BC, et al. Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. J Neurosci 2006;26:10222–31.

48. Rocca MA, Valsasina P, Absinta M, et al. Default-mode network dysfunction and cognitive impairment in progressive MS. Neurology 2010;74:1252–9.

49. Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurol 2005;5:23.

50. Debette S, Beiser A, Hoffmann U, et al. Visceral fat is associated with lower brain volume in healthy middle-aged adults. Ann Neurol 2010;68:136–44.

51. Gunstad J, Paul RH, Cohen RA, et al. Relationship between body mass index and brain volume in healthy adults. Int J Neurosci 2008;118:1582–93.

52. Raji CA, Ho AJ, Parikshak NN, et al. Brain structure and obesity. Hum Brain Mapp 2010;31:353–64.

53. Walther K, Birdsill AC, Glisky EL, Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. Hum Brain Mapp 2010;31:1052–64.

54. Taki Y, Kinomura S, Sato K, et al. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. Obesity (Silver Spring) 2008;16:119–24.

55. Pannacciulli N, Del Parigi A, Chen K, Le DS, Reiman EM, Tataranni PA. Brain abnormalities in human obesity: a voxel-based morphometric study. Neuroimage 2006;31:1419–25.

56. Gazdzinski S, Kornak J, Weiner MW, Meyerhoff DJ. Body mass index and magnetic resonance markers of brain integrity in adults. Ann Neurol 2008;63:652–7.

57. Gazdzinski S, Millin R, Kaiser LG, et al. BMI and neuronal integrity in healthy, cognitively normal elderly: a proton magnetic resonance spectroscopy study. Obesity (Silver Spring) 2010;18:743–8.

58. Marks BL, Katz LM, Styner M, Smith JK. Aerobic fitness and obesity: relationship to cerebral white matter integrity in the brain of active and sedentary older adults. Br J Sports Med 2011;45:1208–15.

59. Mueller K, Anwander A, Möller HE, et al. Sex-dependent influences of obesity on cerebral white matter investigated by diffusion-tensor imaging. PLoS One 2011;6:e18544.

60. Stanek KM, Grieve SM, Brickman AM, et al. Obesity is associated with reduced white matter integrity in otherwise healthy adults. Obesity (Silver Spring) 2011;19:500–4.

61. Xu J, Li Y, Lin H, Sinha R, Potenza MN. Body mass index correlates negatively with white matter integrity in the fornix and corpus callosum: a diffusion tensor imaging study. Hum Brain Mapp 2013;34:1044–52.

62. Willeumier KC, Taylor DV, Amen DG. Elevated BMI is associated with decreased blood flow in the prefrontal cortex using SPECT imaging in healthy adults. Obesity (Silver Spring) 2011;19:1095–7.

63. Volkow ND, Wang GJ, Telang F, et al. Inverse association between BMI and prefrontal metabolic activity in healthy adults. Obesity (Silver Spring) 2009;17:60–5.

64. Whalley LJ, Staff RT, Murray AD, et al. Plasma vitamin C, cholesterol and homocysteine are associated with gray matter volume determined by MRI in non-demented old people. Neurosci Lett 2003;341:173–6.

65. Sinha S, Misra A, Kumar V, et al. Proton magnetic resonance spectroscopy and single photon emission computed tomography study of the brain in asymptomatic young hyperlipidaemic Asian Indians in North India show early abnormalities. Clin Endocrinol (Oxf) 2004;61:182–9.

66. Schmitz SA, O'Regan DP, Fitzpatrick J, et al. MRI at 3 Tesla detects no evidence for ischemic brain damage in intensively treated patients with homozygous familial hypercholesterolemia. Neuroradiology 2007;49:927–31.

67. Schmitz SA, O'Regan DP, Fitzpatrick J, et al. White matter brain lesions in midlife familial hypercholesterolemic patients at 3-Tesla magnetic resonance imaging. Acta Radiol 2008;49:184–9.

68. Soljanlahti S, Autti T, Lauerma K, et al. Familial hypercholesterolemia patients treated with statins at no increased risk for intracranial vascular lesions despite increased cholesterol burden and extracranial atherosclerosis. Stroke 2005;36:1572–4.

69. Williams VJ, Leritz EC, Shepel J, et al. Interindividual variation in serum cholesterol is associated with regional white matter tissue integrity in older adults. Hum Brain Mapp 2013;34:1826–41.

70. Reiman EM, Chen K, Langbaum JB, et al. Higher serum total cholesterol levels in late middle age are associated with glucose hypometabolism in brain regions affected by Alzheimer's disease and normal aging. Neuroimage 2010;49:169–76.

71. Reiman EM, Chen K, Caselli RJ, et al. Cholesterol-related genetic risk scores are associated with hypometabolism in Alzheimer's-affected brain regions. Neuroimage 2008;40:1214–21.

72. Das D, Cherbuin N, Anstey KJ, Sachdev PS, Easteal S. Lifetime cigarette smoking is associated with striatal volume measures. Addict Biol 2012;17:817–25.

73. Gallinat J, Meisenzahl E, Jacobsen LK, et al. Smoking and structural brain deficits: a volumetric MR investigation. Eur J Neurosci 2006;24:1744–50.

74. Brody AL, Mandelkern MA, Jarvik ME, et al. Differences between smokers and nonsmokers in regional gray matter volumes and densities. Biol Psychiatry 2004;55:77–84.

75. Gallinat J, Lang UE, Jacobsen LK, et al. Abnormal hippocampal neurochemistry in smokers: evidence from proton magnetic resonance spectroscopy at 3 T. J Clin Psychopharmacol 2007;27:80–4.

76. Paul RH, Grieve SM, Niaura R, et al. Chronic cigarette smoking and the microstructural integrity of white matter in healthy adults: a diffusion tensor imaging study. Nicotine Tob Res 2008;10:137–47.

77. Yamashita K, Kobayashi S, Yamaguchi S, Koide H. Cigarette smoking and silent brain infarction in normal adults. Intern Med 1996;35:704–6.

78. Rose JE, Behm FM, Westman EC, et al. PET studies of the influences of nicotine on neural systems in cigarette smokers. Am J Psychiatry 2003;160:323–33.

79. Zubieta JK, Heitzeg MM, Xu Y, et al. Regional cerebral blood flow responses to smoking in tobacco smokers after overnight abstinence. Am J Psychiatry 2005;162:567–77.

80. Fowler JS, Volkow ND, Wang GJ, et al. Brain monoamine oxidase A inhibition in cigarette smokers. Proc Natl Acad Sci U S A 1996;93:14065–9.

81. Fowler JS, Volkow ND, Wang GJ, et al. Inhibition of monoamine oxidase B in the brains of smokers. Nature 1996b;379:733–6.

82. Mukhin AG, Kimes AS, Chefer SI, et al. Greater nicotinic acetylcholine receptor density in smokers than in nonsmokers: a PET study with 2-18F-FA-85380. J Nucl Med 2008;49:1628–35.

83. Brody AL, Olmstead RE, London ED, et al. Smoking-induced ventral striatum dopamine release. Am J Psychiatry 2004b;161:1211–8.

84. Kwon HM, Kim BJ, Park JH, et al. Significant association of metabolic syndrome with silent brain infarction in elderly people. J Neurol 2009; 256:1825–31.

85. Kwon HM, Kim BJ, Lee SH, Choi SH, Oh BH, Yoon BW. Metabolic syndrome as an independent risk factor of silent brain infarction in healthy people. Stroke 2006;37:466–70.

86. Segura B, Jurado MA, Freixenet N, Bargalló N, Junqué C, Arboix A. White matter fractional anisotropy is related to processing speed in metabolic syndrome patients: a case-control study. BMC Neurol 2010;10:64.

87. Cavalieri M, Ropele S, Petrovic K, et al. Metabolic syndrome, brain magnetic resonance imaging, and cognition. Diabetes Care 2010;33: 2489–95.

88. Choi HS, Cho YM, Kang JH, Shin CS, Park KS, Lee HK. Cerebral white matter hyperintensity is mainly associated with hypertension among the components of metabolic syndrome in Koreans. Clin Endocrinol (Oxf) 2009;71:184–8.

89. Segura B, Jurado MA, Freixenet N, Falcón C, Junqué C, Arboix A. Microstructural white matter changes in metabolic syndrome: a diffusion tensor imaging study. Neurology 2009;73:438–44.

90. Hoth KF, Gonzales MM, Tarumi T, Miles SC, Tanaka H, Haley AP. Functional MR imaging evidence of altered functional activation in metabolic syndrome. AJNR Am J Neuroradiol 2011;32: 541–7.

91. Struijker Boudier HA, le Noble JL, Messing MW, Huijberts MS, le Noble FA, van Essen H. The microcirculation and hypertension. J Hypertens Suppl 1992;10:S147–56.

92. Vicaut E. Hypertension and the microcirculation: a brief overview of experimental studies. J Hypertens Suppl 1992;10:S59–68.

93. Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HA. Microcirculation in hypertension: a new target for treatment? Circulation 2001;104: 735–40.

94. Gaugler JE, Yu F, Krichbaum K, et al. Predictors of nursing home admission for persons with dementia. Med Care 2009;47:191–8.

95. Athilingam P, King KB. Heart and brain matters in heart failure: a literature review. J N Y State Nurses Assoc 2007;38:13–9.

KEY WORDS brain, cardiovascular, cerebral blood flow, cognitive, diabetes, glucose metabolic rate, gray matter, hyperlipidemia, hypertension, imaging, metabolic syndrome, obesity, smoking, vascular risk factor, white matter

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