Review article

Cardiometabolic determinants of early and advanced brain alterations: Insights from conventional and novel MRI techniques

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ABSTRACT

Cardiometabolic risk factors may be of key importance in the development of future brain diseases like dementia or depression. However, it remains unclear how these risk factors exactly affect the brain. Advanced MR imaging methods such as, diffusion weighted and functional MRI, can provide detailed insights into subtle brain changes, and potentially into early development of disease. In this narrative review, we summarize the available evidence on the associations of cardiometabolic risk factors with subtle changes in brain MRI measures. We found clear evidence that hyperglycemia, physical inactivity, central obesity, and hypertension are associated with both structural and functional brain alterations, while the role of dyslipidemia is far less clear. However, longitudinal evidence that assesses temporality of the associations with more advanced and thus more precise brain imaging methods is needed to improve our insights into the complex etiology of brain diseases.

1. Introduction

Cardiometabolic risk factors may be of key importance in the development of brain diseases like dementia and depression. However, it remains unclear how these risk factors exactly affect the brain. Advanced MR imaging methods can provide detailed insights into subtle brain changes, and thus early development of brain diseases, enhancing our understanding of disease pathology. Subtle brain changes are likely to precede brain dysfunction, and in a later stage, brain diseases (Beason-Held et al., 2013). Cardiometabolic risk factors, like hyperglycemia, physical inactivity and sedentary behavior, central obesity, hypertension, and dyslipidemia, have been identified as risk factors of dementia and depression (Friedman et al., 2014; Tyndall et al., 2016), and their associations have been discussed in previous review articles (Kalaria, 2012; van Bussel et al., 2017). However, no such summary is available on the cardiometabolic determinants of subtle brain alterations as visualized with advanced imaging methods. Therefore, in this narrative review, we summarize the existing evidence on associations between cardiometabolic risk factors and subtle brain changes as assessed by structural and advanced imaging modalities, such as, diffusion weighted MRI (dMRI) and functional MRI (fMRI). These advanced techniques are thought to reflect more subtle tissue and vascular alterations than macroscopically visible lesions displayed by structural MRI.

First, we will introduce the MRI techniques that are presented in literature. Second, we will discuss the association of well-known cardiometabolic risk factors, including hyperglycemia, physical inactivity, sedentary behavior, central obesity, hypertension and dyslipidemia, with structural changes on brain MRI, e.g., with measures of brain atrophy and cerebral small vessel disease (cSVD). Third, their associations with more advanced brain MRI measures, such as diffusion measures and brain connectivity derived from dMRI and fMRI, will be summarised. Finally, we will discuss the findings and their currently available level of evidence.

2. Methods

2.1. Literature search and study selection

We performed an literature search by use of the search terms ‘brain’
2.2. Conventional MRI techniques to detect macrostructural brain changes

Structural brain MRI techniques can detect macroscopically visible morphological brain abnormalities, of which atrophy and features of cSVD are highly relevant for this review. These macrostructural changes are presumably irreversible, but nonetheless important for understanding development of brain diseases.

2.2.1. Brain atrophy

Brain atrophy is a decrease in total or regional brain volume, not caused by a specific macroscopic focal injury such as an infarction or trauma. In general, this loss of volume is thought to be the result of neurodegeneration, e.g., the loss of neurons or other brain cells due to cell death and/or apoptosis (Wardlaw et al., 2013b)(Fjell et al., 2013).

2.2.2. Cerebral small vessel disease

Cerebral small vessel disease (cSVD) refers to lesions in the brain, such as white matter hyperintensities, microbleeds, and lacunar infarcts. According to previous studies, presence of lacunes, white matter hyperintensities, and microbleeds are jointly indicative of an underlying cSVD state, and each studies, presence of lacunes, white matter hyperintensities, and microbleeds on the same study population, the most recent or largest study was included in this review. When possible, we focused on studies performed in large observational population-based cohort studies to maximize generalizability.

2.2.3. White matter hyperintensities

White matter hyperintensities (WMH) are hyper-intense loci on T2-weighted (TSE and FLAIR) MRI scans (Wardlaw et al., 2013b)(Fjell et al., 2013). Larger WMH volumes are associated with worse cognitive function (Tubi et al., 2018). Like brain atrophy, WMH occur more often in older individuals and are strongly associated with cerebrovascular disease and cognitive decline (Debette and Markus, 2010). Wardlaw et al. (Wardlaw et al., 2015) previously discussed the pathogenesis of cSVD features. The main mechanism underlying cSVD-related brain injury, especially WMH, is usually assumed to be ischemia, which results from narrowed or occluded (perforating) arteries. However arterial occlusion might already be a late-stage phenomenon. Currently, earlier phenomena of cSVD pathology are considered to be represented by, systemic endothelium dysfunction (Wardlaw et al., 2013a). For WMH this may be accompanied by demyelination and even axonal loss.

2.2.4. Lacunar infarcts

Lacunar infarcts, or in short lacunes, are round or oval, subcortical, fluid-filled cavities (3-15 mm in diameter) (Wardlaw et al., 2013b) and occur frequently in asymptomatic elderly individuals (Vermeer et al., 2007).

2.2.5. Microbleeds

Microbleeds are small, mostly 2-5 mm in diameter, hypo-intense lesions seen on T2*- or susceptibility-weighted (gradient-echo) MRI (Greenberg et al., 2009). Microbleeds are generally located in the cortico-subcortical junction and deep gray or white matter in the cerebral hemispheres, brainstem, and cerebellum (Wardlaw et al., 2013b).

2.3. Advanced MRI techniques to detect microstructural brain changes

2.3.1. Diffusion MRI

The white matter is organized as a complex network of connected fibers, responsible for efficient information exchange between various brain regions. Alterations in one region may thus affect the function of other regions via the connecting white matter tracts. Therefore, it is important to assess the microstructure of the white matter, which can be visualized by use of dMRI. dMRI can probe white matter fiber architecture, based on the diffusion of water molecules, and yields quantitative measures such as the fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). All these measures reflect microstructural changes related to preferences in diffusion direction relative to the fiber trajectories. It is recommended to analyze a combination of these diffusion metrics, due to their complicated mutual dependence (Tae et al., 2018).

2.3.2. Fractional anisotropy

With respect to the detection of brain changes, the FA is a highly sensitive measure for microstructural changes, however, not very specific to the type of change. FA indicates the directionality of a diffusion process (e.g., due to the orientation of white matter fibers). However, alterations in FA are not unambiguous, as reductions in FA can be either due to decreases in AD and increases in RD or visa versa; FA is furthermore highly influenced by the many crossings of fibers and alterations thereof.

2.3.3. Mean diffusivity

MD indicates the motility of the water molecules. To measure the locally preferred directionality of water diffusion, diffusion-motion

and 'MRI', combined with specific search terms for each category of risk factors, as shown in Supplementary Fig. 1. The inclusion criteria were: full-article research papers and English-written publications, published from inception to May 1, 2019. The following articles were excluded: animal studies, studies on subjects with a specific disease, with a small sample size (case-control N < 10 per group; population-based N < 100), focused on determinant(s) or outcome measures other than cardiometabolic risk factors or brain MRI, conference abstracts without a full text publication, and research protocols. In case of multiple studies on the same study population, the most recent or largest study was included in this review. When possible, we focused on studies performed in large observational population-based cohort studies to maximize generalizability.
sensitized field gradients in multiple angular directions is used, so-called High-Angular-Resolution-Diffusion-Imaging (HARDI). The MD represents an inverse measure of membrane or border density, is independent of direction, and sensitive to cellularity, edema, and necrosis.

2.3.4. Axial and radial diffusivity
AD reflects diffusion along the (long) fiber axis, and gives information about axonal injury and thus decreases when there is axonal damage. RD reflects the diffusion perpendicular to the fiber orientation, and is often most sensitive to impairment of the fiber structure. The RD is often suggested as a surrogate myelin marker and changes when there is myelin damage, and it can be influenced by the geometric properties of the axons (e.g., diameter and density). An increased RD is consistently found in many white matter pathologies, the AD tends to be more variable (Alexander et al., 2011).

2.3.5. Structural connectivity
dMRI can be used to analyze the structure and efficiency of the constellation of white matter fiber tracts, the so-called structural network, by applying graph theory analysis. In graph theory, the brain is represented as a graph, which is a network of nodes (i.e., gray matter brain regions) connected by edges (i.e., white matter tracts between brain regions). The sequence of connections in the network which represent potential routes for communication between brain regions is called a path. The number of connections to one node is called the node degree. The organization of a graph can be characterized by use of graph measures, e.g., clustering coefficient, characteristic path length, global efficiency, and local efficiency. These graph measures describe the efficiency of the white matter network architecture (for an overview, see Table 1). In short, structural connectivity refers to the amount and integrity of white matter tracts between brain areas, thus in general, a lower structural connectivity is a marker of brain pathology.

2.3.6. Functional MRI
fMRI is sensitive to changes in blood oxygenation through the blood oxygen level-dependent (BOLD) signal, which is related to brain function; more oxygenation (indirectly) reflects higher brain activity. fMRI brain activity is thought to locally reflect the coupling between neuronal activity and microvascular blood supply (Lee et al., 2013). In contrast to structural connectivity, functional connectivity relies on statistical dependence of the time signals from different brain regions (which may not be structurally connected). Therefore, a lower functional connectivity is suggested to be a marker of brain dysfunction. fMRI can be used to analyze the temporal correlations between measured time-signals of neuronal activity, to assess collaborations between brain regions, the so-called functional connectivity. Functional connectivity can also expressed in terms of graph measures (Table 1). Neuronal activity can be measured during brain activation (task-based or stimulus-induced) and in rest (resting-state). The latter is used to determine the so-called resting-state networks, consisting of functionally connected regions, which show a high level of correlated BOLD time-signal activity, such as the default mode network (DMN). In task-based fMRI, a cognitive or behavioral task is performed while sensory stimuli (e.g., auditory or visual) are presented during scanning to visualize the brain regions that are involved in the specific tasks.

2.3.7. Perfusion MRI
Perfusion weighted MRI can be used to investigate the blood perfusion of tissues, including ischemic conditions. Lower brain perfusion is a marker for brain diseases, and is associated with cognitive decline. The most used perfusion weighted MRI techniques are dynamic susceptibility contrast (DSC), dynamic contrast enhanced (DCE), and arterial spin labeling (ASL) MR perfusion. Both DSC and DCE require administration of the contrast medium gadolinium, while ASL does not need exogenous contrast. ASL imaging is based on signal loss due to magnetization exchange of labeled water molecules in the blood vessels (Alsop et al., 2015).

3. Results

3.1. Type 2 diabetes and hyperglycemia as risk factor for early brain alterations
Several large cross-sectional and longitudinal observational cohort studies investigated the association of type 2 diabetes mellitus (T2DM) with brain atrophy. T2DM was found to be consistently associated with global brain atrophy in cross-sectional data of the Utrecht Diabetic Encephalopathy Study (Manschot et al., 2007; Manschot et al., 2008; Manschot et al., 2006; Reijmer et al., 2011), The Framingham Heart Study (Debette et al., 2011; Weinstein et al., 2015), The SMART MR study (Tiehuis et al., 2014), The CARDIA Brain MRI study (Launer et al., 2015), The Mayo Clinic Study of Aging (Roberts et al., 2014), UK Biobank (Cox et al., 2019), and The ARIC study (Schneider et al., 2017). This has been confirmed in longitudinal analyses of the Utrecht Diabetic Encephalopathy Study (Brundel et al., 2012), the SMART MR study (Kooistra et al., 2013), and in the PROSPER study, over 3 to 4 years of follow-up (van Elderen et al., 2010).

More specific, T2DM has been associated with smaller gray matter (Cox et al., 2019; Erus et al., 2015; Espeland et al., 2013; Kooistra et al., 2013; Mehta et al., 2014; Moran et al., 2013; Moran et al., 2013; Moran et al., 2013; Reijmer et al., 2011, 2013) and white matter volumes (Manschot et al., 2007; Manschot et al., 2008; Manschot et al., 2006; Reijmer et al., 2011), The Framingham Heart Study (Debette et al., 2011; Weinstein et al., 2015), and also smaller hippocampus volumes (Debette et al., 2011; den Heijer et al., 2003; Filali et al., 2015; Hirabayashi et al., 2016; Moran et al., 2013; Roberts et al., 2014; Weinstein et al., 2015; Zhang et al., 2016b) as compared to normal glucose metabolism (NGM) in these, some population-based) cohort studies. These associations have also been confirmed in longitudinal analyses for decreased gray matter volumes (Erus et al., 2015; Kooistra et al., 2013), increased CSF volumes (Kooistra et al., 2013), and global cortical thinning (Shaw et al., 2017). The follow-up duration of these studies ranged from 40 months (Kooistra et al., 2013) up to 12 years (Shaw et al., 2017). T2DM has also been associated with cSVD characteristics. In multiple large cross-sectional cohort studies an association of T2DM with larger WMH (Brands et al., 2007; Cox et al., 2019; Kooistra et al., 2013; Manschot et al., 2007; Manschot et al., 2008; Manschot et al., 2006; Raffield et al., 2016; Reijmer et al., 2011, 2013; Schneider et al., 2017; Raffield et al., 2016) as compared to normal glucose metabolism (NGM) in these, some population-based) cohort studies. These associations have also been confirmed in longitudinal analyses for decreased gray matter volumes (Erus et al., 2015; Kooistra et al., 2013), increased CSF volumes (Kooistra et al., 2013), and global cortical thinning (Shaw et al., 2017). The follow-up duration of these studies ranged from 40 months (Kooistra et al., 2013) up to 12 years (Shaw et al., 2017).

Table 1
Glossary – Most used terms and measures in graph theory.

| Graph measure              | Description                                                                 |
|----------------------------|-----------------------------------------------------------------------------|
| Of segregation             |                                                                             |
| Clustering coefficient     | Number of connections between nearest neighbors of a node as a proportion of the maximum number of possible connections. |
| Local efficiency           | Inverse shortest path length of connections to neighbors of a specific node; related to clustering coefficient. |
| Characteristic path length | The minimum number of connections that must be traversed on average to go from one region to another. |
| Global efficiency          | Average inverse shortest path length in the network; inversely related to characteristic path length. |
Weinstein et al., 2015) and ischemic lesion volumes (Bissel et al., 2006; Espeeland et al., 2013), and more lacunar infarcts (Schneider et al., 2017) has been established. In longitudinal analyses, T2DM has been associated with increased WMH (Kooistra et al., 2013), and ischemic lesion volumes (Espeeland et al., 2013). Surprisingly, T2DM has not (yet) been associated with microbleeds (Brundel et al., 2014; Moran et al., 2013; van Agtmaal et al., 2018).

A minority of studies used advanced MRI techniques to investigate the association of T2DM with white matter microstructure and (both structural and functional) brain connectivity. By use of dMRI, several case-control studies observed lower FA (Cox et al., 2019; Hsu et al., 2012; Liang et al., 2019; Raffield et al., 2016; Sun et al., 2018; van Bussel et al., 2016a; Weinstein et al., 2015; Xiong et al., 2019; Yau et al., 2010; Yau et al., 2014), and higher MD (Cox et al., 2019; Hsu et al., 2012; Raffield et al., 2016; Sun et al., 2018; van Bussel et al., 2016a; Yau et al., 2014), which indicate altered or impaired fiber microstructure in T2DM. Furthermore, two case-control studies found higher AD (Cox et al., 2019; Hsu et al., 2012; Sun et al., 2018), similarly indicative of injured white matter by axonal injury and disruption of fiber structure.

Van Bussel et al., reported lower structural connectivity, in terms of lower tract volumes between the hippocampi and the frontal lobe, temporal lobe and subcortical gray matter in T2DM compared to NGM as measured by dMRI (van Bussel et al., 2016a). fMRI findings in subjects with T2DM included altered neuronal activity (Cui et al., 2014), lower functional connectivity (Liu et al., 2016; Liu et al., 2018; Sun et al., 2018; Yang et al., 2016) (mainly in frontal and parietal lobes) and lower degree centrality (DC) (Liu et al., 2018) compared to NGM. However, in contradiction to expectations, T2DM was associated with lower characteristic path length (Xu et al., 2019), higher normalized clustering coefficient (CC) (van Bussel et al., 2016b; Xu et al., 2019), and higher local efficiency (Elocal) (van Bussel et al., 2016b) as compared to NGM. A possible explanation for those findings is a compensatory mechanism to counteract (subtle or even subconsciously) cognitive impairment. The authors hypothesized that this compensation is achieved by mobilizing additional neural resources, such as excessive activation of the network and the efficient networking of multiple brain regions. Furthermore, one study found a weaker FC of the posterior cingulate cortex (PCC) and stronger FC to several brain regions in T2DM compared to controls (Tan et al., 2019). Finally, T2DM has been associated with lower blood perfusion (Bangen et al., 2018; Chen et al., 2014; Cui et al., 2017; Xia et al., 2015) measured by use of perfusion and flow MRI techniques.

Very few studies investigated the association of prediabetes, defined as a disturbed fasting or non-fasting glucose metabolism, but not yet full-blown diabetes, with structural or functional brain MRI measures.

In the large cross-sectional ARIC Neurocognitive Study, no association of prediabetes with smaller brain volumes or larger burden of brain vascular pathology was found (Schneider et al., 2017). Meanwhile, in the large cross-sectional population-based Maastricht Study, prediabetes was associated with smaller WM volumes, but not with differences in GM volumes (van Agtmaal et al., 2018). In one case-control study, patients with prediabetes and those with T2DM showed lower GM volumes in the hippocampus, amygdala, and the putamen compared with controls, while no significant differences were found between participants with T2DM and prediabetes (Cui et al., 2019). This indicates that brain changes in T2DM compared to normal glucose metabolism were already present in prediabetes. Only one study reported an association of prediabetes with larger WMH volumes and presence of lacunar infarcts, but found no significant association with cerebral microbleeds (van Agtmaal et al., 2018). In the case-control study of Liang et al., a lower FA was found in prediabetes compared to controls (Liang et al., 2019). Using resting-state fMRI, higher normalized local efficiency was found in participants with prediabetes compared to NGM, hinting at reorganization of the functional networks as compensation for potential cognitive decrements (van Bussel et al., 2016b).

Furthermore, some studies investigated also the association of blood glucose levels on a continuous scale with MRI brain measures. A cross-sectional study reported that higher HbA1c levels were associated with smaller brain volumes and a higher burden of WMH and lacunar infarcts (Schneider et al., 2017). Additionally, elevated glucose levels were associated with lower FA in the right inferior and bilateral superior longitudinal fasciculi (Gonzales et al., 2017). In large population-based studies, higher fasting blood glucose levels were associated with lower cortical thickness (Aikintola et al., 2015; Shaw et al., 2017; van Agtmaal et al., 2018; Wennberg et al., 2016) and lower GM density and FA (Weinstein et al., 2015). One of these was a 12-year follow-up study (Shaw et al., 2017).

In summary, several large cross-sectional and longitudinal population-based studies investigated the association of T2DM with brain changes, and found more atrophy both in gray and white matter, and more severe characteristics of cSVD in T2DM compared to NGM. Fewer studies investigated the association of T2DM with white matter microstructure and connectivity, and found impaired white matter microstructure, and lower structural and functional connectivity in T2DM compared to NGM, which may already be present in prediabetes. Unfortunately, only a few studies investigated continuous glucose measures in relation to brain changes, and most had a cross-sectional design, but did find clear associations. Although these results suggest a causal role for hyperglycemia in early brain changes, longitudinal population-based studies using continuous measures of hyperglycemia are needed to confirm a temporal, and thus potential causal, association of hyperglycemia with early brain damage.

### 3.2. Physical inactivity and sedentary behavior as risk factor for early brain alterations

The association of physical inactivity with structural MRI brain measures has been investigated in large cross-sectional population-based studies, e.g., the AGES-Reykjavik (Arnardottir et al., 2016), SMART-MR (Kooistra et al., 2014), Framingham (Spartano et al., 2019; Tan et al., 2017), LADIS (Baezner et al., 2008; Frederiksen et al., 2015), SHIP (Jochem et al., 2017), MAP (Halloway et al., 2018), and NOMAS (Willey et al., 2011) study. These studies found clear associations between physical inactivity and lower cortical thickness (Afonso et al., 2017; Alosco et al., 2015), specifically in the left prefrontal lobe (Afonso et al., 2017), more brain atrophy (Braskie et al., 2014; Burzynska et al., 2017; Carlson et al., 2015; Doi et al., 2015; Kooistra et al., 2014; Rovio et al., 2016; Spartano et al., 2019; Zhu et al., 2015), and smaller white matter (Arnardottir et al., 2016; Ho et al., 2011) and gray matter volumes (Arenaza-Urquijo et al., 2017; Arnardottir et al., 2016; Boots et al., 2015; Halloway et al., 2018; Jochem et al., 2017; Mueller et al., 2015; Muller et al., 2017; Rovio et al., 2010; Zlatar et al., 2015). Most of these studies used self-reported physical activity measures, while some used objective data as measured by accelerometer devices (Alosco et al., 2015; Arnardottir et al., 2016; Burzynska et al., 2017; Doi et al., 2015; Halloway et al., 2018; Spartano et al., 2019). PA questionnaires only collect subjective information and may therefore over- or underestimate PA levels. Especially light- to moderate-intensity PA are difficult to measure with questionnaires. The longitudinal population-based AGES-Reykjavik study showed that objectively measured physical inactivity was associated with more 5-year GM and WM atrophy (Arnardottir et al., 2016). Comparable results were found in the Cardiovascular Health Study, namely, a longitudinal association of lower self-reported physical activity intensity with more loss of total brain volume over a 9-year period (Braskie et al., 2014). The longitudinal Korean Genome and Epidemiology study found that physical inactivity is associated with brain atrophy (Kim et al., 2018).

Considering cerebral small vessel disease, more physical inactivity has been associated with the presence of silent brain infarcts (Willey et al., 2011), and larger WMH volumes (Boots et al., 2015; Doi et al., 2015; Liang et al., 2019). Furthermore, some studies investigated also the association of blood glucose levels on a continuous scale with MRI brain measures. A cross-sectional study reported that higher HbA1c levels were associated with smaller brain volumes and a higher burden of WMH and lacunar infarcts (Schneider et al., 2017). Additionally, elevated glucose levels were associated with lower FA in the right inferior and bilateral superior longitudinal fasciculi (Gonzales et al., 2017). In large population-based studies, higher fasting blood glucose levels were associated with lower cortical thickness (Aikintola et al., 2015; Shaw et al., 2017; van Agtmaal et al., 2018; Wennberg et al., 2016) and lower GM density and FA (Weinstein et al., 2015). One of these was a 12-year follow-up study (Shaw et al., 2017).

In summary, several large cross-sectional and longitudinal population-based studies investigated the association of T2DM with brain changes, and found more atrophy both in gray and white matter, and more severe characteristics of cSVD in T2DM compared to NGM. Fewer studies investigated the association of T2DM with white matter microstructure and connectivity, and found impaired white matter microstructure, and lower structural and functional connectivity in T2DM compared to NGM, which may already be present in prediabetes. Unfortunately, only a few studies investigated continuous glucose measures in relation to brain changes, and most had a cross-sectional design, but did find clear associations. Although these results suggest a causal role for hyperglycemia in early brain changes, longitudinal population-based studies using continuous measures of hyperglycemia are needed to confirm a temporal, and thus potential causal, association of hyperglycemia with early brain damage.
Physical inactivity has also been associated with diffusion MRI metrics, e.g. a significantly higher FA, and lower MD, AD and RD (Burzynska et al., 2017; Gons et al., 2013; Mueller et al., 2015; Tseng et al., 2013). Only one study investigated the association of physical inactivity on structural connectivity measures. Kim et al. (Kim et al., 2016) found in a cross-sectional study that subjects with a lower level of self-reported physical activity showed significantly lower regional nodal strength in the bilateral middle frontal, bilateral inferior parietal, medial orbitofrontal, and superior and middle temporal gyri, compared to subjects with high levels of self-reported physical activity. In addition, this study found that physical inactivity was associated with lower local efficiency. Using functional MRI measurements, an association of physical inactivity with less fMRI activation was found in a study on obese women after a six-month hypo caloric Mediterranean diet and increased physical activity program (Garcia-Casares et al., 2017). In the 1-year, single-blinded, multicenter randomized controlled LIFE-p trial, an intervention to improve physical activity was compared to health education in sedentary elderly. The intervention on PA was associated with higher fMRI signal only in the inferior frontal gyrus as compared to sedentary groups with health education, 2 years after the intervention ended (Rosano et al., 2010).

Recently, sedentary time has been proposed as an independent risk factor for health outcomes (Brocklebank et al., 2015; Wilmot et al., 2012). Evidence on the association of sedentary behavior and MRI measures is still scarce; however, results from the AGES Reykjavik study indicate that objectively measured PA and sedentary behavior late in life are associated with current and prior cross-sectional measures of white and gray matter atrophy, and that these brain changes over time are associated with PA and sedentary behavior in expected directions (Arnardottir et al., 2016).

In summary, physical inactivity has been associated with more atrophy, the manifestation of cerebral small vessel disease, and lower structural connectivity. Information on sedentary behavior is scarce, but indicates an association with more brain atrophy. Furthermore, longitudinal studies are needed, to further investigate the brain changes over time, and whether lifestyle changes could improve the condition of the brain.

3.3. Central adiposity as risk factor for early brain alterations

A number of large population-based studies have investigated the association between central adiposity and structural brain changes. The studies included in this section focus on both simple, anthropometric methods, such as waist circumference (WC), and waist-hip ratio (WHR), and on more advanced, direct measures of central obesity, such as visceral fat accumulation (VFA) as measured with dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and abdominal MRI scans, all in combination with brain MRI measures. In large cross-sectional (Debette et al., 2010; Debette et al., 2014; Therkelsen et al., 2016) and longitudinal (Driscoll et al., 2012; Janowitz et al., 2015; Kurth et al., 2013; Windham et al., 2017) population-based cohort studies, larger WC and WHR have been associated with lower total brain volume and lower gray matter volume. The Framingham Heart Study Offspring assessed VFA by use of CT, and found an association of more visceral adipose tissue with lower total brain volumes (Debette et al., 2010). Higher VFA measured with abdominal MRI was also associated with global cortical thinning in large cross-sectional population-based studies (Isaac et al., 2011; Veit et al., 2014). Visceral adiposity has also been associated with lower white matter volumes. More specifically, larger WC and WHR were associated with less frontal lobe volume in cross-sectional studies (Debette et al., 2014; Therkelsen et al., 2016), and with lower frontal and temporal lobe volume in one longitudinal study (Driscoll et al., 2012). More visceral adipose tissue measured with abdominal MRI was associated with lower hippocampal and larger ventricular volume in a large cross-sectional population-based study (Isaac et al., 2011). Larger WHR was also associated with lower hippocampal volume according to another cross-sectional population-based study (Isaac et al., 2011; Jagust et al., 2005).

Furthermore, several large cross-sectional population-based cohort studies found an association of VFA with markers of cSVD. In these studies, larger WHR, waist circumference, and VFA have been associated with larger WMH volumes (Anan et al., 2009; Debette et al., 2014; Jagust et al., 2005; Kim et al., 2017; Yamashiro et al., 2014) and lacunar infarcts (Kim et al., 2017; Nagura et al., 2004; Park et al., 2008; Yamashiro et al., 2014). Higher BMI and WHR were associated with larger deep WMH volumes, and to a lower extend with periventricular WMH volumes in the population-based LIFE study (Lampe et al., 2019). A higher visceral-to-subcutaneous fat ratio measured with abdominal CT was associated with cerebral microbleeds (Kwon et al., 2016) in neurologically healthy people. The longitudinal ARIC study found an association of higher WC and WHR with more incident lacunar infarcts after 10-year follow-up, but not with WMH progression (Dearborn et al., 2015).

Evidence on the association of VFA with more advanced measures of brain function is scarce, only associations with diffusion metrics were reported. Higher WC has been associated with lower FA in cross-sectional population-based (Allen et al., 2016; Lou et al., 2014; Speiker et al., 2015; Yau et al., 2016; Yoon et al., 2017; Zhang et al., 2018) and case-control studies (Lou et al., 2014); with higher apparent diffusion coefficient (ADC) in one case-control study (Yau et al., 2010); lower AD in one cross-sectional population-based study (Allen et al., 2016); and higher RD in another cross-sectional population-based study (Verstynen et al., 2013). In contrast, Birdsell et al. found different results, i.e., an association of higher WC with higher FA, and lower MD, AD, and RD (Birdsell et al., 2017).

In short, several large cross-sectional population-based studies assessed the association of central obesity with brain alterations, and found that central obesity was associated with atrophy and markers of cSVD. Only a few longitudinal studies on these associations were conducted, which indicated that central obesity precedes the development of brain atrophy, cSVD, and changes in white matter microstructure. These longitudinal associations need to be investigated further, because this could be a potential target for prevention of brain deterioration. No studies were found that investigated the association of central obesity with structural and functional connectivity, and other functional MRI measures.

3.4. Hypertension and high blood pressure as risk factor for early brain alterations

The brain is known to be more vulnerable to elevated blood pressure or hypertension than other organs, because its microcirculation is characterized by low impedance, which allows the pressure load to penetrate deeply into its microvascular bed (Mitchell, 2008; O’Rourke and Safar, 2005). This (pulsatile) pressure load may cause damage to the smallest blood vessels and thereby cause ischemia and neurodegeneration. Hypertension has been cross-sectionally associated with smaller gray matter volumes (Glodzik et al., 2012), left hemisphere (Salerno et al., 1995) and total brain atrophy (Meusel et al., 2014; Salerno et al., 1992; Strasserburger et al., 1997), thinner cortex (Leritz et al., 2011; Tchistiakova et al., 2014) and larger ventricles (Salerno et al., 1995; Salerno et al., 1992; Shibata et al., 2019; Strasserburger et al., 1997) in population-based cohort studies. Furthermore, both population-based cohort studies (Allan et al., 2015; de Leeuw et al., 2002; King et al., 2014; Kuller et al., 2010; Park et al., 2005; Reed et al., 2006; Shibata et al., 2019; van Dijk et al., 2004), case-control studies (Greenwald et al., 2001; Starchina Iu et al., 2008), and studies on
hypertensive patients (Lee et al., 2007; Scott et al., 2015; Uitterwijk et al., 2017; van Boxtel et al., 2006; White et al., 2018) found an association between hypertension and larger WMH volumes. Only two of these studies had a longitudinal population-based design, and could assess temporality. One study found an association of higher mean arterial pressure with increased WMH volumes after a 28-year follow-up period (Allan et al., 2015), while the other reported progression of periventricular WMHs in participants with hypertension over 4 years of follow-up (Uitterwijk et al., 2017). Hypertension has also been associated with silent cerebral infarctions (Eguchi et al., 2003; Kario et al., 2005; Shibata et al., 2019; Starchina Iu et al., 2008), lacunar infarctions (Shibata et al., 2019; Shintani et al., 1998), and larger perivascular spaces (Shintani et al., 1998) in both cross-sectional (Shibata et al., 2019) and longitudinal (Shintani et al., 1998) population-based studies (Shibata et al., 2019), and large cross-sectional studies including hypertensive patients (Eguchi et al., 2003), in addition to smaller case-control studies (Kario et al., 2005; Starchina Iu et al., 2008).

Evidence on the association of hypertension or blood pressure with more advanced measures of brain function is scarce, only associations with diffusion metrics and changes in cerebral blood flow have been reported. Associations of hypertension with impaired white matter microstructure (Burgmans et al., 2010; Fennema-Notestine et al., 2016; Yau et al., 2013), higher MD (Burgmans et al., 2010) and lower FA in normal appearing white matter (Burgmans et al., 2010; Haight et al., 2018; Yau et al., 2013) have been observed. All these studies had a cross-sectional design, three of these had a large sample size (Fennema-Notestine et al., 2016; Gons et al., 2010; Haight et al., 2018), and two were smaller (n < 100) (Burgmans et al., 2010; Yau et al., 2013). The study by Gons et al. found a lower FA in both normal appearing white matter and white matter hyperintensities, and higher MD in white matter hyperintensities for both categorical (i.e., based on hypertensive status), and continuous blood pressure measures (i.e., systolic and diastolic) (Gons et al., 2010). The study by Fennema-Notestine et al., also had data on hypertension status at an earlier time-point (approximately 5.5 years earlier), and used this information to categorize participants in groups of recent or longer duration of hypertension (Fennema-Notestine et al., 2016). However, no differences between these two groups were observed. Furthermore, an association of hypertension with lower FA (Burgmans et al., 2010; Gons et al., 2010), and hypertension and higher systolic and diastolic blood pressure with lower FA and higher MD in WMH (Gons et al., 2010) was found. Finally, in three case-control studies, hypertension has been associated with lower cerebral blood flow (Dai et al., 2008; Jennings et al., 2005; Wang et al., 2016; Xia et al., 2015).

Taken together, hypertension and elevated blood pressure have been associated with brain atrophy, lower cortical thickness, and cSVD characteristics mostly in cross-sectional studies. Longitudinal population-based analyses are scarce, but do indicate that higher mean arterial pressure is associated with increased WMH volume over time. Furthermore, hypertension has been associated with impaired white matter microstructure, and functional changes in cross-sectional studies. No large population-based studies have investigated the association of hypertension with white matter microstructural impairment yet. To increase knowledge about the temporal, and potentially causal aspects of the association between elevated blood pressure and brain changes, longitudinal population-based studies are needed.

3.5. Dyslipidemia as risk factor for early brain alterations

A number of population-based, case-control, and case studies investigated the association of an adverse lipid profile with early brain changes. In most studies, lipid profiles included information on total, LDL and HDL cholesterol levels, and triglycerides, and for brain outcome measures cortical thickness and markers of cSVD, while studies on atrophy were scarce. We here first summarize findings on total and LDL cholesterol, second on HDL cholesterol and finally on triglycerides. The Strong Heart Heart Study investigated the cross-sectional association of LDL cholesterol levels with brain volumes in a population of American Indians, but found no significant association of LDL cholesterol with total brain and hippocampus volume (Shibata et al., 2019). In contrast to what one might expect, lower LDL cholesterol levels have been associated with GM atrophy in the precentral gyrus and insula cortex in a cross-sectional study (Duan et al., 2016). In agreement with this, in other cross-sectional studies lower LDL cholesterol was associated with cortical thinning in fronto-parietal and occipital areas (Coutinho et al., 2017), within the (left) caudal-middle frontal cortex (Gonzales et al., 2017), and for the total cortex (Leritz et al., 2011). Higher total cholesterol (Breterler et al., 1994; Del Brutto and Mera, 2018; Schmidt et al., 1996; Willey et al., 2014) was reported to be associated with larger WMH volume, in three large population-based and one smaller cross-sectional study. However, another study found no association of LDL cholesterol with WMH volumes, but the majority of their study population used lipid-modifying medication, which might decrease their cholesterol-level-associated risk for cSVD (Raz et al., 2012). Less information is available on the association of cholesterol profile with lacunar infarctions. However, Bezerra et al. (Bezerra et al., 2012) found an association of higher LDL cholesterol with larger lacunes in the cross-sectional population-based ARIC study. Several longitudinal studies have investigated the association of levels of LDL cholesterol with the prevalence of microbleeds, but not all found significant associations. In the population-based Rotterdam Study (Akoudad et al., 2016), a borderline association of high LDL cholesterol levels with prevalence of lobar microbleeds was found. In addition, Lee et al. (Lee et al., 2011) found lower concentrations of LDL cholesterol in patients with a severe degree of microbleeds compared to those without, in a longitudinal study with a follow-up period of 1-5 years. However, in the Strong Heart Study, high serum LDL was not significantly associated with WMH volume, (lacunar) infarcts, and microbleeds (Shibata et al., 2019).

In case-control studies by Cohen et al. (Cohen et al., 2011) and Lou et al. (Lou et al., 2014), obesity-related abnormal plasma cholesterol levels (both high LDL and low HDL) with lower FA in prefrontal brain regions was found. This might indicate that elevated LDL levels contribute to obesity-associated impairment of white matter microstructure. Information on the association of cholesterol levels with functional connectivity is scarce. Only one small cross-sectional study reported a stronger functional connectivity in the DMN in a high total cholesterol group compared to a low cholesterol group, and lower functional connectivity was found in the salience network (SN) (Zhang et al., 2016a).

With regard to HDL cholesterol, Coutinho et al. (Coutinho et al., 2017) reported that lower HDL cholesterol levels were associated with decreased cortical thickness in various brain regions in middle-aged and older adults (40-86 years), which was expected. Lower HDL cholesterol levels were reported to be associated with higher WMH volume, in one large longitudinal and three large cross-sectional population-based studies and two smaller cross-sectional studies (Aljondi et al., 2018; Anan et al., 2009; Carmelli et al., 1999; de Bruijn et al., 2014; Dickie et al., 2016; Longstreth et al., 2005). Lower HDL cholesterol was found to be associated with lacunar infarctions, in one large 3-year follow-up population-based (Gouw et al., 2008), and one smaller cross-sectional study (Takashima et al., 2003).

In the longitudinal AGES-Reykjavik Study (Ding et al., 2015) an association of higher levels of HDL cholesterol with increased risk for lobar, but not deep, microbleeds was found after 5 years.

With regard to triglyceride levels, two cross-sectional studies (Coutinho et al., 2017; Krishnasadas et al., 2013) found that higher triglyceride levels were associated with thinner cortex in multiple brain regions. Three longitudinal studies investigated the association of triglyceride levels with cerebral small vessel disease. In the population-based Rotterdam Study, lower triglyceride levels were associated with an increased 9-year incidence of microbleeds (Akoudad et al., 2016;
This longitudinal association was confirmed in the AGES-Reykjavik Study (Ding et al., 2015) over 5-years of follow-up. Furthermore, the multicenter LADIS study reported that higher triglyceride levels could predict the occurrence of new lacunes over a three-year period (Gouw et al., 2008). These differential results for lacunar infarcts and microbleeds may fit with the hypothesis that microbleeds and lacunes have distinct etiologies.

Studies using advanced MRI techniques were scarce. Only one small cross-sectional study found that lower levels of triglycerides were associated with higher levels of cerebral blood flow as measured with ASL (Jennings et al., 2013).

In conclusion, high LDL cholesterol has been associated with thinner cortex, but higher incidence of lacunar infarcts and microbleeds. On the contrary, high HDL cholesterol was associated with thicker cortex and less white matter hyperintensities, but also with incidence of lacunar infarcts and potentially a higher risk for lobar microbleeds. Studies on diffusion or functional MRI measures are scarce. One study found an association of higher total cholesterol with lower functional connectivity, and one study found an association of higher triglyceride levels with lower cerebral blood flow.

4. Discussion

4.1. Overview and in-depth analysis of the findings

Table 2 provides a condensed systematic overview of the findings in literature about cardiometabolic risk factors in relation to brain volumes and cSVD. The many omissions in the table indicate that not all risk factors have been studied in relation to brain alterations. In general, higher levels of cardiometabolic risk factors considered in this review have been associated to markers of brain atrophy, i.e., smaller total, gray matter and white matter, and larger CSF volumes. Although, the association of altered lipid profile and sedentary behavior with WM, GM, and CSF volumes has been studied too little and needs further investigation. Furthermore, all cardiometabolic risk factors were associated with globally thinner cortex, except for an altered lipid profile. Higher LDL and total cholesterol levels were associated to thicker cortex in some brain regions. With respect to the cSVD characteristics, all cardiometabolic risk factors were associated with larger WMH volumes and the presence of lacunar infarctions. Visceral fat accumulation, altered lipid profile, and hypertension were associated with the presence of microbleeds, while hyperglycemia was not, and for PA and sedentary time, no information was found. These results suggest that all cardiometabolic risk factors are associated with early pathological changes in the brain, in particular with brain volumes and the presence of particular cSVD features. This fits with the notion that all risk factors that are harmful for heart and vasculature, are also harmful for the brain.

Table 3 provides an overview of the main findings for diffusion measures, structural connectivity, and functional connectivity. All cardiometabolic risk factors were associated with lower FA and MD, indicating microstructural changes. For an adverse lipid profile, an association with lower FA was found, but no information was available on MD. Hyperglycemia, less PA and more sedentary behavior were also associated with higher AD and RD, indicating impaired white matter microstructure; and visceral fat accumulation was associated with lower AD and higher RD, indicating axonal and myelin damage. Regarding structural connectivity, limited data were available, as only studies on hyperglycemia and PA were found. Hyperglycemia has been associated with lower overall structural connectivity. In addition, less physical activity and sedentary behavior have been associated to lower nodal strength and local efficiency, indicating less efficient networks. For fMRI, several associations of hyperglycemia with functional MRI measures were found, e.g., lower overall functional connectivity, higher clustering coefficient, higher local efficiency, lower degree centrality,
all indications of network alterations, and lower cerebral blood flow. Furthermore, less physical activity and sedentary behavior have been associated to lower fMRI activation, and a higher functional connectivity in the default mode network (DMN). In addition, an adverse lipid profile was associated to a lower decreased functional connectivity in the salience network (SN). Finally, hypertension was associated with lower functional connectivity. Most omissions in Table 3 are in the field of structural connectivity. Studies on associations of risk factors with white matter structure could probably lead to more insights in microstructural changes.

In addition to the overview in Table 2, we visualised the level of evidence of the observed associations by depicting the study designs found in literature by risk factors in Fig. 2. This figure shows that despite to what we may think, the evidence that cardiometabolic risk factors have a temporal association with brain atrophy. This has been evaluated in longitudinal data for diabetes and physical inactivity, but not for obesity, hypertension and dyslipidemia. In addition, the association of physical inactivity with cSVD needs to be investigated in larger longitudinal studies, to investigate temporal associations. Assessing the associations of cardiometabolic risk factors with more

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**Table 3**

Overview of evidence on the associations between cardiometabolic risk factors and diffusion measures and structural and functional connectivity.

| Diffusion parameters in WM tracts | Structural connectivity | Functional connectivity |
|-----------------------------------|-------------------------|-------------------------|
| FA, MD, AD, RD                   | SC                      | FC/DC/CC/EC/SC/MBF     |

Hyperglycemia

T2DM

Prediabetes

Continuous glucose

Physical inactivity

More sedentary time

Visceral fat accumulation

Hypertension

Dyslipidemia

Total cholesterol

↑LDL

↓HDL

Triglycerides

FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radial diffusivity; SC = structural connectivity; FC = functional connectivity; DC = degree centrality; CC = clustering coefficient; EC = eccentricity; CBF = cerebral blood flow;DMN = default mode network; SN = salience network; ‘n.i.’ means not investigated, ‘=’ means no association found.

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**Fig. 2.** Highest level of evidence in the available literature on the associations between cardiometabolic risk factors and conventional (white symbols) and advanced (gray symbols) MRI measures. Large indicates N > 100; small, N < 100. The size of the symbols indicates the amount of studies in that category: small indicates 1-4; medium, 5-10; large: > 10 studies.
advanced MRI measures as diffusion metrics, structural or function connectivity are in their infancy but coming.

4.2. Future outlook and clinical relevance

As we observe several lacunae in this review, there are a number of opportunities for future studies. First, advanced MRI techniques, including microstructural, functional, and perfusion MRI, may provide more detailed insight into underlying mechanisms that lead from cardiometabolic risk factors to brain dysfunction and disease. These insights may help to develop better treatment strategies to delay or even prevent brain alterations and eventual disease. In addition, the longitudinal association of obesity, hypertension and dyslipidemia with volumetric data needs investigation in order to find support for potential causality. Second, reduction of residual confounding is of key importance to interpret the results of studies. The studies included in this review did this to some extent, at least by matching or adjustments for age and sex. However, cardiometabolic risk factors are interrelated, therefore, an integrated approach where cardiometabolic risk factors are taken into account jointly, would advance this field of research. Third, most advanced MRI outcome measures may represent early changes prior to end-organ damage, which makes them potentially more useful as response markers for intervention studies than volumetric data. This is of particular interest, because cardiometabolic risk factors are modifiable. Fourth, early biomarkers for brain disease may enable us to identify people at risk, to prevent further escalation to functional decrements and eventual disease. Thus, future longitudinal studies are needed to address the usefulness of these novel biomarkers in relation to disease outcomes and risk prediction. Finally, other novel MRI approaches, such as dynamic contrast enhanced (DCE) MRI, to investigate blood-brain-barrier leakage; magnetic resonance spectroscopy (MRS), to investigate the metabolic characteristics of brain alterations; or ultra-high field MRI (> 3Tesla) might provide alternative ways to elucidate early signs and complex pathophysiology of brain diseases.

5. Conclusions

This narrative review indicates clear evidence on the associations of hyperglycemia, central obesity, hypertension, and physical inactivity on brain atrophy, cSVD, and white matter microstructure alterations, although longitudinal data is often lacking. The associations of an adverse lipid profile with MRI markers of the brain are far less clear, as well as the association of relatively novel risk factors as physical inactivity and sedentary behavior. In particular, the evidence from more advanced MRI measures, such as microstructural, functional, and perfusion MRI needs to be applied in longitudinal studies, as insight into more subtle brain alterations, development over time, and subsequent brain dysfunction and disease is needed.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neuropsychologia.2020.04.001.

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