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ORIGINAL RESEARCH

Microvascular Dysfunction and Whole-Brain White Matter Connectivity: The Maastricht Study

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BACKGROUND: Microvascular dysfunction is involved in the development of various cerebral disorders. It may contribute to these disorders by disrupting white matter tracts and altering brain connectivity, but evidence is scarce. We investigated the association between multiple biomarkers of microvascular function and whole-brain white matter connectivity.

METHODS AND RESULTS: Cross-sectional data from The Maastricht Study, a Dutch population-based cohort (n=4326; age, 59.4±8.6 years; 49.7% women). Measures of microvascular function included urinary albumin excretion, central retinal arteriolar and venular calibers, composite scores of flicker light–induced retinal arteriolar and venular dilation, and plasma biomarkers of endothelial dysfunction (intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, and von Willebrand factor). White matter connectivity was calculated from 3T diffusion magnetic resonance imaging to quantify the number (average node degree) and organization (characteristic path length, global efficiency, clustering coefficient, and local efficiency) of white matter connections. A higher plasma biomarkers of endothelial dysfunction composite score was associated with a longer characteristic path length (β per SD, 0.066 [95% CI, 0.017–0.114]) after adjustment for sociodemographic, lifestyle, and cardiovascular factors but not with any of the other white matter connectivity measures. After multiple comparison correction, this association was nonsignificant. None of the other microvascular function measures were associated with any of the connectivity measures.

CONCLUSIONS: These findings suggest that microvascular dysfunction as measured by indirect markers is not associated with whole-brain white matter connectivity.

Key Words: cerebral microcirculation ■ cohort ■ diffusion tensor imaging ■ microvascular dysfunction ■ white matter connectivity

Cerebral disorders such as dementia and late-life depression may, in part, share a microvascular origin.[1–4] A hypothesized pathway by which cerebral microvascular dysfunction may lead to the development of cerebral disorders is via alterations in the structural organization of cerebral white matter networks, also named white matter connectivity.[1] Altered white matter connectivity is an important characteristic

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CLINICAL PERSPECTIVE

What Is New?

- Microvascular dysfunction, as assessed by kidney function, retinal markers, and plasma biomarkers of endothelial dysfunction, was not consistently associated with whole-brain white matter connectivity.
- Only plasma biomarkers of endothelial dysfunction were associated with 1 measure of whole-brain white matter connectivity, but this association was no longer statistically significant after multiple comparison correction.

What Are the Clinical Implications?

- Future studies on the association of direct measures of cerebral microvascular function and altered connectivity are needed.

Nonstandard Abbreviations and Acronyms

CRAE	central retinal arteriolar calibers/equivalents
CRVE	central retinal venular calibers/equivalents
DTI	diffusion tensor imaging

of cognitive dysfunction,[2] dementia,[3] and depression.[4,5] Yet evidence on the association between cerebral microvascular dysfunction and white matter connectivity is scarce.

The cerebral microvasculature is involved in the regulation of many processes, including cerebral perfusion, neurovascular coupling, blood–brain barrier permeability, and cerebral autoregulation.[6] Impairment in any of these functions can be considered cerebral microvascular dysfunction.[6] The brain's white matter may be particularly vulnerable to the effects of microvascular dysfunction because blood perfusion is typically lower in white matter than in gray matter.[7] White matter tracts are crucial for efficient signal trafficking between brain regions, and disruption of these tracts may alter brain function. Whole-brain white matter connectivity can be investigated using diffusion tensor imaging (DTI). DTI can quantify the number (node degree) and organization (characteristic path length, global efficiency, clustering coefficient, and local efficiency) of white matter connections.[8]

Previous studies[9–13] have found an association between markers of cerebral small-vessel disease, notably higher white matter hyperintensity volume, and some measures of altered brain connectivity. However, cerebral small-vessel disease markers are indirect markers that may be related to small-vessel pathology and represent a late disease stage when irreversible brain damage is already present.

Another approach to evaluate the association between microvascular dysfunction and altered connectivity in the brain is to quantify microvascular function noninvasively in various organs other than the brain.[14] Microvascular dysfunction may be a generalized phenomenon,[15] and such markers may, therefore, either directly or indirectly represent microvascular function in the brain. These markers include albuminuria (urinary albumin excretion), central retinal arteriolar and venular calibers/equivalents (CRAE and CRVE), flicker light-induced retinal arteriolar and venular dilation, and plasma biomarkers of endothelial dysfunction (ie, soluble intercellular adhesion molecule-1, soluble vascular adhesion molecule-1, soluble E-selectin, and von Willebrand factor).[14] Retinal arteriolar and venular dilation response and diameters are closely linked to the brain microvasculature, and may reflect its structure and function.[16,17] In addition, to the extent that microvascular dysfunction is a generalized phenomenon,[15] urinary albumin excretion,[18] and plasma biomarkers of endothelial dysfunction[19] may also reflect cerebral microvascular dysfunction. In accordance, previous studies have found associations between each of these markers and presence of structural cerebral small-vessel disease magnetic resonance imaging (MRI) markers.[18,20–25]

Using these proxies of microvascular dysfunction and leveraging cross-sectional data from a large population-based cohort, this study investigated the association between microvascular dysfunction with DTI-determined whole-brain white matter connectivity.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

We used data from the Maastricht Study, an observational population-based cohort study. The rationale and methodology have been described previously.[26] In brief, the study focuses on the pathogenesis, pathophysiology, complications, and comorbidities of type 2 diabetes and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands (province of Limburg). Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known type 2 diabetes status, with an oversampling of individuals

with type 2 diabetes for efficiency reasons. The present report includes cross-sectional data from the first 7689 participants, who completed the baseline survey between November 2010 and December 2017. The examinations of each participant were performed within a time window of 3 months. MRI measurements were implemented from December 2013 onward and are available for 5144 of 7689 participants (66.9%). The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131 088-105 234-PG). All participants gave written informed consent.

Microvascular Function Measures

All participants were asked to refrain from smoking and drinking caffeine-containing beverages 3 hours before the measurements.[14] A light meal was allowed ≥90 minutes before the start of the measurements. For retinal measurements, pupils were dilated with 0.5% tropicamide and 2.5% phenylephrine ≥15 minutes before the start of the examination.

Urinary Albumin Excretion

To assess urinary albumin excretion, participants were requested to collect two 24-hour urine samples. Urinary albumin concentration was measured with a standard immunoturbidimetric assay by an automatic analyzer (due to a change in supplier, by the Synchron LX20 [Beckman Coulter, Brea, CA] and the Cobas 6000 [Roche Diagnostics, Indianapolis, IN]) and multiplied by collection volume to obtain 24-hour urinary albumin excretion.[27] A urinary albumin excretion below the detection limit of the assay was set at 1.5 mg/L (2 mg/L for the Beckman Synchron LX20 and 3 mg/L for the Roche Cobas 6000) before multiplying the collection volume. Only urine collections with a collection time between 20 and 28 hours were considered valid. If needed, urinary albumin excretion was extrapolated to 24-hour excretion. For this study, urinary albumin excretion was preferably based on the average of 2 (available in 92.6% of 4326 included participants) 24-hour collections.

Retinal Microvascular Calibers

Fundus photography of both eyes was performed with the use of an autofocus, shot, and tracker 45-degree camera (Model AFC-230; Nidek, Birmingham, AL) in an optic disc-centered field of view, as described previously.[14] Retinal microvascular calibers were measured using the RHINO software (Eindhoven University of Technology, Eindhoven, the Netherlands).[16] The diameters of the 6 largest arterioles and venules passing through an area 0.5 to 1 disc diameter from the optic margin were measured and summarized as CRAE and CRVE.[14] Between November 2010 and September 2013, either the left or right eye was chosen at random for measurement of CRAE and CRVE. From November 2013 onward, CRAE and CRVE measurements were obtained in both eyes; for these data, we used the average of both eyes for each measurement in the present study (available in 54.7% of 4010 included participants).

Flicker Light–Induced Retinal Arteriolar and Venular Dilation

We measured retinal arteriolar and venular dilation to flicker light exposure by the Dynamic Vessel Analyzer (Imedos, Jena, Germany), as described previously.[14] Investigation of either the left or right eye was chosen at random. A baseline recording of 50 seconds was followed by 40-second flicker light exposure and a subsequent 60-second recovery period. We calculated baseline diameters (in measurement units) as the average diameter during the 20- to 50-second recording. For both the arteriolar and venular dilation, we calculated absolute dilation over baseline using the maximal dilation achieved at time points 10 and 40 seconds during the flicker stimulation period.[28,29]

Plasma Biomarkers of Endothelial Dysfunction

We measured 4 plasma biomarkers of endothelial dysfunction, that is, soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, soluble E-selectin, and von Willebrand factor, as described previously.[14] Soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, and soluble E-selectin were measured in EDTA plasma samples with commercially available 4-plex sandwich immunoassay kits with different standards and antibodies (Meso Scale Discovery, Rockville, MD).[14] Von Willebrand factor was quantified in citrate plasma using ELISA (Dako, Glostrup, Denmark).[14]

Whole-Brain White Matter Connectivity

Brain MRI was performed on a 3T MRI scanner (Magnetom Prisma-fit Syngo MR D13D; Siemens, Erlangen, Germany) using a 64-element head and neck coil for parallel imaging. A 3-dimensional T1-weighted sequence was acquired for anatomic reference. DTI comprised a diffusion sensitized echo-planar imaging sequence, with 3 minimally diffusion-weighted images (β=0 s/mm^2). Preprocessing of the DTI data to calculate structural brain graph measures has been previously explained in detail.[30,31] In short, DTI data were used to perform whole-brain tractography using constrained spherical deconvolution. After transformation to DTI data, the Automated Anatomical Labeling 2 Atlas[32]

was transformed to define 94 (sub)cortical brain regions. Next, connection strength between each pair of brain regions was defined as tract volume normalized to the intracranial volume. A structural brain graph, in which the brain regions were represented as nodes and the connection strength as edges, was created from which the following structural brain connectivity measures were calculated: average node degree, characteristic path length, global efficiency, clustering coefficient, and local efficiency. Average node degree is a measure for the average number of edges connected to a node, calculated as the average of the node degree for each Automated Anatomical Labeling 2 Atlas region.[30] In a network with a high average node degree, brain regions are connected to many other brain regions in that network (ie, strong innervation).[8] Characteristic path length and global efficiency quantify the exchange of information on the whole network scale, and clustering coefficient and local efficiency assess the presence of local densely interconnected groups of brain regions.[8] Characteristic path length was calculated as the minimum number of connections that must be traversed on average to go from one region to another; global efficiency as the inverse of the average shortest path length calculated over the entire brain; clustering coefficient as the number of connections between the nearest neighbors of a region as a proportion of the maximum number of possible connections; and local efficiency as the inverse of the average shorted path connecting all neighbors of a region.[30]

Covariates

We assessed socioeconomic status (education level and income), smoking status (never, former, current), alcohol use (none, low, high), dietary habits, moderate to vigorous physical activity, and prior cardiovascular disease by self-administered questionnaire. Education level was classified into 3 groups: low (none, primary, or lower vocational education only), intermediate (intermediate general secondary, intermediate vocational, or higher general secondary education) and high (higher vocational education or university level of education). Income level was calculated as the household income divided by the square root of the household size. Alcohol use was defined as nonconsumer, low consumer (≤7 alcoholic drinks/wk for women; ≤14 alcoholic drinks/wk for men), or high consumer (>7 alcoholic drinks/wk for women; >14 alcohol drinks/wk for men). Dietary habits were assessed with the Dutch Healthy Diet index sum score, a measure of adherence to the Dutch dietary guidelines 2015.[33] Physical activity was assessed by use of the Community Healthy Activities Model Program for Seniors questionnaire.[34] Medication use was assessed from medication boxes brought to the clinic.[26] Blood pressure, body mass index, and lipid levels were measured using standardized methods as described previously.[26] We defined hypertension as an office blood pressure of ≥140/90 mm Hg, use of antihypertensive medication, or both. We used a 2-hour oral glucose tolerance test[26] to classify participants as having normal glucose metabolism, prediabetes (ie, impaired fasting glucose or impaired glucose tolerance) or type 2 diabetes on the basis of the World Health Organization 2006 criteria.[35] White matter hyperintensity volume was measured on brain MRI, as described previously.[36] Estimated glomerular filtration rate was estimated with the Chronic Kidney Disease Epidemiology Collaboration serum creatinine equation.[37]

Statistical Analysis

Urinary albumin excretion was log-transformed to normalize its skewed distribution. Prior studies have reported different directions of the association between CRAE and brain outcomes. Both larger[38–40] and smaller[38–40] CRAE have been associated with features of cerebral small-vessel disease and dementia. We therefore did not inverse CRAE values. We inversed flicker light–induced retinal dilation so that higher values indicate worse microvascular function.

We calculated composite scores for (1) the flicker light–induced retinal dilation and (2) the plasma biomarkers of endothelial dysfunction, as done previously.[41,42] We hypothesized that the flicker light–induced arteriolar and venular retinal dilation and the plasma biomarkers of endothelial dysfunction each were associated with whole-brain white matter connectivity on the basis of shared underlying mechanisms. Furthermore, using a composite score reduces the influence of the biological variability of the components and increases statistical efficiency. The composite scores were calculated by summation and averaging of the *Z* scores of the flicker light–induced retinal arteriolar and venular dilation, and the 4 plasma biomarkers of endothelial dysfunction, respectively. These averages were then standardized into composite scores.

We used linear regression analysis to estimate standardized regression coefficients and 95% CIs for the association between urinary albumin excretion, CRAE and CRVE, the flicker light–induced retinal dilation composite score, and the plasma biomarkers of endothelial dysfunction composite score on the one hand, and connectivity measures on the other. Assumptions for linear regression analysis were checked and verified (linearity, independence, and homoscedasticity of errors, normal distribution of errors, absence of multicollinearity, and outlier diagnostics). All analyses were adjusted for the following potential confounders: age, sex, and glucose metabolism status (model 1)

and additionally for education level, body mass index, smoking, alcohol use, moderate to vigorous physical activity, dietary habits, total to high-density lipoprotein cholesterol ratio, use of lipid-modifying medication, prior cardiovascular disease, systolic blood pressure, use of antihypertensive medication, and time between baseline examination and MRI examination (model 2). These covariates were selected on the basis of their biological plausibility since they are known to be associated with both microvascular function[43–46] and brain connectivity.[11,30,47] We adjusted all analyses for the time between baseline examination and MRI examination because, for logistical reasons, MRI examinations took place an average of 1.2 years (range, 0.3–5.5 years) after the baseline examinations.

We evaluated whether the investigated associations differed by age, sex, glucose metabolism status, white matter hyperintensity volume, and prior cardiovascular disease by including interaction terms between these variables and the measures of microvascular function in the fully adjusted models (model 2). We additionally stratified all analyses by type 2 diabetes status.

We performed several sensitivity analyses. First, we repeated the analysis with the individual flicker light–induced retinal arteriolar and venular dilation, and the individual plasma biomarkers of endothelial dysfunction instead of using composite scores as determinants. Second, we adjusted for socioeconomic status assessed by income level instead of education level, for mean 24-hour systolic blood pressure instead of office systolic blood pressure, and for waist circumference instead of body mass index. Third, we additionally adjusted for white matter hyperintensity volume. White matter hyperintensity volume may act as a confounder, an antecedent, or a mediator. Fourth, to minimize potential confounding effects by image quality, we additionally adjusted for MRI quality and MRI patch update. Fifth, we used microalbuminuria defined as ≥30 mg/24 h versus <30 mg/24 h as the determinant instead of urinary albumin excretion per mg/24 h.[43] Sixth, we repeated the analysis with flicker light–induced retinal dilation expressed as percentage dilation over baseline on the basis of the average dilation achieved at time points 10 and 40. This analysis was done to account for interindividual variation in the curve shape during dilation.[14] Seventh, we additionally adjusted for estimated glomerular filtration rate. Eighth, we conducted post hoc analyses to evaluate region-specific brain white matter connectivity measures (ie, node degree in the regions anterior cingulate cortex, limbic system, medial temporal lobe, and prefrontal cortex).

Ninth, we repeated the primary analysis with Bonferroni correction for multiple testing. We did not correct for multiple testing in the primary analysis due to the explorative nature of this study. In addition, we performed principal component analysis to test a different method of dimension reduction for the plasma endothelial dysfunction biomarker component score. Pearson correlation coefficients were calculated to explore the correlation between plasma biomarkers of endothelial dysfunction and the flicker light–induced dilatation markers. No missing values were imputed in the data set. We then repeated the primary analysis with the derived component score.

Analyses were performed using SPSS software (version 25; IBM, Chicago, IL). An α level of <0.05 was considered statistically significant in 2-sided tests for both main associations and for interaction terms.

RESULTS

Figure 1 shows the flowchart of the study population. The total study population included 4345 individuals with available data on the whole-brain white matter connectivity measures, all potential covariates, and at least 1 measure of microvascular dysfunction. Urinary albumin excretion was available in 4326, CRAE and CRVE in 4010, flicker light–induced retinal dilation in 3238, and plasma biomarkers of endothelial dysfunction in 2071 individuals. These subgroups based on microvascular dysfunction biomarker availability were comparable regarding age, sex, and cardiovascular risk profile (Table S1). Individuals excluded due to missing data were more likely to be older, less educated, and had a worse cardiovascular risk profile compared with those without missing data.

The Table shows the characteristics of the subpopulation on urinary albumin excretion and according to a higher or lower average node degree. The mean age (SD) was 59.4 (8.6) years, and 49.7% were women (Table). Tables S2 through S4 show the characteristics of the subpopulations on CRAE and CRVE, flicker light–induced retinal dilation, and plasma biomarkers of endothelial dysfunction. Individuals with a lower average node degree compared with those with a higher average node degree were more likely to be older, had a lower education level, and had a worse cardiovascular risk profile.

Urinary albumin excretion, CRAE and CRVE, and the flicker light–induced retinal dilation composite score were not associated with any of the connectivity measures, adjusting for age, sex, and glucose metabolism status (Figure 2, model 1). Further adjustment for lifestyle and cardiovascular factors did not change the results (Figure 2, model 2). A higher plasma biomarkers of endothelial dysfunction composite score was associated with a longer characteristic path length (β per SD, 0.066 [95% CI, 0.017–0.114]) but not with any of the other white matter connectivity measures (Figure 2, models 1 and 2).

We found no consistent interactions of microvascular dysfunction with age, sex, glucose metabolism

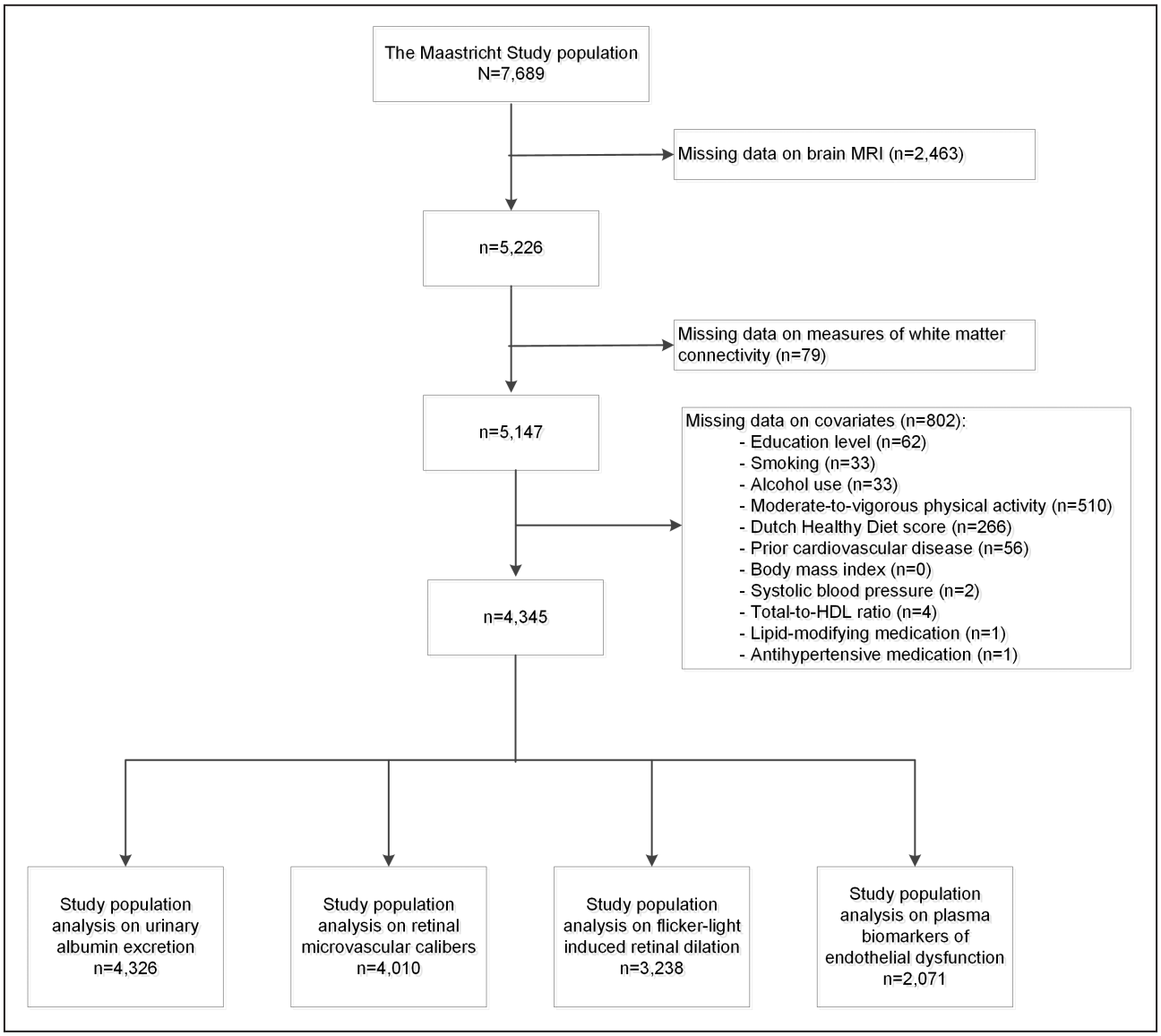

Figure 1. Flowchart derivation of the study populations.
Missing data not mutually exclusive. HDL indicates high-density lipoprotein; and MRI, magnetic resonance imaging.

status, white matter hyperintensity volume, or prior cardiovascular disease with any of the connectivity measures (Table S5). Stratification by type 2 diabetes status led to qualitatively similar results as compared with the primary analysis. Of note, a higher plasma biomarkers of endothelial dysfunction composite score was associated with longer characteristic path length in individuals without type 2 diabetes only (Table S6).

Sensitivity Analysis

Neither flicker light–induced retinal arteriolar or venular dilation were associated with any of the white matter connectivity measures (Figure S1). Of the individual plasma biomarkers of endothelial dysfunction, higher levels of soluble vascular cell adhesion molecule-1 were associated with a longer characteristic path length but not with any of the other white matter connectivity measures (Figure S2). Results showed similar patterns across all additional sensitivity analyses (Tables S7 through S9). When using Bonferroni correction for multiple testing, all *P* values for the primary analysis became nonsignificant, including the *P* value for the analysis on plasma endothelial dysfunction biomarkers and characteristic path length (*P*=0.129). Post hoc analyses did not show evidence for an association between microvascular function measures and region-specific connectivity measures (Table S10). Pearson correlation coefficients showed a moderate correlation between the different plasma biomarkers, and only a

Table. Characteristics of the Subsample of Participants With Available Data on Urinary Albumin Excretion

	Total study population (n=4326)	Average node degree median or greater* (n=2222, 51.4%)	Average node degree less than median* (n=2104, 48.6%)	*P* value†
Demographics				
Age, y	59.4 (8.6)	57.7 (8.4)	61.2 (8.5)	<0.001
Female sex, n (%)	2151 (49.7)	1158 (52.1)	993 (47.2)	0.001
Education level				
Low, n (%)	1336 (30.9)	629 (28.3)	707 (33.6)	0.001
Intermediate, n (%)	1230 (28.4)	646 (29.1)	584 (27.8)	
High, n (%)	1760 (40.7)	947 (42.6)	813 (38.6)	
Lifestyle variables				
Smoking status				
Never, n (%)	1721 (39.8)	946 (42.6)	775 (36.8)	0.001
Former, n (%)	2122 (49.1)	1042 (46.9)	1080 (51.3)	
Current, n (%)	483 (11.2)	234 (10.5)	249 (11.8)	
Alcohol use				
None, n (%)	713 (16.5)	357 (16.1)	356 (16.9)	0.004
Low, n (%)	2550 (58.9)	1361 (61.3)	1189 (56.5)	
High, n (%)	1063 (24.6)	504 (22.7)	559 (26.6)	
Moderate to vigorous physical activity, min/wk	270 (135–480)	285 (180–480)	270 (135–465)	0.001
Dutch Healthy Diet score	77.1 (14.4)	77.0 (14.5)	77.2 (14.4)	0.608
Clinical characteristics				
Glucose metabolism status				
Normal glucose metabolism, n (%)	2814 (65.0)	1560 (70.2)	1254 (59.6)	<0.001
Prediabetes, n (%)	641 (14.8)	321 (14.4)	320 (15.2)	
Type 2 diabetes, n (%)	850 (19.6)	334 (15.0)	516 (24.5)	
Other types of diabetes, n (%)	21 (0.5)	7 (0.3)	14 (0.7)	
Hypertension, n (%)	2178 (50.3)	1022 (46.0)	1156 (54.9)	<0.001
Prior cardiovascular disease, n (%)	528 (12.2)	233 (10.5)	295 (14.0)	<0.001
Body mass index, kg/m^2	26.5 (4.1)	26.4 (4.0)	26.7 (4.2)	0.017
Systolic blood pressure, mm Hg	133.0 (17.3)	131.8 (16.9)	134.2 (17.5)	<0.001
Diastolic blood pressure, mm Hg	75.5 (9.6)	75.9 (9.7)	75.1 (9.5)	0.003
Total to HDL cholesterol ratio	3.6 (1.2)	3.6 (1.2)	3.6 (1.2)	0.269
Lipid-modifying medication, n (%)	1118 (27.5)	518 (23.3)	670 (31.8)	<0.001
Antihypertensive medication, n (%)	1424 (32.9)	623 (28.0)	801 (38.1)	<0.001
eGFR, mL/min/1.73 m^2	82.3 (13.6)	83.3 (13.1)	81.3 (14.1)	<0.001
Microvascular dysfunction measures				
Urinary albumin excretion, mg/24 h	5.3 (3.4–9.6)	5.1 (3.4–9.0)	5.5 (3.5–10.2)	0.001
Central retinal arteriolar calibers, µm	138.5 (19.6)	138.9 (19.1)	138.0 (20.21)	0.131
Central retinal venular calibers, µm	209.0 (29.8)	209.6 (29.0)	208.3 (30.6)	0.161
Flicker light–induced arteriolar dilation, measurement unit	4.49 (3.74)	4.61 (3.74)	4.35 (3.73)	0.042
Flicker light–induced venular dilation, measurement unit	7.58 (4.23)	7.71 (4.24)	7.44 (4.21)	0.056
Flicker light–induced retinal dilation composite score, mean (SD)	0.00 (1.00)	−0.04 (1.01)	0.05 (0.99)	0.010
sICAM-1, ng/mL	343.9 (88.1)	338.9 (82.3)	348.5 (93.0)	0.013
sVCAM-1, ng/mL	424.2 (94.3)	422.4 (92.1)	426.0 (96.4)	0.388
sE-selectin, ng/mL	113.1 (62.1)	109.4 (54.5)	116.5 (68.3)	0.008

(*Continued*)

Table. Continued

	Total study population (n=4326)	Average node degree median or greater* (n=2222, 51.4%)	Average node degree less than median* (n=2104, 48.6%)	*P* value†
von Willebrand factor, n (%)	129.1 (47.0)	125.8 (45.2)	132.2 (48.5)	0.002
Plasma biomarkers of endothelial dysfunction composite score, mean (SD)	0.00 (1.00)	−0.08 (0.89)	0.07 (1.09)	0.001
White matter connectivity measures				
Number of connections				
Average node degree	17.77 (0.35)	18.02 (0.13)	17.50 (0.31)	<0.001
Organization of connections				
Characteristic path length	1.43 (0.14)	1.42 (0.13)	1.44 (0.15)	<0.001
Global efficiency	0.84 (0.03)	0.84 (0.02)	0.84 (0.03)	0.722
Clustering coefficient	2.31 (0.08)	2.27 (0.05)	2.35 (0.08)	<0.001
Local efficiency	1.49 (0.04)	1.47 (0.02)	1.52 (0.04)	<0.001

Data are mean (SD) or median (interquartile range). eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; and sVCAM-1, soluble vascular cell adhesion molecule-1.

*The median of average node degree was 17.83.

†*P* values comparing the group with an average node degree ≥median to the group with an average node degree <median were derived from performing independent sample *t*-tests and Mann–Whitney *U* tests for continuous variables, and Chi-square tests for categorical variables.

weak or no correlation between flicker light–induced retinal arteriolar and venular dilatation on the one hand and the plasma biomarkers on the other (Figure S3). Principal component analysis identified a principal component that explained 45.7% of the total variance with an eigenvalue of 1.8 (Figures S4 and S5). Linear regression analyses using the principal component instead of the plasma biomarkers of endothelial dysfunction composite score led to comparable results (Table S11).

DISCUSSION

In this large population-based study, urinary albumin excretion, CRAE, CRVE, and flicker light–induced retinal dilation, were not associated with whole-brain white matter connectivity, as quantified by the number of connections (average node degree), and the organization of connections, that is, characteristic path length, global efficiency, clustering coefficient, and local efficiency. Endothelial dysfunction, as quantified by four plasma biomarkers (soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, soluble E-selectin, and von Willebrand factor), was associated with a longer characteristic path length, but not with other white matter connectivity measures. After multiple comparison correction, this association turned nonsignificant. A longer characteristic path length is indicative for a topographically less integrated and less efficient network.[48] This result might indicate that endothelial dysfunction contributes to an altered organization of white matter connections.

While we are not aware of other studies that investigated the association between these measures of microvascular dysfunction and white matter connectivity, a few studies[9–11] investigated the association between white matter hyperintensity volume, a well-accepted marker of cerebral small-vessel pathology,[6] and white matter connectivity. For example, a study using UK Biobank data[10] and the Hamburg city health study[9] found that larger white matter hyperintensity volume was associated with *weaker global* efficiency (indicating longer path lengths between brain regions), but they did not evaluate local efficiency. In addition, the Hamburg city health study[9] found that larger white matter hyperintensity volume was associated with a higher clustering coefficient (indicating a higher number of connections between the nearest neighbors of a region). A prior analysis from the Maastricht Study[11] found that larger white matter hyperintensity volume was associated with *higher local* efficiency (indicating stronger/shorter paths between local neighboring brain regions) but not with average node degree or global efficiency. However, these results are difficult to compare because of the different methods used to quantify white matter connectivity, including the use of different brain atlases to define regions and different network thresholding methods. Therefore, this issue requires further study.

A potential association of higher plasma biomarkers of endothelial dysfunction with longer characteristic path length only and not with the other connectivity measures is difficult to interpret but may be explained in several ways. Compared with albuminuria and the retinal measures of microvascular dysfunction, plasma biomarkers of endothelial dysfunction might be more specific or earlier markers of cerebral microvascular dysfunction, as they are highly responsive to inflammation and play an important role in adhesion and

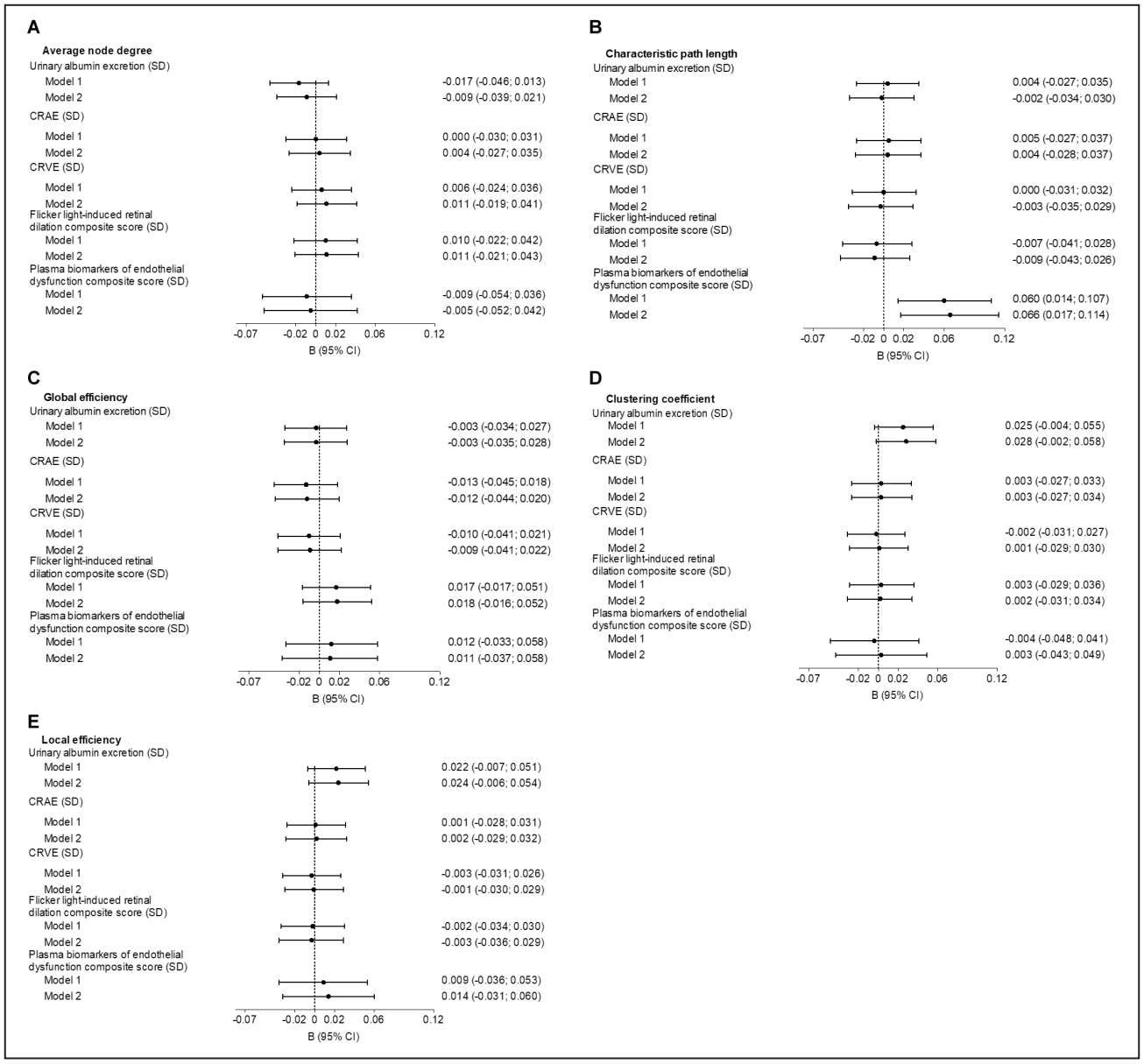

Figure 2. Associations between microvascular function measures and average node degree (A), characteristic path length (B), global efficiency (C), clustering coefficient (D) and local efficiency (E).
Results are expressed as SD difference in the white matter connectivity measures per SD log-transformed mg/24 h higher urinary albumin excretion, per SD larger CRAE and larger CRVE, per SD lower flicker light–induced retinal dilation composite score, and per SD higher plasma biomarkers composite score. Model 1 adjusted for age, sex, and glucose metabolism status. Model 2 additionally adjusted for education level, body mass index, smoking, alcohol use, moderate to vigorous physical activity, dietary habits, total to high-density lipoprotein cholesterol ratio, use of lipid-modifying medication, prior cardiovascular disease, systolic blood pressure, use of antihypertensive medication, and time between baseline examination and magnetic resonance imaging examination. CRAE indicates central retinal arteriolar calibers/equivalents; and CRVE, central retinal venular calibers/equivalents.

migration of leukocytes.[19,49] Aside from that, there may be several reasons why we found an association with characteristic path length only. First, the interscan reproducibility is higher for characteristic path length compared with the other white matter connectivity measures used in this study.[50] This may enhance the ability to detect associations with characteristic path length. Second, characteristic path length is a measure of global connectedness of the brain that quantifies the exchange of information on the whole network scale. It therefore might be an early, more sensitive marker of endothelial dysfunction–related white matter integrity damage than some other white matter connectivity measures that indicate the level of connectivity on a more local scale (ie, local efficiency and clustering coefficient). Third, there may be no relationship between endothelial dysfunction and whole-brain white matter connectivity, and the association with characteristic

path length may represent a false-positive finding, as highlighted by the multiple comparison correction results. Future cross-sectional and longitudinal studies are needed to further understand the role of microvascular dysfunction in the development of cerebral disorders. For instance, studies using more direct measures of cerebral microvascular function such as dynamic contrast-enhanced MRI to assess blood–brain barrier permeability,[51,52] or high-resolution (7T) MRI to assess cerebrovascular reactivity and microvascular perfusion at the tissue level[6] are needed.

Strengths of this study include the large population-based sample, the comprehensive assessment of microvascular function in various microvascular beds, and the assessment of various measures of whole-brain white matter connectivity. The present study also has several limitations. First, the analyses were based on cross-sectional data, limiting the ability to infer temporality. Second, we evaluated the association of microvascular dysfunction with measures of whole-brain connectivity. We cannot exclude the possibility that microvascular dysfunction may affect connectivity in specific brain regions through a network-specific pattern. This issue requires further study. Third, we did not adjust the analyses for multiple testing, and this may have increased the risk of a false-positive finding. Fourth, individuals excluded from the analyses due to missing data were older, had a lower education level, and had a worse cardiovascular risk profile compared with those included. This selection may have contributed to a lower variation in whole-brain white matter connectivity or microvascular function measures and hindered our ability to detect consistent associations. Fifth, the study population mostly consisted of White individuals; therefore, the results may not apply to other racial and ethnic groups.

Conclusions

In the present study, only a composite score of plasma biomarkers of endothelial dysfunction was associated with a longer characteristic path length, that is, a topographically less integrated and less efficient cerebral network. However, this association was no longer statistically significant after multiple comparison correction. These findings suggest that microvascular dysfunction, as quantified by a large set of indirect measures, is not associated with whole-brain white matter connectivity. Future studies should investigate the association between direct measures of cerebral microvascular function, such as dynamic contrast-enhanced MRI to assess blood–brain-barrier permeability or high-resolution (7T) MRI to assess cerebrovascular reactivity and microvascular perfusion at the tissue level, and white matter connectivity.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S11
Figures S1–S5

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