Cerebral Small Vessel Disease Progression Increases Risk of Incident Parkinsonism

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Objective: Cerebral small vessel disease (SVD) is associated with motor impairments and parkinsonian signs cross-sectionally, however, there are little longitudinal data on whether SVD increases risk of incident parkinsonism itself. We investigated the relation between baseline SVD severity as well as SVD progression, and incident parkinsonism over a follow-up of 14 years.

Methods: This study included 503 participants with SVD, and without parkinsonism at baseline, from the RUN DMC prospective cohort study. Baseline inclusion was performed in 2006 and follow-up took place in 2011, 2015, and 2020, including magnetic resonance imaging (MRI) and motor assessments. Parkinsonism was diagnosed according to the UK Brain Bank criteria, and stratified into vascular parkinsonism (VaP) and idiopathic Parkinson's disease (IPD). Linear mixed-effect models were constructed to estimate individual rate changes of MRI-characteristics.

Results: Follow-up for incident parkinsonism was near-complete (99%). In total, 51 (10.2%) participants developed parkinsonism (33 VaP, 17 IPD, and 1 progressive supranuclear palsy). Patients with incident VaP had higher SVD burden compared with patients with IPD. Higher baseline white matter hyperintensities (hazard ratio [HR] = 1.46 per 1-SD increase, 95% confidence interval [CI] = 1.21–1.78), peak width of skeletonized mean diffusivity (HR = 1.66 per 1-SD increase, 95% CI = 1.34–2.05), and presence of lacunes (HR = 1.84, 95% CI = 0.99–3.42) were associated with increased risk of all-cause parkinsonism. Incident lacunes were associated with incident VaP (HR = 4.64, 95% CI = 1.32–16.32).

Interpretation: Both baseline SVD severity and SVD progression are independently associated with long-term parkinsonism. Our findings indicate a causal role of SVD in parkinsonism. Future studies are needed to examine the underlying pathophysiology of this relation.

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Cerebral small vessel disease (SVD) is a well-recognized cause of stroke and cognitive decline.[1,2] Historically, there is relatively little attention for the role of SVD in the decline of motor performance and parkinsonism.[3,4] Recently, severe white mater hyperintensities (WMHs) on magnetic resonance imaging (MRI) and higher level of postmortem indices of cerebrovascular pathologies were found to be associated with more rapid progression of parkinsonism signs.[5] Additionally, high burden of SVD has been reported in patients with parkinsonism, supporting the notion of an important role for SVD in the development of parkinsonism.[6,7] Yet, most studies on SVD and

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parkinsonism were cross-sectional or only assessed SVD at baseline and not its progression over time. They also mainly focused on whether cerebrovascular diseases co-occurred with or contributed to motor impairment severity in patients with already diagnosed parkinsonism.[6,8] So far, because of paucity of longitudinal data, it is unclear whether SVD (progression) precedes and contributes to the onset of parkinsonism. This is an important knowledge gap, because it can hypothesize a potential causal relation between SVD and parkinsonism and provide new targets for prevention and treatment.

Our pilot work indicated that severity of SVD is associated with onset of parkinsonism over a relatively short interval (5 years).[9] However, because of the small number of cases with incident parkinsonism, those results were inconclusive. In addition, due to the relatively short follow-up, patients who had mild parkinsonism symptoms may have been included at baseline of our study despite all efforts to exclude prevalent parkinsonism. Consequently, this may already have contributed to the incidence of parkinsonism, independent of SVD.

To overcome these limitations, we investigated the effect of SVD severity as well as SVD progression on incident all-cause parkinsonism, stratified into idiopathic Parkinson's disease (IPD) and vascular parkinsonism (VaP), during a 14-year follow-up. This approach not only allowed us to study larger numbers of patients with incident parkinsonism, but also to comply with additional criteria for causality[10] by investigating a dose–response temporal relation between severity and progression of SVD and the risk of incident parkinsonism.

Methods

Study Population

This study is embedded within the RUN DMC study, a longitudinal cohort study among individuals with sporadic SVD that investigates the risk factors and clinical outcomes of SVD. The study rationale and protocol of the RUN DMC study has been reported previously.[11] In short, a total of 503 consecutive community-dwelling patients, aged 50 to 85 years, who were referred to the Radboud Neurology outpatient clinic and who underwent cerebral imaging, were screened for baseline inclusion in 2006. SVD diagnosis was based on MRI and included presence of WMH or lacunes.[12] Main exclusion criteria at baseline included presence of dementia, parkinsonism, non SVD-related white matter lesions (eg, multiple sclerosis), and life expectancy of less than 6 months. Follow-up took place in 2011, 2015, and 2020. During all timepoints, patients underwent structured medical questionnaires, physical examination, motor tests, standardized neuropsychological examination, and brain MRI. A flowchart of patient participation in all follow-ups is shown in Figure 1.

The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study and all participants gave written informed consent.

Vascular Risk Factors

Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg during baseline examination or the use of blood pressure lowering agents. Diabetes and hypercholesterolemia were considered to be present if the patient was taking oral glucose-lowering drugs or insulin or lipid-lowering drugs. Information on smoking status was dichotomized into ever (current or former) or never smoking.

MRI Protocol

Images were acquired on 1.5-Tesla MRI (2006: Siemens, Magnetom Sonata; 2011 and 2015: Siemens, Magnetom Avanto) and included the following whole brain scans: 3D T1 MPRAGE imaging (isotropic voxel size 1.0 mm^3); fluid-attenuated inversion recovery (FLAIR) sequences (2006: voxel size 0.5 × 0.5 × 5.0 mm, interslice gap 1.0 mm; 2011 and 2015: voxel size 0.5 × 0.5 × 2.5 mm; interslice gap 0.5 mm); and a transversal T2*-weighted gradient echo sequence (2006: isotropic voxel size 2.5 mm^3, 4 unweighted scans, 30 diffusion weighted scans at b = 900 s/mm^2; 2011 and 2015: 8 unweighted scans, and 60 diffusion weighted scans at b = 900 s/mm^2). The same head coil was used at these 3 timepoints. Full acquisition details have been described previously.[11]

Brain Volumetry Processing

Grey matter volume (GMV), white matter volume (WMV), and CSF probability maps were produced using an SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) tissue segmentation algorithm from T1, corrected for WMH volume.[13] GMV, WMV, and CSF were computed by summing all voxels belonging to that tissue class multiplied by voxel volume in milliliters. The intracranial volume (ICV) was determined by taking the sum of GMV, WMV, and CSF. All volumes were normalized to baseline ICV to account for head size.

MRI Markers of SVD

MRI markers of SVD were rated according to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria.[14] WMH volumes were calculated by a semi-automatic WMH segmentation method and described in detail elsewhere.[15] Segmentations were

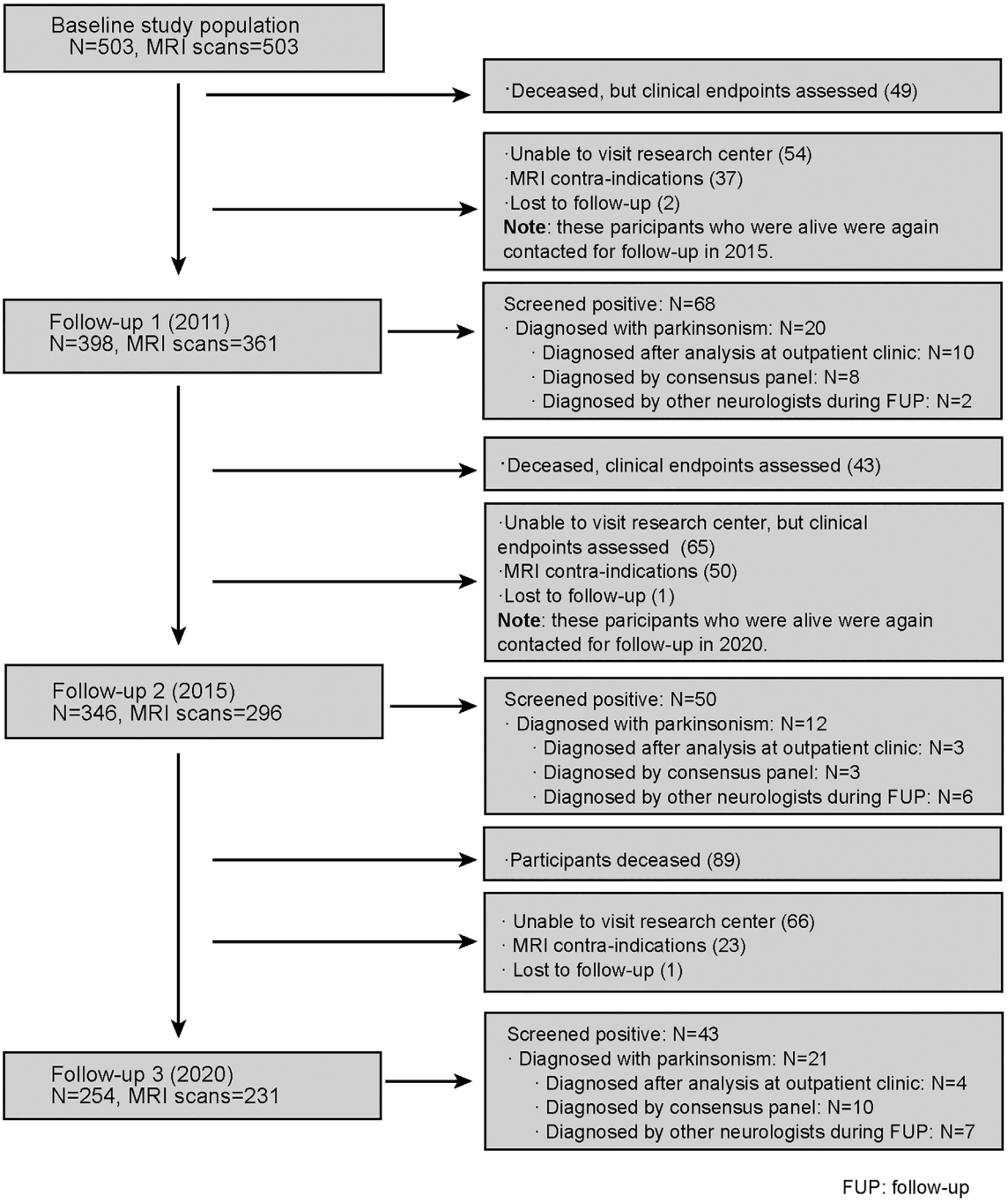

FIGURE 1: Flowchart study design of RUN DMC cohort from 2006 until 2020. FUP = follow-up; MRI = magnetic resonance imaging.

visually checked for segmentation errors by one trained rater, blinded for clinical data. To minimize the effects of changes in FLAIR acquisition sequence parameters, we resliced follow-up FLAIR images to match slice thickness of baseline images using FMRIB's Linear Image Registration Tool (FLIRT), part of the FMRIB Software Library (FSL). WMH volumes were normalized to ICV. We distinguished periventricular WMH (PWMH) and deep WMH (DWMH) using FSL (www.fsl.fmrib.ox.ac.uk/fsl). More specifically, we generated ventricle masks and calculated the geometrical distance from this mask in each voxel using Brain Intensity AbNormality Classification Algorithm (BIANCA) and the command *distancemap*.[16–18] Based on previously validated criteria in literature, we considered voxels within 10 mm distance of the ventricles as PWMH and calculated the corresponding volumes, whereas the volumes of DWMH equates total WMH minus PWMH.

To facilitate consistent identification of incident lacunes, difference images were constructed for T1 and FLAIR images to identify incident lacunes. The images were first full stripped using the Brain Extraction Tool (BET) in FSL. All follow-up images were then registered to the baseline scans. Difference images were generated by subtracting the registered and intensity-normalized baseline T1 and FLAIR images from the corresponding T1 and FLAIR images at the follow-ups. Incident lacunes were defined as a hypointense voxel cluster on a uniform background.[19]

Diffusion Imaging Processing

All diffusion weighted images were denoised using a Local Principal Component Analyses filter,[20] and corrected for cardiac, head motion, and eddy current artifacts simultaneously using the "PATCH" algorithm, as described previously.[21] Peak width of skeletonized mean diffusivity (PSMD) was calculated with the PSMD tool provided at http://www.psmd-marker.com.[22]

Parkinsonism Diagnostic Work-Up

We used a standardized work-up to ascertain incident parkinsonism, comprising serial in-person visits, video examinations, and continuous follow-up of medical records.

Presence of parkinsonian signs was evaluated during the in-person follow-up assessments (2011, 2015, and 2020) by well-trained residents in neurology by using the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-m),[23] verified by a movement disorder specialist (author R.A.J.E.). Parkinsonism was defined as the presence of bradykinesia and at least one of the 3 following signs: tremor, rigidity, or gait and postural instability, according to the UK Parkinson's Disease Society Brain Bank criteria.[24] We assessed the presence of these 4 signs based on scores derived from the UPDRS-m, including limb bradykinesia (based on 8 items: right and left finger taps, handgrip, hand pronation-supination, and leg agility), rigidity (based on 5 items: rigidity of neck and the 4 extremities), tremor (based on 7 items: rest tremor of lip/chin and 4 extremities and action tremor of both arms), and parkinsonian gait (based on 5 items: arise from chair, posture, gait, postural stability, and body bradykinesia). We considered bradykinesia as present when ≥ 1 item on limb bradykinesia had a score of ≥ 2,[23–25] to guarantee a high sensitivity of this main symptom of parkinsonism. The other 3 signs (tremor, rigidity, and gait and postural instability) were considered present when the participant had either ≥ 2 items with a score of ≥ 1, or 1 item with a score of ≥ 2 in that specific category.

Participants were considered screen-positive when (1) they had bradykinesia and one or more of the other 3 signs,[26] according to aforementioned criteria, or (2) had UPDRS-m score ≥ 10, or (3) were already diagnosed with parkinsonism by a neurologist after baseline assessment (2006).

Screened-positive participants were invited for an additional examination by a movement disorder specialist (author R.A.J.E.) to confirm the presence of parkinsonism.

The participants who were screened-positive after the in-person evaluation, but refused additional examination by the movement disorder specialist, were asked whether their UPDRS-m examination could be recorded in a video for an evaluation by a consensus panel consisting of a neurologist specialized in movement disorders (author R.A.J.E.) and a neurologist specialized in cerebrovascular disease (author F.E.de.L.).

For patients who did not participate during follow-up (deceased or refused participation), medical records were retrieved from the general practitioners/treating physicians. Cases in whom parkinsonism was mentioned by treating physicians were evaluated again independently by the consensus panel according to a standardized structured approach, by taking into consideration all available clinical data (medical records), including medical history, medication use, all motor performance scores, neuropsychological examinations, and MRI data from all follow-up timepoints.

The diagnostic criteria of the UK Parkinson's Disease Society Brain Bank[24] were used for IPD, Zijlmans criteria for VaP[27] and the National Institute of Neurological Disorders and Stroke– Society for Progressive Supranuclear Palsy (PSP) criteria for PSP.[24] VaP requires the presence of relevant cerebrovascular disease markers on MRI, operationalized as a Fazekas score ≥ 2 or presence of one or more lacunes in basal ganglia or thalamus.[28] Participants with drug-induced parkinsonism were excluded (n = 4) and not considered as "parkinsonism cases."

For all patients diagnosed with parkinsonism, information from medical records from general practitioners/treating physicians was collected regarding Levodopa response. The Levodopa response was defined as good or poor, based on the judgment of the treating physician.

The date of parkinsonism onset was defined as the date on which the clinical symptoms allowed for the diagnosis. When the date of diagnosis was not exactly known (eg, if the diagnosis was made during the consensus meeting), we used the mid-point between the date of the previous research visit and the date the diagnosis was confirmed. For participants who did not develop parkinsonism, follow-up time was censored at the time of the last visit, the date of the most recently retrieved medical

information from general practitioner mentioning no signs or symptoms of parkinsonism, or death.

Statistical Analysis

Baseline characteristics between participants with and without parkinsonism were compared using the Mann–Whitney U test, t test, or χ^2 where appropriate. WMH volumes were log-transformed to achieve a normal distribution. For comparison of the 4 cardinal motor features (tremor, rigidity, bradykinesia, and gait/posture) between patients with IPD and VaP, the latest available UPDRS scores (after diagnosis) were used.

Person years at risk were calculated from the date of baseline assessment until onset of parkinsonism diagnosis, death, or the date of the last follow-up. We calculated the cumulative incidence of all-cause parkinsonism during follow-up, censoring at death or last available follow-up. Cumulative incidence of all-cause parkinsonism was estimated using Kaplan–Meier analysis, stratified by the severity of MRI markers of SVD (continuous variables were stratified in quartiles). Differences were compared by log-rank test.

To examine whether baseline MRI characteristics of SVD (ie, WMH volume, presence of lacunes, microbleeds, PSMD, GMV, and WMV) volumes are associated with all-cause parkinsonism incidence, Cox regression models were used. Adjustments were made for age, sex, baseline UPDRS score, and territorial infarcts. We did not adjust for vascular risk factors, because we considered them as part of the causal chain between SVD and parkinsonism.[29] In view of the potential competing risk of death, we used the proportional hazards model of Fine-Gray.[30] Schoenfeld residuals were investigated to verify the proportionality of hazards. There were no indications that the proportional hazards assumption was violated. Similar sensitivity analyses were also performed for specifically IPD and VaP.

To explore whether the association between SVD and parkinsonism may reflect a causal effect, we investigated progression of MRI markers of SVD in relation to incident all-cause parkinsonism. Of note, only patients who underwent at least 2 MRI scans at 2006, 2011, and 2015 assessments were included in these analyses. We only included parkinsonism cases that occurred after the second MRI, to ensure use of serial MRI data prior to parkinsonism conversion. We constructed linear mixed effect models to estimate annualized volumetric changes of MRI markers (ie, WMH, PWHM, DWMH volumes, and GMV and WMV volumes). The intercept and slope of each participant's linear trajectory were allowed to vary with both fixed and random effects. The fixed effect of time represents the average annualized volume change across the whole cohort, whereas the random effect of intercept and slope per participant can allow for inter-individual variability. Slopes for each patient were extracted and used for further analyses in Cox regression, in which adjustments were made for adjusted for age, sex, baseline UPDRS score, and baseline presence of territorial infarcts; each MRI marker was additionally adjusted for its baseline measure.

All statistical analyses were performed with R, version 4.1.1.[31]

Results

At baseline, 503 patients were included with a mean age of 65.7 (SD 8.8) years and 201 (44.9%) were men. Parkinsonism as an end point was available for 499 patients (99%); 4 patients were lost to follow-up (3 due to emigration and 1 nonresponder; see Fig 1). In total, 51 participants (10.2%) developed parkinsonism during a median (SD) follow-up time of 13.2 (interquartile range = 8.8–13.8) years, resulting in an incidence rate of 9.0 (95% CI = 6.7–11.8) per 1,000 person-years.

Parkinsonism Diagnosis

Parkinsonism diagnosis was based on real-live examination by a movement disorders neurologist for 31 participants (60.8%), by analyzing recorded videos of UPDRS scores for 11 (21.6%) participants, or were extracted from clinical records for 9 (17.6%) participants. VaP was the most common cause of parkinsonism (33 cases, 64.7%), followed by IPD (17 cases, 33.3%) and PSP (1 case, 2.0%). "A significant difference was found between IPD and Vascular Parkinsonism regarding tremor score, while bradykinesia, rigidity, and gait and postural instability score were non-significantly higher in VaP compared to IPD patients" (Table 1) "An overview of Levodopa response is given in Figure 2. In summary, most of the diagnosed participants (n = 34; 66.67%) did not use Levodopa because their symptoms were still mild, they were mainly diagnosed with vascular parkinsonism, or the participants refused a referral to a neurologist for additional examination and treatment because of various reasons. Of the 17 patients treated with Levodopa, 7 patients (6/7 were diagnosed with vascular parkinsonism) had a poor response on Levodopa and 7 patients (4/7 were diagnosed with IPD) had a good response. In 3 patients, the response was unknown.

SVD Burden and Incidence of Parkinsonism

At baseline, there were no differences in age or prevalence of vascular risk factors among individuals that developed parkinsonism and those who did not (Table 2). Participants who developed parkinsonism had a higher UPDRS

TABLE 1. Differences in Cardinal Features Between Patients Diagnosed With Vascular Parkinsonism and Idiopathic Parkinson's Disease

	Idiopathic Parkinson's disease (N = 13)	Vascular parkinsonism (N = 23)	*p* value
Tremor score (mean ± SD)	3.59 ± 3.69	1.81 ± 2.40	**0.047**
Bradykinesia score (mean ± SD)	6.06 ± 5.93	7.84 ± 5.11	0.276
Rigidity score (mean ± SD)	3.24 ± 3.47	4.12 ± 3.22	0.375
Gait and postural instability score (mean ± SD)	3.69 ± 4.14	5.56 ± 4.17	0.148

Note: Data represent numbers (%), means ± SD, or medians (IQR). For comparison of the 4 cardinal motor features (tremor, rigidity, bradykinesia, and gait/posture) between patients with IPD and VaP, the latest available UPDRS scores (after diagnosis) were used.
Abbreviations: IPD = Idiopathic Parkinson's disease; IQR = interquartile range; UPDRS = Unified Parkinson's Disease Rating Scale; VaP = Vascular parkinsonism.

score and higher burden of MRI markers SVD at baseline (ie, higher WMH volume, higher lacunes and microbleeds prevalence, and higher PSMD values) than those who did not.

The cumulative risk for all-cause parkinsonism was highest in participants with highest quartile of WMH volume, presence of lacunes, and microbleeds, lowest quartile of GMV and WMV, as well as highest quartile of PSMD at baseline (Fig 3).

After adjustment for age, sex, baseline UPDRS score, and presence of territorial infarcts, higher baseline WMH volume (reported as HR): (HR = 1.46 per 1-SD increase, 95% CI = 1.21–1.78), presence of lacunes (HR = 1.84, 95% CI = 1.02–3.31), higher PSMD (HR = 1.66 per 1-SD increase, 95% CI = 1.34–2.05), and lower GMV (HR = 1.82 per 1-SD decrease, 95% CI = 1.25–2.56) at baseline were associated with increased risk of all-cause parkinsonism (Table 3).

Higher WMH volume (HR = 1.71 per 1-SD increase, 95% CI = 1.40–2.08), presence of lacunes (HR = 3.38, 95% CI = 1.41–6.54), presence of microbleeds (HR = 2.86, 95% CI = 1.38–5.91), higher PSMD (HR = 1.92 per 1-SD increase, 95% CI = 1.56–2.40), and lower GMV (HR = 2.04 per 1-SD decrease, 95% CI = 1.32–3.13) were also related to higher risk of VaP (see Table 3).

Higher WMH volume (HR = 0.17 per 1-SD increase, 95% CI = 0.03–1.12) at baseline was associated with lower risk of incident IPD. Higher periventricular WMH and deep WMH volume were associated with higher risk of all-cause and vascular parkinsonism and lower risk of incident IPD (see Table 3).

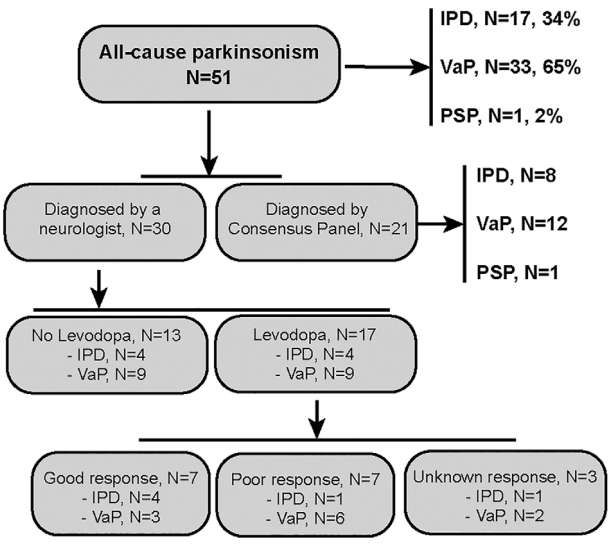

FIGURE 2: : Overview of response to Levodopa treatment of patients with Parkinsonism. IPD = idiopathic Parkinson's disease; PSP = progressive supranuclear palsy; VaP = vascular Parkinsonism.

SVD Progression and Incidence of Parkinsonism

We identified 26 cases with incident all-cause parkinsonism from the 356 subjects with at least 2 MRI scans at the 2006, 2011, and 2015 assessments (16 with VaP and 10 with IPD). In the multivariable Cox regression model, WMH, PMWH, and DMWH progression were associated with incident all-cause parkinsonism. Presence of incident lacunes was significantly associated with incident VaP (HR = 3.17, 95% CI = 1.04–9.65; Table 4).

Discussion

We found a dose–response relation between severity of MRI markers of SVD and long-term all-cause parkinsonism. Furthermore, we found that SVD progression in terms of incident lacunes were independently associated with incident vascular parkinsonism. These observations

TABLE 2. Baseline Characteristics of Patients with and without Incident Parkinsonism

	No parkinsonism	All-cause parkinsonism	*p* value	Vascular parkinsonism	Idiopathic Parkinson's disease	*p* value
Demographics						
Age ± SD	65.5 (8.8)	67.80 (7.94)	0.07	69.42 (6.45)	64.51 (9.84)	**0.039**
Female, N (%)	201 (44.9)	16 (31.4)	0.09	12 (36.4)	4 (23.5)	0.547
Motor performance						
UPDRS ± SD	1.06 (2.11)	2.38 (2.81)	**< 0.001**	2.82 (3.21)	1.38 (1.50)	0.095
Vascular risk factors						
Hypertension, N (%)	325 (72.5)	42 (82.4)	0.18	29 (87.9)	12 (70.6)	0.263
Diabetes, N (%)	63 (14.1)	11 (21.6)	0.22	7 (21.2)	3 (17.6)	1.00
Hypercholesterolemia, N (%)	206 (46.0)	31 (60.8)	0.06	23 (69.7)	7 (41.2)	0.10
Smoking, N (%)	313 (69.9)	39 (76.5)	0.41	24 (72.7)	13 (82.4)	0.685
MRI characteristics						
WMH, ml (IQR)	3.31 (1.18–10.45)	8.85 (2.43–23.26)	**0.001**	16.81 (6.37–26.29)	2.27 (0.64–4.48)	**< 0.001**
DWMH, ml (IQR)	0.88 (0.28, 2.61)	1.97 (0.50, 5.97)	**0.006**	3.82 (1.63, 8.76)	0.34 (0.15, 1.10)	**< 0.001**
PWMH, ml (IQR)	2.35 (0.80, 7.14)	5.46 (2.00, 16.42)	**< 0.001**	12.76 (4.70, 19.15)	1.82 (0.41, 2.29)	**< 0.001**
Presence of lacunes, N (%)	107 (23.9)	24 (47.1)	**0.001**	21 (63.8)	2 (11.8)	**0.001**
Presence of microbleeds, N (%)[a]	68 (15.3)	14 (28.0)	**0.04**	13 (40.6)	1 (5.9)	**0.026**
Presence of territorial infarcts, N (%)	46 (10.3)	11 (21.6)	**0.03**	10 (30.3)	0 (0.0)	**0.030**
PSMD of white matter 10^{-3} mm^2/s (IQR)[b]	3.34 (0.78)	4.07 (1.20)	**< 0.001**	4.50 (1.26)	3.21 (0.42)	**<0.001**
GMV, ml (SD)	609.36 (52.58)	577.95 (44.80)	**< 0.001**	566.22 (34.86)	603.03 (52.87)	**0.005**
WMV, ml (SD)	457.61 (43.14)	429.46 (61.51)	**< 0.001**	421.83 (67.97)	449.98 (37.80)	0.120

Note: Data represent numbers (%), means ± SD, or medians (IQR).
Abbreviations: DWMH = deep white matter hyperintensities; GMV = grey matter volume; IQR = interquartile range; MRI = magnetic resonance imaging; PSMD = peak width of skeletonized mean; PWMH = periventricular white matter hyperintensities; UPDRS = Unified Parkinson's Disease Rating Scale; WMH = white matter hyperintensities; WMV = white matter volume.
[a]Three patients excluded because of insufficient scan quality.
[b]Four patients excluded because of insufficient scan quality. UPDRS scores are baseline scores at start of the study (year 2006).

provide strong evidence for a potential causal role of SVD in the development of parkinsonism.

The contribution of cerebrovascular pathology to parkinsonism is receiving increasing attention. However, controversial reports exist regarding the associations between cerebrovascular diseases and parkinsonism. An epidemiological study showed that traditional cardiovascular risk factors, known to be strongly associated with SVD, are related with a subsequent diagnosis of IPD.[29] These associations could reflect the starting point of a possible causal chain between cerebrovascular pathology and parkinsonism, in which SVD may play an eminent role. So far, most previous studies investigating the relation between SVD and parkinsonism were cross-sectional or only assessed SVD at baseline and not its change over time. Cross-sectionally, SVD has been shown to be

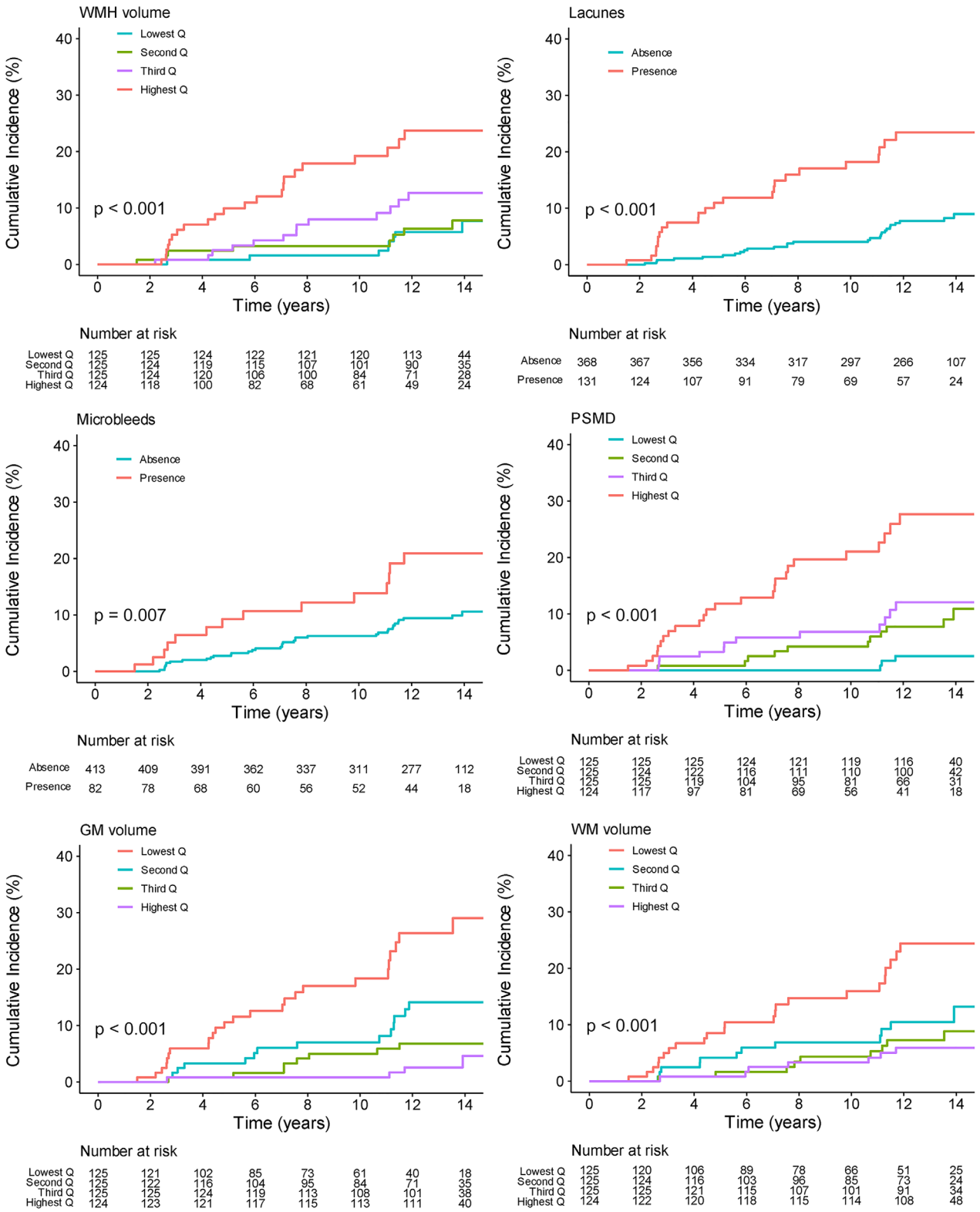

FIGURE 3: : Cumulative risk for all-cause parkinsonism stratified by severity of baseline MRI-characteristics of SVD. GM = grey matter; MRI = magnetic resonance imaging; PSMD = peak width of skeletonized mean diffusivity; WM = white matter; WMH = white matter hyperintensities; SVD = small vessel disease. [Color figure can be viewed at www.annalsofneurology.org]

associated with more severely impaired motor (especially bradykinesia and rigidity) and cognitive function in patients with and without IPD.[32–35] In addition, one longitudinal cohort study found that baseline WMH severity and postmortem cerebrovascular pathology were associated with rapid progression of parkinsonism signs in

TABLE 3. Baseline MRI Markers of SVD and Risk of All-Cause Parkinsonism, Vascular Parkinsonism and Idiopathic Parkinson's Disease

	All-cause Parkinsonism (n = 51)			Vascular Parkinsonism (n = 33)			Idiopathic Parkinson's disease (n = 17)		
MRI characteristics	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
WMH volume (ml) per 1-SD increase[a]	1.46	1.21–1.78	**< 0.001**	1.71	1.40–2.08	**< 0.001**	0.17	0.03–1.12	**0.01**
DWMH volume (ml) per 1-SD increase	1.05	1.02–1.08	**0.01**	1.48	1.24–1.77	**< 0.001**	0.11	0.02–0.88	**0.04**
PWMH volume (ml) per 1-SD increase	1.06	1.03–1.08	**< 0.001**	1.81	1.46–2.25	**< 0.001**	0.19	0.04–0.99	**0.05**
Presence of lacunes, N (%)	1.84	1.02–3.31	**0.04**	3.38	1.41–6.54	**0.002**	0.21	0.03–1.71	0.16
Presence of microbleeds, N (%)[b]	1.79	0.94–3.41	0.09	2.86	1.38–5.91	**0.007**	0.35	0.04–2.72	0.32
PSMD (10^{-3} mm^2/s) per 1-SD increase[c]	1.66	1.34–2.05	**< 0.001**	1.92	1.56–2.40	**< 0.001**	0.73	0.30–1.76	0.36
GMV (ml) per 1-SD decrease	1.82	1.25–2.56	**0.001**	2.04	1.32–3.13	**< 0.001**	1.28	0.68–2.47	0.49
WMV (ml) per 1-SD decrease	1.45	0.97–2.13	0.07	1.38	0.99–1.92	0.21	1.45	0.81–2.56	0.19

Note: Cox proportional hazards analyses for studying association between SVD markers and all-cause parkinsonism. Adjustments were made for age, sex, baseline UPDRS score and presence of territorial infarcts.

Abbreviations: CI = confidence interval; DWMH = deep white matter hyperintensities; GMV = grey matter volume; HR = hazard ratio; MRI = magnetic resonance imaging; PSMD = peak width of skeletonized mean; PWMH = periventricular white matter hyperintensities; SVD = small vessel disease; UPDRS = Unified Parkinson's Disease Rating Scale; WMH = white matter hyperintensities; WMV = white matter volume.

[a]Log-transformed.

[b]Three patients excluded because of insufficient scan quality.

[c]Four patients excluded because of insufficient scan quality.

life.[5] In contrast, one longitudinal population-based study did not find an association between measures of subclinical vascular pathology and incidence of all-cause parkinsonism.[36] This study, however, used less sensitive measures of SVD, such as retinal arteriolar and venular calibers, instead of the standard MRI features of SVD, as defined in the STRIVE criteria.[14] There are also conflicting clinicopathological studies reporting on the relation between the presence of postmortem cerebral SVD pathology and IPD.[37,38] Different methodological issues in tissue staining and SVD features studied can explain the divergent results on SVD and risk of parkinsonism.

One of the major findings in this study, is that incident lacunes were associated with the development of vascular parkinsonism, indicating a temporal association between these 2. These results suggest a direct vascular contribution in the development of vascular parkinsonism. Our findings strengthen the hypothesis that SVD may be causally related to vascular parkinsonism and that it may have a smaller contribution in the development of other primary parkinsonism's (such as IPD). However, this can also be explained by our diagnostic workup as the presence of severe SVD favors a VaP diagnosis on the basis of accepted criteria,[27] resulting in a few IPD cases with severe SVD burden. Of note, all patients with parkinsonism fulfilled the clinical diagnostic criteria of IPD (according to UK Parkinson's Disease Society Brain Bank criteria)[24] but had SVD to such an extent that this qualified for VaP. This may additionally explain the association between WMH burden and lower risk of developing IPD, because patients with more WMH are more likely to be diagnosed with VaP instead of IPD.

Our findings raise the possibility that, like in Alzheimer's dementia,[39] there might be shared pathogenic pathways between cerebrovascular disease and parkinsonism. Several mechanisms may underlie the interaction between SVD and parkinsonism. First, structural SVD lesions located in strategic brain regions (eg, basal ganglia), but also the underlying hypoperfusion in cerebral small vessels may result in widespread dysfunction of multiple brain pathways, including the disruption of dopaminergic and non-dopaminergic pathways (corticostriatal-thalamocortical and nigro-striatal pathways), involved in the pathophysiology of motor and non-motor symptoms in parkinsonism.[7,40] Second, there is increasing evidence for a role of an increased permeability of the blood–brain barrier in SVD. Strikingly, altered blood–brain barrier is also observed in mesencephalic regions (eg, substantia nigra) of patients with IPD, and

TABLE 4. SVD Progression and Risk of All-Cause and Vascular Parkinsonism

	All-cause Parkinsonism			Vascular Parkinsonism		
MRI characteristics	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Annualized WMH (ml/yr) per 1-SD increase[a]	1.18	0.80–1.68	0.34	1.32	0.82–2.05	0.16
Annualized DWMH (ml/yr) per 1-SD increase	1.10	0.78–1.56	0.51	1.29	0.85–1.95	0.14
Annualized PWMH (ml/yr) per 1-SD increase	1.20	0.84–1.70	0.26	1.33	0.87–2.04	0.11
Incident lacunes	1.73	0.52–5.81	0.32	3.17	1.04–9.65	**0.04**
Incident microbleeds	0.86	0.24–2.99	0.83	1.28	0.34–4.83	0.75
Annualized GMV (ml/yr) per 1-SD decrease	1.18	0.70–1.96	0.58	1.18	0.44–1.64	0.69
Annualized WMV (ml/yr) per 1-SD decrease	1.27	0.91–2.13	0.36	1.20	0.43–1.59	0.60

Note: Cox proportional hazards analyses for studying association between progression of MRI markers of SVD and all-cause parkinsonism. Adjustments were made for age, sex, baseline UPDRS score, baseline presence of territorial infarcts, and each progression variable was adjusted for its baseline measure.

Abbreviations: CI = confidence interval; DWMH = deep white matter hyperintensities; GMV = grey matter volume; HR = hazard ratio; MRI = magnetic resonance imaging; PWMH = periventricular white matter hyperintensities; SVD = small vessel disease; WMH = white matter hyperintensities: WMV = white matter volume.

[a]Log-transformed.

might represent a mechanistic link.[2,40,41] Third, cerebral hypoperfusion could also promote Parkinson pathology by inducing α-synuclein aggregation.[29] Experimental studies suggested that cerebral hypoperfusion propels α-synuclein aggregation.[42,43] Aggregation of α-synuclein is to some extent also seen in Alzheimer's dementia, in which cerebral hypoperfusion is also considered to play an important role.[44]

Our study has several limitations. First, not all parkinsonism cases were diagnosed in the same way. For participants with high frailty and other comorbidities who were not able to participate in person, diagnosis of parkinsonism was based on retrieved medical records from general practitioners and treating physicians. This was, for example, also the case for the PSP case, who was diagnosed in an external hospital and was already severely disabled and could therefore not undergo examination and visit our hospital. This is an inevitable limitation one can encounter when investigating in a real-life setting a representative elderly group with SVD. Therefore, to the best we could, the diagnosis of PSP was reconsidered by a clinical panel, including very experienced movement disorder neurologists based on the clinical records and previous collected MRI data. The combination of severe parkinsonism (UPDRS = 34) with a vertical gaze palsy and early dementia was considered indicative of a PSP diagnosis. However, diagnoses based on clinical records only compromised 16.7% of all diagnosed cases. Nevertheless, it could be that we have missed the diagnosis of parkinsonism in some cases who did not visit a doctor, because parkinsonian signs (eg, bradykinesia and gait impairment) are frequently accepted as part of normal aging or may be missed by non-medical personnel. In addition, misclassification of the different parkinsonism subtypes could have occurred, given the nebulous diagnostic borders and meager correlation between the clinical diagnosis and the neuropathological diagnosis of the different etiologies underlying parkinsonism.[27,45,46] Levodopa response is helpful in differentiating between the different subtypes of parkinsonism. In our study, only 17 patients (33.33%) were treated with Levodopa; the majority of patients were not treated because their symptoms were mild, they were mainly diagnosed with vascular parkinsonism, or they refused a referral to a neurologist for additional examination and treatment because of various reasons. Moreover, we did provide data comparing the presence of the 4 cardinal motor features (rated during the latest follow-up) between the VaP and IPD groups. This showed that the tremor score in IPD was significantly higher compared to patients diagnosed with VaP, whereas bradykinesia, rigidity, and gait and postural instability score were nonsignificantly higher in patients with VaP compared to patients with IPD (see Table 1). Although not formally required for diagnosis of IPD according to the 2015 Movement Disorder Society (MDS) criteria, our study lacked striatal dopamine transporter scans (DAT scans). However, a negative DAT scan excludes IPD, but not VaP. Nevertheless, it can be helpful in patient management, as finding of a normal uptake is shown to be associated with no benefit

from medications in over 90% of subjects.[47] Additionally, the numbers of incident IPD in our study were too small to reach sufficient statistical power when analyzing SVD progression in relation to incident IPD. However, all-cause parkinsonism was the primary outcome of this study. Finally, there was a scanner change between 2006 and 2011, which may lead to variable measurements. However, we have minimized this by reslicing the follow-up FLAIR scans to match baseline FLAIR scans.

There are several strengths of this study. First, we investigated for the first time the relation between SVD progression in relation to incident parkinsonism. Second, we present the longest follow-up study of patients with SVD, with only very few subjects lost to follow-up (1.0%) over a follow-up time of 14 years. Third, the longitudinal design provides insights into the long-term effect of cerebral SVD on incident parkinsonism, with data from a large and well-characterized cohort of patients with sporadic SVD, with a comprehensive and standardized clinical and neuroimaging workup. Fourth, because we screened and excluded prevalent parkinsonism patients at baseline, our baseline data on motor performance reflect, if at all, the prodromal phase of parkinsonism.

Our findings set the agenda for future studies, by highlighting remaining knowledge gaps. The pathophysiology of IPD appears to be caused by accelerated neuronal death of primarily dopaminergic neurons, which results from complex interplay of aberrant a-synuclein aggregation, dysfunction of mitochondria, synaptic transport failure, and neuroinflammation. Investigating the link between vascular pathologies and these neurodegenerative processes could provide potential new targets for diagnostic and possibly intervention strategies.[48,49] First, studies that relate SVD burden to functional imaging or neurotransmitter biomarkers are needed to examine the underlying pathophysiology of how SVD can cause parkinsonism. Yet, the clinical consequences of SVD on parkinsonism will vary by the brain regions affected. Therefore, future studies should focus on identifying in which specific brain regions SVD should accumulate to induce parkinsonism. Finally, an important knowledge gap is to investigate interactions between cerebrovascular damage and other neurodegenerative pathologies (eg, α-synuclein aggregation) in the development of parkinsonism.

Given the substantial prevalence and health burden imposed by parkinsonism, developing a firmer understanding of the underlying mechanisms could provide potential modifiable targets for treatment and prevention of parkinsonism in patients with SVD. For example, aggressive medical treatment of vascular risk factors, known to slow down SVD progression,[50] may also reduce occurrence of late-life (vascular) parkinsonism. However, this should be corroborated in randomized intervention studies.

In conclusion, our data in this study implicate that cerebral SVD may have a causal role in development of parkinsonism.

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Author Contributions

M.A.J., A.M.T., and F.E.d.L. contributed to the conception and design of the study. M.A.J., M.C., M.B., S.K.L.D., L.M.Y.G., and R.A.J.E. contributed to the acquisition and analysis of data. M.J. and M.C. contributed to drafting the text and preparing the figures. All authors made a critical revision of the manuscript for important intellectual content.

Potential Conflicts of Interest

The authors declared not conflict of interest.

Data Availability Statement

Data will be available on request.

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