

FEATURED ARTICLE

Small vessel disease more than Alzheimer's disease determines diffusion MRI alterations in memory clinic patients

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*Data used in preparation of this article were obtained from the Dominantly Inherited Alzheimer Network (DIAN) database, the DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) database, and the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within DIAN, DELCODE, and ADNI contributed to the design and implementation of the respective studies and/or provided data but did not participate in analysis or writing of this report. A complete listing of the DIAN consortium, the DELCODE study group, and ADNI investigators can be found in the Supplement (DIAN and DELCODE) and at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf (ADNI).

Sofia Finsterwalder and Naomi Vlegels both contributed equally to the study.

[Correction added on August 22, 2020, after first online publication: the study groups were included in the author listing of the online version of the article. We apologize to the authors and our readers for this error.]

Abstract

Introduction: Microstructural alterations as assessed by diffusion tensor imaging (DTI) are key findings in both Alzheimer's disease (AD) and small vessel disease (SVD). We determined the contribution of each of these conditions to diffusion alterations.

Methods: We studied six samples (N = 365 participants) covering the spectrum of AD and SVD, including genetically defined samples. We calculated diffusion measures from DTI and free water imaging. Simple linear, multivariable random forest, and voxel-based regressions were used to evaluate associations between AD biomarkers (amyloid beta, tau), SVD imaging markers, and diffusion measures.

Results: SVD markers were strongly associated with diffusion measures and showed a higher contribution than AD biomarkers in multivariable analysis across all memory clinic samples. Voxel-wise analyses between tau and diffusion measures were not significant.

Discussion: In memory clinic patients, the effect of SVD on diffusion alterations largely exceeds the effect of AD, supporting the value of diffusion measures as markers of SVD.

KEYWORDS

Alzheimer's disease, biomarker, cerebral small vessel disease, diffusion tensor imaging, free water imaging, white matter

1 | INTRODUCTION

Alzheimer's disease (AD) and cerebral small vessel disease (SVD) are the two leading causes of cognitive decline and dementia.¹ Altered white matter microstructure is considered a key finding in both conditions^{2,3} and has consistently been associated with cognitive deficits.⁴⁻⁶ The most commonly used method to study white matter microstructure in vivo is diffusion tensor imaging (DTI), which quan-

tifies diffusion properties of water molecules in brain tissue.^{7,8} The typical finding described in both AD and SVD is an increase in the extent of water diffusion (mean diffusivity) and a decrease in diffusion directionality (fractional anisotropy), which can be detected both globally and regionally.^{4,5} Despite the wide use of diffusion alterations as efficient disease markers and their strong associations with clinical deficits, little is known about their underlying pathology.

In memory clinic patients, AD and SVD often co-exist.⁹ The extent to which each of these conditions contribute to diffusion magnetic resonance imaging (MRI) alterations is largely elusive. Free water imaging, an advanced diffusion model, improves the specificity of the DTI model and could therefore provide additional insight into the origin of diffusion MRI alterations.¹⁰ As such, free water imaging might be able to disentangle the effects of AD and SVD.¹¹⁻¹⁴ Previous studies using DTI or free water imaging were limited by the lack of biomarker evidence of AD pathology or insufficient consideration of mixed pathology. Assessing the individual contributions of AD and SVD toward diffusion MRI alterations requires a systematic study covering the entire spectrum of “pure AD,” mixed disease, and “pure SVD.”

The uncertainty regarding the origin and interpretation of diffusion alterations in memory clinic patients impedes widespread implementation in research and clinical practice. Therefore, the aim of this study was to determine the effect of AD and SVD on diffusion MRI in a memory clinic setting. We examined associations between biomarkers of AD, MRI markers of SVD, and diffusion measures from both conventional DTI and free water imaging. Six study samples (N = 365 participants) were included to systematically cover the entire spectrum of AD, mixed disease, and SVD, and to account for both cerebrospinal fluid (CSF) and positron emission tomography (PET) markers. In addition to the common memory clinic setting with predominantly mixed disease, our analysis also included patient samples with pure, genetically defined AD or SVD. This enabled us to examine effects of both diseases on diffusion measures without confounding pathology. Analyses were performed separately within each sample to validate results and address generalizability using the six independently recruited samples.

2 | METHODS

2.1 | Participants

We studied six independent samples (N = 365 participants) covering the spectrum of AD, mixed disease, and SVD: four memory clinic samples with mixed disease with a recruitment focus on either AD or SVD, one sample each of genetically defined AD and SVD. Memory clinic samples were drawn from single or multi-center studies, which were selected based on availability of (diffusion) MRI sequences and CSF or PET data. The compilation of samples, subject selection criteria, and exclusions are shown in Figure 1, and further elaborated in sections 2.1.1 to 2.1.3. MRI, CSF, and PET data from subjects of the included samples were obtained within 1 year. Diagnostic criteria used in the AD- and SVD-focused memory clinic samples are summarized in Table S1 in supporting information. All studies were approved by the ethics committees of the respective institutions and all subjects provided written informed consent.

2.1.1 | AD focused samples

We included 89 participants from the German multicentric DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE;

RESEARCH IN CONTEXT

1. Systematic review: Diffusion magnetic resonance imaging (MRI) is widely used to assess white matter microstructure in both Alzheimer's disease (AD) and small vessel disease (SVD). Although AD and SVD frequently co-occur, the vast majority of studies did not consider mixed disease and the individual contributions of these conditions to diffusion MRI alterations have not yet been investigated systematically (as reviewed using Pubmed).
2. Interpretation: SVD more than AD determines diffusion alterations in a memory clinic setting, even in samples in which AD was the clinically predominant disease. Our results validate diffusion measures as markers for SVD.
3. Future directions: Future studies and clinical applications of diffusion MRI need to consider the strong effect of SVD. A more complex parameterization of the fluid compartments, for example, by neurite orientation dispersion and density imaging or a multi-shell model for free water imaging, may further increase the sensitivity in earlier or even asymptomatic stages of SVD.

downloaded in December 2018) with available CSF amyloid beta₁₋₄₀ (A β 40), A β 42, total tau (t-tau), and phosphorylated tau₁₈₁ (p-tau) data. The sample consisted of A β 42-positive healthy controls (A β 42 cut-off see Text S1 in supporting information) and patients with subjective cognitive decline, amnesic mild cognitive impairment, and mild dementia.¹⁵

We further included 53 participants from the multicentric AD Neuroimaging Initiative (ADNI, phase 3; downloaded in December 2018 at <http://adni.loni.usc.edu>) with available A β [¹⁸F]-florbetapir and tau [¹⁸F]AV-1451 flortaucipir (PET). The sample consisted of amyloid-positive (cut-off see Text S1) healthy controls and patients with amnesic mild cognitive impairment and mild dementia (<http://adni.loni.usc.edu>).

2.1.2 | SVD focused samples

We included 39 participants from the University Medical Center Utrecht, the Netherlands (prospective Utrecht Vascular Cognitive Impairment study, UVCI) with available CSF data for A β 42, t-tau, and p-tau. The sample consisted of patients with subjective cognitive decline, mild cognitive impairment, and dementia and with no evidence of a primary etiology other than neurodegenerative disease or sporadic SVD and a high burden of SVD on MRI.¹⁶

We further included 39 participants from the Samsung Medical Center, Seoul, Republic of Korea (Seoul Vascular Cognitive Impairment study, SVCI) with available A β [¹⁸F]-florbetaben and tau [¹⁸F]AV-1451

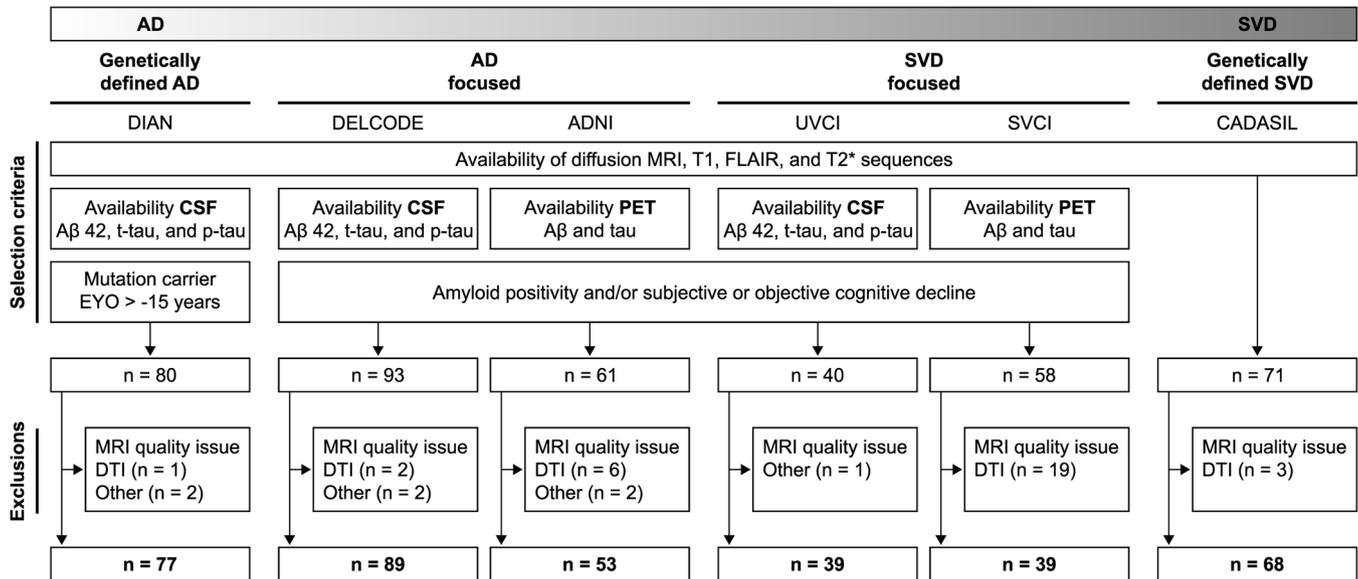


FIGURE 1 Study concept and participant selection flowchart. Samples cover the entire spectrum of Alzheimer's disease (AD), mixed disease, and small vessel disease (SVD). ADNI, Alzheimer's Disease Neuroimaging Initiative; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSF, cerebrospinal fluid; DELCODE, DZNE-Longitudinal Cognitive Impairment and Dementia Study; DIAN, Dominantly Inherited Alzheimer's Network; DTI, diffusion tensor imaging; EYO, estimated years from symptom onset; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; PET, positron emission tomography; p-tau, phosphorylated-tau₁₈₁; SVCI, Seoul Vascular Cognitive Impairment study; t-tau, total tau; UVCi, Utrecht Vascular Cognitive Impairment study

flortaucipir (PET). The sample consisted of patients with objective cognitive impairment and a high burden of SVD on MRI.^{17,18}

2.1.3 | Genetically defined samples

As a genetically defined AD sample, we included 77 participants from the multicentric Dominantly Inherited Alzheimer Network (DIAN, data freeze 11; downloaded in August 2018).¹⁹ DIAN is a longitudinal cohort study of individuals at risk of developing autosomal dominant AD. Here we included *PSEN1* (n = 59), *PSEN2* (n = 5), and *APP* (n = 13) mutation carriers with available A β 40, A β 42, t-tau, and p-tau CSF data. In our study, subjects had to be < 15 years from estimated symptom onset to increase sensitivity to detect AD and SVD marker alterations in proximity to the onset of AD symptoms.^{5,20}

As a genetically defined SVD sample, we included 68 patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) recruited from a single-center study in Munich.⁴ Although CSF or PET data were not available in this dataset, we included CADASIL to judge the effect sizes of SVD markers in genetically defined SVD.

2.2 | MRI

All MRI data were obtained on three Tesla systems. All samples included diffusion MRI, T1-weighted, fluid-attenuated inversion recovery (T2-weighted), and gradient echo (T2*-weighted) sequences. While each study used a standardized protocol, acquisition parameters

differed across studies. The MRI protocols have been published previously for DIAN,⁵ DELCODE,²¹ ADNI,²² UVCi,²³ SVCI,¹⁷ and CADASIL.¹¹ Diffusion MRI sequence parameters for all samples are summarized in Table S2 in supporting information. All diffusion images were processed with the same pipeline as described in Text S2 in supporting information. Global diffusion measures were calculated as mean of all voxels within a white matter skeleton. Regional analyses were based on voxel-wise diffusion measures.

2.3 | AD markers

We used A β and tau (CSF or PET) as biomarkers of AD. Details on CSF assays, PET tracers, and calculations of PET standardized uptake value ratio (SUVR) scores have previously been published for DIAN,⁵ DELCODE,¹⁵ ADNI (<http://adni.loni.usc.edu>), UVCi,²⁴ and SVCI.¹⁸

For the main analyses we used continuous CSF and PET measures. For a subgroup analysis in amyloid-positive individuals, we used study specific A β cut-off values. See Text S1 for details.

2.4 | SVD markers

We used an established total SVD score (ordinal variable)²⁵ and white matter hyperintensity (WMH) volume (continuous variable) as MRI markers of SVD. The total SVD score summarizes the presence or severity of SVD lesions on an ordinal scale, that is, WMH, lacunes, microbleeds, and enlarged perivascular spaces.²⁵ Two trained raters (SF, NV) assessed these lesions according to the STRIVE

(Standard for Reporting Vascular Changes on Neuroimaging) consensus criteria:² WMHs were rated using the Fazekas scale,²⁶ the number of lacunes was determined on fluid-attenuated inversion recovery and T1-weighted images, the number of cerebral microbleeds on T2*-weighted gradient echo images, and the number of enlarged perivascular spaces in the basal ganglia on a single T1-weighted axial image slice with the highest number of perivascular spaces.²⁷

WMH volume was calculated from a previously described semi-automated segmentation pipeline.⁴

2.5 | Statistical analyses

All statistical analyses were performed in R (version 3.5.1).²⁸ The statistical significance level was set at $\alpha < 0.05$.

Associations between AD biomarkers, SVD markers, age, sex (independent variables), and global diffusion measures (dependent variables) were first assessed by simple linear regression analyses within each sample. Variables were power transformed in case of non-normal distribution (Shapiro-Wilk test).

To perform multivariable analysis in the presence of multicollinearity (ie, intercorrelations among disease markers, Figure S1 in supporting information), we used random forest regressions (R package "party"; version 1.3-2).²⁹ This method allowed us to assess the contribution of each AD biomarker, SVD marker, age, and sex to diffusion alterations, while accounting for all other variables. For each sample, we calculated 1501 conditional inference trees with unbiased variable selection and default parameters as previously described.¹¹ We calculated conditional variable importance together with a 95% confidence interval from 100 repetitions.

An effect of $A\beta$ on diffusion measures might be mediated by vascular pathology, in particular cerebral amyloid angiopathy, that is, $A\beta$ accumulation in perforating vessels.³⁰ To address this possibility, we performed a post-hoc mediation analysis (R package "lavaan"; version 0.6 to 4)³¹ in samples in which simple regression analysis showed an effect of $A\beta$ on diffusion measures. Diffusion measures were entered as dependent variables, $A\beta$ as independent variable, WMH volume as mediator, and age as covariate. Standard errors were based on bootstrapping (1000 iterations).

Because amyloid pathology has been shown to strengthen the association between tau accumulation and structural tract alterations as assessed by diffusion measures,³² we performed two additional analyses within each sample. First, we conducted a sensitivity analysis restricted to amyloid-positive individuals by repeating simple regression analyses. Second, we assessed the interaction effect of tau \times $A\beta$ on diffusion measures.

Finally, because tau is a localized pathology starting in the entorhinal cortex,³³ we also performed regional analyses between voxel-wise diffusion measures and tau in the PET samples, that is, ADNI and SVCI. We used permutation test theory with a standard general linear model as implemented in "randomise" (FSL). We assessed associations between both global tau PET SUVR scores as well as regional tau PET SUVR scores in the entorhinal cortex and voxel-wise diffusion measures. The number of permutations was set at 5000. Significant voxels within the

skeletonized diffusion measure maps were identified using threshold-free cluster enhancement with 2D optimization and $P < .05$, corrected for multiple comparisons.

3 | RESULTS

Sample characteristics are summarized in Table 1. As expected, patients with genetically defined AD or SVD were considerably younger than memory clinic patients.

3.1 | SVD shows stronger associations than AD with diffusion alterations in simple regression analyses

In simple regressions, both SVD markers, that is, WMH volume and total SVD score, were consistently and strongly associated with conventional DTI measures (FAu, MDu; range of R^2_{adj} , [0.08 to 0.79]) and FW (range of R^2_{adj} , [0.18 to 0.76]) across all six samples (Figure 2, Tables S3–5 in supporting information). In contrast, AD biomarkers, that is, CSF and PET data, were not or only weakly associated with conventional DTI measures and FW (range of R^2_{adj} , [0.04 to 0.18]; Figure 2, Tables S3–5). Results were largely consistent across study samples, with a notable exception in the sample of genetically defined AD (DIAN). Here, effect sizes for $A\beta$ 42 (CSF) were similar to the effect sizes of WMH volume (Figure 2, Table S5). Associations between $A\beta$ 42, WMH volume, and diffusion measures in DIAN and DELCODE were further addressed in a post-hoc mediation analysis (see section 3.3).

3.2 | SVD and age contribute most to diffusion alterations in multivariable analyses

Using random forest regression as a multivariable method, we assessed the contribution of each AD biomarker and SVD marker to diffusion measures, while accounting for multicollinearity. In all memory clinic samples, SVD markers showed higher variable importance than AD biomarkers for alterations of conventional DTI measures (FAu and MDu; Figure 3) and FW (data not shown; nearly identical to MDu). The opposite was found only in DIAN, in which AD biomarkers showed higher variable importance. For tissue measures (FAT and MDt), interpretation of random forest regressions was not feasible, because variable importances were zero or almost zero in all samples (data not shown).

3.3 | White matter hyperintensities partially mediate the effect of $A\beta$ on diffusion alterations in genetically defined AD

For diffusion measures significantly associated with $A\beta$ 42 (CSF) in the simple regression analysis, that is, in DIAN and DELCODE, we performed a post hoc mediation analysis to explore whether these

TABLE 1 Sample characteristics

	Genetically defined AD					Genetically defined SVD
	DIAN (n = 77)	AD focused DELCODE (n = 89)	ADNI (n = 53)	SVD focused UVCI (n = 39) SVCI (n = 39)		
Age, years	42 (14)	72 (9)	78 (13)	74 (12)	79 (10)	55 (11)
Female, n (%)	40 (52)	36 (40)	25 (47)	13 (33)	28 (72)	44 (65)
Diagnosis, n (%) HC, SCD, MCI, dementia	na	4 (4), 37 (42), 33 (37), 15 (17)	22 (42), na, 23 (43), 8 (15)	0 (0), 3 (8), 18 (46), 18 (46)	0 (0), na, 22 (56), 17 (44)	na
CDR, n (%) 0, 0.5, 1, 2, 3	38 (49), 29 (38), 9 (12), 1 (1), 0 (0)	29 (33), 52 (59), 7 (8), 0 (0), 0 (0) ^a	22 (42), 23 (43), 6 (11), 2 (4), 0 (0)	1 (3), 30 (77), 8 (20), 0 (0), 0 (0)	0 (0), 26 (67), 7 (18), 6 (15), 0 (0)	57 (84), 9 (13), 1 (1), 1 (1), 0 (0)
A β -positive, n (%)	46 (60)	44 (49)	37 (70)	22 (56)	19 (49)	na
DTI						
FAu, mm ² /s	0.45 (0.03) [0.38, 0.49]	0.46 (0.03) [0.36, 0.52]	0.45 (0.04) [0.38, 0.50]	0.44 (0.04) [0.36, 0.48]	0.42 (0.04) [0.35, 0.50]	0.40 (0.06) [0.27, 0.49]
MDu, 10 ⁻⁴ mm ² /s	7.84 (0.64) [7.27, 9.31]	7.68 (0.59) [6.71, 9.72]	8.21 (0.63) [7.35, 9.77]	8.05 (0.82) [7.23, 9.72]	9.66 (0.76) [8.48, 11.0]	9.40 (1.61) [7.79, 12.89]
FAt, mm ² /s	0.55 (0.02) [0.52, 0.58]	0.56 (0.02) [0.52, 0.60]	0.57 (0.02) [0.54, 0.60]	0.56 (0.02) [0.52, 0.57]	0.59 (0.01) [0.56, 0.63]	0.55 (0.02) [0.50, 0.59]
MDt, 10 ⁻⁴ mm ² /s	5.92 (0.07) [5.80, 6.01]	5.97 (0.10) [5.51, 6.14]	6.01 (0.63) [5.94, 6.09]	5.82 (0.15) [5.63, 5.99]	6.00 (0.04) [5.91, 6.12]	5.97 (0.03) [5.89, 6.03]
FW, mm ² /s	0.18 (0.05) [0.14, 0.28]	0.16 (0.04) [0.11, 0.29]	0.20 (0.05) [0.13, 0.31]	0.22 (0.06) [0.16, 0.35]	0.25 (0.04) [0.17, 0.31]	0.29 (0.11) [0.17, 0.51]
AD markers						
CSF						
A β 40, ng/L	7634 (4516) [2215, 15622]	7942 (3229) [3721, 13358]	-	na	-	-
A β 42, ng/L	436 (332) [174, 1424]	498 (380) [183, 1317]	-	619 (279) [363, 1641]	-	-
T-tau, ng/L	97 (132) [8, 563]	425 (369) [98, 1477]	-	524 (368) [140, 1274]	-	-
P-tau, ng/L	56 (66) [14, 163]	51 (39) [16, 192]	-	67 (47) [19, 166]	-	-
PET						
[¹⁸ F]-florbetapir SUVR	-	-	1.18 (0.36) [0.90, 1.70]	-	na	-
[¹⁸ F]-florbetaben SUVR	-	-	na	-	1.38 (0.49) [1.11, 2.17]	-
[¹⁸ F]AV-1451 SUVR	-	-	1.10 (0.13) [0.86, 1.67]	-	1.11 (0.16) [0.89, 1.60]	-
SVD markers						
WMHvol, mL	2.22 (3.05) [0.00, 30.47]	2.78 (5.36) [0.03, 34.50]	3.35 (8.29) [0.00, 77.24]	15.72 (1.85) [1.34, 67.27]	32.19 (21.03) [10.48, 71.20]	71.27 (73.74) [1.09, 257.74]
SVD score, n (%) 0, 1, 2, 3, 4	67 (87), 9 (12), 1 (1), 0 (0), 0 (0)	23 (26), 33 (37), 28 (31), 3 (3), 2 (2)	8 (15), 17 (32), 18 (34), 8 (15), 2 (4)	4 (10), 15 (39), 11 (28), 6 (15), 3 (8)	0 (0), 0 (0), 0 (0), 0 (0), 39 (100)	0 (0), 16 (24), 19 (28), 17 (25), 16 (24)

Note: For numeric variables median (interquartile range) [min, max] is shown, except for age. ^aDELCODE: CDR of 1 subject missing.

Abbreviations: AD, Alzheimer's disease; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CDR, clinical dementia rating; DELCODE, DZNE-Longitudinal Cognitive Impairment and Dementia Study; DIAN, Dominantly Inherited Alzheimer's Network; DTI, diffusion tensor imaging; FAu, uncorrected fractional anisotropy; FAt, free water corrected tissue compartment of fractional anisotropy; FW, free water content; HC, healthy control; MCI, mild cognitive impairment; MDu, uncorrected mean diffusivity; MDt, free water corrected tissue compartment of mean diffusivity; na, not available; p-tau, phosphorylated- tau₁₈₁; SCD, subjective cognitive decline; SUVR, standardized uptake value ratio; SVD, small vessel disease; SVCI, Seoul Vascular Cognitive Impairment study; SVD score, total SVD score; t-tau, total tau; UVCI, Utrecht Vascular Cognitive Impairment study; WMHvol, white matter hyperintensity volume.

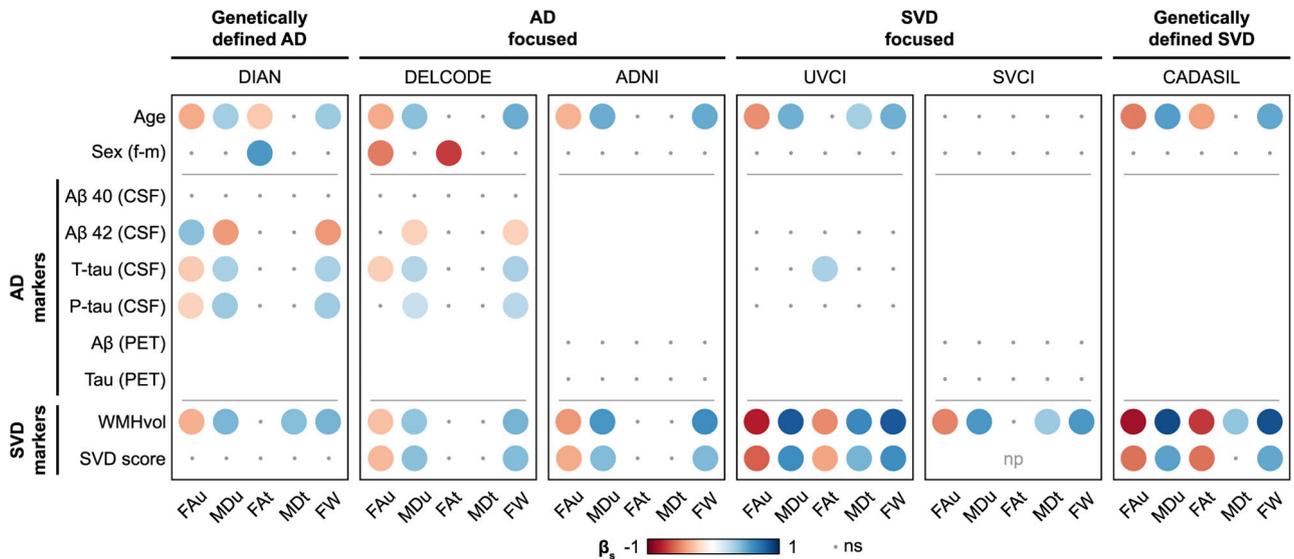


FIGURE 2 Simple regression analyses. Simple linear regression analyses between diffusion measures and Alzheimer's disease (AD) biomarkers or small vessel disease (SVD) markers. Standardized beta is represented by color. ADNI, Alzheimer's Disease Neuroimaging Initiative; β_s , standardized beta; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSF, cerebrospinal fluid; DELCODE, DZNE-Longitudinal Cognitive Impairment and Dementia Study; DIAN, Dominantly Inherited Alzheimer's Network; FAU, uncorrected fractional anisotropy; FAT, free water corrected tissue compartment of fractional anisotropy; FW, free water content; MDu, uncorrected mean diffusivity; MDT, free water corrected tissue compartment of mean diffusivity; np, not possible (all patients had the maximum score); ns, not significant; PET, positron emission tomography; p-tau, phosphorylated- tau₁₈₁; SVCI, Seoul Vascular Cognitive Impairment study; SVD score, total SVD score; t-tau, total tau; UVCi, Utrecht Vascular Cognitive Impairment study; WMHvol, white matter hyperintensity volume

associations might be mediated by vascular pathology, such as cerebral amyloid angiopathy. In DIAN, the effect of A β 42 on MDu and FW was indeed partially mediated by WMH volume (MDu: $\beta_s = -0.06$, standard error [SE] = 0.03, $P = .030$; FW: $\beta_s = -0.06$, SE = 0.03, $P = .026$). However, we also found a direct effect of A β 42 on MDu and FW (MDu: $\beta_s = -0.30$, SE = 0.12, $P = .005$; FW: $\beta_s = -0.30$, SE = 0.11, $P = .005$). For FAU, mediation analysis was not significant. As a further indication for the presence of cerebral amyloid angiopathy, most (8 out of 9) DIAN participants with cerebral microbleeds showed a strictly lobar distribution, and one participant had disseminated cortical superficial siderosis.

In DELCODE, in which simple regression analysis showed only weak effects of A β 42, none of the mediation analyses were significant (all $P > .136$).

3.4 | Tau is not associated with diffusion alterations in amyloid-positive individuals

It was recently reported that A β might strengthen the association between tau accumulation and diffusion alterations.³² We addressed this aspect in a sensitivity analysis restricted to amyloid-positive individuals (Tables S6–8, Figure S2 in supporting information). Simple linear regressions between tau and diffusion measures in amyloid-positive individuals were not significant, except for DIAN ($n = 46$; p-tau and MDu, $\beta_s = 0.32$, $R^2_{adj.} = 0.08$, $P = .031$; p-tau and FW, $\beta_s = 0.31$, $R^2_{adj.} = 0.07$, $P = .038$). In correspondence with the full DIAN sample, tau showed effect sizes comparable to those found for WMH volume (WMH volume and MDu, $\beta_s = 0.35$, $R^2_{adj.} = 0.10$, $P = .017$; WMH

volume and FW, $\beta_s = 0.37$, $R^2_{adj.} = 0.12$, $P = .011$). None of the tau \times A β interaction models with diffusion measures as dependent variables were significant in any of the samples (all $P > .051$).

3.5 | Regional tau is not associated with diffusion alterations

Tau is a localized pathology starting in the entorhinal cortex³³ and previous literature suggests localized effects of tau on white matter microstructure.^{32,34,35} We therefore performed regional analyses in the PET samples, that is, ADNI and SVCI, which allowed us to assess local tau load. Associations between regional tau PET SUVR scores in the entorhinal cortex or global tau PET SUVR scores and voxel-wise diffusion measures were not significant.

4 | DISCUSSION

We investigated the effect of AD and SVD on brain microstructure assessed by diffusion measures. As a unique feature, our study included six independently recruited samples covering the entire spectrum of AD, mixed disease, and SVD. The main finding is that in memory clinic patients, diffusion MRI alterations are largely determined by SVD. Results were consistent across all memory clinic samples, illustrating the robustness of our findings. Our study facilitates the interpretation of diffusion MRI alterations and the development toward clinical application.

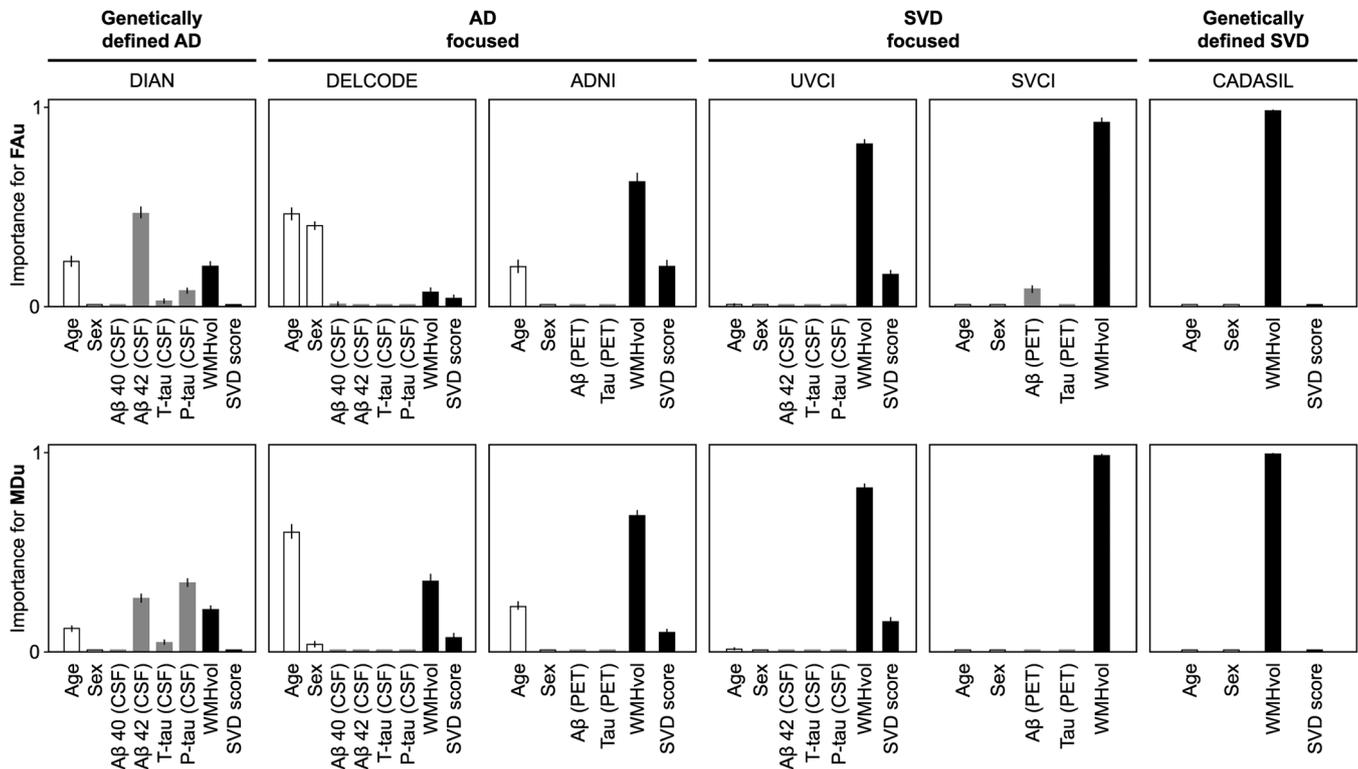


FIGURE 3 Multivariable analyses. Random forest regression analyses for estimating the relative variable importance of Alzheimer's disease (AD) biomarkers (gray bars), small vessel disease (SVD) markers (black bars), age and sex (white bars) with regard to conventional diffusion tensor imaging (DTI) measures (uncorrected fractional anisotropy (FAu), uncorrected mean diffusivity (MDu) while accounting for all other variables (conditional importance). Lines indicate the 95% confidence interval for the conditional variable importance. ADNI, Alzheimer's Disease Neuroimaging Initiative; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSF, cerebrospinal fluid; DELCODE, DZNE-Longitudinal Cognitive Impairment and Dementia Study; DIAN, Dominantly Inherited Alzheimer's Network; FAu, uncorrected fractional anisotropy; MDu, uncorrected mean diffusivity; p-tau, phosphorylated-tau₁₈₁; SVCI, Seoul Vascular Cognitive Impairment study; SVD score, total SVD score; T-tau, total tau; UVCI, Utrecht Vascular Cognitive Impairment study; WMHvol, white matter hyperintensity volume

The strong effect of SVD on diffusion measures was evident in all of the six study samples. In contrast, an association between AD and diffusion measures was only detectable in DELCODE and DIAN. While in DELCODE effect sizes of AD biomarkers were considerably smaller than those of SVD markers, effect sizes of A β 42 and WMH volume were similar in DIAN. Multivariable analyses using random forest regression showed a higher importance of SVD markers for diffusion alterations in all memory clinic samples. The only sample in which AD biomarkers had a higher variable importance was DIAN. As expected for a genetically defined sample, these patients are considerably younger than typical memory clinic patients and less likely to show age-related comorbidities, such as SVD. Still, mediation analysis in DIAN suggested a vascular contribution to diffusion alterations also in this population, as the effect of A β on diffusion alterations was partially mediated by WMH volume. This might indicate a contribution of cerebral amyloid angiopathy, a specific subtype of SVD caused by deposition of A β in perforating vessels.³⁰ Because the DIAN sample also included asymptomatic mutation carriers up to 15 years before estimated symptom onset, another explanation is that the association between A β and diffusion measures is strongest in early, preclinical AD, before A β reaches its plateau level. This view is supported by a

recent study demonstrating an association between A β and diffusion measures over the adult lifespan in cognitively healthy participants.³⁶ Conversely, a ceiling effect might hamper the detection of associations with A β in later disease stages.

Overall, we conclude that while the effect of AD on diffusion measures is apparent in DIAN patients with pure and early AD, the presence of SVD in the memory clinic samples masks the effect of AD on diffusion measures.

Seemingly in contrast with our results, associations between AD biomarkers and alterations of white matter microstructure as assessed by DTI have been previously reported in memory clinic patients,^{13,14,32,34,37-39} although some studies found no association.^{40,41} Importantly, however, only one of these studies accounted for SVD. Hence, the effect of AD on diffusion alterations might have been overestimated. Only Strain et al.³⁴ considered biomarkers of both diseases and found an association between tau PET (but not A β PET) in temporal regions and diffusion measures in temporal white matter projections, independent of WMHs. In line with our results, the effect size for WMH volume was larger than effect sizes of AD biomarkers. By considering both diseases, we conclude that SVD determines diffusion alterations to a much larger extent

than AD, even in samples in which AD was the clinically predominant disease. The strong effect of SVD has implications for future studies, which will need to take SVD into account as an important confounder, as well as for the interpretation of diffusion MRI alterations in clinical routine.

In the current study, neither the regional analysis nor the analysis in amyloid-positive individuals, in which the effect of tau was expected to be stronger,³² indicated a significant association between tau and diffusion measures. In *post mortem* studies, white matter alterations in AD patients have been attributed to axonal degeneration secondary to cortical deposition of hyperphosphorylated tau.^{42,43} Yet, *post mortem* studies by design examine patients in very late stages of AD, while our memory clinic patients were mostly in earlier disease stages. Thus, it is conceivable that our patients have not yet reached the disease stage in which associations between tau and axonal degeneration can be detected.

By design, our memory clinic samples were heterogeneous, which in our view accurately reflects a real-life memory clinic setting. To study pure forms of AD and SVD, we included genetically defined samples. Furthermore, the sensitivity analysis in subgroups with amyloid-positive individuals allowed us to study memory clinic patients who met the biological definition of AD. Although statistical power was reduced, the strong effect of SVD on diffusion measures was also confirmed in these subgroups.

Our finding that diffusion alterations are predominantly driven by SVD is also supported by a genome-wide association study in the population-based UK Biobank. Polygenic risk scores for altered DTI measures were associated with SVD-related stroke and major depressive disorder, but not with AD.⁴⁴ The study thus provided genetic evidence that mechanisms underlying diffusion alterations are shared with cerebrovascular disease.

Another aim of this study was to investigate whether free water imaging allows us to disentangle the contribution of SVD and AD. The finding that SVD markers showed strongest associations with FW corroborates previous results indicating that diffusion alterations in SVD patients are predominantly driven by an increase in the free water content.¹¹ However, our current analysis did not provide evidence that AD biomarkers are reflected in the tissue compartment. The latter result is in contrast to studies suggesting that AD-related neurodegeneration of the white matter might be specifically represented in free water corrected tissue measures: Tissue measures were associated with conversion from mild cognitive impairment to dementia in AD patients¹² and showed A β -related longitudinal changes.¹⁴ It should be noted that the current study was cross-sectional and thus we cannot exclude that the tissue compartment holds valuable information for longitudinal studies.^{12,14} Furthermore, multi-shell diffusion data, which would be necessary for more complex parametrization of the fluid compartments,⁴⁵⁻⁴⁷ was not available in the study samples. This would have allowed us to control for the effects of capillary blood flow (intravoxel incoherent motion) in the free water estimation.⁴⁷

A limitation of our study is that elevated tau (especially in CSF) is not specific for AD as it could also indicate other tauopathies, such

as Pick's disease, corticobasal degeneration, or progressive supranuclear palsy. However, the tau PET tracer ([¹⁸F]AV-1451) used mostly binds to tau deposits specific for AD.⁴⁸ Also, the focus on recruitment of clinical AD, for example, by including amnesic mild cognitive impairment in DELCODE and ADNI, clearly enriched for AD rather than other tauopathies. Another limitation is the lack of AD biomarkers in the CADASIL sample. Yet, the purpose of the CADASIL sample was to judge the effect sizes of SVD markers in genetically defined disease, that is, in young patients with pure SVD. Interestingly, we found similar effect sizes as in SVD-focused samples with mixed pathology, in particular the UVCI sample. While we also included voxel-based analyses to identify regional associations, our study mostly focused on global, whole-brain averages of diffusion measures. Thus, we cannot exclude that analyses in specific subregions will yield different results. Because of limitations in the diffusion MRI acquisition protocols (no reversed phase-encoding, directions not sampled on entire sphere), we were not able to correct for susceptibility-induced distortions or to use a more modern approach for correction of eddy current-induced distortions, motion, and outlier slices.⁴⁹ Finally, the lack of pathological confirmation of the presence and extent of AD and SVD pathology originates from the paucity of autopsy studies with high-quality, standardized *ante mortem* diffusion MRI.

The main strength of our analysis is the inclusion of multiple samples from different countries and ethnicities, covering the entire spectrum of AD, mixed disease, and SVD. This has enabled us to independently validate results and to assess both CSF and PET biomarkers of AD in a robust manner. The differences in study protocols among the six samples, such as MRI acquisition, biomarker assessment techniques, and recruitment strategies indicate that our results might be generalizable to other populations along the spectrum of AD and SVD. We also included younger individuals with genetically defined disease to minimize confounding by other age-related pathologies. Finally, the state-of-the-art diffusion imaging analysis pipeline included modern preprocessing techniques and rigorous control for confounding by CSF partial volume effects, which is crucial in patients with atrophy and therefore enlarged CSF spaces.

In conclusion, we demonstrate that the effect of SVD on diffusion alterations largely exceeds the effect of AD. Our systematic analysis contributes to the interpretation of diffusion MRI in memory clinic patients and further advances its application in clinical practice. We validate diffusion measures as markers for SVD and as valuable tools to assess the vascular contribution to AD and dementia, which still needs to be adequately explored.⁵⁰ Building upon our findings, future studies could assess if more advanced parameterization of diffusion processes, such as biophysical diffusion models, further increases the sensitivity in earlier or even asymptomatic stages.

ACKNOWLEDGMENTS

We would like to thank all the researchers and the support staff from the DIAN (https://dian.wustl.edu/wp-content/uploads/2019/04/DIAN-TU-Publications_Acknowledgement_V14.pdf), DELCODE, ADNI, Utrecht VCI study group, Seoul VCI study group, and CADASIL

study for their contributions to the present study. Investigators within DIAN, DELCODE, and ADNI contributed to the design and implementation of the respective studies and/or provided data but did not participate in analysis or writing of this report. A complete listing of the DIAN consortium and the DELCODE study group can be found in Tables S9 and 10 in supporting information and ADNI investigators at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. Members of the Utrecht VCI study group involved in the present study (in alphabetical order by department): University Medical Center Utrecht, the Netherlands, Department of Neurology: E. van den Berg, J. M. Biesbroek, M. Brundel, W. H. Bouvy, L. G. Exalto, C. J. M. Frijns, O. Groeneveld, S. M. Heringa, R. Heinen, N. Kalsbeek, L. J. Kappelle, J. H. Verwer; Department of Radiology/Image Sciences Institute: J. de Bresser, H. J. Kuijf, A. Lee-mans, P. R. Luijten, M. A. Viergever, K. L. Vincken, J. J. M. Zwanenburg; Department of Geriatrics: H. L. Koek; Hospital Diaconessenhuis Zeist, the Netherlands: M. Hamaker, R. Faaij, M. Pleizier, E. Vriens. We acknowledge the altruism of the study participants and their families.

The study was funded by a cross-border grant from the Alzheimer Forschung Initiative e.V. (#16018CB)/Alzheimer Nederland AN WE.03-2016-1. BG and MDu were supported by the German Research Foundation (DU1626/1-1). The research of GJB is also supported by VICI grant 918.16.616 from NWO, the Netherlands Organization for Scientific Research. DIAN: Data collection and sharing for this project was supported by The Dominantly Inherited Alzheimer's Network (DIAN, U19AG032438) funded by the National Institute on Aging (NIA), the German Center for Neurodegenerative Diseases (DZNE), Raul Carrea Institute for Neurological Research (FLENI). Partial support by the Research and Development Grants for Dementia from Japan Agency for Medical Research and Development, AMED, and the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI). This article has been reviewed by DIAN Study investigators for scientific content and consistency of data interpretation with previous DIAN Study publications. DELCODE: The DELCODE study was funded by the German Center for Neurodegenerative Diseases (DZNE), Study-ID: BN012DZNE. We acknowledge support from the Max-Delbrück-Centrum für Molekulare Medizin in der Helmholtz-Gemeinschaft (MDC) and the Freie Universität Berlin Center for Cognitive Neuroscience Berlin (CCNB). ADNI: Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI; National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bio-engineering, and through generous contributions from the following: AbbVie; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnos-

tics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. SVCI: This research was funded by Research of Korea Centers for Disease Control and Prevention (2018-ER6203-01).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Finsterwalder S, Vlegels N, Gesierich B, et al. Small vessel disease more than Alzheimer's disease determines diffusion MRI alterations in memory clinic patients. *Alzheimer's Dement.* 2020;1-12.
<https://doi.org/10.1002/alz.12150>