

# BMJ Open Biopsychosocial model of resilience in young adults with multiple sclerosis (BPS-ARMS): an observational study protocol exploring psychological reactions early after diagnosis

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## ABSTRACT

**Introduction** Multiple sclerosis (MS), the most common neurological disease causing disability in young adults, is widely recognised as a major stress factor. Studies have shown that the first years after the diagnosis are distressing in terms of adjustment to the disease and that MS negatively affects patients' psychological well-being, quality of life (QoL) and social functioning. However, the links between disease-specific variables at diagnosis, resilience and psychological adjustment of patients with MS remain largely unexplored, especially in adolescents and young adults. This observational study aims to fill the gap of knowledge on biopsychosocial characteristics and resilience of young adults with MS to evaluate the relationship among these variables and to develop a biopsychosocial model of resilience.

**Methods and analysis** Biological and clinical characteristics of young adults newly diagnosed with MS will be investigated by collecting clinical information, performing neurological examinations, MRI and analysing cerebrospinal fluid and blood biomarkers (eg, measures of inflammation), body composition, gut microbiota and movement/perceptual markers. Psychosocial characteristics (eg, psychological distress, coping strategies), QoL, psychological well-being and resilience will be assessed by self-report questionnaires. Comparative statistics (ie, analysis of variance or unpaired samples t-test, correlation and regression analyses) will be applied to evaluate the relationship among biological, psychological and social factors. The results are expected to allow a comprehensive understanding of the determinants of resilience in young patients with MS and to inform resilience interventions, tailored to young patients' specific needs, aiming to reduce the risk of maladaptive reactions to the disease and to improve psychological well-being and QoL.

**Ethics and dissemination** The study has been approved by the Verona University Hospital Ethics Committee (approval number: 2029CESC). The findings will be

## Strengths and limitations of this study

- This study provides a novel research approach to patients with multiple sclerosis (MS), exploring the relationship between disease-specific variables, resilience and psychological adjustment after diagnosis.
- Study results are expected to expand the understanding of resilience determinants in young adults with MS and to inform resilience interventions with the potential of improving patients' quality of life, well-being and adherence to MS care strategies.
- The present study has the advantage of recruiting patients with MS at a young age, early after diagnosis and before disease-modifying therapy initiation, therefore limiting the impact of long-standing disease and treatment on psychosocial characteristics.
- The methodological approach is multidisciplinary and it favours an integrated vision of MS presentation from different perspectives.
- Study limitations include the cross-sectional design preventing prospective evaluation of the variables of interest and the scarcity of preliminary data to support the expected connections between biological and psychological characteristics of patients with MS.

disseminated through scientific publications in peer-reviewed journals, conference presentations, social media and specific websites.

**Trial registration number** ClinicalTrials.gov (NCT03825055).

## INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system pathologically characterised by the presence

of scattered areas of demyelination and axonal loss in the brain and spinal cord.<sup>1</sup> Depending on the location and the accrual rate of such lesions, patients with MS experience episodes of diverse neurological symptoms, which are typically reversible in the early phase of the disease but tend to be replaced by a relentless progression of disability in more advanced stages.<sup>2</sup> Being diagnosed with MS represents a major life event influencing individual functioning and emotional well-being. For many patients, the first years after the diagnosis are particularly distressing in terms of adjustment to the disease, may negatively affect quality of life (QoL) and social functioning and may lead to psychological symptoms, such as distress, anxiety and depression.<sup>3–6</sup> However, the findings regarding psychopathology among adolescents and young adults with MS are ambiguous with two studies reporting similar levels of depression and anxiety between young patients and their healthy peers.<sup>7,8</sup>

Since MS is usually diagnosed in young adults (20–40 years old) and increasingly in adolescents,<sup>9,10</sup> it is important to consider that the personal development, which is crucial for young adults, may be affected and overshadowed by the diagnosis. Various areas of life, such as education, work, relationships and social participation, need to be adjusted to gain a new sense of coherence that necessarily has to include MS.<sup>7,11–13</sup> Studies examining patients' adjustments to MS demonstrated a wide range of possible reactions to the diagnosis and different levels of resilience. Indeed, evidence indicates that higher levels of resilience are related to lower psychopathology in adults newly diagnosed with MS.<sup>14</sup> Considering the association between social support and mental health outcomes, a recent longitudinal study<sup>15</sup> highlighted the mediating role of resilience in this relationship in patients with MS. However, the amount of received social support may depend on the functional limitations associated with MS, which may reduce participation in social life.<sup>16,17</sup> As Southwick *et al.*<sup>18</sup> stated, 'determinants of resilience include a host of biological, psychological, social, and cultural factors that interact with one another to determine how one responds to stressful experiences'.

Personality traits have been studied as individual factors that can account for differences in health, well-being and overall QoL in MS. While some authors did not find different personality traits between patients with MS and healthy subjects, others described 'Type D personality', defined by high neuroticism, low extraversion, sometimes low conscientiousness, and, to a lesser extent, low agreeableness, in this category of patients.<sup>19–22</sup> In a sample of 119 adults with MS, trait mindfulness was linked to adaptive coping styles and increased resilience coping skills and higher resilience.<sup>23</sup>

Furthermore, literature has highlighted the important role of coping strategies in the life of patients with MS. A systematic review by Keramat Kar *et al.*<sup>24</sup> demonstrated that patients with MS, especially in the beginning, apply mainly emotional and avoidance coping strategies and tend to use, compared with healthy subjects, fewer active

coping strategies. Even if coping strategies of patients with MS have been widely investigated, also in relation to psychological constructs, such as personality traits, cognitive impairment and QoL,<sup>25</sup> the impact of disease-related variables on the coping strategies of patients with MS and, in particular, on resilience mechanisms, remains largely underexamined. Only one systematic review<sup>26</sup> showed a consistent association between coping strategies of patients diagnosed with life-threatening diseases, such as cancer, HIV/AIDS or MS and post-traumatic growth, which might be considered a dimension of resilience.<sup>27</sup>

Illness perception, defined as the pattern of cognitive representations created by patients facing a new health threat,<sup>28</sup> is considered another factor potentially influencing the adjustment to MS.<sup>29,30</sup> These beliefs can influence coping behaviour, since negative illness perceptions are related to worse adjustment outcomes, slower recovery and increased future disability.<sup>28</sup> For this reason, illness perception may influence the ability to be resilient facing the new MS diagnosis.

There is solid evidence that stressful life events are a triggering factor for MS relapses.<sup>31,32</sup> While some earlier studies have also suggested an association between distress and the onset of MS,<sup>33,34</sup> a recent article could not confirm this finding.<sup>21</sup>

Further, Benedict and colleagues<sup>19</sup> conducted a study on 120 subjects with MS of any duration to assess the association between clinical and psychological factors and QoL. The findings indicated that self-reported health-related QoL was most strongly predicted by measures of depression, whereas employment status was primarily predicted by measures of cognitive function.

Also, sociodemographic factors, such as gender, age, education and occupational status, need to be considered when studying differences in adapting to MS and resilience, as done in a recent review of coping with MS.<sup>24</sup>

None of the validated diagnostic and prognostic tools that are used in MS clinical practice (eg, type of clinical onset, brain and spinal cord MRI characteristics, IgG oligoclonal bands in the cerebrospinal fluid (CSF) and evoked potentials) have been specifically explored as possible modifiers of patients' psychological characteristics or vice versa. However, it could be hypothesised that clinical and paraclinical features of MS directly or indirectly influence patient's resilience strategies, by interfering with psychological adjustment or other mechanisms still to be investigated in the MS population.<sup>35</sup> In addition, investigational biomarkers—including neurofilament light chain and cytokines in CSF/serum,<sup>36,37</sup> microRNA expression in cells and tissues,<sup>38,39</sup> oxidative stress markers in body fluids,<sup>40,41</sup> gut microbiota composition,<sup>42,43</sup> body composition<sup>44,45</sup> and neurophysiological markers of motor–perception interactions<sup>46,47</sup>—are linked to diverse pathophysiological processes of MS, which could have direct or indirect connections to psychological factors, coping strategies, well-being and ultimately QoL.

A comprehensive understanding of the concept of resilience in the MS field and of related factors, which may

enhance or reduce resilience, are essential for improving patients' well-being. The role of disability-specific, biological, psychological and social factors should be explored adopting the well-established biopsychosocial model of Engel.<sup>48</sup> Recently, Black and Dorstyn<sup>16</sup> tested a biopsychosocial model of resilience in 196 adults with MS. While positive affect and self-efficacy showed a direct effect on resilience, fatigue severity, physical dependence and social support had an indirect effect. However, the authors acknowledged that more than half of the variance could not be explained by the identified variables and therefore suggested to explore in future studies other key elements of resilience from a biopsychosocial perspective.

There is only scant research about resilience in patients with MS and its influencing factors, particularly in adolescents and young adults. Up to now, to our knowledge, only one Italian study<sup>7</sup> assessed resilience in adolescents and young adults newly diagnosed with MS. Moreover, rarely<sup>16</sup> have been biological, psychological and social factors potentially associated with resilience explored in a holistic biopsychosocial model.

Thus, investigating resilience in this population is innovative and extremely relevant for the following reasons: (1) youth is a critical period for the individual's future development and well-being; (2) MS is the most common neurological disease causing disability in young people<sup>49</sup> and increasingly recognised in adolescents; (3) early interventions, focusing on young patients' resilience, are crucially needed to prevent a worsening of potential psychological problems later on in life and to improve psychological well-being and QoL.

## OBJECTIVES

Drawing on the above outlined literature, the aims of the biopsychosocial characteristics and resilience of young adults with MS (BPS-ARMS) are threefold:

Research objective 1: To assess the biological, psychological and social characteristics of a sample of young adults newly diagnosed with MS.

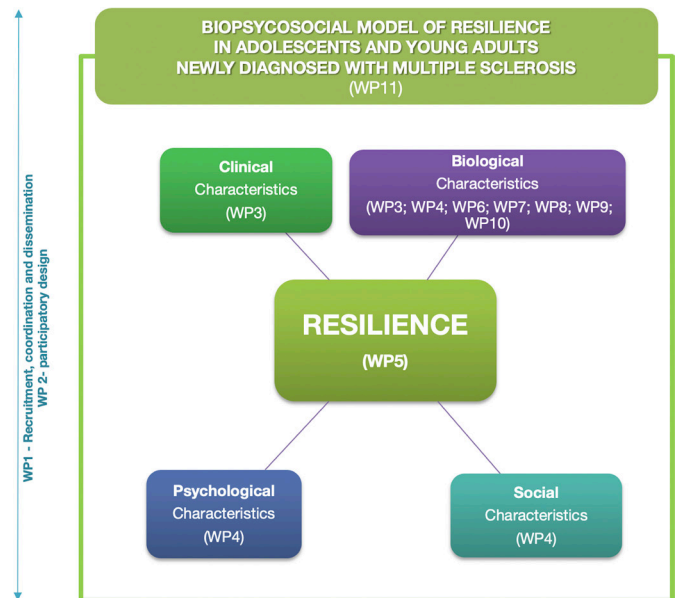
Research objective 2: To explore the resilience strategies and QoL in a sample of young adults newly diagnosed with MS.

Research objective 3: To investigate the association between biopsychosocial characteristics and resilience to develop a biopsychosocial model of resilience in young adults newly diagnosed with MS.

## METHODS

### Study design

The BPS-ARMS project has an observational design. It will last for 3 years, following two main consequential phases (start date: 26 February 2019, planned end date: 26 August 2021). In the first phase, biopsychosocial factors will be collected and resilience strategies and QoL assessed. In the second one, the relationship between biopsychosocial factors and resilience will be explored and consequently a



**Figure 1** Overview of the BPS-ARMS work packages. BPS-ARMS, biopsychosocial characteristics and resilience of young adults with MS.

biopsychosocial model of resilience in young adults newly diagnosed with MS will be developed. Eleven specific work packages (WP) will be accomplished during these two phases (figure 1).

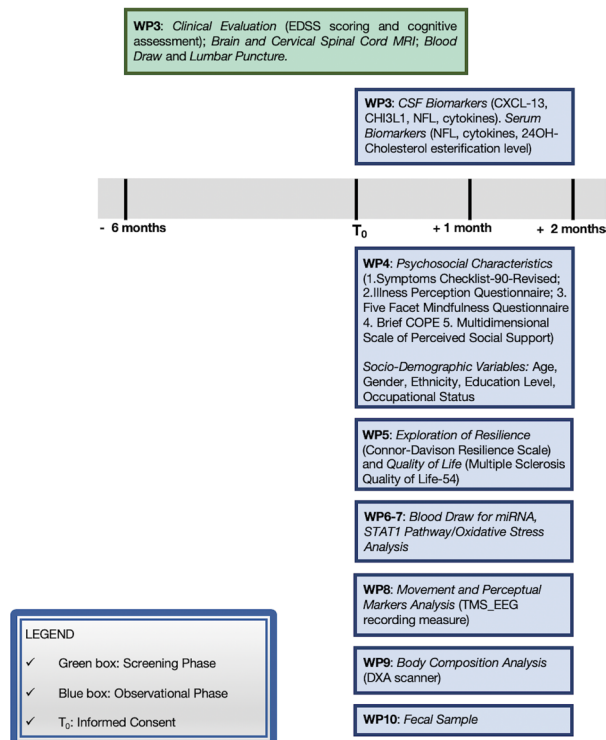
For each WP, different actions will be performed according to the flowchart (figure 2). WP1 actions include recruitment, coordination and dissemination of the results. WP2 aims to achieve an effective, constant collaboration between researchers, patients and healthcare providers (participatory design). WP3 is dedicated to the screening phase for the eligibility of patients and collection of clinical and MRI characteristics of young patients and analysis of protein biomarkers and 24OH-Cholesterol. WP4 aims to collect the psychosocial characteristics of young patients. WP6, 7, 8, 9 and 10 aim to collect all the biological variables not included in WP3.

Research actions of WP3 and WP6–10 are summarised in table 1. WP4 procedures are reported in table 2. Exploration of resilience and QoL will be performed in WP5 and, considering the results of the previous WPs, WP11 procedures will allow developing the biopsychosocial model of resilience.

### Sample and setting

The BPS-ARMS project will be implemented in the Multiple Sclerosis Regional Center of the Azienda Ospedaliera Universitaria Integrata of Verona—Borgo Roma Hospital (Veneto Region, Italy—Hub for Verona Province).

Patients will be enrolled according to the following inclusion criteria: age range 18–40 years; MS diagnosis in the 2 years prior to study inclusion, according to the revised McDonald Criteria<sup>50</sup>; MRI of the brain in the 6 months prior to or within 1 month after screening visit, according to the protocol described below; Italian speakers.



**Figure 2** Flowchart of data collection according to each WP. COPE, Coping Orientation to the Problems Experienced; CSF, cerebrospinal fluid; DXA, dual-energy X-ray absorptiometry; EDSS, Expanded Disability Status Scale; EEG, electroencephalography; miRNA, microRNA; NFL, neurofilament light chain; TMS, transcranial magnetic stimulation; WP, work package.

We will exclude patients with: clinically relevant cognitive deficits as evaluated by the treating neurologist; treatment with any disease-modifying therapy for MS at inclusion and by completion of study procedures

(maximum 2 months from consent); steroids administration up to 30 days prior to inclusion is allowed.

The effective sample size, required to allow the regression models to be reliably estimated, is 150–180 patients. On the basis of the setting catchment area (ie, 1800 patients with MS annually for Verona province), we estimate that the required numerosity of eligible patients will be reached in a time period of 30 months.

## Recruitment procedures

Eligible patients will be consecutively enrolled by the neurologists and residents working at the MS Center of Borgo Roma Hospital, Verona. During the first visit at the MS Center, the neurologists/residents will explain the study to eligible patients, and the consent form will be signed. During this visit, sociodemographic and clinical information will be collected, according to routine clinical practice. Within 1 month from consent, patients will start a screening phase, which is part of the typical diagnostic work-up of patients with suspected MS (WP3). After screening completion, fulfilment of inclusion criteria and absence of exclusion criteria, patients will be enrolled or excluded from the study accordingly. Within 1 month from screening completion, patients included in the study will undergo a blood draw from a peripheral vein at the MS Center, and a faecal sample will be collected (WP 3, 6, 7 and 10). During the same visit, a psychological battery of tests will be performed (questionnaires for both WP4 and WP5). Within 1 month from screening completion, patients can decide to be involved in additional study procedures, regarding the analysis of movement and perceptual markers as well as body composition as measured by dual-energy X-ray absorptiometry (WP8 and WP9) at the dedicated laboratories of the University of Verona. All the aforementioned procedures will

**Table 1** Summary of the clinical and biological variables collected in WPs 3,6,7,8,9,10

Work package	Description
WP3	Recruitment and screening phase; collection of clinical, MRI and CSF data of patients; analysis of NFL in serum/CSF by Simoa, Quanterix; analysis of inflammatory cytokine panel in serum/CSF by Bioplex, BioRad <sup>37</sup> ; analysis of 24OH-Cholesterol esterification level in serum <sup>61</sup>
WP6	Analysis of microRNA levels in exosomes from serum samples. Candidate miRNAs to be analysed (miR-15b-5p, miR-374a-5p, miR-342-3p, miR-30b-5p, miR-223-3p, miR-433-3p, miR-432-5p, miR-23a-3p, miR-485-3p and let-7i) have been selected from previous studies indicating them as potential biomarkers for MS. <sup>38,39</sup>
WP7	Oxidative stress markers analysis. The concentration of glutathione and glutathione disulphide (GSH/GSSG), of nitrite/nitrate (NO <sub>2</sub> <sup>-</sup> /NO <sub>3</sub> <sup>-</sup> ) as well as levels of lipid peroxidation and of oxidative post-translation modification of proteins will be evaluated in plasma. The activation of STAT1 signalling (phosphoTyr701-STAT1/STAT1 ratio and levels of S-glutathionylated STAT1) will be analysed in PBMC. <sup>40,62</sup>
WP8	Movement and perceptual markers analysis. <sup>46,47</sup> Upper extremities motor evoked potentials obtained by transcranial magnetic stimulation in two tasks (ie, rest and motor imagery)
WP9	Body composition analysis. <sup>44,45</sup> Bone mineral content, fat-free soft tissue mass, fat mass and percentage of fat mass will be measured by dual-energy X-ray absorptiometry
WP10	Gut microbiota composition. <sup>42,43</sup> A faecal sample will be collected at enrollment and analysed to assess microbiome composition using the percentage of bacterial subgroups at the genus level and protein concentration resulting from metaproteomics experiments.

CSF, cerebrospinal fluid; MS, multiple sclerosis; NFL, neurofilament light chain; PBMC, peripheral blood mononuclear cell; WP, work package.

**Table 2** Summary of the psychological variables and self-report questionnaires (WP4)

Measure	Questionnaire	Description of the questionnaires and variables
Symptoms of psychopathology	SCL-90-R <sup>63</sup>	SCL-90-R is a 90-item questionnaire, designed to evaluate, on a 5-point Likert scale. A broad range of psychological problems and symptoms of psychopathology. The primary assessed dimensions are somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism.
Mindfulness traits	The Italian short form of FFMQ-SF <sup>64 65</sup>	The FFMQ-SF with 24 items is used to assess major aspects of mindfulness skills: observing, describing, acting with awareness, non-judging and non-reactivity. Items are measured on a 5-point Likert scale.
Coping strategies	The Brief COPE <sup>66-68</sup>	The Brief COPE includes 28 items, organised in 14 subscales, each composed of 2 items. Each item is evaluated on a 4-point scale from 1 to 4.
Illness perception	The Brief IPQ <sup>29 69-71</sup>	The Brief IPQ-R is a 9-item instrument developed to provide a quantitative measurement of the components of illness representations, evaluated on a 5-point Likert scale.
Psychosocial functioning and stressful life events	PSI <sup>72 73</sup>	The PSI is a scale made of 55 items providing a comprehensive assessment of stress, well-being, distress and illness behaviour.
Social support	The Italian version of MSPSS <sup>74 75</sup>	The MSPSS, a 12-item measure of social support, measures on a 6-point Likert scale the level of perceived social support of various sources (eg, family, friends and significant others).

COPE, Coping Orientation to the Problems Experienced; FFMQ-SF, Five Facet Mindfulness Questionnaire Short Form; IPQ, Illness Perception Questionnaire; MSPSS, Multidimensional Scale of Perceived Social Support; PSI, Psychosocial Index; SCL-90-R, Symptoms Checklist 90 items Revised.

be completed within 2 months from informed consent to guarantee timely access to the more appropriated MS treatment for each patient as discussed between the treating neurologist and the patient according to clinical practice. Study procedures will not influence treatment decisions.

### Variables and procedures

The primary endpoint of the study is the resilience of patients with MS, assessed using the Connor-Davison Resilience Scale (CD-RISC).<sup>51</sup> This instrument is specifically designed to examine resilience features in adolescents and adults. The CD-RISC is composed of 25 items and evaluated on a 5-point Likert scale (ranging from 0 'not true at all' to 4 'true nearly all of the time'), with higher scores reflecting higher levels of resilience. This instrument has been selected because of its good psychometric properties.<sup>51</sup> Further, it showed the highest quality in a methodological review<sup>52</sup> evaluating 15 resilience questionnaires. The psychometric properties of the Italian version of the 25-item CD-RISC will be described by using item response theory analysis on our sample of patients with MS. To validate this scale in the Italian language, a confirmatory factor analysis (CFA) will be performed. Furthermore, this questionnaire has already been used with patients with MS<sup>15 16 23 53</sup> and translated into Italian.

The secondary endpoint is QoL, assessed using the Italian version of the Multiple Sclerosis Quality of Life-54 (MSQOL-54).<sup>54</sup> The MSQOL-54 is a multidimensional health-related QoL measure that combines both generic and MS-specific items, such as fatigue and cognitive function.<sup>54-56</sup> The

instrument generates 12 scores (ie, physical function, role limitations—physical, role limitations—emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall QoL and sexual function) along with two summary scores (ie, physical health and mental health) derived from a weighted combination of scale scores. There are also two single-item measures: satisfaction with sexual function and change in health. The Italian version of MSQOL-54 is easy to administer and well accepted by patients.

All variables collected in the WPs 3, 4 and 6–10 (eg, clinical, psychosocial, MRI and laboratory data) are used to describe the sample and considered as potential predictors of resilience through Exploratory Factor Analysis (EFA).

The following sociodemographic variables will be collected at the recruitment for each patient through a case report form: age, gender, ethnicity, education level and occupational status.

Table 1 recaps the clinical and biological variables for all WPs, with the exception of WP4, for which table 2 describes measures and the questionnaires used to collect the psychological measures. For the variables collected in WPs 3 and 6–10, preliminary measurements, obtained on biological samples of healthy subjects in the laboratories of the research team, will be used as the qualitative reference. This will allow setting up the methods for biomarkers analysis for each WP.

### **Patient and public involvement statement. Participatory design: research partnership with patients and associations**

Patients and the public were first involved in the conclusive phase of protocol preparation during a meeting with Verona representatives of the Italian Multiple Sclerosis Association (AISM) and during a public event organised by the University of Verona in September 2018. Psychological variables and outcome measures were developed based on the response to a preliminary survey that was conducted in a sample of patients with MS attending the Verona MS centre in 2017.

The Verona section of AISM will be involved in the recruitment process through disseminating information to patients and caregivers regarding the study. A patients advisory board (PAB) composed by young patients with MS and representatives of AISM will be established. The recruitment will be performed at the beginning of the project in the clinical centres and MS associations of patients and relatives. The PAB will collaborate and supervise all the research phases (including the discussion, interpretation and dissemination of results) through regular meetings and consultations.

The participatory design of the study (WP2) will increase the ecological validity of our results and improve trust and collaboration among the MS stakeholders as a potential starting point for future research and care planning.

### **Planned analysis**

An integrated database will be created and checked for completeness across all the collected biopsychosocial variables. It will be possible to merge the databases (ie, of WP3, WP4 and so on) using the unique study subject identifier. The statistical power analysis used to identify the sample size is based on the number of subjects per variable (SPV) approach.<sup>57 58</sup> The literature indicates 10 as the minimum value of SPV. In the present study, we have set SPV at 15, given that we analyse one relevant variable (ie, indicator) for each WP (ie, WP3–WP10) and five clinical and socio-demographic characteristics (sex, age, education level, Expanded Disability Status Scale score and the number of T2 lesions on brain MRI). These characteristics will be analysed a priori in the regression models due to the relevance for the resilience of patients with MS.

Since the relationship between resilience and biological variables has been scarcely investigated in the literature, the handling of missing data could be problematic, particularly in case of missing not at random.<sup>59</sup> For this reason, only the variables with an amount of missing data <10% will be included in the analysis so that the results can be considered robust and accurate.

To identify the indicator for each WP to be included in the final biopsychosocial model of resilience, an EFA will be performed using each WP variable measured as factors. The first factor (ie, the one explaining most of the variability) will be selected as the indicator for the specific WP. Applying generalised linear regression models, we will preliminarily explore (1) the relationship among the different WP indicators and (2) the relationship

between each WP indicator and resilience. The selected WP indicators will be jointly explored using multivariable models to quantify the main relationships. The results of the regression analyses will lead to the development of a biopsychosocial model of resilience. Given the paucity of evidence in this field, we will proceed gradually in the design of the model, applying different statistical techniques according to the critical issues that will potentially emerge from the preliminary descriptive analysis. If the main assumptions of Structural Equation Models (ie, the sample size of groups, the normality of frequency distribution of the variables of interest, the absence of outliers) will be satisfied, it will be possible to perform also CFAs. This method will allow the goodness of fit of our biopsychosocial model to be assessed.

The same procedure will be applied at the secondary endpoint of the study to build a biopsychosocial model of QoL. Statistical analyses will be carried out using Stata V.15.<sup>60</sup>

## **ETHICS AND DISSEMINATION**

### **Ethics and safety**

The project will be conducted according to the approved protocol. All data collected during the project will be handled fairly, and the databases will remain strictly confidential, anonymised, password protected and stored in locked and secured facilities at the Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona.

In detail, patients who sign the informed consent form and comply with all of the inclusion criteria will be assigned a unique study subject identifier (ie, a pseudonym or alias). Only the authorised study personnel will have access to the matching between the subject identifier and patient identity. The study subject identifier will remain the same during the whole study and will allow the proper handling of the patients' data and samples without using sensitive personal identifiers. Data will be collected in a dedicated case report form and entered into an electronic database for analysis.

The collected biological samples will be stored at the Neuropathology Laboratory of the University Hospital of Verona for 10 years and may be used for additional research conducted at the University of Verona and related to the present study. Following the completion of the study, leftover samples sent to the laboratories of the "Centro Interuniversitario di Ricerca sui Peptidi Bioattivi" (CIRPEB, Research Centre on Bioactive Peptides), Napoli (see WP3) will be destroyed after analysis.

### **Dissemination plan**

A dissemination plan will be established in the first phase of the project in agreement with all the involved researchers during a dedicated meeting. The dissemination target will be different stakeholders (eg, other researchers, patients, MS representatives and associations, healthcare professionals, the general public). Each dissemination product will be tailored to these different

target groups in terms of objectives, methods, timeline and language (eg, youth-friendly language and format). Facebook and specific websites will be used to disseminate the materials of the project. The use of these social media channels will allow a broader dissemination of the project results. The scientific community will be reached through scientific publications in national and international preferably open access journals and presentations at national and international scientific conferences. Items for dissemination in any format including publications will not contain any information that could lead to the identification of the patients.

**Contributors** All the authors were involved in planning and conceptualising the project providing their specific contribution according to the different disciplines. AG, MR, VD, FG, EB, MC, ACDP, PC, MD, PF, SF, MGL, R Magliozzi, GM, R Marriotti, SM, CM, MGR and AS were involved in the acquisition of data. AG, MR, MAM, VD, IMB, FG, EB, MC, ACDP, PC, MD, PF, SF, MGL, R Magliozzi, GM, R Marriotti, SM, CM, MGR, LDP, FS and AS were involved in the analysis and interpretation of the data. AG, VD, IMB and MR drafted the manuscript. MAM provided her expertise on the methodological elements. All authors reviewed and approved the final manuscript. In their role as team leaders, MR and AG supervised the entire project. In their role as project managers, LDP and FS coordinated the general organisation and institutional aspects of the project.

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**Competing interests** None declared.

**Patient and public involvement statement** Patients or the public were involved in our work.

**Patient consent for publication** Not required.

**Ethics approval** BPS-ARMS has been approved by the Ethical Committee of Verona and Rovigo Province (Azienda Ospedaliera Universitaria Integrata di Verona)—study registration number: Prog. 2029CESC.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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