Modifiable cardiovascular risk factors and axial motor impairments in Parkinson disease

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ABSTRACT

Objective: Cardiovascular comorbidities associate with neurodegeneration in the elderly and may contribute to extranigral pathologies and medically refractory axial motor features in Parkinson disease (PD).

Methods: We explored differences in the estimated rate of axial motor feature accrual between patients with PD with and without elevated cardiovascular risk factors as estimated by the Framingham General Cardiovascular Disease risk-scoring algorithm in a cross-sectional cohort study. All participants underwent motor evaluations with the Movement Disorders Society revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS), [^{11}C]dihydrotetrabenazine (DTBZ) monoaminergic brain PET imaging, and MRI.

Results: Participants with PD with elevated Framingham risk (FR) scores (n = 63, 74.1%) showed higher unadjusted rates of total MDS-UPDRS (t = 3.60, p = 0.0006) and axial motor scores (t = 3.98, p = 0.0001) per estimated year of motor symptoms compared to participants with normal-range risk scores (n = 22, 25.9%). After controlling for sex, Montreal Cognitive Assessment score, frontal leukoaraiosis severity, and striatal DTBZ activity, elevated risk factor status was associated with the rate of accrual of axial motor impairments (R^2 = 0.206; t = 2.62, p = 0.011) but not with total MDS-UPDRS motor score (R^2 = 0.198; t = 1.51, p = 0.135). Frontal leukoaraiosis was associated with the rate of axial and total MDS-UPDRS scores per year of symptoms and also with elevated systolic blood pressure (R^2 = 0.291; t = 2.30, p = 0.024) in a separate risk-factor model.

Conclusion: Cardiovascular risk factors may contribute to axial motor features in PD. Early modification of cardiovascular risk factors, including hypertension, deserves further study as a novel disease-modifying strategy in PD. ***Neurology*® 2014;82:1514–1520**

GLOSSARY

BMI = body mass index; **DR** = dopamine-resistant; **DTBZ** = dihydrotetrabenazine; **DVR** = distribution volume ratio; **FLAIR** = fluid-attenuated inversion recovery; **FR** = Framingham risk; **MDS-UPDRS** = Movement Disorders Society revised Unified Parkinson's Disease Rating Scale; **MLR** = multivariable linear regression; **MoCA** = Montreal Cognitive Assessment; **PD** = Parkinson disease; **VOI** = volume of interest.

Idiopathic Parkinson disease (PD) manifests with a variety of motor and nonmotor features. Advanced PD typically involves the development of dopamine medication–related motor fluctuations as well as dopamine-resistant (DR) features of axial motor impairments and progressive cognitive impairment.[1,2] While the presence of these features marks the onset of advancing PD, the rate at which DR features develop varies significantly between patients and is not predicted easily.[3] Although nigrostriatal dopaminergic denervation is a key pathologic hallmark of PD, increasing evidence[4–6] suggests that neurodegeneration in other regions of the nervous system, collectively termed extranigral neurodegeneration, may account for many DR motor features of PD, including axial motor impairments.

Cardiovascular risk factors, including hypertension, diabetes, and obesity, are implicated as risk factors for neuronal injury in healthy elderly individuals and in those with dementia.[7,8]

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Cardiovascular risk factors may similarly promote the development of extranigral pathology in PD, including frontal white matter hyperintensities detectable with MRI.

We employed a cross-sectional cohort study to explore differences in the estimated rate of development of axial motor impairments between participants with PD with well-controlled cardiovascular risk factors for age and sex—as determined by the 10-year general cardiovascular disease Framingham risk (FR) score—and those with elevated FR scores. We hypothesized that elevated FR scores would correlate with frontal leukoaraiosis severity and the more rapid development of critical DR disease features of axial motor impairments.

METHODS **Participants.** This cross-sectional study involved 85 participants with idiopathic PD. This sample size represents the number of participants with PD in our single-center cohort with matching clinical, PET, and MRI evaluations sufficient for analysis. All participants met UK Brain Bank clinical diagnostic criteria for PD.[9] No participants met diagnostic criteria for vascular parkinsonism.[10] All participants displayed typical patterns of nigrostriatal dopaminergic denervation with monoaminergic dihydrotetrabenazine (DTBZ) PET imaging. Participants were recruited from movement disorders clinics at the University of Michigan Medical Center and the Veterans Affairs Ann Arbor Health System between 2009 and 2013. Demographic information for all participants is presented in table 1. All participants underwent the Movement Disorders Society revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor examination in the practically defined "off" state. A 5-item axial motor subscore was calculated using the sum of the following items on the MDS-UPDRS motor examination[11]: 3.1 Speech, 3.9 Arising from a Chair, 3.10 Gait, 3.12 Postural Stability, and 3.13 Posture using the Levy et al.[12] criteria. All other MDS-UPDRS motor examination items were categorized as nonaxial. Motor subtypes including tremor-predominant, postural instability and gait difficulty–predominant, and indeterminate were calculated using recently published guidelines for the MDS-UPDRS motor examination.[13] All participants provided a detailed clinical history including a history of their parkinsonian motor symptoms. As in previously reported cross-sectional studies exploring PD feature heterogeneity,[14,15] an estimated rate of motor features accrued per year was calculated by dividing the axial and total MDS-UPDRS motor scores by the number of years of PD motor symptoms.

Framingham risk score assessment. All participants underwent a detailed medical history and examination, including an

Table 1 Participant demographics

Clinical characteristics	Mean (SD) or frequency		
	Overall cohort	Low-risk participants (n = 22)	Elevated-risk participants (n = 63)
Age, y	64.6 (7.1)	63.3 (8.1)	65.0 (6.7)
Sex, M/F[a]	60/25	10/12	50/13
Duration of motor symptoms[a,b]	5.6 (4.0)	8.4 (3.0)	4.6 (4.9)
Hoehn & Yahr Scale, n[c]			
1.0	3	0	3
1.5	5	0	5
2.0	21	7	14
2.5	39	12	27
3.0	15	2	13
4.0	2	1	1
MDS-UPDRS motor score	36.3 (14.6)	40.2 (15.0)	35.0 (14.4)
MDS-UPDRS motor score/year of motor symptoms[a,b]	9.8 (7.8)	6.3 (3.7)	11.1 (8.5)
Axial motor subscore	4.3 (2.6)	4.6 (2.3)	5.1 (3.1)
Axial motor subscore/year of motor symptoms[a,b]	1.3 (1.2)	0.7 (0.5)	1.5 (1.3)
Motor subtype prevalence (PIGD/ID/tremor)[c]	36/5/44	7/1/14	29/4/30
Levodopa dose equivalents[b]	670.9 (570.8)	751.8 (725.2)	642.7 (510.0)
Montreal Cognitive Assessment	26.0 (2.3)	26.6 (2.1)	25.8 (2.4)
Individual 10-year Framingham risk score[a,b]	22.6% (14.1)	10.6% (5.9)	26.8% (13.7)

Abbreviations: ID = indeterminate subtype; MDS-UPDRS = Movement Disorders Society revised Unified Parkinson's Disease Rating Scale; PIGD = postural instability and gait difficulty–predominant subtype; tremor = tremor-predominant subtype.
[a] $p < 0.05$ for differences between low-risk participants and elevated-risk participants.
[b] Satterthwaite t test due to unequal variances.
[c] Fisher exact test.

assessment of medical comorbidities, current medications, and a standardized measurement of height and weight to calculate body mass index (BMI) as well as sphygmomanometer measurement of resting blood pressure while seated. This information—specifically age, sex, smoking status, BMI, systolic blood pressure, diabetes status, and use of antihypertensive medications—was used to calculate the simplified 10-year Framingham General Cardiovascular Disease Risk Score (FR score) (http://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php).[16] Smoking status data were missing for 4 participants—in these cases, participants were assumed to be nonsmokers for the purposes of FR scoring.

The 2 distinct FR scores derived included an individualized percentage risk score aimed at estimating the 10-year likelihood of cardiovascular events ("individual" score) and a "normative" score derived by setting all cardiovascular risk factor parameters to within the normal range, given an individual's fixed age and sex.[16] Because FR scoring algorithms differ by sex, treating FR score as a continuous variable was not possible. Participants were grouped into 2 categories where low-risk individuals (n = 22) were defined as those in whom the ratio of individual/normative FR score was ≤1.0 and elevated-risk individuals (n = 63) were those in whom the ratio was >1.0. Dichotomizing the cohort in this fashion allowed us to explore specific associations not simply with higher risk scores, but with elevated modifiable cardiovascular risk burden and heterogeneity in motor progression among participants with PD.

Standard protocol approvals, registrations, and patient consents. The study was approved by the institutional review boards of the University of Michigan and the Ann Arbor Veterans Affairs Medical Center. Written informed consent was obtained from all participants.

Imaging. ***DTBZ PET imaging.*** DTBZ PET imaging was performed in 3D imaging mode using an ECAT Exact HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquires 63 transaxial slices (slice thickness 2.4 mm; intrinsic in-plane resolution 4.1 mm full-width at half maximum over a 15.2 cm axial field of view). A NeuroShield (Scanwell Systems, Montreal, Canada) head-holder/shielding unit was attached to the patient bed to reduce the contribution of detected photon events originating from the body outside the scanner field of view.[17] Before beginning radioligand injections, a 5-minute transmission scan was acquired using rotating ^{68}Ge rods for attenuation correction of emission data using the standard vendor-supplied segmentation and reprojection routines.

No-carrier-added (+)-[^{11}C]DTBZ (250–1,000 Ci/mmol at the time of injection) was prepared as reported previously.[18] Dynamic PET scanning was performed for 60 minutes immediately following a bolus injection of 55% of 555 MBq (15 mCi) of (+)-[^{11}C]DTBZ dose (containing less than 50 μg of cold DTBZ mass) over the first 15–30 seconds of the study, while the remaining 45% of the dose was continuously infused over the next 60 minutes, resulting in stable arterial tracer levels and equilibrium with brain tracer levels after 30 minutes.[19] A series of 15 scan frames over 60 minutes were obtained as follows: 4 × 30 seconds; 3 × 1 minute; 2 × 2.5 minutes; 2 × 5 minutes; and 4 × 10 minutes.

MRI. All participants underwent brain MRI on a 3T Philips Achieva system (Philips, Best, the Netherlands) utilizing an 8-channel headcoil. This protocol has been described previously by our group.[20] Participants with findings of a previous large-artery stroke, tumor, demyelination, or findings suggestive of an atypical parkinsonian disorder were excluded from this study. T1-weighted and volumetric fluid-attenuated inversion recovery (FLAIR) sequences were obtained.

Frontal leukoaraiosis burden MRI analysis. Bifrontal leukoaraiosis burden was calculated in all participants using an automated routine involving the analysis of coregistered FLAIR and T1-weighted MRI sequences for each participant.[20,21] This method uses cerebellar white matter, a region relatively unaffected by age-associated leukoaraiosis, as a reference region for comparison of frontal white matter hyperintensities. FLAIR-based white matter hyperintensities were defined as 1.65 standard deviations greater than the reference region mean in intensity for bilateral frontal regions for each individual participant.[20,21] As in our previous studies, frontal white matter hyperintensity burden was normalized by the frontal white matter volume and transformed using the natural log to account for a non-normal distribution of data values. Leukoaraiosis values $\times 10^5$ are presented in tables 2 and 3.

PET analysis. Interactive data language image analysis software (Research Systems, Inc., Boulder, CO) was used to manually trace the striatal volume of interest (VOI) on MRI to include the caudate nucleus and putamen of each hemisphere. Total striatal distribution volume ratio (DVR) was defined as the mean of bilateral caudate and putaminal regions. All image frames were spatially coregistered within participants with a rigid-body transformation to reduce the effects of participant motion during the imaging session. These motion-corrected PET frames were spatially coregistered to the T1-weighted MRI using standard coregistration procedures in SPM8b implemented in Matlab 2010b (The MathWorks, Natick, MA). Time activity curves for each VOI were generated from the spatially aligned PET frames. [^{11}]C-DTBZ vesicular monoamine transporter type 2 DVR was then estimated by using the Logan plot graphical

Table 2 Multivariable linear regression for estimated rate of motor progression

	Annual rate of total MDS-UPDRS motor examination progression (R^2 = 0.198)				Annual rate of axial MDS-UPDRS motor examination progression (R^2 = 0.206)			
	β	Standard error	t Test	*p* Value	β	Standard error	t Test	*p* Value
Female sex	1.73	1.96	0.88	0.379	0.56	0.30	1.90	0.062
Striatal DTBZ DVR	5.45	2.91	1.87	0.065	0.072	0.44	0.16	0.870
Frontal leukoaraiosis ($\times 10^5$)	2.86	1.22	2.35	0.022[a]	0.40	0.19	2.15	0.035[a]
Montreal Cognitive Assessment	−0.62	0.35	−1.77	0.081	−0.03	0.05	−0.50	−0.617
Elevated risk factor status	3.15	2.09	1.51	0.135	0.83[a]	0.31	2.62	0.011[a]

Abbreviations: DTBZ = dihydrotetrabenazine; DVR = distribution volume ratio; MDS-UPDRS = Movement Disorders Society revised Unified Parkinson's Disease Rating Scale.
[a] $p < 0.05$.

Table 3 Multivariable linear regression for frontal leukoaraiosis severity

	Frontal leukoaraiosis severity ($\times 10^5$) ($R^2 = 0.291$)			
	β	Standard error	*t* Test	*p* Value
Female sex	0.344	0.157	2.18	0.032[a]
Age	0.032	0.011	2.95	0.004[a]
Diabetes status	0.165	0.309	0.53	0.595
Systolic blood pressure	0.012	0.005	2.30	0.024[a]
Use of antihypertensives	0.148	0.151	0.99	0.327
Smoking status	0.455	0.295	1.54	0.127
Body mass index	−0.179	0.019	−0.95	0.344

[a] $p < 0.05$.

analysis method[22] with the time activity curves as the input function and neocortex as reference tissue.[19,22–24]

Statistical analysis. Chi-square tests, the Fisher exact test, and 2-sample pooled and Satterthwaite *t* tests were used to compare demographic characteristics between participants with and without elevated FR scores. Multivariable linear regression (MLR) analysis was used to explore differences in the estimated rate of axial and total motor feature accrual between low-risk and elevated-risk participants. There was a sex difference between groups, which was controlled for in the MLR analysis. This analysis also controlled for potential confounder effects of Montreal Cognitive Assessment (MoCA) scores, striatal DTBZ DVR, and frontal leukoaraiosis severity. MoCA scores were chosen as a covariate to account for cognitive differences that might explain differential axial motor performance. By controlling for striatal DTBZ and frontal leukoaraiosis, we were able to explore the effects of dopaminergic neuropathology and a manifestation of nondopaminergic, vascular-linked pathology, respectively, on estimated rate of motor feature accrual. After finding significant associations between axial motor accrual rates and vascular-linked leukoaraiosis burden, an exploratory MLR analysis was conducted to determine the influence of each of the individual item components of the FR score on frontal leukoaraiosis burden. Age, BMI, and systolic blood pressure were treated as continuous variables in this model, while all other covariates were categorical. Each of the MLR analyses met the assumptions of normal distribution of residuals, constant variance, and the absence of multicollinearity. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS Demographic characteristics are presented in table 1. Eighty percent of participants (68/85) were Hoehn & Yahr stage 2.5 or less. According to MoCA operative cutoff scores validated in PD,[25] 1 out of 85 participants met criteria for dementia and 33 (n = 6 low-risk vs n = 27 high-risk; $\chi^2 = 1.67$, $p = 0.196$) met criteria for mild cognitive impairment. Although disease duration was noted to be shorter in elevated-risk participants, there were no differences between groups in age, Hoehn & Yahr score, axial or total UPDRS motor scores, or MoCA scores. As expected, participants in the high-risk group differed significantly ($p < 0.05$) from those in the low-risk group in BMI (29.2 ± 4.5 vs 24.3 ± 3.3), proportion of diabetic participants (6/63 vs 0/22), proportion of current smokers (6/63 vs 0/22), and mean systolic blood pressure (127.1 ± 14.1 vs 112.4 ± 9.4). There were no differences in levodopa dose equivalents between participants in the elevated-risk group compared to those in the low-risk group (642.7 ± 510.0 vs 751.8 ± 725.2; $t = 0.65$, $p = 0.52$).[26] The proportion of women was higher in the low-risk group. Low-risk participants had lower axial and total UPDRS motor scores/year compared to elevated-risk participants. Low-risk participants showed a lower mean striatal DTBZ DVR (1.81 ± 0.22 vs 1.97 ± 0.30; $t = 2.32$, $p = 0.023$) compared to elevated-risk participants. There was a nonsignificant trend toward greater leukoaraiosis scores in the elevated-risk group ($2.3 \times 10^{-5} \pm 7.2 \times 10^{-6}$ vs $2.0 \times 10^{-5} \pm 6.1 \times 10^{-6}$; $t = 1.80$, $p = 0.076$).

Multivariable linear regression was used to investigate differences between the 2 groups in the rate of axial and total motor scores per year (table 2). Elevated FR score factor status associated with greater axial motor feature rate but not with total MDS-UPDRS motor score rate. Lower striatal DTBZ DVR showed a nonsignificant trend towards association with the rate of total motor score but no correlation with rate of axial motor feature accrual. Frontal leukoaraiosis burden associated strongly with both total and axial motor feature accrual rate even after accounting for elevated FR status.

To explore whether the relationship between leukoaraiosis and the estimated rate of MDS-UPDRS total motor feature accrual was attributable to the axial-specific portion of the motor examination alone, we created a separate dependent variable to estimate the annual rate of progression of all nonaxial components of the MDS-UPDRS motor examination. In this model ($R^2 = 0.187$, $F = 3.65$, $p = 0.005$), frontal leukoaraiosis burden ($\times 10^5$) ($\beta = 2.39$, $t = 2.25$, $p = 0.027$) and striatal DTBZ DVR ($\beta = 5.19$, $t = 2.05$, $p = 0.044$) showed significant

associations with the estimated rate of nonaxial motor progression. There were no associations seen between estimated rate of nonaxial motor accrual and sex ($\beta = 1.23$, $t = 0.72$, $p = 0.47$), MoCA score ($\beta = -0.53$, $t = -1.76$, $p = 0.08$), or elevated cardiovascular risk factor status ($\beta = 2.39$, $t = -1.31$, $p = 0.19$).

A multivariable regression model explored the association between frontal leukoaraiosis and individual item elements of the 10-year General Cardiovascular Disease FR score (table 3). Female sex, advanced age, and elevated systolic blood pressure all associated with increased frontal leukoaraiosis severity. No associations were seen between frontal leukoaraiosis burden and diabetes status, smoking status, antihypertensive use, age, or BMI. A post hoc comparison of frontal leukoaraiosis burden between sexes showed a nonsignificant trend with greater leukoaraiosis severity seen in women ($2.4 \times 10^{-5} \pm 8.5 \times 10^{-6}$ vs $2.1 \times 10^{-5} \pm 6.1 \times 10^{-6}$; $t = 1.74$, $p = 0.092$).

DISCUSSION Modifiable cardiovascular risk factors are increasingly recognized as a driver of neuropathology in degenerative dementias, including Alzheimer disease.[7] Our results suggest that cardiovascular comorbidities may play a pathogenic role in exacerbating axial motor impairments in PD, independent of nigrostriatal dopaminergic denervation. Elevated Framingham cardiovascular risk scores and frontal leukoaraiosis both independently predicted higher estimated rates of axial motor impairments, suggesting heterogeneous mechanisms that may extend beyond isolated microvascular disease.

Frontal leukoaraiosis strongly predicted the rate of advancement in axial, nonaxial, and total motor scoring. These findings require validation in a longitudinal PD cohort but raise questions about the potential role of extranigral pathology not only on influencing the heterogeneous presentation of PD features but also variable rates of advancing motor disability. Cross-sectional diffusion tensor imaging studies in early PD have shown a preferential breakdown of frontal white matter pathways, suggesting that such pathology may advance in parallel with nigrostriatal dopaminergic terminal loss.[27,28] Our results add to these findings and raise the possibility that vascular-mediated neuropathology may be a mediator of variable rates of disease progression in PD through additive effects superimposed upon already-present dopaminergic terminal loss. Frontal leukoaraiosis most likely contributes to DR motor features not by altering transmission through the direct or indirect pathway per se but rather by altering the integrity of corticostriatal and cortical–cortical connections leading to dysfunction of downstream targets of dopaminergic therapies. Alternatively, it may represent an indirect staging marker for various types of unobserved vascular-related brain pathology.

As expected, frontal leukoaraiosis pathology was associated with age and elevated blood pressure. Interestingly, frontal leukoaraiosis burden was also associated with female sex. Greater progression of deep white matter hyperintensities in women has been reported previously in healthy elderly individuals.[29] The greater degree of frontal leukoaraiosis seen among women in our study could conceivably relate to sex-specific factors influencing white matter susceptibility or to other inherent sex differences in neuronal projection system integrity in PD. We previously reported that men with PD have roughly 6% lower caudate dopaminergic and neocortical cholinergic innervation than women[30]—it is possible that women with PD may manifest with relatively distinctive disease-specific features, whose pathogenesis is more closely tied to acquired risk factors. Further validation of our sex–leukoaraiosis findings is needed.

Although our study specifically explored leukoaraiosis, cardiovascular comorbidities contribute to a wide variety of neuropathologies in the elderly, including macroscopic findings of diffuse cortical atrophy,[31] CNS inflammatory states,[32] and possibly cellular-level changes including dysregulation of CNS insulin signaling or amyloid peptide metabolism.[33,34]

Limitations of our study include its cross-sectional nature, which introduces the possibility of recall bias on the part of participants asked to recall when their parkinsonian motor symptoms began. Of note, we use the term "estimated rate of axial motor burden per year" as an assessment of rise over run—namely, accumulated motor burden over duration of motor disease rather than a reflection of the true slope of disease progression. It is likely that the true slope of motor decline seen in early PD reflects a much more complex linear or nonlinear model whose precise nature is outside of the scope of this study. We also acknowledge that we employed the simplified FR score, which uses BMI rather than serum high-density lipoprotein. This simplified score, however, has shown good validity relative to the full score,[16] and is widely used in primary care settings. Elevated FR scoring may also associate with other unmeasured factors including diet and exercise. We dichotomized the cohort into low-risk and elevated-risk groups based upon a novel scoring system using the ratio of individual to normative FR scores. Using the ratio of individual/normative score allowed us to more reasonably categorize participants into those with excess treatable cardiovascular risk vs those with well-controlled cardiovascular risk. Parsing the group in this fashion provides a better focus on the specific role of potentially alterable cardiovascular risk factors, which can have great treatment implications for clinical practice. A significant limitation of the raw FR scores is that

they tend to give significant weight to an individual's specific age and sex—2 factors whose relative distributions differ in PD compared to the US population at large. Future studies would likely benefit from in-depth serologic testing to explore potential pathologic associations of more impaired glucose tolerance, hyperlipidemia, or systemic inflammation in PD.

Our results may have significant implications for future disease-modifying trials in PD. Modification of cardiovascular risk factors may be a plausible strategy to delay or mitigate the emergence of morbid axial motor impairments. Although leukoaraiosis is one possible mechanism for vascular-related neuronal injury in PD, its natural history is well-studied in non-PD elderly.[35] While leukoaraiosis burden may have only modest clinical significance for healthy elderly,[36] the impact of leukoaraiosis-linked axial motor disability in PD may be substantial. Interactive effects between neurodegeneration and cardiovascular impairments, including elevated blood pressure, are well-established for dementias and may represent novel opportunities to advance disease modification in neurodegenerative disorders through improvement of treatable cardiovascular risk factors. Given its unique clinical appearance in early stages and the strong long-term risk for dementia,[37] idiopathic PD may represent a uniquely promising neurologic condition in which to attempt a clinical trial of aggressive cardiovascular risk factor modification aimed at altering long-term clinical outcomes.

Comorbid and modifiable cardiovascular risk factors associate with the estimated rate of accrual of axial motor impairments in PD. These results should be evaluated in longitudinal studies. These findings suggest that modifying cardiovascular risk factors in early PD may represent a novel and potentially impactful disease-modifying strategy.

AUTHOR CONTRIBUTIONS

Vikas Kotagal: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, statistical analysis. Roger L. Albin: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, obtaining funding. Martijn L.T.M. Muller: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision. Robert A. Koeppe: study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Kirk A. Frey: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision, obtaining funding. Nicolaas I. Bohnen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision, obtaining funding.

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