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Common brain structural alterations associated with cardiovascular disease risk factors and Alzheimer's dementia: Future directions and implications

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Abstract

Recent reports suggest declines in the age-specific risk of Alzheimer's dementia in higher income Western countries. At the same time, investigators believe that worldwide trends of increasing mid-life modifiable risk factors [e.g., cardiovascular disease (CVD) risk factors] coupled with the growth of the oldest age groups in the world may nonetheless lead to an increase in Alzheimer's dementia. Thus, understanding the overlap in neuroanatomical profiles associated with CVD risk factors and AD may offer more relevant targets for investigating ways to reduce the growing dementia epidemic than current targets specific to isolated AD-related neuropathology. We hypothesized that a core group of common brain structural alterations exist between CVD risk

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factors and Alzheimer's dementia. Two co-authors conducted independent literature reviews in PubMed using search terms for CVD risk factor burden (separate searches for 'cardiovascular disease risk factors', 'hypertension', and 'Type 2 diabetes') and 'aging' or 'Alzheimer's dementia' with either 'grey matter volumes' or 'white matter'. Of studies that reported regionally localized results, we found support for our hypothesis, determining 23 regions commonly associated with both CVD risk factors and Alzheimer's dementia. Within this context, we outline future directions for research as well as larger cerebrovascular implications for these commonalities. Overall, this review supports previous as well as more recent calls for the consideration that both vascular and neurodegenerative factors contribute to the pathogenesis of dementia.

Keywords

cardiovascular disease; cerebrovascular disease; Alzheimer's dementia; neuroimaging; connectomics; cognition

The relationship between vascular disease and Alzheimer's dementia has been discussed for decades (de la Torre, 2010; Jellinger, 2010; Kalaria, 2010), with work from bench to bedside (de la Torre, 2010) attempting to elucidate the interplay of vascular dysfunction and dementia (see de la Torre, 2018 for review). As part of this larger corpus, it has been documented that mid-life, and to a lesser extent, late-life cardiovascular disease (CVD) risk factors increase the risk for and development of dementia including Alzheimer's dementia (Beauchet et al., 2013; Bendlin et al., 2010; Li et al., 2016; Raz, Knoefel, & Bhaskar, 2016; Suzuki et al., 2019; Tolppanen, Solomon, Soininen, & Kivipelto, 2012). In fact, CVD risk factors are no longer seen as more relevant to vascular dementia as once thought, but rather reflective of cerebrovascular alterations that may not only contribute to Alzheimer's dementia (Nelson, Sweeney, Sagare, & Zlokovic, 2016), but may also be seen as a common etiology shared among all dementias (Raz et al., 2016). Yet drug development and recent NIA-AA research criteria for Alzheimer's disease (Jack et al., 2018) continue to focus primarily on amyloid- or tau-based biomarkers despite the fact that they may not reflect the complete picture of neuropathological alterations present in individuals with Alzheimer's dementia at death (Kapasi, DeCarli, & Schneider, 2017; Yarchoan et al., 2012). For example, over 230 different combinations of neuropathologies that have been reported to date (Boyle et al., 2018). Thus, considering the potential overlap of brain structural alterations associated with CVD risk factors *and* Alzheimer's dementia may offer relevant, more inclusive, targets for drug development and clinical trials, including trials of already available drugs on the market for CVD risk factor management (e.g., Sprint Mind Investigators for the SPRINT Research Group, 2019).

The two-hit vascular hypothesis for Alzheimer's disease (Zlokovic, 2011) includes CVD risk factors as part of 'hit one' that leads to the blood-brain barrier dysfunction and reduced cerebral blood flow that precedes dementia, with 'hit two' characterized by an increase in beta-amyloid amplifying neuronal dysfunction, neurodegeneration and disease. As such, we reviewed the literature for commonalities between grey and white matter as well as subcortical structural alterations associated with CVD risk factors and Alzheimer's dementia to better understand the structural commonalities of regional vulnerabilities associated with

the early stages of disease. More specifically, two co-authors conducted independent literature reviews in PubMed using search terms for CVD risk factor burden (separate searches for ‘cardiovascular disease risk factors’, ‘hypertension’, and ‘Type 2 diabetes’) and ‘aging’ or ‘Alzheimer’s dementia’ with either ‘grey matter volumes’ or ‘white matter’. We hypothesized that our review of studies reporting regionally localized results would reveal a set of overlapping brain structural alterations across studies of CVD risk factors and Alzheimer’s dementia. Results of this review are placed within the larger context of the relationship between vascular disease and Alzheimer’s dementia. Additionally, we discuss future directions for structural neuroimaging research strategies incorporating commonalities across CVD risk factors and Alzheimer’s dementia for a more holistic approach to understanding cognitive aging and dementia. Lastly, we describe the larger cerebrovascular implications of this work. It is our belief that only within this more integrated framework to brain aging, i.e., one that considers a more complete picture of the neuroanatomical alterations associated not only with Alzheimer’s dementia but also CVD risk factors and how they relate to real-world cognitive outcomes, will we be able to move beyond increasingly isolated and unsuccessful clinical trials to slow and ultimately stop risk for and development of Alzheimer’s dementia.

Literature Review

Neuroimaging of Grey Matter and Subcortical Structures

Cardiovascular Disease Risk ——Studies examining composite CVD risk factor burden scores that incorporate multiple risk factors such as hypertension, Type 2 diabetes mellitus, smoking, hypercholesterolemia, and obesity, report relationships between increased CVD risk factor burden and decreased regional grey matter and subcortical structures (Table 1, Column A). For example, increased CVD risk factor burden was associated with decreased frontal and more posterior regional brain volumes as well as the hippocampal volumes across participants between the fourth to eight decades of life (Cardenas et al., 2012; Debette et al., 2011; Gonzales et al., 2017; Lamar et al., 2015; Leritz et al., 2011). A review of the literature by Friedman and colleagues further confirms that in individuals without a history of overt cardiovascular disease, the presence of CVD risk factors is associated with these same structural brain changes (Friedman et al., 2014). Lastly, cumulative CVD risk factor burden has also been associated with a reduction of subcortical volumes in the hippocampus, and several subcortical structures including the nucleus accumbens, caudate, putamen, pallidum, and thalamus (Cox et al., 2019). While composite CVD risk factor burden scores are useful in conceptualizing cumulative risk, they do not reveal the separate contributions of individual CVD risk factors such as hypertension and diabetes mellitus to grey matter structural alterations in the aging brain.

Mid-life CVD risk factors including hypertension and diabetes mellitus have been linked to late-life alterations in whole brain as well as regional grey matter and subcortical structures, with less, albeit still robust, evidence suggesting late-life CVD risk factors are also associated with late-life structural alterations (see Table 1, Column A and Friedman et al., 2014 for review). For example, hypertension has been associated with cross-sectional differences and increased rates of change in whole brain atrophy in older adults (Firbank et

al., 2007; Wiseman et al., 2004) as well as specific hippocampal vulnerability (Firbank et al., 2007; Wiseman et al., 2004). In a qualitative review of approximately 30 studies conducted in mid- to late-life adults (i.e., 45 to 80 years of age), hypertension as well as higher blood pressure in individuals without hypertension were associated with reductions in frontal, parietal, and temporal lobe volumes as well as hippocampal volumes (Beauchet et al., 2013). More recently, an analysis of approximately 10,000 mid- to late-life participants in the UK Biobank revealed that hypertension was linked to alterations in global brain outcomes as well as regionally specific alterations within the frontal and temporal lobes and subcortical structures including the pallidum, accumbens, thalamus, putamen, hippocampus, and amygdala (Cox et al., 2019). A recent study in the mid-life CARDIA cohort confirmed the basal ganglia-thalamic signature of elevated blood pressure exposure (Jenkins et al., 2020).

Many of these same results have been reported for mid- and late-life adults with diabetes mellitus (see Table 1, Column A; and Moulton, Costafreda, Horton, Ismail, & Fu, 2015 for review). Diabetes mellitus has been associated with decreased whole brain volumes, particularly grey matter volumes (Bryan et al., 2014; Reitz et al., 2017); an association recently highlighted in a systematic review (Wu, Lin, Zhang, & Wu, 2017). Additionally, work detailing cerebral localization of diabetes mellitus associates has reported reductions within frontal and temporal regions, in the presence of mid- (e.g., Bruehl et al., 2009; Moran et al., 2013) as well as late-life diabetes mellitus (e.g, Erus et al., 2015; Kumar et al., 2008), although, more severe diabetes mellitus has been associated with smaller volumes of all lobes (Schneider et al., 2017). Regional implications of longer duration diabetes mellitus include middle and inferior frontal gyri, precentral and posterior cingulate cortices, as well as middle and inferior temporal cortices in young-old to older adults (Erus et al., 2015; Moran et al., 2013). There are also multiple reports of associations between diabetes mellitus and volumetric reductions in the limbic system (Erus et al., 2015) including the hippocampus (X. Cui, Abduljalil, Manor, Peng, & Novak, 2014; Moran et al., 2013; Reitz et al., 2017; Roberts et al., 2014; Y. W. Zhang et al., 2015), the amygdala, as well as subcortical structures including the putamen (Cox et al., 2019; D. Cui et al., 2019), the caudate, thalamus, and nucleus accumbens (Chen et al., 2017; Cox et al., 2019). Thus, CVD risk factors combined or in isolation have been associated with reductions in several of the same brain regions, some of which are also implicated in risk for and development of Alzheimer's dementia as outlined below.

Alzheimer's Dementia Risk and Development ––—Initial studies as well as more recent work investigating risk for and development of Alzheimer's dementia point to the importance of key brain regions to cognitive decline and incident dementia (Table 1, Column B). For example, volume loss in the hippocampus is either associated with or predictive of Alzheimer's dementia (Apostolova et al., 2010; den Heijer et al., 2010; Fox et al., 1996; Zeifman et al., 2015). Furthermore, longitudinal staging of brain structural alterations suggest that early in the development of the disease, there is atrophy of the hippocampus and subsequent atrophic changes in the amygdala (Eskildsen et al., 2013). In fact, loss of hippocampal and amygdala volume along with volume loss within the posterior cingulate gyrus, the inferior parietal lobe and the superior frontal lobe appear to have better prognostic accuracy for conversion from an at-risk state of mild cognitive impairment (MCI) to

Alzheimer's dementia (Zeifman et al., 2015) when compared to clinical ratings scores used in the Alzheimer's Disease Neuroimaging Initiative (ADNI: Aksu, Miller, Kesidis, Bigler, & Yang, 2011). These results are consistent with the cortical signature of Alzheimer's dementia put forth by Dickerson and colleagues (Dickerson et al., 2009) who reported alterations in the medial and inferior temporal lobes, posterior cingulate-precuneus, superior parietal, and superior and inferior frontal regions formed a structural phenotype of participants with Alzheimer's dementia. This structural phenotype not only correlates with disease severity ante-mortem (Dickerson et al., 2009), but also mirrors the topography of neuropathology found post-mortem. Despite the anatomic similarities, relatively less work has been done comparing the neuroimaging phenotype of Alzheimer's dementia with the neuroimaging phenotype of CVD risk factors in older adults.

Commonalities Across CVD risk factors and Alzheimer's dementia ——As a result of this review, several grey matter, cortical and subcortical structures appear to be consistently associated with CVD risk factor burden, hypertension, or diabetes mellitus, as well as Alzheimer's dementia (Table 1). More specifically, 23 areas appeared to be commonly, congruently associated with our select indices of CVD risk and Alzheimer's dementia. These areas include the superior frontal gyrus, inferior frontal gyrus (pars opercularis, pars triangularis, pars orbitalis), rostral and caudal middle frontal gyrus, caudal and rostral anterior, posterior, and isthmus cingulate cortex, entorhinal cortex, supramarginal gyrus, middle and inferior temporal gyrus, hippocampus, amygdala, superior and inferior parietal cortex, the basal ganglia (caudate, putamen, pallidum, and accumbens), and precuneus. Although other regions showed overlap, the congruence of these areas was not as consistent across all studies reviewed as the 23 regions listed above and outlined in Table 1. A recent empirical investigation of over 8,000 participants in the UK Biobank to determine common, overlapping grey matter regions between modifiable risk factors for dementia and Alzheimer's dementia further supported our decision making (Suzuki et al., 2019) as do reports that cardiovascular disease risk factors (Silbert et al., 2018), especially diabetes mellitus (Schneider et al., 2017; Zeifman et al., 2015; Y. Zhang et al., 2014), are associated with the cortical signature of Alzheimer's dementia.

Neuroimaging of White Matter

Cardiovascular Disease Risk ——CVD risk factor burden is also associated with white matter alterations (see Wassenaar, Yaffe, van der Werf, & Sexton, 2019 for a recent review). In a large population-based lifespan sample, a cardiovascular disease risk score revealed a causal relationship between overall burden and white matter hyperintensities (Habes et al., 2016) and more nuanced diffusion-tensor imaging (DTI) derived white matter integrity (Habes et al., 2018). Furthermore, in large-scale studies of older adults, mid-life vascular risk exposure including hypertension, current smoking, and diabetes mellitus were associated with greater white matter hyperintensity volume (Debette et al., 2011) and reduced white matter tract integrity within both association and commissural fibers in late-life (de Groot et al., 2015). Lastly, a recent study reported that mid- as well as late-life cardiovascular disease risk factors commonly included in quantifications of total burden were associated with changes in white matter over time (Scharf et al., 2019).

Individually, hypertension and diabetes mellitus are associated with increased white matter hyperintensities (Debette et al., 2011; Firbank et al., 2007; Iadecola et al., 2016; Marseglia et al., 2019; Meusel et al., 2014) predominantly within parietal and frontal (for hypertension; Fennema-Notestine et al., 2016; Salvado et al., 2019) or temporal and frontal (for diabetes; Moran et al., 2013) white matter regions. Furthermore, DTI-derived fractional anisotropy also reveals a loss of white matter integrity associated with these same CVD risk factors (Gonzales et al., 2017; Haight et al., 2018; Hoogenboom et al., 2014; Jacobs et al., 2013). Research done in a cross-sectional study of late-middle-aged men found that individuals reporting a longer duration of hypertension showed lower DTI-derived measures of white matter integrity within several association fibers connecting anterior to posterior regions of brain including the inferior and superior longitudinal fasciculi (McEvoy et al., 2015) with more recent studies suggesting these associations may exist independent of age (Sabisz et al., 2019). Similar findings have been noted in more diverse samples both cross-sectionally (Gonzales et al., 2017; Kennedy & Raz, 2009) and longitudinally (R. Wang et al., 2015).

There is increasing evidence suggesting that these white matter alterations may manifest earlier than originally thought. For example, investigators have shown tissue damage when investigating white matter integrity in 30–40 year old adults with elevated blood pressure (Munoz Maniega et al., 2017; Weinstein et al., 2015) and blood glucose (Maillard et al., 2012). These findings suggest that alterations to white matter integrity may manifest earlier putting, mid-life to young-old adults at increased risk for earlier pathological aging, lending credence to an emerging hypothesis that early effects on white matter integrity may confer a vulnerability across the lifespan (Jefferson, 2020). When coupled with findings relating CVD risk factors to alterations in regional white matter integrity that are also associated with risk for and development of Alzheimer's dementia (see below), the assumption that CVD risk factors influence vascular forms of dementia exclusively is changing (Nelson et al., 2016; Raz et al., 2016), further supporting the role of CVD risk factors in dementia regardless of etiology (Hachinski, 2019; Nelson et al., 2016; Raz et al., 2016).

Alzheimer's Dementia Risk and Development ——Over the past two decades, a literature has emerged showing the importance of white matter alterations to risk for (Bangen et al., 2018; Bryan et al., 2014; Carmichael et al., 2010; Lee et al., 2016) and development of Alzheimer's dementia (Delano-Wood et al., 2009; Libon et al., 2008; Price et al., 2012; Tosto et al., 2015). For example, periventricular white matter hyperintensities, more prominent in Alzheimer's dementia than normal aging (Damulina et al., 2019; Sundar, Manwatkar, Joshi, & Bhandarkar, 2019), appear early in the course of dementia with white matter damage moving more distally to include deep white matter and finally white matter closer to the cortex over time with increasing disease severity (Spilt et al., 2006; Zimmerman, Fleming, Lee, Saint-Louis, & Deck, 1986). Although a recent study suggested that maternal family history of Alzheimer's disease was associated with higher white matter hyperintensity volumes within temporal and occipital regions (Salvado et al., 2019), frontal (Kao, Chou, Chen, & Yang, 2019) and parietal white matter have emerged in non-familial late-onset studies as key regions of vulnerability associated with Alzheimer's dementia (Brickman, 2013; Kao et al., 2019). For example, white matter hyperintensity burden within frontal and parietal regions has been shown to associate with amyloid-PET in these same

regions (Graff-Radford et al., 2019). Furthermore, higher parietal white matter hyperintensity volumes have been reported to predict increasing levels of CSF-derived t-tau (Tosto et al., 2015), and when combined with low baseline levels of t-tau led to faster rates of entorhinal cortex atrophy and faster conversion to Alzheimer's dementia (Tosto et al., 2015). Superior and inferior parietal, as well as rostral and caudal middle frontal, supramarginal, and precuneus white matter hyperintensity burden appear to distinguish MCI and Alzheimer's dementia (Lindemer, Greve, Fischl, Augustinack, & Salat, 2017) with parietal white matter hyperintensity volume predicting Alzheimer's dementia (Brickman et al., 2012; Brickman et al., 2015) and frontal, as well as temporal white matter hyperintensities pointing to a decreasing time-to-Alzheimer's conversion (Lindemer, Greve, Fischl, Augustinack, Salat, et al., 2017).

Commonalities Across CVD risk factors and Alzheimer's dementia ——When taken together, the alterations of white matter, for example, regionally distributed white matter hyperintensities within the parietal lobe, appear to be associated with both CVD risk factor burden including hypertension and diabetes mellitus, as well as Alzheimer's dementia (Table 2). While few studies noted a strong role for temporal lobe white matter alterations across disease states (Lindemer, Greve, Fischl, Augustinack, Salat, et al., 2017), others have advocated for a shared vulnerability to white matter alterations within frontal as well as parieto-occipital white matter regions(Kao et al., 2019). Additionally, infarcts within select subcortical structures including the basal ganglia and caudate, reported for both CVD risk factor burden and Alzheimer's disease (Olazaran et al., 2014), may disconnect temporal from frontal regions allowing for disruptions within either region to exert their effect (Catani & Mesulam, 2008; Geschwind, 1965a, 1965b).

Directions for Future Research and Larger Cerebrovascular Implications

The congruent alterations in grey matter, subcortical structures, as well as white matter discussed above suggests the need for a more integrated approach to structural neuroimaging that includes multi-modal capture and analytic integration of these distinct findings, both to understand the brain at a more holistic level, but also to decipher how CVD risk factors and Alzheimer's dementia may be associated with similar brain regions and the role this may play on behavior. Thus, we will turn our attention away from a review of the literature to place findings of this review within a larger context, discuss future directions for research, and implications for the field.

Previous studies investigating cerebral hypo-perfusion, that is, decreased blood flow through the brain, as it relates to grey matter atrophy in risk for as well as development of Alzheimer's dementia confirm results of this review as it relates to common regional involvement across vascular and Alzheimer's disease processes (de la Torre, 2018) and suggest potential rationale for our noted regional congruence, a topic we will return to toward the end of this review. Using arterial spin-labeling investigators reported decreased regional cerebral blood flow within the posterior cingulate and precuneus across MCI and Alzheimer's dementia compared to controls, as well as reductions in inferior parietal, superior temporal and frontal regions for Alzheimer's dementia compared to MCI and controls (Dai et al., 2009). Interestingly, increases in rCBF in this same study were seen

within multiple subcortical and basal ganglia structures including the hippocampus, amygdala, caudate, putamen, and global pallidus for MCI, suggesting an attempt at compensation for vulnerability in the at-risk stage (Dai et al., 2009). These results, and the results of similar such perfusion studies (see Montagne et al., 2016 for review), involve nearly all 23 regions highlighted by the current review. Thus, a link between the vascular components of Alzheimer's dementia, established via rCBF and patterns of atrophy in Alzheimer's dementia in the past, is confirmed and extended to include congruent regions of involvement across CVD risk factors and Alzheimer's dementia in the current manuscript.

In contrast to the multi-modal imaging across neurovascular dysfunction in Alzheimer's dementia noted above, much of the work to date focused exclusively on structural brain aging, CVD risk factor burden, and Alzheimer's dementia has focused on a single neuroimaging modality approach. This is despite the fact that the landscape of brain aging research is rapidly changing (e.g., Montagne et al., 2016) to incorporate a more nuanced approach to gray *and* white matter structures. Advances in image analytics, through the application of graph theory have made possible the ability to examine the structural connectivity of grey matter, subcortical structures or white matter as it relates to indices of interest (Rubinov & Sporns, 2010). These advanced neuroimaging methods allow analysis of brain structure in a more integrated form, including but not limited to system properties of how the brain exchanges information (efficiency), how strong connections are between brain regions (strength), how important regions are to effective network communication (hubness), and how groups of brain regions preferentially interact to form communities (modularity). Information on these metrics of brain network integrity may fill gaps in the literature related to the interplay of cortical grey matter, subcortical structures, and white matter brain structures common to CVD risk factor burden and risk for and development of Alzheimer's dementia in older adults.

We believe one such approach to understand the interplay of grey matter, subcortical structures, and the white matter that connects them is via tract-based structural connectomics, that is, using the cortical grey matter and subcortical volumes common to CVD risk factor burden and risk for and development of Alzheimer's dementia to determine the integrity of white matter tract-based streamlines connecting these brain regions. Within the normal aging literature, tract-based structural connectomics have been used to predict brain age (Lin et al., 2016), investigate regional importance for brain network efficiency, and particularly relevant to the results of the present review, better understand reductions in network strength between frontal and temporal regions (e.g., Zhao et al., 2015). Likewise, studies have used this analytic approach to outline regions critically important for efficient network communication (e.g., temporal and prefrontal, precentral and precuneus, superior and inferior parietal grey matter regions as well as limbic and basal ganglia structures) and the changes in such communication associated with normal aging (Betzel et al., 2014; Perry et al., 2015; Sun et al., 2015), MCI, and Alzheimer's dementia (Daianu et al., 2015; Daianu et al., 2013; Jacquemont et al., 2017; Mallio et al., 2015; Nir et al., 2015; Yan et al., 2018). Many of these reported regional associations are those that show congruent alterations across CVD risk factors and risk for, as well as development of Alzheimer's dementia as reported in the current review.

We recently took a more directed approach to tract-based structural connectomics as it relates to the 23 ROIs common to both CVD risk factors and Alzheimer's dementia. In a community-based cohort of non-demented older adults (n=94; ~68 years of age, ~29 on the MMSE). Our investigation (Boots et al., 2019) revealed that CVD risk factors differentially impact the efficiency and nodal strength of the tract-based structural connectome within AD-associated regions in fully adjusted models that included a term for white matter hyperintensity burden (i.e., total volume). More specifically, higher CVD risk factor burden was associated with lower efficiency within the left hippocampus and right pars opercularis, and higher efficiency in the right supramarginal gyrus as well as lower nodal strength in bilateral rostral middle frontal gyri, bilateral hippocampi, the thalamus bilaterally, right pars triangularis, and left amygdala (Boots et al., 2019). Furthermore, the tract-based structural connectome metric of nodal strength for left and right hippocampi mediated the association between CVD risk factor burden and cognition, specifically attention and information processing, while this same metric for the left middle frontal gyrus mediated the association between CVD risk factor burden and attention and information processing, as well as executive function (Boots et al., 2019). While this work highlights a means by which tract-based structural connectomics may provide insight into the structural vulnerabilities and the brain-behavior relationships common to both CVD risk factors and Alzheimer's dementia, it is not the only method of multi-modal integration available (Liu et al., 2015; Sui, Adali, Yu, Chen, & Calhoun, 2012; Valdes-Sosa, Kotter, & Friston, 2005), and readers are encouraged to consider what works best for their research interests as well as the MRI modalities used to support their work.

Conclusion

While a discussion of the possible underlying pathophysiology linking common cerebral structures associated with CVD risk factors and Alzheimer's dementia is beyond the scope of this review, as is an outline of the potential temporal nature of theses alterations over time, multiple empirical (e.g., Thompson et al., 2003) and conceptual (e.g., Zlokovic, 2011) studies as well as Special Issue collections exist (Murphy, Corriveau, & Wilcock, 2016), relating to one or both of these disease states. The focus of this review, however, was to present evidence of the overlap between grey, white, and subcortical structural alterations associated with CVD risk factors as well as risk for and development of Alzheimer's dementia. Given the two-hit vascular hypothesis for Alzheimer's disease (Zlokovic, 2011) includes CVD risk factors as part of 'hit one', and the results of previous studies investigating hypoperfusion in Alzheimer's dementia (see Montagne et al., 2016 for review), we advocate that the congruent structural imaging findings reported in this study as related to both CVD risk factors and Alzheimer's dementia further support the consideration of the role CVD risk factors play across dementia subtypes including Alzheimer's disease.

Only with a continued more integrated approach to neurodegeneration will we be able to move beyond increasingly isolated and unsuccessful clinical trials to slow risk for and ultimately stop development of Alzheimer's dementia. This position is further supported by the fact that several large-scale intervention trials of modifiable CVD risk factors including targeted foci, for example, the SPRINT MIND trial (Systolic Blood Pressure Intervention Trial – Memory and cognition in Decreased Hypertension: SPRINT Research Group et al.,

2019), as well as multidomain interventions including diet, exercise, and vascular risk monitoring, for example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER: Kivipelto et al., 2013), have reported success in reducing age-related neurodegeneration. More specifically, targeting lower levels of systolic blood pressure led to smaller increases in white matter hyperintensity burden over approximately 4 years (SPRING Research Group et al., 2019), and a multidomain 2-year intervention that included vascular risk monitoring led to improved cognitive functioning (Ngandu et al., 2015), regardless of participant characteristics including global mental status (Rosenberg et al., 2018). Thus, by considering a more complete picture of neuropathological alterations present in individuals with Alzheimer's dementia including those associated with CVD risk factors, more relevant, more inclusive, and more successful clinical trials may follow.

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Table 1.

23 grey matter and subcortical regions associated with both cardiovascular disease risk factors and Alzheimer's dementia

		Column A	Column B
number and corresponding name(s) of 23 regions of interest		***Cardiovascular Disease Risk Factors references***	***Alzheimer's dementia references***
1	superior frontal gyrus	(Beauchet et al., 2013; Bruehl et al., 2009; Cox et al., 2019; Debette et al., 2011; Friedman et al., 2014; Gianaros, Greer, Ryan, & Jennings, 2006; Glodzik et al., 2012; Gonzales et al., 2017; Kumar et al., 2008; Lamar et al., 2015; Leritz et al., 2011; Y. Zhang et al., 2014)	(Aksu, Miller, Kesidis, Bigler, & Yang, 2011; Dickerson et al., 2009; Kiuchi et al., 2014; Pini et al., 2016; Wang et al., 2015)
2–4	inferior frontal gyrus (pars opercularis, pars triangularis, pars orbitalis)	(Beauchet et al., 2013; Bruehl et al., 2009; Cox et al., 2019; Debette et al., 2011; Erus et al., 2015; Friedman et al., 2014; Glodzik et al., 2012; Gonzales et al., 2017; Kumar et al., 2008; Lamar et al., 2015; Leritz et al., 2011; Moran et al., 2013)	(Dickerson et al., 2009; Kiuchi et al., 2014; Moller et al., 2013)
5–6	middle frontal gyrus (rostral and caudal)	(Beauchet et al., 2013; Bruehl et al., 2009; Cox et al., 2019; Debette et al., 2011; Erus et al., 2015; Friedman et al., 2014; Gonzales et al., 2017; Kumar et al., 2008; Lamar et al., 2015; Leritz et al., 2011; Moran et al., 2013; Y. Zhang et al., 2014)	(Kiuchi et al., 2014; Pini et al., 2016)
7–10	cingulate cortex (caudal and rostral anterior, posterior, isthmus)	(Beauchet et al., 2013; X. Cui, Abduljalil, Manor, Peng, & Novak, 2014; Erus et al., 2015; Gianaros et al., 2006; Leritz et al., 2011; Moran et al., 2013; Raji et al., 2010; Y. Zhang et al., 2014)	(Aksu et al., 2011; Dickerson et al., 2009; Kiuchi et al., 2014; Moller et al., 2013; Pini et al., 2016; Wang et al., 2015; Zeifman et al., 2015)
11	entorhinal cortex	(Beauchet et al., 2013)	(Pini et al., 2016; Whitwell et al., 2013)
12	supramarginal gyrus	(Beauchet et al., 2013; Leritz et al., 2011)	(Dickerson et al., 2009; Kiuchi et al., 2014)
13–14	middle and inferior temporal gyrus	(Beauchet et al., 2013; Bruehl et al., 2009; Cox et al., 2019; Erus et al., 2015; Gianaros et al., 2006; Kumar et al., 2008; Moran et al., 2013; Raji et al., 2010; Y. Zhang et al., 2014)	(Aksu et al., 2011; Dickerson et al., 2009; Kiuchi et al., 2014; Moller et al., 2013; Pini et al., 2016; Whitwell et al., 2013; Zeifman et al., 2015)
15	hippocampus	(Beauchet et al., 2013; Cardenas et al., 2012; Cox et al., 2019; X. Cui et al., 2014; Debette et al., 2011; Firbank et al., 2007; Friedman et al., 2014; Gonzales et al., 2017; Lamar et al., 2015; Leritz et al., 2011; Moran et al., 2013; Moulton, Costafreda, Horton, Ismail, & Fu, 2015; Raji et al., 2010; Reitz et al., 2017; Roberts et al., 2014; Wiseman et al., 2004; Y. W. Zhang et al., 2015)	(Aksu et al., 2011; Apostolova et al., 2010; den Heijer et al., 2010; Eskildsen et al., 2013; Fox et al., 1996; Moller et al., 2013; Pini et al., 2016; Whitwell et al., 2013; Zeifman et al., 2015)
16	amygdala	(Beauchet et al., 2013; Cox et al., 2019; D. Cui et al., 2019)	(Aksu et al., 2011; Eskildsen et al., 2013; Pini et al., 2016)
17–18	superior and inferior parietal cortex	(Beauchet et al., 2013; Cox et al., 2019)	(Dickerson et al., 2009; Moller et al., 2013; Whitwell et al., 2013)
19–22	basal ganglia (caudate, putamen, pallidum, accumbens)	(Chen et al., 2017; Cox et al., 2019; D. Cui et al., 2019; Moran et al., 2013; Moulton et al., 2015; Raji et al., 2010)	(Pini et al., 2016)
23	precuneus	(Moran et al., 2013; Y. Zhang et al., 2014)	(Dickerson et al., 2009; Kiuchi et al., 2014; Moller et al., 2013)

NOTE: Table was compiled based on independent literature reviews by two co-authors via PubMed using search terms for CVD risk factor burden (separate searches for 'cardiovascular disease risk factors', 'hypertension', and 'Type 2 diabetes') and 'aging' or 'Alzheimer's dementia' with either 'grey matter volumes' or 'white matter'.

Table 2.

Common regional involvement of white matter hyperintensities associated with both cardiovascular disease risk factors and Alzheimer's dementia

		Column A	Column B
		Cardiovascular Disease Risk Factors references	***Alzheimer's dementia references***
WMH	Generally	(Debette et al., 2011; Firbank et al., 2007; Habes et al., 2016; Iadecola et al., 2016; Marseglia et al., 2019; Reitz et al., 2017; Scharf et al., 2019)	(Bangen et al., 2018; Brickman et al., 2018; Carmichael et al., 2010; Damulina et al., 2019; Delano-Wood et al., 2009; Lee et al., 2016; Libon et al., 2008; Price et al., 2012; Sundar, Manwatkar, Joshi, & Bhandarkar, 2019)
	By Lobe		
	Frontal	(Fennema-Notestine et al., 2016; Jacobs et al., 2013; Kennedy & Raz, 2009; Salvado et al., 2019)	(Graff-Radford et al., 2019; Kao, Chou, Chen, & Yang, 2019; Lindemer, Greve, Fischl, Augustinack, Salat, et al., 2017; Lindemer, Greve, Fischl, Augustinack, & Salat, 2017)
	Temporal	(Debette et al., 2011; Jacobs et al., 2013; Moran et al., 2013)	(Lindemer, Greve, Fischl, Augustinack, Salat, et al., 2017; Salvado et al., 2019)
	Parietal	(Fennema-Notestine et al., 2016; Jacobs et al., 2013)	(Brickman et al., 2012; Brickman et al., 2014; Brickman et al., 2015; Graff-Radford et al., 2019; Lindemer, Greve, Fischl, Augustinack, & Salat, 2017; Tosto et al., 2015)
	Occipital	(Jacobs et al., 2013; Kennedy & Raz, 2009)	(Salvado et al., 2019)

NOTE: Table was compiled based on independent literature reviews by two co-authors via PubMed using search terms for CVD risk factor burden (separate searches for 'cardiovascular disease risk factors', 'hypertension', and 'Type 2 diabetes') and 'aging' or 'Alzheimer's dementia' with either 'grey matter volumes' or 'white matter'.