ORIGINAL RESEARCH ARTICLE

Cerebral Perfusion and the Risk of Dementia

A Population-Based Study

BACKGROUND: Cerebral hypoperfusion has previously been associated with mild cognitive impairment and dementia in various cross-sectional studies, but whether hypoperfusion precedes neurodegeneration is unknown. We prospectively determined the association of cerebral perfusion with subsequent cognitive decline and development of dementia.

METHODS: Between 2005 and 2012, we measured cerebral blood flow by 2-dimensional phase-contrast magnetic resonance imaging in participants of the population-based Rotterdam Study without dementia. We determined the association of cerebral perfusion (mL/100mL/min) with risk of dementia (until 2015) using a Cox model, adjusting for age, sex, demographics, cardiovascular risk factors, and apolipoprotein E genotype. We repeated analyses for Alzheimer disease and accounting for stroke. We used linear regression to determine change in cognitive performance during 2 consecutive examination rounds in relation to perfusion. Finally, we investigated whether associations were modified by baseline severity of white matter hyperintensities.

RESULTS: Of 4759 participants (median age 61.3 years, 55.2% women) with a median follow-up of 6.9 years, 123 participants developed dementia (97 Alzheimer disease). Lower cerebral perfusion was associated with higher risk of dementia (adjusted hazard ratio, 1.31; 95% confidence interval per standard deviation decrease, 1.07–1.61), similar for Alzheimer disease only, and unaltered by accounting for stroke. Risk of dementia with hypoperfusion was higher with increasing severity of white matter hyperintensities (with severe white matter hyperintensities; hazard ratio, 1.54; 95% confidence interval, 1.11–2.14). At cognitive reexamination after on average 5.7 years, lower baseline perfusion was associated with accelerated decline in cognition (global cognition: β=−0.029, P=0.003), which was similar after excluding those with incident dementia, and again most profound in individuals with higher volume of white matter hyperintensities (P value for interaction=0.019).

CONCLUSIONS: Cerebral hypoperfusion is associated with accelerated cognitive decline and an increased risk of dementia in the general population.

Frank J. Wolters, MD
Hazel I. Zonneveld, MD
Albert Hofman, PhD
Aad van der Lugt, PhD
Peter J. Koudstaal, PhD
Meike W. Vernooij, PhD
M. Arfan Ikram, PhD
On Behalf of the Heart-Brain Connection Collaborative Research Group

Correspondence to: M. Arfan Ikram, PhD, Erasmus University Medical Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail m.a.ikram@erasmusmc.nl

Sources of Funding, see page 727

Key Words: Alzheimer disease ■ cerebral blood flow ■ cerebral perfusion ■ dementia ■ epidemiology ■ small-vessel disease

Clinical Perspective

What Is New?

- Lower cerebral perfusion is associated with accelerated cognitive decline and increased risk of dementia in the general population.
- This association may be modified by hypertension and cerebral small-vessel disease, possibly reflecting impaired arteriolar and capillary function.

What Are the Clinical Implications?

- Although these findings can in part reflect early signs of neurodegeneration, the 10-year follow-up period in our study also supports a role of hypoxia in the pathophysiology of cognitive decline and dementia.
- This calls for further long-term study and evaluation of optimizing cerebral perfusion as a means to prevent cognitive deterioration (eg, in patients with heart failure and carotid artery stenosis).

About 47 million people worldwide are living with dementia, and this number is predicted to increase to 131 million by 2050.[1] Consequently, the socioeconomic burden of dementia will increase enormously unless preventive or curative measures can be established. Vascular disease is an important contributor to dementia, including Alzheimer disease (AD),[2,3] but the underlying pathophysiological mechanisms remain largely unknown. Because vascular risk factors have an important effect on cerebral hemodynamics, cerebral hypoperfusion has been suggested as a potential link between vascular damage and dementia and is a potential target for preventive interventions.[4,5] Various cross-sectional studies have indeed reported lower perfusion in patients with mild cognitive impairment or dementia,[6–10] but the temporal relationship of these findings is debated.[11,12] Hypoperfusion may contribute to neurodegeneration by inducing neuronal energy crisis, whereas loss of brain tissue can lead to hypoperfusion because of reduced metabolic demand. In fact, we recently found in a large longitudinal imaging study that smaller brain volume precedes decline in cerebral blood flow, whereas low flow is associated with accelerated brain atrophy in elderly individuals.[13] Moreover, lower perfusion has been associated with more decline on the Mini-Mental State Examination in the years preceding flow measurement,[14] but to date no studies have determined the risk of developing dementia after a baseline measurement of cerebral blood flow.

Cerebral hypoperfusion has particularly been implicated in small-vessel disease, which is a major risk factor for dementia.[15,16] Hypoperfusion is suggested to play an important role in the pathophysiology of small-vessel disease through ischemia and inflammation.[12,17] In addition, hypoperfusion may be particularly detrimental to neurons in the presence of capillary dysfunction or arteriolar disease because of concomitant impaired vasoreactivity,[18] blood-brain barrier dysfunction,[19] and less efficient extraction of oxygen and other diffusible nutrients.[20] A cross-sectional study in patients with manifest arterial disease indeed found that hypoperfusion was particularly associated with worse executive function in the presence of more extensive white matter hyperintensities.[21] However, whether this also applies to other cognitive domains or to associations with subsequent cognitive decline and development of dementia is unknown.

In a prospective population-based cohort study, we aimed to determine the association of cerebral perfusion with subsequent cognitive decline and development of dementia, and investigate whether this association varies with severity of small-vessel disease.

METHODS

Setting

This study is embedded within the Rotterdam Study, a large population-based cohort study in The Netherlands.[22] The original study population consisted of 7983 participants ≥55 years of age from the Ommoord area, a suburb of Rotterdam. The cohort was subsequently expanded with 3011 persons (≥55 years of age) in the year 2000, and an additional 3932 persons (≥45 years of age) in 2005, thus including 14926 participants in the cohort. From August 2005 onward, all participants without contraindications are invited for magnetic resonance imaging (MRI). Contraindications include presence of iron-based metal implants, other internal metallic objects, severe claustrophobia, recent surgery, or the inability to lie flat for the duration of the scan. The current study includes all eligible participants, who underwent a baseline MRI between 2005 and 2012 (N=5163; 88.3% of invitees). The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study and executed by the Ministry of Health, Welfare, and Sports of The Netherlands. Written informed consent was obtained from all participants.

MRI Scan Protocol

MRI of the brain was performed on a 1.5 T scanner (General Electric Healthcare) using an 8-channel head coil.[23] We acquired high-resolution axial T1-weighted sequence, proton density-weighted sequence, and fluid attenuated inversion recovery sequence. For flow measurement, 2D phase-contrast imaging was performed as described previously.[24] In brief, a sagittal 2D phase-contrast angiographic scout image was performed. On this scout image, a transverse imaging plane perpendicular to both the precavernous portion of the internal carotid arteries and the middle part of the basilar artery was chosen for a 2D gradient-echo phase-contrast sequence (repetition time=20 ms, echo time=4 ms, field of view=19 cm2, matrix=256×160, flip angle=8°, number of excitations=8,

Circulation. 2017;136:719–728. DOI: 10.1161/CIRCULATIONAHA.117.027448

bandwidth=22.73 kHz, velocity encoding=120 cm/sec, slice thickness=5 mm). Acquisition time was 51 seconds and no cardiac gating was performed.[25]

Assessment of total cerebral blood flow, brain volume, and markers of small-vessel disease: Flow was calculated from the phase-contrast images using interactive data language-based custom software (Cinetool version 4; General Electric Healthcare). Two independent, experienced technicians drew all the manual regions of interest and performed subsequent flow measurements (inter-rater correlations >0.94 for all vessels).[24] This method for blood flow measurement was established in 1998,[26] and subsequent reports have demonstrated good accuracy and reproducibility.[24,25] Recently, phase contrast imaging has been shown to correlate well with arterial spin labeling measures of cerebral perfusion,[27,28] although absolute estimates tend to be higher than with arterial spin labeling and somewhat more variable.[27] For the assessment of brain volume, the structural MR sequences (T1-weighted, proton density-weighted, and fluid attenuated inversion recovery) were transferred to a Linux workstation. Pre-processing steps and the classification algorithm have been described previously.[29] Quantification of cerebrospinal fluid, total parenchymal volume, and white matter hyperintensity (WHM) volume were done using an automated tissue segmentation method, based on a k-nearest-neighbor brain tissue classifier algorithm.[29] All segmentation results were visually inspected and if needed manually corrected. Parenchymal brain volume was calculated by adding up gray and white matter volumes, converted to milliliters. We calculated total brain perfusion (mL/min per 100 mL) by dividing total cerebral blood flow (mL/min) by each individual's brain volume (mL) and multiplying the result by 100. All scans were furthermore rated by trained research physicians, blinded to clinical data, for the presence of cerebral microbleeds (defined as small round to ovoid areas of focal signal loss on T2 susceptibility-weighted images), cortical infarcts, lacunar infarcts (defined as focal lesions ≥3 and <15 mm in size with similar signal intensity as cerebrospinal fluid on all sequences and, when located supratentorially, a hyperintense rim on fluid-attenuated inversion recovery).

Cognitive Function Assessment

Cognitive function was assessed in detail at baseline and follow-up with a neuropsychological test battery comprising the letter-digit substitution task (number of correct digits in 1 minute), the verbal fluency test (animal categories), the Stroop test (error-adjusted time in seconds), a 15-word learning test (immediate and delayed recall), and Purdue pegboard task.[30] For all participants, z-scores were calculated for each test separately by dividing the difference between the individual and mean test scores by the standard deviation. We derived scores on cognitive domains for memory (word learning test), information processing (Stroop reading and color naming task and letter-digit substitution task [weighted half]), executive function (Stroop interference task, verbal fluency test, and letter-digit substitution task [weighted half]), and motor function (Purdue pegboard test). To obtain a measure of global cognitive function, we furthermore calculated a standardized compound score (G-factor) using principal component analysis, including each of the cognitive tests described previously.[30] The G-factor explained 47.4% of the variance in cognitive test scores in the population. The average interval between baseline assessment and reexamination was 5.7 years, limiting any practice effects. In fact, the average test performance showed a decline on all tests during the study period (data not shown).

Dementia Screening and Surveillance

Participants were screened for dementia at baseline and follow-up examinations every 4 to 5 years using a 3-step protocol.[31] Screening was done using the Mini-Mental State Examination and the Geriatric Mental Schedule organic level. Those with a Mini-Mental State Examination score <26 or a Geriatric Mental Schedule score >0 subsequently underwent examination and informant interview using the Cambridge Examination of Mental Disorders in the Elderly. The total cohort was also continuously monitored for dementia through computerized linkage of medical records from general practitioners and the regional institute for outpatient mental healthcare with the study database. For all suspected cases of dementia, a consensus panel led by a consultant neurologist (PJK) decided on the final diagnosis in accordance with standard criteria for dementia (*Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*), and (National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association). Follow-up for dementia was virtually complete by January 2015 (96.1% of potential person-years). Participants were censored within this follow-up period at date of dementia diagnosis, death, or last follow-up, whichever came first.

Other Measurements

We assessed educational attainment (classified into lower, further, and higher education), civil status, residential situation (ie, independent or with care), history of smoking (ie, current, former, never), and use of antihypertensive or lipid-lowering medication at baseline by interview. Systolic and diastolic blood pressures were measured twice on the right arm with a random-zero sphygmomanometer; the mean of these readings was used for analyses. Mean arterial pressure was calculated by the sum of diastolic pressure and one-third times the difference between systolic and diastolic pressure. Fasting serum lipid levels were measured at baseline. Diabetes mellitus was defined as the use of blood glucose-lowering medication at baseline or a fasting serum glucose level ≥126 mg/dL. Body mass index was computed from measurements of height and weight (kg/m2). Carotid stenosis (≥50%) was assessed by Doppler ultrasound. History of stroke was assessed at baseline by interview and verified using medical records, and participants were continuously monitored for occurrence of incident stroke through computerized linkage of medical records from general practitioners and nursing home physicians with the study database. Ethnicity was determined from genotype. Apolipoprotein E (*APOE*) genotype was determined by polymerase chain reaction on coded DNA samples in the original cohort and by biallelic Tacqman assays (rs7412 and rs429358) for the expansion cohorts. In 177 participants with missing *APOE* status from this blood sampling, genotype was determined by genetic imputation (Illumina 610K and 660K chip; imputation with Haplotype Reference Consortium reference panel [v1.0] with Minimac 3). Overall, *APOE* genotype

was determined in 97.6% of participants and classified into homozygote ε3 carriers, ε2 carriers (ie, ε2/2 and ε2/3), and ε4 carriers (ie, ε2/4, ε3/4, and ε4/4).

Statistical Analysis

Analyses included all participants without dementia who underwent MRI. Missing covariable data (maximum 10%) were imputed using 5-fold multiple imputation with an iterative Markov chain Monte Carlo method based on determinant, outcome, and included covariables. Distribution of covariates was similar in the imputed versus nonimputed dataset.

We first determined the association between various cardiovascular risk factors and baseline cerebral perfusion by using linear regression.

We then assessed change in cognitive test scores between examination rounds in relation to perfusion using linear regression with test score at reexamination as the dependent variable while adjusting for baseline test score, age, age,^{2} sex, educational attainment, ethnicity, household income, smoking, mean arterial pressure, antihypertensive drugs, serum total cholesterol and high-density lipoprotein, lipid-lowering drugs, diabetes mellitus, body mass index, and *APOE* genotype. We repeated these analyses stratified by median age (61.3 years of age) and after exclusion of participants who were diagnosed with dementia before the repeated cognitive assessment. Finally, we assessed effect modification by white matter hyperintensities (WMH) volume at baseline for global cognition and separate cognitive domains. To avoid overfitting of the models in the latter stratified analyses, adjustment for covariables other than baseline test score, age, and sex was done by means of propensity scores.

Next, we determined the association between cerebral perfusion and incident dementia using Cox proportional hazard models. Competing risk of death was taken into account by modeling the cause-specific hazards, censoring individuals without dementia at date of death. The proportional hazard assumption was met. We assessed risk of dementia per quartile of cerebral perfusion as well as continuously per standard deviation decrease. There was no indication of nonlinearity in the association between perfusion and dementia (Figure I in the online-only Data Supplement). All analyses were adjusted for age^2 and sex. We verified that age was sufficiently controlled for by comparing results with those from a model using cubic splines and repeating the analyses with age rather than follow-up time as the time scale (Table I in the online-only Data Supplement). To minimize confounding by cardiovascular disease, in a second model, we further adjusted for smoking history, mean arterial pressure, use of antihypertensive medication, serum total cholesterol and high-density lipoprotein, use of lipid-lowering medication, diabetes mellitus, body mass index, and *APOE* genotype. In this model, we furthermore controlled for ethnicity, educational attainment, civil status, and living condition. We repeated the analyses, assessing AD only, excluding all participants with prior clinical stroke or MRI defined cortical infarct at baseline while censoring for incident clinical stroke during follow-up, with delayed entry after 1, 2, 3, and 4 years from baseline and excluding participants with carotid artery stenosis >50%. In addition, we examined potential mediation by small-vessel disease by further adjusting for MRI markers of cerebral small vessel disease (ie, WMH volume, cerebral microbleeds, and lacunar infarcts). Finally, we explored effect modification by age, sex, baseline levels of mean arterial pressure, and WMH volume at baseline by stratifying analyses and testing for multiplicative interaction (entering perfusion and WMH volume as continuous variables in the model). To avoid overfitting of the models in the stratified analyses, adjustment for aforementioned covariables was done by means of propensity scores. We visualized the association between perfusion and dementia by mean arterial pressure, creating 3-dimensional mesh plots (using negative exponential smoothing, second-degree polynomial, and nearest neighbor bandwidth method).

Analyses were done using IBM SPSS Statistics version 23.0 (IBM Corp.) apart from analyses using splines and age as a time scale for which we used R statistical software version 3.1.1 (packages rms and survival). The 3-dimensional mesh plots were created using SigmaPlot version 8.0 (Systat Software). Alpha level (type 1 error) was set at 0.05.

RESULTS

Of 5010 eligible participants, no reliable measure of cerebral blood flow could be obtained in 58 (1.2%) persons because of incorrect positioning of the phase-contrast imaging plane. In addition, parenchymal volume computations were unreliable in 193 (3.9%) participants because of inadequate quality of obtained images, thus leaving 4759 (95.0%) individuals for analysis. Baseline characteristics of participants are presented in Table 1.

Cerebral perfusion was lower with advancing age and lower in men compared with women (Table II in the online-only Data Supplement). Most cardiovascular risk factors were individually associated with perfusion at baseline, whereas after adjustment for other risk factors associations with use of antihypertensive medication, cholesterol level, and current smoking remained statistically significant (Table II in the online-only Data Supplement).

Of 4707 participants (98.9%) who underwent detailed cognitive assessment at baseline, 3700 (78.6%) had repeated assessment at follow-up (mean interval 5.7 years). Lower cerebral perfusion at baseline was associated with accelerated decline in global cognition, particularly in memory and executive function (Table 2). Across domains, effect estimates for perfusion increased with escalating severity of WMH (*P* value for interaction of perfusion and WMH with respect to global cognition=0.019; Figure 1). Associations were also stronger in older compared with younger participants (*P* value for interaction=0.018; Table 2). Results were similar when excluding participants who were diagnosed with dementia before cognitive reassessment (Table III in the online-only Data Supplement).

During a mean follow-up time of 6.9 years, 123 individuals developed dementia, of whom 97 (78.9%) had AD. Follow-up for dementia was virtually complete for all 4759 participants (96.1% of potential person-

Table 1. Baseline Characteristics (N=4759)

	Overall Sample	Cognitive Reexamination	No Cognitive Reexamination
Age, y	63.7 (±10.8)	62.2 (±9.7)	69.1 (±12.8)
Female sex	2625 (55.2%)	2031 (54.9%)	565 (56.1%)
White ethnicity	4156 (97.3%)	3219 (97.0%)	891 (98.5%)
Smoking			
Former	2300 (48.6%)	1807 (49.1%)	474 (47.4%)
Current	995 (21.0%)	731 (19.9%)	249 (24.9%)
Systolic blood pressure, mm Hg	139 (±21)	138 (±20)	143 (±23)
Diastolic blood pressure, mm Hg	82 (±11)	82 (±11)	82 (±12)
Mean arterial pressure, mm Hg	101 (±13)	101 (±13)	102 (±14)
Antihypertensive medication	1616 (34.2%)	1130 (30.8%)	462 (46.2%)
Cholesterol, mg/dL	215 (±41)	216 (±41)	211 (±41)
High-density lipoprotein cholesterol, mg/dL	56 (±16)	56 (±16)	54 (±15)
Lipid-lowering medication	1129 (23.9%)	848 (23.1%)	267 (26.7%)
Diabetes mellitus	519 (11.1%)	368 (10.1%)	146 (14.9%)
Body -mass index, kg/m^2	27.4 (±4.2)	27.5 (±4.1)	27.4 (±4.4)
Educational attainment			
Lower	2180 (46.2%)	1621 (44.2%)	531 (53.1%)
Further	1440 (30.5%)	1129 (30.8%)	295 (29.5%)
Higher	1100 (23.3%)	918 (25.0%)	174 (17.4%)
Civil status			
Living with spouse or partner	3540 (74.8%)	2870 (77.9%)	636 (63.7%)
Widowed, divorced, or never married	1191 (25.2%)	813 (22.1%)	363 (36.3%)
Residential care	270 (5.7%)	155 (4.2%)	110 (11.0%)
APOE genotype			
ε3/ε3	2726 (58.7%)	2127 (58.8%)	574 (58.8%)
ε2/ε2 or ε2/ε3	604 (13.0%)	472 (13.0%)	122 (12.5%)
ε2/ε4, ε3/ε4, or ε4/ε4	1315 (28.3%)	1020 (28.2%)	281 (28.8%)
Carotid artery stenosis (≥50%)	208 (4.4%)	112 (3.1%)	91 (9.2%)
Cerebral perfusion, mL/100mL/min	56.3 (±9.7)	56.7 (±9.5)	54.9 (±10.1)

Values are depicted as mean±SD for continuous variables and n (%) for categorical variables. *APOE* indicates apolipoprotein E.

years). Of incident dementia cases, 25 were preceded by a clinical stroke or had evidence of cortical infarction on baseline MRI.

Lower cerebral perfusion at baseline was associated with a higher risk of all-cause dementia (adjusted hazard ratio [aHR], 1.31, 95% confidence interval [CI] per standard deviation decrease, 1.07–1.61), with similar effect estimates for AD (Table 3). There was no evidence of nonlinearity in the association between perfusion and dementia (Figure I in the online-only Data Supplement).

Table 2. Cognitive Test Performance at Follow-Up in Relation to Baseline Cerebral Perfusion

	All Participants β for Change (95% CI)	Age <61 y β for Change (95% CI)	Age ≥61 y β for Change (95% CI)
Global cognition	−0.029 (−0.048 to −0.010)	−0.010 (−0.032 to 0.013)	−0.056 (−0.089 to −0.022)
Memory	−0.031 (−0.056 to −0.006)	−0.013 (−0.045 to 0.019)	−0.047 (−0.086 to −0.008)
Information processing	−0.007 (−0.024 to 0.009)	0.003 (−0.017 to 0.023)	−0.020 (−0.047 to 0.007)
Executive function	−0.017 (−0.033 to −0.001)	−0.013 (−0.032 to 0.007)	−0.025 (−0.052 to 0.002)
Motor function	−0.001 (−0.026 to 0.027)	0.014 (−0.026 to 0.055)	−0.025 (−0.051 to 0.001)

Results are stratified by the median age of 61.3 years. Model adjusted for age,[2] sex, educational attainment, ethnicity, civil status, residential care, smoking, mean arterial pressure, antihypertensive drugs, serum total cholesterol and high-density lipoprotein, lipid-lowering drugs, diabetes mellitus, body mass index, and apolipoprotein E genotype. Betas reflect the effect of cerebral perfusion (per standard deviation decrease) on standardized cognitive test scores at follow-up examination adjusted for baseline cognitive test score. CI indicates confidence interval.

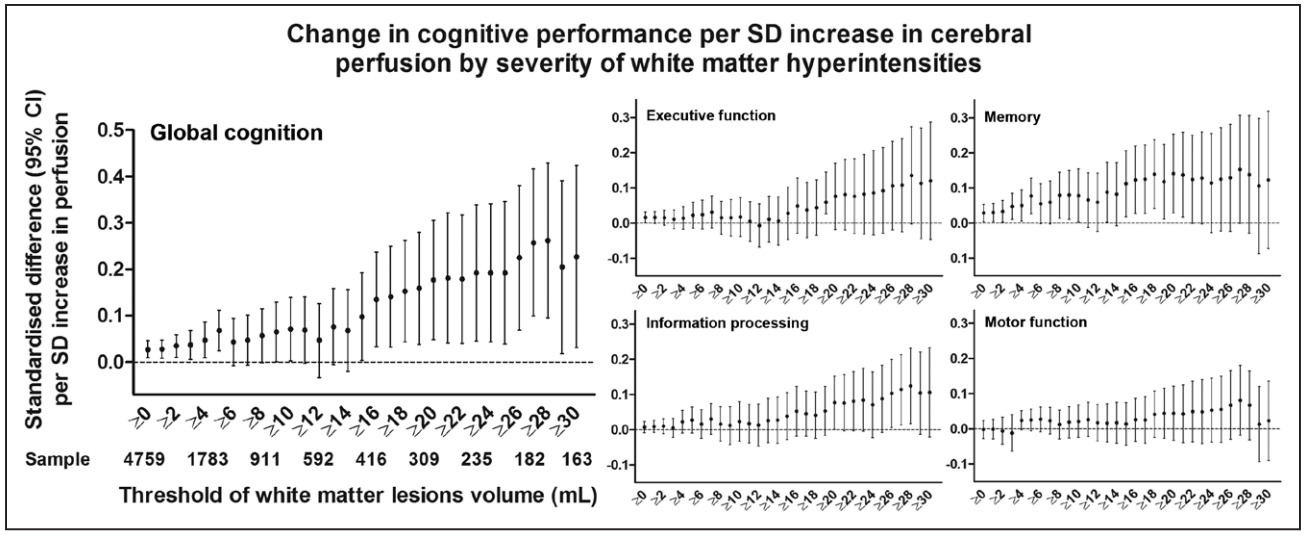

Figure 1. Change in cognitive performance during follow-up in relation to baseline perfusion by severity of white matter hyperintensities.

Results are shown for global cognition and separate cognitive domains. Moving right along the x-axis limits the included population to those with at least the specified volume of white matter hyperintensities on baseline magnetic resonance imaging (ranging from the full sample of 4759 individuals with ≥0 mL to a sample of 163 individuals with ≥30 mL). Each dot represents the estimated change in cognitive test performance per 1 standard deviation (SD) increase in perfusion in this specified population. CI indicates confidence interval.

Results were unaffected by excluding prevalent stroke and censoring at time of incident stroke (aHR, 1.33; 95% CI, 1.06–1.68). Analyses with delayed study entry, excluding the first year of follow-up, resulted in mildly reduced estimates, which remained grossly stable with additional exclusion of the second, third, and fourth years of follow-up (HRs, 1.26, 1.24, 1.21, and 1.25, respectively). Overall effect estimates were mildly attenuated after excluding participants with ≥50% carotid artery stenosis (aHR, 1.23; 95% CI, 0.99–1.53) and when adjusting for MRI markers of small-vessel disease (aHR, 1.25; 95% CI, 1.02–1.54; Table 4). Risk estimates for dementia were much higher for measures of cerebral blood flow, not accounting for parenchymal volume (Table IV in the online-only Data Supplement).

The association between cerebral perfusion and risk of dementia was more profound with increasing burden of WMH on MRI (Table 4; with severe WMH: aHR, 1.54; 95% CI, 1.11–2.14), although a formal test for multiplicative interaction was not statistically significant (*P*=0.24). This trend was similar when excluding all participants with clinical stroke or stroke on MRI at baseline (Table V in the online-only Data Supplement). In addition, dementia risk estimates for low perfusion were higher in those with higher blood pressure levels at baseline (Figure 2; *P* value for interaction with mean arterial pressure=0.039). This trend was consistently seen for systolic and diastolic pressure (Figure 2; for a full table, see Table VI in the online-only Data Supplement) and persisted after additional adjustment for WMH volume (data

Table 3. Risk of Dementia in Relation to Baseline Cerebral Perfusion

	All-Cause Dementia			Alzheimer Disease		
	n/N	Model I* HR (95% CI)	Model II† HR (95% CI)	n/N	Model I* HR (95% CI)	Model II† HR (95% CI)
Quartiles of perfusion						
$Q1_{<50\ mL/100mL/min}$	51/1189	2.28 (1.20–4.32)	2.27 (1.19–4.32)	41/1189	2.15 (1.06–4.33)	2.08 (1.02–4.26)
$Q2_{50–55\ mL/100mL/min}$	40/1190	2.35 (1.23–4.49)	1.95 (1.01–3.77)	31/1190	2.13 (1.04–4.37)	1.63 (0.78–3.41)
$Q3_{56–62\ mL/100mL/min}$	20/1190	1.27 (0.62–2.61)	1.20 (0.59–2.47)	15/1190	1.13 (0.51–2.51)	1.03 (0.46–2.30)
$Q4_{>62\ mL/100mL/min}$	12/1190	Reference	Reference	10/1190	Reference	Reference
P trend		0.002	0.002		0.007	0.008
Per SD decrease	123/4759	1.30 (1.07–1.58)	1.31 (1.07–1.61)	97/4759	1.26 (1.01–1.57)	1.28 (1.01–1.62)

CI indicates confidence interval; HR, hazard ratio; n, number of cases of dementia; and N, sample size.

*Adjusted for age and sex.

†Model I with additional adjustment for educational attainment, ethnicity, civil status, residential care, smoking, mean arterial pressure, antihypertensive drugs, serum total cholesterol and high-density lipoprotein, lipid-lowering drugs, diabetes mellitus, body mass index, and apolipoprotein E genotype.

Table 4. Risk of Dementia in Relation to Baseline Cerebral Perfusion Adjusted for Imaging Markers of Small-Vessel Disease and by Severity of White Matter Hyperintensities on Magnetic Resonance Imaging

	Adjustment for Small-Vessel Disease*		By Severity of White Matter Hyperintensitiest		
	n/N	HR (95% CI)	None to Mild (n/N=40/3439)	Moderate (n/N=40/763)	Severe (n/N=39/443)
Quartiles of perfusion					
Q1	50/1166	2.08 (1.08–4.00)	1.18 (0.43–3.23)	3.14 (0.91–10.77)	4.36 (1.29–14.72)
Q2	37/1164	1.94 (1.00–3.77)	1.26 (0.45–3.53)	2.60 (0.73–9.35)	1.96 (0.51–7.58)
Q3	20/1160	1.19 (0.58–2.45)	1.71 (0.67–4.38)	2.45 (0.65–9.32)	1.66 (0.42–6.68)
Q4	12/1155	Reference	Reference	Reference	Reference
P trend		0.007	0.98	0.083	0.003
Per SD decrease	119/4645	1.25 (1.02–1.54)	1.07 (0.76–1.51)	1.30 (0.93–1.84)	1.54 (1.11–2.14)

CI indicates confidence interval; HR, hazard ratio; n, number of cases of dementia; and N, total number of individuals in group.

*Adjusted for age sex, educational attainment, ethnicity, civil status, residential care, smoking, mean arterial pressure, antihypertensive drugs, serum total cholesterol and high-density lipoprotein, lipid-lowering drugs, diabetes mellitus, body mass index, apolipoprotein E genotype, volume of white matter hyperintensities, presence of lacunar infarcts, and cerebral microbleeds.

† Adjusted by means of propensity score. Categories are based on an approximately equal number of cases across categories (cutoffs at 6 mL and 15 mL, respectively).

not shown). There was no effect modification of the association between cerebral perfusion and risk of dementia by age or sex (data not shown).

DISCUSSION

In this large population-based study, we found that lower cerebral perfusion at baseline was associated with accelerated cognitive decline and a higher risk of developing dementia during on average 7 years of follow-up. These associations were most profound in individuals with a higher burden of WMH or higher mean arterial pressure at baseline.

Prior studies have almost invariably shown associations of hypoperfusion with mild cognitive impairment and AD in cross-sectional studies[6–9] and more rapid decline in cognition after diagnosis of dementia in a longitudinal study.[10] Lower perfusion is often attributed to neurodegeneration and can indicate neuronal dysfunction and synaptic failure. The first signs of neurodegeneration are likely to occur years before the diagnosis of dementia, and cerebral perfusion may consequently fall well before clinical symptoms of dementia arise. Nevertheless, our findings show that the association of perfusion with cognitive decline extends well into the presymptomatic phase of the disease and could therefore precede and also contribute to neuronal cell loss and neurodegeneration. Both sides of this medal are supported by a recent longitudinal imaging study, in which smaller brain volume precipitated decline in cerebral blood flow and low flow predisposed to accelerated brain atrophy in elderly individuals.[13] In line with these findings, we found the strongest associations of hypoperfusion with cognitive decline in those >60 years of age, which extended to individuals who did not (yet) develop dementia.

Various potential underlying mechanisms can link hypoxia to (neuronal) cell death, many of which are related to the activation of hypoxia-inducible transcription factors. Hypoxia-inducible transcription factors can lead to increased expression of various inflammatory cytokines,[32] and the subsequent activation of microglia,[33] release of proinflammatory neurotoxic factors, and oxidative stress may explain part of the observed link between neuroinflammation and AD.[34] Furthermore, hypoxia-inducible transcription factors render endothelial cells responsive to various proangiogenic factors, as seen in the white matter of patients with AD.[35] These proangiogenic factors are important for maintaining blood-brain barrier integrity through regulating endothelial cell and pericyte function in angiogenesis,[36] and dysfunction of these vital components of the neurovascular unit has been implicated in neurodegeneration with AD.[36] Moreover, hypoxia can result in aberrant angiogenesis and microvascular degeneration in humans by pathways associated with advanced vascular degeneration and poor β-amyloid clearance in mice.[37] Cerebral blood flow correlates with amyloid burden across the spectrum from cognitively healthy to AD,[38] which could be in part consequential and in part contributing to impaired amyloid clearance. Certain areas in the brain, such as the metabolically highly active hippocampi, may be particularly vulnerable to hypoxia, which could explain their role in early AD[39] and the marked associations we found with memory function in our study. Future studies may focus more specifically on such regions, refine insight in these pathways, and investigate whether cerebral perfusion or hypoxia mediates associations of, for instance, heart failure and atrial fibrillation with dementia.

Hypoperfusion is widely implicated in the etiology of cerebral small-vessel disease, but once again the temporality of the association is under debate.[12,17,40] The mild

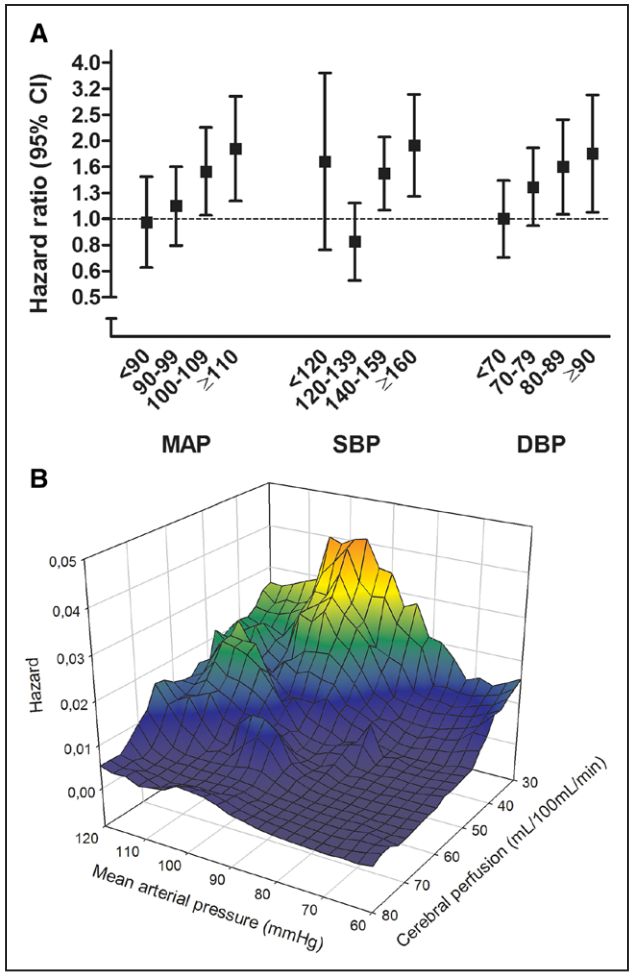

Figure 2. Association between cerebral perfusion and risk of dementia by blood pressure levels at baseline (A), and graphically (3-dimensionally) depicted for mean arterial pressure (B).

CI indicates confidence interval; DBP, diastolic blood pressure; MAP, mean arterial pressure; and SBP, systolic blood pressure.

attenuation of risk estimates by adjusting for markers of cerebral small-vessel disease in our study may in that respect reflect confounding or partial mediation of the association between hypoperfusion and dementia by small-vessel disease. In addition, small-vessel disease may modify an effect of hypoperfusion on neuronal cell loss. In line with a previous cross-sectional study of executive functioning,[21] we observed stronger associations in individuals with a higher degree of WMH at baseline. WMH have been related to blood-brain barrier permeability,[41] diminished vasoreactivity,[42] and a state of impaired extraction of oxygen and other nutrients, in which hypoperfusion could be especially hazardous to meeting metabolic demand.[20] Diminished blood-brain barrier function may render amyloid clearance more dependent on interstitial bulk flow,[43] whereas in mouse models of AD, vascular dysfunction and hypoperfusion led to impaired drainage of interstitial fluid and β-amyloid clearance.[44] Of particular relevance to brain tissue, encased as it is by the skull, is its low interstitial compliance, causing small increases in interstitial volume to lead to large increases in interstitial pressure. Consequently, increases in arterial pressure may be required to maintain the hydrostatic pressure gradient and fluid filtration. This might underlie the observed interaction between perfusion and arterial blood pressure in our study. Yet high blood pressures may also reflect long-standing hypertension and its detrimental consequences on (micro)vascular integrity and function.[45] The potential interplay between blood pressure, arteriolar and capillary dysfunction, and neuronal hypoxia warrants further investigation. It is important to note, somewhat counterintuitively, that hyperperfusion might also lead to lower oxygen extraction in the presence of relatively mild-moderate capillary dysfunction, requiring suppression of blood flow to optimize metabolism.[46] In those individuals, perfusion may be reduced as a mechanism to optimize oxygen extraction. Repeated scan data in future studies may aid to further explore this possibility.

Although we believe our findings are valid, certain limitations to our study must be taken into account. First, 2-dimensional phase contrast flow measurement does not allow region-specific assessment of cerebral perfusion, which is likely more sensitive in detecting associations with cognitive decline. Also, we could not differentiate between gray and white matter perfusion. Although phase contrast imaging measures of perfusion correlate well with arterial spin labeling,[27,28] absolute estimates tend to be higher and somewhat more variable.[27] However, such a systematic deviation would not influence obtained relative risks, and a larger variability would only lead to dilution of effect estimates. Second, we could not measure cerebellar blood flow because flow in the basilar artery was measured distally of the posterior and anterior inferior cerebellar arteries. Third, although follow-up for dementia was nearly complete (96%), attrition for cognitive reexamination was substantial (21%). Because those participants lost to follow-up were older, had worse risk profiles, and had lower cerebral perfusion, this most likely led to an underestimation of the association of perfusion with decline in test performance. Response rate to MRI invitation in our study was 88.3%, and nonparticipants were also older than those who did undergo brain imaging. Fourth, given the long presymptomatic phase of dementia, the median 7 years of follow-up is still relatively short, and therefore we cannot completely rule out reverse causation. Finally, the vast majority of our population is of European ancestry, potentially limiting generalizability to other ethnicities.

In conclusion, cerebral hypoperfusion is associated with accelerated cognitive decline and increased risk of dementia in the general population. These findings support a role of cerebral hypoperfusion in the patho-

Circulation. 2017;136:719–728. DOI: 10.1161/CIRCULATIONAHA.117.027448

physiology of dementia. Further studies are warranted to unravel mechanisms in relation to blood pressure and small-vessel disease and assess the potential of cerebral perfusion as a target for prevention of cognitive decline.

ACKNOWLEDGMENTS

The dedication and commitment by which study participants, general practitioners, and pharmacists of the Ommoord district contributed to the Rotterdam Study are gratefully acknowledged. The authors thank all staff at the Rotterdam Study Research Center, facilitating assessment of participants throughout the years, and Frank J. A. van Rooij as data manager. All authors made a substantial intellectual contribution to the study design (AH, MWV, MAI), acquisition of data (FJW, HIZ, AL, PJK), analysis and interpretation of data (FJW, HIZ, MWV, MAI), drafting of the manuscript (FJW), or revising it critically for important intellectual content (HIZ, AH, AL, PJK, MWV, MAI). All authors approved the final version of the manuscript for publication. MAI had full access to the data in the study and takes responsibility for data integrity and accuracy of data analysis.

SOURCES OF FUNDING

The Heart Brain Connection collaborative research group is supported by The Netherlands Cardiovascular Research Initiative (CVON2012-06). The Rotterdam Study is sponsored by the Erasmus Medical Center and Erasmus University Rotterdam, The Netherlands Organization for Scientific Research, The Netherlands Organization for Health Research and Development, the Research Institute for Diseases in the Elderly, The Netherlands Genomics Initiative, the Ministry of Education, Culture, and Science, the Ministry of Health, Welfare, and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. Further support was obtained from The Netherlands Consortium for Healthy Ageing and the Dutch Heart Foundation (2012T008). This research was further supported by funding from the European Union Seventh Framework Program (FP7/2007e2013) under grant agreement no. 601055, VPH-Dare@IT (FP7-ICT-2011-9e601055), and funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 667375 (Co-STREAM) and no. 678543 (European Research Council-funded project: ORACLE). None of the funding organizations or sponsors was involved in study design, collection, analysis, and interpretation of data, in writing of the report, or in the decision to submit the article for publication.

DISCLOSURES

None.

AFFILIATIONS

From Department of Epidemiology (F.J.W., H.I.Z., A.H., M.W.V., M.A.I.), Department of Neurology (F.J.W., P.J.K., M.A.I.), Department of Radiology and Nuclear Medicine (H.I.Z., A.v.d.L., M.W.V., M.A.I.), Erasmus Medical Center, Rotterdam, The Netherlands; and Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA (F.J.W., A.H.).

FOOTNOTES

Received January 18, 2017; accepted May 2, 2017.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.027448/-/DC1.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Circulation is available at http://circ.ahajournals.org.

REFERENCES

1. Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M; Alzheimer's Disease International. World Alzheimer Report 2016. September 2016. http://www.alz.co.uk/research/WorldAlzheimerReport2016.pdf. Accessed October 26, 2016.
2. Gardener H, Wright CB, Rundek T, Sacco RL. Brain health and shared risk factors for dementia and stroke. *Nat Rev Neurol*. 2015;11:651–657. doi: 10.1038/nrneurol.2015.195.
3. Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. *Nat Rev Cardiol*. 2015;12:267–277. doi: 10.1038/nrcardio.2014.223.
4. la Torre de JC. Cerebral hemodynamics and vascular risk factors: setting the stage for Alzheimer's disease. *J Alzheimers Dis*. 2012;32:553–567.
5. Drachman DA. The amyloid hypothesis, time to move on: Amyloid is the downstream result, not cause, of Alzheimer's disease. *Alzheimers Dement*. 2014;10:372–380. doi: 10.1016/j.jalz.2013.11.003.
6. Binnewijzend MA, Kuijer JP, Benedictus MR, van der Flier WM, Wink AM, Wattjes MP, van Berckel BN, Scheltens P, Barkhof F. Cerebral blood flow measured with 3D pseudocontinuous arterial spin-labeling MR imaging in Alzheimer disease and mild cognitive impairment: a marker for disease severity. *Radiology*. 2013;267:221–230. doi: 10.1148/radiol.12120928.
7. Johnson NA, Jahng GH, Weiner MW, Miller BL, Chui HC, Jagust WJ, Gorno-Tempini ML, Schuff N. Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. *Radiology*. 2005;234:851–859. doi: 10.1148/radiol.2343040197.
8. van de Haar HJ, Jansen JFA, van Osch MJP, van Buchem MA, Muller M, Wong SM, Hofman PA, Burgmans S, Verhey FR, Backes WH. Neurovascular unit impairment in early Alzheimer's disease measured with magnetic resonance imaging. *Neurobiol Aging*. 2016;45:190–196.
9. Alsop DC, Detre JA, Grossman M. Assessment of cerebral blood flow in Alzheimer's disease by spin-labeled magnetic resonance imaging. *Ann Neurol*. 2000;47:93–100.
10. Benedictus MR, Leeuwis AE, Binnewijzend MA, Kuijer JP, Scheltens P, Barkhof F, van der Flier WM, Prins ND. Lower cerebral blood flow is associated with faster cognitive decline in Alzheimer's disease. *Eur Radiol*. 2017;27:1169–1175. doi: 10.1007/s00330-016-4450-z.
11. Mazza M, Marano G, Traversi G, Bria P, Mazza S. Primary cerebral blood flow deficiency and Alzheimer's disease: shadows and lights. *J Alzheimers Dis*. 2011;23:375–389. doi: 10.3233/JAD-2010-090700.
12. Shi Y, Thrippleton MJ, Makin SD, Marshall I, Geerlings MI, de Craen AJ, van Buchem MA, Wardlaw JM. Cerebral blood flow in small vessel disease: a systematic review and meta-analysis. *J Cereb Blood Flow Metab*. 2016;36:1653–1667. doi: 10.1177/0271678X16662891.
13. Zonneveld HI, Loehrer EA, Hofman A, Niessen WJ, van der Lugt A, Krestin GP, Ikram MA, Vernooij MW. The bidirectional association between reduced cerebral blood flow and brain atrophy in the general population. *J Cereb Blood Flow Metab*. 2015;35:1882–1887. doi: 10.1038/jcbfm.2015.157.
14. Ruitenberg A, den Heijer T, Bakker SL, van Swieten JC, Koudstaal PJ, Hofman A, Breteler MM. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. *Ann Neurol*. 2005;57:789–794. doi: 10.1002/ana.20493.
15. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010;341:c3666.

16. Akoudad S, Wolters FJ, Viswanathan A, de Bruijn RF, van der Lugt A, Hofman A, Koudstaal PJ, Ikram MA, Vernooij MW. Association of cerebral microbleeds with cognitive decline and dementia. *JAMA Neurol*. 2016;73:934–943. doi: 10.1001/jamaneurol.2016.1017.
17. Yata K, Tomimoto H. Chronic cerebral hypoperfusion and dementia. *Neurology and Clinical Neuroscience*. 2014;2:129–134.
18. Wolters FJ, de Bruijn RF, Hofman A, Koudstaal PJ, Ikram MA; Heart Brain Connection Collaborative Research Group. Cerebral vasoreactivity, apolipoprotein E, and the risk of dementia: a population-based study. *Arterioscler Thromb Vasc Biol*. 2016;36:204–210. doi: 10.1161/ATVBAHA.115.306768.
19. Zhao Z, Nelson AR, Betsholtz C, Zlokovic BV. Establishment and dysfunction of the blood-brain barrier. *Cell*. 2015;163:1064–1078. doi: 10.1016/j.cell.2015.10.067.
20. Østergaard L, Engedal TS, Moreton F, Hansen MB, Wardlaw JM, Dalkara T, Markus HS, Muir KW. Cerebral small vessel disease: capillary pathways to stroke and cognitive decline. *J Cereb Blood Flow Metab*. 2016;36:302–325. doi: 10.1177/0271678X15606723.
21. Appelman AP, van der Graaf Y, Vincken KL, Mali WP, Geerlings MI. Combined effect of cerebral hypoperfusion and white matter lesions on executive functioning: the SMART-MR study. *Dement Geriatr Cogn Disord*. 2010;29:240–247. doi: 10.1159/000289813.
22. Hofman A, Brusselle GG, Darwish Murad S, van Duijn CM, Franco OH, Goedegebure A, Ikram MA, Klaver CC, Nijsten TE, Peeters RP, Stricker BH, Tiemeier HW, Uitterlinden AG, Vernooij MW. The Rotterdam Study: 2016 objectives and design update. *Eur J Epidemiol*. 2015;30:661–708. doi: 10.1007/s10654-015-0082-x.
23. Ikram MA, van der Lugt A, Niessen WJ, Koudstaal PJ, Krestin GP, Hofman A, Bos D, Vernooij MW. The Rotterdam Scan Study: design update 2016 and main findings. *Eur J Epidemiol*. 2015;30:1299–1315. doi: 10.1007/s10654-015-0105-7.
24. Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Vrooman HA, Hofman A, Krestin GP, Breteler MM. Total cerebral blood flow and total brain perfusion in the general population: the Rotterdam Scan Study. *J Cereb Blood Flow Metab*. 2008;28:412–419. doi: 10.1038/sj.jcbfm.9600526.
25. Spilt A, Box FM, van der Geest RJ, Reiber JH, Kunz P, Kamper AM, Blauw GJ, van Buchem MA. Reproducibility of total cerebral blood flow measurements using phase contrast magnetic resonance imaging. *J Magn Reson Imaging*. 2002;16:1–5. doi: 10.1002/jmri.10133.
26. Buijs PC, Krabbe-Hartkamp MJ, Bakker CJ, de Lange EE, Ramos LM, Breteler MM, Mali WP. Effect of age on cerebral blood flow: measurement with ungated two-dimensional phase-contrast MR angiography in 250 adults. *Radiology*. 1998;209:667–674. doi: 10.1148/radiology.209.3.9844657.
27. Dolui S, Wang Z, Wang DJ, Mattay R, Finkel M, Elliott M, Desiderio L, Inglis B, Mueller B, Stafford RB, Launer LJ, Jacobs DR Jr, Bryan RN, Detre JA. Comparison of non-invasive MRI measurements of cerebral blood flow in a large multisite cohort. *J Cereb Blood Flow Metab*. 2016;36:1244–1256. doi: 10.1177/0271678X16646124.
28. Clark LR, Berman SE, Rivera-Rivera LA, Hoscheidt SM, Darst BF, Engelman CD, Rowley HA, Carlsson CM, Asthana S, Turski P, Wieben O, Johnson SC. Macrovascular and microvascular cerebral blood flow in adults at risk for Alzheimer's disease. *Alzheimers Dement (Amst)*. 2017;7:48–55. doi: 10.1016/j.dadm.2017.01.002.
29. Vrooman HA, Cocosco CA, van der Lijn F, Stokking R, Ikram MA, Vernooij MW, Breteler MM, Niessen WJ. Multi-spectral brain tissue segmentation using automatically trained k-Nearest-Neighbor classification. *Neuroimage*. 2007;37:71–81. doi: 10.1016/j.neuroimage.2007.05.018.
30. Hoogendam YY, Hofman A, van der Geest JN, van der Lugt A, Ikram MA. Patterns of cognitive function in aging: the Rotterdam Study. *Eur J Epidemiol*. 2014;29:133–140. doi: 10.1007/s10654-014-9885-4.
31. de Bruijn RF, Bos MJ, Portegies ML, Hofman A, Franco OH, Koudstaal PJ, Ikram MA. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. *BMC Med*. 2015;13:132. doi: 10.1186/s12916-015-0377-5.
32. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N Engl J Med*. 2011;364:656–665. doi: 10.1056/NEJMra0910283.
33. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neurosci*. 2007;8:57–69. doi: 10.1038/nrn2038.
34. Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. *Nat Rev Neurosci*. 2015;16:358–372. doi: 10.1038/nrn3880.
35. Barker R, Ashby EL, Wellington D, Barrow VM, Palmer JC, Kehoe PG, Esiri MM, Love S. Pathophysiology of white matter perfusion in Alzheimer's disease and vascular dementia. *Brain*. 2014;137(Pt 5):1524–1532. doi: 10.1093/brain/awu040.
36. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci*. 2011;12:723–738. doi: 10.1038/nrn3114.
37. Wu Z, Guo H, Chow N, Sallstrom J, Bell RD, Deane R, Brooks AI, Kanagala S, Rubio A, Sagare A, Liu D, Li F, Armstrong D, Gasiewicz T, Zidovetzki R, Song X, Hofman F, Zlokovic BV. Role of the MEOX2 homeobox gene in neurovascular dysfunction in Alzheimer disease. *Nat Med*. 2005;11:959–965. doi: 10.1038/nm1287.
38. Mattsson N, Tosun D, Insel PS, Simonson A, Jack CR Jr, Beckett LA, Donohue M, Jagust W, Schuff N, Weiner MW; Alzheimer's Disease Neuroimaging Initiative. Association of brain amyloid-β with cerebral perfusion and structure in Alzheimer's disease and mild cognitive impairment. *Brain*. 2014;137(Pt 5):1550–1561. doi: 10.1093/brain/awu043.
39. Reitz C, Brickman AM, Brown TR, Manly J, DeCarli C, Small SA, Mayeux R. Linking hippocampal structure and function to memory performance in an aging population. *Arch Neurol*. 2009;66:1385–1392. doi: 10.1001/archneurol.2009.214.
40. Gregg NM, Kim AE, Gurol ME, Lopez OL, Aizenstein HJ, Price JC, Mathis CA, James JA, Snitz BE, Cohen AD, Kamboh MI, Minhas D, Weissfeld LA, Tamburo EL, Klunk WE. Incidental cerebral microbleeds and cerebral blood flow in elderly individuals. *JAMA Neurol*. 2015;72:1021–1028. doi: 10.1001/jamaneurol.2015.1359.
41. Topakian R, Barrick TR, Howe FA, Markus HS. Blood-brain barrier permeability is increased in normal-appearing white matter in patients with lacunar stroke and leucoaraiosis. *J Neurol Neurosurg Psychiatry*. 2010;81:192–197. doi: 10.1136/jnnp.2009.172072.
42. Bakker SL, de Leeuw FE, de Groot JC, Hofman A, Koudstaal PJ, Breteler MM. Cerebral vasomotor reactivity and cerebral white matter lesions in the elderly. *Neurology*. 1999;52:578–583.
43. Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, Axel L, Rusinek H, Nicholson C, Zlokovic BV, Frangione B, Blennow K, Ménard J, Zetterberg H, Wisniewski T, de Leon MJ. Clearance systems in the brain-implications for Alzheimer disease. *Nat Rev Neurol*. 2015;11:457–470. doi: 10.1038/nrneurol.2015.119.
44. Arbel-Ornath M, Hudry E, Eikermann-Haerter K, Hou S, Gregory JL, Zhao L, Betensky RA, Frosch MP, Greenberg SM, Bacskai BJ. Interstitial fluid drainage is impaired in ischemic stroke and Alzheimer's disease mouse models. *Acta Neuropathol*. 2013;126:353–364. doi: 10.1007/s00401-013-1145-2.
45. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol*. 2013;12:483–497. doi: 10.1016/S1474-4422(13)70060-7.
46. Østergaard L, Aamand R, Gutiérrez-Jiménez E, Ho YC, Blicher JU, Madsen SM, Nagenthiraja K, Dalby RB, Drasbek KR, Møller A, Brændgaard H, Mouridsen K, Jespersen SN, Jensen MS, West MJ. The capillary dysfunction hypothesis of Alzheimer's disease. *Neurobiol Aging*. 2013;34:1018–1031. doi: 10.1016/j.neurobiolaging.2012.09.011.