



Original article

Childhood trauma and treatment compliance in people with multiple sclerosis: The mediating role of physician–patient rapport

Ambra Salvati^{a,1}, Alessandra Cicia^{b,*,1} , Assunta Bianco^b, Matteo Lucchini^b, Marco Bisurgi^b, Claudio Imperatori^{c,2}, Benedetto Farina^{c,2}, Massimiliano Mirabella^{b,2}

^a Centro Clinico Janet, Rome, Italy

^b Multiple Sclerosis Research Center “Anna Paola Batocchi”, Catholic University of the Sacred Heart, Rome, Italy

^c Experimental and Applied Psychology Laboratory, Department of Health and Life Sciences, European University of Rome, Italy

ARTICLE INFO

Keywords:

Childhood trauma

Multiple sclerosis

Treatment adherence

The physician–patient rapport

ABSTRACT

Background: The role of childhood trauma (CT) and its impact on therapeutic adherence in patients with multiple sclerosis (MS) has been poorly explored. The aim of this study was to investigate the association between CT and treatment adherence, and to test the potential mediating role of the physician–patient rapport in this association. **Methods:** Two hundred and five patients with MS were enrolled and completed self-report measures assessing the main study variables. Mediation models analyzing the direct and indirect effects of CT on treatment adherence through the physician–patient rapport were performed while controlling for socio-demographic and clinical confounding factors.

Results: The models showed that the total effect of CT on treatment adherence was significant ($B = -0.050$, $p < .001$) and that this association was mediated by lower interpersonal physician–patient connection ($B = -0.014$, $p = .019$).

Conclusions: These findings suggest that CT may negatively affect treatment adherence in patients with MS and that this association is significantly mediated by difficulties in the physician–patient interpersonal connection, highlighting the importance of targeted psychological interventions to improve disease management and patient care.

1. Introduction

Childhood trauma (CT), such as physical, sexual, and emotional abuse and neglect, is associated not only with an increased risk of developing many chronic physical diseases (Nelson et al., 2020), but there is also evidence that in several cases it negatively affects treatment response and adherence (Bellis et al., 2024). CT significantly hinders the relationship with physicians and treatment adherence due to difficulties in regulating emotions and behaviors, poor self-care skills, a sense of distrust in oneself and others, and difficulty trusting care relationships (Farina and Schimmenti, 2025). Multiple sclerosis (MS) is a chronic inflammatory disease in which treatment adherence represents a key component of disease management and one of the most important modifiable factors influencing clinical outcomes (Rodriguez de Antonio et al., 2025). The complexity of MS extends beyond physical disability,

as cognitive and behavioral involvement is frequent and psychiatric comorbidities are commonly reported (Menculini et al., 2023). These features may influence patients' engagement with care and adherence to prescribed therapies (Washington and Langdon, 2022). As in other neuroinflammatory and autoimmune diseases, CT is recognized as playing a possible role in determining the disease and its course, severity and management of MS (Vitturi et al., 2023), but this role has been scarcely studied (Bruce et al., 2010; Khaw et al., 2021; Polick et al., 2022). In particular, there are still limited data on the role of CT and its relational consequences in influencing treatment adherence, which is known to be a critical component in the management of this disease (Patti, 2010). Investigating factors associated with therapeutic compliance, including psychosocial and relational aspects, may provide clinically relevant insights into mechanisms that contribute to variability in treatment behaviors in this medical condition. With this in mind, the

* Corresponding author.

E-mail addresses: cicia.alessandra@gmail.com (A. Cicia), massimiliano.mirabella@unicatt.it (M. Mirabella).

¹ These authors contributed equally to this work.

² These authors jointly supervised this work.

<https://doi.org/10.1016/j.msard.2026.107387>

Received 5 March 2026; Received in revised form 24 June 2026; Accepted 9 July 2026

Available online 10 July 2026

2211-0348/© 2026 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

aim of this study is to investigate, in patients with MS, the association between CT and treatment adherence, and to test the potential mediating role of interpersonal physician-patient connection in this association.

2. Methods

2.1. Participants

According to the sample size guidelines of [Fritz and MacKinnon \(2007\)](#), assuming small/medium effect sizes for both the “a” and “b” paths (i.e., 0.26) in the mediation model, the analyses required minimum sample size of 162 with the percentile bootstrap procedure to provide a statistical power of 0.80.

Between December 2024 and December 2025, 205 patients with MS attending the Multiple Sclerosis Center of the Policlinico Universitario Agostino Gemelli IRCCS, Rome, were consecutively enrolled in this observational study. Eligibility criteria included: i) age ≥ 18 years, ii) a diagnosis of relapsing multiple sclerosis (RMS) according to the 2017 McDonald criteria ([Thompson et al., 2018](#)), iii) the provision of written informed consent. Exclusion criteria comprised the presence of language barriers or any condition potentially affecting comprehension or the accurate completion of questionnaires. Patients were recruited during routine clinical visits. After providing written informed consent, participants completed a set of electronic questionnaires administered via tablet.

The study protocol was approved by the Comitato Etico Territoriale Lazio Area 3 – Rome (approval issued on November 6, 2024; administrative resolution dated November 21, 2024) and was registered on ClinicalTrials.gov (identifier: NCT06718920) on December 2, 2024. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Assessment procedure

All patients had a confirmed diagnosis of MS at the time of enrolment. Sociodemographic (i.e., biological sex, age, educational level, occupation, marital status) and clinical data (i.e., alcohol use and tobacco use, current MS medications status, and medical comorbidity) were collected at the study entry. Neurological disability was assessed at enrolment and using the Expanded Disability Status Scale (EDSS; [Kurtzke, 1983](#)). Patients were also asked to complete the following self-report measures: The Childhood Trauma Questionnaire - Short Form (CTQ-SF; [Scher et al., 2001](#)), the “rapport” dimension of the Medical Interview Satisfaction Scale (MISS-21; [Meakin and Weinman, 2002](#)) and the Morisky Medication Adherence Scale (MMAS; [Morisky et al., 2008](#)). A detailed description of these tools as well as of the diagnostic work-up is provided in the **Supplementary Materials**.

3. Statistical analysis

All analyses were performed using the SPSS (20.0) statistical package (IBM, Armonk, NY, USA). The association between the main study variables was investigated using Pearson’s r correlation coefficient. To investigate whether the association between CT and medication adherence was mediated by physician-patient rapport, a single mediation analysis was performed by means of the “Model 4” method of SPSS Macro Process v3.5 ([Hayes, 2012](#)) using 5000 bootstrap samples. In this model CTQ total score was set as the independent variable, MMAS total score as the dependent variable, and MISS-21 rapport dimension as the mediator. Potential socio-demographic and clinical data were included as covariates. Following [Baron and Kenny \(1986\)](#), three separate paths were reported: i) path a (i.e., the direct effect of CT on MISS-21 rapport dimension), ii) path c' (i.e., the direct effect of CTQ on MMAS total score), iii) path c (i.e., the total effect of CT on MMAS total score, summing the direct and indirect effect). Path b (i.e., the association of

MISS-21 rapport dimension with MMAS total score) and path ab (i.e., the indirect effect of CT on medication adherence through interpersonal physician-patient connection) are also shown graphically.

4. Results

The descriptive statistics of the current sample and the zero-order correlations are reported in [Table 1](#) and **Supplementary Table 1**, respectively.

The results of mediational model (i.e., CTQ total score as the independent variable, MMAS total score as the dependent variable, and MISS-21 rapport dimension as the mediator) is shown graphically in [Fig. 1](#) and reported in full in **Supplementary Table 2**. The total effect was negative and significant [$B = -.042$, $SE = .014$ (95% CI: $-.069$; $-.015$), $p = .002$], suggesting that higher CTQ scores were associated with lower medication adherence. Moreover, the effect of CTQ scores were negative and significant on physician-patient rapport [$B = -.181$, $SE = .046$ (95% CI: $-.271$; $-.090$), $p < .001$]. In turn, physician-patient rapport was positively associated with medication adherence [$B = .082$, $SE = .021$ (95% CI: $.041$; $.123$), $p < .001$]. The direct effect of CT on medication adherence was negative and significant [$B = -.027$, $SE = .014$ (95% CI: $-.054$; $-.0002$), $p = .048$]. The indirect effect via physician-patient rapport was also negative and significant [$B = -.015$, $BootSE = .006$ (95% CI: $-.028$; $-.005$) $p = .012$] suggesting that the association between CT and medication adherence was significantly mediated by lower interpersonal physician-patient connection.

5. Discussion

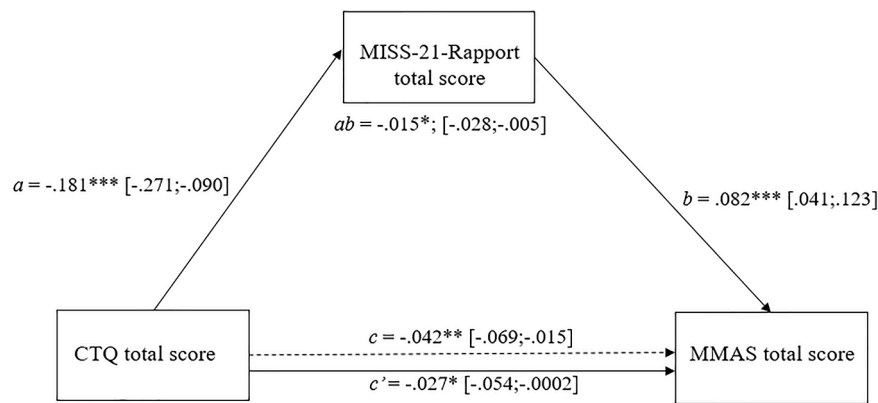
The results of this study confirm that CT can affect treatment adherence in patients with MS, regardless of the severity of their disability and medication status. Furthermore, as expected, our study showed that this association is significantly mediated by lower scores in patients’ perceived interpersonal connection and trust during the

Table 1
Descriptive statistics of the sample (N = 205).

Age – M $\pm$ SD / Median (IQR)	38.36 $\pm$ 10.00 / 37 (31.50–46)
Females – N (%)	154 (75.1)
Unemployed – N (%)	44 (21.5)
Bachelor’s Degree or higher – N (%)	121 (59.0)
Married or living with partner – N (%)	110 (53.7)
Socioeconomic status (SES)*	
Low – N (%)	17 (8.3)
Medium – N (%)	115 (56.1)
High – N (%)	73 (35.6)
Tobacco use – N (%)	58 (28.3)
Alcohol use – N (%)	63 (30.7)
Current MS medications	
None medications – N (%)	14 (6.8)
Higher Efficacy medications – N (%)	163 (79.5)
Low/Moderate Efficacy medications – N (%)	28 (13.7)
MS medication route of administration	
Intravenous – N (%)	148 (72.2)
Oral – N (%)	41 (20.0)
Subcutaneous – N (%)	2 (1.0)
Medical or psychiatric comorbidity – N (%)	28 (13.7)
CTQ Total score – M $\pm$ SD / Median (IQR)	35.37 $\pm$ 8.83 / 32 (30–38)
CTQ denial dimension – M $\pm$ SD / Median (IQR)	11.28 $\pm$ 2.81 / 12 (10–13)
MISS-21 rapport dimension – M $\pm$ SD / Median (IQR)	24.25 $\pm$ 4.14 / 26 (22–28)
MMAS Total score – M $\pm$ SD / Median (IQR)	7.26 $\pm$ 1.29 / 8 (7–8)
EDDS Total score – M $\pm$ SD / Median (IQR)	1.95 $\pm$ 1.20 / 1.5 (1–2.5)

Note: * SES was calculated using education, employment status, and area of residence according to [d’Errico et al. \(2017\)](#).

Abbreviation: M= mean; SD= standard deviation; IQR= Interquartile Range; MS= Multiple Sclerosis; CTQ= Childhood Trauma Questionnaire; MISS-21= Medical Interview Satisfaction Scale; MASS= Morisky Medication Adherence Scale; EDSS= Expanded Disability Status Scale.



$$R^2 = .243; F_{13; 191} = 4.711***$$

Fig. 1. Graphical representation of the results from the mediation model.

Abbreviation: CTQ= Childhood Trauma Questionnaire; MISS-21= Medical Interview Satisfaction Scale; MASS: Morisky Medication Adherence Scale; MS= Multiple Sclerosis; EDSS= Expanded Disability Status Scale.

Note: The reported estimates were obtained controlling for potentially competing factors (i.e., sex, age, educational level; alcohol use and tobacco use, occupation, marital status, EEDS total score, current MS medications status, denial subscale of the CTQ and medical comorbidity).

*= $p < .05$; **= $p < .01$; ***= $p < .001$.

interaction with their physician (i.e., the MISS-21 rapport dimension total score).

It has been widely demonstrated that the presence of CT negatively affects treatment adherence for several reasons: emotional and behavioral difficulties, poor coping resources, feelings of mistrust and helplessness, and an increased risk of developing concomitant psychiatric disorders such as anxiety and depression, which further reduce adherence (Corallo et al., 2019). One of the most typical consequences of CT that creates the greatest clinical difficulties in the treatment of physical illnesses is a lack of trust in others, particularly caregivers and doctors. These difficulties are caused by the fact that over 90% of child abuse is perpetrated by one or both parents, which generates negative expectations and problems in subsequent care relationships (Farina and Schimmenti, 2025).

In patients with MS, effective disease management depends on sustained adherence to treatment and scheduled clinical monitoring. However, psychosocial factors, including emotional, cognitive, and relational dimensions, may meaningfully interfere with patients' engagement in clinical care and compromise the continuity of treatment over time (Patti, 2010; Rodriguez de Antonio et al., 2025; Washington and Langdon, 2022). Furthermore, it should be considered that traumatic experiences during childhood may also have broader implications for MS disease course, potentially through both psychological (e.g., dysfunctional coping strategies) and biological mechanisms (e.g., long-lasting alterations in stress-response systems and inflammatory processes) that may be involved in MS-related outcomes (Mitsonis et al., 2009; Polick et al., 2022).

Thus, regardless of its limitations (e.g. the use of self-reports, the cross-sectional approach which preclude to establish the cause-effect relationship between the study variables), our findings are have important clinical implications. Specifically, physicians should be increasingly aware of the potential presence of CT in patients with MS, as these experiences are likely underrecognized in routine clinical practice, and consider incorporating CT assessment into clinical evaluation to identify patients who may benefit from targeted psychological interventions (Bruce et al., 2010).

Our results underscore the importance of considering relational and psychological dimensions within routine clinical management (Rodriguez de Antonio et al., 2025; Washington and Langdon, 2022), as

they may represent modifiable targets to improve adherence and optimize long-term care in this population. Future studies should investigate whether targeted psychological interventions for people with MS and a history of CT may improve treatment adherence and clinical outcomes. Moreover, further research is needed to examine whether different types of CT may differentially influence these associations. A person-centered approach integrating psychological assessment into MS care may contribute to improved disease management.

CRediT authorship contribution statement

Ambra Salvati: Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Alessandra Cicia:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Assunta Bianco:** Investigation, Project administration, Writing – review & editing. **Matteo Lucchini:** Project administration, Writing – review & editing. **Marco Bisurgi:** Data curation, Writing – review & editing. **Claudio Imperatori:** Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Benedetto Farina:** Conceptualization, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Massimiliano Mirabella:** Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Role of funding source

This research did not receive any specific funding source. No funding source had any role in the design of the study, data collection, analysis or interpretation of the data, writing of the manuscript, or the decision to submit the article for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.msard.2026.107387](https://doi.org/10.1016/j.msard.2026.107387).

References

- Baron, R.M., Kenny, D.A., 1986. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J. Pers. Soc. Psychol.* 51, 1173–1182. <https://doi.org/10.1037//0022-3514.51.6.1173>.
- Bellis, M.A., Hughes, K., Ford, K., Sharp, C., Hill, R., 2024. Associations between adverse childhood experiences and trust in health and other information from public services, professionals and wider sources: national cross sectional survey. *BMJ Public Health* 2, e000868. <https://doi.org/10.1136/bmjph-2023-000868>.
- Bruce, J.M., Hancock, L.M., Arnett, P., Lynch, S., 2010. Treatment adherence in multiple sclerosis: association with emotional status, personality, and cognition. *J. Behav. Med.* 33, 219–227. <https://doi.org/10.1007/s10865-010-9247-y>.
- Corallo, F., Bonanno, L., Di Cara, M., Rifici, C., Sessa, E., D'Aleo, G., Lo Buono, V., Venuti, G., Bramanti, P., Marino, S., 2019. Therapeutic adherence and coping strategies in patients with multiple sclerosis: an observational study. *Medicine* 98, e16532. <https://doi.org/10.1097/MD.00000000000016532>.
- d'Errico, A., Ricceri, F., Stringhini, S., Carmeli, C., Kivimäki, M., Bartley, M., McCrory, C., Bochud, M., Vollenweider, P., Tumino, R., Goldberg, M., Zins, M., Barros, H., Giles, G., Severi, G., Costa, G., Vineis, P., 2017. Socioeconomic indicators in epidemiologic research: a practical example from the LIFEPAth study. *PLoS One* 12, e0178071. <https://doi.org/10.1371/journal.pone.0178071>.
- Farina, B., Schimmenti, A., 2025. The psychopathological domains of attachment trauma: a proposal for a clinical conceptualization. *Clin. Neuropsychiatry* 22, 351–373. <https://doi.org/10.36131/cnforitieditore20250501>.
- Fritz, M.S., Mackinnon, D.P., 2007. Required sample size to detect the mediated effect. *Psychol. Sci.* 18, 233–239. <https://doi.org/10.1111/j.1467-9280.2007.01882.x>.
- Hayes, A.F., 2012. PROCESS: a versatile computational tool for observed variable mediation, moderation, and conditional process modeling.
- Khaw, Y.M., Majid, D., Oh, S., Kang, E., Inoue, M., 2021. Early-life-trauma triggers interferon-beta resistance and neurodegeneration in a multiple sclerosis model via downregulated beta1-adrenergic signaling. *Nat. Commun.* 12, 105. <https://doi.org/10.1038/s41467-020-20302-0>.
- Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 33, 1444–1452. <https://doi.org/10.1212/wnl.33.11.1444>.
- Meakin, R., Weinman, J., 2002. The 'Medical interview satisfaction scale' (MISS-21) adapted for British general practice. *Fam. Pract.* 19, 257–263. <https://doi.org/10.1093/fampra/19.3.257>.
- Menculini, G., Mancini, A., Gaetani, L., Bellingacci, L., Tortorella, A., Parnetti, L., Di Filippo, M., 2023. Psychiatric symptoms in multiple sclerosis: a biological perspective on synaptic and network dysfunction. *J. Neurol. Neurosurg. Psychiatry* 94, 389–395. <https://doi.org/10.1136/jnnp-2022-329806>.
- Mitsonis, C.I., Potagas, C., Zervas, I., Sfigos, K., 2009. The effects of stressful life events on the course of multiple sclerosis: a review. *Int. J. Neurosci.* 119, 315–335. <https://doi.org/10.1080/00207450802480192>.
- Morisky, D.E., Ang, A., Krousel-Wood, M., Ward, H.J., 2008. Predictive validity of a medication adherence measure in an outpatient setting. *J. Clin. Hypertens (Greenwich)* 10, 348–354. <https://doi.org/10.1111/j.1751-7176.2008.07572.x>.
- Nelson, C.A., Scott, R.D., Bhutta, Z.A., Harris, N.B., Danese, A., Samara, M., 2020. Adversity in childhood is linked to mental and physical health throughout life. *BMJ* 371, m3048. <https://doi.org/10.1136/bmj.m3048>.
- Patti, F., 2010. Optimizing the benefit of multiple sclerosis therapy: the importance of treatment adherence. *Patient Prefer Adherence* 4, 1. <https://doi.org/10.2147/ppa.s8230>.
- Polick, C.S., Polick, S.R., Stoddard, S.A., 2022. Relationships between childhood trauma and multiple sclerosis: a systematic review. *J. Psychosom. Res.* 160, 110981. <https://doi.org/10.1016/j.jpsychores.2022.110981>.
- Rodríguez de Antonio, L.A., Fernández de Córdoba-García, R., Herrero-Munoz, N., Ontanon-Nasarre, A., García-Castanon, I., 2025. Treatment adherence in patients with multiple sclerosis: risk factors. *Neurol. (Engl. Ed.)* 40, 353–360. <https://doi.org/10.1016/j.nrleng.2025.04.013>.
- Scher, C.D., Stein, M.B., Asmundson, G.J., McCreary, D.R., Forde, D.R., 2001. The childhood trauma questionnaire in a community sample: psychometric properties and normative data. *J. Trauma. Stress* 14, 843–857. <https://doi.org/10.1023/A:1013058625719>.
- Thompson, A.J., Banwell, B.L., Barkhof, F., Carroll, W.M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M.S., Fujihara, K., Galetta, S.L., Hartung, H.P., Kappos, L., Lublin, F.D., Marrie, R.A., Miller, A.E., Miller, D.H., Montalban, X., Mowry, E.M., Sorensen, P.S., Tintore, M., Traboulsee, A.L., Trojano, M., Uitdehaag, B.M.J., Vukusic, S., Waubant, E., Weinshenker, B.G., Reingold, S.C., Cohen, J.A., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 17, 162–173. [https://doi.org/10.1016/S1474-4422\(17\)30470-2](https://doi.org/10.1016/S1474-4422(17)30470-2).
- Vitturi, B.K., Rahmani, A., Dini, G., Montecucco, A., Debarbieri, N., Bandiera, P., Ponzio, M., Battaglia, M.A., Brichetto, G., Inglese, M., Persechino, B., Durando, P., 2023. Work barriers and job adjustments of people with Multiple sclerosis: a systematic review. *J. Occup. Rehabil.* 33, 450–462. <https://doi.org/10.1007/s10926-022-10084-1>.
- Washington, F., Langdon, D., 2022. Factors affecting adherence to disease-modifying therapies in multiple sclerosis: systematic review. *J. Neurol.* 269, 1861–1872. <https://doi.org/10.1007/s00415-021-10850-w>.