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Comparative impact of mental and cardiovascular comorbidities on adverse outcomes in people with MS

Madeleine France-Ratcliffe [a,c], Stephanie L. Harrison [d,e], Leona A. Verma [b,f,g], Azmil H. Abdul-Rahim [b,i,j], Linsay McCallum [k], Garry McDowell [b,f], Carolyn A. Young [g,h], Benjamin J.R. Buckley [a,b,i,*]

[a] Cardiovascular Health Sciences, Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool L3 5UX, United Kingdom
[b] Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
[c] Department of Sport and Exercise Sciences, Institute of Sport, Manchester Metropolitan University, Manchester, United Kingdom
[d] Registry of Senior Australians Research Centre, College of Nursing and Health Sciences, Flinders University, Bedford Park, Australia
[e] Registry of Senior Australians Research Centre, South Australian Health and Medical Research Institute, Adelaide, Australia
[f] Liverpool John Moores University, School of Pharmacy and Biomolecular Sciences, Liverpool L3 3AF, United Kingdom
[g] Molecular and Integrative Biology, Institute of Systems, University of Liverpool, Liverpool, United Kingdom
[h] Walton Centre NHS Foundation Trust, Liverpool, United Kingdom
[i] Department for Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, UK
[j] Stroke Division, Department of Medicine for Older People, Whiston Hospital, Mersey and West Lancashire Teaching Hospitals NHS Trust, Prescot, UK
[k] School of Cardiovascular & Metabolic Health, University of Glasgow, Glasgow, UK

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ABSTRACT

Background: Comorbidities may exacerbate disease burden in people with Multiple Sclerosis (pwMS), yet their influence on disease progression and patient-reported outcomes (PROs) remains poorly understood. Understanding how comorbidities relate to progression and PROs can inform personalised care.
Objectives: Identify comorbidity profiles in pwMS and assess their impact on MS type progression and PROs.
Methods: This observational study analysed UK MS Register data from 2011 to 2025. Hierarchical clustering was based on cardiovascular and mental health comorbidities. Logistic and linear regression examined associations between clusters, comorbidities, progression and PROs.
Results: Cluster analysis in 5944 pwMS identified 3 clusters: 1 (no comorbidities, $n = 4278$), 2 (100% cardiovascular, 5% mental health, $n = 910$), and 3 (98% mental health, 24% cardiovascular, $n = 756$). Amongst participants with relapsing-remitting MS at baseline ($n = 4942$), compared to cluster 1, cluster 2 showed no difference in odds (OR 1.15, 95%CI: 0.93–1.43) whilst cluster 3 greater odds (OR 1.90, 95%CI: 1.53–2.35) of progressing to secondary-progressive MS, after adjusting for age, gender, and time since diagnosis. Depression showed the strongest association with progression. Comorbidities were associated with worse PROs, with anxiety and depression linked to lower psychological and physical symptoms.
Conclusions: Mental health conditions clustered with cardiovascular multimorbidity consistently associated with poorer MS progression and prognosis, emphasising the need for integrated mental health management in pwMS.

1. Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative condition characterised by a diverse array of symptoms, including fatigue, impaired mobility, and unpredictable disease progression, all of which can significantly impact patients' quality of life (QoL) and mental health [1–3]. Research consistently demonstrates that people with MS (pwMS) experience lower health-related QoL (HRQoL) compared to the general

* Corresponding author at: Cardiovascular Health Sciences, Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool Centre for Cardiovascular Science, Liverpool L3 5UX, United Kingdom.
E-mail address: b.j.buckley@ljmu.ac.uk (B.J.R. Buckley).

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population [4–7].

PwMS are at risk of experiencing progression in their disease course, transitioning from relapsing-remitting MS (RRMS) to more progressive forms. Approximately 85% of patients initially present with RRMS, characterised by episodes of acute worsening of function followed by partial or complete recovery [8]. Within two decades, around half of these patients will progress to secondary progressive MS (SPMS) [9], a form marked by at least six months of steady clinical deterioration that occurs independently of relapses [10]. Primary progressive MS (PPMS), which affects 10–15% of the MS population, is progressive from onset [11]. Research has identified higher age, male gender, longer disease duration, and greater disability as measured by Expanded Disability Status Scale (EDSS), as risk factors for MS progression [12]. Importantly, patients who transition from RRMS to SPMS report significantly worse QoL and higher levels of fatigue compared to patients who remained having RRMS [13].

A range of clinical and demographic factors have been associated with reduced health-related QoL in pwMS, extending beyond the core symptoms of the disease [14,15]. The type of MS also plays a role, with SPMS related with greater EDSS scores compared to RRMS [16]. Other factors, including older age, female sex, higher EDSS scores, and shorter time since last relapse, have been identified as predictors of lower QoL [17]. Additionally, multimorbidity, more common in pwMS than the general population [18], can exacerbate MS disease course by delaying diagnosis, accelerating disability progression, and complicating treatment adherence and management [19,20]. In a study of 8274 pwMS, 34% reported having at least one comorbidity, with hypertension being the most common [21]. Notably, comorbidities have been strongly associated with poorer health, disability, and QoL trajectories in pwMS, often contributing to a clinical profile at diagnosis resembling that of late-stage disease [22]. Given the impact of transition of RRMS to SPMS on HRQoL and fatigue [13], further research is needed to understand the interaction between specific comorbidities and health outcomes to drive development of more targeted interventions and improve outcomes for pwMS.

By employing a hierarchical clustering approach, we aimed to identify comorbidity profiles in pwMS to investigate their impact on MS type progression and patient reported outcomes (PROs). We employed hierarchical clustering to identify distinct comorbidity phenotypes within the pwMS population. Unlike individual comorbidity analyses that assess each condition independently, clustering reveals how comorbidities naturally co-occur and interact, providing insights into real-world multimorbidity patterns. This approach enables comparison between different comorbidity profiles and their relative impact on outcomes.

2. Methods

2.1. Study design

The UK MS Register (UKMSR), launched in 2011 and funded by the MS Society was used. Details of participant recruitment and study design have been previously described [23]. The data is stored in a Microsoft SQL Server, and Structured Query Language (SQL) queries were used to extract, clean, and aggregate relevant data for analysis. All patient data were anonymised prior to inclusion in the register, and remote access technology was employed to enable researchers to analyse data securely without compromising confidentiality. Participant demographic characteristics, self-reported disease type, and lifestyle information are gathered at recruitment, and participants are asked to complete PROs every 6 months (detailed below).

2.2. Participants

Data were extracted from the UKMSR in July 2025. Participants were eligible if they were aged 18 years or older, resided in the UK, had a diagnosis of MS confirmed by a neurologist based on the McDonald Criteria [24], and agreed to the terms of service [25], which outline the Register's responsibility for the data usage and storage.

2.3. Measures

Demographic information were obtained at recruitment: age, gender, ethnicity, occupation, education, year of MS onset, MS type at diagnosis (and date of diagnosis), current MS type (and date of recording), smoking history, and the presence of cardiovascular (self-report of high cholesterol, high blood pressure, heart trouble [*e.g.* angina, congestive heart failure, or coronary artery disease], peripheral vascular disease, or diabetes mellitus), and mental health comorbidities (self-report of depression or anxiety).

Participants were invited to complete a series of online questionnaires every six months. The questionnaires included: Fatigue Severity Scale (FSS) [26], Hospital Anxiety and depression scale (HADS) [27], Web version of the Expanded Disability Status Scale (web-EDSS) [28], MS impact scale (MSIS-29 V1/2) [29], and the Multiple Sclerosis Walking Scale-12 (MSWS) [30]. Please refer to the supplementary material 1 for further information regarding these measures.

2.4. Statistical analyses

Statistical analyses were conducted in RStudio (R v4.1.3 (2022−03−10)), within the UKMSR secure online portal. Descriptive statistics are reported as percentages, unless otherwise specified. To account for multiple comparisons, *p*-values were adjusted using the Benjamini-Hochberg (BH) false discovery rate (FDR) correction [31], applied within five pre-specified families of related tests. FDR-adjusted p-values <0.05 were considered statistically significant.

2.4.1. Hierarchical cluster analysis

Hierarchical clustering is an unsupervised machine learning technique used to group individuals into clusters based on shared characteristics, facilitating the identification of distinct clusters within a population. It is particularly useful in exploring complex, multivariate datasets where the aim is to uncover natural groupings without predefining the number of clusters. The approach iteratively combines similar individuals or variables into clusters, visualising the relationships and hierarchical structure through a dendrogram (Fig. 1). Hierarchical clustering was selected to identify naturally occurring patient subgroups based on comorbidity patterns, rather than examining comorbidities as isolated variables. This approach reveals how comorbidities cluster together in real-world patients and enables direct comparison of outcomes between distinct comorbidity profiles.

We investigated MS progression and PROs across different clusters. Variables included in the clustering were high blood pressure, high cholesterol, diabetes mellitus (type 1 and 2), peripheral vascular disease (PVD), heart trouble (such as angina, congestive heart failure, or coronary artery disease), anxiety, and depression. Clustering was performed using the *hclust* function from the R *stats* package with *Ward-linkage* method. The number of clusters was decided based on visual inspection of the dendrogram (Fig. 1) and using the *NbClust* R package, [32].

2.4.2. MS type progression

To assess MS type progression (a binary outcome), logistic binomial family) were used throughout including all participants with RRMS at diagnosis who had not already progressed to SPMS before their baseline assessment. First, cluster group was entered as the sole predictor with cluster 1 as the reference as this group included no cardiovascular or mental health comorbidities. This analysis was repeated with cluster 2 as the reference to explore differences between clusters 2 and 3 (mental health *vs* cardiovascular clusters). Subsequently, individual comorbidities were entered simultaneously in a multivariable logistic regression model (high blood pressure, high cholesterol, diabetes, PVD, heart

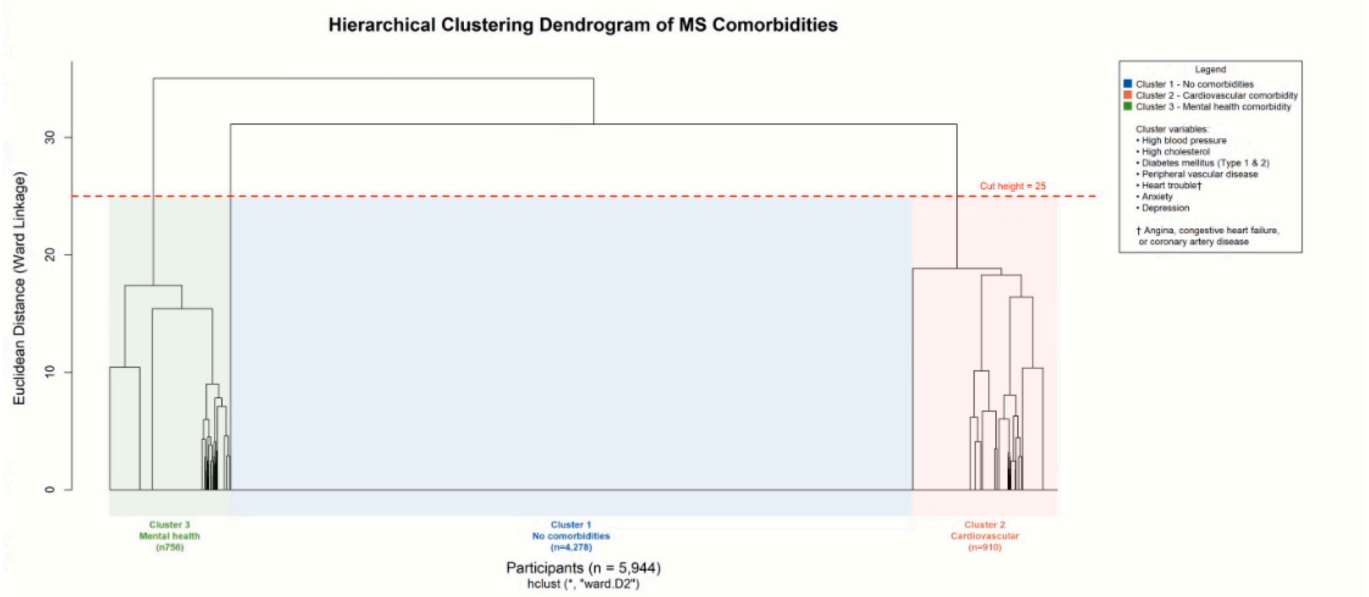

Fig. 1. Dendrogram of people with multiple sclerosis clustered according to cardiovascular and mental health comorbidities. Clustering variables: high blood pressure, high cholesterol, diabetes mellitus (Type 1 & 2), peripheral vascular disease, heart trouble (angina, congestive heart failure, or coronary artery disease), anxiety, and depression. PwMS were grouped into three clusters at a Euclidean distance of 25: Cluster 1 (blue; $n = 4278$; no comorbidities), Cluster 2 (red; $n = 910$; cardiovascular comorbidities), and Cluster 3 (green; $n = 756$; mental health comorbidities). *Note: The middle cluster (Cluster 1; no cardiovascular or mental health comorbidities) appears visually compressed because it is large and highly homogeneous; cluster contains zero variance across comorbidity variables (every value is 0).* (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

trouble, anxiety, depression) without cluster stratification. Age, gender, and time since diagnosis were added as covariates to the multivariable logistic regression model (adjusted model 1) as these variables differed significantly between clusters and are plausible confounders of the relationship between comorbidity and MS progression. Additionally, we performed a sensitivity analysis including baseline web-EDSS as a covariate in the multivariable logistic regression model due to the observed differences across clusters and its potential role as a marker of disease severity (adjusted model 2). BH FDR correction was applied separately to: the cluster group comparisons (Family 1; three tests per model: cluster 2 *vs* 1, cluster 3 *vs* 1, and cluster 3 *vs* 2 in the adjusted and unadjusted models), and the individual comorbidity associations with MS progression (Family 2; seven tests per model, applied to the adjusted and unadjusted models).

To address the time-dependent nature of MS progression, Kaplan-Meier survival analysis and Cox proportional hazards regression were conducted in participants with RRMS at diagnosis ($n = 4831$), after excluding those with missing time-to-event or cluster data ($n = 163$). The outcome of interest was time from baseline assessment to SPMS. Kaplan-Meier curves were generated to visualise the probability of remaining RRMS over time across clusters, and differences between curves were assessed using the log-rank test. Cox proportional hazards regression was subsequently used to estimate hazard ratios (HR) and 95% confidence intervals for the association between cluster and time to SPMS, with cluster 1 (no comorbidity) as the reference category. A separate multivariable Cox regression model examined the association between individual comorbidities and time to SPMS. Models were repeated following adjustment for age, gender, and time since MS diagnosis. Survival analyses were conducted using the *survival* and *survminer* packages in R.

2.4.3. Patient reported outcomes

To assess PROs (continuous outcomes), linear regression models were used. Each model included cluster group, baseline questionnaire score, time between baseline and latest questionnaire completions, age, gender, time since diagnosis, and MS progression as predictors of the latest questionnaire score. Estimated marginal means were calculated using the *emmeans* package, and pairwise comparisons between categories of MS progression (no change or progression) were performed. BH FDR correction was applied to the cluster group (cluster 2 *vs* 1 and cluster 3 *vs* 1) and MS progression predictor *p*-values across the seven PRO models, with correction applied separately within each predictor across models (Family 3).

Finally, a multiple linear regression model was used to determine the impact of different cardiovascular and mental health comorbidities on latest questionnaire scores with and without adjustment for age, gender, time since diagnosis and time between baseline and latest questionnaire completions. BH FDR correction was applied within each PRO outcome separately across the seven comorbidity predictors (Family 4).

To examine whether findings were robust across age categories, unadjusted logistic and linear regression analyses were repeated in participants stratified by age category (<60 and ≥ 60 years).

3. Results

3.1. Participants

The initial sample included 24,318 pwMS. After excluding participants with incomplete demographic data (including those who answered 'Prefer not to say' for gender) and those who completed fewer than two questionnaires per type, 5944 eligible participants remained. Missing data were as follows: age ($n = 0$), gender ($n = 30$), onset year ($n = 2116$), diagnosis year ($n = 1548$), MS type at diagnosis ($n = 2252$), MS type now ($n = 2908$) and the date of recording ($n = 1686$), ethnicity ($n = 815$), occupation ($n = 2376$), education ($n = 2450$), and smoking history ($n = 6540$). Supplementary material 2 shows demographic characteristics of the ineligible participants, though should be interpreted with caution given the large amounts of missing data. Amongst the eligible 5944 participants, 75.7% ($n = 4501$) were female, and the mean age was 57 ± 12 years. 84.0% of participants were initially diagnosed with RRMS (first diagnosis). Amongst the ineligible participants, 73.3% ($n = 13,473$) were female, and the mean age was 57 ± 13

years, whilst fewer participants were initially diagnosed with RRMS in comparison to the eligible participants (67.9%). Amongst all eligible and ineligible participants, the mean interval between MS type at diagnosis and answering the question about their current MS type was 12 ± 10 years.

3.2. Cluster analysis

The cluster analysis for the sample of 5944 eligible participants identified three distinct clusters (Fig. 1): Cluster 1; latest year of diagnosis, greater percentage of individuals with RRMS now, no cardiovascular comorbidities or mental health comorbidities ($n = 4278$), cluster 2; a slightly older cluster with the least number of individuals having RRMS at diagnosis and now, and 100% of individuals having cardiovascular comorbidities ($n = 910$), and cluster 3; 98% had mental health comorbidities, 24% had cardiovascular comorbidities ($n = 756$). Cluster group demographic and clinical characteristics are presented in Table 1, pairwise standardised mean differences (SMD) between all groups were calculated using the *tableone* package in R Studio and the maximum absolute SMD was reported.

3.3. Primary outcomes

Amongst those with RRMS at diagnosis ($n = 4994$), 1091 (22%) progressed to SPMS, whilst 3903 (78%) reported no change. Individuals who had progressed from RRMS at diagnosis to SPMS prior to baseline assessment ($n = 69$) were excluded from the logistic regression analyses, leaving $n = 4942$.

3.3.1. Family 1: cluster group and MS type progression

In the unadjusted logistic regression model, there were significantly higher odds of MS progression in cluster 2 compared to cluster 1 (OR 2.33, 95%CI: 1.94, 2.80, BH-adjusted $p < 0.001$), and in cluster 3 compared to cluster 1 (OR 2.11, 95%CI: 1.75, 2.54, BH-adjusted $p < 0.001$). There was no significant difference between the odds of MS progression in cluster 3 compared to cluster 2 (OR 0.91, 95%CI: 0.72, 1.14, BH-adjusted $p = 0.406$). After adjusting for age, gender, and time since diagnosis (adjusted model 1), there was no significant difference between the odds of MS progression in cluster 2 compared to cluster 1 (OR 1.15, 95%CI: 0.93, 1.43, BH-adjusted $p = 0.192$). There were significantly higher odds of MS progression in cluster 3 compared to cluster 1 (OR 1.90, 95%CI: 1.53, 2.35, BH-adjusted $p < 0.001$) Moreover, cluster 3 was at a significantly higher odds of MS progression compared to cluster 2 (OR 1.64, 95%CI: 1.25, 2.16, BH-adjusted $p < 0.001$). In sensitivity analyses including baseline web-EDSS as a covariate (adjusted model 2), associations between clusters and MS progression were attenuated, and neither cluster 2 (OR 0.90, 95% CI: 0.70, 1.14) nor cluster 3 (OR 1.21, 95% CI: 0.95, 1.54) remained significantly associated with progression compared to cluster 1. When unadjusted and stratified by age category, cluster 2 and cluster 3 were associated with MS progression in both age < 60 (OR 1.92, 95%CI: 1.30, 2.79; OR 2.39, 95%CI: 1.80, 3.15, respectively) and ≥ 60 years (OR 1.32, 95%CI: 1.05, 1.65; OR 1.95, 95%CI: 1.47, 2.60, respectively) compared to cluster 1 (supplementary material 3).

3.3.2. Family 2: individual comorbidities and MS type progression

When assessing the impact of individual comorbidities on MS progression in the full cohort (not stratified by cluster), an unadjusted multivariable logistic regression model found that presence of high cholesterol (OR 1.97, 95%CI: 1.49, 2.58, BH-adjusted $p < 0.001$), high blood pressure (OR 1.65, 95%CI: 1.33, 2.04, BH-adjusted $p < 0.001$), and depression (OR 2.09, 95%CI: 1.67, 2.60, BH-adjusted p < 0.001) were significantly associated with increased odds of MS progression compared to no presence of these comorbidities. Presence of diabetes (OR 1.35, 95%CI 0.94, 1.92, BH-adjusted $p = 0.119$), heart trouble (OR 1.58, 95%CI: 1.03, 2.38, BH-adjusted $p = 0.056$), PVD (OR 2.32, 95%CI:

Table 1
Demographic characteristics of the Clusters.

	Cluster 1 (%) $n = 4278$	Cluster 2 (%) $n = 910$	Cluster 3 (%) $n = 756$	P-Value	SMD
Age (years); mean (SD)	55 (12)	65 (9)	57 (11)	<0.001	0.595
Female	77	65	80	<0.001	0.224
MS Diagnosis					
Time since diagnosis (years); mean	15	20	18	<0.001	0.297
MS type at diagnosis				<0.001	0.233
RRMS at diagnosis	86	74	86		
PPMS at diagnosis	10	18	9		
SPMS at diagnosis	4	8	6		
MS type now				<0.001	0.354
RRMS now	69	48	59		
PPMS now	10	18	9		
SPMS now	20	33	32		
Benign now	1	2	0		
Ethnicity				0.009	0.199
British	89	95	91		
Irish	2	1	2		
Asian	1	1	1		
African / Caribbean	1	1	1		
Mixed Race	1	1	1		
Other Ethnicity	6	2	4		
Education				<0.001	0.168
Secondary school	16	18	20		
Occupational certificate or diploma	29	37	33		
University bachelor's degree	28	24	24		
Postgraduate degree	22	15	18		
Other education	5	5	5		
Occupations				<0.001	0.210
Managerial	21	21	15		
Professional	30	31	26		
Associate professional and technical	10	10	10		
Administrative	18	18	21		
Skilled trade	4	6	5		
Caring, leisure and other service	7	6	11		
Sales and customer service	6	6	9		
Process plant and machine operatives	1	1	1		
Elementary occupations	1	1	2		
Smoking history				<0.001	0.137
Never smoked	56	50	47		
Past smoker	37	44	44		
Current smoker	7	6	9		
Comorbidities					
With cardiovascular comorbidities	0	100	24	<0.001	NA
With mental health comorbidities	0	5	98	<0.001	4.959
High cholesterol	0	35	12	<0.001	0.703
High blood pressure	0	67	18	<0.001	1.283
Heart trouble	0	16	1	<0.001	0.446
PVD	0	0	3	<0.001	0.188
Diabetes	0	20	4	<0.001	0.508
Degree of physical impairment					

(*continued on next page*)

Table 1 (*continued*)

	Cluster 1 (%) $n = 4278$	Cluster 2 (%) $n = 910$	Cluster 3 (%) $n = 756$	P-Value	SMD
High web-EDSS score at baseline	37	60	58	<0.001	0.316
High MSWS score at baseline	10	18	16	<0.001	0.149

Web-EDSS; web version of the expanded disability status scale, MS; multiple sclerosis, MSWS; multiple sclerosis walking scale, RRMS; Relapsing-remitting multiple sclerosis, PPMS; Primary-progressive multiple sclerosis, SPMS; Secondary-progressive multiple sclerosis. SMD for cardiovascular comorbidities is reported as NA as one group has no variation. Benign is used to describe a version of RRMS with very mild or no attacks separated by long periods with no symptoms. Heart trouble was defined as angina, congestive heart failure, or coronary artery disease. Occupation definitions: mangers (e.g. Office, IT, Purchasing, Healthcare or other mangers); professional (e.g. Chemists, Civil Engineers, Electronics Engineers, Dentists, Doctors, Nurses, Social Workers); associate professional and technical (e.g. Nurses, Laboratory technicians, IT Support, Radiographers, Artists, Authors); administrative (e.g. Clerks, Secretaries, Personal Assistants, Receptionists); skilled trade (e.g. Farmers, Electricians, Industrial Operators, Plumbers, Mechanics, Aircraft Engineers, Painters); caring, leisure and other service (e.g. Healthcare, Childcare, looking after animals, housekeeping and hairdressing); sales and customer service (e.g. Sale and Retail assistants, Call centre workers, Debt collectors, Housekeepers); process plant and machine operatives (e.g. Machine operators, Textile Process Operators, Electroplaters, Plant workers); elementary occupations (e.g. Forestry workers, Farm workers, Labourers, Waitresses, Porters, Bar staff, Shelf Filler, Traffic Wardens).

0.79, 6.90, BH-adjusted $p = 0.121$), and anxiety (OR 0.76, 95%CI: 0.56, 1.04, BH-adjusted $p = 0.119$), were not significantly associated. When assessing the impact of individual comorbidities on MS progression in the full cohort with age, gender and time since diagnosis as covariates (not stratified by cluster), the presence of depression (OR 1.94, 95%CI: 1.51, 2.49, BH-adjusted $p < 0.001$) was significantly associated with higher odds of MS progression compared to without depression. Presence of diabetes (OR 1.40, 95%CI 0.95, 2.06, BH-adjusted $p = 0.304$), PVD (OR 0.90, 95%CI: 0.27, 2.95, BH-adjusted $p = 0.853$), high cholesterol (OR 1.13, 95%CI: 0.83, 1.53, BH-adjusted $p = 0.743$), high blood pressure (OR 1.07, 95%CI: 0.84, 1.35, BH-adjusted $p = 0.743$), heart trouble (OR 0.79, 95%CI: 0.49, 1.27, BH-adjusted $p = 0.743$), and anxiety (OR 1.09, 95%CI: 0.77, 1.54, BH-adjusted p = 0.743), were not significantly associated (Fig. 2). When stratified by age category, depression remained a significant predictor of MS progression in both those aged <60 and ≥ 60. High blood pressure was significantly associated with MS progression only in those aged <60 (OR 1.75, 95%CI: 1.14, 2.62), whilst high cholesterol was significantly associated only in those aged ≥60 (OR 1.54, 95%CI: 1.12, 2.11) (supplementary material 3).

We conducted Cox proportional hazards regression to analyse time from baseline assessment to SPMS. In the adjusted models, cluster group or presence of independent comorbidities were not associated with earlier progression to SPMS. Kaplan-Meier curves demonstrated no significant differences in time to SPMS across the three clusters (log-rank $p = 0.12$, supplemental material 4.1). Full results are reported in supplementary material 4.

3.3.3. Family 3: cluster group, MS progression and patient-reported outcomes

In participants with RRMS at baseline, baseline questionnaire score was a significant predictor of latest questionnaire score for all PROs ($P < 0.001$). Time between baseline and latest questionnaire completion was a significant predictor for web-EDSS, MSWS, MSIS-psychological, HADS-Anxiety, and HADS-Depression. After BH correction within each predictor across all seven PRO models (family 3), MS progression was a significant predictor for all PROs (full results in supplementary file 5). Clusters 2 and 3 were associated with significantly higher scores for all PROs after adjusting for baseline scores, age, gender, time since diagnosis, time between baseline and latest questionnaire completion, and MS type progression, compared to reference cluster 1. When stratified by age category, cluster was significantly associated with worse scores for FSS, HADS-Anxiety, HADS-Depression, MSIS-Psychological and MSWS in both those aged <60 and ≥ 60 years. Web-EDSS and MSIS-Physical were significantly associated with cluster in those aged <60 only (supplementary material 3). Linear regression in the entire cohort ($n = 5944$) similarly found that MS progression associated with significantly higher PRO scores in all questionnaires, however there was no association with FSS scores (supplementary file 6).

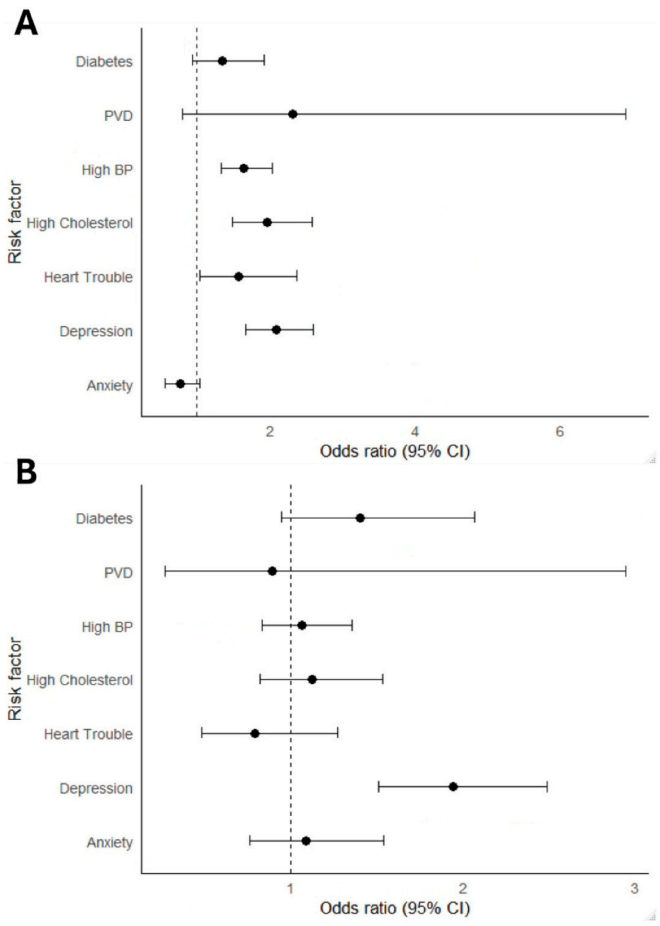

Fig. 2. Odds ratios and 95% confidence intervals for the association between individual comorbidities and MS progression (relapsing-remitting to secondary-progressive MS). A; unadjusted multivariable logistic regression model, B; adjusted logistic regression model including age, gender, and time since diagnosis as covariates. Reference category is absence of each individual comorbidity. Demographic covariates are not displayed for clarity.

3.4. Secondary outcomes

3.4.1. Family 4: individual comorbidities and patient-reported outcomes

Multiple linear regression analyses in all participants ($n = 5944$) revealed that, before and after adjusting for time between baseline, age, gender, time since diagnosis, and questionnaire completions, comorbidities were negatively associated with latest questionnaire scores for some, but not all, PROs (Table 2). For physical disability and functioning outcomes, diabetes and depression showed the most consistent independent associations. Diabetes and high blood pressure were independently associated with worse web-EDSS scores (adjusted B 0.83, 0.26,

Table 2
Associations between individual comorbidities and latest questionnaire scores, derived from multiple linear regression models.

Patient Reported Outcome	Unadjusted B	Unadjusted SE	Unadjusted BH-corrected P-value	Adjusted B	Adjusted SE	Adjusted BH-corrected P-value
Web-EDSS						
High cholesterol	0.39	0.12	<0.001	−0.07	0.11	0.528
High blood pressure	0.69	0.09	<0.001	0.26	0.08	0.003
Heart trouble	0.59	0.17	<0.001	0.10	0.15	0.529
PVD	1.09	0.39	0.006	0.44	0.36	0.315
Diabetes	0.89	0.14	<0.001	0.83	0.13	<0.001
Anxiety	0.02	0.13	0.845	0.27	0.12	0.038
Depression	0.77	0.09	<0.001	0.62	0.09	<0.001
FSS						
High cholesterol	0.18	0.78	0.817	−0.15	0.78	0.852
High blood pressure	2.19	0.58	<0.001	1.87	0.59	0.004
Heart trouble	2.23	1.12	0.065	1.72	1.12	0.172
PVD	2.81	2.65	0.337	1.71	2.65	0.605
Diabetes	2.09	0.98	0.056	2.13	0.97	0.050
Anxiety	3.26	0.85	<0.001	3.51	0.85	<0.001
Depression	6.57	0.64	<0.001	6.24	0.64	<0.001
HADS-A						
High cholesterol	−0.35	0.26	0.301	0.13	0.25	0.673
High blood pressure	−0.10	0.19	0.639	0.34	0.19	0.137
Heart trouble	0.65	0.37	0.181	1.11	0.37	0.006
PVD	0.41	0.87	0.639	0.80	0.86	0.492
Diabetes	−0.26	0.32	0.587	−0.13	0.32	0.673
Anxiety	2.74	0.28	<0.001	2.51	0.28	<0.001
Depression	2.34	0.21	<0.001	2.39	0.21	<0.001
HADS-D						
High cholesterol	0.14	0.25	0.574	−0.01	0.25	0.965
High blood pressure	0.66	0.18	<0.001	0.56	0.19	0.004
Heart trouble	1.36	0.35	<0.001	1.20	0.36	0.001
PVD	1.18	0.84	0.187	0.96	0.84	0.298
Diabetes	1.05	0.31	<0.001	1.06	0.31	0.001
Anxiety	1.20	0.27	<0.001	1.29	0.27	<0.001
Depression	2.82	0.20	<0.001	2.78	0.20	<0.001
MSIS-Physical						
High cholesterol	2.47	1.12	0.033	−1.05	1.07	0.382
High blood pressure	5.60	0.84	<0.001	2.23	0.81	0.011
Heart trouble	6.78	1.61	<0.001	2.87	1.54	0.087
PVD	8.40	3.82	0.033	3.12	3.63	0.391
Diabetes	7.69	1.41	<0.001	7.09	1.33	<0.001
Anxiety	1.87	1.22	0.126	3.66	1.17	0.004
Depression	10.20	0.92	<0.001	8.52	0.88	<0.001
MSIS-Psychological						
High cholesterol	−0.27	1.00	0.788	0.11	1.01	0.915
High blood pressure	1.13	0.75	0.233	1.54	0.76	0.077
Heart trouble	5.24	1.44	<0.001	5.46	1.45	<0.001
PVD	3.76	3.42	0.380	3.32	3.42	0.387
Diabetes	1.15	1.26	0.420	1.43	1.26	0.359
Anxiety	7.26	1.10	<0.001	7.23	1.10	<0.001
Depression	12.13	0.82	<0.001	12.07	0.83	<0.001
MSWS						
High cholesterol	2.46	0.82	0.004	−0.75	0.76	0.476
High blood pressure	4.57	0.62	<0.001	1.64	0.57	0.007
Heart trouble	3.84	1.18	0.002	0.15	1.09	0.889
PVD	6.44	2.80	0.025	1.26	2.57	0.728
Diabetes	5.36	1.03	<0.001	4.81	0.94	<0.001
Anxiety	0.26	0.90	0.771	2.50	0.82	0.006
Depression	5.51	0.67	<0.001	5.18	0.62	<0.001

Web-EDSS; Web version of the expanded disability status scale, FSS; Fatigue Severity Scale, HADS-A; Hospital Anxiety and depression scale (Anxiety score), HADS-D; Hospital Anxiety and depression scale (Depression score), MSIS-Physical; MS impact scale (Physical component), MSIS-Psychological; MS impact scale (Psychological component), MSWS; Multiple Sclerosis Walking Scale. Each model included all comorbidities simultaneously as predictors (high blood pressure, high cholesterol, diabetes, peripheral vascular disease, heart trouble, anxiety, and depression) before (unadjusted) and after (adjusted) adding age, gender, and time since diagnosis as covariates. B represents the unstandardised regression coefficient, indicating the mean difference in latest questionnaire score associated with the presence of each comorbidity compared to its absence. SE represents the standard error of the coefficient.

respectively), higher MSIS-physical scores (adjusted B 7.09, 2.23, respectively), and worse walking ability (adjusted B 4.81, 1.64, respectively). Associations between high cholesterol, heart trouble, and PVD and physical outcomes were largely attenuated after adjustment for age, gender, time since diagnosis, and questionnaire completions. FSS was independently associated with anxiety (adjusted B 3.51), depression (adjusted B 6.24), and high blood pressure (adjusted B 1.87), with depression demonstrating the largest effect. Mental health comorbidities demonstrated robust independent associations across multiple PROs, while diabetes and high blood pressure were the physical comorbidities most consistently associated with worse physical disability and functioning.

4. Discussion

By using a hierarchical clustering approach to identify distinct clusters of pwMS, this study sought to investigate how comorbidity profiles impact MS progression and PROs. In addition, it sought to identify key comorbidities that may inform targeted secondary prevention for pwMS.

Three primary clusters emerged: cluster 1 was characterised by the absence of cardiovascular and mental health comorbidities, providing a meaningful reference group for understanding the impact of different multimorbidity patterns; cluster 2 comprised of pwMS with universal cardiovascular comorbidity (100%) and a low prevalence of mental health comorbidity (5%); and cluster 3 was defined by a high prevalence of mental health comorbidity (98%) and moderate cardiovascular multimorbidity (24%). Amongst participants with RRMS at baseline (n = 4942), participants in cluster 2 ('cardiovascular comorbidity' cluster) showed no difference in odds of MS progression compared to cluster 1 ('healthy' cluster), whilst participants in cluster 3 ('mental health comorbidity' cluster) showed 90% higher odds compared to cluster 1 after adjusting for age, gender, and time since diagnosis. Interestingly, cluster 3 also showed a significantly higher odds (64%) of MS progression in comparison to cluster 2. These findings emphasise a need for mental health screening and management, which should be a priority for pwMS.

After additional adjustment for baseline webEDSS, associations between clusters and MS progression were attenuated and no longer statistically significant. This suggests that baseline disability may account for a substantial proportion of the differences in progression risk observed between clusters. As such, the identified phenotypes may reflect underlying disease severity, of which EDSS is one clinical manifestation. However, because disability may also lie on the causal pathway between phenotype and progression, adjustment for webEDSS could represent partial overadjustment, and these findings should be interpreted with caution. Kaplan-Meier curves revealed no significant differences in the time from baseline assessment to MS progression across clusters. However, as the UKMSR was established in 2011, maximum follow-up from baseline assessment was ~15 years, potentially resulting in insufficient follow-up time to detect any meaningful differences between clusters, underscoring the need for longer-term longitudinal data.

When assessing the impact of individual comorbidities, depression (109%), high cholesterol (97%), and high blood pressure (65%) were associated with higher odds of MS progression in the full cohort. After adjustment for age, gender and time since diagnosis, depression (94%) was the only remaining comorbidity associated with increased odds of MS progression. Poor mental health has been identified as a potential risk factor for MS progression, rather than merely a consequence of advancing disease [33]. Previous research has also highlighted differences in QoL across MS types, with individuals experiencing progressive forms of MS expressing greater concern about the unpredictable nature of their symptoms and describing relapses as significantly disruptive to daily life [34]. Multiple studies have also documented relapses as traumatic experiences [35,36]. While cardiovascular comorbidities, such as peripheral vascular disease [37], hypertension [20,37,38], hypercholesterolemia [20,37], diabetes [20,37,38], and heart disease [20,37] have consistently been reported to be associated with an increased risk of disability progression in MS, these associations may be confounded by age and disease duration, which are themselves strongly associated with both cardiovascular risk and MS progression. Previous research has found the largest increases in comorbidities over an average of 20.5 years after MS onset were in hypertension (+21.9%) and high cholesterol (+16.3%) [39]. Individual analyses identified depression as the primary high-risk comorbidity for MS progression after adjustment for demographic factors. Moreover, the cluster analyses revealed that pwMS with cardiovascular-dominant comorbidity profiles (cluster 2) showed no significant difference in progression risk compared to the healthy cluster, whilst those with mental-health dominant profiles (cluster 3) showed significantly higher odds of progression compared to both cluster 1 and cluster 2. It is important to acknowledge that cluster 3 represents a multimorbidity cluster dominated by mental health but also includes substantial additional cardiovascular comorbidity burden. Together, these findings suggest that mental health comorbidity represents a robust independent contributor to MS progression.

Approximately 50% of individuals with RRMS are expected to transition to SPMS after 15 years, and 75% after 25 years [40]. As highlighted in previous research, the transition from RRMS to SPMS is often accompanied by poorer QoL and greater fatigue [13,41–43], with these disparities detectable even prior to the diagnosed transition [13]. Consistent with previous research, our study observed significantly poorer PRO scores, including web-EDSS, FSS, MSWS, MSIS-physical component, MSIS-psychological component, HADS-anxiety, and HADS-depression scores, in participants who transitioned from RRMS to SPMS. Disease type closely correlates with EDSS scores [41,44–48] and previous research identified higher EDSS scores as a significant predictor of MS type progression [12]. A UKMSR study (n = 15,976) demonstrated worsened MSWS and MSIS scores before and following MS progression, even during the RRMS stage [49]. Previous studies have identified factors such as older age, female sex, shorter time since last relapse, disease duration, and current MS treatments as contributors to worse physical health outcomes [17,42,46]. Unlike previous findings, the current study found a significant association between MS progression and HADS-anxiety scores after adjusting for age, gender and time since diagnosis. This contrasts with a meta-analysis of 32 studies reporting that higher anxiety levels in pwMS were associated with younger age, female sex, not using MS medication, and a diagnosis of RRMS [50], which would suggest anxiety is more prevalent in earlier stages of MS. The significant association observed in the present study may reflect the broader psychological burden of disease progression captured when demographic factors are accounted for. Notably, only 21% of participants in the current study with RRMS at baseline reported progression to SPMS, despite estimates suggesting that approximately 50% of people with RRMS eventually progress [40]. This discrepancy may reflect sampling bias.

When examining the impact of cluster on PROs in the present cohort, we found that cluster 2 (cardiovascular comorbidity) and cluster 3 (mental health comorbidity) were associated with significantly greater physical and psychological symptoms compared to cluster 1 (healthy). Notably, 24% of participants in cluster 3 also presented with at least one cardiovascular comorbidity/risk factor (*i.e.*, had mental and cardiovascular multimorbidity), therefore the observed physical impairment may be, at least in part, attributable to overlapping health conditions. Amongst 185 pwMS, the presence of at least one vascular comorbidity has been linked to poorer physical health-related QoL, independent of level of physical disability [51]. Furthermore, evidence suggests a cumulative effect, whereby an increasing number of comorbidities is associated with progressively lower health-related QoL [18,52]. This aligns with prior research indicating that comorbidities consistently correlate with poorer QoL and higher disability [18,38,52]. And the findings in this study emphasise a particular importance of

cardiovascular and mental health multimorbidity.

Notably, the findings in the present study revealed that the associations between cardiovascular and mental health comorbidities and PROs varied by comorbidity type. For example, diabetes was associated with worse web-EDSS, FSS, HADS-depression, MSIS-physical, and MSWS scores, and heart trouble was associated with worse MSIS-psychological, HADS-anxiety, and HADS-depression scores. Meanwhile, high blood pressure was associated with worse web-EDSS, FSS, HADS-depression, MSIS-physical, and MSWS scores. High cholesterol and PVD were not significantly associated with PROs. Further, anxiety and depression were associated with worse web-EDSS, FSS, MSIS-physical, and MSWS scores. These findings suggest that anxiety and depression could exacerbate physical disability in pwMS, potentially through reduced motivation, fatigue, and lower engagement in physical activity [53]. It is equally plausible that individuals with reduced walking ability accumulate more comorbid diagnoses and increased physical disability. Previous research has found that mental health disorders were strongly associated with overall health-related QoL in pwMS [52]. This highlights the interconnected nature of psychological and physical health in MS and underscores the need for integrated management strategies that address both mental health and physical function to improve QoL. These results support the value of exploring multimorbidity management as possible contributors to patient outcomes in MS.

4.1. Limitations

Several limitations of this study require acknowledgement. First, the sample is based on voluntary participation in the registry, which may introduce selection bias and limit the generalisability of the findings. Although prior validation by Middleton and colleagues (2018) supports the UKMSR's representativeness to a clinical population, self-reported data, such as PROs, comorbidities and smoking history may still be under- or over-reported which may impact the reliability of these findings [23]. The absence of a control group prevents direct comparison of comorbidity prevalence and PROs with those of the general population. Missing data introduces selection bias and, while the study captures a range of physical and psychological PROs, it does not measure pain, an aspect known to be inadequately captured by the EDSS but important for a comprehensive understanding of MS impact [54]. Finally, comorbidity phenotypes were defined using baseline covariates, and MS progression was assessed prospectively during follow-up, establishing clear temporal ordering between exposure and outcome. Therefore, within the analytic framework of this study, reverse causation is unlikely. However, as comorbidities were assessed at a single time point and may have been present prior to baseline, we cannot fully exclude residual confounding or pre-existing disease dynamics that preceded study entry. While our longitudinal design strengthens inference regarding temporal relationships, causal conclusions remain limited in the absence of time-varying comorbidity assessment and interventional study designs. In addition, the limited follow-up duration of the registry (~15 years) may be insufficient to detect meaningful differences in progression between clusters, highlighting the need for longer-term longitudinal data for survival analyses.

5. Conclusion

Mental health conditions clustered with cardiovascular multimorbidity consistently associated with poorer MS progression and prognosis. Mental health comorbidities associated with a greater overall burden of physical and psychological symptoms across all patient-reported outcomes. Depression showed particularly pronounced associations, linked not only with psychological distress but also with increased physical symptom severity, highlighting its wide-ranging impact on disease burden in pwMS. These findings emphasise of the need for structured mental health screening and management as part of routine MS care, and the importance of holistic, multimorbidity-focused strategies that address both mental health and cardiovascular health to improve overall quality of life and potentially influence disease trajectory in pwMS.

Data sharing and data accessibility

Datasets analysed in the current study were accessed under a specific license and funded by the MS Society (174) and therefore are not publicly available. Due to data protection regulations, open distribution of the data is restricted.

CRediT authorship contribution statement

Madeleine France-Ratcliffe: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Stephanie L. Harrison:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization. **Leona A. Verma:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Azmil H. Abdul-Rahim:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Linsay McCallum:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Garry McDowell:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Carolyn A. Young:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Benjamin J.R. Buckley:** Writing – review & editing, Validation, Supervision, Methodology, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2026.126007.

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