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Brain atrophy and strategic lesion location increases risk of parkinsonism in cerebral small vessel disease

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ABSTRACT

Introduction: Incident parkinsonism in patients with comparable cerebral small vessel disease (SVD) burden is not fully explained by presence of SVD alone. We therefore investigated if severity of SVD, SVD location, incidence of SVD and/or brain atrophy plays a role in this distinct development of parkinsonism.
Methods: Participants were from the RUN DMC study, a prospective cohort of 503 individuals with SVD. Parkinsonism was diagnosed according to the UKPDS brain bank criteria. Fine and Gray method was used to assess the association between SVD and incident parkinsonism. Differences in white matter hyperintensities (WMH) progression and brain atrophy were calculated with a linear mixed effect analysis.
Results: After a median follow-up of 8.6 years, 32 of 501 participants developed parkinsonism (6.4%). The highest WMH load was found in the frontal lobe for both groups. Presence of more than one lacune at baseline was higher in the group who developed parkinsonism, especially in the frontal lobe (22% versus 3%, $p < 0.001$) and basal ganglia (12.5% versus 1%, p-value < 0.001). The annual rate of total brain atrophy was significantly higher for those who developed parkinsonism compared to those who did not (8.7 ml [95%CI 7.1–10.3] and 4.9 ml [95%CI 4.5–5.3], respectively). While WMH progression was not different, incidence of lacunes and microbleeds was higher in the group with parkinsonism.
Conclusion: The risk of parkinsonism in patients with SVD is especially increased when WMH and lacunes are present in the frontal lobe. A higher brain atrophy rate might further increase this risk.

1. Introduction

Markers of cerebral small vessel disease (SVD), such as cerebral microbleeds, white matter hyperintensities (WMH) and lacunes of presumed vascular origin (lacunes) are common in both the general elderly population [1,2] and in patients with Parkinson's disease [3,4].

The presence of parkinsonism in patients with advanced SVD is well recognized in clinical practice, but formal evidence from longitudinal studies is scarce. An increase in WMH has been associated with worsening of motor performance in patients with parkinsonism [4–6] and we recently demonstrated presence of SVD at baseline is associated with *incident* parkinsonism [7]. However, only few patients with SVD develop parkinsonism, suggesting that additional factors play a role.

One factor might be the location of SVD, as for instance WMH in the frontal lobe [8] and lacunes in the basal ganglia [9], have been associated with mild parkinsonian signs in cross-sectional studies. When only SVD at strategic locations may lead to parkinsonism, this might explain why patients with similar SVD lesion load differ profoundly in motor symptoms. Another factor might be a difference in WMH progression or brain atrophy. Brain atrophy has been proposed as disease

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modifier by researchers investigating cognition in patients with SVD. A higher brain volume might attenuate the impact of WMH pathology on cognition [10]. We hypothesize a similar mechanism for the differential development of parkinsonism in patients with equal SVD burden at baseline. A higher brain volume at baseline might initially prevent deterioration of motor function caused by SVD, but this effect may diminish with advancing brain atrophy and/or WMH progression.

We therefore investigated the difference in baseline SVD location, baseline SVD severity, incidence of SVD and WMH progression between those who developed parkinsonism and those who did not.

2. Methods

2.1. Study population

The RUN DMC study is a prospective cohort study investigating the causes and consequences of SVD in 503 independent functioning elderly. The detailed study protocol and rationale has been described previously [11]. SVD was defined as the presence of WMH and/or lacunes on cerebral imaging [12]. All consecutive patients referred to our outpatient clinic who underwent diagnostic cerebral imaging for different reasons (e.g. TIA, cognitive disturbances) were eligible for participation. Inclusion criteria were: Age 50–85 years and presence of SVD. Main exclusion criteria were: parkinsonism, dementia and SVD mimics. Baseline measurements were in 2006. In 2011 and 2015 participants were invited for a follow-up assessment. Information on survival and event status were collected up to the 11th of September 2015. This information could be obtained from 501 participants, since 2 participants were lost to follow-up. This study has been approved by the Medical Review Ethics Committee region Arnhem-Nijmegen and a written informed consent was obtained from all participants.

2.2. MRI protocol

Image were acquired on a 1.5-T scanner (baseline: Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany; 2011 and 2015 follow-up: Magnetom Avanto Tim (76 × 32), Siemens Medical Solutions, Erlangen, Germany). The same head coil was used at all time points. The protocol included: T1-weighted 3D MPRAGE, Fluid-attenuated inversion recovery (FLAIR) sequence and transversal T2*weighted gradient echo sequence. A detailed description of the MRI protocol has been given previously [11].

2.3. MRI markers

All SVD features were rated according to the STRIVE (STandards for ReportIng Vascular changes on nEuroimaging) criteria [12]. Lacunes and microbleeds were rated manually on respectively FLAIR and T2* imaging by trained raters blinded for clinical data. WMH were segmented with a semi-automated program [13]. In addition, for its clinical applicability, a modified Fazekas scale [14] was used to grade WMH, with the following categories: mild (no or only punctate lesions), moderate (beginning confluent lesions) and severe (large confluent lesions).

For lesion location WMH were segmented with a Talaraich Daemon based atlas (WFU pickatlas, version 3.0.5), using Statistical Parametric Mapping 12 (SPM12, http://www.fil.ion.ucl.ac.uk/spm/). Binary WMH maps simultaneously with FLAIR images were first co-registered to corresponding T1 images and subsequently normalized to MNI space. Proportion of voxels marked as WMH were then calculated in each anatomical region with the aforementioned atlas. The location of microbleeds and lacunes was rated manually.

Gray matter, white matter and cerebrospinal fluid volume maps were obtained by segmenting T1 images using SPM12. All volumes were normalized to the intracranial volume, to adjust for head size. To correct for inter-scanner effect, all normalized brain volumes in 2011 or 2015 were corrected using the difference in intracranial volume between baseline and follow-up.

2.4. Parkinsonism definition and sub classification

Parkinsonism was defined as the presence of bradykinesia and at least one of the following symptoms: tremor, rigidity, parkinsonian gait and/or postural instability, according to the UK Parkinson's Disease Society (UKPDS) Brain Bank criteria [15]. We used the bradykinesia definition 'slowness of initiation *with* reduction in speed *and* amplitude of the movement', as described in the UKPDS brain bank criteria. Parkinsonism was further classified as idiopathic Parkinson's disease (IPD), progressive supranuclear palsy (PSP) of vascular parkinsonism (VP). The diagnostic criteria of the UK Parkinson's Disease Society Brain Bank [15] were used for IPD, National Institute of Neurological Disorders and Stroke– Society for Progressive Supranuclear Palsy criteria for PSP [15] and Zijlmans criteria for VP [16]. Zijlmans criteria requires the presence of relevant cerebrovascular lesions on neuroimaging, which was defined in our study as a modified Fazekas score of > 2 or the presence of lacunes in basal ganglia or thalamus.

2.5. Parkinsonism case finding

The flowchart summarizes our method and results of our efforts to find parkinsonism cases (Fig. 1). A short description is provided in the online supplement (eMethods I). An in depth description of the screening methods has been reported previously [7].

2.6. Other measurements

We used the MMSE score and a previously described compound score using an extensive neuropsychological test battery (Cognitive index) to assess global cognitive status [11]. For the assessment of sleep quality and depressive symptoms we have used respectively the SCOPA-Sleep scale [17] and the CES-D [18].

2.7. Statistical analysis

Baseline characteristics, SVD severity, incident SVD markers were compared between those who developed parkinsonism and those who did not. When appropriate the χ [2] test or Fisher exact test was used for nominal variables and the two-sided independent T-test or Mann-Whitney *U* test for continuous variables.

Cumulative risk of parkinsonism was estimated using Gray's method [19], with death as a competing risk. Person-years at risk were calculated from date of baseline assessment until transition to parkinsonism, death, date lost to follow-up or date of last follow-up visit, whichever came first. Participants who did not develop parkinsonism or died were censored. Risk of parkinsonism with 95% confidence intervals at specific time points were calculated with the CumIncidence R-function [20].

Hazard ratios for incident of any parkinsonism and vascular parkinsonism separately were calculated for MRI markers with death as a competing risk using the cmprsk package (Gray, 2014) of the R project. In model 1 these analyses were adjusted for age, UPDRS-m score and presence of territorial infarction. In model 2 total brain volume was added to model 1. As a sensitivity analysis we repeated the analyses including only those who had an in-person evaluation (eTable II).

Difference in annual rate of WMH progression and brain atrophy between patients with and without parkinsonism was calculated with a linear mixed effect analysis with maximum likelihood estimation using the lme4 package (Bates, 2015) of the R project. For this analysis the following data was available (year: total number of participants (number with parkinsonism)): 2006: 501 (32), 2011: 352 (20), 2015: 294 (13).

For the calculation of annual change in brain and WMH volume, the

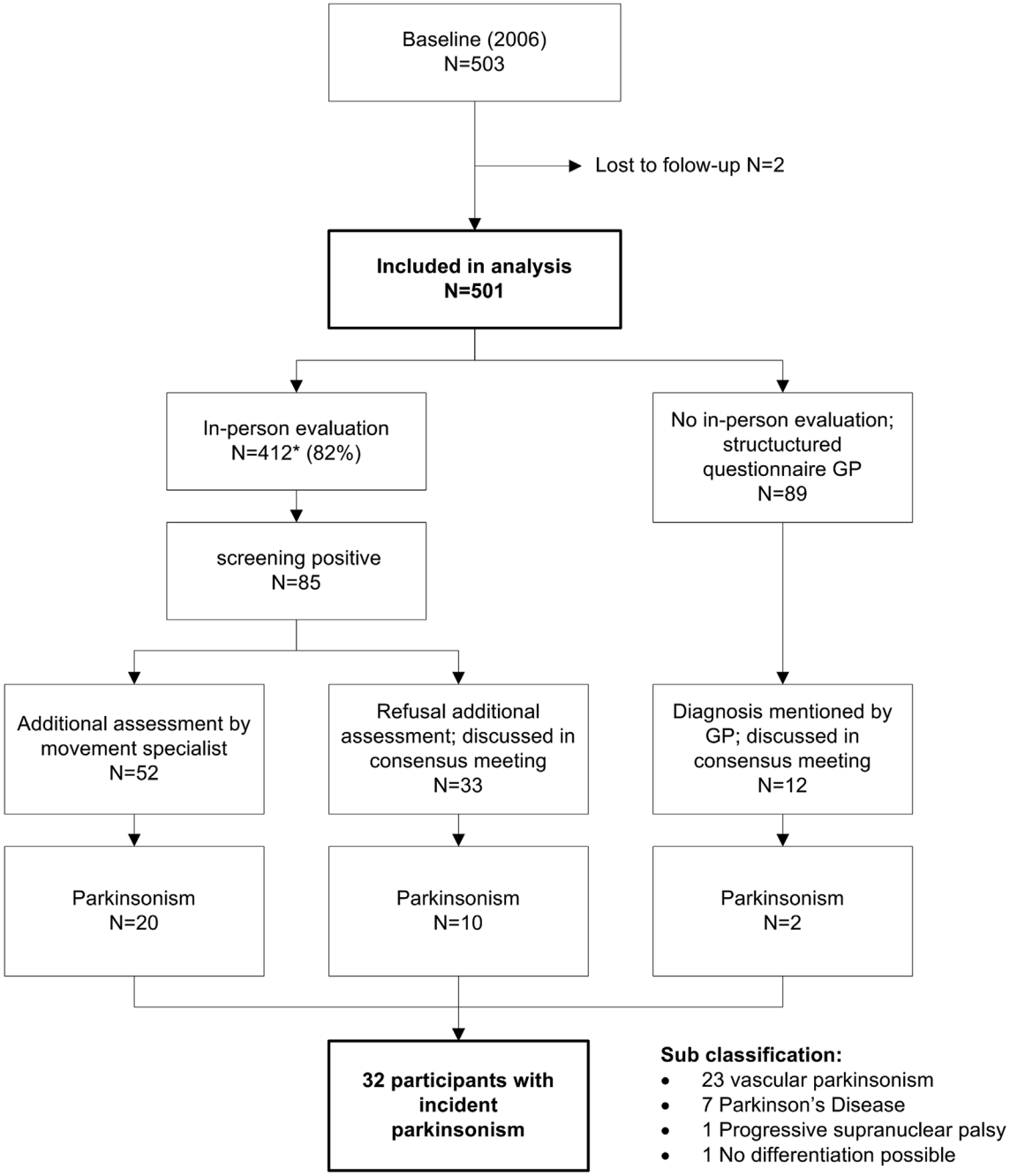

Fig. 1. Flowchart of parkinsonism case finding. GP = general practitioner. * follow-up visit in 2011 and 2015: 326, only visit in 2011: 72, only visit in 2015: 14.** Reasons of those who were not able to visit the follow-up were (number of subjects): deceased (49), perceived as high burden (21), severe comorbidity (18), unknown (1).

following model was used; sex, baseline age (centered around 65), follow-up time in years, parkinsonism during follow-up (yes/no) and the interaction follow-up time x parkinsonism during follow-up were entered as fixed effects, with random intercepts per subject and random slopes of follow-up time by subjects. *P*-values were obtained by likelihood ratio tests of this model against a model without the interaction term follow-up time x parkinsonism during follow-up. We used a normal linear model for brain volumes and a lognormal linear model for WMH volume. An example of the R code is provided in the online supplement (eMethods II).

For all final models standardized marginal residual plots were inspected for outliers, homoscedasticity, normality and linearity. For all volumes no obvious deviations were found.

All statistical analyses were performed using IBM SPSS Statistics version 22 or R version 3.1.1. (www.R-project.org).

3. Results

3.1. Incidence of parkinsonism and baseline characteristics

Of 501 participants, 32 developed parkinsonism (6.4%) during a median follow-up of 8.6 years [IQR 5.7; 8.8]. The cumulative risk of parkinsonism was 3.8% [95%CI 2.4–5.7%] after 5 years and 6.4% [95%CI 4.5–8.8%] after 8 years. These 32 patients with parkinsonism were further classified as having vascular parkinsonism (n = 23), Parkinson's Disease (n = 7) and progressive supranuclear palsy (n = 1).

Table 1
Association of baseline structural MRI markers with incident any parkinsonism and vascular parkinsonism.

	Risk of any parkinsonism (N = 32)		Risk of vascular parkinsonism (n = 23)	
	Model 1	Model 2	Model 1	Model 2
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
A. SVD markers				
WMH				
Mild	1	1	1	1
Moderate	1.3 (0.46–3.5)	1.2 (0.40–3.3)	3.6 (0.93–14.25)	3.3 (0.79–13.5)
Severe	4.0 (1.5–10.7)**	3.0 (1.1–8.3)*	11.1 (2.8–44.0)***	8.2 (1.9–35.4)**
Lacune				
None	1	1	1	1
1	1.2 (0.43–3.4)	0.98 (0.34–2.8)	1.8 (0.51–6.1)	1.3 (0.36–4.9)
> 1	4.0 (1.6–9.7)**	3.3 (1.4–7.7)**	6.7 (2.3–18.9)***	5.2 (1.9–14.0)**
Microbleed				
None	1	1	1	1
1	0.91 (0.26–3.6)	0.63 (0.18–2.2)	1.4 (0.38–5.2)	0.86 (0.23–3.2)
> 1	2.5 (0.86–7.3)	2.3 (0.80–6.4)	4.0 (1.2–12.9)*	3.5 (1.1–11.1)*
B. Lacune location				
Frontal lobe	2.4 (1.1–5.3)*	2.2 (1.0–4.9)*	3.1 (1.2–8.1)*	3.1 (1.2–7.8)*
Other lobes	1.3 (0.51–3.2)	1.1 (0.41–2.7)	1.8 (0.67–4.7)	1.5 (0.51–4.1)
Basal ganglia	2.1 (0.83–5.3)	1.9 (0.73–4.8)	2.6 (0.92–7.1)	2.2 (0.79–6.5)
Other deep	1.5 (0.38–5.6)	1.1 (0.30–4.1)	2.0 (0.50–7.7)	1.5 (0.38–5.6)
Infratentorial	0.79 (0.19–3.1)	0.78 (0.19–3.3)	1.0 (0.25–4.2)	1.0 (0.24–4.4)
C. WMH location				
Frontal lobe	1.8 (1.3–2.7)**	1.7 (1.2–2.4)**	2.7 (1.7–4.2)***	2.4 (1.2–3.7)***
Other lobes	1.5 (1.1–2.1)*	1.4 (1.0–1.9)*	2.3 (1.5–3.5)***	2.0 (1.4–3.0)***
Limbic	1.5 (1.0–2.3)*	1.6 (1.1–2.4)*	2.0 (1.2–3.4)**	2.2 (1.4–3.6)**
Other deep	1.7 (1.1–2.8)*	1.8 (1.1–2.8)*	2.5 (1.4–4.5)**	2.5 (1.4–4.2)**
Infratentorial	1.1 (0.73–1.8)	1.1 (0.69–1.7)	1.4 (0.81–2.4)	1.3 (0.75–2.3)

WMH = white matter hyperintensities, SVD = Small Vessel Disease. Model 1 is adjusted for age, UPDRS-m score and presence of territorial infarction. Model 2 is additionally adjusted for total brain volume. *P*-values: * < 0.05, ** < 0.01, *** < 0.001.

In one case no further differentiation was made due to inconclusive clinical information. During follow-up nine patients received levodopa, six of them had no or only a mild response and levodopa was discontinued. Reasons for not receiving levodopa therapy were: patient declined neurological evaluation at outpatient clinic (n = 10), little effect expected (n = 5), contraindications (n = 5, e.g. severe hypotension, visual hallucinations) and in two cases the reasons were unclear.

All small vessel disease markers, age, and baseline UPDRS-m score were different between those who developed parkinsonism and those who did not at the baseline. Besides cognitive markers other non-motor symptoms were not different between the two groups (supplementary eTable I).

3.2. Baseline SVD severity and location

Both the presence of severe WMH (HR 4.0 [95% CI 1.6–9.7] compared to mild lesions) and the presence of more than lacune (HR 4.0 [95% CI 1.6–9.7]) were associated with any parkinsonism (Table 1; model 1), even after adjusting for total brain volume (Table 1; model 2). When the analyses were restricted to vascular parkinsonism these associations were stronger (Table 1).

The highest WMH load was found in the frontal lobe for both groups with a significant higher median of 6.9 ml [IQR 2.4; 14.5] in those with parkinsonism compared to 1.5 ml [IQR 0.5; 4.9] in those without (p-value < 0.001) (Fig. 2). The presence of more than one lacune at baseline was higher in the group of patients who developed parkinsonism, especially in the frontal lobe (22% versus 3% for those without parkinsonism, p-value < 0.001) and basal ganglia (12.5% versus 1% for those without parkinsonism, p-value < 0.001). No significant differences between the two groups were found for microbleeds. (Fig. 2).

In both model 1 and 2, the hazard ratio was highest for number of lacunes in the frontal lobe (HR 2.4 [95% CI 1.1–5.3]) and basal ganglia (HR 2.1 [95% CI 0.83–5.3]) compared to those who had no lesions in these areas. For WMH, all locations, except for infratentorial lesions, were associated with any parkinsonism (Table 1).

3.2.1. Sensitivity analyses

When analyses for baseline SVD markers and SVD location are repeated for the group who had an in-person evaluation (n = 412), the results show stronger associations between SVD markers and any or vascular parkinsonism (eTable II).

3.3. Longitudinal changes in SVD

Those who developed parkinsonism had a significant higher incidence of both lacunes and microbleeds in the interval 2006–2011 and 2006–2015 (eTable III). For the interval 2006–2011 this difference was due to a higher incidence of lacunes in the lobar and basal ganglia regions (eTable III).

Those who developed parkinsonism had a higher total brain atrophy rate of 8.7 ml per year [95%CI 7.1–10.3] compared with those without parkinsonism (atrophy rate of 4.9 ml per year, [95%CI 4.5–5.3], p-value < 0.001) (Table 2). This difference in atrophy rate was present in both white and gray matter. No significant difference in annual percentage increase in WMH volume was found. However due to the difference in median baseline WMH volume between those who developed parkinsonism and those who did not, the absolute WMH progression might be different. After 9 year, this would be 7.4 ml (6.9 ml *1.084^9 - 6.9 ml) for a 65 year old male who developed parkinsonism and 2.4 ml (3.0 ml *1.067^9 - 3.0 ml) for a 65 year old male who did not develop parkinsonism.

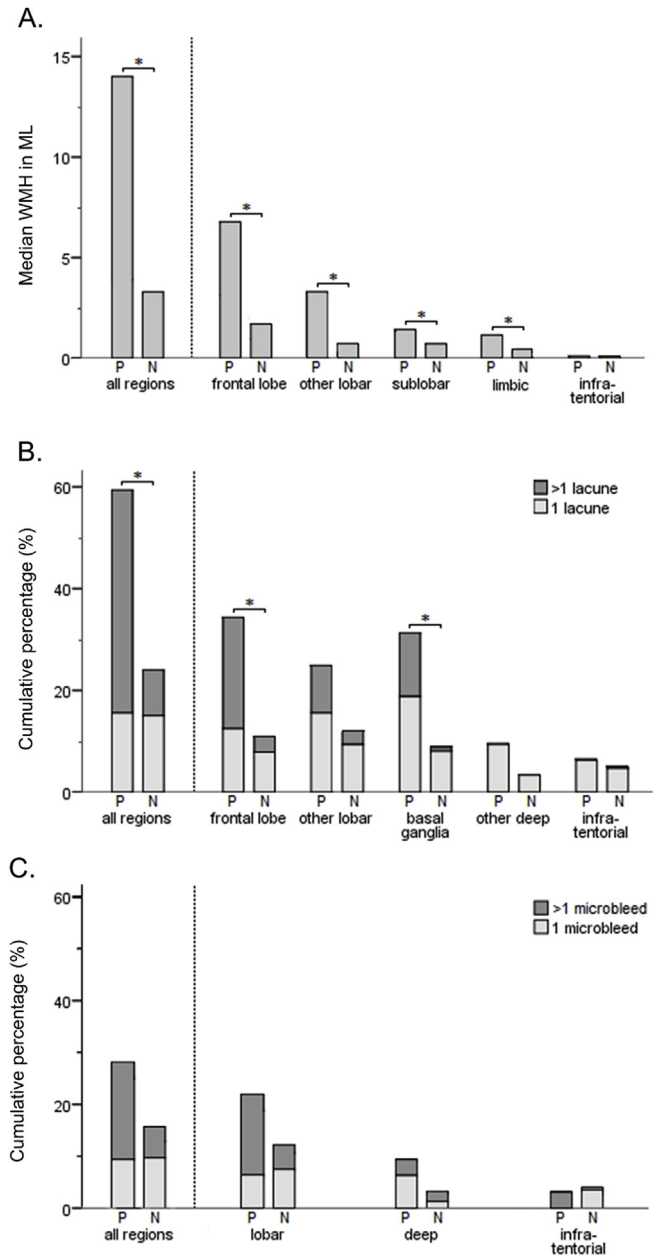

Fig. 2. Comparison of SVD burden between participants with and without parkinsonism. Panel A: White matter hyperintensities, B: Lacunes, C: Microbleeds. Bars with a P represent participants with parkinsonism (n = 32 for panel A–C), bars with N represent participants without parkinsonism (n = 469 for panel A and B, n = 465 for panel C). *p-value < 0.01. p-values were calculated with the Mann Whitney *U* test (panel A) or chi squared test (panel B and C).

4. Discussion

This nine year prospective study shows that brain atrophy, baseline SVD severity and a higher incidence of SVD, particularly in the frontal lobe and basal ganglia, are related with incident parkinsonism.

Our study showed that those who developed parkinsonism had both a higher baseline SVD lesion load and a higher incidence of SVD. The association of baseline lacune presence with incident parkinsonism is largely driven by lacunes located in the frontal lobe and basal ganglia. While WMH in all lobes were associated with incident parkinsonism. Strategic located WMH and lacunes (in frontal lobe and basal ganglia) likely contribute to parkinsonism by disrupting striato-thalamo-cortical circuits [21,22].

In our previous study we found an association between both baseline white and gray matter volume and incident parkinsonism [7]. The brain reserve hypothesis [23,24] provides a potential explanation for our findings of a lower baseline total brain volume and a faster total brain atrophy rate in those who developed parkinsonism. In this hypothesis brain reserve is the capacity to functionally compensate for neurodegeneration and is captured for instance by brain size [24]. A higher brain volume might be able to compensate for symptoms of parkinsonism at baseline, however with increasing brain atrophy this effect may diminish and as a consequence parkinsonism may develop.

This could also explain why some patients, with an otherwise equal SVD burden at baseline, develop parkinsonism and others do not. In these patients a lower baseline total brain volume and subsequent higher total brain atrophy might increase the risk of parkinsonism. Brain atrophy might be influenced by SVD itself, since both lacunes [25] and WMH [26,27] have been associated with a decrease of focal gray matter volume. This remote effect may accelerate the development of parkinsonism even further.

Although we did find a higher incidence of lacunes and microbleeds, we did not find a difference in annual percentage of WMH between those who developed parkinsonism and those who did not during follow up. In addition the difference in WMH progression after 9 years was rather small, especially in comparison with total brain atrophy after 9 years. An explanation could be that WMH progression is not sensitive enough to capture all relevant changes in the white matter associated with clinical symptoms of parkinsonism. This is supported by a weak association between WMH progression and gait [28]. Furthermore in a recent study we did not find an association between WMH progression and gait decline, while changes in the microstructural integrity of the white matter were associated [29]. Another explanation might be that other factors such as brain atrophy surpasses the effect of WMH progression when a certain threshold of SVD is reached.

Strengths of our study are the long median follow-up duration of 8.6 years, the high number of in-person evaluations of 82% and the almost complete (99%) collection of data on the outcome. Furthermore, the follow-up evaluations of parkinsonism were done by trained physicians with an excellent inter-rater agreement. In addition the collection of data in a single center reduced methodological bias. To further increase the validity of our results we treated mortality as a competing risk.

Table 2
Annual change of structural MRI features during 9-year follow-up.

	Parkinsonism		No Parkinsonism	
	Baseline volume	Annual change	Baseline volume	Annual change
Total brain volume	1011 (991–1032)	8.7 (7.1–10.3)***	1050 (1044–1057)	4.9 (4.5–5.3)
Gray matter volume	578 (563–592)	4.1 (3.0–5.2)**	596 (591–601)	2.4 (2.1–2.6)
White matter volume	434 (420–449)	4.8 (3.8–5.8)***	455 (451–460)	2.5 (2.3–2.7)
WMH volume	6.9 (4.5–10.7)	8.4% (7.7–9.1%)	3.0 (2.6–3.4)	6.7% (3.7–9.6%)

WMH = white matter hyperintensities. Baseline volumes are represented in ml for males with an age of 65. For brain volumes mean annual change is represented as atrophy in ml/year (95% confidence interval), for WMH the mean annual change is represented as increase in percentages/year (95% confidence interval). *P*-values: * < 0.05, ** < 0.01, *** < 0.001.

Finally, we believe our results have a high external validity to elderly patients presenting with SVD on diagnostic cerebral imaging following a general neurologic consult.

A limitation of our study is the usage of two different case finding methods. Both methods yielded a different percentage of parkinsonism cases: 8% with in-person evaluation in contrast to 2% with structured questionnaires. Since participants who did not attend follow-up were older and had a higher SVD load at baseline, it is likely the second method underestimated the number of parkinsonism cases and may have attenuated the association of SVD and parkinsonism. This is illustrated by the results of the sensitivity analyses which show stronger associations between SVD and parkinsonism when only participants with an in-person evaluation were included. Data of limited participants were available for the longitudinal MRI analysis, especially in the group who developed parkinsonism during follow-up. These results should therefore be interpreted with caution. Finally, our participants did not undergo dopamine transporter imaging since dopamine transporter imaging is not a routine part of diagnostic examination of parkinsonism in the Netherlands. As parkinsonism is a clinical diagnosis this would not affect the incidence of parkinsonism in our population, however we were not able to investigate the interaction between nigrostriatal loss and cerebral small vessel disease.

Recently new criteria have been proposed for vascular parkinsonism subtypes by an expert working group [30]. Although this has been concluded before these new criteria has been published we believe the presented cases would adhere to these new criteria. All vascular parkinsonism cases had gait and balance disturbances, extensive white matter hyperintensities and/or lacunes in basal ganglia.

Future studies with inclusion of biomarkers of other neurodegenerative processes important in the development of parkinsonism (e.g. degeneration of dopamine cells in the substantia nigra, alpha synuclein deposition) could provide a more integrated picture of the development of parkinsonism. Furthermore, in contrast to WMH volume, more sensitive markers of white matter abnormalities like those obtained with diffusion tensor imaging might be able capture relevant changes, even before the development of parkinsonism. These diffusion tensor imaging parameters are promising candidates since they are both associated with incident parkinsonism [7] and worsening of diffusion parameters is described in early Parkinson's Disease patients, when compared to healthy controls [31].

In conclusion, the risk of parkinsonism in patients with SVD is especially increased when confluent WMH lesions or more than one lacune is present. This risk is further increased when lacunes or WMH lesions are present in the frontal lobe. A higher total brain atrophy rate might further increase the risk of incident parkinsonism. Future studies should unravel the effect of progression of SVD on gray and white matter atrophy, preferably combined with conventional markers of parkinsonism.

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Potential conflicts of interests

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MB, AT, HvdH, EvL, MG, IvU, BP, DN, and RE declare no conflicts of interest.

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MB was involved in data collection, data management, data analysis, interpretation, drafting and revising the manuscript. AM was involved in data collection, analysis and interpretation and revising the manuscript. HvdH, EvL, IvU were involved in data collection and revising the manuscript. MG and BP were involved in imaging analysis and revising the manuscript. DN and EvD were involved in study concept and design and revising the manuscript. RE was involved in data collection, data interpretation and manuscript revision. F-EdL is the principal investigator of the RUN DMC study, obtained funding, was involved in study concept and design, contributed to data analysis, interpretation and manuscript preparation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.11.010.

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