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ORIGINAL ARTICLE

Vascular risk factors are associated with grey matter atrophy in secondary progressive multiple sclerosis

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Abstract

Background: Comorbidities including vascular risk factors can be associated with whole and regional brain atrophy in multiple sclerosis (MS). This has been examined in mixed MS cohorts in prospective or observational studies; however, the association between vascular comorbidities (VCM) in secondary progressive MS (SPMS) and brain atrophy has been less well studied. The aim was to investigate the cross-sectional and longitudinal association between VCM, comorbidity burden and brain atrophy in SPMS.

Methods: Post hoc analysis of 445 participants from the MS–Secondary Progressive multi-arm trial (MS-SMART)–a multi-arm multicentre phase-2b randomised placebo-controlled trial of three agents in SPMS (NCT01910259). VCM (hypertension, hyperlipidaemia) but also asthma, hypothyroidism and osteoporosis were recorded. Regional and whole brain volume (WBV), and percentage brain volume change were calculated using SIENAX and SIENA, respectively. Multiple linear regression was used to investigate the cross-sectional and longitudinal relationships between VCM, overall comorbidity count and whole brain, grey matter (GM) and white matter (WM) atrophy.

Results: The cohort was predominantly female (67%), mean age 55 with median EDSS 6.0. In total, 13% and 9% had hypertension and hyperlipidaemia, respectively. In

cross-sectional regression models, VCM was associated with decreased cortical GM volume [(hypertension $\beta = -0.30$, 95%CI −0.54 to −0.06, $p = 0.01$) (hyperlipidaemia $\beta = -0.37$, 95%CI −0.64 to −0.09, $p = 0.008$)]; but not WBV. Having ≥2 comorbidities was also associated with decreased cortical GM volume ($\beta = -0.36$, 95%CI −0.61 to −0.10, $p = 0.007$). No relationship was observed between VCM/comorbidity count and whole brain or GM atrophy rate over 96 weeks.

Conclusions: People with SPMS with VCM or increased overall comorbidity burden showed reduced whole brain and especially cortical grey matter volumes, but no significant impact on subsequent 2-year atrophy rate was detected.

KEYWORDS
comorbidities, multiple sclerosis, secondary progressive

INTRODUCTION

The importance of comorbidities in multiple sclerosis (MS) is increasingly recognised and clearly presents an additional therapeutic strategy to reduce disease progression. Comorbidities are common, with many studies demonstrating their increased prevalence and incidence in different MS phenotypes compared to age and sex matched control populations [1–4]. These include vascular comorbidities (VCM), for example hypertension, diabetes, hyperlipidaemia; non-vascular physical comorbidities, for example chronic lung disease; and autoimmune disease (e.g. inflammatory bowel disease). Previous studies have demonstrated that VCM and overall increased comorbidity burden are associated with increased relapse risk, faster rate of disability progression and decreased quality of life [4–7]. VCM in MS are also associated with brain atrophy in cohorts with early relapse onset MS or in mixed MS cohorts containing predominantly clinically isolated syndrome and relapsing remitting MS. [8–12] However, the effect of VCM on whole brain and regional atrophy measures in pure secondary progressive MS (SPMS) has been much less well studied.

Spinal cord atrophy is strongly associated with disability progression in progressive forms of the disease [13], but also here, it remains unknown whether VCM and comorbidity burden are associated with spinal cord atrophy.

We examined whether the presence of VCM and overall comorbidity burden were associated with decreased whole brain (and regional) volume and spinal cord area at baseline as well as atrophy rate in an SPMS population.

METHODS

Study design, setting and participants

This was a post hoc analysis of participants ($n = 445$) recruited into the MS-SMART trial from 13 sites across the United Kingdom. The Multiple Sclerosis–Secondary Progressive multi-arm trial (MS-SMART) was a phase-2b multi-arm multicentre, randomised placebo-controlled trial of the neuroprotective potential of amiloride, fluoxetine and riluzole in SPMS. Results of this trial have been published previously (NCT01910259) with no effect of trial agents on reducing whole brain atrophy over 96 weeks, compared with control [14, 15]. In brief, SPMS participants were eligible if aged 25–65 with an Expanded Disability Status Scale (EDSS) score of 4.0–6.5 with evidence of progression over the last 2 years. Participants were randomised 1:1:1:1 to placebo, amiloride, fluoxetine or riluzole. The primary outcome measure was the percentage brain volume change (whole brain atrophy) over 2 years. Participants were not on disease modifying treatments. Further details of the study protocol including complete eligibility criteria and outcome measures have been described previously [14, 15]. Participants were followed over 96 weeks. Blood pressure (BP) in mmHg was measured at screening, week 48 and week 96.

Those at the Queen Square MS Centre, University College London (UCL) were also invited to take part in Advanced MRI substudy which included spinal cord imaging ($n = 142$). From here on, participants from the UCL site in the Advanced MRI substudy will be referred to as the UCL cohort and will be referred to specifically, whilst analysis including MS-SMART participants from all sites will be referred to as the 'whole MS-SMART' cohort (which includes the UCL cohort).

STANDARD PROTOCOL APPROVALS AND PATIENT CONSENTS

Consent was obtained for all participants according to the Declaration of Helsinki. Ethical approval was provided by the Scotland A Research Ethics Committee [13/SS/0007].

Comorbidity status

The presence or absence of baseline comorbidities was recorded at the initial screening visit as per study protocol. These were VCM–hypertension, hyperlipidaemia, also physical comorbidities—asthma,

hypothyroidism and osteoporosis. The data were provided by participants and where possible, corroborated using medical and GP records. Once a comorbidity was recorded at screening, it was assumed to be present for the entire trial duration due to the chronic nature of the conditions.

MRI acquisition and analysis

MRI acquisition was undertaken on 3Tesla scanners (at all study centres), and a standardised MRI acquisition protocol including dual echo PD/T2-weighted, T2-weighted FLAIR and 3D T1-weighted was completed in all participants. The MRI acquisition protocols at all study centres have been published previously.[14] T2 and 3DT1 were first registered, then lesion filled. Tissue segmentation was completed using geodesic information flows. [16] T2 lesion segmentation was performed using semi-manual method with Jim7 (Xinapse, UK) over PD/T2 images. Normalised whole brain volume (WBV), white matter volume (WMV), deep grey matter (dGMV) and cortical grey matter volume (cGMV) were calculated at baseline using SIENAX [17]. Whole brain atrophy over 96 weeks was measured as percentage brain volume change (PBVC) using SIENA [17]. Regional atrophy over 96 weeks was measured indirectly as percentage change using values derived from SIENAX at baseline and 96 weeks. Full details of acquisition parameters and MR analysis pipelines have been described elsewhere [14]. All participants were scanned using the same scanner at baseline and 96 weeks.

Cervical cord imaging in the UCL cohort was acquired using a T1-weighted 3D-phase sensitive inversion recovery (PSIR) sequence. Images were acquired in the axial plane without parallel imaging containing 16 contiguous slices, FOV = 256 × 256 mm^2, matrix = 512 × 256, TR = 8 ms/TE = 3.7 ms/TI = 843.6 ms, number of averaged signals = 3 with voxel dimensions 0.5 × 0.5 × 3 mm. The cervical cord was imaged in the axial-oblique plane from C2-C4 with centre of the imaging volume positioned at the level of C2-3 intervertebral disc plane. Mean upper cervical cord area (MUCCA) was calculated using the active surface model on Jim software (v7.0, Xinapse Systems, UK) from the 3D-PSIR image using the method as previously described by Kearney [18]. In brief, a manual mark (centred at C2-C3) was placed at the centre of the five intermediate 3-mm thick slices of the 3D-PSIR scan. Jim software was then used to automatically detect the cord edge and provide a marked cord area contour for each of the five selected slices which were then averaged to calculate the final MUCCA [18].

Statistical analysis

Participant demographics, characteristics and MRI measures were summarised using descriptive statistics. Missing data are reported but not imputed. Baseline comorbidities were analysed as (i) individual VCM (hypertension, hyperlipidaemia) were recorded as binary (present/absent) variables; and (ii) comorbidity count included both VCM and the other physical comorbidities—asthma, hypothyroidism and osteoporosis (0, 1, 2 or more) to enable comparison with previous studies (categorical variable with no comorbidity as reference) [6]. The comorbidity count groups was truncated at two or more due to the low number of participants with ≥3 comorbidities.

In the baseline cross-sectional analysis, the dependent variables (MRI measures) were WBV, cGMV, dGMV and WMV (all continuous). For the UCL cohort, the dependent MRI variable was baseline MUCCA. When measuring change over 96 weeks, the dependent variable was percentage brain volume change for whole brain atrophy or the respective brain regions (white matter, grey matter). In the UCL cohort, spinal cord atrophy was measured by calculating percentage change in MUCCA from baseline to 96 weeks.

Our analysis involved three stages. First, we compared differences in the baseline cross-sectional MRI measures in those with and without each individual VCM and by comorbidity count using univariable analysis with Student's *t*-test, Mann–Whitney *U*-test, one-way ANOVA or Kruskal–Wallis as appropriate. Second, VCM that showed a univariate association in the first stage were examined using multiple linear regression models. The dependent variable was the baseline MRI measure, and the independent variable of interest was the presence/absence of the individual VCM or comorbidity count. Third, significant baseline cross-sectional associations in the second stage were further investigated by exploring the association between the respective baseline VCM and the change in MRI measure over 96 weeks where the corresponding baseline outcome measure was added as an independent variable. Models were adjusted for age (continuous), sex (female as reference), ethnicity (white Caucasian as reference), disease duration (continuous) and baseline T2LV (continuous). BMI (categorised as underweight<18.5 kg/m^2, healthy[reference] 18.5–24.9 kg/m^2, overweight 25.0–29.9 kg/m^2 and obese≥30 kg/m^2) was also added as a covariate of specific interest given its close association with metabolic syndrome and other VCM.

In additional analyses requested by reviewers, we examined the association between degree of hypertension [baseline mean arterial pressure (MAP), systolic BP (SBP) averaged across the trial duration both as continuous variables] and dependent variables (where significant); adjusted models for study centre, examined the relationship between VCM and lesion volume, re-analysed significant models without T2 lesion volume as a covariate and investigated the association between VCM and brain volume measures in the UCL cohort.

Results are reported as both effect sizes (standardised coefficients (β) with standardised 95% confidence intervals) and unstandardised coefficients(B). Distributional assumptions in the regression analyses were assessed by visual inspection of residual plots, normality examined by normal probability plots and highly leveraged data observations identified using Cook's distance. Multicollinearity was examined using variable inflation factors.

Statistical analysis was completed using R statistical software 4.0.3 (https://www.r-project.org) [19]. Statistical analysis for the UCL cohort was completed using Python (SciPy 1.9.2 and statsmodels 0.13.2). All

statistical tests and confidence intervals were two-sided. 95% confidence intervals were calculated with the significance of raw *p*-values assessed based on a 5% significance level. No adjustment for multiplicity was made as comparisons were based on specific a priori hypotheses.

RESULTS

Participants

Cohort demographics are demonstrated in Table 1. In total, 52/445 (11%) did not undergo primary outcome assessment (PBVC) at 96 weeks. This was due a variety of reasons including: withdrawal before MRI (14/52), loss to follow-up (13/52), MRI scan not done (16/52) and image quality issues (6/52). There were also three deaths that were unrelated to the investigational medical products used in the trial [15]. The percentage loss to follow-up was 5–9% across all study groups. The median PBVC from baseline to 96 weeks was −1.15 (IQR −2.04 to −0.54; $n=393$).

In total, 166/445 (37%) had at least one comorbidity with hypertension (13%) being the most common comorbidity present amongst all participants. When examining characteristics by the presence or absence of one or more comorbidity, 63% had none of the recorded comorbidities, 26% had 1, 11% had ≥2 comorbidities (Table 1). Baseline MAP was higher in those with hypertension (105 vs. 97, $p<0.001$). Mean SBP (139 vs. 128, $p<0.001$) and mean MAP (102 vs. 95, $p<0.001$) were also higher in those with hypertension (taken as an average across measurements from screening, 48 and 96 weeks). In those with hypertension, baseline MAP in those on treated was 105 compared to 104.6 in those not on active treatment ($p=0.74$). Across the trial duration, mean MAP in those on treatment for hypertension was 102.6, 103.7 in those not receiving any treatment ($p=0.82$). In those with hyperlipidaemia, 30/41 were on statin treatment for dyslipidaemia.

In the UCL cohort, 142 and 122 participants were eligible for analysis at baseline and 96 weeks, respectively, with the demographics and characteristics showing overlap with the whole MS-SMART cohort (Table 1).

TABLE 1 Baseline demographics and characteristics of whole MS-SMART and UCL cohorts.

Characteristic	Whole MS-SMART ($n=445$)	UCL cohort ($n=142$)
Age in years, mean (SD)	54.5 (7.0)	54.9 (6.9)
Female sex, *n* (%)	298 (67%)	94 (67%)
Ethnicity, *n* (%)		
White	427 (96%)	135 (95%)
Black	5 (1%)	2 (1%)
Asian	10 (2%)	5 (4%)
Other	3 (0.7%)	0 (0%)
Disease duration in years, mean (SD)	21.6 (9.7)	22.7 (9.5)
Body mass index, *n* (%)		
Underweight (<18.5)	22 (5%)	9 (6%)
Healthy (18.5–24.9)	204 (46%)	80 (56%)
Overweight (25.0–29.9)	136 (31%)	41 (29%)
Obese (≥30)	81 (18%)	11 (8%)
EDSS, median (IQR)	6.0 (5.5–6.5)	6.0 (5.5–6.5)
Normalised WBV, mL, mean (sd)	1422.6 (83.6)	1412.0 (87.1)
T2 lesion volume, cm^3, median (IQR)	10.3 (4.1–18.6)	10.6 (4.6–19.2)
MUCCA, mm^3, mean (sd)	N/A	68.5 (9.3)
Individual comorbidities, *n* (%)		
Asthma	31 (7%)	13 (9%)
Hypertension	60 (13%)	21 (15%)
Hyperlipidaemia	41 (9%)	19 (13%)
Osteoporosis	22 (5%)	6 (4%)
Hypothyroidism	41 (9%)	19 (13%)
Total comorbidity count, *n* (%)		
0 comorbidities	279 (63%)	77 (54%)
1 comorbidities	115 (26%)	47 (33%)
2+ comorbidities	51 (11%)	18 (13%)

Abbreviations: EDSS, Expanded Disability Status Scale; IQR, interquartile range; MUCCA, mean upper cervical cord area; SD, standard deviation; WBV, whole brain volume.

Whole brain volume: Whole MS-SMART cohort

In the first stage cross-sectional univariable analysis, baseline WBV was lower in those with hypertension and hyperlipidaemia ($p=0.01$, $p=0.007$, respectively). There was no difference in WBV with increasing overall comorbidity count (Figure 1, Table S2).

However, in the second stage cross-sectional analysis using multiple linear regression, there was no association between hypertension, hyperlipidaemia and WBV after adjusting for covariates. In both models, male sex ($\beta=-0.54$), non-white Caucasian ethnicity ($\beta=-0.90$ to -1.05), longer disease duration ($\beta=-0.15$), higher lesion volume ($\beta=-0.27$) and being overweight ($\beta=-0.50$) or obese ($\beta=-0.73$ to -0.75) were also associated with decreased whole brain MRI volume (Tables S3 and S4).

In the third stage analysis, there was no association between VCM, overall comorbidity count and percentage brain volume change from baseline to 96 weeks.

Grey matter volume: Whole MS-SMART cohort

In the first stage cross-sectional univariable analysis, cGMV at baseline were lower in those with hypertension ($p=0.001$, 95%CI [10.74–42.90]), hyperlipidaemia ($p<0.001$, 95%CI [22.96,52.41]) and

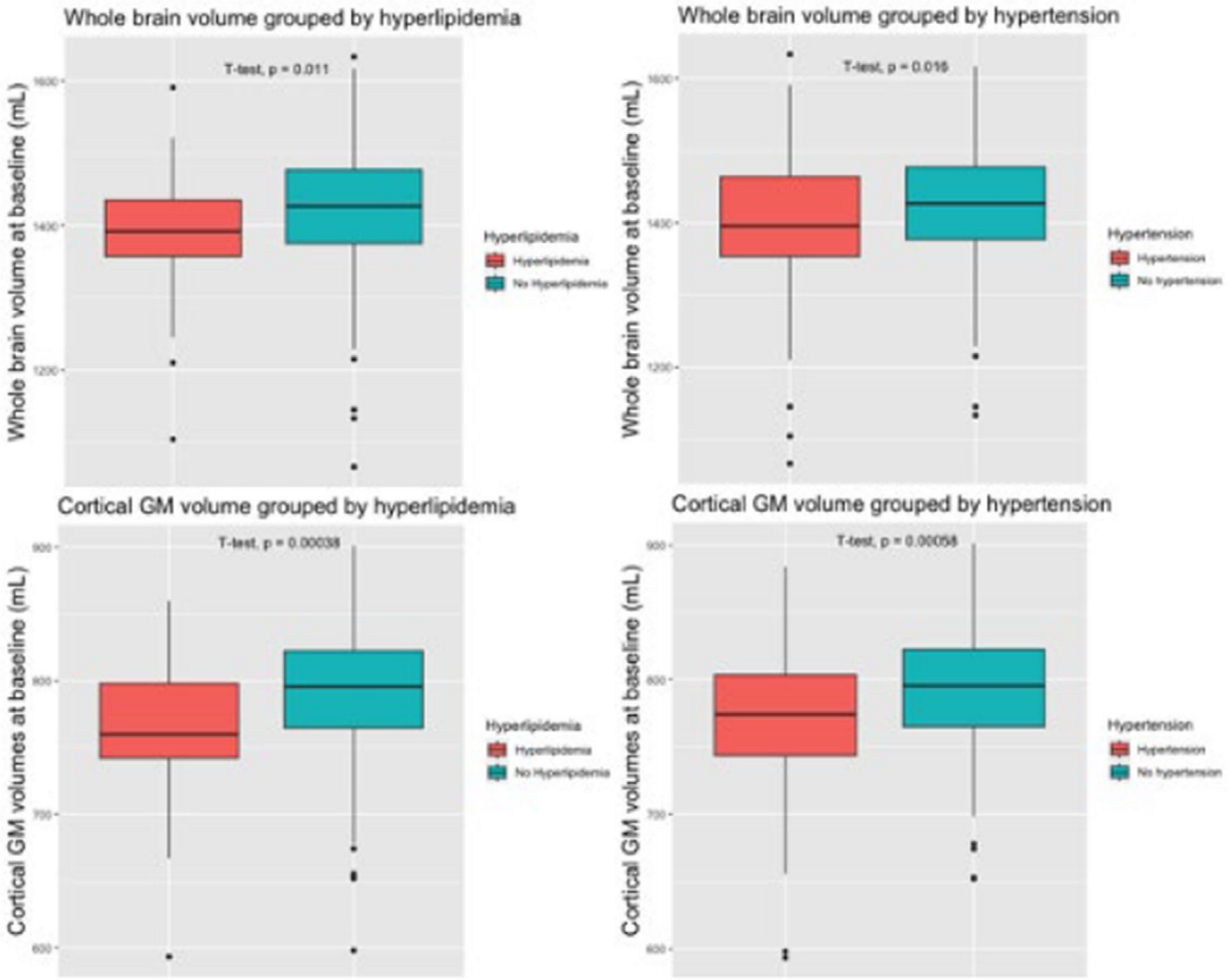

FIGURE 1 Differences in baseline whole brain volume and cortical grey matter volume in those with hypertension and hyperlipidaemia ($n = 445$).

≥2 comorbidities ($p < 0.001$) (Figures 1, 2 and Table S2). There were no associations with dGMV.

In the second stage analysis, having hypertension ($\beta = -0.25$, 95%CI −0.51 to 0.00, $p = 0.05$), hyperlipidaemia ($\beta = -0.35$, 95%CI −0.64 to −0.06, $p = 0.017$) and ≥2 comorbidities ($\beta = -0.18$, 95%CI −0.32 to −0.03, $p = 0.017$) were all associated with cGMV that were 0.25, 0.35 and 0.18 standard deviations (or 13.2 mL, 16.0 mL and 15.8 mL) lower, respectively, after adjusting for model covariates (Tables S5–S7). In all three models, being male ($\beta = -0.62$ to −0.65), BMI in the overweight ($\beta = -0.63$ to −0.64) or obese range ($\beta = -0.93$ to −0.96), increased lesion volume ($\beta = -0.24$ to −0.25) and non-white ethnicity ($\beta = -0.80$ to −0.94) was associated with decreased cGMV. There was no association between VCM, overall comorbidity count and cGM atrophy from baseline to 96 weeks.

In additional analyses, baseline MAP (B = −0.76, 95%CI −1.17 to −0.35, $p < 0.001$) and mean SBP (B = −0.36, 95%CI −0.65 to −0.08, $p = 0.012$) were both associated with decreased cortical GM volumes in unadjusted models. There was no association after adjusting for covariates. When re-examining the models without T2 lesion volume as a covariate, VCM (both hypertension and hyperlipidaemia) remained significantly associated with cGMV (Table S8). In models adjusted for study centre, hyperlipidaemia ($\beta = -0.27$, 95%CI 0.00–0.53, $p = 0.046$) remained associated with decreased cGM volume, whilst hypertension showed borderline significance ($\beta = -0.22$, 95%CI −0.01 to 0.45, $p = 0.06$) (Tables S9 and S10).

White matter volume: Whole MS-SMART cohort

There were no differences in WMV between those with and without each VCM and those with ≥2 comorbidities (Table S2).

Lesion volume: Whole MS-SMART cohort

There was no association between VCM and lesion volume (Table S11).

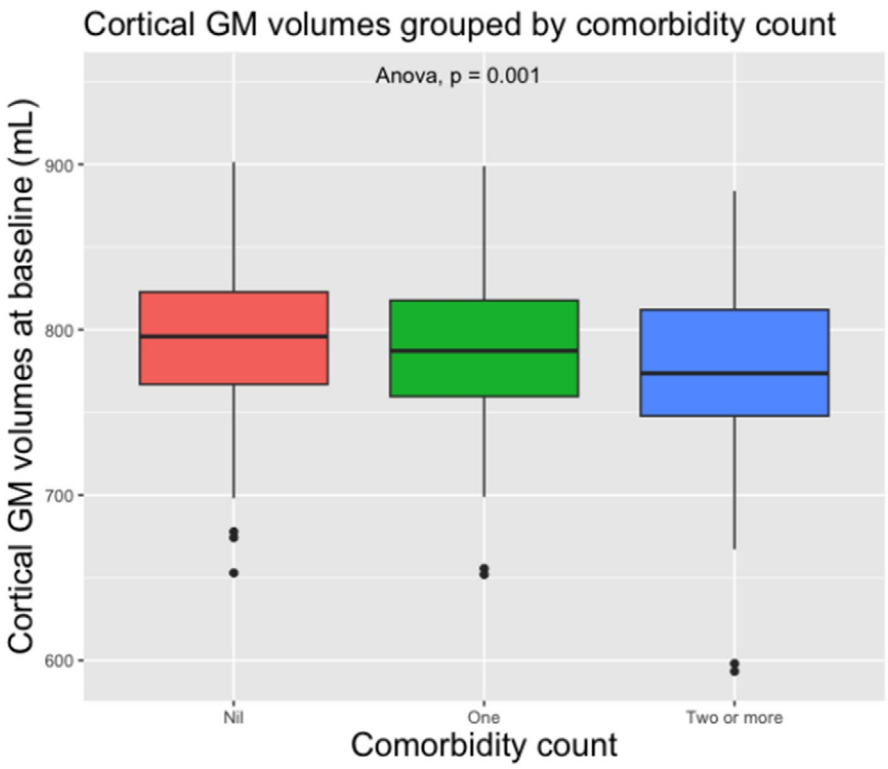

FIGURE 2 Differences in cortical grey matter volume by comorbidity count ($n = 445$).

Cervical spinal cord area: UCL cohort

There was no association between VCM, overall comorbidity count and baseline MUCCA; nor was there an association between VCM/overall comorbidity count and spinal cord atrophy over 96 weeks (Table S12).

In an additional analysis of the UCL cohort, VCM was not associated with baseline cGM volume ($n = 142$).

DISCUSSION

Our study shows that VCM and increasing comorbidity burden negatively impact cGMV rather than other cranial or spinal cord regions, though no effect on subsequently atrophy rates was seen. No other relationships were observed either at baseline or longitudinally.

Comorbidities and whole brain volume

Three previous studies in cohorts with progressive forms of MS (PMS) have demonstrated decreased WBV or brain parenchymal fraction in those with specific VCM, whilst one study did not identify an association [8, 12, 20].

In cross-sectional analyses, Kappus et al. studied 489 patients of whom 33% (163/489) had PMS showing that smoking was associated with decreased WBV (adjusting for age, sex, race, disease duration and treatment) [8], whilst Fitzgerald et al. examined 11,507 (26–35% PMS, 7–17% self-reported severe disease course) patients in a cross-sectional study that showed 19% reduction in brain parenchymal fraction in those with dyslipidaemia (propensity score matched for demographic variables, disease duration, BMI, socioeconomic variables) [11]. In two studies that also included longitudinal analysis, Lorefice et al. studied 326 patients (34/326 [10%] PMS) demonstrating decreased WBV in those with hypertension (~mean difference = 52 mL) and diabetes mellitus (~mean difference = 48 mL) compared to MS controls after adjustment for sex, age, disease duration, EDSS and MS subtype [12]. They also showed that the presence of 1 VCM increased annualised percentage brain volume change over a mean follow-up of 2.4 years [20]. Jakimovski et al. studied 194 participants with MS (median EDSS = 2.5) of which 49 (25%) had PMS. They did not find any association between hypertension, hyperlipidaemia and WBV (adjusting for age, sex and disease duration) [12]. The differing results with our study are likely explained by several reasons. First and likely the most significant factor is that previous studies included a wider range of VCM including diabetes, heart disease and smoking status. This is also further highlighted in a recent study by Williams et al. of 218 SPMS patients demonstrating that each additional year of prematurely achieved cardiovascular risk (measured using validated composite risk score-QRISK3) was associated with a 2.73 mL reduction in WBV [21]. Second, compared to our cohort of progressing SPMS (median EDSS = 6.0), these previous studies included predominantly relapsing MS with lower age (mean = 44–48 years) and levels of disability (median/mean EDSS = 2.5–3.3) [8, 12, 20]. Third, there was variability in the adjustment for confounding factors and whilst all three adjusted for demographic and clinical variables, they did not all include additional confounding factors such as BMI or lesion load [8, 12,

20]. Last, the follow-up duration for two studies differed (mean 2.4–5.1 years) compared to 96 weeks in our study, and the study by Lorefice followed up only 90 of the original 326 participants longitudinally [12, 20].

BMI in the overweight (25.0–29.9) or obese range (≥30) was also associated with WBV that were 0.50 to 0.73 standard deviations lower compared to the healthy (reference) category. Decreased WBV is also seen in people without MS but with elevated BMI above the health range [22]. It remains unclear as to whether elevated BMI decreases WBV via mechanisms specific to MS or whether there are other processes occurring common to people with and without MS. High BMI is associated with a pro-inflammatory state and subsequent increases in cytokines such as TNF-alpha, IL-6 and IL-1β may link elevated BMI and WB atrophy in MS. [23] More recently, glucagon-like peptide (GLP) has been associated with T-cell mediated inflammation and TNF-alpha. GLP-1 receptor agonists were then shown in animal models to attenuate TNF-alpha activation thereby carrying promise as a potential treatment in central neuroinflammatory disorders [24].

Comorbidities and grey matter volume

We demonstrate that VCM and increasing overall comorbidity burden are associated with decreased cGMV in SPMS. This is consistent with several previous studies that have found VCM (−4.73%; 36 mL lower) and increasing comorbidity burden (−10.10%) to be associated with decreased cGMV in relapsing or mixed MS cohorts [8, 9, 11, 20]. It is also consistent with a recent cross-sectional analysis of a similar UK SPMS cohort ($n = 218$, median EDSS = 6.0) enrolled into a phase III randomised control trial (MS-STAT2 NCT03387670). That study demonstrated that increased modifiable cardiovascular risk (measured using prematurely achieved QRISK3) was associated with decreased cGM volumes (beta coefficient 1.6 mL/year) [21]. The fact we did not find associations between VCM and dGMV is in keeping the two previous studies of PMS that examined both cGMV and dGMV with Fitzgerald also finding an association with cGMV but not dGMV [8, 11].

We postulate that VCM (and BMI above healthy range) may affect cGM volume via its effect on cerebral vasculature which may be mediated via endothelial dysfunction, lipohyalinsation, oxidative damage and hypoperfusion [23]. Some recent work has demonstrated associations between serum adipokines and decreased cGMV in a mixed MS cohort; however, evidence supporting a direct link between raised BMI, adipokines and brain atrophy was not found [25]. Several studies across different MS disease courses demonstrate an association between VCM and cGM, but not dGM. This may be evidence of a link between VCM, raised BMI and the subpial inflammation that has now been recognised to cause cortical damage [26]. To date, no studies have examined the mechanisms through which comorbidities may mediate parenchymal damage in MS, particularly that affecting cGM. There is, however, a consistent association between VCM and elevated BMI across multiple MS phenotypes suggesting that addressing VCM and BMI may have the potential to decrease cGM damage in MS. The elucidation of these mechanisms may provide more targeted approaches to achieve this goal.

None of the VCM nor increasing overall comorbidity burden were associated with cGM atrophy over 96 weeks. This is consistent with the only study by Jakimovski (outlined above) that reported on GMV percentage change over mean 5.4 years [12]. Our ability to detect this longitudinal change in future studies may have been enhanced by recording additional VCM such as diabetes, smoking status and ischaemic heart disease, and having a longer follow-up period.

Comorbidities and white matter volume

We found no association between comorbidities and WMV. This is in generally in keeping with previous studies that examined the association between various VCM and WMV in either early relapse onset MS or mixed MS cohorts [8, 11, 12, 20].

Comorbidities and spinal cord measures

There have been no previous studies that have examined the effect of comorbidities on spinal cord area in PMS. Finding no association between VCM, increasing number of overall comorbidities and decreased cross-sectional spinal cord volume either in the cross-sectional or the longitudinal analysis suggests that VCM mediate their effect via the brain atrophy in SPMS. This may reflect the multiple anastomoses in the spinal vasculature that provide compensation against the negative endothelial effects of VCM, similar to reasons that spinal cord ischaemic is relatively rare compared to the brain [27].

Strengths and limitations

The strengths of this our paper are the recruitment of a large cohort with SPMS across many regions in the United Kingdom with standardised measurements and data collection as part of randomised controlled trial.

There are however several limitations. First, we relied predominantly on patient histories when recording comorbidities and whilst we attempted to corroborate this with GP records, this was not always possible. However, BP recordings from the study were significantly higher in those recorded as having hypertension. Second, we did not include the development of comorbidities during the 96-week trial period in this study as we were more interested in the association between baseline comorbidities and outcomes at 96 weeks. Third, we would have liked to record a wider range of VCM including diabetes mellitus, smoking history and previous vascular events, but this was not part of the study. This is an important point as a subsequent cross-sectional analysis of a similar SPMS UK cohort from the

Phase III MS-STAT2 trial (NCT03387670) with a wider range of VCM including lipid levels demonstrated that cumulative vascular risk (measured using QRISK3) was associated with decreased WBV and cGMV [21]. However, the comorbidities we recorded are in keeping with consensus recommendations [28].

In summary, VCM and increased overall comorbidity burden are associated with decreased cGMV in SPMS. Whilst independently contributing to decreased cGMV in this SPMS cohort, VCM and increased comorbidity burden do not appear to increase the rate of brain atrophy once in the secondary progressive phase of MS. The effects of comorbidities are likely mediated via the brain with no direct impact on the spinal cord.

AUTHOR CONTRIBUTIONS

Nevin A. John: Conceptualization; methodology; data curation; investigation; formal analysis; writing – original draft; writing – review and editing; visualization. **Yingtong Li:** Formal analysis; writing – review and editing. **Floriana De Angelis:** Data curation; formal analysis; resources; writing – review and editing; visualization. **Jonathan Stutters:** Software; data curation; project administration; resources; writing – review and editing. **Ferran Prados:** Methodology; software; data curation; investigation; formal analysis; project administration; writing – review and editing. **Anisha Doshi:** Data curation; writing – review and editing. **Alberto Calvi:** Data curation; writing – review and editing. **Thomas Williams:** Data curation; writing – review and editing. **Domenico Plantone:** Data curation; writing – review and editing. **Thanh Phan:** Formal analysis; writing – review and editing; supervision. **Claudia A. M. Gandini Wheeler-Kingshott:** Supervision; conceptualization; methodology; formal analysis; funding acquisition; resources; writing – review and editing. **Frederik Barkhof:** Conceptualization; methodology; software; formal analysis; supervision; funding acquisition; writing – review and editing. **Jeremy Chataway:** Conceptualization; methodology; funding acquisition; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

FDA, JS, FP, AC, AE, TW, DP, AD, CWK and TP have no competing interests to declare. NAJ is a local principal investigator on commercial MS studies funded by Novartis, Roche and Sanofi. He has received speakers honoraria from Merck and congress sponsorship covering registration and travel from Novartis. FB serves on the editorial boards of Brain, European Radiology, Journal of Neurology, Neurosurgery & Psychiatry, Neurology, Multiple Sclerosis and Neuroradiology, and serves as consultant for Bayer Shering Pharma, Sanofi-Aventis, Biogen-Idec, TEVA Pharmaceuticals, Genzyme, Merck-Serono, Novartis, Roche, Synthon, Jansen Research and Lundbeck. CAGW-K has received research grants (PI and co-applicant) from Spinal Research, Craig H. Neilsen Foundation, EPSRC, Wings for Life, UK MS Society, Horizon2020, NIHR/MRC, MRC and is a shareholder of Queen Square Analytics. In the last 3 years, JC has received support from the Efficacy and Evaluation (EME) Programme, a Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership and the Health Technology Assessment (HTA) Programme (NIHR), the UK MS Society, the US National MS Society and the Rosetrees Trust. He is supported in part by the National Institute for Health Research, University College London Hospitals, Biomedical Research Centre, London, UK. He has been a local principal investigator for a trial in MS funded by the Canadian MS society. A local principal investigator for commercial trials funded by: Actelion, Biogen, Novartis and Roche; has received an investigator grant from Novartis; and has taken part in advisory boards/consultancy for Azadyne, Biogen, Celgene, Janssen, MedDay, Merck, NervGen, Novartis and Roche.

DATA AVAILABILITY STATEMENT

The dataset from this study is held securely by UCL. Access may be granted via authorisation from the Executive Committee and facilitated by contacting Dr. John.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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