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ORIGINAL ARTICLE

Cardiovascular risk factors in secondary progressive multiple sclerosis: A cross-sectional analysis from the MS-STAT2 randomized controlled trial

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Abstract

Background and purpose: There is increasing evidence that cardiovascular risk (CVR) contributes to disability progression in multiple sclerosis (MS). CVR is particularly prevalent in secondary progressive MS (SPMS) and can be quantified through validated composite CVR scores. The aim was to examine the cross-sectional relationships between excess modifiable CVR, whole and regional brain atrophy on magnetic resonance imaging, and disability in patients with SPMS.

Methods: Participants had SPMS, and data were collected at enrolment into the MS-STAT2 trial. Composite CVR scores were calculated using the QRISK3 software. Prematurely achieved CVR due to modifiable risk factors was expressed as QRISK3 premature CVR, derived through reference to the normative QRISK3 dataset and expressed in years. Associations were determined with multiple linear regressions.

See Appendix for investigator group details.

Results: For the 218 participants, mean age was 54 years and median Expanded Disability Status Scale was 6.0. Each additional year of prematurely achieved CVR was associated with a 2.7 mL (beta coefficient; 95% confidence interval 0.8–4.7; $p = 0.006$) smaller normalized whole brain volume. The strongest relationship was seen for the cortical grey matter (beta coefficient 1.6 mL per year; 95% confidence interval 0.5–2.7; $p = 0.003$), and associations were also found with poorer verbal working memory performance. Body mass index demonstrated the strongest relationships with normalized brain volumes, whilst serum lipid ratios demonstrated strong relationships with verbal and visuospatial working memory performance.

Conclusions: Prematurely achieved CVR is associated with lower normalized brain volumes in SPMS. Future longitudinal analyses of this clinical trial dataset will be important to determine whether CVR predicts future disease worsening.

KEYWORDS

cardiovascular risk, comorbidity, multiple sclerosis, progressive multiple sclerosis, secondary progressive multiple sclerosis

INTRODUCTION

There is increasing evidence to support the importance of cardiovascular risk (CVR) factors in the pathogenic evolution of multiple sclerosis (MS). These are prevalent within the MS population, particularly in those with secondary progressive MS (SPMS), and have been reported to be associated with current and future measures of MS severity [1–7].

Validated composite CVR scores are more accurate in predicting an individual's overall future risk of a cardiovascular event compared to individual risk factors alone [8]. The use of such composite scores may therefore be more favourable compared to examining individual risk factors alone in people with MS.

The Framingham Risk Score (FRS) is one such composite measure that has previously been investigated in people with MS [9]. Whilst that analysis did not include biochemical contributions to risk (particularly lipid ratios), the FRS was found to be higher in people with SPMS compared to relapsing–remitting MS (RRMS) and was associated with higher Expanded Disability Status Scale (EDSS) [4]. A prospective follow-up of the same cohort over 4.6 years found that those with a higher baseline FRS were more likely to experience relapses, reach EDSS 6.0 or have their disease-modifying therapy escalated [10]. A separate study (84% RRMS) reported that higher FRS (again quantified without lipid data) was associated cross-sectionally with smaller whole brain volume [11]. Longitudinally, in participants with the highest brain volume at baseline (90th centile or above), higher FRS was associated with a faster subsequent rate of brain atrophy over 1 year [11].

A limitation of using composite CVR scores is their strong association with non-modifiable risk factors, such as age and gender [9]. Within National Health Service (NHS) England, it is recommended that CVR is assessed using the QRISK3 composite score [12, 13]. This model was derived from a cohort study using data from English general practitioner (GP) practices, including 7.89 million patients in the derivation cohort and 2.67 million patients in the validation cohort [14]. QRISK3 quantifies the estimated risk of a cardiovascular event in the next 10 years, but importantly it also allows quantification of *prematurely achieved* CVR (QRISK3_PCR). This is determined through comparison of patient data to the modelled CVR score derived from age, gender and ethnicity matched healthy controls from the QRISK3 derivation cohorts. The QRISK3_PCR variable therefore provides a quantification (expressed in years) of prematurely achieved CVR attributable to modifiable risk factors, relative to age, gender and ethnicity matched data.

The aims of this study were to examine the cross-sectional relationships between a comprehensive composite score of excess modifiable CVR, using the QRISK3_PCR variable, and imaging and clinical measures of MS disease severity. A clinical trial cohort of people with SPMS was included, in whom CVR was likely to be prevalent [4]. As additional exploratory outcomes, which individual components of CVR contribute most to these relationships were then investigated.

METHODS

Participants

Participants included in this analysis were all recruited into the MS-STAT2 randomized controlled trial (NCT03387670) at the lead University College London (UCL) site. All participants gave written informed consent, and MS-STAT2 was approved by the NHS national research ethics committee (London Westminster Research Ethics Committee, 09/10/2017, ref: 17/LO/1509) and conducted according to the Declaration of Helsinki [15].

MS-STAT2 is an ongoing multicentre, interventional phase 3 randomized controlled trial assessing high-dose simvastatin

versus placebo as a treatment for slowing the progression of disability in patients with SPMS. Eligible participants are 25–65 years of age with EDSS 4.0–6.5, with a confirmed diagnosis of SPMS and evidence of ongoing disability progression. The main exclusions included ongoing use of immunosuppressive disease-modifying therapy (with the exception of siponimod) or current use of a statin. Where a patient's screening assessments suggested significantly elevated CVR (absolute QRISK3 > 10%), they could only be enrolled if, following discussion with their GP, it was agreed that the 50% risk of being on placebo for 3 years would not compromise their general medical care. From a total of 315 participants recruited at the UCL MS-STAT2 site, 218 were additionally recruited into an optional magnetic resonance imaging (MRI) substudy and included in this analysis.

Baseline assessments

Participants underwent a systematic assessment of CVR, together with clinical evaluations of MS severity, before the first dose of trial medication. CVR measures included patient demographics, previous medical history, current medication, blood pressure, body mass index (BMI), smoking status and lipid and renal profiles. Lipid profiles included total cholesterol, low-density lipoprotein and high-density lipoprotein. In line with current recommendations on the assessments of CVR, the lipid profile was expressed as the total cholesterol to high-density lipoprotein ratio and was derived from non-fasting samples [16]. Clinical assessments were performed by trained neurologists and included EDSS, timed 25-ft walk, timed nine-hole peg test, Symbol Digit Modalities Test, California Verbal Learning Test II (CVLT-II), Brief Visuospatial Memory Test, Revised and Sloan Low Contrast Letter Acuity.

QRISK3 cardiovascular risk

QRISK3% (the predicted risk of a cardiovascular event in the next 10 years) was calculated using the online QRISK3 software platform, incorporating all of the above stated CVR parameters [12]. The QRISK3% therefore represents an estimate of CVR, including modifiable and non-modifiable risk factors. QRISK3_PCR was calculated as the difference between the patient's actual age and the age at which a healthy person of the same sex and ethnicity would be predicted to achieve the same level of QRISK3%. The QRISK3 software defines a healthy person as someone with no adverse clinical indicators (smoking, diabetes etc.), a lipid ratio (total cholesterol/high-density lipoprotein) of 4.0, a systolic blood pressure of 125 and a BMI of 25, and predicts the age at which such healthy subject would achieve a level of QRISK3% based upon data from its derivation and validation cohorts. Each negative year of QRISK3_PCR therefore represents the subject achieving a level of CVR a year earlier than would be expected through ageing alone, compared to healthy sex and ethnicity matched controls.

Magnetic resonance imaging

The 218 participants enrolled at baseline in the MRI sub-study were all imaged on a 3 T Philips Ingenia CX MR system before the first dose of trial medication. 3D sagittal T1-weighted (3DT1) magnetization-prepared rapid acquisition gradient echo and 3D sagittal fluid-attenuated inversion recovery images both with 1 mm^3 isotropic voxels were included. Lesions were automatically segmented via nicMSlesions [16] and quality checked by expert clinicians. These lesion masks were then used for lesion filling on the 3DT1 scans [17, 18]. Geodesic Information Flows (GIFv2) was then applied to the filled 3DT1 scans to produce brain tissue segmentation and parcellation, which was used to calculate regional volumes [19]. Normalized whole brain volume was calculated using SIENAX [20].

Statistical analysis

Inspection of the following variables demonstrated a skewed distribution which could be normalized through $\log_2$ transformation: QRISK3%, T2 hyperintense lesion volume (T2LV), systolic blood pressure, lipid ratio and BMI. In all analyses, a 1 unit increase in these variables therefore represents a doubling of their value.

To assess whether our participants had achieved a level of CVR earlier than would be predicted in healthy sex and ethnicity matched controls through ageing alone, each participant's age was compared with the paired age at which QRISK3 predicted such controls would achieve the same QRISK3%. This was assessed with a paired two-sample *t* test with unequal variance and Wilcoxon exact matched pairs signed-rank test.

The pre-specified primary outcome of this analysis was to assess the relationship between QRISK3_PCR as the predictor and normalized whole brain volume as the dependent variable. This was assessed through multiple linear regression. The following covariates were included, because of their established relationship with normalized brain volumes: T2LV, MS duration (time since symptom onset) and age. Sex was not included as a covariate in the analysis as QRISK3_PCR is derived relative to sex matched control data from the QRISK3 population. To confirm that the relationship between QRISK3 predictor variables and normalized brain volumes persisted independently of the established relationship between sex and normalized brain volumes, sensitivity analyses were conducted where normalized brain volumes were expressed as sex-specific *t* scores. To test for collinearity between predictors and covariates, variance inflation factors were calculated for all multivariate models, and univariate linear regression models or two-sample *t* tests with unequal variance were constructed to directly examine the relationship between individual predictors. It is well established that covariates can introduce substantial confounding even with a low degree of collinearity, producing unreliable estimates of coefficients [21]. Where relationships between individual predictors were identified, the multivariate models were therefore repeated following the

exclusion of each predictor in turn, in order to assess its effect on model coefficients.

Pre-specified secondary analyses included repeating the above models but with normalized regional brain volumes (normalized grey matter volume, cortical grey matter volume, deep grey matter volume, white matter volume) as the dependent variable.

Exploratory analyses included repeating the above models but with clinical outcomes as the dependent variable. Additional exploratory analyses then included repeating the above models including each of the individual CVR components from the QRISK3 composite scores as predictors, instead of the composite scores themselves. In these models, a reverse stepwise multiple linear regression approach was taken, excluding variables until all variables made statistically significant contributions, removal of further variables caused >1% loss of R^2, or when removal was judged to meaningfully change the coefficients of the other remaining variables [22]. In these models, ethnicity was dichotomized into white or non-white due to the small number of participants in each individual non-white category. Similarly, smoking status was dichotomized into never regularly smoked versus ever regularly smoked. In all models assessing cognitive outcomes, participant years in education was included as an additional covariate, in accordance with established practices within the literature [23, 24]. Whilst the inclusion of multiple secondary and exploratory analyses will increase the family-wise type-I error rate, it does not increase the individual per-comparison-wise error rate of each test [25]. The results of the secondary and exploratory analyses should not, however, be generalized beyond the precise relationships assessed [25].

For all models, assumptions were assessed through examination of the normality of residuals and residual versus fitted plots to exclude heteroscedasticity. Data were inspected for particularly influential outliers via analysis of datapoint leverage. Where evidence was identified of datapoints with high leverage or outlying residuals, data were inspected for accuracy, and sensitivity analyses were performed following the exclusion of these participants [26]. Models with EDSS as the dependent variable violated assumptions on the normality of residuals. Estimates were therefore derived through bias corrected and accelerated bootstrap with 10,000 replications.

RESULTS

Cohort characteristics

Characteristics of the cohort are shown in Table 1, including variables contributing to CVR.

Degree of prematurely achieved cardiovascular risk

Eighty of 941 (8.5%) patients considered for the MS-STAT2 trial at UCL were excluded prior to formal screening due to already taking a statin. 487 were excluded due to other eligibility issues (see Williams et al. [27]). Of the remaining 374 candidates, six (1.6%) were excluded from randomization as their GP felt their high QRISK3% meant they required treatment with a statin outside of the trial. Despite this potentially biasing the cohort towards those with a

TABLE 1 Characteristics of the UCL MS-STAT2 MRI cohort at baseline—demographics, MS variables, QRISK3 variables and components of cardiovascular risk.

	UCL MS-STAT2 MRI cohort ($n = 218$)
Age (years, SD)	54.0 (7.2)
Sex: female	75.2%
Ethnicity: white	94.4%
MS duration (years, SD)	23.7 (9.5)
EDSS (step score, median, IQR)	6 (4.5 to 6.0)
25FW (s; median, IQR)	11.8 (8.0 to 18.4)
9HPT (s; median, IQR))	30.1 (25.6 to 38.4)
SLCLA 2.5% (count, SD)	26.3 (10.2)
Educational years (SD)	15.5 (3.6)
SDMT (count, SD)	44.3 (11.3)
CVLT-II (count, SD)	47.6 (12.0)
BVMT-R (count, SD)	20.3 (8.0)
T2LV (mL, median, IQR)	21.0 (12.4 to 36.1)
nWBV (mL, SD)	1423.7 (73.6)
nGMV (mL, SD)	841.7 (41.9)
nCGMV (mL, SD)	795.2 (39.4)
nDGMV (mL, SD)	46.44 (3.8)
nWMV (mL, SD)	582.1 (37.5)
QRISK3% (median, IQR)	4.1 (2.6 to 6.7)
QRISK3_PCR (years, median, IQR)	−1 (−4 to +1)
BMI (kg/m^2, median, IQR)	24.7 (21.3 to 28.2)
Smoking (% ever regularly)	41.7%
T2DM	0.9%
CKD stage ≥3	1.8%
Anti-hypertensives (*n*)	11.5%
Migraine	3.2%
Regular steroids	1.4%
Lipid ratio (total cholesterol/HDL, median, IQR)	3.1 (2.5 to 4.1)
Systolic blood pressure (median, mmHg)	128 (119 to 141)

Note: Data reported as mean (SD) unless otherwise stated. Medians are reported with interquartile range (IQR) unless stated.

Abbreviations: 25FW, timed 25-ft walk; 9HPT, timed nine-hole peg test; BMI, body mass index; BVMT-R, Brief Visuospatial Memory Test, Revised; CKD, chronic kidney disease; CVLT-II, California Verbal Learning Test II; EDSS, Expanded Disability Status Scale; HDL, high-density lipoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; nCGMV, normalized cortical grey matter volume; nDGMV, normalized deep grey matter volume; nGMV, normalized grey matter volume; nWBV, normalized whole brain volume; nWMV, normalized white matter volume; QRISK3%, QRISK3 predicted risk of a cardiovascular event in the next 10 years; QRISK3_PCR, QRISK3 derived premature cardiovascular risk; SDMT, Symbol Digit Modalities Test; SLCLA 2.5%, Sloan Low Contrast Letter Acuity 2.5%; T2DM, type 2 diabetes mellitus; T2LV, T2 hyperintense lesion volume; UCL, University College London.

lower CVR, the cohort demonstrated significantly greater excess CVR compared to healthy control data from the QRISK3 population: patient age (54.0 years, 95% confidence interval [CI] 53.0–55.0) was significantly younger than the expected age at which healthy sex and ethnicity matched controls would be predicted to achieve the same level of QRISK3% (56.2 years, 95% CI 55.1–57.4, $p<0.001$). This manifests as a median QRISK_PCR value of −1 years (interquartile range −4 to +1 years) in this cohort, with 58% having a negative QRISK_PCR value and hence modifiable CVR achieved prematurely compared to the QRISK3 healthy control population.

Relationship between covariates: CVR, age, sex and T2LV

As expected, QRISK3% was strongly associated with age. For each additional year of age, QRISK3% increased by 0.12 (95% CI 0.11–0.13) doublings ($p<0.001$), with age alone accounting for 59.4% of the variability in $\log_2$ QRISK3. Importantly, however, there was insufficient evidence to support a relationship between QRISK3_PCR and participant age (coefficient +0.00 [−0.08 to 0.09], $p=0.975$), confirming that QRISK3_PCR is a measure of modifiable CVR, independent of age.

Similarly, as expected, QRISK3% was higher in males (2.37%) compared to females (1.87%; $p<0.001$). On the QRISK3_PCR variable, derived through comparison to healthy sex and ethnicity matched controls, males maintained a slightly greater degree of prematurely achieved CVR compared to females (males −3.61 [−5.06 to −2.16] years vs. females −1.80 [−2.43 to −1.17] years, $p=0.025$).

No significant relationships were found between any of the CVR variables (QRISK3%, QRISK3_PCR or any of their individual subcomponents) and T2LV.

Relationship between cardiovascular risk and normalized brain volumes

The relationship between prematurely achieved CVR (QRISK3_PCR) and normalized whole and regional brain volumes is shown in Table 2.

The primary analysis revealed that each additional year of prematurely achieved CVR was associated with a 2.73 (95% CI 0.77–4.68) mL reduction in normalized whole brain volume ($p=0.006$). Secondary analyses suggested that this relationship was strongest for the cortical grey matter, where each additional year of prematurely achieved CVR was associated with a 1.60 (95% CI 0.54–2.67) mL reduction in normalized volume ($p=0.003$). For comparison, the same models suggested that each doubling of T2LV was associated with an 11.1 (6.8–15.3) mL reduction in normalized cortical grey matter volume ($p<0.001$; Table 2). All significant relationships persisted after normalized brain volumes were expressed after adjusting for sex (see Table S1).

TABLE 2 Relationship between the degree of prematurely achieved cardiovascular risk and normalized whole and regional brain volumes.

Dependent variable	Predictors				R^2
	QRISK3_PCR	$\log_2$ T2LV	MS duration	Age	
nWBV	2727.9 +772.3 to +4683.6 $p=0.006$	−25778.6 −33612.9 to −17944.3 $p<0.001$	−434.7 −1440.6 to +571.3 $p=0.395$	−1119.2 −2419.0 to +180.6 $p=0.091$	21.9%
nGMV	1662.5 +538.4 to +2786.6 $p=0.004$	−13082.4 −17589.0 to −8575.7 $p<0.001$	−97.6 −675.9 to +480.7 $p=0.740$	−1082.7 −1832.1 to −333.2 $p=0.005$	20.4%
nCGMV	+1601.0 +535.3 to +2666.8 $p=0.003$	−11075.3 −15347.9 to −6802.7 $p<0.001$	−70.0 −618.3 to +478.2 $p=0.801$	−1119.6 −1830.1 to −409.1 $p=0.002$	18.8%
nDGMV	61.4 −27.3 to +150.1 $p=0.174$	−2007.1 −2362.6 to −1651.5 $p<0.001$	−27.6 −73.2 to +18.0 $p=0.234$	36.9 −22.2 to 96.0 $p=0.220$	39.0%
nWMV	1104.5 130.7 to 2078.2 $p=0.026$	−12428.3 −16332.2 to −8524.4 $p<0.001$	−314.3 −815.2 to +186.7 $p=0.218$	−113.5 −762.7 to 535.7 $p=0.731$	19.7%

Note: Results are derived from five separate multiple linear regression models each including baseline data from the 218 participants in the UCL MS-STAT2 MRI sub-study. The relationship between QRISK3_PCR and nWBV was the primary analysis; all other analyses were pre-specified secondary analyses. For each model, normalized whole or regional brain volume is the dependent variable, and QRISK3_PCR is the predictor. In all models, age, MS duration (from symptom onset) and baseline $\log_2$ T2LV are included as covariates. For each predictor and covariates, the coefficient estimate and 95% confidence interval, together with the p value, are presented, plus the R^2 value for the overall model. All volumes are reported as mm^3. For QRISK3_PCR, a more negative value represents the patient achieving a greater degree of prematurely achieved CVR; hence the positive coefficients between QRISK3_PCR and normalized volumes represent a greater degree of prematurely achieved CVR being associated with smaller normalized volumes.

Abbreviations: $\log_2$T2LV, $\log_2$ of T2-weighted lesion volume; MRI, magnetic resonance imaging; MS, multiple sclerosis; nCGMV, normalized cortical grey matter volume; nDGMV, normalized deep grey matter volume; nGMV, normalized grey matter volume; nWBV, normalized whole brain volume; nWMV, normalized white matter volume; QRISK3_PCR, QRISK3 premature cardiovascular risk.

Relationship between cardiovascular risk and clinical disability

Exploratory analyses assessing the relationship between prematurely achieved CVR (QRISK3_PCR) and measures of clinical disability are shown in Table 3. There was little evidence to support any relationships between prematurely achieved CVR and measures of physical disability. Greater prematurely achieved CVR, however, was associated with poorer verbal working memory: each additional year of prematurely achieved CVR was associated with a 0.45 (0.13–0.77) points worse CVLT-II performance ($p=0.006$). A relationship of borderline significance was also present between excess prematurely achieved CVR and poorer Brief Visuospatial Memory Test performance (0.22, 0.00 to +0.44, $p=0.052$).

Relationship between individual components of cardiovascular risk and both clinical and imaging measures of disease severity

Final models assessing the relationships between individual components of CVR and imaging or clinical MS severity variables are shown in Tables 4 and 5. When CVR components were included separately, they explained a greater degree of variability in normalized brain volumes compared to including the composite QRISK3 scores alone. Beyond T2LV, age and sex, BMI and ethnicity were consistently associated with normalized brain volumes. BMI was also significantly associated with measures of lower limb physical disability (EDSS and timed 25-ft walk). Lipid ratio, in contrast, was associated with verbal and visuospatial working memory performance.

DISCUSSION

The cross-sectional relationships between prematurely achieved CVR and imaging and clinical measures of MS severity in people with SPMS have been analysed. Our primary and secondary analyses suggest that greater prematurely achieved CVR, quantified through the QRISK3_PCR variable, is significantly associated with lower normalized brain volumes, particularly lower cortical grey matter volume. Furthermore, exploratory analyses suggested this prematurely achieved CVR may be associated with poorer memory performance, particularly for verbal working memory. On

TABLE 3 Relationship between the degree of prematurely achieved cardiovascular risk and clinical disability measures.

Dependent variable	Predictors				
	QRISK3_PCR	$\log_2$T2LV	MS duration	Age	R^2
EDSS	−0.02 −0.04 to +0.01	+0.09 −0.03 to +0.20	+0.01 +0.00 to +0.03	−0.01 −0.03 to +0.00	5.2%
25FW	2.89 −32.55 to +38.34 $p=0.872$	−141.0 −283.03 to +0.96 $p=0.052$	−1.23 −19.46 to +17.01 $p=0.895$	+3.60 −19.96 to +27.16 $p=0.763$	1.9%
9HPT	+0.16 −0.10 to +0.41 $p=0.231$	−2.37 −3.39 to −1.34 $p<0.001$	−0.03 −0.16 to +0.11 $p=0.694$	+0.29 +0.12 to +0.46 $p=0.001$	14.1%
SDMT	+0.17 −0.10 to +0.45 $p=0.209$	−5.79 −6.88 to −4.70 $p<0.001$	−0.01 −0.15 to +0.126 $p=0.844$	−0.04 −0.22 to +0.14 0.649	36.7%
CVLT-II	+0.45 +0.13 to +0.77 $p=0.006$	−4.00 −5.29 to −2.71 $p<0.001$	−0.01 −0.17 to +0.16 $p=9.45$	+0.15 −0.07 to +0.36 $p=0.181$	21.5%
BVMT-R	+0.22 −0.00 to +0.44 $p=0.052$	−2.45 −3.34 to −1.56 $p<0.001$	−0.04 −0.15 to +0.08 $p=0.527$	−0.02 −0.17 to +0.13	15.7%
SLCLA 2.5%	+0.13 −0.15 to +0.41 $p=0.351$	−2.69 −3.80 to −1.57 $p<0.001$	−0.26 −0.40 to −0.12 $P<0.001$	−0.01 −0.20 to 0.18 $p=0.894$	18.5%

Note: Results are derived from seven separate multiple linear regression models each including baseline data from the 218 participants in the UCL MS-STAT2 MRI sub-study. All models should be considered exploratory. For each model a separate clinical measure is the dependent variable as indicated, and QRISK3_PCR is the predictor. In all models, age, MS duration (from symptom onset) and baseline $\log_2$T2LV are included as covariates. For all cognitive measures, educational years was additionally included as a covariate. For each predictor and covariates, the coefficient estimate and 95% confidence interval, together with the p value, are presented, plus the R^2 value for the overall model. EDSS estimates are produced via bias corrected and accelerated bootstrap; hence p values cannot be calculated but may be inferred from the 95% confidence interval of the coefficients. Both 25FW and 9HPT are expressed as a speed (with units ft/s × 1000 and $s^{-1} \times 1000$, respectively). All other variables are included as raw scores. As previously for QRISK3_PCR, a more negative value represents the patient achieving a greater degree of prematurely achieved CVR.

Abbreviations: 25FW, timed 25-ft walk; 9HPT, timed nine-hole peg test; BVMT-R, Brief Visual Memory Test, Revised; CVLT-II, California Verbal Learning Test II; EDSS, Expanded Disability Status Score; $\log_2$T2LV, $\log_2$ of T2-weighted lesion volume; MRI, magnetic resonance imaging; MS, multiple sclerosis; QRISK3_PCR, QRISK3 premature cardiovascular risk; SDMT, Symbol Digit Modalities Test; SLCLA 2.5%, Sloan Low Contrast Letter Acuity 2.5%; UCL, University College London.

TABLE 4 Final models following reverse stepwise multiple linear regression with individual cardiovascular risk components as predictors, against the dependent variable of normalized whole and regional brain volumes.

	nWBV	nGMV	nCGMV	nDGMV	nWMV
Log_2T2LV	−27,946.9 −34,817.1 to −21,076.7 $p<0.001$	−14,375.8 −18,176.5 to −10,575.0 $p<0.001$	−12,265.3 −15,864.0 to −8666.5 $p<0.001$	−2109.7 −2444.7 to −1774.7 $p<0.001$	−13,146.7 −16,819.5 to −9473.9 $p<0.001$
Age	−2026.5 −3134.7 to −918.3 $p<0.001$	−1576.0 −2189.6 to −962.4 $p<0.001$	−1580.2 −2161.2 to −999.1 $p<0.001$	–	–
Sex	+33,419.0 +15,133.5 to +51,704.6 $p<0.001$	+24,249.6 +14,142.6 to +34,356.6 $p<0.001$	+23,067.4 +13,497.6 to +32,637.2 $p<0.001$	1191.7 +309.7 to +2073.7 $p=0.008$	–
Ethnicity	−77,433.3 −110,902.5 to −43,964.1 $p<0.001$	−44,255.3 −62,743.8 to −25,766.8 $p<0.001$	−42,332.4 −59,838.2 to −24,826.5 $p<0.001$	−1945.4 −3548.6 to −342.2 $p=0.018$	−31,660.4 −49,229.1 to −14,091.7 $p<0.001$
Log_2BMI	−78,391.1 −106,277.6 to −50,504.5 $p<0.001$	−49,262.3 −64,671.7 to −33,852.9 $p<0.001$	−46,814.8 −61,405.2 to −32,224.5 $p<0.001$	−2442.5 −3799.8 to −1085.2 $p<0.001$	−31,399.7 −46,257.2 to −16,542.3 $p<0.001$
Log_2lipid ratio	–[a]	–	–	–	–[a]
R^2	39.7%	43.2%	42.2%	45.8%	27.5%

Note: Results are derived from the five final separate multiple linear regression models, each with a different normalized brain volume region as the dependent variable. All cardiovascular risk variables contained within the QRISK3 composite score were initially included as predictors, and reverse stepwise removal of non-contributory variables was performed as described. In the final models, all variables were either significantly associated with the dependent variable or their removal resulted in >1% loss in R^2 or was deemed to materially affect the relationship of the remaining predictors. T2LV was included as an additional covariate in all models.

Abbreviations: ethnicity, white = 1, non-white = 2; log_2BMI, log_2 of body mass index (kg/m^2); log_2lipid ratio, total cholesterol/high-density lipoprotein; log_2T2LV, log_2 of T2-weighted lesion volume; nCGMV, normalized cortical grey matter volume; nDMGV, normalized deep grey matter volume; nGMV, normalized grey matter volume; nWBV, normalized whole brain volume; nWMV, normalized white matter volume; sex, male = 1, female = 2.

[a]When combined with BMI, lipid ratio was significantly associated with nWBV and nWMV, but the two variables introduced multicollinearity. BMI remained independently associated with nWBV without lipid ratio and when examined in a univariate linear regression model; lipid ratio was only significant when included with BMI, and displayed no evidence of a univariate relationship with nWBV or nWMV. Lipid ratio was therefore excluded from the final model.

investigating which aspects of CVR may be the most influential, higher BMI was found to be strongly associated with lower brain volumes and a greater degree of lower limb disability, whilst higher lipid ratios, as for greater prematurely achieved CVR, were associated with poorer memory performance.

In all, 10% of potential trial participants were excluded from the UCL MS-STAT2 cohort due to pre-existing statin use or unacceptably high CVR. The overall SPMS population is therefore expected to have a higher burden of CVR than those included in this study—although our cohort, with a median QRISK_PCR value of −1 years (interquartile range −4 to +1 years), still maintained a significantly greater excess CVR than healthy control data from the QRISK3 population. One might therefore expect the impact of prematurely achieved CVR across the whole SPMS population to be even greater than estimated here, although this will require confirmation with further research in less selective observational cohorts.

It should be recognized that whilst the relationships described between QRISK3_PCR and MS severity variables (such as normalized cortical grey matter volume or CVLT-II) were statistically significant, the degrees of variability accounted for by excess CVR were modest. For example, in univariate analyses without other covariates, QRISK3_PCR only explained 3.5% of the variability in cortical grey matter volume. This is to be expected, however, given the established relationship between other quantifiable aspects of MS severity, such as neuroinflammatory variables (e.g., T2LV, T1-gadolinium enhancing lesions, neurofilament light concentrations) and subsequent brain atrophy [28, 29]. In terms of magnitude, however, our data suggest that 10 additional years of prematurely achieved CVR were associated with a similar degree of cortical grey matter volume loss as a doubling of T2LV: 16.0 (95% CI 5.4–26.7) mL per 10 years of prematurely achieved CVR, compared to 11.1 (95% CI 6.8–15.3) mL for each doubling of T2LV. The finding that excess CVR may be associated with poorer working memory performance, whilst exploratory, lends support to the potential clinical significance of the relationships between prematurely achieved CVR and brain volumes.

The models including individual components of CVR explained more variability in brain volumes than the models including the composite QRISK3_PCR scores. This suggests that whilst the QRISK3-derived scores have been extensively validated against future cardiovascular events, they may need to be optimized for prediction of outcomes in people with SPMS. Our exploratory analyses therefore suggest that the value of the QRISK3 score, in terms of predicting relevant MS outcomes, may be less than the sum of its parts, with higher BMI and potentially higher lipid ratios being particularly important aspects.

TABLE 5 Final models following reverse stepwise linear regression with individual cardiovascular risk components as predictors, against the dependent variables of MS clinical and cognitive disability.

Predictors	EDSS	25FW speed	9HPT speed	SLCLA 2.5%	SDMT	CVLT-II	BVMT-R
Log_2T2LV	+0.10 −0.01 to +0.20	−136.4 −272.69 to −1.15 $p=0.048$	−2.42 −3.42 to −1.41 $p<0.001$	−3.13 −4.25 to −2.00 $p<0.001$	−5.82 −6.89 to −4.76 $p<0.001$	−4.04 −5.29 to −2.78 $p<0.001$	−2.51 −3.38 to −1.64 $p<0.001$
Age	+0.29 +0.00 to +0.58	–	+0.27 +0.11 to +0.43 $p=0.001$	–	–	–	–
Sex	–	−566.4 −922.7 to −210.1 $p=0.002$	–	–	–	–	–
Smoking	–	–	–	–	–	−2.51 −5.42 to +0.40 $p=0.090$	–
Log_2lipid ratio	–	–	–	–	–	−4.21 −6.98 to −1.45 $p=0.003$	−2.19 −4.11 to −0.27 $p=0.026$
Ethnicity	+0.48 +0.08 to +0.81	−564.9 −1213.1 to +83.4 $p=0.087$	–	–	–	–	−4.34 −8.53 to −0.16 $p=0.042$
Log_2BMI	+0.44 +0.03 to +0.85	−840.6 −1389.3 to −292.0 $p=0.003$	–	–	–	–	–[a]
R^2	6.4%	10.2%	13.5%	12.4%	36.2%	20.4%	17.7%

Note: Results are derived from the seven final separate multiple linear regression models, each with a different clinical outcome measure as the dependent variable. As for the MRI analysis, all cardiovascular risk variables contained within the QRISK3 composite score were initially included as predictors, and reverse stepwise removal of non-contributory variables was performed as described. In the final models, all variables were either significantly associated with the dependent variable or their removal resulted in >1% loss in R^2 or was deemed to materially affect the relationship of the remaining predictors. T2LV was included as an additional covariate in all models.

Abbreviations: 25FW, timed 25-ft walk (ft/s×1000); 9HPT, timed nine-hole peg test (s^{-1}×1000); BMI, body mass index (kg/m^2); BVMT-R, Brief Visual Memory Test, Revised; CVLT-II, California Verbal Learning Test II; EDSS, Expanded Disability Status Score; ethnicity, white=1, non-white=2; lipid ratio, total cholesterol/high-density lipoprotein; log_2T2LV, log_2 of T2-weighted lesion volume; MRI, magnetic resonance imaging; MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test; SLCLA 2.5%, Sloan Low Contrast Letter Acuity 2.5%; smoking, never=0, ever=1; T2DM, type 2 diabetes mellitus (absent=0, present=1).

[a]When combined with lipid ratio, BMI was significantly associated with BVMT-R, but the two variables introduced multicollinearity. Lipid ratio remained independently associated with BVMT-R without BMI, but BMI did not when lipid ratio was excluded. BMI was therefore excluded from the final model.

No significant associations were found between CVR variables and T2LV. A previous cross-sectional observational study in a mixed cohort (60% RRMS) found that the presence of hypertension, smoking, heart disease and a BMI >25 kg/m^2, in various combinations, was associated with higher T2LV, but predominantly in people with RRMS [30]. Another longitudinal study in those with a clinically isolated syndrome found higher lipid profiles were associated with increased risk of new lesion formation [31]. Other studies, however, have not replicated these relationships [3]. Certainly, the absence of significant relationships between CVR variables and T2LV in our study does not refute these previous findings, and the study may be underpowered to detect modest relationships. In healthy controls, CVR has an established association with white matter hyperintensities, presumably mediated via cerebral small vessel disease [32]. One possible interpretation is therefore that whilst CVR appears to be associated with T2 lesion variables earlier in the course of disease, by the advanced disease stage included in this study (SPMS, disease duration 24 years) T2LV predominantly represents neuroinflammatory lesions, as shown in previous histological studies [33]. Further studies are warranted, however, to further explore this relationship.

There is established literature supporting the relationship between higher BMI and aspects of MS severity, including cross-sectional and longitudinal changes in grey matter volumes [34–39]. This is not necessarily an MS-specific effect, as similar results, particularly between higher BMI and lower grey matter volumes, have been found in people without MS [40–48]. Interestingly, given our finding of a relationship between greater prematurely achieved CVR or higher lipid ratios and worse verbal working memory performance, one previous study of predominantly RRMS found that higher FRS is also associated with poorer CVLT-II performance [49]. Whilst lipid ratios were not included, in further support of our findings, higher total cholesterol was also associated with poorer CVLT-II performance [49]. This again may not be an MS-specific effect, as studies in people without MS have reported a relationship between mid- and late-life CVR,

including cholesterol and smoking, with future incidence of dementia and cortical amyloid burden [50, 51]. Our findings, and those of others, may therefore represent an extension of these same processes in people with SPMS, or they may represent a particular additional vulnerability of people with SPMS to the cognitive impacts of such CVRs. The possibility that people with MS may be particularly vulnerable to cerebral small vessel disease has been suggested by a histology case–control study [52]. People with MS had higher rates of small vessel disease, and a stronger relationship between measures of peripheral cardiovascular disease and cerebral small vessel disease, compared to controls [52]. One possible interpretation of this literature and our data is therefore that greater prematurely achieved CVR may contribute to accelerated brain atrophy and poorer memory performance due to a particular vulnerability of people with SPMS to the mechanisms of cerebral small vessel disease. This interpretation is speculative, however, and requires exploration in further research.

The main limitation of this work is the cross-sectional design. At present, it is not therefore possible to comment on causality and whether the observed relationships are relevant to ongoing changes in our participants' MS severity. A major advantage of investigating CVR within this MS-STAT2 clinical trial cohort, however, is first that longitudinal clinical and MRI follow-up is ongoing, with the 3-year dataset due to be completed in 2025. Secondly, the randomization between high-dose simvastatin and placebo will allow further investigation of causality, given that simvastatin is an established and probably pleiotropic modifier of CVR [53].

CONCLUSIONS

In this cross-sectional analysis of people with SPMS from the UCL MS-STAT2 trial cohort, a greater degree of prematurely achieved CVR was cross-sectionally associated with lower normalized brain volumes, particularly for cortical grey matter, and worse working memory performance. Raised BMI and lipid ratios appeared to be key contributors to the relationship between CVR and MS severity measures, and it is suggested that composite CVR scores may require optimizing to better predict important MS severity endpoints. Whilst this cross-sectional analysis cannot comment on causality, longitudinal follow-up of the cohort is ongoing, within which the randomization between high-dose simvastatin versus placebo will allow important future conclusions to be drawn on whether prematurely achieved CVR is a relevant modifiable target for treatment in SPMS.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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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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APPENDIX

MS-STAT2 INVESTIGATORS

Jeremy Chataway, Thomas Williams, Nevin John, Floriana De Angelis, Alberto Calvi, Alessia Bianchi, Sarah Wright, Madiha Shatila, Anisha Doshi, Wallace Brownlee, Claudia A M Gandini Wheeler-Kingshott, Frederik Barkhof, Olga Ciccarelli, Jonathan Stutters, Ferran Prados Carrasco, Antonio Ricciardi, Marios Yiannakas, David MacManus, Megan Wynne, Marie Braisher (Queen Square Multiple Sclerosis Centre, University College London and University College London Hospitals NHS Foundation Trust, London, UK); James Blackstone, Leanne Hockey, Josephine Parker, Jennifer Flight (Comprehensive Clinical Trials Unit, Institute of Clinical Trials and Methodology, University College London, London, UK); Chris Frost, Jennifer Nicholas (Centre for Statistical Methodology, London School of Hygiene and Tropical Medicine, London, UK); Stuart Nixon and Judy Beveridge (patient representatives); Siddharthan Chandran, Peter Connick, Dawn Lyle (Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, UK); Ian Galea, Elisabeth Jarman (University Hospital Southampton NHS Foundation Trust, Southampton, UK); Helen Ford, Linford Fernandes, Maruthi Vinjam (Leeds Teaching Hospitals NHS Trust, Leeds, UK); Sue Pavitt (Dental Translational and Clinical Research Unit, University of Leeds, Leeds, UK); Basil Sharrack, David Paling (Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK); Abdullah Shehu, Tarunya Arun, Mohamed Belhag (University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK); Owen Pearson, Gillian Ingram, Christopher Rickards (Swansea Bay University Health Board, Swansea, UK); Gavin McDonnell, Stella Hughes (Belfast Health and Social Care Trust, Belfast, UK); Cord Spilker (Bradford Teaching Hospitals Foundation Trust, Bradford, UK); Leonora Fisniku, Julia Aram (Brighton and Sussex University Hospitals NHS Trust, Brighton, UK); Claire Rice (North Bristol NHS Trust, Bristol, UK); Stefano Pluchino, Luca Peruzzotti-Jametti (Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK); Sreedharan Harikrishnan, Nikki Guck (East Kent Hospitals University NHS Foundation Trust, Canterbury, UK); Neil Robertson, Emma Tallantyre (University Hospital of Wales, Cardiff, UK); Timothy Harrower (Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK); Paul Gallagher (NHS Greater Glasgow and Clyde, Glasgow, UK); Fayyaz Ahmed (Hull University Teaching Hospitals NHS Trust, Hull, UK); Carolyn Young, Heike Arndt (The Walton Centre NHS Foundation Trust, Liverpool, UK); Eli Silber (Lewisham and Greenwich NHS Trust, London, UK); Richard Nicholas (Imperial College Healthcare NHS Trust, London, UK); Martin Duddy (Royal Victoria Infirmary, Newcastle upon Tyne Hospital NHS Foundation Trust, Newcastle, UK); Martin Lee (Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK); Nikos Evangelou, Christopher Allen (Nottingham University Hospital NHS Trust, Nottingham, UK); Matthew Craner, Ruth Geraldes (Oxford University Hospitals NHS Foundation Trust, Oxford, UK); Jeremy Hobart (University Hospitals Plymouth NHS Trust, Plymouth, UK); Charles Hillier (University Hospitals Dorset NHS Foundation Trust, Poole, UK); Suresh Chhetri (Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK); Miriam Mattoscio, Abhijit Chaudhuri (Barking, Havering and Redbridge University Hospitals NHS Trust, Romford, UK); Seema Kalra (University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK); Agne Straukiene (Torbay and South Devon NHS Foundation Trust, Torbay, UK); David Rog (Salford Royal NHS Foundation Trust, Manchester, UK).