SVEUČILIŠTE U SPLITU
MEDICINSKI FAKULTET

Ana Jerković

POVEZANOST TJELESNE ONESPOSOBLJENOSTI, KVALITETE SPAVANJA, DEPRESIVNOSTI, ANKSIOZNOSTI I UMORA KOD OSOBA S MULTIPLOM SKLEROZOM

Doktorski rad

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Doktorski rad

Mentorica:
dr. sc. Maja Rogić Vidaković, viša znanstvena suradnica

Split, 2026.

Ova disertacija izrađena je u sklopu sveučilišnog poslijediplomskog doktorskog studija Translacijska istraživanja u biomedicini Medicinskog fakulteta Sveučilišta u Splitu pod vodstvom dr. sc. Maje Rogić Vidaković, više znanstvene suradnice. Istraživanja su provedena pri Laboratoriju za humanu i eksperimentalnu neurofiziologiju, Zavoda za neuroznanost, Medicinskog fakulteta Sveučilišta u Splitu u okviru istraživačkog projekta Hrvatske zaklade za znanost (broj projekta HRZZ-2022-10-6203) te programskog financiranja znanosti Sveučilišta u Splitu.

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"Kad vam oduzmu sve ostat će vam dvije ruke; sklopite ih na molitvu, pa ćete tada biti najjači!"

bl. Alojzije Stepinac

POSVETA

Uspomeni na oca – u tihoj skromnosti njegove mudrosti i brige.

Branko Šuto Super (1957.–2020.)

SADRŽAJ

1. POPIS OZNAKA I KRATICA

AUC – površina ispod krivulje (engl. Area Under the Curve)

CIS – Klinički izolirani sindrom (engl. Clinically isolated syndrome)

CFA – konfirmatorna faktorska analiza (engl. Confirmatory Factor Analysis)

COVID-19 – korona virus (engl. Coronavirus disease 2019)

DASS-21 – Ljestvica depresije, anksioznosti i stresa – 21 čestica (engl. Depression, Anxiety and Stress Scale – 21 items)

EBV - Epstein-Barr virus

EFA – eksploratorna faktorska analiza (engl. Exploratory Factor Analysis)

EDSS – Proširena ljestvica stupnja onesposobljenosti (engl. Expanded Disability Status Scale)

FSS – Ljestvica težine umora (engl. Fatigue Severity Scale)

HADS – Bolnička ljestvica anksioznosti i depresije (engl. Hospital Anxiety and Depression Scale)

HLA - humani leukocitni antigen

HPA – Hipotalamo-hipofizo-adrenalna os

MS – multipla skleroza (engl. Multiple Sclerosis)

MSIS-29 – Ljestvica utjecaja multiple skleroze – 29 čestica (engl. Multiple Sclerosis Impact Scale – 29 items)

MSWS-12 – Ljestvica hodanja – 12 čestica (engl. Multiple Sclerosis Walking Scale – 12 items)

MRI – Magnetska rezonancija (engl. Magnetic Resonance Imaging)

PCA – analiza glavnih komponenti (engl. Principal Component Analysis)

PPMS – Primarno progresivna multipla skleroza (engl. primary progressive multiple sclerosis)

PSQI – Pittsburgov indeks kvalitete spavanja (engl. Pittsburgh Sleep Quality Index)

ROC – ROC krivulja (engl. Receiver Operating Characteristic)

RRMS – Relapsno remitentna multipla skleroza (engl. relapsing-remitting multiple sclerosis)

SPMS – Sekundarno progresivna multipla skleroza (engl. secondary progressive multiple sclerosis)

SŽS – središnji živčani sustav

T3 – Trijodtironin

T4 – Tiroksin

UMSH - Udruge multiple skleroze Hrvatske

1. PREGLED OBJEDINJENIH RADOVA

I. Jerković A, Safić IS, Pavelin S, Pleić N, Duka Glavor K, Vujović I, Šoda J, Duranović J, Rogić Vidaković M. Disability and Non-Motor Symptoms in Multiple Sclerosis: Exploring Associations and Predictive Factors. Brain Sci. 2025 Oct;15:1122. doi:10.3390/brainsci15101122

II. Jerković A, Nikolić Ivanišević M, Šimić N, Poljičanin A, Đogaš Z, Rogić Vidaković M. Psychometric properties of the Croatian version of the Multiple Sclerosis Walking Scale (MSWS-12). Disabil Rehabil. 2023 Oct;45(20):3373-3378. doi: 10.1080/09638288.2022.2132301.

III. Jerković A, Proroković A, Matijaca M, Katić AĆ, Košta V, Mihalj M, Dolić K, Đogaš Z, Vidaković MR. Validation of the fatigue severity scale in Croatian population of patients with multiple sclerosis disease: Factor structure, internal consistency, and correlates. Mult Scler Relat Disord. 2022 Feb;58:103397. doi: 10.1016/j.msard.2021.103397.

IV. Jerković A, Proroković A, Matijaca M, Vuko J, Poljičanin A, Mastelić A, Ćurković Katić A, Košta V, Kustura L, Dolić K, Đogaš Z, Rogić Vidaković M. Psychometric Properties of the HADS Measure of Anxiety and Depression Among Multiple Sclerosis Patients in Croatia. Front Psychol. 2021 Nov 30;12:794353. doi: 10.3389/fpsyg.2021.794353.

2. UVOD

2.1. Multipla skleroza: epidemiologija, etiologija i patofiziologija

Multipla skleroza (MS) je upalno-degenerativna bolest središnjeg živčanog sustava (SŽS), za sada još uvijek nepoznatog uzroka, koju karakteriziraju demijelinizirajuće lezije bijele tvari i degeneracija neurona. Posljedice neuroinflamatornih i neurodegenerativnih mehanizama jesu neurološki ispadi, pojava različitih simptoma (motoričke i senzoričke disfunkcije, kognitivna oštećenja, poremećaji raspoloženja, umor), kliničke manifestacije i napredovanje bolesti (1–7). Globalno, MS pogađa oko 1,89 milijuna ljudi, s prevalencijom od približno 23,9 slučajeva na 100 000 stanovnika (8,9). Najviše stope zabilježene su u Sjevernoj Americi i Zapadnoj Europi (npr. Švedska 219/100 000, Kanada 182), s regionalnim varijacijama (npr. u SAD-u, sjeverne savezne države imaju dvostruko veću incidenciju od južnih) i predviđanjima daljnjeg porasta broja oboljelih od MS-a (10,11).

Prema podacima Hrvatskog zavoda za javno zdravstvo, u Hrvatskoj s MS-om živi više od 8 500 osoba (stopa prevalencije 220,9/100 000 stanovnika), a broj oboljelih svake godine raste (12). Bolest se najčešće javlja kod mlađih odraslih osoba, između 20. i 40. godine života, te značajno utječe na kvalitetu života oboljelih i njihovih obitelji (12,13). Žene su češće pogođene (159,6/100 000 naspram 69,7/100 000 kod muškaraca) (14), a regionalne razlike u prevalenciji MS-a pokazuju više stope oboljelih u Hrvatskoj u unutrašnjosti (npr. Gorski kotar do 122/100 000) u odnosu na obalu, slično globalnom trendu (14).

Uzroci MS-a danas se opisuju kao rezultat složene interakcije naslijeđene osjetljivosti i okolišnih utjecaja, pri čemu nijedan pojedinačni čimbenik nije dovoljan sam za sebe, nego se bolest razvija kada se poklopi određena kombinacija genetskih varijanti, imunološke disfunkcije te virusnih i životnih faktora u osjetljivom razvojnom razdoblju (15–18). Genetska komponenta MS-a vidljiva je kroz povećan rizik obolijevanja u rodbini prvog koljena i veću podudarnost bolesti u jednojajčanih u odnosu na dvojajčane blizance, što ukazuje da nasljeđe ima važnu, ali ne i isključivu ulogu u nastanku bolesti (19).

Genomska istraživanja su do 2025. godine identificirala više od 200 neovisnih genetskih varijanti koje svaka pojedinačno samo blago povećava rizik oboljevanja od MS-a, ali njihov se učinak zbraja u ukupni poligenski rizik (20). Najsnažnije je povezan alel HLA-DRB1*15:01 u području glavnog sustava tkivne podudarnosti humanog leukocitnog antigena (HLA), pri čemu osobe koje nose barem jednu kopiju ovog alela imaju približno tri

puta veći relativni rizik razvoja MS-a u odnosu na one koje ga nemaju (20). Većina prepoznatih rizičnih varijanti smještena je u genima koji reguliraju funkciju T-limfocita, B-limfocita i stanica urođenog imuniteta, što dodatno podupire shvaćanje MS-a kao primarno autoimune bolesti imunološkog sustava koja tek posljedično dovodi do oštećenja SŽS-a (16,20).

Premda genetski čimbenici značajno povećavaju rizik, većina osoba s rizičnim alelima nikada ne razvije MS, što ukazuje da je za nastanak bolesti nužan i utjecaj okolišnih čimbenika poput infekcije virusom Epstein–Barr (EBV), pušenja, nedostatka vitamina D i smanjene izloženosti sunčevoj svjetlosti te prekomjerne tjelesne mase u adolescenciji (15,17). Velike epidemiološke studije pokazuju da osobe koje su preboljele infekciju EBV-om (infektivna mononukleoza) imaju višestruko veći rizik razvoja MS-a (21–23). Pušenje, osobito dugotrajno i u većim kumulativnim dozama, dodatno povisuje vjerojatnost razvoja bolesti i ubrzava njezinu progresiju, vjerojatno kombinacijom sistemske upale, oksidacijskog stresa i specifičnih imunoloških promjena (17), dok se nedostatak vitamina D i život u područjima s manje sunčeve svjetlosti povezuju s većim rizikom MS-a, što upućuje na to da redovita izloženost ultraljubičastom zračenju i dovoljna razina vitamina D pomažu imunološkom sustavu da zadrži toleranciju prema vlastitim (auto)antigenima (17,24).
U novijim radovima važnu pozornost privlače i raspodjela tjelesne mase, sastav crijevnog mikrobioma te rani životni utjecaji (primjerice infekcije u djetinjstvu), koji preko kronične niskogradijentne upale, promjena u metaboličkim putovima i epigenetskih modifikacija mogu dugoročno mijenjati reaktivnost imunološkog sustava i doprinijeti nastanku autoreaktivnih limfocita (17,24). Način na koji je tjelesna masa raspoređena, sastav crijevnog mikrobioma i rani životni utjecaji (npr. učestalost infekcija u djetinjstvu) mogu mijenjati imunološki sustav i tako utjecati na rizik razvoja MS-a (25–27). Pretilost u djetinjstvu i adolescenciji povezuje se s oko dvostruko većim rizikom razvoja MS-a u mlađoj odrasloj dobi (26). Smatra se da taj učinak proizlazi iz kronične niskogradijentne upale i povišenih razina hormona masnog tkiva poput leptina, koji potiču proliferaciju autoreaktivnih T-limfocita, pojačavaju lučenje proupalnih citokina i istovremeno smanjuju broj i funkciju regulatornih T-stanica, čime se dugoročno pomiče ravnoteža imunološkog sustava prema proupalnom i autoreaktivnom profilu (26).
Studije crijevnog mikrobioma dosljedno pokazuju da osobe s MS-om imaju disbiozu, odnosno promijenjen sastav i metabolizam crijevnih bakterija, u usporedbi sa zdravim ispitanicima (25,27). Ovakva disbioza povezuje se s pojačanom aktivacijom Th1 i Th17

stanica, narušenom funkcijom crijevne barijere i promijenjenom produkcijom kratkolančanih masnih kiselina, što zajedno stvara proinflamatorno okruženje koje može sniziti prag za pokretanje autoimunog odgovora (25,27).

MS je bolest u kojoj poremećaji imunološkog sustava u genetski osjetljivih osoba, pod utjecajem okolišnih čimbenika, dovode do aktivacije autoreaktivnih limfocita i kroničnog upalno-degenerativnog procesa u SŽS-u (16,20). Autoreaktivni T-limfociti i B-limfociti gube imunološku toleranciju prema vlastitim antigenima, prolaze klonalnu aktivaciju na periferiji (limfni organi i tkiva izvan SŽS-a) te nakon narušavanja krvno-moždane barijere ulaze u SŽS i iniciraju imunološki posredovano oštećenje mijelina i oligodendrocita (16). U ranim fazama bolesti dominira upalna demijelinizacija s formiranjem tipičnih lezija bijele i sive tvari, pri čemu se već tada zbiva aksonska transekcija i subklinička neurodegeneracija (16,28). Kako bolest napreduje, upalna aktivnost postaje sve više kronična i lokalizirana unutar SŽS-a, uz trajnu aktivaciju mikroglije, oksidacijski stres, mitohondrijsku disfunkciju i progresivni gubitak aksona i neurona (28).
Zbroj upalno-demijelinizacijskih i neurodegenerativnih mehanizama objašnjava zašto se kod iste osobe istodobno mogu javiti relapsno-remitirajuća pogoršanja i polagana, klinički često slabo izražena progresija bolesti. Ta progresija se u praksi očituje postupnim pogoršanjem motoričkih funkcija, kognitivnih sposobnosti i emocionalnog funkcioniranja, čak i u razdobljima bez jasnih relapsa (28,29).

2.2. Klinička slika i oblici multiple skleroze

MS karakterizira heterogena klinička slika i varijabilni tijek bolesti. Demijelinizacijske lezije u SŽS-u uzrokuju širok spektar simptoma ovisno o lokalizaciji oštećenja – od optičkog neuritisa (20-50% prvih simptoma) i senzornih parestezija do motoričke slabosti, spastičnosti, ataksije i umora (30).

Simptomi se manifestiraju akutno u relapsima (pogoršanja trajanja >24h) ili progresivno, s primarnim neurološkim ispadima poput Lhermitteovog znaka, internuklearne oftalmoplegije i parapareza, te sekundarnim patopsihološkim ishodima kao što su depresivnost (do 50%), anksioznost (21-35%) i kognitivni poremećaji (40-70%) koji značajno smanjuju kvalitetu života (31,32). MS se manifestira u različitim oblicima, najčešće relapsno remitirajućim (RRMS), sekundarno (SPMS) i primarno progresivnim tipom bolesti (PPMS) te klinički izoliranim sindromom (CIS) (33). Dijagnoza se temelji na kombinaciji kliničkih nalaza, magnetske rezonancije i laboratorijskih biomarkera, prema

McDonaldovim kriterijima (34). Opsežna patologija sive tvari moždane kore i drugih regija središnjeg živčanog sustava smatra se ključnim čimbenikom koji doprinosi brojnim složenim neurološkim simptomima povezanim s napredovanjem MS-a, uključujući poremećaje motoričkog i senzoričkog sustava (2,4), disfunkciju mokraćnog sustava i pridružene komorbiditete (35), kroničnu bol (36), kognitivne i psihološke poremećaje te povećanu razinu umora (2,4,37–40).

Relapsno remitirajuća multipla skleroza (RRMS) je najčešći oblik MS-a (85% dijagnoza), obilježen ponavljajućim relapsima (napadi traju 24h+) praćenim remisijama, uz fokalne lezije bijele tvari vidljive na magnetskoj rezonanciji (engl. Magnetic Resonance Imaging, MRI) (T2-hiperintenzivne, gadolinij-pozitivne) i relativno bolju prognozu, gdje oko 70-80% pacijenata ima EDSS <3 nakon 10 godina od dijagnoze, uz rizik prelaska u sekundarno progresivnu MS (SPMS) nakon 15-20 godina (33,41,42). Relapsi su senzorički (35-50%), motorički (30-40%) ili vidni, uz umor kao većinom dominantan simptom (70-90%) (38,41,43).

Sekundarno progresivna MS (SPMS) razvija se kod 50-70% RRMS pacijenata nakon 10-20 godina od početka bolesti (prosječno 15 godina), prelazeći u kontinuiranu progresiju s rijetkim relapsima (u aktivnom SPMS), većom atrofičnom sivom tvari, lezijama i brzim napretkom EDSS (medijan EDSS 5.0-6.0 pri dijagnozi SPMS, EDSS 6 nakon 5-10 godina od dijagnoze ili prvih simptoma), gdje dominantni simptomi uključuju motorički invaliditet, spastičnost, ataksiju i kognitivni pad (44,45).

Primarno progresivna MS (PPMS, 10-15% slučajeva) počinje postupno bez relapsa, s kasnijim početkom (prosječna dob 40 godina), naglaskom na leđnu moždinu i kortikalnu demijelinizaciju, manje gadolinijskih pozitivnih lezija i lošijom prognozom (EDSS 6 u prosjeku 14 godina od dijagnoze ili prvih simptoma), gdje simptomi uključuju progresivnu paraparezu nogu (70%), ataksiju, umor i poremećaj sfinktera (46,47).

CIS (engl. Clinically Isolated Syndrome, klinički izolirani sindrom) je prva klinička epizoda demijelinizacijske bolesti (≥24h, bez prethodnih epizoda), poput sindroma optičkog neuritisa, mijelitisa ili moždanog stabla, koji može biti prva manifestacija MS-a (konverzija u 60-80% ako MRI pokazuje više lezija), ali nisu još zadovoljeni kriteriji za dijagnozu MS-a jer nedostaje diseminacija u vremenu (lezije nastale u različitim vremenskim intervalima) (34,48).

2.3. Depresivnost, anksioznost, umor i spavanje kod osoba s MS-om

Depresija, anksioznost i stres ubrajaju se među najčešće psihološke korelate MS-a, s učestalošću depresije od 25–65%, anksioznosti od 20–54% te stresa oko 45% (49–51). Kod osoba s MS-om, depresivnost, anksioznost i stres često su povezani s umorom, koji se javlja s prevalencijom od 36,5 do 78,0% (52–54), kognitivnim oštećenjima prisutnima u 45-70% oboljelih (50), te poremećajima spavanja, koji se javljaju do 67% češće nego u općoj populaciji (55–57). Umor, kao jedan od najdominantnijih simptoma u ambulantnom praćenju MS-a, karakterizira multifaktorijalna patofiziologija, te uključuje fizičke i psihičke čimbenike (52). Osjećaju umora najčešće pridonose različiti komorbiditeti (58) te štetni učinci lijekova, depresivnost i poremećaji spavanja (59).

Depresivnost i anksiozni poremećaji česti su kod osoba s MS-om te postoji značajna korelacija između razine umora i depresivnosti kod MS osoba (60). Procjenjuje se da oko 50% osoba s MS-om razvije depresiju i to u bilo kojem periodu tijekom (progresije) bolesti (61). Opći čimbenici rizika za depresiju, kao što su (mlađa) dob, (ženski) spol i obiteljska anamneza, manje su povezani s depresijom uzrokovanom MS-om nego što su u općoj populaciji (61). Simptomi depresije su: osjećaj umora, poremećaj pamćenja i koncentracije, nesanica, razdražljivost i gubitak apetita. To su ujedno i simptomi koji se mogu preklapati s MS-om, što otežava diferencijalnu dijagnozu (62). Pretpostavlja se da postoje neki zajednički mehanizmi patogeneze i patofiziologije depresije i MS-a, odnosno promjene vezane uz neuroinflamatorne, neurodegenerativne i neuroendokrine mehanizame (63). Međutim, sve je veći broj istraživanja koji potvrđuju važnost psihosocijalnih čimbenika u riziku od razvoja depresije kod osoba s MS-om. Prema bihevioralnom modelu depresije (64), depresivni simptomi proizlaze iz promjena u obrascima ponašanja osobe, kao što je smanjena uključenost u ugodne aktivnosti, socijalno povlačenje i izbjegavanje. Drugim riječima, bolest će dovesti do depresije ukoliko interferira s urednim psihičkim i fizičkim funkcioniranjem osobe (65). Arnett i sur. (66) su na temelju pregleda empirijskih studija zadnjih dvadeset godina zaključili da biokemijski čimbenici koji su povezani s MS-om (neuroinflamacija, neurodegeneracija, neuroendokrine promjene) samo jednim dijelom objašnjavaju rizik od depresije kod osoba s MS-om. Uobičajene posljedice MS-a, kao što su umor, invaliditet, kognitivna deterioracija i bol, u slabim su korelacijama s depresijom pa se pretpostavlja da postoji utjecaj psihosocijanih varijabli moderatora koji utječu na snagu i smjer tog odnosa (66). Kada je utjecaj moderatorskih varijabli u adaptivnom smjeru, tada uobičajene MS posljedice vjerojatno neće dovesti do depresije, odnosno kada je njihov

utjecaj u maladaptivnom smjeru, postoji vjerojatnost razvoja depresivnog poremećaja.

Novija istraživanja upućuju na to da poremećaji spavanja u MS-u mogu imati ulogu moderatora koji pridonose pogoršanju psihološkog stresa i umora (67,68). Navedeni poremećaji spavanja kod osoba s MS-om obuhvaćaju teškoće s usnivanjem, skraćeno trajanje sna i smanjenu učinkovitost spavanja (67), što se može očitovati i polisomnografskom abnormalnošću u vidu skraćene N2 faze sna (69). Lošija kvaliteta sna dovodi do poremećaja motoričkog sustava kao što su motorička slabost, spastičnost i teškoće u koordinaciji, te do poremećaja psihološkog funkcioniranja, depresivnosti, anksioznosti i umora (56). Dugoročno gledano, kvaliteta spavanja kod osoba s MS-om ostaje relativno stabilna, a depresija se ističe kao jedan od glavnih prediktora lošijeg sna, što dodatno narušava kvalitetu života oboljelih (68). Kvaliteta spavanja pritom predstavlja važan pokazatelj ukupne kvalitete života osoba s MS-om (56). Depresivnost, anksioznost i stres značajno pridonose razvoju poremećaja spavanja i umora (69), no unatoč njihovoj važnosti, ovi simptomi su često izuzeti u procjeni stupnja tjelesne onesposobljenosti (engl. *Expanded Disability Status Scale,* EDSS) (70) kod osoba s MS-om.

2.4. Procjena stupnja (ne)motoričke onesposobljenosti

EDSS je kvantitativna skala kojom se procjenjuje stupanj tjelesne onesposobljenosti kod bolesnika s MS-om, težina bolesti i njezin progres u određenom vremenskom razdoblju. Skala se proteže od 0,0 (bez neuroloških znakova bolesti) do 10,0 (smrt uslijed MS-a), sa stupnjevima od 0,5, a temelji se na kliničkom neurološkom pregledu kojim se ocjenjuju osam funkcionalnih sustava (engl. *Functional System*, FS): vizualni, funkcije moždanog debla, piramidalni, cerebelarni, senzorni, funkcije crijeva i mjehura, moždane funkcije – umor, kognitivne sposobnosti, depresija, te osma kategorija koja obuhvaća procjenu pokretljivosti/hodanja (Slika 1) (71,72).

Konačna EDSS vrijednost ne odražava jednostavan zbroj oštećenja u pojedinim funkcionalnim sustavima, već se dobiva usklađivanjem funkcionalnih FS-nalaza s kriterijima za hodanje i samostalnost u aktivnostima svakodnevnog života, tako da su u srednjim i višim rangovima (npr. 4,0–7,0) kriteriji mobiliteta i korisničko korištenje pomoćnih sredstava (štapa, kolica) ključni za određivanje brojke skale. U donjem dijelu ljestvice (0,0–4,0) težište se nalazi na kliničkom oštećenju u funkcionalnim sustavima, dok se od 4,0 nadalje težina EDSS-a sve više određuje ograničenjem udaljenosti i vremena hodanja te stupnjem nemogućnosti nezavisne pokretljivosti (72,74,75). U svakodnevnoj kliničkoj i istraživačkoj praksi EDSS se najčešće koristi kao glavni

klinički parametar za praćenje progresije bolesti, klasifikaciju kohorta bolesnika i evaluaciju učinkovitosti terapija; u kliničkim ispitivanjima porast EDSS-a za barem 0,5 ili 1,0 bod u određenom vremenskom razdoblju (npr. 3–6 mjeseci) često se uzima kao pokazatelj trajne kliničke progresije, ovisno o početnoj razini invalidnosti (76–78).

Slika 1. Funkcionalni sustavi prema EDSS-u.

Slika prikazuje EDSS osam funkcionalnih sustava kod MS-a prema Kurtzke JF (72) *i Kappos L* (73). *(Sliku je izradila autorica doktorskog rada).*

Uz to, važno je uočiti i ograničenja EDSS-a u kontekstu psiholoških i kognitivnih aspekata MS-a. Kad je riječ o cerebralnom FS-u u sklopu EDSS procjene, depresija se ne uključuje u izračun FS-a niti izračun ukupnog EDSS-a, dok se evaluacija umora često izostavlja zbog poteškoća u objektivnoj procjeni simptoma umora (79). Iako je EDSS najčešće korišteni klinički alat za procjenu tjelesne onesposobljenosti kod osoba s MS-om, osjetljivost EDSS ljestvice je ograničena, osobito kada je riječ o procjeni depresivnosti, anksioznosti, umora, kognitivnih teškoća i funkcijskih teškoća u gornjim ekstremitetima, što može dovesti do nepotpune kliničke slike i podcjenjivanja stvarnog stanja pacijenta (57,80–82).

Povezanost tjelesne onesposobljenosti, kvalitete spavanja, depresivnosti, anksioznosti i umora kod osoba s MS-om još uvijek nije u potpunosti istražena. Dok neka istraživanja pokazuju značajnu povezanost viših stupnjeva tjelesne onesposobljenosti s izraženim teškoćama spavanja, depresivnošću, anksioznošću i umorom kod osoba s MS-om (55,67,83–85), drugi nalazi ostaju nedosljedni (86,87). Rezultati istraživanja također upućuju na niže korelacije između EDSS-a, depresivnosti, anksioznosti, te kognitivnih teškoća (2,49,82,86). Navedeno ukazuje na ograničenja EDSS ljestvice, kojom se prvenstveno procjenjuju motoričke funkcije i hodanje, dok kvaliteta spavanja, depresivnost, anksioznost i umor nisu dovoljno zastupljeni u okviru EDSS procjene (49,88). Spavanje, umor i depresivnost međusobno su povezani i značajno utječu na kvalitetu života oboljelih, a zajednički patološki mehanizmi, poput oštećenja aksona, mogu biti temelj za pojavu navedenih simptoma (89). Posebno je važno naglasiti ulogu kvalitete spavanja, koja ne samo da snažno korelira s depresivnošću, anksioznošću i umorom, već i direktno utječe na funkcionalne kapacitete i opću dobrobit kod osoba s MS-om (68). Kvaliteta spavanja ne predstavlja isključivo sekundarni prateći simptom, već predstavlja ključni čimbenik koji značajno utječe na ishod MS-a (89).

U kliničkoj praksi se mjere samoprocjene kvalitete spavanja, depresivnosti, anksioznosti i umora prikupljaju u svega 28-32% europskih MS registara, dok se EDSS koristi kao standardna mjera procjena tjelesne onesposobljenosti MS bolesnika (90). Neki od upitnika koji se često koriste u procjeni simptomatologije MS-a koja nije primarno vezana uz motorički status su: Pittsburg indeks kvalitete spavanja (engl. *Pittsburgh Sleep Quality Index*, PSQI) (55,91–93), Bolnička ljestvica anksioznosti i depresije (engl. *Hospital Anxiety and Depression Scale,* HADS) (94), Skala depresivnosti, anksioznosti i stresa (engl. *Depression Anxiety and Stress Scale – 21*, DASS-21) (57,94–98), Ljestvica težine umora (engl. *Fatigue Severity Scale,* FSS) (99–104), Ljestvica za procjenu hodanja kod multiple skleroze (engl. *Multiple Sclerosis Walking Scale – 12*, MSWS-12)(105–108), te Skala utjecaja multiple skleroze na svakodnevni život (engl. *Multiple Sclerosis Impact Scale – 29,* MSIS-29) (57,107,109,110).

Procjena simptomatologije MS-a koja nije primarno vezana uz motorički status u Republici Hrvatskoj bila je otežana zbog ograničene dostupnosti validiranih instrumenata za MS populaciju, posebice negdje do pojave COVID-19 (engl. *Coronavirus disease 2019*) (111,112).

3. CILJEVI OBJEDINJENIH RADOVA

Zbog nedostatka jasnih dokaza o povezanosti tjelesne onesposobljenosti i prateće MS simptomatologije (depresivnosti, anksioznosti, umora, narušene kvalitete spavanja) koja nije primarno vezana uz motoričke funkcije, definirani su ciljevi istraživanja:

1. Primarni cilj istraživanja je ispitati povezanost tjelesne onesposobljenosti, kvalitete spavanja, depresivnosti, anksioznosti i umora kod osoba s MS-om.
2. Sekundarni cilj istraživanja je ispitati psihometrijske karakteristike instrumenata za procjenu depresivnosti i anksioznosti (Bolnička ljestvica anksioznosti i depresije; engl. *Hospital Anxiety and Depression Scale*, HADS) (94), umora (Ljestvica težine umora; engl. *Fatigue Severity Scale,* FSS) (101) i hodanja (Ljestvica hodanja; engl. *Multiple Sclerosis Walking Scale,* MSWS-12) (106) kod osoba s MS-om u Republici Hrvatskoj.

4. HIPOTEZE OBJEDINJENIH RADOVA

H_1: Kvaliteta spavanja bit će značajan prediktor razine depresivnosti, anksioznosti i umora kod osoba s MS-om, neovisno o dobi, spolu i stupnju tjelesne onesposobljenosti.

H_2: Bolnička ljestvica anksioznosti i depresije (engl. *Hospital Anxiety and Depression Scale*, HADS), Ljestvica težine umora (engl. *Fatigue Severity Scale*, FSS) te Ljestvica hodanja (engl. *Multiple Sclerosis Walking Scale*, MSWS-12) pokazat će zadovoljavajuće psihometrijske karakteristike (stabilnu faktorsku strukturu, adekvatnu internu konzistentnost te konvergentnu i divergentnu valjanost) kod osoba s MS-om u Republici Hrvatskoj.

5. PREGLED METODOLOGIJE OBJEDINJENIH RADOVA

5.1. Ispitanici

Istraživanja su provedena kao presječne studije s kombiniranim pristupom koji je uključivao korištenje standardiziranih upitnika. Bolnički uzorak činili su oboljeli s MS-om koji su sudjelovali tijekom redovitih neuroloških kontrola na Klinici za neurologiju KBC-a Split te na Odjelu za neurologiju Opće bolnice Zadar. Dodatno, ispitanici su regrutirani putem Udruge multiple skleroze Hrvatske (UMSH) i povezanih organizacija. Prikupljeni su demografski podaci (dob, spol, obrazovanje, komorbiditeti i terapija) te klinički podaci specifični za MS (trajanje bolesti, tip MS-a i EDSS rezultat).

U Tablici 1 prikazan je broj osoba s MS-om i broj kontrolnih ispitanika koji su sudjelovali u istraživanjima.

Tablica 1. Broj ispitanika prema cilju objedinjenih radova.

Cilj	Objedinjeni rad	Osobe s MS-om	Kontrolna grupa
I.	Povezanost depresivnosti, anksioznosti, umora i kvaliteta spavanja s EDSS-om (113)	n=469	n=369
II.	HADS, provjera psihometrijskih karakteristika (81)	n=179	n=999
II.	FSS, provjera psihometrijskih karakteristika (114)	n=179	n=999
II.	MSWS-12, provjera psihometrijskih karakteristika (115)	n=148	-

EDSS – Proširena ljestvica statusa onesposobljenosti; FSS – Ljestvica težine umora; HADS – Bolnička ljestvica anksioznosti i depresije; MSWS-12 – Ljestvica hodanja kod multiple skleroze.

5.2. Korišteni instrumenti

U okviru objedinjenih istraživanja korišteni su sljedeći instrumenti: Bolnička ljestvica anksioznosti i depresije (engl. *Hospital Anxiety and Depression Scale*, HADS) (94), Ljestvica težine umora (engl. *Fatigue Severity Scale*, FSS) (101), Pittsburghov indeks kvalitete spavanja (engl. *Pittsburgh Sleep Quality Index*, PSQI) (55) te MSWS-12 (engl. *Multiple Sclerosis Walking Scale*, MSWS-12) (106).

U Tablici 2 prikazani su korišteni instrumenti u pojedinim znanstvenim radovima razvrstani prema cilju objedinjenih radova.

Tablica 2. Korišteni instrumenti prema cilju objedinjenih radova.

Cilj	Objedinjeni rad	Instrumentarij
I.	Povezanost depresivnosti, anksioznosti, umora i kvaliteta spavanja s EDSS-om (113)	PSQI, HADS, FSS
II.	HADS, provjera psihometrijskih karakteristika (81)	HADS, MSIS-29
II.	FSS, provjera psihometrijskih karakteristika (114)	FSS, MSIS-29
II.	MSWS-12, provjera psihometrijskih karakteristika (115)	MSWS-12, MSIS-29, DASS-21

DASS-21 – Ljestvica depresije, anksioznosti i stresa, FSS – Ljestvica težine umora, HADS – Bolnička ljestvica anksioznosti i depresije, MSIS-29 – Ljestvica utjecaja multiple skleroze, MSWS-12 – Ljestvica hodanja kod multiple skleroze, PSQI – Pittsburghov indeks kvalitete sna.

5.2.1. Bolnička ljestvica depresije i anksioznosti - HADS

Bolnička ljestvica depresije i anksioznosti HADS (94) je ljestvica samoprocjene koja se sastoji od dvaju subskala: HADS-A za mjerenje anksioznosti i HADS-D za mjerenje depresivnosti, pri čemu svaka subskala sadrži po sedam čestica. Ispitanici na svaku tvrdnju odgovaraju na Likertovoj ljestvici od četiri stupnja (0–3), navodeći koliko su se često osjećali na određeni način tijekom prethodnog tjedna. Čestice pod brojevima 1, 3, 5, 7, 9, 11 i 13 pripadaju subskali anksioznosti, dok čestice 2, 4, 6, 8, 10, 12 i 14 čine subskalu depresivnosti. Ukupni rezultat svake subskale dobiva se zbrajanjem bodova odgovarajućih čestica unutar pojedine subskale. Prema interpretaciji Pais-Ribeiro i suradnika (98), rezultati od 0 do 7 ukazuju na „normalne" vrijednosti, rezultati od 8 do 10 označavaju „blagu", od 11 do 14 „umjerenu", a od 15 do 21 „izraženu" razinu anksioznosti ili depresivnosti.

HADS (81,94) se preferira kao instrument za ranu detekciju depresivnosti i anksioznosti kod osoba s MS-om (116). Prema TOP smjernicama (116,117) HADS se navodi kao opcija za rano prepoznavanje depresije kod MS-a uz Beckovu ljestvicu depresije (BDI, engl. *Beck Depression Inventory*) (118,119). Za razliku od BDI (120,121), HADS ne uključuje pitanja o

tjelesnim simptomima karakterističnih za MS (fizički umor, poremećaji sna, bol), koji mogu dovesti do lažno povišenih rezultata na BDI-ju (94,122,123). HADS-om se procjenjuju isključivo psihološki aspekti depresivnosti i anksioznosti, primjerice anhedonija i napetost. Osim toga, HADS rezultati pokazuju bolju prediktivnu valjanost za funkcionalne ishode poput radne sposobnosti, tjelesne onesposobljenosti i brzine kognitivne obrade informacija (122).

Dodatne prednosti HADS-a su kraće trajanje ispunjavanja (14 stavki, 5 min) i jasna podjela na dvije subskale (HADS-D, subskala depresivnosti i HADS-A, subskala anksioznosti), što olakšava diferencijalnu procjenu depresivnosti i anksioznosti (94,122). S druge strane, HADS je manje osjetljiv u razlikovanju stupnjeva težine depresivnosti u usporedbi s BDI, koji je detaljniji, ali zahtjevniji za pacijente i može precjenjivati depresivnost zbog uključivanja tjelesnih aspekata MS-a (118,119,122). Za razliku od BDI-ja, HADS je precizniji u procjeni depresivnosti i anksioznosti kod osoba s MS-om zbog kratkoće, praktičnosti i smanjene interferencije s tjelesnim simptomima MS-a (116).

5.2.2. Ljestvica težine umora - FSS

Ljestvica težine umora FSS (101) je ljestvica samoprocjene koja se sastoji od devet čestica namijenjenih procjeni razine umora tijekom prethodnoga tjedna kod osoba s MS-om. Ispitanici na svako pitanje na skali odgovaraju na Likertovoj ljestvici (1–7), pri čemu vrijednost 1 označava potpuno neslaganje, a vrijednost 7 potpuno slaganje s navedenom tvrdnjom. Ukupni rezultat dobiva se zbrajanjem svih čestica i dijeljenjem dobivenog zbroja s ukupnim brojem čestica, čime se dobiva prosječna vrijednost. Istraživanja su pokazala da se izraženiji umor kod osoba s MS-om identificira graničnim vrijednostima FSS ≥ 4 i ≥ 5 (99,102,104).

FSS (101,114) predstavlja zlatni standard za procjenu umora kod osoba s MS-om zbog visoke unutarnje konzistentnosti (Cronbach $\alpha > 0,90$) i pouzdanosti dokazane u više istraživanja (99,100,104,124,125). Za razliku od ljestvica dizajniranih za procjenu zdravstvenog statusa, kvalitete života ili funkcioniranja u općoj populaciji, bez specifičnosti za određenu bolest ili stanje (122), FSS bolje razlikuje umor kod osoba s MS-om u odnosu na kontrolne ispitanike jer mjeri isključivo težinu i utjecaj umora na svakodnevni život (104,126).

5.2.3. Ljestvica hodanja - MSWS-12

Ljestvica hodanja MSWS-12 (106) je ljestvica samoprocjenje koja mjeri utjecaj MS-a na kvalitetu hodanja. Sastoji se od 12 čestica koje procjenjuju stupanj ograničenja hodanja uzrokovanog MS-om tijekom prethodna dva tjedna. Ispitanici na svaku tvrdnju odgovaraju

odabirom broja koji najbolje opisuje njihovo trenutno stanje na Likertovoj ljestvici (1 = nimalo, 2 = malo, 3 = umjereno, 4 = dosta i 5 = izrazito). Ukupni rezultat se može transformirati u raspon od 0 do 100, pri čemu se od ukupnog rezultata oduzima minimalni mogući rezultat (12), zatim se dobivena vrijednost dijeli razlikom između maksimalnog mogućeg (60) i minimalnog mogućeg rezultata (12), te se rezultat množi sa 100. Niži rezultat ukazuje na manji utjecaj bolesti na hodanje, dok viši rezultat označava veći stupanj oštećenja hodanja.

MSWS-12 (106,115) objektivno kvantificira percipirane poteškoće u hodanju specifične za MS (12 stavki pokrivajući brzinu, koordinaciju, ravnotežu). Kratkoća i dokazana pouzdanost (Cronbach $\alpha > 0{,}90$) omogućuju učinkovitu primjenu MSWS-12 u kliničkim i istraživačkim uvjetima, posebno kod pacijenata s RRMS i SPMS, gdje su problemi s mobilnošću česti. U odnosu na generičke, opće ljestvice npr. *Timed 25-Foot Walk* (127), MSWS-12 uključuje subjektivni doživljaj poteškoća u hodanju, što je ključno za procjenu funkcionalnog utjecaja bolesti (106). Istraživanja su pokazala da je ljestvica MSWS-12 u visokoj korelaciji s EDSS-om (105,107,108,128) posebice kod pacijenata s umjerenim invaliditetom (EDSS 3-6), kod kojih se ljestvicom MSWS-12 bolje diferenciraju svakodnevne poteškoće u pokretljivosti (106).

5.2.4. Pittsburghov indeks kvalitete spavanja – PSQI

Pittsburghov indeks kvalitete spavanja PSQI (91) standardizirani je instrument za subjektivnu procjenu kvalitete spavanja kroz sedam komponenti: subjektivnu kvalitetu spavanja, latenciju spavanja, trajanje spavanja, učinkovitost spavanja, prisutnost poremećaja spavanja, upotrebu lijekova za spavanje te dnevnu disfunkciju. Većina čestica ocjenjuje se na Likertovoj ljestvici (0–3), dok su za četiri čestice predviđeni numerički odgovori. Globalni rezultat, čiji se raspon kreće od 0 do 21, dobiva se zbrajanjem rezultata pojedinih komponenti, pri čemu vrijednost veća od 5 upućuje na lošiju kvalitetu spavanja.

Jerković i sur. (2022) (55) ispitali su valjanost, pouzdanost i faktorsku strukturu PSQI-a kod osoba s MS-om u Republici Hrvatskoj. PSQI je posebno prikladan za procjenu kvalitete spavanja kod osoba s MS-om jer pouzdano diskriminira loše od dobrih spavača (ROC analiza nije odredila jasno definiranu graničnu vrijednost, no globalni rezultat veći od 5 smatra se indikativnim za lošu kvalitetu spavanja), pokazuje metričku stabilnost između pacijenata s MS-om i kontrolne skupine, uz istovremenu visoku osjetljivost na specifične poremećaje povezane s MS-om, što potvrđuju značajne korelacije s EDSS-om i umorom (67,129–131).

6.2.5. Ljestvica depresije, anksioznosti i stresa (DASS-21) i Ljestvica utjecaja multiple skleroze (MSIS-29)

U svrhu ispitivanja konvergentne, konkurentne i inkrementalne valjanosti upitnika HADS, FSS i MSWS-12, u objedinjenim istraživanja (81,114,115) su dodatno primijenjene dvije ljestvice samoprocjene: Skala depresije, anksioznosti i stresa – 21, DASS-21 (96) te Skala utjecaja multiple skleroze, MSIS-29 (109).

DASS-21 sadrži tri subskale (depresija, anksioznost i stres) po sedam čestica, a ispitanici procjenjuju učestalost opisanih stanja tijekom prethodnog tjedna na Likertovoj ljestvici (0–3). Hrvatska verzija instrumenta pokazala je zadovoljavajuću pouzdanost kod osoba s MS-om (57).

MSIS-29 (57) procjenjuje subjektivni utjecaj MS-a na fizičko i psihološko funkcioniranje kroz dvije subskale (tjelesni utjecaj, $MSIS_{PHYS}$: 20 čestica; psihološki utjecaj, $MSIS_{PSY}$: 9 čestica). Tvrdnje se ocjenjuju na Likertovoj ljestvici (1–5), a viši rezultat označava veći percipirani utjecaj MS-a na fizičko i/ili psihološko funkcioniranje osobe.

5.3. Statističke metode

Deskriptivna statistika korištena je za prikaz osnovnih obilježja uzorka i distribucije podataka u objedinjenim radovima. Izračunate su mjere središnje tendencije (aritmetička sredina i medijan) te mjere raspršenosti (standardna devijacija i interkvartilni raspon).

Za usporedbu srednjih vrijednosti između skupina primijenjeni su parametrijski i neparametrijski testovi, ovisno o distribuciji podataka i homogenosti varijance. T-test za nezavisne uzorke korišten je kada su bile zadovoljene pretpostavke normalne distribucije i homogene varijance, dok je analiza varijance (ANOVA) primijenjena za usporedbu više od dvije skupine istovremeno. Leveneov test korišten je za provjeru homogenosti varijanci između skupina. Kada pretpostavke parametrijskih testova nisu bile zadovoljene, korištene su neparametrijski testovi, Mann–Whitney U test i Kruskal–Wallisov H test.

Povezanosti između varijabli ispitane su Pearsonovim koeficijentom korelacije (r) za parametrijske podatke, te Spearmanovim koeficijentom ranga (ρ) za ordinalne ili neparametrijski distribuirane podatke. Dobivene vrijednosti korelacija interpretirane su u skladu s Cohenovim smjernicama: slaba povezanost (0.10–0.29), umjerena (0.30–0.49) i jaka (≥0.50) (132).

Za procjenu prediktivnih odnosa između varijabli primijenjeni su hijerarhijski regresijski modeli. Ova metoda omogućuje postupno uključivanje skupina prediktora u model (npr. kvaliteta sna) zbog utvrđivanja doprinosa svake skupine objašnjenju varijance kriterijske varijable (npr. depresivnosti, anksioznosti ili umora). Značajnost regresijskog modela i pojedinačnih prediktora testirana je na razini $p < 0.05$, a veličina učinka procijenjena je pomoću standardiziranih beta koeficijenata (β) i koeficijenata determinacije (R^2).

U provjeri psihometrijskih karakteristika korištenih instrumenata primijenjene su faktorske analize. Eksploratorna faktorska analiza (EFA; engl. *Exploratory Factor Analysis*) korištena je za ispitivanje latentne strukture upitnika i identifikaciju faktorskih uzoraka (115), analiza glavnih komponenti (PCA; engl. *Principal Component Analysis*) za smanjenje dimenzionalnosti i maksimizaciju objašnjene varijance (114), dok je konfirmatorna faktorska analiza (CFA; engl. *Confirmatory Factor Analysis*) služila za provjeru teorijski pretpostavljenog faktorskog modela i procjenu prikladnosti modela (81). Pouzdanost mjernih instrumenata procijenjena je Cronbachovim α koeficijentom, pri čemu su vrijednosti iznad 0.70 smatrane zadovoljavajućima (133).

ROC analiza (engl. *Reciever Operating Curve*) primijenjena je zbog procjene diskriminativnu valjanosti primijenjenih instrumenata. Procijenjena je površina ispod krivulje (AUC; engl. *Area Under the Curve*), pri čemu veće vrijednosti (≥0.80) upućuju na dobru

sposobnost diskrimnacije. Na temelju provedenih analiza određene su optimalne granične vrijednosti (*cut-off* vrijednosti).

Tablica 3 prikazuje sažeti pregled statističke analize prema cilju objedinjenih radova.

Tablica 3. Korištene statističke metode prema cilju objedinjenih radova.

Cilj	Objedinjeni rad	Statističke metode
I.	Povezanost depresivnosti, anksioznosti, umora i kvaliteta spavanja s EDSS (113)	Hijerarhijski regresijski modeli, korelacijske analize (Pearson, Spearman), t-test, Kruskal-Wallis H, Z-vrijednost, $p<0.05$
II.	HADS, provjera psihometrijskih karakteristika (81)	CFA; Cronbach α (>0.7), korelacijske analize, ROC analiza, hijerarhijska regresija, t-test, Mann-Whitney U test, ANOVA, Levene test, $p<0.05$
II.	FSS, provjera psihometrijskih karakteristika (114)	PCA, Cronbach α (>0.7), t-test, ANOVA, ROC analiza, $p<0.05$
II.	MSWS-12, provjera psihometrijskih karakteristika (115)	EFA, Cronbach α (>0.7), hijerarhijska regresijska analiza, korelacijske analize, t-test, ANOVA, $p<0.05$

ANOVA – Analiza varijance; CFA – Konfirmatorna faktorska analiza; Cronbach α – Cronbach alfa; EFA – eksplorativna faktorska analiza; PCA – Analiza glavnih komponenti; ROC – ROC analiza; Z-standardizirana vrijednost; p < 0,05 – vjerojatnost greške manja od 5%.

7. PREGLED REZULTATA OBJEDINENIH RADOVA

7.1. **Primarni cilj istraživanja** (113)

7.1.1. Povezanost depresivnosti, anksioznosti, umora i kvaliteta spavanja s EDSS-om kod osoba s MS-om

Rezultati primarnog cilja objedinjenih radova pokazali su umjereno do snažne korelacije između umora (FSS), anksioznosti (HADS-A), depresije (HADS-D) i globalnog PSQI-a. EDSS rezultati značajno su, ali slabo korelirali sa FSS ($r = 0.266$; $p < 0.001$), HADS-D ($r = 0.294$; $p < 0.001$) i globalnim PSQI ($r = 0.153$; $p < 0.004$), bez statističke značajnosti za HADS-A ($p = 0.056$) (Tablica 4).

Prosječni rezultati za HADS-D ($H = 15.07$; $p < 0.001$), FSS ($H = 13.56$; $p < 0.001$) i globalni PSQI ($H = 6.35$; $p = 0.002$) bili su viši kod ispitanika s MS-om i težim stupnjevima EDSS-a, dok za HADS-A nije dobivena statistički značajna razlika ($H = 2.45$; $p = 0.088$).

Tablica 4. Pearsonove korelacije između EDSS, FSS, HADS-A, HADS-D i globalnih PSQI rezultata kod osoba s MS-om.

	HADS-A	HADS-D	PSQI global	EDSS
FSS	0.517 (<0.001)	0.577 (<0.001)	0.399 (<0.001)	0.266 (<0.001)
HADS-A	–	0.665 (<0.001)	0.474 (<0.001)	0.095 (0.056)
HADS-D		–	0.466 (<0.001)	0.294 (<0.001)
PSQI global			–	0.153 (0.004)

Vrijednosti predstavljaju Pearsonove koeficijente korelacije s odgovarajućim p-vrijednostima u zagradama. EDSS – Proširena ljestvica stupnja onesposobljenosti; FSS – Ljestvica težine umora, HADS – Bolnička ljestvica anksioznosti i depresije, MSWS-12 – Ljestvica hodanja kod multiple skleroze, PSQI – Pittsburghov indeks kvalitete sna.

7.1.2. Kvaliteta spavanja kao prediktor razine depresivnosti, anksioznosti i umora kod osoba s MS-om

Hijerarhijske linearne regresijske analize s tri modela (osnovni model 1, model 2 prilagođen za dob i spol, te model 3 potpuno prilagođen za dob, spol i EDSS) pokazale su da globalni PSQI rezultati predstavljaju stabilan prediktor anksioznosti (HADS-A; $\beta = 0.527$, $p < 0.001$), depresije (HADS-D; $\beta = 0.480$, $p < 0.001$) i umora (FSS; $\beta = 0.151$, $p < 0.001$), objašnjavajući 21.2%–26.3% varijance. EDSS je značajan prediktor HADS-D ($\beta = 0.435$, $p < 0.001$) i FSS-a ($\beta = 0.170$, $p < 0.001$), dok su

dob i spol uglavnom bili neznačajni, osim spola kod FSS-a ($\beta = -0.484$, $p = 0.024$).

Višestruki regresijski modeli za pojedinačne PSQI komponente (PSQI1-PSQI7), prilagođeni za dob, spol i EDSS, pokazali su da dnevna disfunkcija (PSQI7) predstavlja najkonzistentniji prediktor anksioznosti (HADS-A; $\beta = 1.990$, $p < 0.001$), depresije (HADS-D; $\beta = 2.220$, $p < 0.001$) i umora (FSS; $\beta = 0.675$, $p < 0.001$), nakon poremećaja spavanja (PSQI5; $\beta = 0.426–1.161$, $p \leq 0.003$) te upotrebe lijekova za spavanje (PSQI6; $\beta = 0.169–0.668$, $p \leq 0.035$) (Tablica 5).

Tablica 5. PSQI komponente kao prediktori HADS-A, HADS-D i FSS uz kovarijate.

Prediktori		Zavisne varijabla/kriterij		
		HADS-A	HADS-D	FSS
PSQI1	*Subjektivna kvaliteta spavanja*	0.545 (0.066)	0.487 (0.081)	0.129 (0.267)
PSQI2	*Latencija spavanja*	0.064 (0.775)	0.026 (0.903)	0.003 (0.969)
PSQI3	*Trajanje spavanja*	0.106 (0.715)	-0.353 (0.198)	-0.140 (0.218)
PSQI4	*Efikasnost spavanja*	0.044 (0.845)	0.256 (0.228)	0.067 (0.445)
PSQI5	*Poremećaji spavanja*	1.161 (0.002)	0.833 (0.017)	0.426 (0.003)
PSQI6	*Upotreba lijekova za spavanje*	0.658 (0.001)	0.668 (0.001)	0.169 (0.035)
PSQI7	*Dnevna disfunkcija*	1.990 (<0.001)	2.220 (<0.001)	0.675 (<0.001)
	Dob	-0.015 (0.414)	0.036 (0.044)	0.010 (0.163)
	Spol (Muško)	-0.792 (0.130)	0.287 (0.561)	-0.388 (0.057)
	EDSS	0.101 (0.302)	0.383 (<0.001)	0.161 (<0.001)
	Broj opservacija	373	373	377
	Prilagođeni R^2	0.372	0.427	0.326
	F-statistika	23.081	28.726	19.183

Vrijednosti predstavljaju regresijske koeficijente s odgovarajućim p-vrijednostima u zagradama. Svi modeli prilagođeni su za dob, spol i EDSS. p-vrijednosti < 0,05 smatraju se statistički značajnim; EDSS – Proširena ljestvica stupnja onesposobljenosti; FSS – Skala težine umora; HADS-A – Bolnička ljestvica anksioznosti i depresije – anksioznost; HADS-D – Bolnička ljestvica anksioznosti i depresije – depresija; PSQI – Pittsburghov indeks kvalitete sna.

7.2. Sekundarni cilj istraživanja (81,114,115)

7.2.1. HADS, provjera psihometrijskih karakteristika

Hrvatska verzija HADS-a pokazala jedobre psihometrijske karakteristike kod 179 osoba s MS-om. Unutarnja konzistentnost bila je visoka (Cronbach α = 0.82 za HADS-A; 0.83 za HADS-D), a CFA je potvrdila dvofaktorsku strukturu HADS ljestvice (RMSEA = 0.051).

Konvergentna valjanost HADS-a umjerena je (r = 0.33–0.69 s MSIS-29), s jačim korelacijama s psihološkom subskalom MSIS-29 ljestvice. Prosječne vrijednosti HADS-A i HADS-D značajno su više kod osoba s MS-om nego u kontrolnoj skupini (Z_{HADS-A} = 6.98, p<0.01; Z_{HADS-D} = 8.588, p<0.01), što potvrđuje konkurentnu valjanost HADS ljestvice.

ROC analiza pokazala je dobru diskriminativnu valjanost (AUC = 0.664–0.702; granična vrijednost HADS-D > 7; granična vrijednost HADS-A > 6).

Hijerarhijska regresija pokazala je da HADS-A i HADS-D doprinose objašnjenju varijance MSIS-29 nakon demografskih i kliničkih varijabli unesenih u prvom koraku analize (dob, spol, EDSS, tip MS-a, trajanje bolesti) (ΔR^2 = 18% za fizički utjecaj, $MSIS\text{-}29_{PHYS}$ i ΔR^2 = 40% za psihološki utjecaj, $MSIS\text{-}29_{PSY}$) čime se potvrđuje inkrementalna valjanost HADS ljestvice u procjeni utjecaja MS-a.

Tablica 6. Psihometrijske karakteristike Bolničke ljestvice anksioznosti i depresije (HADS) kod osoba s MS-om u Republici Hrvatskoj.

Psihometrijska karakteristika	HADS-A (anksioznost)	HADS-D (depresija)
Cronbach *α*	0.82	0.83
Faktorska struktura	18.66% varijance	21.85% varijance
Konvergentna valjanost	r=0.33 ($MSIS\text{-}29_{PHYS}$) r=0.69 ($MSIS\text{-}29_{PSY}$)	r=0.54 ($MSIS\text{-}29_{PHYS}$) r=0.61 ($MSIS\text{-}29_{PSY}$)
Konkurentna valjanost	Z_{HADS-A} = 6.98, p<0.01	Z_{HADS-D} = 8.588, p<0.01
ROC	AUC = 0.664; *cutoff* >7	AUC = 0.702; *cutoff* > 6
Inkrementalna valjanost	ΔR^2 = 0.18–0.40 (MSIS-29)	ΔR^2 = 0.18–0.40 (MSIS-29)

$MSIS\text{-}29_{PHYS}$ – fizička subskala Ljestvice utjecaja multiple skleroze – 29 čestica; $MSIS\text{-}29_{PSY}$ – psihološka subskala Ljestvice utjecaja multiple skleroze - 29 čestica; FSS – Skala težine umora; HADS-A – Bolnička ljestvica anksioznosti i depresije – anksioznost; HADS-D – Bolnička ljestvica anksioznosti i depresije – depresija; ROC – ROC analiza; AUC – područje ispod krivulje; cutoff – granična vrijednost; Z – Mann-Whitney U test; ΔR^2 – promjena koeficijenta determinacije; r – koeficijent korelacije; p – razina statističke značajnosti.

7.2.2. FSS, provjera psihometrijskih karakteristika

Hrvatska verzija FSS-a pokazala je odlične psihometrijske karakteristike kod 179 osoba s MS-om. Potvrđena je visoka unutarnja pouzdanost (Cronbach α = 0.93) i jednodimenzionalna struktura FSS ljestvice (55.7% varijance).

Konkurentna i konvergentna valjanost FSS potvrđene su značajnim razlikama između MS i kontrolnih ispitanika, te korelacijama s fizičkom ($MSIS\text{-}29_{PHYS}$; r = 0.60) i psihološkom ($MSIS\text{-}29_{PSY}$; r = 0.50) subskalom MSIS-29 ljestvice.

Prosječne vrijednosti FSS-a značajno su više kod osoba s MS-om nego u kontrolnoj skupini (t = 12.6; p < 0.001), što potvrđuje konkurentnu valjanost FSS ljestvice.

Rezultati ROC analize pokazali su da je optimalna granična vrijednost FSS ljestvice između 4 i 5, pri čemu test postiže relativno visoku osjetljivost i specifičnost. (AUC = 0.785; ≥4).

Tablica 7. Psihometrijske karakteristike Ljestvice umora (FSS) kod osoba s MS-om u Republici Hrvatskoj.

Psihometrijska karakteristika	FSS (umor)
Cronbach α	0.93
Faktorska struktura	Jednodimenzionalna, 55.7% varijance
Konvergentna valjanost	r=0.60 ($MSIS\text{-}29_{PHYS}$) r=0.50 ($MSIS\text{-}29_{PSY}$)
Konkurentna valjanost	t = 12.6; p < 0.001
ROC	AUC = 0.785; *cutoff* ≥4

MSIS-29PHYS – fizička subskala Ljestvice utjecaja multiple skleroze – 29 čestica; MSIS-29PSY – psihološka subskala Ljestvice utjecaja multiple skleroze - 29 čestica; ROC – ROC analiza; AUC – područje ispod krivulje; cutoff – granična vrijednost; r – koeficijent korelacije; p – razina statističke značajnosti.

7.2.3. MSWS-12, provjera psihometrijskih karakteristika

Hrvatska verzija MSWS-12 pokazala je odlične psihometrijske karakteristike kod 148 osoba s MS-om. Potvrđena je visoka unutarnja pouzdanost (Cronbach α = 0.98), a faktorskom analizom potvrđena je jednodimenzionalna struktura ljestvice (81.2% objašnjene varijance).

Konvergentna valjanost MSWS-12 potvrđena je značajnim umjerenim korelacijama s psihološkom subskalom ($MSIS\text{-}29_{PSY}$; r = 0.47) i visokim značajnim korelacijama sa fizičkom subskalom ($MSIS\text{-}29_{PHYS}$; r = 0.82), naglašavajući primarno povezanost MSWS-12 s fizičkim aspektima bolesti. Slabe korelacije MSWS-12 i DASS-21 ($r_{depresija}$ = 0.27, $r_{anksioznost}$ = 0.25 i r_{stres} = 0.20) potvrđuju

diskriminativnu valjanost MSWS-12. Odnosno, MSWS-12 ne mjeri isto što i DASS-21 (depresiju, anksioznost i stres), već specifično funkcionalna ograničenja osoba s MS-om.

Prosječna vrijednost MSWS-12 značajno korelira s EDSS-om ($r = 0.44$, $p < 0.01$), što potvrđuje konkurentnu valjanost ljestvice.

Hijerarhijska regresija pokazala je da MSWS-12 značajno doprinosi objašnjenju varijance MSIS-29 nakon demografskih i kliničkih varijabli unesenih u prvom koraku analize (dob, EDSS, tip MS-a, trajanje bolesti): $\Delta R^2 = 45\%$ za fizički utjecaj ($MSIS\text{-}29_{PHYS}$) i $\Delta R^2 = 24\%$ za psihološki utjecaj ($MSIS\text{-}29_{PSY}$), čime se potvrđuje inkrementalna valjanost MSWS-12 u procjeni funkcionalnih ograničenja hodanja kod osoba s MS-om.

Tablica 8. Psihometrijske karakteristike Ljestvice hodanja (MSWS-12) kod osoba s MS-om u Republici Hrvatskoj.

Psihometrijska karakteristika	MSWS-12 (hodanje)
Pouzdanost (Cronbach α)	0.98
Faktorska struktura	Jednodimenzionalna; 81.2% varijance
Konvergentna valjanost	$r = 0.82$ ($MSIS\text{-}29_{PHYS}$) $r = 0.47$ ($MSIS\text{-}29_{PSY}$)
Diskriminativna valjanost	$r = 0.27$ (DASS-21 depresija) $r = 0.25$ (DASS-21 anksioznost) $r = 0.20$ (DASS-21 stres)
Konkurentna valjanost	$r = 0.44$ (EDSS)
Inkrementalna valjanost	$\Delta R^2 = 0.45$ ($MSIS\text{-}29_{PHYS}$); $\Delta R^2 = 0.24$ ($MSIS\text{-}29_{PSY}$)

HADS-A/D – Bolnička skala anksioznosti i depresije; MSIS-29PHYS – fizička subskala Ljestvice utjecaja multiple skleroze – 29 čestica; MSIS-29PSY – psihološka subskala Ljestvice utjecaja multiple skleroze - 29 čestica; MSWS-12 – Skala hodanja multiple skleroze-12; DASS-21 – Ljestvica anksioznosti, depresije i stresa-21; ΔR² – promjena koeficijenta determinacije; r – koeficijent korelacije; p – razina statističke značajnosti.

8. ZNANSTVENI DOPRINOS OBJEDINJENIH RADOVA

Objedinjeni radovi donose sljedeće znanstvene doprinose:

1) Kvaliteta spavanja predstavlja samostalni i značajni prediktor izraženosti depresivnosti, anksioznosti i umora kod osoba s MS-om, neovisno o dobi, spolu i stupnju tjelesne onesposobljenosti.
2) Dokazan je diferencirani utjecaj pojedinih komponenti kvalitete spavanja na izraženost depresivnosti, anksioznosti i umora kod osoba s MS-om.
3) Rezultati istraživanja ukazuju da bi uz kliničku EDSS procjenu onesposobljenosti bilo korisno uključiti procjenu prateće simptomatologije (depresivnost, anksioznost, umor i kvalitete spavanja) koja nije obuhvaćena EDSS procjenom osoba s MS-om.

9. SAŽETAK

Uvod: Multipla skleroza (MS) kronična je autoimuna bolest središnjeg živčanog sustava obilježena demijelinizacijom, neuroinflamacijom i neurodegeneracijom, koja globalno pogađa oko 2.8 milijuna ljudi. Iako *Expanded Disability Status Scale* (EDSS) standardno procjenjuje tjelesnu onesposobljenost, osjetljivost ove skale ograničena je za nemotoričke simptome poput depresivnosti, anksioznosti, umora i poremećaja spavanja. Primarni cilj je ispitati povezanost tjelesne onesposobljenosti, kvalitete spavanja, depresivnosti, anksioznosti i umora kod osoba s MS-om. Sekundarni cilj je ispitati psihometrijske karakteristike instrumenata za procjenu depresivnosti i anksioznosti (Bolnička ljestvica anksioznosti i depresije; HADS), umora (Ljestvica težine umora; FSS) i hodanja (Ljestvica hodanja; MSWS-12) kod osoba s MS-om u Republici Hrvatskoj.

Metode: Istraživanja su provedena kao presječne studije pomoću standardiziranih upitnika.Uzorak su činili oboljeli sMS-om s Klinike za neurologiju KBC-a Split, Odjela za neurologiju Zadar te članovi Udruge multiple skleroze Hrvatske (UMSH) i povezanih organizacija. Prikupljeni su demografski podaci (dob, spol, obrazovanje, komorbiditeti i terapija) te klinički podaci specifični za MS (trajanje bolesti, tip MS-a i EDSS rezultat). U okviru primarnog cilja korišteni su instrumenti: HADS, FSS te PSQI (Pittsburgh indeks kvalitete spavanja). U okviru sekundarnog cilja korišteni su instrumenti: HADS, FSS i MSWS-12.

Rezultati: Depresivnost, anksioznost, umor i kvaliteta spavanja značajno su korelirani kod osoba s MS-om, dok je povezanost tjelesne onesposobljenosti (EDSS) s depresivnošću, anksioznošću, umorom i kvalitetom spavanja slaba ($r = 0.15–0.29$). Nadalje, depresivnost i kvaliteta spavanja bili su lošiji na višim stupnjevima EDSS-a, dok je umor bio izraženiji na srednjim stupnjevima EDSS-a (4.5–6.5). Kvaliteta spavanja pokazala se kao nezavisni prediktor depresivnosti, anksioznosti i umora kod osoba s MS-om. Subskale PSQI kojima se procijenjuje dnevna disfunkcija, poremećaji spavanja i upotreba lijekova za spavanje, značajan su prediktor depresivnosti, anksioznosti i umora kod osoba s MS-om. Sekundarni ciljevi potvrdili su zadovoljavajuće psihometrijske karakteristike HADS, FSS i MSWS-12 kod osoba s MS-om.

Zaključak: Kvaliteta spavanja predstavlja značajan i nezavisni prediktor razine depresivnosti, anksioznosti i umora kod osoba s MS-om, neovisno o dobi, spolu i tjelesnoj onesposobljenosti. Dokazan je diferencirani utjecaj pojedinih komponenti kvalitete spavanja na izraženost depresivnosti, anksioznosti i umora kod osoba s MS-om. Rezultati istraživanja ukazuju da bi uz kliničku EDSS procjenu onesposobljenosti bilo korisno uključiti procjenu prateće simptomatologije (depresivnost, anksioznost, umor i kvalitete spavanja) koja nije obuhvaćena EDSS procjenom kod osoba s MS-om.

10. SUMMARY

Title: Association between physical disability, sleep quality, depression, anxiety and fatigue in people with multiple sclerosis

Introduction: Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by demyelination, neuroinflammation, and neurodegeneration, affecting approximately 2.8 million people worldwide. Although the *Expanded Disability Status Scale* (EDSS) standardly assesses physical disability, the sensitivity of this scale is limited for non-motor symptoms such as depression, anxiety, fatigue, and sleep disturbances. The primary aim was to examine the relationship between physical disability, sleep quality, depression, anxiety, and fatigue in individuals with MS. The secondary aim was to investigate the psychometric properties of instruments for assessing depression and anxiety (*Hospital Anxiety and Depression Scale*; HADS), fatigue (*Fatigue Severity Scale*; FSS), and walking (*Multiple Sclerosis Walking Scale*; MSWS-12) in individuals with MS in the Republic of Croatia.

Methods: The research was conducted as cross-sectional studies using a combined approach via online and paper questionnaires. The sample consisted of MS patients from the Clinic of Neurology, University Hospital Center Split, Department of Neurology Zadar, as well as members of the Croatian Multiple Sclerosis Association (UMSH) and related organizations. Demographic data (age, gender, education, comorbidities, and therapy) and MS-specific clinical data (disease duration, MS type, and EDSS score) were collected. For the primary aim, the following instruments were used: HADS, FSS, and PSQI (Pittsburgh Sleep Quality Indeks). For the secondary aim, the instruments used were: HADS, FSS, and MSWS-12.

Results: Depression, anxiety, fatigue, and sleep quality were significantly correlated in individuals with MS, while the relationship between physical disability (EDSS) and depression, anxiety, fatigue, and sleep quality was weak ($r = 0.15–0.29$). Furthermore, depression and sleep quality were worse at higher EDSS levels, while fatigue was more pronounced at moderate EDSS levels (4.5–6.5). Sleep quality proved to be an independent predictor of depression, anxiety, and fatigue. PSQI subscales assessing daytime dysfunction, sleep disturbances, and use of sleep medications were significant predictors of depression, anxiety, and fatigue. The secondary aims confirmed satisfactory psychometric properties of HADS, FSS, and MSWS-12.

Conclusion: Sleep quality represents a significant and independent predictor of depression, anxiety, and fatigue levels in individuals with MS, regardless of age, gender, and physical disability. A differentiated impact of individual sleep quality components on the expression of depression, anxiety,

and fatigue in individuals with MS has been demonstrated. The research results indicate that, in addition to clinical EDSS disability assessment, it would be useful to include assessment of accompanying symptomatology (depression, anxiety, fatigue, and sleep quality) not covered by EDSS assessment in individuals with MS.

11. LAIČKI SAŽETAK

Multipla skleroza (MS) je kronična bolest mozga i leđne moždine koja može uzrokovati različite tjelesne i psihičke poteškoće. Iako se u praksi najčešće procjenjuje tjelesna onesposobljenost (npr. poteškoće u hodanju), mnogi oboljeli imaju i druge simptome poput umora, lošeg sna, anksioznosti i depresivnosti, koji često ostaju nedovoljno prepoznati.

Ovo istraživanje imalo je dva cilja. Prvi je bio ispitati kako su međusobno povezani tjelesna onesposobljenost, kvaliteta spavanja, depresivnost, anksioznost i umor kod osoba s MS-om. Drugi cilj bio je provjeriti koliko su pouzdani upitnici koji se koriste za mjerenje tih simptoma na populaciji oboljelih osoba s MS-om u Hrvatskoj.

U istraživanju su sudjelovale osobe s MS-om iz više zdravstvenih ustanova i udruga u Hrvatskoj. Sudionici su ispunili upitnike o raspoloženju, umoru, kvaliteti spavanja i hodanju, a prikupljeni su i osnovni zdravstveni podaci.

Rezultati su pokazali da su depresivnost, anksioznost, umor i loša kvaliteta spavanja međusobno povezani. Međutim, tjelesna onesposobljenost bila je samo slabo povezana s tim simptomima. Posebno se istaknulo da loša kvaliteta spavanja ima važnu ulogu – ona može predvidjeti razinu depresivnosti, anksioznosti i umora, neovisno o težini bolesti ili dobi osobe. Također, određeni aspekti spavanja, poput dnevne iscrpljenosti i poremećaja sna, dodatno su povezani s lošijim psihičkim stanjem.

Zaključno, rezultati upućuju na to da je, uz procjenu tjelesnog stanja, važno redovito pratiti i kvalitetu spavanja, umor te psihičko zdravlje osoba s MS-om. Takav pristup može pomoći u boljem razumijevanju bolesti i kvalitetnijem liječenju.

12. LAY SUMMARY

Title: Association between physical disability, sleep quality, depression, anxiety and fatigue in people with multiple sclerosis

Multiple sclerosis (MS) is a chronic disease of the brain and spinal cord that can cause various physical and psychological difficulties. Although physical disability (e.g., walking difficulties) is most commonly assessed in clinical practice, many patients also experience other symptoms such as fatigue, poor sleep, anxiety, and depression, which often remain insufficiently recognized.

This study had two main aims. The first was to examine how physical disability, sleep quality, depression, anxiety, and fatigue are interrelated in people with MS. The second aim was to determine how reliable the questionnaires used to measure these symptoms are in a population of people with MS in Croatia.

The study included people with MS from several healthcare institutions and patient organizations in Croatia. Participants completed questionnaires on mood, fatigue, sleep quality, and walking ability, and basic clinical and demographic data were also collected.

The results showed that depression, anxiety, fatigue, and poor sleep quality are mutually related. However, physical disability was only weakly associated with these symptoms. Poor sleep quality emerged as particularly important, as it can predict the level of depression, anxiety, and fatigue, regardless of disease severity or age. In addition, specific aspects of sleep, such as daytime dysfunction and sleep disturbances, were further associated with poorer psychological status.

In conclusion, the findings indicate that, in addition to assessing physical status, it is important to regularly monitor sleep quality, fatigue, and mental health in people with MS. Such an approach may contribute to a better understanding of the disease and to more comprehensive and effective treatment.

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14. ŽIVOTOPIS

OSOBNI PODACI

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OBRAZOVANJE

2003.- 2008.	Sveučilište u Zadru, Odjel za psihologiju
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RADNO ISKUSTVO

24. 12.2015.- do danas	Osnovna škola Petar Berislavić Trogir (40 sati tjedno) *mjesto stručnog suradnika psihologa*
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rujan 2008.–svibanj 2009.	Odsjek za psihologiju Filozofskog fakulteta Sveučilišta u Mostaru, mjesto *mlađeg asistenta*

OSTALI POSLOVI

2025./2026. (I semestar)	Fakultet elektrotehnike, strojarstva i brodogradnje Sveučilišta u Splitu, vanjska suradnica na kolegiju *Komunikacijske vještine*
2016.- do danas	Poslovni edukator - *autorica stručnih članaka iz područja psihologije*
2014. – do danas	Sveučilište u Zadru, Odjel za nastavničke studije u Gospiću – *suradnja na znanstveno-istraživačkim poslovima*
2011./2021.	Centar za održivi razvoj Imotski, voditeljica radionica u projektu *Prevencija ovisnosti-vršnjačko savjetovanje*
2013.-2019.	Centar za socijalnu skrb Gospić, Imotski, Kaštela, Trogir vanjski suradnik, voditelj mjere *nadzora nad* i*zvršavanjem roditeljske skrbi*
2010. (II semestar)	Učiteljski fakultet u Rijeci, Odsjek za učiteljski studij u Gospiću, vanjski suradnik u izvođenju kolegija *Trening socijalnih vještina*

VJEŠTINE

Aktivno korištenje Statistica Soft paketa/ SPSS za obradu podataka

Engleski: aktivno u govoru i pismu

OSTALE INFORMACIJE:

Položeni stručni ispiti:	Napredovanje u zvanje:
4.11. 2010. – AZOO	15.10.2020. – stručni suradnik mentor
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IZVORNI ZNANSTVENI RADOVI (Ukupno: 19)

1. Jerković A, Safić IS, Pavelin S, Pleić N, Duka Glavor K, Vujović I, et al. Disability and Non-Motor Symptoms in Multiple Sclerosis: Exploring Associations and Predictive Factors. Brain Sci. 2025;15(10):1122.

2. Režić Mužinić N, Markotić A, Pavelin S, Polančec D, Buljubašić Šoda M, Bralić A, et al. Expression of CD40 and CD192 in Classical Monocytes in Multiple Sclerosis Patients Assessed with Transcranial Magnetic Stimulation. Biomedicines. 2023;11(10):2870.

3. Rogić Vidaković M, Ćurković Katić A, Pavelin S, Bralić A, Mikac U, Šoda J, et al. Transcranial Magnetic Stimulation Measures, Pyramidal Score on Expanded Disability Status Scale and Magnetic Resonance Imaging of Corticospinal Tract in Multiple Sclerosis. Bioengineering. 2023;10(10):1118.

4. Rogić Vidaković M, Ćurković Katić A, Jerković A, Šoda J, Košta V, Režić Mužinić N, et al. Neurophysiological impairment in multiple sclerosis patient confirmed by transcranial magnetic stimulation of the central nervous system but not with electrical stimulation of peripheral nervous system. Artif Organs. 2022;46(3):E182-E186.

5. Jerković A, Nikolić Ivanišević M, Šimić N, Poljičanin A, Đogaš Z, Rogić Vidaković M. Psychometric properties of the Croatian version of the Multiple Sclerosis Walking Scale (MSWS-12). Disabil Rehabil. 2022:1-6.

6. Ahmetović H, Jerković A, Rogić Vidaković M, Košta V. The comparison of mechanical thrombectomy and symptomatic therapy on early outcome of acute ischemic stroke in patients older than 80 years: a retrospective cohort study. Clin Neurol Neurosurg. 2022;221:107378.

7. Jerković A, Pavelin S, Šoda J, Vujović I, Rogić Vidaković M. Symptom-Level Disability Status Assessed with an Electronic Unsupervised Patient-Reported Expanded Disability Status Scale (ePR-EDSS) in Multiple Sclerosis Patients—The Example of Croatia. J Clin Med. 2022;11(14):4081.

8. Jerković A, Mikac U, Matijaca M, Košta V, Ćurković Katić A, Dolić K, et al. Psychometric Properties of the Pittsburgh Sleep Quality Index (PSQI) in Patients with Multiple Sclerosis: Factor Structure, Reliability, Correlates, and Discrimination. J Clin Med. 2022;11(7):2037.

9. Jerković A, Matijaca M, Proroković A, Šikić A, Košta V, Ćurković Katić A, et al. Information Processing Speed Assessed with Letter Digit Substitution Test in Croatian Sample of Multiple Sclerosis Patients. Diagnostics. 2022;12(1):111.

10. Jerković A, Proroković A, Matijaca M, Ćurković Katić A, Košta V, Mihalj M, et al. Validation of the Fatigue Severity Scale in Croatian population of patients with multiple sclerosis disease: Factor structure, internal consistency, and correlates. Mult Scler Relat Disord. 2022;58:103397.

11. Jerković A, Proroković A, Matijaca M, Vuko J, Poljičanin A, Mastelić A, et al. Psychometric properties of the HADS measure of anxiety and depression among multiple sclerosis patients in Croatia. Front Psychol. 2021;12:794353.

12. Nikčević-Milković A, Jurković D, Jerković A. Construction and validation of the parental assessment questionnaire for children's emotional competence (URPEKD). Život Šk. 2020;66(1):11-22.

13. Šoda J, Rogić Vidaković M, Lorincz J, Jerković A, Vujović I. A Novel Latency Estimation Algorithm of Motor Evoked Potential Signals. IEEE Access. 2020;8:193356-193374.

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15. Rogić Vidaković M, Kostović A, Jerković A, Šoda J, Russo M, Stella M, et al. Using Cutaneous Receptor Vibration to Uncover the Effect of Transcranial Magnetic Stimulation (TMS) on Motor Cortical Excitability. Med Sci Monit. 2020;26:e923166.

16. Nikčević-Milković A, Jerković A, Brala-Mudrovčić J. Ispitivanje nekih komponenti samoregulacije učenja u domenama čitanja i pisanja kod učenika različite dobi i roda. Napredak. 2018;159(1-2):73-99.

17. Nikčević-Milković A, Jerković A, Rukavina M. Stanje, problemi i potrebe rada s darovitim učenicima u osnovnim školama u Republici Hrvatskoj. Magistra Iadertina. 2017;11(1):9-34.

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2014;155(4):375-398.

19. Nikčević-Milković A, Jerković A. Učestalost i oblici elektroničkog zlostavljanja učenika viših razreda osnovnoškolske dobi u tri različite školske sredine. Školski vjesnik. 2016;65(1):75-94.

PREGLEDNI ZNANSTVENI RAD (Ukupno:1)

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15. PRESLIKE OBJEDINJENIH RADOVA

I. Jerković A, Safić IS, Pavelin S, Pleić N, Duka Glavor K, Vujović I, Šoda J, Duranović J, Rogić Vidaković M. Disability and Non-Motor Symptoms in Multiple Sclerosis: Exploring Associations and Predictive Factors. Brain Sci. 2025 Oct;15:1122. doi:10.3390/brainsci15101122

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Article

Disability and Non-Motor Symptoms in Multiple Sclerosis: Exploring Associations and Predictive Factors

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Abstract

Background/Objectives: The relationship between multiple sclerosis (MS) disability and co-occurring non-motor symptomatology is not well understood. This study examined the association between disability status and non-motor symptoms—sleep quality, depression, anxiety, and fatigue—in people with multiple sclerosis (MS), as well as the contribution of sleep quality to the prediction of fatigue, depression, and anxiety in MS. Methods: A cross-sectional study included 469 MS and 369 control subjects. Disability status of MS subjects was assessed with the Expanded Disability Status Scale (EDSS), while fatigue, depression, anxiety, and sleep quality were evaluated with the Fatigue Severity Scale (FSS), the Hospital Anxiety and Depression Scale (HADS), and the Pittsburgh Sleep Quality Index (PSQI), respectively. Statistical analyses encompassed group comparisons, Pearson correlations, and hierarchical regression models adjusted for age, sex, and EDSS. Results: The results show that MS subjects exhibited higher FSS, HADS-D, and PSQI scores than controls, with intercorrelations and only weak associations with EDSS severity (r = 0.15–0.29). Moreover, PSQI global and HADS-D scores increased with higher EDSS severity, while FSS scores peaked in the moderate EDSS range (4.5–6.5). Global PSQI score independently predicted FSS, HADS-D, and HADS-A. Daytime dysfunction, sleep disturbances, and sleep medication use significantly predicted FSS, HADS-D, and HADS-A scores. Conclusions: Study findings highlight the role of sleep quality in exacerbating depression, anxiety, and fatigue in MS.

Keywords: multiple sclerosis; sleep; fatigue; depression; anxiety; disability evaluation

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1. Introduction

Multiple sclerosis (MS) is a chronic, disabling neurological autoimmune disorder of the central nervous system (CNS) characterized by demyelination, neuroinflammation, and neurodegeneration [1–6], and it affects 1.89 million people, with the global prevalence of

23.9 cases per 100,000 population (Khan & Hashim, 2025). MS organizations (National Multiple Sclerosis Society) estimate that 2.8 million people suffer from MS, with an estimated number of 500,000–700,000 MS in Europe [7].

Extensive pathology in the gray matter of the cerebral cortex and other CNS regions is thought to be responsible for various complex neurological indices associated with disease progression in motor and sensory systems [2,4], lower urinary tract symptoms and related comorbidities [8], chronic pain [9], disruption in cognitive and psychological functioning, and increased level of fatigue [2,4,10–14]. Depression, anxiety, and stress are frequent psychological symptoms of MS (prevalence of 25–65%, 20–54%, and 44.8%, respectively) [15,16], often associated with fatigue (prevalence from 36.5 to 78.0%) [17], cognitive impairment (prevalence of 45–70%) [15], and sleep disorders (up to 67% more common than in the general community) [18]. Emerging evidence positions sleep disturbances as key mediators and moderators, exacerbating psychological distress and fatigue independently of disability progression [19]. These disturbances include poor sleep initiation, reduced duration, and efficiency [19], alongside polysomnographic abnormalities such as diminished stage N2 sleep [20]. Critically, sleep quality independently clusters with MS symptoms and predicts quality of life [18], while depression, anxiety, and stress explain 37% of sleep disorder variance and 35% of fatigue risk [21]. Despite their interconnectedness, co-occurrence symptoms are overlooked by the Expanded Disability Status Scale (EDSS) [22].

The EDSS is based on a clinical neurological examination, including seven functional systems (FS: visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder, and cerebral) and assessment of walking range (ambulation) [23,24]. Regarding the cerebral FS score, depression is not considered in FS and EDSS calculations, and fatigue evaluation is often omitted due to the neurologist's difficulties in objectively assessing fatigue. Despite being the most widely used clinical tool in MS clinical trials, EDSS has limitations, including less sensitivity in assessing symptoms of depression, anxiety, fatigue, cognitive disturbances, and difficulties in upper limb function [25,26].

The relationship between EDSS scores and co-occurring symptoms remains inconsistent across studies. While some research demonstrates a significant association between higher EDSS scores and increased levels of depression, anxiety, sleep problems, and fatigue [19,27–29], other studies report no clear correlation [30,31]. Importantly, even when statistically significant, correlations between EDSS scores and co-occurring symptoms in MS are generally low, highlighting the limitations of the EDSS, which somehow prioritizes motor function and ambulation over non-physical symptoms [2,11,26,30]. In clinical practice, patient-reported measures such as depression, anxiety, and fatigue are collected by only 28–32% of European MS registries, whereas EDSS and other disability measures are routinely included [7].

Given the limitations of EDSS and inconsistent findings on the relationship between co-occurring symptoms in MS, the present study aims to address this gap by comparing the relationship of MS disability status with non-motor symptoms (depression, anxiety, fatigue, and sleep quality) in MS subjects. Notably, sleep problems have been shown to independently predict non-motor symptoms, mediating the effects of disability on mood and quality of life [18]. Therefore, the study also examines the contribution of individual components of sleep quality (assessed by the Pittsburgh Sleep Quality Index, PSQI) [32], concerning MS disability status (EDSS), depression and anxiety (evaluated with the Hospital Anxiety and Depression Scale, HADS) [33], and fatigue (evaluated with the Fatigue Severity Scale, FSS) [34].

2. Materials and Methods

2.1. Study Procedure

A cross-sectional study design using a mixed-methods approach was used; therefore, online surveys were combined with paper-based questionnaires. Paper-based questionnaires were given to MS subjects at regular neurologic visits at the Department of Neurology at the University Hospital Split (n = 115) and the Department of Neurology, General Hospital Zadar (n = 354). This study included a total of 469 MS subjects, members of the Association of Multiple Sclerosis Societies of Croatia (AMSSC). The control subjects were recruited through online social media communities (n = 369).

Participation in the study was voluntary and anonymized, with exclusion criteria encompassing a history of psychiatric disorders or other neurological conditions other than MS. During screening, 5.54% of MS subjects and 1.31% of control subjects were excluded (e.g., psychiatric and neurological disorders). Data collection spanned from 1 October to 30 November 2024.

2.2. Demographic Information and Disease-Related Variables

Demographic characteristics (age, sex, and handedness), educational attainment, comorbidities, and medications for comorbid conditions were recorded for all participants. For individuals with MS, disease-specific data were collected, including disease duration, MS subtype, EDSS scores, and current immunomodulatory therapies.

2.3. Participants

Demographic and clinical data are presented in Table 1. The mean age of individuals with MS was 42.7 ± 10.8 years (range: 18–78), with females comprising 85% of the cohort. The majority of subjects with MS had completed high school (53.7%), while 31.1% held a graduate degree.

According to the McDonald criteria [35,36], the distribution of MS subtypes was as follows: relapsing-remitting MS (75.3%), primary progressive MS (12.8%), secondary progressive MS (7.8%), and Clinically Isolated Syndrome (CIS) (0.4%). The median EDSS score was 2 [Q1–Q3: 1–4], and the mean disease duration was 8.39 ± 7.74 years. Immunomodulatory therapy was administered to 72.9% of MS subjects, with comorbidities reported in 29% of MS subjects, most commonly endocrine, metabolic, and circulatory system disorders.

The control group consisted of 369 participants with a mean age of 42.3 ± 11.7 years (range: 18–75), of whom 82% were female. Graduate degrees were held by 61.2%, while 23.3% had completed high school. Comorbidities were present in 25.7% of control subjects, predominantly endocrine, metabolic, and circulatory disorders.

Table 1. Baseline characteristics of MS and control subjects.

	MS (n = 469)	**Control (n = 369)**
Age in years, mean (SD)	42.7 (10.8)	42.3 (11.7)
Age, range	18–78	18–75
Sex, n (%)		
Women	398 (84.8)	304 (82.4)
Men	71 (15.2)	65 (17.6)
Right-hand dominance, n (%)	438 (93.4)	344 (93.2)
Education, n (%)		
Primary school	8 (1.7)	0
Secondary school	252 (53.7)	85 (23.3)
Professional study	31 (6.6)	24 (6.3)
Undergraduate study	32 (6.9)	34 (9.2)
Graduate study	131 (27.9)	189 (51.2)

Table 1. *Cont.*

	MS (n = 469)	Control (n = 369)
Postgraduate study	15 (3.2)	37 (10.0)
Comorbidity, n (%)	136 (29.0)	95 (25.7)
FSS, mean (SD)	5.01 (1.68)	4.02 (1.37)
HADS-A, mean (SD)	8.18 (4.49)	8.19 (2.97)
HADS-D, mean (SD)	7.02 (4.31)	5.48 (3.51)
PSQI global, mean (SD)	7.75 (4.04)	5.97 (3.14)
MS type, n (%)		
RRMS	353 (75.3)	-
PPMS	60 (12.8)	
SPMS	19 (7.8)	
CIS	2 (0.4)	
EDSS, median (Q1–Q3)	2 (1–4)	-
Duration of MS, mean (SD)	8.39 (7.74)	-
Immunomodulatory drug, n (%)	342 (72.9)	-

Values are presented as mean (SD) and median (Q1–Q3) for continuous variables and absolute frequency (relative frequency) for categorical variables. CIS, Clinically Isolated Syndrome; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; HADS-A, Hospital Anxiety and Depression Scale (anxiety subscale); HADS-D, Hospital Anxiety and Depression Scale (depression subscale); Q1, first quartile; Q3, third quartile; PPMS, primary progressive multiple sclerosis; PSQI, Pittsburgh Sleep Quality Index; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPM, secondary progressive multiple sclerosis.

2.4. Questionnaires

2.4.1. Fatigue Severity Scale (FSS)

The FSS, developed by Krupp et al. [34], is a 9-item questionnaire assessing subjective fatigue perception. Each item is rated on a 7-point Likert scale (1 = strong disagreement to 7 = strong agreement), with total scores calculated as the mean of all items. Fatigue in MS is a multidimensional symptom, encompassing physical, cognitive, and psychosocial aspects. However, most widely used fatigue scales, such as the Fatigue Severity Scale (FSS), primarily measure the severity and impact of physical fatigue, with limited coverage of cognitive or psychosocial fatigue [37,38]. The validated Croatian version demonstrated excellent internal consistency (Cronbach's $\alpha = 0.93$) and a unidimensional structure [39]. A cut-off score of ≥ 4 identifies clinically significant fatigue in MS subjects, with high sensitivity and specificity [40–42].

2.4.2. Hospital Anxiety and Depression Scale (HADS)

The HADS, developed by Zigmond and Snaith [33], comprises two seven-item subscales measuring anxiety (HADS-A) and depression (HADS-D). In MS subjects, the HADS has demonstrated robust psychometric properties. Honarmand and Feinstein [43] found that a cut-off score of eight or greater on either subscale provides high sensitivity and specificity for detecting major depression and generalized anxiety disorder, confirming the scale's utility as a screening tool in this population. These findings have been supported by subsequent studies, which highlight the HADS' effectiveness for identifying clinically significant psychiatric symptoms in MS [44–46].

The Croatian version of the HADS exhibits excellent internal consistency (Cronbach's $\alpha = 0.82$–0.83) and supports a two-factor structure, aligning with the original scale's design [47]. Psychometric analyses further confirm good convergent and incremental validity, with significant correlations observed between HADS subscales and measures of MS impact. For the Croatian MS sample, optimal cut-off scores have been identified as >7 for anxiety and >6 for depression, slightly lower than the original threshold, to maximize diagnostic accuracy in this specific population [47].

2.4.3. The Pittsburgh Sleep Quality Index (PSQI)

The PSQI, developed by Buysse et al. [32], evaluates sleep quality across seven components: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication use, and daytime dysfunction. Most items use a 4-point scale (subscores 0–3), while four require numeric responses. The global score (0–21) is derived from subscores, with >5 indicating poor sleep quality [48]. Jerković et al. [39] validated PSQI on the MS population, showing excellent reliability (Cronbach's $\alpha = 0.83$) and a two-factor structure.

2.5. Statistical Analyses

All statistical analyses were performed using R version 4.1.3. [49]. Descriptive statistics were calculated to summarize demographic, clinical, and questionnaire-based variables. Group differences (MS vs. controls) were assessed using independent t-tests (continuous variables) and χ^2 tests (categorical variables), as well as the Kruskal–Wallis H test for comparisons across more than two groups defined by disability severity. The classification of EDSS scores into mild (0–4), moderate (4.5–6.5), and severe (7–10) is based on the degree of disability and mobility impairment [24]. Average standardized scores (z-values) for the PSQI, FSS, HADS-A, and HADS-D were used to depict the distribution of symptom severity across EDSS categories, serving as the basis for the graphical presentation.

Given the exploratory nature of this study, the analyses were designed to examine potential associations among variables rather than to test specific hypotheses. Pearson correlations examined relationships between FSS, HADS-A, HADS-D, PSQI components, and EDSS in the MS cohort. Hierarchical linear regression models assessed associations of sleep quality with depression, anxiety, and fatigue. Models included blocks with predictors and covariates (age, sex, and EDSS). Results are reported as unstandardized coefficients (β) and adjusted R^2. Controls were excluded from these models. Causal inference methods were not applied due to the cross-sectional design of the study, which limits the ability to establish cause-and-effect relationships. The level of statistical significance was set at 0.05.

3. Results

3.1. Group Differences and Symptom Interrelations

The demographic characteristics and disease-related variables of MS and the control group subjects are presented in Table 1. No statistically significant differences were observed in sex ($p = 0.384$) or age distribution ($p = 0.582$) between the examined groups (Table 1). Subjects with MS showed significantly higher FSS (5.01 ± 1.68 vs. 4.02 ± 1.37; $p < 0.001$), HADS-D (7.02 ± 4.31 vs. 5.48 ± 3.51 in controls), and PSQ global scores compared to control subjects (PSQI: 7.75 ± 4.04 vs. 5.97 ± 3.14; $p < 0.001$) (Table 2). HADS-A scores did not differ between groups ($p = 0.961$) (Table 2).

Table 2. Mean group comparison between MS (**n** = 469) and control ($n = 369$) subjects.

	MS Mean (SD)	Control Mean (SD)	*p*-Value
FSS	5.01 (1.68)	4.02 (1.37)	$<2.2 \times 10^{-16}$
HADS-A	8.18 (4.49)	8.19 (2.97)	0.961
HADS-D	7.02 (4.31)	5.48 (3.51)	1.83×10^{-8}
PSQI global	7.75 (4.04)	5.97 (3.14)	1.717×10^{-12}

Values are presented as mean (SD). HADS-A, Hospital Anxiety and Depression Scale (anxiety subscale); HADS-D, Hospital Anxiety and Depression Scale (depression subscale); PSQI, Pittsburgh Sleep Quality Index; FSS, Fatigue Severity Scale. *p*-values represent results of independent sample *t*-tests.

In the MS group, moderate to strong intercorrelations were observed between FSS, HADS-A, HADS-D, and PSQI global (Table 3). EDSS scores were significantly, but weakly associated with FSS (r = 0.266, <0.001), HADS-D (r = 0.294, <0.001), and PSQI global

(r = 0.153; $p < 0.004$), while the association of EDSS with HADS-A did not reach statistical significance ($p = 0.056$, $p > 0.05$).

Table 3. Pearson correlations between EDSS, FSS, HADS-A, HADS-D, and PSQI global scores in MS.

	HADS-A	HADS-D	PSQI Global	EDSS
FSS	0.517 (<0.001)	0.577 (<0.001)	0.399 (<0.001)	0.266 (<0.001)
HADS-A	-	0.665 (<0.001)	0.474 (<0.001)	0.095 (0.056)
HADS-D	-	-	0.466 (<0.001)	0.294 (<0.001)
PSQI global	-	-	-	0.153 (0.004)

Values represent Pearson correlation coefficients with corresponding *p*-values shown in parentheses. HADS-A, Hospital Anxiety and Depression Scale (anxiety subscale); HADS-D, Hospital Anxiety and Depression Scale (depression subscale); PSQI, Pittsburgh Sleep Quality Index; FSS, Fatigue Severity Scale, EDSS, Expanded Disability Status Scale.

The results show that mean scores for HADS-D (H = 15.07, $p < 0.001$), FSS (H = 13.56, $p < 0.001$), and PSQI (H = 6.35, $p = 0.002$) were higher in MS subjects with more severe EDSS levels, whereas anxiety (HADS-A) showed no significant differences (H = 2.45, $p = 0.088$). Mean (SD) scores for depression (HADS-D) increased with greater EDSS severity: from 6.51 (±4.27) in the mild group, to 8.93 (±4.41) in the moderate group, and 8.73 (±4.92) in the severe group. Similarly, mean (SD) FSS rose from 4.88 (±1.67) in mild cases to 5.74 (±1.41) in moderate and 5.73 (±1.83) in severe cases. The global mean (SD) PSQI scores also showed a progressive increase, rising from 7.55 (±3.21) in the mild group to 8.91 (±3.45) in the moderate group and reaching 10.33 (±4.12) in the severe group.

Figure 1 shows that average standardized PSQI global scores and HADS-D scores increased gradually with higher EDSS severity scores. FSS increased markedly in the moderate EDSS severity stratum and remained elevated at severe EDSS, while HADS-A scores showed minimal variation across EDSS severity levels.

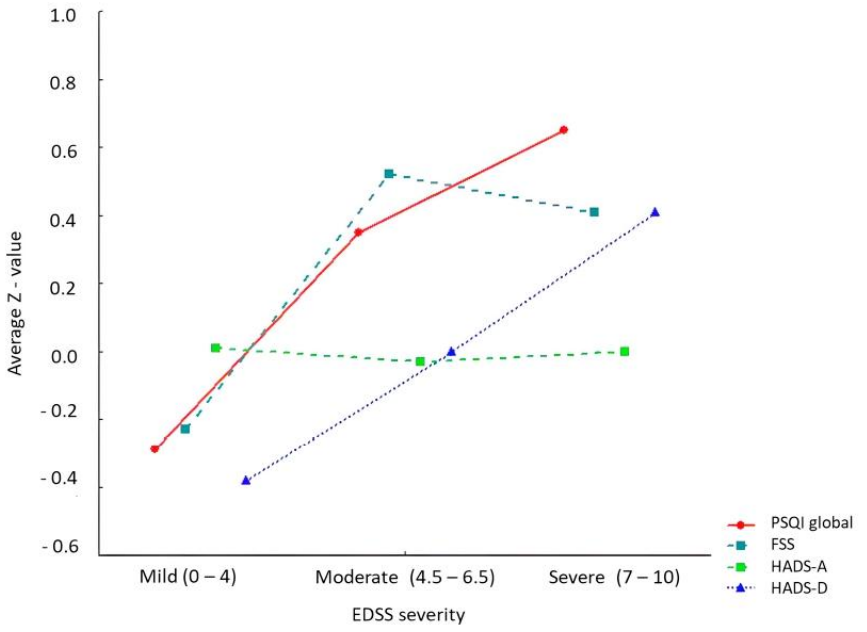

Figure 1. Average standardized scores (Z-values) of FSS, HADS-A, HADS-D, PSQI across EDSS severity stratum. Legend: FSS(Fatigue Severity Scale); HADS-A (Hospital Anxiety and Depression Scale—anxiety subscale); HADS-D (Hospital Anxiety and Depression Scale—depression subscale); PSQI (Pittsburgh Sleep Quality Index); EDSS (Expanded Disability Status Scale).

3.2. Regression Analysis

Hierarchical linear regression analyses revealed global PSQI scores as a robust and consistent predictor of anxiety symptoms (HADS-A) across all models (Table 4). In the unadjusted model (Model 1), PSQI scores demonstrated a strong positive association with HADS-A ($\beta = 0.528$, $p < 0.001$), explaining 22.3% of the variance in HADS-A outcomes. Subsequent adjustment for age and sex (Model 2) yielded negligible attenuation in effect size ($\beta = 0.519$, $p < 0.001$), with the model retaining comparable explanatory power (adjusted $R^2 = 0.220$).

Table 4. Hierarchical linear regression models predicting HADS-A from PSQI global and covariates.

Predictor Variables	Dependent Variable: HADS-A		
	(1)	(2)	(3)
PSQI global	0.528 (<0.001)	0.519 (<0.001)	0.527 (<0.001)
Age		−0.022 (0.227)	−0.026 (0.193)
Sex (Male)		−1.072 (0.05)	−1.033 (0.069)
EDSS			0.122 (0.249)
Observations	461	441	386
Adjusted R^2	0.223	0.220	0.240
F-statistic	132.812 (df = 1; 459)	42.362 (df = 3; 437)	31.467 (df = 4; 381)

Values represent regression coefficients with corresponding *p*-values in parentheses. EDSS, Expanded Disability Status Scale; HADS-A, Hospital Anxiety and Depression Scale (anxiety subscale); PSQI, Pittsburgh Sleep Quality Index. Model 1 includes PSQI only; Model 2 adds age and sex; Model 3 adds EDSS. *p*-values < 0.05 are considered statistically significant and are marker in bold text.

The fully adjusted model (Model 3), which incorporates EDSS alongside demographic covariates, further confirms the stability of this relationship. PSQI scores remained a significant predictor of HADS-A ($\beta = 0.527$, $p < 0.001$), with the final model accounting for 24% of the variance in anxiety symptoms. Age, sex, and EDSS were not statistically significant predictors in the final model.

Further analyses confirmed the global PSQI score as a stable predictor of HADS-D across all models (Table 5). In the unadjusted model (Model 1), the PSQI demonstrated a strong positive association with depression ($\beta = 0.499$, $p < 0.001$), accounting for 21.5% of the variance in outcomes (adjusted $R^2 = 0.215$). After adjusting for age and sex (Model 2), the strength of the association remained unchanged ($\beta = 0.489$, $p < 0.001$), with age emerging as a significant covariate ($\beta = 0.051$, $p = 0.003$), indicating that higher age was associated with greater depressive symptom severity.

Table 5. Hierarchical linear regression models predicting HADS-D from PSQI global and covariates.

Predictor Variables	Dependent Variable: HADS-D		
	(1)	(2)	(3)
PSQI global	0.499 (<0.001)	0.489 (<0.001)	0.480 (<0.001)
Age		0.051 (0.003)	0.028 (0.147)
Sex (Male)		0.505 (0.326)	0.148 (0.788)
EDSS			0.435 (<0.001)
Observations	461	441	386
Adjusted R^2	0.215	0.221	0.263
F-statistic	127.094 (df = 1; 459)	42.593 (df = 3; 437)	35.434 (df = 4; 381)

Values represent regression coefficients with corresponding *p*-values in parentheses. EDSS, Expanded Disability Status Scale; HADS-D, Hospital Anxiety and Depression Scale (depression subscale); PSQI, Pittsburgh Sleep Quality Index. Model 1 includes PSQI only; Model 2 adds age and sex; Model 3 adds EDSS. *p*-values < 0.05 are considered statistically significant and are marked in bold text.

In the fully adjusted model (Model 3), which included EDSS, the global PSQI score retained its statistical significance as an independent predictor ($\beta = 0.480$, $p < 0.001$).

Simultaneously, EDSS showed a robust association with HADS-D (β = 0.435, $p < 0.001$). The final model accounted for 24.8% of the variance in HADS-D scores, with PSQI remaining a key factor within the multivariate analysis.

Hierarchical regression analyses identified global PSQI scores as a significant predictor of FSS across all models (Table 6). In the unadjusted model (Model 1), poorer PSQI demonstrated a strong positive association with fatigue (β = 0.166, $p < 0.001$), explaining 15.7% of the variance in FSS outcomes. Controlling for age and sex (Model 2) resulted in a minor reduction in the sleep-fatigue association (β = 0.153, $p < 0.001$), as neither demographic factor demonstrated independent predictive significance in the adjusted model.

Table 6. Hierarchical linear regression models predicting FSS from PSQI global and covariates.

Predictor Variables	**Dependent Variable: FSS**		
	(1)	(2)	(3)
PSQI global	0.166 (<0.001)	0.153 (<0.001)	0.151 (<0.001)
Age		0.017 (0.018)	0.009 (0.227)
Sex (Male)		−0.266 (0.195)	− 0.484 (0.024)
EDSS			0.170 (<0.001)
Observations	464	445	390
Adjusted R^2	0.157	0.150	0.212
F-statistic	87.288 (df = 1; 462)	27.030 (df = 3; 441)	27.114 (df = 4; 385)

Values represent regression coefficients with corresponding *p*-values in parentheses. EDSS, Expanded Disability Status Scale; PSQI, Pittsburgh Sleep Quality Index; FSS, Fatigue Severity Scale. Model 1 includes PSQI only; Model 2 adds age and sex; Model 3 adds EDSS. *p*-values < 0.05 are considered statistically significant and are marked in bold text.

The fully adjusted model (Model 3), incorporating EDSS, revealed two key findings: (1) the PSQI global score remained a robust independent predictor of fatigue (β = 0.151, $p < 0.001$), and (2) EDSS emerged as a significant contributor to fatigue severity (β = 0.170, $p < 0.001$). Notably, male sex exhibited an inverse relationship with fatigue in this final model (β = −0.484, $p = 0.024$), suggesting potential sex-specific moderators in fatigue etiology.

Three separate multiple regression models were conducted to examine whether individual PSQI components predicted HADS-A, HADS-D, and FSS while adjusting for age, sex, and EDSS. Across all three outcomes, daytime dysfunction (PSQI7) was the most consistent and robust predictor, significantly associated with higher scores on HADS-A (β = 1.990, $p < 0.001$), HADS-D (β = 2.220, $p < 0.001$), and FSS (β = 0.675, $p < 0.001$) (Table 7). Sleep disturbances (PSQI5) also showed significant associations with all three outcomes: HADS-A (β = 1.161, $p = 0.002$), HADS-D (β = 0.833, $p = 0.017$), and FSS (β = 0.426, $p = 0.003$). Similarly, use of sleep medication (PSQI6) was a significant predictor of HADS-A (β = 0.658, $p = 0.001$), HADS-D (β = 0.668, $p = 0.001$), and FSS (β = 0.169, $p = 0.035$).

Other components such as subjective sleep quality (PSQI1) and sleep duration (PSQI3) were not significantly associated with any of the HADS-A, HADS-D, and FSS ($p > 0.05$), except for a marginal association between PSQI1 and HADS-D (β = 0.487, $p = 0.081$). Among demographic covariates, age was significantly associated only with HADS-D (β = 0.036, $p = 0.044$), while no significant associations were observed for HADS-A (β = −0.015, $p = 0.414$) or FSS (β = 0.010, $p = 0.163$). Sex emerged as a borderline-significant predictor of FSS (β = −0.388, $p = 0.057$), suggesting lower FSS scores among males, while demonstrating no predictive utility for HADS-A (β= −0.792, $p = 0.130$) or HADS-D (β = 0.287, $p = 0.561$) in fully adjusted models. EDSS was a significant predictor of HADS-D scores (β = 0.383, $p < 0.001$) and FSS (β = 0.161, $p < 0.001$), but not HADS-A (β = 0.101, $p = 0.302$). The final models explained 37.2% of the variance in HADS-A, 42.7% in HADS-D, and 32.6% in FSS (Table 7).

Table 7. Multiple regression models analyzing PSQI subscales as predictors of HADS-A, HADS-D, and FSS and covariates.

Predictor Variables	Dependent Variable		
	HADS-A	HADS-D	FSS
PSQI1 (Subjective quality)	0.545 (0.066)	0.487 (0.081)	0.129 (0.267)
PSQI2 (Sleep latency)	0.064 (0.775)	0.026 (0.903)	0.003 (0.969)
PSQI3 (Sleep duration)	0.106 (0.715)	−0.353 (0.198)	−0.140 (0.218)
PSQI4 (Sleep efficiency)	0.044 (0.845)	0.256 (0.228)	0.067 (0.445)
PSQI5 (Sleep disturbances)	1.161 (0.002)	0.833 (0.017)	0.426 (0.003)
PSQI6 (Use of sleep medications)	0.658 (0.001)	0.668 (0.001)	0.169 (0.035)
PSQI7 (Daytime dysfunction)	1.990 (<0.001)	2.220 (<0.001)	0.675 (<0.001)
Age	−0.015 (0.414)	0.036 (0.044)	0.010 (0.163)
Sex (Male)	−0.792 (0.130)	0.287 (0.561)	−0.388 (0.057)
EDSS	0.101 (0.302)	0.383 (<0.001)	0.161 (<0.001)
Observations	373	373	377
Adjusted R^2	0.372	0.427	0.326
F-statistic	23.081 (df = 10; 362)	28.726 (df = 10; 362)	19.183 (df = 10; 366)

Values represent regression coefficients with corresponding *p*-values in parentheses. All models are adjusted for age, sex, and EDSS. *p*-values < 0.05 are considered statistically significant and are marked in bold text. EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; HADS-A, Hospital Anxiety and Depression Scale (anxiety subscale); HADS-D, Hospital Anxiety and Depression Scale (depression subscale); PSQI, Pittsburgh Sleep Quality Index.

4. Discussion

The present study confirms that MS subjects experience significantly higher levels of fatigue, depressive symptoms, and poor sleep quality compared to control subjects, while anxiety levels do not differ significantly between groups. These results are consistent with previous research highlighting the high prevalence of non-motor symptoms in MS, such as depression, anxiety, fatigue, and sleep disturbances, which often co-occur and exacerbate the overall impact of the MS [3,16–19,21,27,50].

The study demonstrated robust intercorrelations between FSS, HADS-D, and PSQI global scores, and a positive association of FSS, HADS-D, and PSQI with EDSS severity. However, the correlations between EDSS and FSS, HADS-D, and PSQI were generally weak, which is in line with prior findings [19,27–29], suggesting that the EDSS, while widely used, inadequately captures the full spectrum of non-motor MS symptomatology [2,6,11,16,25–30].

Sleep quality and depression showed progressive worsening with higher EDSS severity scores, while fatigue reached its highest levels in MS subjects with moderate EDSS severity (EDSS 4.5–6.5). Anxiety levels remained consistent across all severity strata (EDSS $\leq$ 4; EDSS 4.5–6.5; EDSS $\geq$ 7), a finding that aligns with previous findings [19,51,52] and underscores the heterogeneity of anxiety symptoms in MS, as well as their potentially distinct etiological mechanisms compared to depression and fatigue [50].

The novel finding of the present study relates to sleep quality (PSQI global), found to be a robust predictor of fatigue (FSS), anxiety (HADS-A), and depression (HADS-D),

even after controlling for age, sex, and disability status (EDSS). Among PSQI components, daytime dysfunction, sleep disturbances, and use of sleep medication were the most robust and consistent predictors of fatigue (FSS), depression (HADS-D), and anxiety (HADS-A) in our MS sample. These results additionally contribute to the understanding of the complex association of sleep quality with depression, anxiety, and fatigue [18,19,21,27,29]. Compared to our present study findings, previous studies reported findings on the following: (a) correlations between poor sleep, anxiety, and fatigue [19]; (b) psychometric properties of PSQI on MS samples [39]; and (c) sleep disturbances forming a unique impact on quality of life [18]. In contrast to our findings, Ozdogar et al. [19] used the version of PSQI previously not validated on the MS sample and reported on 52 MS subgroups that anxiety was significantly higher in the poor sleep quality group, with no significant differences observed for fatigue or depression. In the present study, however, we used the PSQI version previously validated on MS sample [39], and in contrast to Ozdogar et al. [19], both fatigue and depression were found to be significantly elevated among MS subjects with poorer sleep quality. Additionally, our study findings detected specific PSQI components strongly predicting depression, anxiety, and fatigue in MS, independent of EDSS score. Furthermore, Laslett et al. [18] investigated sleep quality in MS using the global PSQI score as well as applying a previously non-validated PSQI scale on the MS sample [32], and demonstrating that poorer sleep independently predicts reduced quality of life, even after accounting for symptoms such as depression and fatigue. In contrast, the present study investigated sleep quality by accounting for all PSQI components in predicting the severity of non-motor symptoms (fatigue, depression, and anxiety), while controlling disability status (EDSS). The current findings suggest that daytime dysfunction was the best predictor of fatigue, while sleep disturbances were more closely linked to anxiety. Additionally, certain aspects of sleep quality, such as the use of sleep medication, were significantly associated with the severity of depressive symptoms in MS.

Therefore, our findings further highlight that sleep problems (daytime dysfunction, sleep disturbances, and use of sleep medication) not only co-occur with depression, anxiety, and fatigue but also significantly predict their severity in MS. This underscores the clinical importance of granular, component-level sleep assessment and integrated psychological interventions to effectively address the complex interplay between sleep and non-motor symptoms in MS.

The limitations of this study should be acknowledged. The cross-sectional design precludes any inference of causality between disability status, depression, anxiety, fatigue, and sleep quality. To clarify the directionality, temporal dynamics, and complex interplay of MS disability and co-occurring non-motor symptoms, future longitudinal studies might employ objective sleep measures [19,29] and cognitive evaluation, in addition to standardized EDSS disability scoring, and validated instruments for assessing depression, anxiety, sleep quality, and fatigue in MS subjects.

Overall, the present study provide findings on: (a) moderate to strong intercorrelation between FSS, HADS-D, HADS-A and PSQI, (b) positive association of FSS, HADS-D, and PSQI with EDSS severity, (c) a steady increase in PSQI global and HADS-D scores with higher EDSS severity, (d) a pronounced elevation of FSS scores at moderate EDSS severity (EDSS 4.5–6.5), (e) generally weak correlation between EDSS and FSS, HADS-D, HADS-A and PSQI, (f) EDSS as significant predictor of HADS-D and FSS scores, (g) global PSQI score as independent predictor of FSS and HADS-D, and HADS-A, and (h) daytime dysfunction, sleep disturbances, and sleep medication use as significantly predictors of FSS, HADS-D, and HADS-A.

5. Conclusions

The present study demonstrates an interrelation among PSQI, FSS, and HADS-D scores, with a progressive increase in these scores observed at higher EDSS severity levels, confirming a significant association between disability status (EDSS) and non-motor symptoms (fatigue, depression, and sleep quality) in the MS sample. Daytime dysfunction, sleep disturbances, and sleep medication use were identified as consistent and robust predictors of depression, anxiety, and fatigue, independent of demographic factors and EDSS. In the end, the present study findings clarify the complex interplay between MS disease disability and non-motor symptomatology, highlighting the role of sleep quality in exacerbating depression, anxiety, and fatigue in MS.

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Abbreviations

The following abbreviations are used in this manuscript:

AMSSC	Association of Multiple Sclerosis Societies of Croatia
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
EDSS	Expanded Disability Status Scale
FS	Functional Score
FSS	Fatigue Severity Scale
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale (anxiety subscale)
HADS-D	Hospital Anxiety and Depression Scale (depression subscale)

MS	Multiple Sclerosis
PSQI	Pittsburgh Sleep Quality Index

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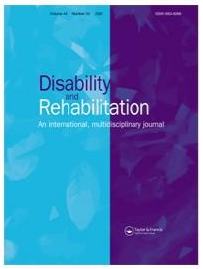

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ORIGINAL ARTICLE

Psychometric properties of the Croatian version of the Multiple Sclerosis Walking Scale (MSWS-12)

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ABSTRACT

Purpose: Walking difficulties in people with multiple sclerosis (pwMS) are one of the most pronounced predictors affecting patients' quality of life. The study objective was to determine the psychometric properties of the Croatian version of the Multiple Sclerosis Walking Scale (MSWS-12) among pwMS in Croatia and to examine the association between MSWS-12 and Depression, Anxiety, and Stress Scale-21 (DASS-21), and Multiple Sclerosis Impact Scale-29 (MSIS-29).

Materials and methods: A cross-sectional study included a sample of pwMS ($N = 148$). Psychometric properties were examined by estimating the validity and reliability of the MSWS-12. The predictive validity of MSWS-12 and demographic and disease-related factors were assessed by a hierarchical regression model using MSIS-29 and DASS-21 as criterion variables.

Results: Scale reliability was good for the MSWS-12 scale, expressed by Cronbach's alpha coefficient ($\alpha = 0.98$). Correlations between MSWS-12 and DASS-21 (0.20–0.27) and between MSWS-12 and MSIS-29 subscales (0.47–0.83) provided initial support for the convergent validity. Factor analysis demonstrated the unidimensional structure of the MSWS-12.

Conclusions: The Croatian version of the MSWS-12 is a reliable, valid, and clinically useful tool for assessing walking impairments in pwMS.

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Multiple sclerosis; Multiple Sclerosis Walking Scale-12; Depression; Anxiety; and Stress Scale-21; Multiple Sclerosis Impact Scale-29; psychometrics

➤ IMPLICATIONS FOR REHABILITATION

- Walking difficulties in people with multiple sclerosis (pwMS) are one of the most pronounced predictors affecting patients' quality of life.
- Multiple Sclerosis Walking Scale (MSWS-12) is a measure of the disease's impact on walking abilities from the patient's perspective.
- MSWS-12 is a reliable scale for assessing walking speed, endurance, and gait quality in multiple sclerosis and is validated in several languages (Korean, Italian, Brazilian, and Persian).
- The Croatian version of the MSWS-12 is a reliable, predictive, and valid tool for screening walking impairments in pwMS.

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system with a prevalence reaching two per 100 000 in Japan and 100 per 100 000 in Northern Europe and North America [1]. The main characteristic of MS is the inflammatory destruction of myelin which leads to the development of lesions (plaques) in the brain, spinal cord, or optic nerve. The clinical picture is characterized by muscle spasticity and weakness, fatigue, sensory impairments, and walking disability [2]. Among people with multiple sclerosis (pwMS), gait dysfunctions, and imbalance are prevalent, with 50–80% having slowed movements, delayed responses to postural changes, reduced gait speed, stability, and walking problems. Low physical activity levels affect everyday activities of pwMS and are one of the more pronounced predictors of quality of life [2].

Some of the commonly used measures for assessing gait in pwMS are the Expanded Disability Status Scale (EDSS) [3], the Timed 25-Foot Walk (T25FW) test [4], and the 12-item Multiple Sclerosis Walking Scale (MSWS-12) [5]. The EDSS and T25FW measures are used by physicians in evaluating the mobility of pwMS, while the MSWS-12 measures disease impact on walking abilities from the patient's perspective [5]. MSWS-12 is a reliable scale for assessing walking speed, endurance, and gait quality in MS [6–8] and is validated in several languages like Korean [9], Italian [10], Brazilian [11], and Persian [12]. Furthermore, the studies have shown strong correlations of the MSWS-12 scores with the T25FW test scores [8]. A correlation was also found between MSWS-12

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scores and spatial and temporal parameters of walking such as walking speed, cadence, step length, step time, the base of support, and percentage of the gait cycle spent in double support [8].

The purpose of the present study was to evaluate the psychometric properties of the Croatian version of the MSWS-12 (factor structure, validity, and reliability) in a sample of pwMS. The study compared the Croatian version of the MSWS-12 with published data on the psychometric properties of the MSWS-12 [8]. The predictive validity of MSWS-12 and demographic and disease-related factors were evaluated using the Multiple Sclerosis Impact Scale (MSIS-29) [13–16] and Depression, Anxiety, and Stress Scale-21 (DASS-21) [13,17–19] as criterion variables.

Patients and methods

Study design

A cross-sectional design was used to collect data related to the impact of MS on walking quality, demographic, and MS disease-related data. The study was conducted as an online survey.

Participants

We recruited 148 pwMS registered in the Association of Multiple Sclerosis Societies of Croatia (AMSSC) and the non-governmental association MS TIM Croatia. Patients who had psychiatric and all other neurological conditions other than MS were filtered and excluded from further analysis. All procedures performed in this study were conducted according to the local Ethics Committee (Class: 003-08/20-03/0005, No. 2181-198-03-04-20-0028) with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Before commencing with the online survey, participants were informed about the study details. Participation was voluntary and anonymous. Patients' demographic and disease characteristics are summarized in Table 1. Most pwMS were right-handed (95%) and with secondary education degrees (57%). The median EDSS score was 3 ± 4 (range, 0–9). Eighteen percent of patients suffered from other autoimmune conditions (i.e., psoriasis, asthma, rhinitis, etc.).

Sample size justification

A *post hoc* G power test was performed to determine if the sample size was adequate for multiple regression analysis. The results of the *post hoc* G power test showed that the estimated power was 0.87, which confirmed the adequacy of the study sample size [20].

Table 1. Demographic and disease characteristics of pwMS ($N = 148$).

	Value
Female/male (%)	87/13
Age (mean ± SD)	41.2 ± 11.4
Duration of the disease in years (mean ± SD)	8.0 ± 9.1
Type of MS (RRMS/SPMS/PPMS/PRMS) (%)	76/2/3/2
EDSS (0–4.5)/EDSS (5–9.5) (%)	78.4/21.6
Comorbid diseases (Y/N)	46/102
Immunomodulatory medication (Y/N)	77/71
Education (primary/secondary/undergraduate/graduate) (%)	2/58/16/24

SD: standard deviation; Y: yes; N: no; RRMS: relapsing-remitting MS; SPMS: secondary progressive MS; PPMS: primary-progressive MS; PRMS: progressive-relapsing MS.

Data collection and rationale

The participants filled out online questionnaires via the Google Survey from 1 March 2020 until 20 April 2020. Data collection before completing self-report scales included the following: demographic data (age, gender, handedness), educational level (primary school degree; secondary school degree; undergraduate degree; graduate degree); disease-related factors including: duration of the disease, classification of MS types RRMS, SPMS, PPMS, and PRMS; the EDSS score (0–10) (fully preserved mobility (0–4.5) or partially or fully impaired mobility (5–9.5), comorbidity, and immunomodulatory medication intake. Even though the PRMS form is not used since the year 2014 [21] in the classification of MS types, the PRMS type was retained in the analysis since three subjects with MS stated PRMS type.

Participants completed three self-report scales: MSWS-12 [5] scale for evaluating walking quality, the psychological scale DASS-21 [13,17–19] assessing depression, anxiety, and stress, and MSIS-29 [13,15,16] for capturing the psychological and physical impact of the MS disease.

The Multiple Sclerosis Walking Scale (MSWS-12)

The Multiple Sclerosis Walking Scale (MSWS-12) is a self-report scale that measures the impact of MS on walking quality [5]. It consists of 12 items/questions regarding the limitations to walking due to MS during the past two weeks. For each statement, the patient answered by circling the number that best describes his/her condition on a five-point Likert scale (1 = not at all, 2 = a little, 3 = moderately, 4 = quite a lot, and 5 = extremely). A total score can be generated and transformed to a 0–100 scale by subtracting the minimum score possible (12) from the patient's score, dividing by the maximum score possible (60) minus the minimum possible (12), and multiplying the result by 100. Walking improvement on the MSWS-12 is indicated by lower change scores. A higher score indicates a higher impact of MS on walking.

Depression, Anxiety, and Stress Scale-21

The DASS-21 is a self-report scale capturing depression, anxiety, and stress [17]. The DASS-21 is a set of three subscales (depression, anxiety, and stress) each containing seven items. The patient had to read each item and estimate the extent to which the content of the item related to him/her over the past week. Patient answers by circling the number on a four-point Likert scale (0 = did not apply to me at all, 1 = applied to me to some degree or some of the time, 2 = applied to me to a considerable degree or a good part of the time, and 3 = applied to me very much or most of the time). The sum of all items on each subscale yields a scale's score result verified with the cut-off scores for conventional severity labels (normal, moderate, severe, and extremely severe) on depression, anxiety, and stress subscale. The Croatian version of DASS-21 in pwMS was validated previously by the authors [13].

Multiple Sclerosis Impact Scale (MSIS-29)

The Multiple Sclerosis Impact Scale (MSIS-29) is a self-report scale capturing MS disease impact from a patient's physical and psychological perspective [14]. The scale is structured into two subscales, a 20-item scale for measuring physical impact and a nine-item scale for measuring the psychological impact of the disease. The "physical impact" subscale consists of items from 1 to 20. The subscale "psychological impact" consists of items from 21 to 29.

For each item, the patient had to estimate disease impact on his/her everyday life in the past two weeks and answer on a five-point Likert scale (1 = not at all, 2 = a little, 3 = moderately, 4 = quite a bit, and 5 = extremely). The patient's scores on two subscales generated by summing scores from individual items can be transformed to a scale of 0–100, with higher scores indicating a more severe disease burden. The Croatian version of the MSIS-29 in pwMS was validated previously by the authors [13].

Translation and cultural adaptation

For the purpose of translating the English version of the MSWS-12 to the Croatian language, the following guidelines were consulted: "Guidelines for translating and adapting psychological instruments" [22], and "Development, validation and translation of psychological tests for translating and validating instruments" [23].

The two authors of this study, natives of the Croatian language (NŠ, MNI), separately translated the MSWS-12 questionnaire from English to Croatian. Next, the English language professor (University of Zadar) compared both translated versions and produced the final version of the questionnaire. Another independent English language professor (University of Zadar) who had no insight into the original English version translated the last Croatian version of the questionnaire back into the English language, completing the final adaptation of the Croatian version of MSWS-12. The MSWS-12 translated into the Croatian language with the original version in English can be found in the Supplementary material.

Statistical analysis

The normality of each scale distribution was tested using parameters of skewness and kurtosis. Results indicated acceptable values for the parametric statistic. Group comparisons were carried out by *t*-tests and analysis of variance (ANOVA), depending on how many groups were compared. The *post hoc* Bonferroni test was also calculated. Correlation analyses were conducted using Pearson's *r* coefficient. Descriptive statistics of relevant patient characteristics and applied scales were summarized by *N*, percentage, mean and standard deviations. Psychometric properties were examined by estimating the validity, reliability, and factor structure of the MSWS-12 scale. To assess the dimensional structure of the MSWS, we conducted an exploratory factor analysis using the maximum-likelihood estimation method. The predictive validity of MSWS-12 and relevant disease-related factors was investigated by the hierarchical regression model using MSIS-29 subscales (physical and psychological) and DASS-21 subscales (depression, anxiety, and stress) as the criterion variables. Age, EDSS, type of MS, duration of the disease since diagnosis were entered into the first step, while MSWS-12 was added in the second step. In all analyses, a p value of <0.05 was considered statistically significant. Data analysis was performed using software Statistica 13.5.0.17 (TIBCO Software Inc., Palo Alto, CA).

Results

Psychometric properties of the MSWS-12

Internal consistency

The Cronbach α value for the MSWS-12 scale indicates high internal consistency ($\alpha = 0.98$) (Table 2). Average inter-item correlation for MSWS-12 was 0.82 while individual inter-item correlations are given in Table 3, and these values range from 0.71 to 0.94 (Table 3).

Table 2. Psychometric properties of the MSWS-12 scale, results for comparative MS study, and relevant correlation coefficients.

Psychometric properties	Values
Data quality	
Valid *N*	148
Scaling assumptions	
Mean scores	29.0
SD	15.4
Item total correlations	0.80–0.93
Acceptability	
Scale range (theoretical)	0–100
Score range	0–100
Mean score ± SD	35.4 ± 31.9
Skewness	0.67
Kurtosis	–0.83
Internal consistency reliability	
Cronbach's α	0.98
Correlations	
MSWS-12 and EDSS	0.44**
MSWS-12 and DASS-21 depression	0.27**
MSWS-12 and DASS-21 anxiety	0.25**
MSWS-12 and DASS-21 stress	0.20**
MSWS-12 and MSIS-29 physical impact	0.82**
MSWS-12 and MSIS-29 psychological impact	0.47**
Comparison to other study	
Mean score ± SD for MSWS-12 of Pilutti et al. [8]	39.5 ± 28.9
Comparison of MSWS-12 scores of our study with Pilutti et al. [8]	$t(146)=1.31$; $p = 0.17$

*$p < 0.05$.
**$p < 0.01$.

Factor structure

Factor analysis demonstrated the unidimensional structure of the MSWS-12 scale. Guttman-Kaiser's criterion is used to exclude factors with eigenvalue of less than 1. A single factor was extracted with eigenvalues of 9.7, explaining 81.2% of the total variance (Table 4). Moreover, factor loadings were all above the 0.30 cut-off criterion. In Table 4, factor loadings and each item translation are given.

Convergent and concurrent validity

Table 2 includes data on the MSWS-12 scale's psychometric properties, comparative MS value [8], and correlations among MSWS-12, MSIS-29, and DASS-21 scores. Convergent validity was demonstrated by the correlation of the DASS-21 and the MSIS-29 subscales with MSWS-12 (Table 2). Both MSIS-29 subscales are correlated with MSWS-12, noting that the correlations of MSWS-12 are higher with the physical impact on MSIS-29 ($r = 0.82$; $p < 0.01$) compared to moderate significant correlations with the psychological impact on MSIS-29 ($r = 0.48$; $p < 0.01$) (Table 2). MSWS-12 scale has low significant correlations with DASS-21 subscales (0.20–0.27).

Moreover, concurrent validity was demonstrated by comparing mean scores of the MSWS-12 scales to results (mean and standard deviation) of the published study (Table 2). No significant mean differences ($t(146)=1.31$, $p = 0.17$) were found between our MS sample and MS sample in the study of Pilutti et al. [8] (Table 2). Concurrent validity is also supported by the obtained correlation between the overall score on the MSWS-12 scale and the EDSS score ($r = 0.44$; $p < 0.01$).

Table 3. Inter-item correlations for MSWS-12 scale ($N = 148$).

MSWS item	MSWS 1	MSWS 2	MSWS 3	MSWS 4	MSWS 5	MSWS 6	MSWS 7	MSWS 8	MSWS 9	MSWS 10	MSWS 11	MSWS 12
MSWS 1	–	0.79	0.86	0.83	0.80	0.87	0.87	0.78	0.74	0.85	0.88	0.83
MSWS 2		–	0.78	0.76	0.73	0.76	0.76	0.62	0.62	0.78	0.80	0.74
MSWS 3			–	0.87	0.78	0.80	0.81	0.79	0.76	0.83	0.82	0.80
MSWS 4				–	0.85	0.86	0.87	0.79	0.74	0.82	0.81	0.78
MSWS 5					–	0.83	0.83	0.77	0.71	0.78	0.79	0.79
MSWS 6						–	0.94	0.78	0.76	0.87	0.86	0.81
MSWS 7							–	0.77	0.71	0.85	0.85	0.80
MSWS 8								–	0.90	0.82	0.83	0.81
MSWS 9									–	0.83	0.81	0.81
MSWS 10										–	0.94	0.87
MSWS 11											–	0.91
MSWS 12												–

All correlations are significant at $p < 0.001$.

Table 4. English and Croatian version of MSWS-12 items and factor loadings.

MSWS item		Factor 1
MSWS 1	Limited your ability to walk?	
	Ometala vašu sposobnost da hodate?	0.92
MSWS 2	Limited your ability to run?	
	Ometala vašu sposobnost da trčite?	0.81
MSWS 3	Limited your ability to climb up and down stairs?	
	Ometala vašu sposobnost da se penjete uz i silazite niz stepenice?	0.90
MSWS 4	Made standing when doing things more difficult?	
	Učinila stajanje za vrijeme obavljanja nekih radnji otežanim?	0.91
MSWS 5	Limited your balance when standing or walking?	
	Narušavala vašu ravnotežu tijekom stajanja i hodanja?	0.87
MSWS 6	Limited how far you are able to walk?	
	Ograničavala udaljenost koju ste mogli prehodati?	0.93
MSWS 7	Increased the effort needed for you to walk?	
	Povećala napor uložen u hodanje?	0.92
MSWS 8	Made it necessary for you to use support when walking indoors (e.g., holding on to furniture, using a stick, etc.)?	
	Trebali ste koristiti potporu prilikom kretanja u zatvorenom prostoru (npr. pridržavanje uz namještaj, upotreba štapa …)?	0.88
MSWS 9	Made it necessary for you to use support when walking outdoors (e.g., using a stick, a frame, etc.)?	
	Trebali ste koristiti potporu prilikom kretanja na otvorenom (npr. upotreba štapa, hodalice …)?	0.85
MSWS 10	Slowed down your walking?	
	Usporila vaše hodanje?	0.94
MSWS 11	Affected how smoothly you walk?	
	Utjecala na normalan hod?	0.95
MSWS 12	Made you concentrate on your walking?	
	Trebali ste se koncentrirati na hodanje?	0.90
Variance (%)		81.2

Multiple regression analysis

MSIS-29 subscales as a criterion variable

The results of hierarchical regression analysis are presented in Table 5. For the physical MSIS-29 subscale, the first set of predictors (age, EDSS, MS type, disease duration) explained 21% of the variance ($F(4/143)=11{,}09$; $p < 0.01$) where age and EDSS were significant. Both of these predictors have positive β, meaning that older people and those with higher EDSS scores report a higher impact of MS on physical health. In addition, introducing the MSWS-12 score in the second step significantly contributed ($F(5/142)=64.53$; $p < 0.01$) to explaining the variance of physical health (45%), thus achieving a total high amount of 67% of the explained variance of this criterion variable. For the psychological MSIS-29 subscale, the first set of predictors was not significant ($F(4/143)=1.36$; $p > 0.05$), but the MSWS-12 scores, included in a second step ($F(5/142)=11.36$; $p < 0.01$), explained 24% of the variance.

DASS-21 subscales as a criterion variable

For DASS-21 subscales as criterion variables, in the first step, age, EDSS, MS type, and disease duration were set up as predictor variables, and in the second step result on the MSWS-12 scale. For all three DASS-21 subscales (depression, anxiety, and stress), the first set of predictors was not significant ($F_{depression}(4/143)=1.26$, $p > 0.05$; $F_{anxiety}(4/143)=0.80$, $p > 0.05$; $F_{stress}(4/143)=0.82$, $p > 0.05$), while the result on the MSWS-12 scale in the second step explained 6% of the variance of depression ($F(5/142)=3.36$, $p < 0.01$), 10% of the variance of anxiety ($F(5/142)=4.58$, $p < 0.01$), and 5% of the variance of stress $F(5/142)=2.55$, $p < 0.05$) (Table 5).

Discussion

The present study aimed to examine the reliability and validity of the MSWS-12 in Croatian-speaking pwMS. This is the first report on translation and cross-cultural adaptation of the MSWS-12 into Croatian language. Psychometric properties of the MSWS-12 in our sample indicated that the scale had excellent internal consistency and good convergent and concurrent validity. The internal consistency of the MSWS-12 item scores (Cronbach's alpha coefficient ($\alpha = 0.98$) was in line with the previous findings reporting Cronbach's alpha coefficients of $\alpha = 0.98$ [9]; $\alpha = 0.97$ [8,10], $\alpha = 0.96$ [12]; $\alpha = 0.94$ [5,11]. Further, factor analysis demonstrated the unidimensional structure of the MSWS-12 scale, which is comparable to previously reported findings [5].

The MSWS-12 is a widely used patient-reported measure of walking ability in pwMS, which has its value in clinical neurological settings and clinical research trials [5,24]. Evidence from MS studies supports its robust measurement performance [25–27].

Table 5. Hierarchical regression analysis with DASS-21 and MSIS-29 scales as criterion variables.

		MSIS-29				DASS-21					
		Physical scale		Psychological scale		Depression		Anxiety		Stress	
		Step 1	Step 2	Step 1	Step 2	Step 1	Step 2	Step 1	Step 2	Step 1	Step 2
Predictors		β	β	β	β	β	β	β	β	β	β
Step 1	Age	0.35**	0.06	0.09	−0.12	−0.06	−0.16	−0.08	−0.22	−0.04	−0.13
	Time since diagnosis	−0.12	−0.08	−0.19	−0.16	−0.13	−0.12	0.16	−0.14	−0.16	−0.15
	Type MS	0.06	−0.06	−0.03	−0.11	0.11	0.07	0.01	−0.04	0.02	−0.01
	EDSS	0.23**	0.01	0.14	−0.05	0.15	0.06	0.12	0.00	0.11	0.02
	Adj. R^2	0.21**		0.01		0.02		0.01		0.00	
Step 2	MSWS-12		0.82**		0.59**		0.29**		0.38**		0.27**
	Adj. R^2		0.67**		0.25**		0.07**		0.11**		0.05**
	ΔR^2		0.45**		0.24**		0.06**		0.10**		0.05**

β: standardized regression coefficient; ΔR^2: change in the coefficient of determination; adjusted R^2: coefficient of determination adjusted for the number of predictors in the model.
*$p < 0.05$.
**$p < 0.01$.

The MSWS-12 is the only patient-based instrument specific for the measurement of different aspects of walking compared to the objective walking measures and has been suggested to be more responsive to changes in walking ability [24] than either the EDSS [3] or T25FW [4] measuring the walking speed in MS patients.

The present study provides additional support for the validity of the MSWS-12 as a self-report measure that captures psychological and physical health quality information for pwMS. Previously, the MSWS-12 score was associated with T25FW scores (i.e., walking speed) [5,7] and walking quality (assessed as spatio-temporal parameters of gait) [8]. The findings of present study emphasized evidence for convergent validity of the MSWS-12 scale that was demonstrated by the lower correlation between the MSWS-12 and DASS-21 in comparison to correlations between the MSWS-12 and MSIS-29 (Table 2). These results were somewhat expected since the DASS-21 scale measures only psychological constructs (depression, anxiety, and stress). On the other hand, the correlation between the MSWS-12 and MSIS-29 was stronger since MSIS-29 measures the psychological impact of the disease and the physical impact of the disease on the MS subject. The conducted hierarchical regression analysis indicates that the MSWS-12 scale contributes to the explanation of MSIS-29 and DASS-21 variance. This evidence suggests that the MSWS-12 scale is a clinical useful tool for predicting the impact of MS on physical and psychological health (MSIS-29) and somewhat less effective in predicting the levels of depression, anxiety, and stress (DASS-21).

There are a few study limitations to discuss. A possible limitation to this study is it was conducted online, and it was not possible to confirm the status of MS by the neurological examination report. Due to data protection, we could not request an official statement with the EDSS score given by the neurologist. This shortcoming did not affect the data since the questionnaires were sent officially to associations whose members are pwMS. Further, although the study covered a heterogeneous group of pwMS from all over Croatia, most participants had an RRMS and were females. Future studies could consider a more heterogeneous sample considering MS type and gender. The third limitation refers to the test–retest reliability, which was not conducted since the survey was conducted online, and due to data protection, we were not able to collect personal e-mail addresses for the second round filling of the MSWS-12 by the same MS participants.

Conclusions

In conclusion, MSWS-12 proved to be a valid and reliable scale for assessing walking abilities in pwMS. The present study's findings also point to the clinical usefulness of the MSWS-12 application with EDSS, MSIS-29, and DASS-21 for the assessment of disability level and impact of MS disease on physical and psychological functioning.

Ethical approval

Permission to undertake the work: All procedures performed in studies involving human participants were according to the Ethics Committee of School of Medicine University of Split (Class: 003-08/20-03/0005, No. 2181-198-03-04-20-0028) with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Disclosure statement

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Data availability statement

Due to the privacy of patients, the data can be obtained on request from the corresponding author.

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Original article

Validation of the fatigue severity scale in Croatian population of patients with multiple sclerosis disease: Factor structure, internal consistency, and correlates

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ABSTRACT

Background: Fatigue is a common symptom in people with multiple sclerosis (MS) and is evaluated and monitored with self-report questionnaires. The objective of this study was to determine the psychometric properties of the Croatian version of the Fatigue Severity Scale (FSS) in people with MS.

Material and methods: This is a retrospective cohort study conducted as an online survey from December 16, 2020, until January 13, 2021. A total of 179 people with MS and 999 control subjects completed FSS and self-administered questionnaires capturing information of demographic, education level, disease-related variables (duration of the disease, MS type, the expanded disability status scale (EDSS), and Multiple Sclerosis Impact Scale-29 (MSIS-29). Psychometric properties were examined by estimating the validity, reliability, and factor structure of the FSS scale in people with MS.

Results: The Croatian version of the FSS had excellent internal consistency (Cronbach's α value 0.93). Factor analysis demonstrated a unidimensional structure. The concurrent validity of the FSS appeared to be satisfactory due to the significant differences between people with MS and control subjects ($p < .05$). The correlations between FSS and MSIS-29 physical ($r = 0.60$) and psychological ($r = 0.50$) subscale results confirmed the convergent validity of the FSS scale. Results also indicated that the best cut-off score is between 4 and 5 with a relatively high sensitivity and specificity.

Conclusions: The Croatian version of FSS was shown to have excellent psychometric properties in people with MS and can be used in the research and clinical settings evaluating fatigue in people with MS in Croatia.

1. Introduction

Fatigue has often been defined as tiredness, lack of energy, and a feeling of physical, mental, and emotional exhaustion (Davis and Walsh, 2010). Fatigue is distinguished from symptoms of major depression (Corfield et al., 2016; Ormstad et al., 2020) and extremity weakness or an evident physical lack of strength (Krupp and Pollina, 1996; Capone et al., 2020). Fatigue is highly prevalent and detected in people with multiple sclerosis (MS), affecting their quality of life (Minden et al., 2006; Weiland et al., 2015; Manjali et al., 2019). In the last twenty years, the pathogenetic basis of fatigue has been evaluated in MS, pointing to the involvement of the cortico-subcortical pathway centered on the thalamus (Capone et al., 2020). While this mechanism has been suggested as a possible cause of MS-related fatigue, it is worth considering the multifactorial nature of fatigue and other possible influencing factors (e.g., depression, inflammation) (Langeskov-Christensen et al., 2017; Penner I.K, and Friedemann Paul, F. (2017).

According to the Multiple Sclerosis International Federation (MSIF) (Director et al., 2012), two types of fatigue are distinguished, physical (motor) fatigue, characterized by muscle weakness and difficulties to perform daily tasks, and cognitive fatigue, characterized by difficulties in thinking, concentration, and memory. The prevalence of fatigue

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ranges from 76% to 92% in people with MS (Minden et al., 2006; Weiland et al., 2015; Krupp et al., 1988; Brañas et al., 2000;Rooney, Wood, Moffat, and Paul, 2019). Various screening instruments have been used to evaluate fatigue in clinical and non-clinical populations of people with MS, including the self-report scales such as the Fatigue Severity Scale (FSS) (Krupp et al., 1989; Lerdal et al., 2007; Hjollund et al., 2007; Ferentinos et al., 2011; Rosti-Otajärvi et al., 2017; Gavrilov et al., 2018), Modified Fatigue Impact Scale (MFIS) (MS Council, 1998), and Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner, Raselli, Stöcklin, Opwis, Kappos, and Calabrese, 2009). The FSS is the most frequently used questionnaire for evaluating fatigue developed by Krupp et al. (1989) for the use in patients with MS and patients with systemic lupus erythematosus. The FSS, a nine-item questionnaire, primarily focuses on the motor aspects of fatigue, the main emphasis being the assessment of the fatigue severity and impact on the patients daily living and monitoring fatigue evaluation during the time. The FSS is, therefore, a unidimensional instrument, compared to multidimensional questionnaires such as the MFIS (MS Council, 1998) assessing fatigue impact on motor, cognitive and psychosocial performance, and the FSMC (Penner, Raselli, Stöcklin, Opwis, Kappos, and Calabrese, 2009) assessing the impact of fatigue symptoms on daily functioning with respect to the motor and cognitive aspects. The FSS has been so far validated other than English (Krupp et al., 1988; Krupp et al., 1989), on Turkish (Armutlu et al., 2007), Swiss (Valko et al., 2008), Persian (Azimian et al., 2009), Arabic (Al-Sobayel et al., 2016), Finish (Rosti-Otajärvi et al., 2017) and Russian (Gavrilov et al., 2018), reporting high internal consistency of FSS (Cronbach α of 0.89 to 0.96) (Rosti-Otajärvi et al., 2017; Amtmann et al., 2012; Bakalidou et al., 2014; Behrangrad and Yoosefinejad, 2021).

2. Study goals and hypotheses

Given the importance of fatigue in people with MS for understanding patient health and safety, this study had two goals. The first goal was to examine the psychometric properties of a Croatian version of the FSS. Psychometric properties were examined by estimating the validity, reliability, and factor structure of the FSS scale in people with MS. The second goal was to explore associations of the FSS with a set of predictor variables among people with MS and control subjects. The FSS scores in people with MS in Croatia were compared with a non-clinical population (control subjects) and published data on FSS validation in people with MS (Valko et al., 2008; Gavrilov et al., 2018). The convergent validity of FSS was investigated using the Multiple Sclerosis Impact Scale (MSIS-29) (Hobart et al., 2001), the most used outcome measure in the clinical settings assessing the physical and psychological impact of MS disease from a patient perspective (McGuigan and Hutchinson, 2004; Glaser et al., 2019).

3. Material and methods

3.1. Participants

The people with MS were recruited by advertising through the Association of Multiple Sclerosis Societies of Croatia (AMSSC) and non-governmental MS associations and various groups on Facebook, WhatsApp, and Viber applications. The control subjects were recruited by using the snowball method. Persons who did not have MS and had psychiatric and neurological diseases and belonged to the control group were filtered and excluded from further analysis. A total of 179 people with MS and 999 control subjects participated in the study.

The demographic factors, education level, and disease-related factors for people with MS and control subjects are presented in Table 1. In the group of people with MS, 84% were female with a mean age of 41.3 ± 11.5 years, and 16% were men with a mean age of 42.7 ± 9.9 years. Most people with MS were righthanded (92.7%) and between 35 and 49 years old (49%). Most of the MS participants had high school degrees (49.1%) and graduate university degrees (23.5%). Most of the MS subjects were diagnosed with MS disease between 0 and 5 years (41.4%), 26.7% of people with MS were diagnosed between 6 and 11 years, and 31.8% reported over 11 years of MS diagnosis. The mean duration of the disease for all people with MS was 8.7 ± 7.2. According to Lubling et al. (2014) classification of MS types, a majority of the subjects declared to have relapsing-remitting MS (RRMS) (70.4%), while others reported having secondary progressive MS (SPMS) (7.8%), and primary progressive MS (PPMS) (10.6%). Certain people with MS (11.2%) did not provide information on the type of MS. People with MS entered EDSS score if it was known to them according to the clinical neurological assessment. Overall, 53.5% of participants with MS did not provide information on the EDSS. The median EDSS score for people with MS that provided information was 3.5 ± 3.5. Of 179 people with MS, 51.8% had comorbidities, including endocrine, nutritional, and metabolic diseases (9.9%) and diseases of the circulatory system (7.8%).

Table 1
Characteristics of study participants.

	Control subjects (N = 999)	People with MS (N = 179)
Age in years (mean±SD)	39.9 ± 10.2,	41.6 ± 11.3,
Age (range)	20–74	19–75
Sex		
Female (mean±SD)	39.8 ± 10.3	41.3 ± 11.5
Male (mean±SD)	40.3 ± 10.1	42.7 ± 9.9
MS type (%)		
RRMS		70.4%
SPMS		7.8%
PPMS		10.6%
Not known		11.2%
Years of MS disease (mean±SD)		8.7 ± 7.2
EDSS (median±IQR, range)		3.5 ± 3.5 0–9
Self-report scales (mean±SD)		
FSS	3.7 ± 1.4	5.1 ± 1.3
MSIS-29 PHYS		46.6 ± 17.2
MSIS-29 PSY		24.3 ± 8.8

Abbreviations: SD - standard deviation; IQR – interquartile range; EDSS - Expanded Disability Status Scale; RRMS- relapsing-remitting multiple sclerosis; SPMS-secondary progressive multiple sclerosis; PPMS- primary progressive multiple sclerosis; MSIS-29 PHYS- Physical subscale; MSIS-29 PSY- Psychological subscale.

In the control group, 81% of participants were women with a mean age of 39.8 ± 10.3 years, and 19 percent (19%) were men with a mean age of 40.3 ± 10.1 years. Most of the control subjects were righthanded (93.4%) and between 35 and 49 years old (51%), and most of them had graduate university degrees (43.7%) and high school degrees (25.6%). Of 999 control subjects, 27.6% had comorbidities, of which the most common were endocrine, nutritional, and metabolic diseases (8.2%) and diseases of the circulatory system (5.2%).

The data were collected via a Google Forms survey from December 16, 2020, until January 13, 2021. All procedures performed in studies involving human participants were in accordance with the ethical standards of The Ethics Committee of the University of Split School of Medicine, Class: 003–08/20–03/0005, No. 2181–198–03–04–20–0028 and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Before commencing with the survey, participants were informed about the study details. Participation was voluntary and anonymous.

3.2. Demographic information and disease-related variables

The participants were characterized by:

a) demographic information: age (younger 19–34 years, middle 35–45 years, older 35–75 years), sex, handedness;

b) educational level (primary school degree, secondary school degree, professional degree, undergraduate university degree, specialist graduate professional degree, graduate university degree, postgraduate specialization degree, postgraduate doctoral degree);
c) disease-related factors including duration of the disease since diagnosis; classification of MS according to MS types defined by Lublin et al. (2014): relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and primary progressive multiple sclerosis (PPMS); and the Expanded Disability Status Scale (EDSS) score (McDonald et al., 2001).

3.3. Questionnaires

3.3.1. Fatigue severity scale (FSS)

The Fatigue Severity Scale (FSS) (Krupp et al., 1988) is a 9-item self-report questionnaire used to assess fatigue during the past week in people with MS. The grading for each item ranges from 1 to 7, with 7 indicating strong agreement and 1 indicating complete disagreement. The scoring is calculated by adding up all the answers and dividing them by nine (average value). A cut-off score of $\geq$4 and $\geq$5 for clinically relevant fatigue was used (Lerdal et al., 2007; Armutlu et al., 2007; Valko et al., 2008).

3.3.2. Multiple sclerosis impact Scale- 29 (MSIS-29)

The Multiple Sclerosis Impact Scale (MSIS-29) is a self-report scale capturing MS disease's impact from a patient's physical and psychological perspective (Hobart et al., 2001). The scale is structured into two subscales, a 20-item scale for measuring physical impact (MSIS-29 PHYS) and a 9-item scale for measuring the psychological impact (MSIS-29 PSY) of the disease. The MSIS-29 PHYS subscale consists of items from 1 to 20. The MSIS-29 PSY consists of items from 21 to 29. The subject with MS is instructed to read each statement about the impact of MS disease on his/her everyday life in the past two weeks. For each statement, the subject's task is to circle the number that best describes his/her condition and answer on a five-point Likert scale (1 = not at all, 2 = a little, 3 = moderately, 4 = quite a bit, and 5 = extremely). The Croatian version of the MSIS-29 scale was used (Rogić Vidaković et al., 2021).

3.4. Translation and cultural adaptation

We have translated FSS following existing recommendations, methodological approaches, and guidelines in the process of translating, adapting, and cross-validating instruments (Sousa and Rojjanasrirat, 2011). One author of this study (MRV), and one independent Professor of Croatian language (Professor Daria Matijević), both natives in the Croatian language, translated the FSS questionnaire from English to Croatian. Next, the English language professor (DB) compared both translated versions of FSS in the Croatian language and produced the final version of the questionnaires. Another independent English language professor (University of Split) who had no insight into the original English version translated the last Croatian version of the questionnaires back into the English language, completing the final adaptation of the Croatian version of FSS used in this study (Appendix A. Supplementary material).

3.5. Validation procedure

Internal consistency of the FSS scale was estimated by Cronbach's alpha coefficients and inter-item correlations. Exploratory factor analysis was performed in people with MS to explore the dimensional structure of the FSS scale. Convergent validity was demonstrated by the correlation between FSS and MSIS-29 subscales. Concurrent validity was evaluated with comparisons of FSS scores between people with MS and control subjects. Furthermore, comparisons were also provided between published data on psychometric properties of the FSS (Valko et al., 2008; Gavrilov et al., 2018). Valko et al. (2008) included 188 people with MS in Switzerland (67% female; mean age 45 ± 13 years), while Gavrilov et al. (2018) included 85 people with MS (53% female; mean age 37.6 ± 10.2 years). Psychometric properties of FSS were compared in the whole sample of participants estimating the receiver operating characteristics (ROC) curve and the area under the curve (AUC) relative to the different possible cut-off scores.

3.6. Statistical analyses

Parameters of skewness and kurtosis were tested for FSS and MSIS-29 scales. Parameters indicated acceptable values for the parametric statistic. Mean value comparisons between our study and other studies using the FSS scale (18,20) in people with MS and differences between relevant disease-related variables were carried using *t*-tests, Chi-square test, and variance analysis (*ANOVA*). The post hoc Bonferroni test was also calculated when using multiple comparisons. Levene's test was used to assess the equality of variances between groups. Correlation analyses were conducted using Pearson's *r* coefficient and Spearman rank-order correlation (ρ). Descriptive statistics of relevant participants' characteristics and applied scales were summarized by *N*, percentage, mean and standard deviations, median and interquartile range. Psychometric properties were examined by estimating the factor structure, validity, and reliability of the FSS. A principal factor analysis (comm.=multiple R-square) was used to evaluate the dimensional structure of FSS. In all calculations, a *p*-value of <0.05 was considered statistically significant. Data analysis was performed using the software Statistica 12.

4. Results

4.1. Overview results

The demographic characteristics and disease-related variables of people with MS and control subjects are summarized in Table 1. No significant sex (χ^2=0.05, $p = .82$, $p > .05$) and age (t=−4.84, df=1390, $p > .05$) differences were found between people with MS and control subjects. The scores on FSS (t=−2.38, df=177, $p < .05$) varied significantly by MS type in people with MS. People with RRMS type (mean±sd=4.97 ± 1.37) reported less fatigue on FSS scale than people with SPMS (mean±sd=5.84 ± 0.87) and PPMS (mean±sd=5.82 ± 0.95). Further, in people with MS, significant differences were found between different age groups for FSS ($F = 29.5$; $p < .001$). Post hoc results suggest an increase in fatigue in older people with MS than younger and middle-aged ($p_{\text{younger vs.older}}<0.001$; $p_{\text{midle age vs.older}}<0.001$). In people with MS, no significant difference was found in FSS score in regard to sex ($t = 0.33$, df=177, $p > .05$).

4.2. Psychometric properties of the FSS

4.2.1. Factor analysis and internal consistency

Factor analysis demonstrated the unidimensional structure of the FSS scale. Guttman-Kaiser's criterion was used to exclude factors with an eigenvalue of less than 1. A single factor was extracted whit eigenvalues of 5.02, explaining 55.7% of the total variance (Table 2). Moreover, factor loadings were all above the 0.30 cut-off criterion. In Table 2, factor loadings and each item translation are given. Expressed by Cronbach's α coefficients, FSS scale ($\alpha = 0.91$) and MSIS-29 subscales ($\alpha_{\text{MSIS-PHYS}} = 0.82$; $\alpha_{\text{MSIS-PSY}} = 0.81$) had excellent internal consistency. Inter-item correlations for FSS and MSIS-29 subscales were >0.3, meaning that all items on each scale correlate very well with the scale overall.

4.2.2. Convergent validity

Convergent validity was demonstrated by the correlations of the FSS scale and the MSIS-29 subscales in people with MS. Results showed a significant moderate correlation of the FSS scale with MSIS-29 physical

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Table 2
The English and the Croatian version of FSS items and factor loadings (N = 1178).

FSS item		Factor 1
FSS1	My motivation is lower when I am fatigued.	
	Motivacija mi je niža kad sam umoran/a.	0.41
FSS2	Exercise brings on my fatigue.	
	Vježba mi izaziva umor.	0.37
FSS3	I am easily fatigued.	
	Lako se umorim.	0.66
FSS4	Fatigue interferes with my physical functioning.	
	Umor ometa moje fizičko funkcioniranje.	0.75
FSS5	Fatigue causes frequent problems for me.	
	Umor mi često stvara probleme.	0.86
FSS6	My fatigue prevents sustained physical functioning.	
	Umor me sprječava u kontinuiranom fizičkom radu.	0.87
FSS7	Fatigue interferes with carrying out certain duties and responsibilities.	
	Umor me ometa u obavljanju određenih dužnosti i odgovornosti.	0.85
FSS8	Fatigue is among my most disabling symptoms.	
	Umor je jedan od simptoma koji me najviše onesposobljavaju.	0.84
FSS9	Fatigue interferes with my work, family, or social life.	
	Umor ometa moj rad, obiteljski ili društveni život.	0.86
Variance (%)		55.7

($r = 0.60, p < .01$) and psychological ($r = 0.50, p < .01$) subscale. The convergent validity of the FSS is supported by a significant correlation with EDSS ($\rho = 0.34$; $p < .05$), which indicates that fatigue severity is more pronounced in people with a higher EDSS score. No significant correlations were found between FSS and the duration of the disease ($r = 0.21$; $p > .05$) and FSS and age ($r = 0.13$; $p > .05$).

4.2.3. Concurrent validity

The FSS efficiently discriminated people with MS from the control subjects. The FSS mean values obtained in the present study for people with MS are significantly higher (t=−12.6, df=1175, $p < .001$; Levene's $F = 0.43$; $p < .05$) than those reported in control subjects (Fig. 1). Moreover, when using the FSS cut-off score of ≥4, 81.6% of people with MS have more expressed fatigue compared to 42.1% in the control subjects. When using a cut-off point of ≥5, 56.4% of people with MS scored five or higher on FSS compared to 21.0% in the control subjects.

Furthermore, the mean scores of the FSS from the present study were compared to the results of Valko et al. (2008)(20) and Gavrilov et al. (2018)(18) (Table 3). The FSS score was significantly higher in the present sample of MS subjects than in people with MS reported by Valko et al. (2008) ($t = 2.91, p < .01$) and Gavrilov et al. (2018) ($t = 5.05, p < .01$).

The results of the ROC curve are reported in Table 4. They show that the best cut-off score is between 4 and 5, with relatively high sensitivity and specificity. Youden index (a commonly used measure of overall diagnostic effectiveness which occurs at the cut-point that optimizes the marker's differentiating) was 0.4277, associated with the criterion of 4.257 (sensitivity 76.02, specificity 66.75) and the highest and statistically significant AUC (area under ROC curve; 0.785; $p < .001$).

Table 3
The FSS results from the present study and comparisons between published studies.

Comparisons between studies		FSS	Age (years)	EDSS	Years of MS
Current study	Mean	5.12	41.3 ±	3.4 ±	8.7 ±
N = 179 / 84% Female	(SD)	(1.38)	11.5	2.8	7.2
Valko et al. (2008) N =	Mean	4.66	45.0 ±	3.6 ±	11.1 ±
188 / 67% Female	(SD)	(1.64)	13.0	2.3	9.8
	t	2.91			
	df	365			
	p	<0.01			
Gavrilov et al. (2018)	Mean	4.1	37.6 ±	2.9 ±	
N = 85 / 53% Female	(SD)	(1.6)	10.2	1.6	
	t	5.05			
	df	262			
	p	<0.01			

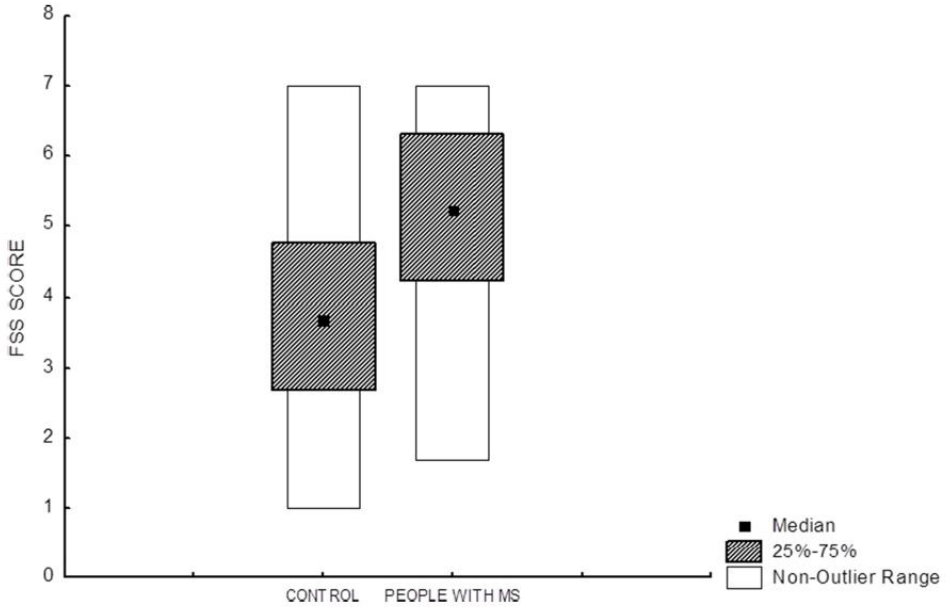

Fig. 1. Boxplots of FSS scores in people with MS and control subjects.

Table 4
Psychometric properties of the FSS at different cut-off scores.

FFS scores	Sensitivity	Specificity	+LR	-LR
1	99.76	2.83	1.03	0.08
2	98.28	12.66	1.13	0.08
3	95.28	31.05	1.38	0.15
4	82.39	58.73	2.00	0.30
5	55.35	82.31	3.13	0.54
6	27.36	95.68	6.33	0.76
7	7.23	99.37	11.50	0.93

+LR likelihood ratio for a positive result, -LR likelihood ratio for a negative result.

5. Discussion

The present study examined the psychometric properties of the FSS in a Croatian sample of people with MS, revealing sufficient validity and reliability evidence (Valko et al., 2008; Gavrilov et al., 2018; Azimian et al., 2009; Behrangrad and Yoosefinejad, 2021; Mills et al., 2009). The fatigue was slightly pronounced in people with MS in the present study compared to Valko et al. (2008) and Gavrilov et al. (2018), which might be related to a higher percentage of female participants with MS in our sample or due to other psychological measures like depression, anxiety, stress, or sleeping quality, which were not evaluated in the present study (Broch et al., 2021). Even though in our study we did not provide the differences in the fatigue between male and female MS subjects, similar as other authors (Rosti-Otajärvi et al., 2017), the larger studies investigating the prevalence of fatigue in people with MS are reporting higher prevalence of fatigue in female MS subjects compared to men MS subjects (Broch et al., 2021). Broch et al. (2021) showed that fatigue is associated with female sex and level of disability, as well as with anxiety, depression, and excessive daytime sleepiness.The present study confirms the findings from published studies on FSS validation in people with MS compared to fatigue levels in control subjects (Armutlu et al., 2007; Valko et al., 2008; Gavrilov et al., 2018; Behrangrad and Yoosefinejad, 2021). The FSS score for people with MS was higher than for control subjects, indicating more pronounced fatigue associated with MS disease (Krupp and Pollina, 1996; Brañas et al., 2000; Minden et al., 2006; Armutlu et al., 2007; Lerdal et al., 2007; Valko et al., 2008; Weiland et al., 2015; Gavrilov et al., 2018). Since the FSS predominantly evaluates the fatigue severity based on the impact of fatigue on physical (motor) function, perhaps these scores may be influenced by the impaired physical function pronounced in people with MS (Hobart et al., 2013).

The FSS scores exhibited moderate correlations with physical and psychological MSIS-29 subscales, which is in line with reported findings (Wood et al., 2013;Rooney, Wood, Moffat, and Paul, 2019). Correlations between FSS and MSIS-29 scales indicate that fatigue is associated with higher levels of disease impact from a physical and psychological perspective which provides evidence for convergent validity of the FSS. In line with reported findings (Flachenecker et al., 2002; Pittion--Vouyovitch et al., 2006; Valko et al., 2008; Mills et al., 2009), FSS score correlated with the degree of physical disability (EDSS score) but not with age and duration of the disease.

Further, the present study confirmed the one-dimensionality of the FSS as demonstrated by previous findings (Lerdal et al., 2007; Ferentinos et al., 2011; Amtmann et al., 2012; Rosti-Otajärvi et al., 2017; Gavrilov et al., 2018; Behrangrad and Yoosefinejad, 2021). The percentage of the total variance of the FSS scale is comparable to prior results (Lerdal et al., 2007; Gavrilov et al., 2018).

Further, since the original FSS from Krupp et al. (1989) did not have clear cut-off values or grading of fatigue severity, we have calculated the receiver operating characteristics (ROC) curve and the area under the curve (AUC) relatively to the different possible cut-off scores for FSS. The results indicated that the best cut-off score is between 4 and 5, with relatively high sensitivity and specificity.

The present study has limitations that need to be considered. A possible limitation would be the time of conducting the survey. Namely, the study was conducted during the COVID-19 pandemic and series of earthquakes that hit Croatia. However, we assume that COVID-19 and the earthquakes did not significantly affect the FSS scores in people with MS. A comparison with previous studies (Rooney et al., 2019; Smedal et al., 2011) shows similarities in the prevalence of anxiety, stress, and fatigue in the MS population independently of external factors not related to MS. The second limitation of the study was that it was conducted online, and it was not possible to confirm the status of MS by the neurological examination report. Due to data protection, we were not able to request an official report, with EDSS score given by the neurologist. We believe that this shortcoming did not affect the data since the questionnaires were sent officially to associations whose members are people with MS. Only a few subjects did not suffer from MS, and their data were initially filtered and excluded from further analysis.

To summarize the significance, the validated FSS on the Croatian population of people with MS will primarily serve the clinical practice and the research as the diagnostic instrument for assessing the fatigue severity and impact and monitoring fatigue evolution over time. The present study's findings also point to the clinical usefulness of the FFS use with the MSIS-29 as the self-report scales for monitoring the fatigue severity and impact on the physical and psychological functioning of the MS patient.

6. Conclusion

The Croatian FSS represents a psychometrically sound unidimensional measure of fatigue in people with MS. Collectively, the previous studies (Krupp et al., 1988; Krupp et al., 1989; Rosti-Otajärvi et al., 2017; Gavrilov et al., 2018; Valko et al., 2008; Bakalidou et al., 2014; Amtmann et al., 2012; Behrangrad and Yoosefinejad, 2021) and the present study support the importance of monitoring fatigue in patients with MS disease to develop a fuller and more integrative understanding of the experience, and outcomes of fatigue during the disease progress. The Croatian version of FSS, therefore, proved to be valid and reliable for assessing fatigue severity in people with MS.

Conflict of Interest

The authors have no competing interests to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103397.

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Psychometric Properties of the HADS Measure of Anxiety and Depression Among Multiple Sclerosis Patients in Croatia

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Depression and anxiety are common complaints in patients with multiple sclerosis (MS). The study objective was to investigate the factor structure, internal consistency, and correlates of the Croatian version of the Hospital Anxiety and Depression Scale (HADS) in patients with MS. A total of 179 patients with MS and 999 controls were included in the online survey. All subjects completed the HADS and self-administered questionnaires capturing information of demographic, education level, disease-related variables, and the Multiple Sclerosis Impact Scale-29 (MSIS-29). Psychometric properties were examined by estimating the validity, reliability, and factor structure of the HADS in patients with MS. The two HADS subscales (anxiety and depression) had excellent internal consistencies (Cronbach's α value 0.82–0.83), and factor analysis confirmed a two-factor structure. The convergent validity of the HADS subscales appeared to be good due to the significant correlations between HADS and MSIS-29. Receiver operating characteristic (ROC) analysis indicates that the HADS subscales have a significant diagnostic validity for group differentiation. Hierarchical regression analysis using MSIS-29 subscales as criterion variables showed consistent evidence for the incremental validity of the HADS. The HADS is a reliable and valid self-assessment scale in patients with MS and is suggested to be used in clinical monitoring of the psychiatric and psychological status of patients with MS.

Keywords: Hospital Anxiety and Depression Scale (HADS), psychometrics, depression, multiple sclerosis, anxiety

INTRODUCTION

Multiple sclerosis (MS) has a high prevalence of depression, anxiety, and stress comorbidities (Marrie et al., 2018; Karimi et al., 2020). Comorbid depression and anxiety disorders affect more than 20% of the MS population (Beiske et al., 2008; Fiest et al., 2015; Marrie et al., 2015, 2018; Karimi et al., 2020). Various screening instruments have been used to evaluate depression, anxiety, and

stress in a clinical population of people with MS (pwMS) and non-clinical populations, including the Beck Depression Inventory-II (BDI-II) (Beck and Steer, 1990; Watson et al., 2014), Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983; Honarmand and Feinstein, 2009), and Depression, Anxiety, and Stress Scale-21 (DASS-21) (Lovibond P.F. and Lovibond S.H., 1995; Lovibond S.H. and Lovibond P.F., 1995; Rogić Vidaković et al., 2021). The HADS is one of the most commonly used scales for assessing anxiety and depression among patients in a general hospital setting (Zigmond and Snaith, 1983; Mitchell et al., 2010). Watson et al. (2014) validated anxiety and depression measures in pwMS, confirming HADS as an appropriate questionnaire to assess depression and anxiety in pwMS. Recently Rogić Vidaković et al. (2021) reported psychometric properties of the DASS-21 scale in pwMS. The normative data for the HADS in pwMS were provided in pwMS in different languages (Honarmand and Feinstein, 2009; Atkins et al., 2012; Watson et al., 2014; Marrie et al., 2018; Pais-Ribeiro et al., 2018). A systematic review of the structure of the HADS (Cosco et al., 2012) found inconsistencies in the latent structure of the scale, which were mainly related to the different latent variable analysis methods [exploratory factor analysis and confirmatory factor analysis (CFA)] used for HADS. Regarding factor structure of HADS in pwMS MS, Pais-Ribeiro et al. (2018) conducted CFA and exploratory factor analysis providing support for a two-factor HADS structure in pwMS. There have also been specific problems in the translated versions and cross-cultural use of the HADS (i.e., authors from the same country do not apply the identical versions of HADS translations) (Wichowicz and Wieczorek, 2011; Maters et al., 2013; Watrowski and Rohde, 2014). The HADS has been validated in a diverse group of subjects, including those in primary care patients (el-Rufaie and Absood, 1995), geriatric patients (Flint and Rifat, 1996), or cancer patients (Mitchell et al., 2010). In addition, specific HADS cut-off points have been established for patients with cancer (Ibbotson et al., 1994), gynecological disorders (Abiodun, 1994), stroke (Johnson et al., 1995), and for pwMS (Honarmand and Feinstein, 2009). In previous studies conducted in Croatia, the HADS has been used in medical conditions other than MS (Filipovic-Grcic et al., 2010; Vuletić et al., 2011; Ostojić et al., 2014; Pokrajac-Bulian et al., 2015; Miljanović et al., 2017), but no study determined psychometric properties for the Croatian version of the HADS in pwMS. Two studies conducted in Croatia with HADS stated the origin of the Croatian version of HADS (Miljanović et al., 2017; Galić et al., 2020), and so far, only Miljanović et al. (2017) investigated metric properties of HADS in terminal cancer patients but having relatively smaller convenient sample size without a control group.

OBJECTIVE

The purpose of this online survey, was to evaluate the metric properties of the Croatian version of the HADS in terms of validity, reliability, and factor structure in pwMS. The study compared HADS subscales with a non-clinical population (control healthy subjects) and published data in pwMS (Watson et al., 2014; Pais-Ribeiro et al., 2018). The study also investigated the incremental validity of HADS using the Multiple Sclerosis Impact Scale-29 (MSIS-29) (Hobart et al., 2001) and relevant demographic and disease-related variables as the criterion variables.

MATERIALS AND METHODS

Study Population and Procedure

The subjects with MS were recruited by advertising through the Association of Multiple Sclerosis Societies of Croatia (AMSSC). A total of 179 pwMS and 999 control subjects were included in the online survey. The demographic factors, education level, and disease-related factors for pwMS and control subjects are presented in **Table 1**. In the group of pwMS, 84% were women with a mean age of 41.3 ± 11.5 years, and 16% were men with a mean age of 42.7 ± 9.9 years. Most pwMS were right-handed (92.7%) and 35–49 years old (49%). Most pwMS had high school degrees (49.1%) and graduate university degrees (23.5%). Most of the pwMS were diagnosed with MS disease between 0 and 5 years (41.4%), 26.7% were diagnosed between 6 and 11 years, and 31.8% reported having MS over 11 years. The mean duration of the disease for pwMS was 8.7 ± 7.2. A majority of the people declared to have relapsing-remitting MS (RRMS) (70.4%), while others reported having secondary progressive MS (SPMS) (7.8%) and primary progressive MS (PPMS) (10.6%). Some pwMS (11.2%) did not provide information on the type of MS. The median Expanded Disability Status Scale (EDSS) score for all pwMS was 3.5 ± 3.5. Of the 179 pwMS, 51.8% had comorbidities, of which the most common were endocrine, nutritional, and metabolic diseases (9.9%) and diseases of the circulatory system (7.8%).

In the group of control subjects, 81% of participants were women with a mean age of 39.8 ± 10.3 years, and 19 percent (19%) were men with a mean age of 40.3 ± 10.1 years. Most of the controls were right-handed (93.4%) and between 35 and 49 years old (51%), and most of them had graduate university degrees (43.7%) and high school degrees (25.6%). Of a total, 27.6% of people had comorbidities, of which the most common were endocrine, nutritional, and metabolic diseases (8.2%) and diseases of the circulatory system (5.2%).

The data were collected *via* a Google Forms survey from December 16, 2020, until January 13, 2021.

Measurements and Data Collection

Demographic Information and Disease-Related Variables

The participants were characterized by demographic information (age, sex, and handedness), educational, and disease-related factors, including duration of the disease, MS type (Lublin et al., 2014), and the score on the EDSS (McDonald et al., 2001).

Hospital Anxiety and Depression Scale (HADS)

The HADS (Zigmond and Snaith, 1983) is a self-report scale consisting of two subscales, one measuring anxiety with seven items (HADS-A) and one measuring depression with seven items

(HADS-D). The subject gives answers to each question on a 4-point (0–3) Likert scale and answering how he/she has been feeling in the past week. Items 1, 3, 5, 7, 9, 11, 13 belong to the anxiety subscale, while items: 2, 4, 6, 8, 10, 12, 14 belong to the depression subscale. The total score is obtained by summing the scores within each subscale. According to Pais-Ribeiro et al. (2018) interpretation, the score 0–7 represents "normal," 8–10 "mild," 11–14 "moderate," and 15–21 "severe." In the present study, the cut-off score of ≥8 and of ≥11 was used for HADS subscales (Botega et al., 1995; Bjelland et al., 2002; Honarmand and Feinstein, 2009; Brennan et al., 2010; Watson et al., 2014; Litster et al., 2016).

Multiple Sclerosis Impact Scale-29

The MSIS-29 is a self-report scale capturing MS disease's impact from a patient's physical and psychological perspective (Hobart et al., 2001; Rogić Vidaković et al., 2021). The MSIS-29 is a self-report scale capturing MS disease's impact from a patient's physical and psychological perspective. The scale is structured into two subscales, a 20-item scale for measuring physical impact and a 9-item scale for measuring the psychological impact of the disease. The "physical impact" subscale consists of items from 1 to 20. The subscale of "psychological impact" consists of items from 21 to 29. The patient is instructed to read each statement about the disease's impact on his/her everyday life in the past 2 weeks. For each statement, the patient's task is to circle the number that best describes his/her condition and answering on a 5-point Likert scale (1 = not at all, 2 = a little, 3 = moderately, 4 = quite a bit, and 5 = extremely. The patient's scores on two subscales generated by summing individual items can be transformed to a scale of 0–100, with higher scores indicating a more severe disease burden.

TABLE 1 | Characteristics of study participants.

	Control subjects (*N* = 999)	pwMS (*N* = 179)
Age in years (mean ± SD)	39.9 ± 10.2	41.6 ± 11.3
Age (range)	20–74	19–75
Sex		
Female	81%	84%
Male	19%	16%
MS type		
RRMS		70.4%
SPMS		7.8%
PPMS		10.6%
Not known		11.2%
Years of MS disease (mean ± SD)		8.7 ± 7.2
EDSS (median ± IQR, range)		3.5 ± 3.5, 0–9
EDSS*		2.5 ± 2.5
EDSS**		6 ± 2
Self-report scales (mean ± SD)		
HADS-A	6.5 ± 3.6	8.8 ± 4.1
HADS-D	5.1 ± 3.1	7.8 ± 3.9
MSIS-29 PHYS		46.6 ± 17.2
MSIS-29 PSY		24.3 ± 8.8

SD, standard deviation; IQR, interquartile range; EDSS, Expanded Disability Status Scale; EDSS, fully preserved mobility 0–4.5; EDSS**, partially or fully impaired mobility 5–9.5; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale; MSIS-29 PHYS, MSIS-29 Physical subscale; MSIS-29 PSY, MSIS-29 Psychological subscale.*

TABLE 2 | Score classification percentages of HADS anxiety and depression subscales for pwMS and control subjects.

	Control subjects		pwMS	
	HADS-A (%)	HADS-D (%)	HADS-A (%)	HADS-D (%)
(0–7) normal	65.7	79.7	41.4	50.3
(8–10) mild	21.3	12.9	22.9	21.8
(11–14) moderate	9.6	7.2	26.8	24.0
(15–21) severe	3.4	0.2	8.9	3.9
≥8	34.3%	20.3%	58.6%	49.8%
≥11	13%	7.4%	35.7%	27.9%

HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale.

Translation and Cultural Adaptation

Croatian translation of the HADS questionnaire was used in the evaluation of anxiety and depression in patients suffering from oncological (Miljanović et al., 2017) and neurological (Vuletić et al., 2011; Ostojić et al., 2014) diseases or other conditions (Filipovic-Grcic et al., 2010). Recently, HADS was used in the general Croatian population during the COVID-19 infection (Galić et al., 2020). Among the mentioned studies that used the Croatian translation of HADS, two studies stated the origin of the translated version of the HADS questionnaire. Miljanović et al. (2017) used the purchased Croatian translation of HADS from Mapi Research Trust, and Galić et al. (2020) used the translated Croatian version of HADS from Pokrajac-Bulian et al. (2015).

The reason why our group initiated the HADS translation procedure is the fact that the translation of HADS from Mapi Research Trust is not entirely in the spirit of the Croatian language according to the authors' opinion, and all authors of this study agreed not to use it in the present study. Also, the Croatian version of HADS from Mapi Research Trust is not publicly free of charge to the research community. Further, since Pokrajac-Bulian et al. (2015) did not detail the process of translating HADS into Croatian, having a relatively small sample size of obese people, and the main aim of the study was not the validation of HADS in the Croatian population, we did not consider it appropriate.

Therefore, our group translated HADS following current recommendations, methodological approaches, and guidelines in the process of translating, adapting, and cross-validating instruments (Sousa and Rojjanasrirat, 2011). One author of this study (MRV) and Professor of English language (Professor Dalibora Behmen – DB, from the University of Split School of Medicine), both natives in the Croatian language, translated the HADS from English to Croatian. Next, the English language professor (DB) compared both translated versions of HADS in the Croatian language and produced the final version of the questionnaires. Another independent English language professor (University of Split) who had no insight into the original English

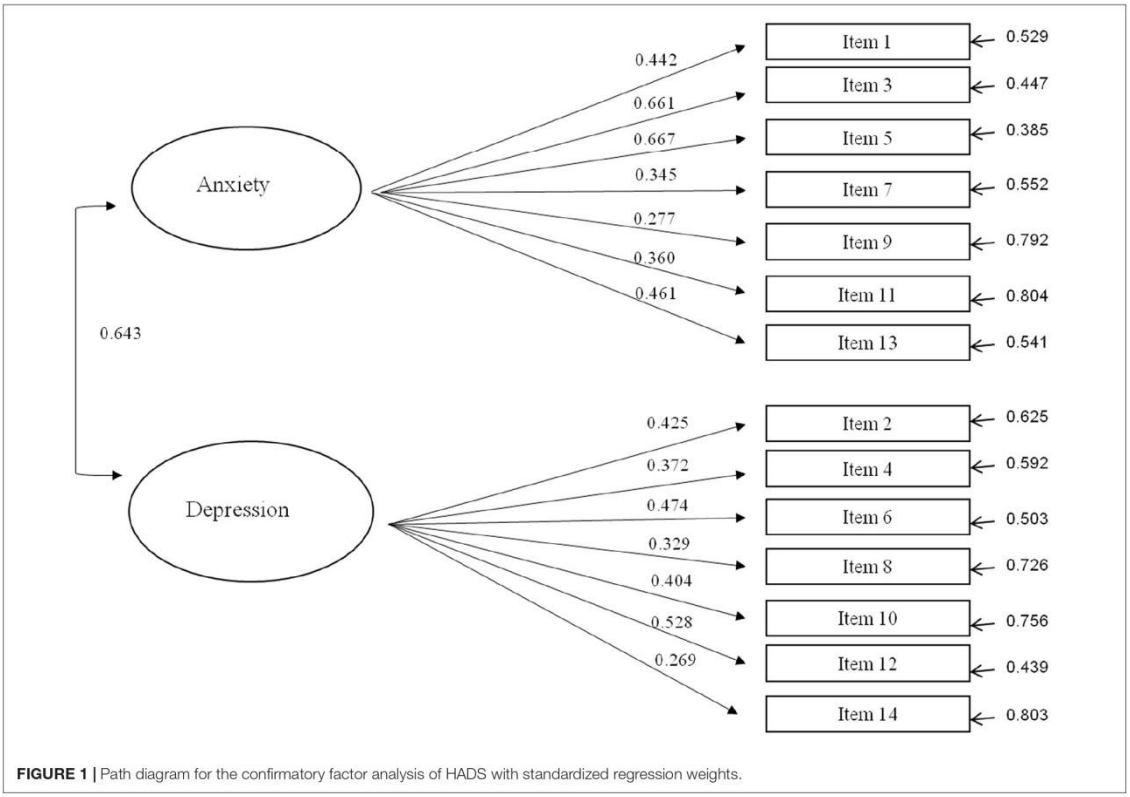

FIGURE 1 | Path diagram for the confirmatory factor analysis of HADS with standardized regression weights.

version translated the last Croatian version of the questionnaires back into the English language, completing the final adaptation of the Croatian version of HADS used in this study (**Supplementary Material**).

Validation Procedure

Internal consistency of HADS was estimated by Cronbach's alpha coefficients and inter-item correlations. CFA was carried out to test the validity of the two-factor and one-factor models. Data were analyzed by using the generalized least square (GLS) method and the maximum likelihood (ML) estimator. Several criteria [ML Chi-square, root mean square (RMS) standardized residual, Steiger Lind RMSEA, and McDonald non-centrality index] are reported with an emphasis on the root mean square error of approximation (RMSEA), the most commonly used fit index. Convergent validity was demonstrated by the correlation between HADS and MSIS-29 subscales. Concurrent validity was assessed by comparisons between a group of pwMS and control subjects. A receiver operating characteristic (ROC) curve was used to determine the optimum cut-off score for each HADS subscales – the score that yielded the best balance between sensitivity and specificity. Furthermore, comparisons were also provided between published data on psychometric properties of the HADS (Watson et al., 2014; Pais-Ribeiro et al., 2018). Pais-Ribeiro et al. (2018) offered psychometric properties of HADS, analyzing a sample of 380 pwMS (63.9% female; mean age 40.0 ± 10.9 years; range: 16–71 years) from the outpatient Neuroimmunology Clinic at a Central Hospital in Porto, Portugal, while Watson et al. (2014) included 34 pwMS (71%) female and (29%) male; mean age 48.5 (11.1) from England.

The incremental validity of HADS was assessed by the hierarchical regression model using the MSIS-29 and relevant demographic and disease-related factors as criterion variables. Age, sex, EDSS, type of MS, duration of the disease were entered into the first step, while the scores on HADS subscales were added in the second step.

Statistical Analyses

Parameters of skewness and kurtosis were tested for HADS and MSIS-29 scales. Results indicated acceptable values for the parametric statistic. Mean value comparisons between our study and published studies using HADS (Watson et al., 2014; Pais-Ribeiro et al., 2018) in pwMS and differences between relevant disease-related variables were carried using *t*-tests, Chi-square test, Mann–Whitney *U* test, Kruskal–Wallis test, and variance analysis (ANOVA). The *post hoc* Bonferroni test was calculated when using multiple comparisons. Levene's test was used to assess the equality of variances between

groups. Correlation analyses were conducted using Pearson's r coefficient and Spearman rank-order correlation (ρ). Descriptive statistics of relevant participants' characteristics and applied scales were summarized by *N*, percentage, mean and standard deviations, median, and interquartile range. Psychometric properties were examined by estimating internal consistency, factor structure, convergent, concurrent, and incremental validity of the HADS. In all calculations, a *p*-value of <0.05 was considered statistically significant. Data analysis was performed using the software Statistica 12.

RESULTS

Overview Results

The demographic characteristics, disease-related variables, and mean results on self-rating scales (HADS and MSIS-29) of pwMS and healthy subjects are shown in **Table 1**. No significant sex ($\chi^2 = 0.05$, $p = 0.82$, $p > 0.05$) and age ($t = -4.84$, $df = 1390$, $p > 0.05$) differences were found between pwMS and control subjects. The scores on HADS depression ($t = -2.34$, $df = 177$, $p < 0.05$) and MSIS-29 physical ($t = -2.94$, $df = 177$, $p < 0.01$) subscales varied significantly by MS type in pwMS. People with RRMS type ($Mean_{HADS-D} = 7.4$; $Mean_{MSIS-PHYS} = 43.9$) were less depressed and had better physical health than people with SPMS ($Mean_{HADS-D} = 10.0$; $Mean_{MSIS-PHYS} = 55.9$) and PPMS ($Mean_{HADS-D} = 10.1$; $Mean_{MSIS-PHYS} = 56.4$). For women, HADS scores on depression subscale varied significantly with MS type. The women with RRMS were less depressed [$\chi^2_{(df=3)} = 8.81$; $p < 0.05$] than women with SPMS and PPMS. However, the sex differences were found in pwMS in achievement on the HADS depression subscale, indicating that the male participants have a higher depression score than females with MS ($t = -2.10$, $df = 177$, $p < 0.05$). Further, in pwMS, significant differences were found between different age groups (19–34; 35–39; and 40–75 years) for HADS depression subscales ($F = 12.34$; $p < 0.001$) and MSIS-29 physical impact subscale ($F = 12.16$; $p < 0.001$). *Post hoc* results suggest an increase in depression and poorer physical health in older pwMS than younger pwMS ($p_{younger\ vs.\ older} < 0.001$; $p_{midle\ age\ vs.\ older} = 0.04$; $p < 0.05$; $p_{midle\ age\ vs.\ younger} = 0.04$; $p < 0.05$).

Further, the participants who suffer from MS for a more extended period (more than 11 years) have poorer physical health on the MSIS-29 than those who are younger and suffer from MS for a shorter period, less than 5 years ($F = 3.29$, $p < 0.05$). Furthermore, when levels of physical health and depression were compared for types of MS (1-participants with RRMS; 2-participants with other types of MS/SPMS, PPMS, MS type not provided), a significant difference was also found ($t_{depression} = 2.34$, $df = 177$, $p < 0.05$; $t_{physical} = -2.54$, $df = 177$, $p < 0.001$). Participants with RRMS had better physical health and were less depressed than people with SPMS, PPMS, and those who did not provide information on MS type.

Table 2 presents the score classification percentages of HADS anxiety and depression subscales for pwMS and control subjects. According to score classification for the HADS depression subscale, 49.8% of the pwMS exhibited a score of ≥8 compared to 20.3% of control subjects. For HADS anxiety score, 58.6% of pwMS presented a score ≥8, compared to 34.3% of control subjects. Moreover, based on the score of ≥11, for the HADS depression subscale, 27.9% of pwMS exhibited moderate or severe depression compared to 7.4% of control subjects. For the HADS anxiety subscale, 35.7% of pwMS presented a score ≥11 compared to 13% of control subjects. The prevalence of depression in pwMS seems to be higher in comparison to anxiety.

Psychometric Properties of the Hospital Anxiety and Depression Scale (HADS)

Internal Consistency

Expressed by Cronbach's α coefficients, both HADS subscales ($\alpha_{HADS-A} = 0.82$ to $\alpha_{HADS-D} = 0.83$) and MSIS-29 subscales ($\alpha_{MSIS-PHYS} = 0.82$ to $\alpha_{MSIS-PSY} = 0.81$) had excellent internal consistency. Values for both HADS and MSIS-29 scales are considered indicative of good reliability. Inter-item correlations for HADS and MSIS-29 scales were >0.3, meaning that all items on each subscale correlate very well with the scale overall.

Factor Analysis of the Hospital Anxiety and Depression Scale (HADS)

Indicated by almost all obtained fitting parameters except for a slightly higher ratio between Chi-square and corresponding *df* (Kenny, 2020), CFA confirmed the original structure of the HADS in general (**Figure 1** and **Table 3**). Namely, HADS, as expected, shows a primarily two-factor structure (separate dimensions of anxiety and depression) with mutually significantly correlated factors. HADS-A subscale explained 18.66% of factor variance and with HADS-D subscale 21.85% of the variance. The CFA for the one-factor solution was also reported (**Table 3**), but all fit indices support the retention of the two-factor solution. The Steiger Lind RMSEA index was used as the main and most commonly used criteria for accepting models. Cut-off RMSEA

TABLE 3 | Fit indices for one-factor and two-factor model of HADS (CFA).

	One-factor solution	Two-factor solution
ML Chi-square	752.03 (*df* = 77)	128.315 (*df* = 28)
RMS standardized residual	0.059	0.024
Steiger Lind RMSEA	0.107	0.051
McDonald non-centrality index	0.643	0.93

Rms, root mean square; Rmsea, root mean square error of approximation; Ml, maximum likelihood.

TABLE 4 | Pearson correlation coefficient for HADS and MSIS-29 scale (*N* = 179).

	HADS-A	HADS-D	MSIS-29 PHYS	MSIS-29 PSY
HADS-A	–	0.54**	0.33**	0.69**
HADS-D		–	0.54**	0.61**
MSIS-29 PHYS			–	0.57**
MSIS-29 PSY				–

***p < 0.01; HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale; MSIS-29 PSY-MSIS-29 Psychological subscale.*

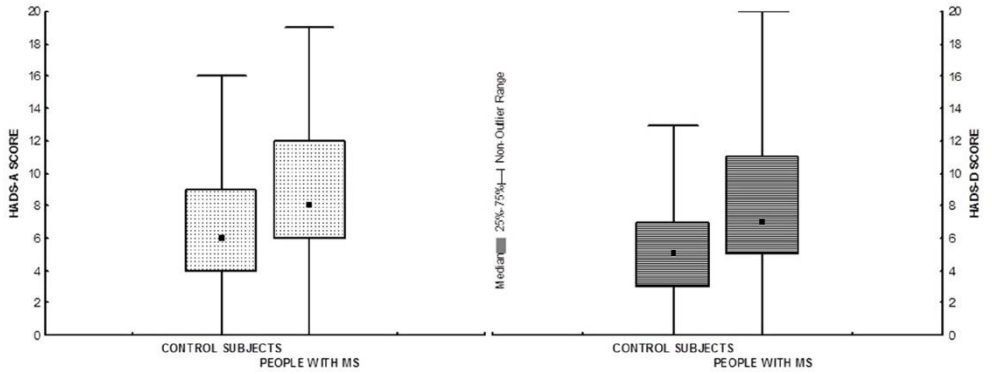

FIGURE 2 | Box plots showing medians and interquartile range of HADS scores in pwMS and control subjects. HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale.

value of <0.05 indicates a "close fit," and that <0.08 suggests a reasonable model–data fit (e.g., Browne and Cudeck, 1993; Jöreskog and Sörbom, 1993).

Convergent Validity of the Hospital Anxiety and Depression Scale (HADS)

Convergent validity was demonstrated by the correlations of the HADS subscales and the MSIS-29 subscales (**Table 4**) for pwMS. HADS anxiety and depression subscales have a significant moderate correlation ($r = 0.54$; $p < 0.001$). Moreover, both HADS subscales are correlated with MSIS-29 subscales, noting that the correlations of HADS subscales are higher with the psychological MSIS-29 subscale ($r = 0.61$–0.69; $p < 0.01$) compared to the physical MSIS-29 subscale ($r = 0.33$–0.54; $p < 0.01$). Correlation coefficients between HADS subscales and MSIS-29 subscales indicate weak and moderate correlations.

Concurrent Validity

Concurrent validity was demonstrated by differences between MS and control subjects. HADS mean values for pwMS were significantly higher (Mann–Whitney U test; $z_{\text{anxiety}} = 6.98$, $p < 0.01$; $z_{\text{depression}} = 8.588$, $p < 0.01$) than those reported in control subjects (**Figure 2**). A non-parametric test was done because Levene's test for homogeneity of variances was significant (both HADS-A and HADS-D). Further, compared to the results of the current study with Watson et al. (2014) and Pais-Ribeiro et al. (2018), depression and anxiety were not equally represented (**Table 5**). The results on both subscales were significantly higher in our sample than those presented by Pais-Ribeiro et al. (2018), and the difference is significantly more pronounced when it comes to HADS-D. Compared to Watson et al. (2014), there were no significant differences in depression levels, while the difference in anxiety exists (small effect size).

Receiver operating characteristic analysis (**Table 6**) indicated that for the HADS-A, the highest value of the Youden Index ($J = 0.245$) was obtained for a cut-off point of >7 and the HADS-D at the cut-off point of >6 ($J = 0.328$). For the HADS-A, the statistically significant AUC was 0.664 ($p < 0.001$) with a 95% confidence interval of 0.635–0.692. For the HADS-D, AUC was 0.702 ($p < 0.001$) with 95% confidence interval 0.675–0.728. Both parameters (J and AUC) indicate that the HADS-A and the HADS-D have a significant diagnostic validity for group differentiation.

Incremental Validity

Table 7 represents the results of multiple hierarchical regression analyses and the incremental validity of the HADS. Results indicate whether HADS-A and HADS-D contribute to the explanation of MSIS-29 variance (incremental validity) in relation to some examined sociodemographic variables, MS type, and EDDS.

For the physical impact on the MSIS-29, the first set of predictor variables (age, sex, EDSS, MS type, and disease duration) only sex had a significant β coefficient. Step 2, which included HADS subscales, revealed that these variables

TABLE 5 | The HADS results from the present study and comparisons between published studies.

		HADS-A	HADS-D
Present study $N = 179$	Mean (SD)	8.82 (4.11)	7.80 (3.99)
Watson et al. (2014) $N = 34$	Mean (SD)	7.2 (5.4)	8.1 (5.9)
	t	1.99	0.37
	df	211	211
	p	0.04; $p < 0.05$	0.71; $p > 0.05$
Pais-Ribeiro et al. (2018) $N = 380$	Mean (SD)	7.94 (4.31)	5.63 (4.01)
	t	2.29	5.98
	df	557	557
	p	0.02; $p < 0.5$	0.00; $p < 0.001$

HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale.

TABLE 6 | Psychometric properties of HADS-A and HADS-D at different cut-off scores (ROC analysis).

	Sensitivity (95% CI)	Specificity (95% CI)	+LR	−LR
HADS-A scores				
≤6	65.92 (58.5–72.8)	54.44 (51.1–57.7)	1.45	0.63
≤7	58.66 (51.1–66.0)	65.39 (62.2–68.5)	1.69	0.63
≤8	48.04 (40.5–55.6)	73.38 (70.4–76.2)	1.81	0.71
≤9	43.02 (35.7–50.6)	80.94 (78.2–83.4)	2.26	0.70
≤10	35.75 (28.7–43.2)	87.19 (84.8–89.3)	2.79	0.74
≤11	27.37 (21.0–34.5)	90.25 (88.1–92.1)	2.81	0.80
≤12	20.11 (14.5–26.7)	93.32 (91.5–94.9)	3.01	0.86
HADS-D scores				
≤6	61.45 (53.9–68.6)	71.37 (68.5–74.2)	2.15	0.54
≤7	49.72 (42.2–57.3)	79.58 (76.9–82.0)	2.43	0.63
≤8	43.58 (36.2–51.2)	85.39 (83.0–87.5)	2.98	0.66
≤9	35.20 (28.2–42.7)	89.19 (87.1–91.0)	3.26	0.73
≤10	27.93 (21.5–35.1)	92.49 (90.7–94.0)	3.72	0.78
≤11	21.23 (15.5–28.0)	96.30 (94.9–97.4)	5.73	0.82
≤12	12.85 (8.3–18.7)	98.70 (97.8–99.3)	9.87	0.88

+, LR likelihood ratio for a positive result; −, LR likelihood ratio for a negative result; CI, confidence interval.

contribute to the explanation of an additional 18% of physical impact variance. Among these predictors, only HADS depression had significant β, which is positive, meaning that the greater depression is accompanied by greater physical impact (**Table 7**). For the psychological impact on the MSIS-29, age, among predictors included in the first step, significantly predicted psychological impact, accounting for 13% of the variance. Simultaneously, HADS depression and anxiety subscales entered in the second step explained 40% of the psychological impact variance. Anxiety and depression subscale significantly contributed to the explanation of the criterion variable. For both criterion variables (MSIS-29 physical and psychological impact) HADS has been shown to have significant incremental validity in the explanation of MSIS-29, especially when it comes to the second criterion, MSIS-29 psychological impact. The additional contribution of physical impact is 13%, and for psychological impact, even 40%.

DISCUSSION

Anxiety and depressive disorders are among the most common psychiatric illnesses highly comorbid with each other and considered to belong to the broader category of internalizing disorders (Kalin, 2020). More than 50% of the patients with major depression have significant anxiety and were considered to have anxious depression (Fava et al., 2004; Beijers et al., 2019). When looking into a healthy population compared to pwMS in terms of developing mood disorders, the risk of depression, anxiety, and stress are higher in MS patients than in healthy subjects (Pham et al., 2018). The etiology of MS disease is not yet known and factors such as immune system deficiency, genetic predisposition, lack of vitamin D, Epstein-Barr virus, family background, geographical region, stress, and lifestyle play a role in this disease (Dehghani and Kazemi Moghaddam, 2015). Besides mood disorders, relevant clinical symptoms of MS include disturbances in motor functions (e.g., tremor, weakness, and spasticity), sensory deficits (e.g., pain), visual impairments (e.g., diplopia and optic neuritis), vascular dysfunctions, obesity, and cognitive impairments (e.g., attention deficits, working memory impairments, information processing). Karimi et al. (2020) investigated 87 MS patients in Iran and showed that 47.1% had moderate depression, 39.1% had moderate anxiety, and 44.8% had moderate stress. A study in Canada (Pham et al., 2018)

TABLE 7 | Multiple hierarchical regression analyses for the incremental validity of HADS and relevant variables on MSIS-29 subscales.

		MSIS-29 PHYS		MSIS-29 PSY	
		Step 1	Step 2	Step 1	Step 2
Predictors		β	β	β	β
Step 1	Age	0.07	0.05	−0.37**	−0.40*
	Sex	0.32**	0.22*	0.16	0.01
	Duration of the disease	0.17	0.10	0.11	0.01
	Type MS	0.11	0.14	0.01	0.04
	EDSS	0.05	0.08	0.05	0.09
Step 2	R^2	0.19		0.13	
		$F(5,80) = 3.71\ p < 0.001$	$F(5,80) = 2.50\ p < 0.04$		
	HADS-A		0.14		0.20*
	HADS-D		0.36**		0.54**
	R^2		0.37		0.54
			$F(7,79) = 6.52\ p < 0.001$	$F(7,78) = 13.00\ p < 0.001$	
	ΔR^2		0.18		0.40
			$F(7,79) = 11.18\ p < 0.001$	$F(7,78) = 34.36\ p < 0.001$	

*HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale; MSIS-29 PHYS, MSIS-29 Physical subscale; MSIS-29 PSY, MSIS-29 Psychological subscale; β, standardized regression coefficient; R^2, coefficient of determination; ΔR^2, change in the coefficient of determination; *$p < 0.05$, CI = 95%; **$p < 0.01$, CI = 98%.*

showed 30% of MS patients suffered from anxiety, and 16.3% were affected with depression. The results of a study in the United States (Boeschoten et al., 2017) revealed 20.6% of MS patients suffered from depression. A significant factor responsible for MS relapses is stressful life events (Brown et al., 2005; Stamoula et al., 2021). From a clinical point of view, it is therefore recommended to monitor psychological constructs such as depression, anxiety, and stress in pwMS (Glaser et al., 2019). According to a literature search, it is evident that scales such as DASS-21 (Lovibond P.F. and Lovibond S.H., 1995; Lovibond S.H. and Lovibond P.F., 1995) and HADS (Zigmond and Snaith, 1983) were mainly used for detecting depression, anxiety, and stress in pwMS. Recently psychometric properties for DASS-21 were published in pwMS (Rogić Vidaković et al., 2021), while psychometric properties for HADS in pwMS have been available on different languages from earlier years (Honarmand and Feinstein, 2009; Atkins et al., 2012; Watson et al., 2014; Marrie et al., 2018; Pais-Ribeiro et al., 2018). What it has to bear in mind is that HADS was not initially developed in pwMS. Instead, it is created as a self-report rating scale for evaluating depression and anxiety in patients with a general medical condition, but can be regarded as a useful screening instrument to detect potential psychological disturbances in pwMS (Honarmand and Feinstein, 2009; Watson et al., 2014).

By exploring the factor structure of the HADS, the present study confirmed a two-dimensionality of the HADS in a large community and patient samples (Mykletun et al., 2001; Norton et al., 2013), as well as in samples of pwMS (Pais-Ribeiro et al., 2018). Internal consistency, using Cronbach's alpha, for the two dimensions was good, 0.80 for anxiety and 0.81 for depression in the study of Pais-Ribeiro et al. (2018), while in the present study, the Cronbach's alpha, for the two dimensions was also good, 0.82 for anxiety and 0.83 for depression. A systematic review study conducted by Cosco et al. (2012) pointed out that previous findings on the latent structure of the HADS have been somewhat inconsistent factor structure with 25 of the 50 reviewed studies revealing a two-factor structure, 5 studies revealing unidimensional, 17 studies revealing three-factor, and 2 studies revealing four-factor structures. According to the findings of Cosco et al. (2012), different latent variable analysis methods gained correspondingly different structures: exploratory factor analysis studies revealed primarily two-factor structures, CFA studies revealed primarily three-factor structures, and item response theory studies revealed primarily unidimensional structures. Regarding factor structure of HADS in MS research, Pais-Ribeiro et al. (2018) conducted CFA and exploratory factor analysis and provided support for the bifactor model. The present study confirmed a two-factor structure, and several fit indices that were used support the retention of the two-factor solution.

Parameters of ROC analysis indicate that the HADS-A and the HADS-D have a significant diagnostic validity for group differentiation. Although the HADS depression scale shows slightly better concurrent validity than HADS anxiety, the accuracy of both measures to distinguish emotional disorder is not very high. Therefore, the present study provided data for the optimum cut-off score of >7 for HADS-A and a cut-off score of >6 for HADS-D. The cut-off score of >7 for HADS-A is similar to findings of Nicholl et al. (2001) and Honarmand and Feinstein (2009), while the cut-off score of >6 for HADS-D was slightly lower compared to other studies using HADS in pwMS (Honarmand and Feinstein, 2009; Watson et al., 2014). When looking into studies using HADS in different samples of patients (not including pwMS) like cancer patients or psychiatric illnesses, the sensitivity and specificity of HADS-A and HADS-D with a threshold of 8+ were most often found to be in the range of 0.70–0.90. The variation in optimal cut-off values and sensitivity and specificity might be due to differences in HADS translations used, samples and procedures in administration, and method analysis of HADS (Bjelland et al., 2002; Cosco et al., 2012).

Both HADS subscales had excellent internal consistencies and good convergent validity expressed by inter-correlations between the HADS and the MSIS-29 subscales. Results of regression analysis suggest that the HADS showed incremental validity in relation to age, sex, MS type, and EDSS.

Further, we have to acknowledge several limitations of the study. The possible limitation of the study would be the time of conducting the survey. Namely, the study was conducted during the COVID-19 pandemic (1 year after the first lockdown in Croatia) and a series of earthquakes that hit Croatia, causing specific problems regarding the governmental social distancing measures and collective trauma effects. Although the study was conducted during COVID-19 disease and strong earthquakes in the eastern part of Croatia (Perinja and Zagreb region), we assume that COVID-19 and earthquakes did not significantly affect the HADS results in pwMS and control subjects. Galić et al. (2020) assessed depression and anxiety in the general population with HADS 3 weeks after the first registered cases of COVID-19 in Croatia. In line with the study of Galić et al. (2020), observed values of depression were similar to the results of control subjects in the present study, with less pronounced anxiety in the present study. Further, a comparison with the previous studies shows a higher prevalence of depression and anxiety in pwMS independently of specific external factors not related to the MS disease (Dahl et al., 2004; Karimi et al., 2020). Another possible limitation is that HADS was not used as a paper–pencil assessment but rather as an online survey. The advantage of the online survey was the possibility to reach a higher number of MS patients. The paper–pencil assessment of HADS would last longer since we could access the MS patients once a week at the University Hospital of Split during the regular control examinations at the Department of Neurology. An approximate number of MS patients that we could reach weekly would be approximately three to five. The second problem was that during regular control visits at the Department of Neurology, the MS patients are not registered at specific hours but are intermingled with other patients having other neurological diseases. Therefore, we believe by conducting an online survey, we reached a satisfactory number of MS patients in a shorter period and got a more appropriate sample size avoiding possible erroneous findings which might occur in the process of determining psychometric properties of the HADS, in particular the identification of the correct structure of the questionnaire (e.g., number of dimensions and items in each dimension).

CONCLUSION

The HADS is shown to be a reliable and valid patient-self report scale that captures meaningful psychological and physical clinical correlates of MS disease.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the School of Medicine, University of Split. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AJ: conceptualization, data curation, formal analysis, methodology, project administration, resources, and writing – original draft. APr: supervision, methodology, and writing – original draft. MM, KD, and ZĐ: supervision and writing – original draft. JV, AM, AĆ, VK, and LK: methodology, project administration, and resources. APo: methodology and project administration. MRV: conceptualization, data curation, formal analysis, methodology, project administration, resources, supervision, and writing – original draft. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.794353/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.