Physical activity is related to the structural integrity of cerebral white matter

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ABSTRACT

Objective: To investigate the relation between physical exercise and the microstructural integrity of cerebral white matter.

Methods: Four hundred forty individuals with cerebral small-vessel disease, aged between 50 and 85 years, without dementia, were included and underwent MRI scanning. Physical exercise was assessed with a structured questionnaire. The cross-sectional relation between physical exercise and the microstructural integrity of the white matter was assessed by applying Tract-Based Spatial Statistics to diffusion tensor imaging parameters.

Results: Being more physically active was negatively related to the mean, axial, and radial diffusivity in numerous regions of the white matter, indicative of higher white matter integrity.

Conclusions: These data indicate an association between physical activity and the integrity of the cerebral white matter's microstructure. Prospective studies are required to investigate a possible causal association between physical activity and cognitive decline. *Neurology*® 2013;81:971–976

GLOSSARY

AD = axial diffusivity; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FLAIR** = fluid-attenuated inversion recovery; **MD** = mean diffusivity; **MET** = metabolic equivalent; **NAWM** = normal-appearing white matter; **RD** = radial diffusivity; **SVD** = small-vessel disease; **TBSS** = Tract-Based Spatial Statistics; **WML** = white matter lesion.

As the incidence of dementia increases with age, research on modifiable risk factors has become an important health care priority.[1,2] Such a factor could be physical activity, which reportedly has a beneficial effect on cognitive function, although others could not replicate this finding.[1,3]

Physical activity may reduce cerebrovascular events because of better control of cardiovascular risk factors.[4] It could also be that physical activity maintains the quality/structure of the white matter at the level of microstructural integrity of the normal-appearing white matter (NAWM) that cannot be assessed with conventional imaging.

Loss of microstructural integrity is typically reflected by a reduction in fractional anisotropy (FA) and/or increase in mean diffusivity (MD),[5] which can result from different combinations of changes in axial diffusivity (AD) and radial diffusivity (RD). Important limitations in using whole-brain, voxel-based analysis are the spurious effects of the smoothing[6] and the possible misalignment caused by the spatial normalization procedure.[7] This is especially a common problem in elderly people because of atrophy and ventricular enlargement. Tract-Based Spatial Statistics (TBSS) mitigates these 2 problems.[7] The rationale behind the TBSS method is that the analysis is restricted to those white matter voxels that constitute the skeleton (core) of the brain's connectional architecture and that this skeleton can be matched more accurately across subjects.

Our hypothesis was that physical activity is positively related to the cerebral white matter's microstructure. Our objective was to investigate this microstructure in relation to physical activity among elderly subjects with small-vessel disease (SVD).

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METHODS

Study population. This study is embedded within the Radboud University Nijmegen Diffusion Tensor and MRI Cohort Study, a prospective cohort study that was designed to investigate risk factors and cognitive, motor, and mood consequences of functional and structural brain changes as assessed by MRI among elderly with cerebral SVD. The primary study outcome of the longitudinal part of this study is the development of dementia or parkinsonism.

Cerebral SVD is characterized on neuroimaging by either white matter lesions (WMLs) or lacunar infarcts. Symptoms of SVD can be acute, such as TIAs or lacunar syndromes, or subacute manifestations, such as cognitive, motor (gait), and/or mood disturbances.[8] Because the onset of cerebral SVD is often insidious, clinically heterogeneous, and typically with mild symptoms, it has been suggested that the selection of subjects with cerebral SVD in clinical studies should be based on these more consistent brain imaging features.[9] Accordingly, in 2006, consecutive patients referred to the Department of Neurology between October 2002 and November 2006, were selected for participation.

Inclusion criteria were a) age between 50 and 85 years, and b) cerebral SVD on neuroimaging (WML and/or lacunar infarct[s]). Subsequently, the above-mentioned acute or subacute clinical symptoms of SVD were assessed by standardized structured assessments. Patients who were eligible because of a lacunar syndrome were included only >6 months after the event to avoid acute effects on the outcomes.

Exclusion criteria were a) dementia (American Psychiatric Association, 2000); b) parkinson(ism),[10,11] c) intracranial hemorrhage; d) life expectancy of <6 months; e) intracranial space occupying lesion; f) (psychiatric) disease interfering with cognitive testing or follow-up; g) recent or current use of acetylcholine-esterase inhibitors, neuroleptic agents, L-dopa, or dopa-agonists/antagonists; h) non-SVD–related WML mimics (e.g., multiple sclerosis); i) prominent visual or hearing impairment; j) language barrier; and k) MRI contraindications or known claustrophobia.

From 1,004 invited individuals, 727 were eligible and 525 agreed to participate. Complete information, including a cerebral MRI scan was obtained from 503 individuals because in 22 individuals exclusion criteria were found during their visit to our research center (14 with unexpected claustrophobia, one died before MRI scanning, one was diagnosed with multiple sclerosis, in one there was a language barrier, one subject fulfilled the criteria for Parkinson disease, and 4 met the dementia criteria), yielding a response of 71.3% (503/705) for the original cohort of the study. These 503 individuals had symptoms of TIA or lacunar syndrome (n = 219), cognitive disturbances (n = 245), motor disturbances (n = 97), depressive symptoms (n = 100), or a combination thereof.

Standard protocol approvals, registrations, and patient consents. All participants signed an informed consent form. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

Assessment of physical activity. Leisure-time physical activity was assessed with a questionnaire that has been proven valid and useful in other large studies.[2,12] Subjects were asked to estimate the average amount of time per week during the past year spent on the following activities: running (≤10 min/mile); jogging (>10 min/mile); walking outdoors; racquet sports; lap swimming; bicycling; aerobic dance or use of exercise machines; other vigorous activities (e.g., lawn mowing); and low-intensity exercise (e.g., yoga, stretching, toning). Participants were also asked to indicate their usual outdoor walking pace: easy (>30 min/mile), normal (21–30 min/mile), brisk (16–20 min/mile), or very brisk (≤15 min/mile). A metabolic equivalent (MET) value was assigned to each activity according to accepted standards.[13]

One MET is proportional to the energy expended while sitting quietly. MET values were 9.8 for running; 7 for jogging; 7.3 for racket sports; 7 for lap swimming; 4 for bicycling; 5.5 for aerobic dance and/or use of exercise machines; 6 for other vigorous activities; and 4 for low-intensity exercise. MET values for walking varied by reported pace, from 2.8 METs for easy pace to 5 METs for very brisk pace. For each activity, we estimated the energy expended in MET-hours/week, by multiplying its MET value by the time spent performing it.[2]

Other covariates. Systolic and diastolic blood pressure were measured 3 times in supine position after 5 minutes of rest; the average of these 3 measurements was used. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and/or the use of blood pressure–lowering agents.[14] Information on blood pressure–lowering medication was collected by means of a structured, computerized questionnaire, which was filled out by a resident in neurology.

Height and weight were measured in light clothing without shoes, and body mass index was calculated as weight divided by height (in meters) squared. Information on smoking behavior (current, former, and never) was obtained through a standardized, structured questionnaire, which was checked during the interview. Diabetes mellitus and hypercholesterolemia were considered to be present if the participant was taking oral glucose-lowering drugs or insulin or lipid-lowering drugs, respectively. Level of education was considered an additional confounder.

Conventional MRI analysis. MRI scans of all subjects were acquired on a single 1.5-tesla scanner (Magneton Sonata; Siemens Medical Solutions, Erlangen, Germany). The protocol included a 3-dimensional T1 magnetization-prepared rapid gradient-echo sequence (repetition time/echo time/inversion time = 2,250/3.68/850 milliseconds; flip angle 15°; voxel size 1.0 × 1.0 × 1.0 mm), a fluid-attenuated inversion recovery (FLAIR) sequence (repetition time/echo time/inversion time = 9,000/84/2,200 milliseconds; voxel size 1.0 × 1.2 × 5.0 mm, plus an interslice gap of 1 mm), and a diffusion tensor imaging (DTI) sequence (repetition time/echo time = 10,100/93 milliseconds, voxel size 2.5 × 2.5 × 2.5 mm, 4 unweighted scans, 30 diffusion-weighted scans with b-value of 900 s/mm^2).

White matter signal hyperintensities on FLAIR scans, which were not, or only faintly, hypointense on T1-weighted images, were considered WMLs, except for gliosis surrounding infarcts. WMLs were manually segmented on FLAIR images by 2 trained raters. Total WML volume was calculated by summing the segmented areas multiplied by slice thickness. Lacunar infarcts were rated and defined as areas with a diameter >2 mm and <15 mm with low signal intensity on T1 and FLAIR, ruling out enlarged perivascular spaces and infraputaminal pseudolacunes.[15–17] All imaging analyses were performed by raters blinded to clinical information. In a random sample of 10%, interrater variability for total WML volume yielded an intraclass correlation coefficient of 0.99; intra- and interrater reliability for number of lacunar infarcts a weighted κ of 0.80 and 0.88. We computed gray and white matter tissue and CSF probability maps using Statistical Parametric Mapping 5 (Wellcome Department of Cognitive Neurology, University College London, UK) unified segmentation routines on the T1 images.[18] Binary tissue maps were created by thresholding the probability maps at 0.5. Total gray and white matter volumes were calculated by summing all voxel volumes that belonged to that class. Total brain volume was taken as the sum of total gray and total white matter volume.

DTI analysis. Diffusion data were first preprocessed using an in-house–developed algorithm for patching artifacts from cardiac and head motion.[19] In short, this iteratively reweighted least-squares algorithm produces robust diffusion tensor estimates and provides weightings that are used to detect and correct head and cardiac motion artifacts in the diffusion-weighted data. Next, affine misalignments from eddy currents and subject motion were corrected simultaneously by minimization of the residual diffusion tensor errors.[20] Using DTIFit within the Functional MRI of the Brain Diffusion Toolbox, we created the FA, MD, AD, and RD images, which were then fed into the TBSS pipeline.[7] In short, an FA skeleton was created by thinning the mean FA image based on the FA values. Subsequently, this skeleton was thresholded at 0.3 to include the major white matter tracts and to account for the intersubject variability. All normalized FA data were then projected onto this skeleton. By applying the projection vectors from each subject's FA-to-skeleton transformation, we projected the images of MD, AD, and RD onto the mean FA skeleton. During the normalization procedures, the images were not modulated with the Jacobian of the spatial transformations (i.e., not corrected for the brain volume). These data were then fed into voxel-wise, cross-subject statistics. The volume-averaged FA and MD were calculated in the NAWM and WMLs. All images were visually checked for motion artifacts and coregistration errors. The final sample resulted in 440 subjects after additional exclusion of 63 subjects because of excessive motion artifacts or the presence of territorial infarcts.

Statistical analysis. The χ^2 tests and analysis of variance were used to compare subject characteristics by quartile of physical activity. Physical activity was expressed as the sum of all energy expended on the different leisure activities, calculated in MET-hours/week. The baseline characteristics were presented as mean ± SD; for the skewed distributed parameters, the median and interquartile ranges were calculated.

We performed linear regression analyses to investigate the relation between physical activity and WML volume, adjusted for age, sex, education, normalized total brain volume, and cardiovascular risk factors, including hypertension and/or the use of antihypertensive drugs, body mass index, diabetes mellitus, the use of lipid-lowering drugs, and smoking status.

For the TBSS analyses, we assessed voxel-wise regression coefficients between the skeletal DTI parameters (FA, MD, RD, and AD) and physical activity, while adjusting for age, sex, education, normalized total brain volume, and cardiovascular risk factors.

We performed the voxel-wise analysis for the TBSS data using a permutation-based statistical interference tool for nonparametric approach as a part of Functional MRI of the Brain Software Library.[7,21] The number of the permutation tests was set at 5,000, and significant associations were determined using the threshold-free cluster-enhancement with a threshold of $p < 0.05$, corrected for the multiple comparisons.[22]

Mean differences in FA and MD by quartile of physical activity were calculated in both NAWM and WMLs, adjusted for age, sex, education, and cardiovascular risk factors. These analyses were performed using SPSS statistical software, version 19.0 (IBM Corp., Armonk, NY).

RESULTS Table 1 presents the baseline characteristics of the total study population. Subjects were of similar age across quartiles of physical activity. Compared with subjects in lower quartiles of physical activity, subjects in higher quartiles had a lower blood

Table 1 Characteristics of the study population by quartiles of physical activity

	Quartiles of physical activity (MET-h/wk)			
Characteristics[a]	1 (<34, 0) (n = 104)	2 (34.0–55.0) (n = 113)	3 (55.1–84.5) (n = 111)	4 (>84.5) (n = 112)
Age,[b] y	67.9 (9.0)	66.0 (8.5)	63.2 (8.3)	63.8 (9.0)
Women, n (%)	46 (44.2)	48 (42.5)	60 (54.1)	47 (42.0)
Education,[c] n (%)	93 (89.4)	102 (90.3)	101 (91.0)	103 (92.0)
MMSE score	28.0 (1.7)	28.2 (1.6)	28.4 (1.4)	28.2 (1.6)
Systolic blood pressure,[d] mm Hg	144.7 (23.4)	142.7 (22.0)	136.5 (18.4)	136.9 (17.2)
Diastolic blood pressure, mm Hg	78.8 (9.9)	78.4 (9.8)	77.6 (8.9)	78.7 (8.9)
Use of antihypertensive drugs,[d] n (%)	67 (64.4)	62 (54.9)	53 (47.7)	45 (40.2)
Use of lipid-lowering drugs, n (%)	50 (48.1)	46 (40.7)	48 (43.2)	49 (43.8)
Diabetes,[b] n (%)	24 (23.1)	18 (15.9)	5 (4.5)	13 (11.6)
Body mass index,[d] kg/m^2	28.2 (4.2)	27.2 (4.0)	26.5 (4.5)	26.5 (3.9)
Alcohol intake, U/wk	8.3 (10.6)	8.2 (9.4)	7.6 (8.7)	6.2 (8.0)
Smoking status, n (%)				
Never	34 (32.7)	32 (28.3)	30 (27.0)	38 (33.9)
Former	51 (49.0)	66 (58.4)	68 (61.3)	55 (49.1)
Current	19 (18.3)	15 (13.3)	13 (11.7)	19 (17.0)

Abbreviations: MET = metabolic equivalent; MMSE = Mini-Mental State Examination.
[a] Data are means and standard errors unless indicated as percent.
[b] Association with physical activity ($p < 0.001$).
[c] Beyond primary school.
[d] Association with physical activity ($p < 0.05$).

pressure and were less likely to use antihypertensive medication. Diabetes and depressive symptoms were less prevalent in more active subjects.

Physical activity was negatively linearly related to total WML volume ($\beta = -0.04$ [95% confidence interval: -0.01 to -0.07]; $p = 0.013$). Being more physically active was negatively related to the MD in both NAWM and WMLs. We found significantly higher levels of microstructural integrity (expressed by MD) in higher quartiles compared with the lowest quartiles of physical activity (mean difference for highest quartile $= -0.15$ mm^2/s $\times 10^{-7}$ and -0.23 mm^2/s $\times 10^{-7}$ in NAWM and WML; p trend $= 0.001$) (table 2).

The figure shows the relation between the voxelwise analysis of the FA, MD, AD, and RD and physical activity ($p < 0.05$, corrected for multiple comparisons). No significant relations were found between FA and physical activity, whereas in almost all voxels of the skeleton, significant relations were found between MD, AD, and RD and physical activity. This was true after adjustment for age, sex, and normalized total brain volume (model 1) and after additional adjustment for cardiovascular risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, body mass index, and smoking status (model 2).

DISCUSSION In this large cross-sectional study, physical activity in participants with SVD was related to WML volume on conventional FLAIR and to white matter microstructural integrity using whole-brain voxel analysis and TBSS. Lower levels of physical activity were associated with higher MD, AD, and RD in multiple regions of the white matter skeleton, reflecting impaired microstructural integrity. These regions were located in both NAWM and WMLs. We did not find such an association for FA. The same results were found for analyses in total NAWM and WMLs.

Some methodologic issues need to be considered. Because of the cross-sectional nature of our study, one cannot draw conclusions for directionality and causality. Although we used a structured questionnaire to assess daily leisure-time physical activity, the use of MET values may not reflect the exact amount of energy expended; some subjects perform activities more vigorously than others. It could also be that our results have been influenced by recall bias using self-reports of physical activity. This may especially be the case in preexisting cognitive impairment, which could cause a reduction in physical activity, such that our findings could reflect reverse causation. However, we consider this very unlikely to have occurred, given our relatively low mean age of the total study population (65.2 years) and high mean Mini-Mental State Examination score (28.2) at baseline. Furthermore, health conditions such as a history of emphysema or chronic obstructive pulmonary disease, fatigue, or a history of osteoarthritis were not taken into account, and could have therefore limited subjects' daily exercise. For instance, subjects with knee problems could have a lower microstructural integrity of the white matter because of their physical limitations, rather than being physically less active due to cognitive impairment. We consider it unlikely that this misclassification could have influenced our results. However, if any, it would have led to an underestimation of the presumed relation between exposure and outcome.

Strong elements of our study include its large sample size, the single-center design, the use of a single scanner, and the high response rate. Furthermore, a structured assessment of the risk factor was used and all associations were corrected for possible confounders, strongly related to SVD and brain structural deficits. We believe our findings have high external validity for other individuals with SVD; however, our findings cannot be generalized to healthy individuals older than 50 years from the general population because they were not included in our study.

The lack of an association in the present study between FA and physical activity may initially seem counterintuitive, but this may presumably be attributable to a simultaneous increase in both AD and RD. Consequently, the FA (which is a function of this ratio) will remain relatively unchanged. This is

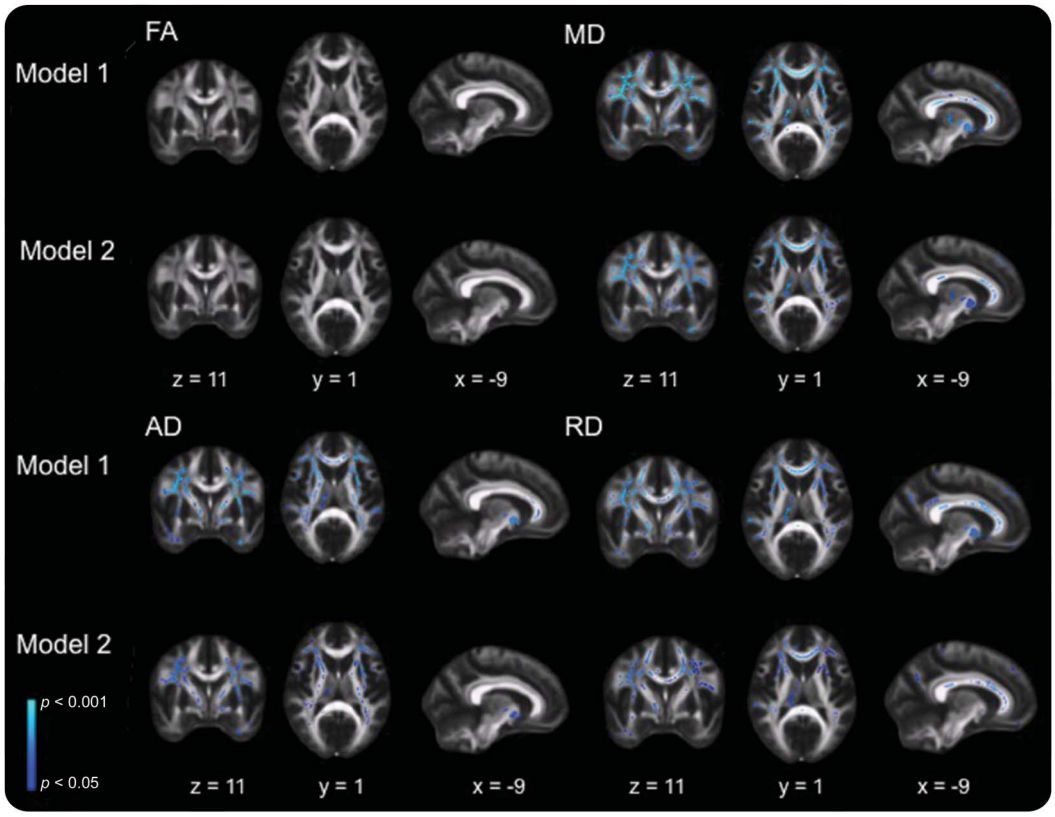
Table 2 Mean differences in DTI parameters in NAWM and WMLs by quartile of physical activity[a]

	Quartile of physical activity				
DTI parameters	1 (lowest)	2	3	4 (highest)	p Value for trend
FA in NAWM	Reference	0.15 (−0.32 to 0.61)	0.27 (−0.22 to 0.75)	0.34 (−0.14 to 0.82)	0.15
FA in WMLs	Reference	−0.07 (−0.83 to 0.69)	0.17 (−0.62 to 0.96)	−0.05 (−0.82 to 0.73)	0.95
MD in NAWM	Reference	−0.06 (−0.14 to 0.03)	−0.09 (−0.17 to 0.00)	−0.15 (−0.23 to −0.06)	0.001
MD in WMLs	Reference	−0.01 (−0.15 to 0.13)	−0.11 (−0.26 to 0.03)	−0.23 (−0.37 to −0.09)	0.001

Abbreviations: DTI = diffusion tensor imaging; FA = fractional anisotropy; MD = mean diffusivity; NAWM = normal-appearing white matter; WML = white matter lesion.

[a] Values are estimated mean differences (95% confidence interval) between the reference (lowest quartile of physical activity) and each quartile, calculated by analysis of variance. FA = $\times 10^{-2}$; MD = mm^2/s $\times 10^{-7}$.

Figure Association between DTI parameters and physical activity



Voxel-wise analysis of the FA, positively related with physical activity, and MD, AD, and RD negatively associated with physical activity. Adjusted for age, sex, education, and normalized total brain volume (model 1), or age, sex, education, normalized total brain volume, and cardiovascular risk factors (model 2), thresholded at $p < 0.05$ and corrected for multiple comparisons. The statistical maps are superimposed onto the spatially normalized (Montreal Neurological Institute stereotactic space) FA and MD maps. AD = axial diffusivity; DTI = diffusion tensor imaging; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity

in line with a previous study, which showed that nonfractional measures of diffusivity (AD, RD, and MD) were more sensitive than FA for assessing microstructural integrity changes in (early) Alzheimer disease.[23] Patterns of changes in FA, MD, AD, and RD may give information on the underlying histopathologic mechanisms leading to loss of white matter microstructural integrity, but the exact processes remain poorly understood. Although a reduction in FA and a predominant increase in AD are believed to reflect demyelination and axonal loss,[5] it has been suggested that different pathologies, different stages of disease, or the rate of degeneration can also differentially affect the tensor.[23] Therefore, any interpretation of the underlying neuropathologic correlates in DTI remains speculative.

We are not aware of other studies investigating the relation between physical activity and the microstructural integrity of cerebral white matter. There is emerging evidence from observational studies that physical activity may have a protective effect on the risk of cognitive decline and dementia; however, results from intervention studies are less clear.[24]

Our findings among patients without dementia who have SVD may suggest that lower cognitive performance could be the result of a lower microstructural integrity of cerebral white matter and FLAIR-visible WMLs because of less stringent physical activity.

A possible biological mechanism for the association between physical activity and integrity of the cerebral white matter could be that physical activity exerts a positive influence on cardiovascular risk factors, such as hypertension, diabetes, obesity, and dyslipidemia and may improve cerebral blood flow.[4,25] It seems very plausible that cerebral microstructural changes, assessed with DTI, reflect pathology that is under the influence of these vascular risk factors, thereby contributing to cognitive decline. Evidence for the relation between impaired microstructural integrity and cognition in subjects with SVD has been found in previous DTI studies.[26–28]

This study showed that lower levels of physical activity were associated with a lower microstructural integrity of multiple white matter fibers connecting different cortical and subcortical regions, independent of education and cardiovascular risk factors. Future

longitudinal studies are needed to investigate the causal relation between physical activity and microstructural impairment of cerebral white matter assessed with DTI in relation to cognitive decline.

AUTHOR CONTRIBUTIONS

R.A.R. Gons and A.M. Tuladhar: acquisition of data, analysis and interpretation. K.F. de Laat and A.G.W. van Norden: acquisition of data. E.J. van Dijk, D.G. Norris, and M.P. Zwiers: critical revision of the manuscript for important intellectual content. F.-E. de Leeuw: study concept and design, study supervision, and critical revision of the manuscript for important intellectual content.

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DISCLOSURE

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