Journal of Statistics on Health Decision

EXTENDED ABSTRACT

A34 Body mass index in patients with Multiple Sclerosis: a meta-analysis

Laura J. J. O. Castro[1], Alexandre L. Pereira[1], Nuno F.L.O. Ribeiro[1],

[1]University of Aveiro, Department of Medical Sciences, Campus Universitário de Santiago, Agra do Crastro, Edifício 30, 3810-193, Aveiro Portugal

Introduction

Multiple sclerosis (MS) is a type of central nervous system autoimmune illness. The disease's principal characteristic is damage to myelin and axons, which causes neurological impairment, notably in people in their third and fifth decades of life [1],[2]. Weight (in kilograms) per square meter is used to compute the body mass index (BMI) [3],[4]. It is a measure of tissue mass that plays a role in some neurodegenerative illnesses including Huntington's disease. However, the various processes by which BMI impacts MS are still not completely understood. Obesity in adolescence is one of the factors that has been linked to the risk of MS [5],[6]. Furthermore, a higher BMI appears to be linked to a poor MS prognosis. Overweight and obese MS patients have been found to have higher disease activity, while MS patients with an abnormal lipid profile, indicating a change in lipid metabolism, had acquired more impairment [7],[8],[9].

The etiology of this disease is not yet known but there are multiple environmental factors that have been shown to be associated with an increased risk of developing multiple sclerosis: infection by the Epstein-Barr virus, smoking, low levels of vitamin D and changes in the intestinal microbiome [10],[11]. There are several mechanisms that explain the increased risk of autoimmune pathology associated with obesity: adipocytes secrete high levels of TNF-alpha and IL-6, which are proinflammatory and induce a dysregulation between the levels of Th17 and Treg cells, in addition to the deficit of vitamin D that is more frequent in obese people, also contributing to the pro-inflammatory state [12].

There is a lot of information about the possible triggers for multiple sclerosis however there is a lack of knowledge regarding the pathogenic mechanisms responsible for the course of the disease which can be illustrated by the few explicit data concerning the influence of BMI on the progression of the disease. In practical terms, it would be more clinically valuable the discovery of evidences that elucidate if between the loss or gain of weight which has the better therapeutic effect for the patients with MS. Will the progression of the disease be slower? Will they be less incapacitated if they lose weight? Multiple sclerosis is a neuroinflammatory and neurodegenerative disease and there are neurodegenerative diseases, such as Huntington's disease, referred to above, or Amyotrophic Lateral Sclerosis in which weight loss can be harmful to patients.

From this point of view, this meta-analysis is mainly dedicated in the characterization of the population with MS based in their BMI. In a near future, new studies should be devoted in correlation of these data with disease activity and functional status of patients (EDSS or annualized rate of outbreaks, if this information is present in the studies).

Methods

Literature search strategy

Initially, the authors of the article that was chosen ("Body mass index in patients with Multiple Sclerosis: a meta-analysis" by Efthimios Dardiotis et al [13]) performed a systematic research of the literature in the online database PubMed to identify related studies between the beginning of the database and January 2018, using the following search terms with multiple combinations: "Body Mass Index", "Multiple Sclerosis", "MS" and "BMI". Subsequently, it was carried out a search in order to find more recent articles to complement the data up to January 2021. To accomplish this, the same database was used with the following search terms: "BMI" and "Multiple Sclerosis".

Data extraction

The titles and the abstracts of the search results were firstly screened. The full texts of the eligible studies were then assessed. The data from each selected study were obtained through research, which includes the following variables: main author, year of publication, country, sample size, mean and standard deviation (SD) of body mass and mean age index levels. EDSS scores were extracted when available.

Keywords:
Body Mass Index, Multiple Sclerosis, Meta-analysis, MS, BMI, Systematic Review

Corresponding author:
Laura Castro
lauracastro@ua.pt

Supplementary material:
Available online: Link
Table A1; Figures A1 to A6)

Conflict of interest:
The authors declare no conflict of interests.

First published: 22JUN2021

Inclusion criteria

The articles were selected in this meta-analysis based on the following inclusion criteria: casecontrol studies, studies with data from patients with MS and healthy controls; age over 18 years; detailed data (including mean and standard deviation) on the BMI in both the MS and control groups; studies in human beings; studies written in English. On the other hand, studies were excluded if they were review articles, did not have a control group, or contained overlapping or insufficient data.

Statistical analysis

The Z test was used to evaluate the SMD (Standardized Mean Difference) and the 95 % CI for the difference in mean BMI between patients with MS and control groups. Statistical significance was defined as a value less than 0.05 ($p < 0.05$). Cochran's Q and I^2 tests were used to determine heterogeneity. The random effects model was used when there was a lot of heterogeneity, such as pvalues less than 0.10 and/or I^2 more than 75%. Funnel plots were used to visualize the publishing bias.

All statistical analyses were performed using RStudio Version 4.0.3.

Results

Description of the included studies

336 studies, published between 1997 and January 2021, were found after searching the PubMed database and screening references. Following the screening of titles, abstracts, and full texts, 175 research were left to be assessed for eligibility. The following research and patient groups were then excluded: 63 studies in which there were no healthy control groups; There are 48 studies that do not provide the BMI for people with MS or healthy controls; 25 researches involving BMI groupings or height and weight measurements; 6 studies included pediatric MS patients; 2 studies only provided BMI at the age of 20. According to the adopted criteria, the quantitative synthesis in the first stage of the meta-analysis contained 31 trials with 3248 MS patients and 3561 healthy controls. The second section contained 26 research with 1914 MS patients and 2227 healthy controls. Finally, 24 papers with 1671 MS patients and 1994 healthy people were included in the meta-analysis's final section. The process of study selection is presented in a flow diagram (Figure 1).

The characteristics of the 31 studies included in the first part of the research can be found at Table A1 (supplementary material). The studies were published between 1997 and 2020. All of them were case-control studies. EDSS scores were available for all studies except 8. The BMI was calculated from patients' body weight and height (kg/m^2) during the disease.

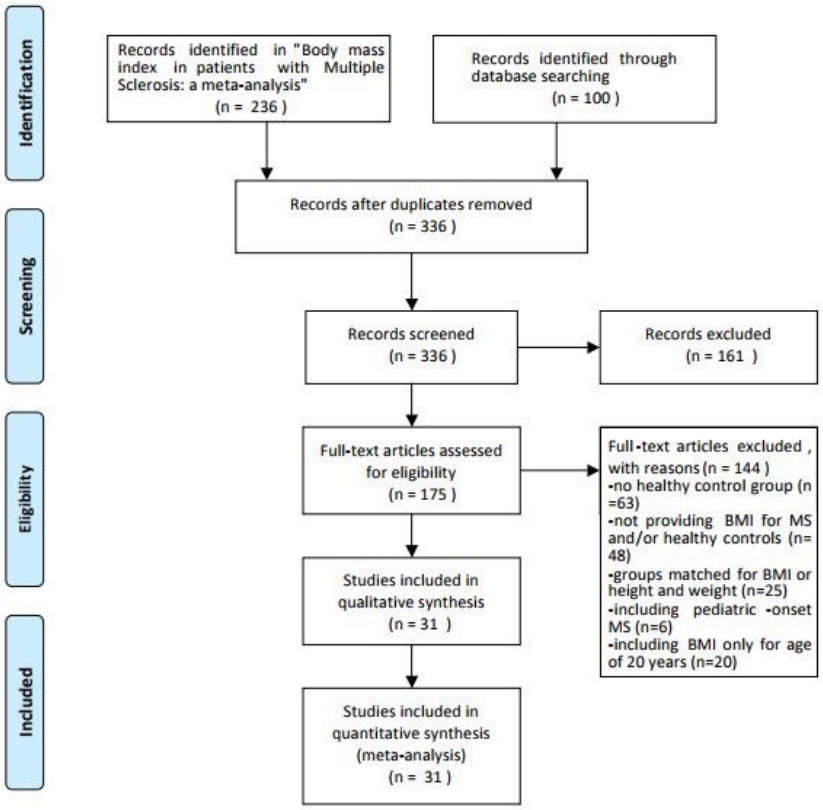

Figure 1 - Flow chart presenting the selection process of the eligible studies for the meta-analysis.

Meta-analysis results

From the analysis made to the forest plot, present in Figure 2, it was found that the mean BMI in patients with MS during the course of the disease is significantly lower than the healthy controls. The Cochran Q statistic was used to assess heterogeneity between studies, and subsequently quantified with I^2, which was used to estimate the effect of heterogeneity between studies. According to the Cochran test, it was possible to conclude that there is heterogeneity between the studies since the p-value (<0.0001) is less than 0.1. Considering the value of I^2, it appears that the heterogeneity is high (89.7%). As there is a high heterogeneity, the most appropriate model to use is the random effects model.

Subsequently, the publication bias was analyzed by using the funnel plot (Figure A1, supplementary material), the Egger test and the Begg and Mazumdar test. When observing the funnel plot, it is concluded that it does not present significant graphic asymmetry. As the p-values for the Egger test and the Begg and Mazumbar test (0.7096 and 0.7467, respectively) are greater than 0.05, the presence of publication bias is not suspected.

In addition, the Rosenthal test was performed in order to complement the results in relation to the publication bias and it was possible to observe that, as expected, the publication bias did not constitute a problem since the calculated FSN (464) was very higher than the cutoff value (165). The Trim and Fill test was also performed and, as no studies were added, it appears that there are no relevant studies that have not been analyzed.

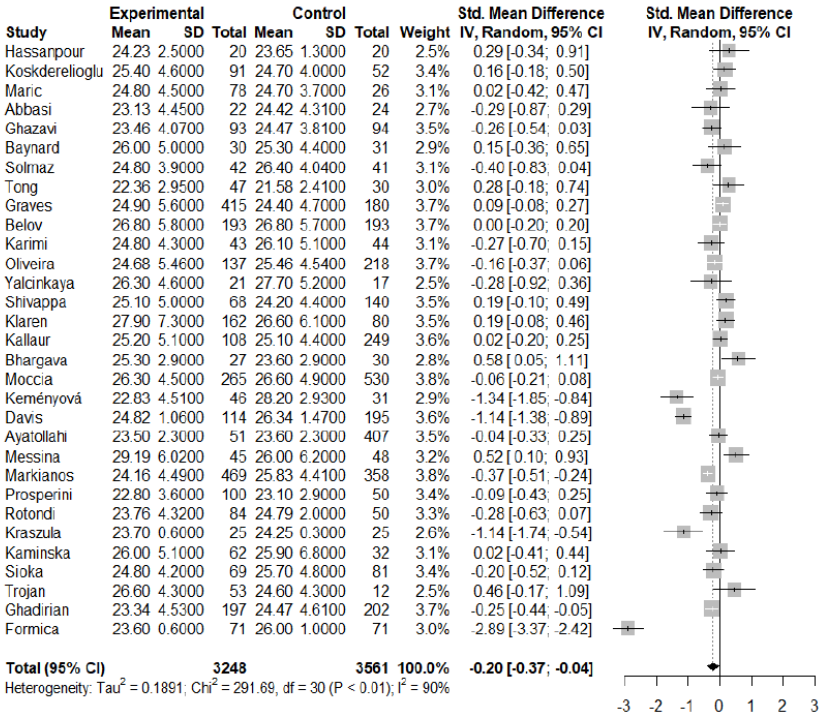

Figure 2 - Forest plot: SMD of BMI between MS patients and healthy controls.

Sensitivity analysis results

Then, a sensitivity analysis was performed based on the analysis excluding individual studies. It is possible to see in figure 3 that whenever CIs do not intersect the null effect line, omitting the effects of individual studies, the effect is statistically significant. The opposite occurs in the Formica study, since it intersects the null effect line, and it is not possible to state that it is statistically significant, which reveals some lack of agreement in the data set.

Influence analysis results

Finally, an influence analysis was performed (Figure A2, supplementary material) in order to find out if there were atypical studies. This test identifies the most influential studies on the overall result, that is, the studies that most contribute to the levels of heterogeneity found in the analysis. Through this analysis it is concluded that 5 studies are considered atypical (Davis, Formica, Graves, Moccia and Markianos). With the knowledge of the existence of atypical studies, it was decided to withdraw them and execute the meta-analysis again, with the objective of determining the weight of these studies in the meaning of the overall result. When looking at the forest plot (Figure A3, supplementary material), it appears that, without the

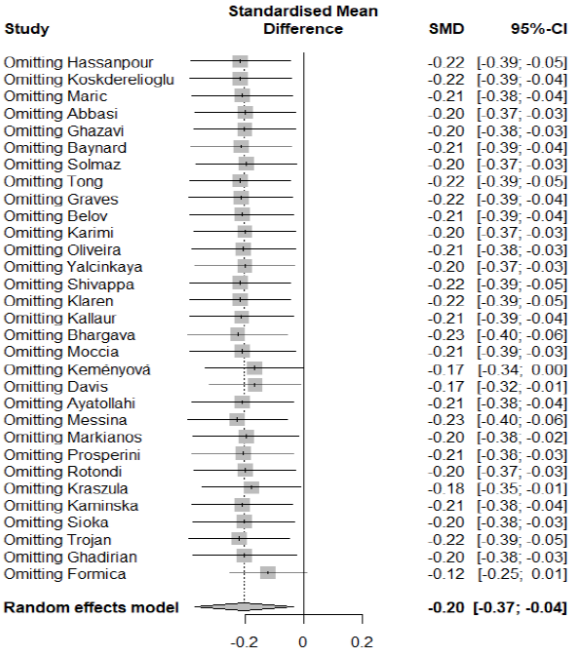

Figure 3 - Forest plot: SMD of BMI between MS patients and healthy controls, omitting individual studies.

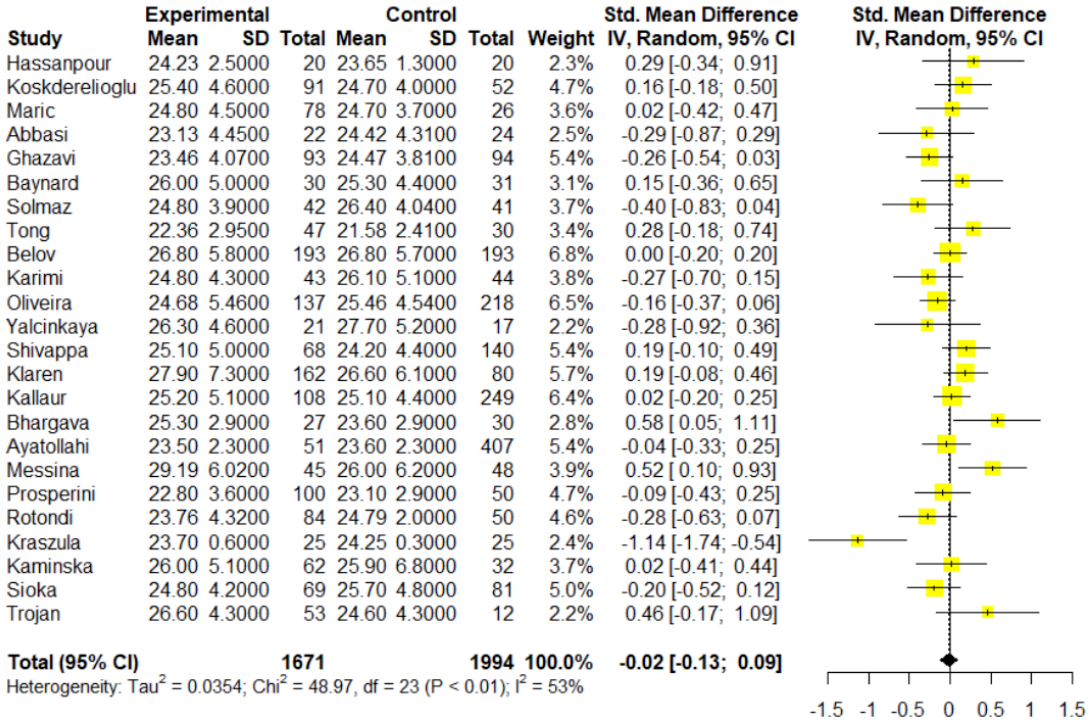

Figure 3 - Forest plot: SMD de BMI between MS patients during the course of the disease and healthy controls, without 7 atypical studies.

atypical studies, the effect is no longer significant compared to the data set with the atypical values. It was decided to carry out a second analysis of influence (Figure A4, supplementary material) in order to investigate whether atypical studies still existed. In this sense, the existence of two more atypical studies (Keményova and Ghadirian) was identified. To obtain a data set without atypical studies, the meta-analysis was performed again, with the 24 studies. Looking at the forest plot (Figure 4), it is interpreted that, without the atypical studies, the effect is still not significant when compared with the data set of the forest plot of the set with 26 studies.

Meta-regression results

In order to explain the heterogeneity of this meta-analysis, a meta-regression was effectuated using the maximum likelihood method. In this sense, two co variables of the sample were studied: the region, which

classifies the country from each group of individuals of the selected studies in developed or in development and the year of publication of the study. The vif values obtained point to the lack of multicollinearity between the co-variables. The observation of the bubble plot (Figure A5, supplementary material) and the baujat plot (Figure A6, supplementary material), leads to believe that the study 31 (Formica) is related to the high heterogeneity present in this meta-analysis, since it stands out for presenting the greatest atypicality.

Discussion:

The main purpose of this work was to investigate if there was a link between mean BMI and MS in this meta-analysis. The average BMI of MS patients, during the course of the disease, was considerably lower in comparison to the healthy controls in the initial half of the study. It includes a higher number of sick and healthy people in relation to the earlier research. In total, 3248 MS patients and 3561 healthy controls were incorporated in this meta-analysis. At first appearance, BMI appears to be unhealthy in MS patients compared to healthy controls, but after a more thorough examination of the available data, it was discovered that there are some studies that are inconsistent, particularly in the case of Formica. In fact, the study of sensitivity, the study of effect, and the analysis of meta-regression all agreed that this article has an impact on the data set's heterogeneity. When it comes to BMI in MS patients, there is a lot of debate. Several studies have linked a high BMI during adolescence and childhood to an increased chance of getting MS [14]. In adulthood, however, there is no clear link [6]. The majority of research on BMI during the course of the disease found no link, with only a handful demonstrating that MS patients had either a lower or higher BMI than controls. Two studies in particular (Messina and Klaren) found that patients had a higher BMI. Overall, the findings of the study are far from unanimous. Despite the notion that obesity is a risk factor for MS, our findings show that BMI in MS patients is much lower during the disease. Nonetheless, the accumulation of handicap, combined with limited independence and other eating problems, may all contribute to a lower BMI over time. Obesity has been associated to an increase in autoimmune and immune-mediated illnesses [15]. As an endocrine organ, adipose tissue produces adipokines including leptin, adiponectin, and resistin, which cause inflammation and are linked to autoimmune illnesses like MS [15]. Obesity prevalence and the connection between obesity and the risk of MS, on the other hand, varies greatly amongst populations [16]. Individuals who are genetically inclined to having a high BMI have also been associated to an increased risk of MS [17]. All of the foregoing show that MS is a systemic immune-mediated illness in which BMI plays a significant role in the genesis and progression. In theory, dietary variables can affect MS through a number of pathophysiological routes [18]. Diet may influence MS pathophysiology processes such as inflammation, remyelination, neuronal repair, and neuroprotection, to name a few [18]. Diet and metabolite synthesis, which may impact vascular MS risk factors, could be to blame for these effects [19].

There are some drawbacks to this study. For all research participants analyzed in this analysis, detailed information on characteristics of the included studies, such as type of MS, degree of impairment, and disease duration, was not accessible. Furthermore, factors such as ethnicity, EDSS score, and/or disease duration may have influenced the estimated relationships, which were not assessed in the current meta-analysis. Finally, lifestyle factors such as smoking and drinking, which were not recognized in all of the included research, can be blamed for the substantial heterogeneity between the researches. This study adds to the body mass index (BMI) disparity between MS patients and healthy people, reinforcing the assumption that BMI is an important parameter to consider in MS. Furthermore, these findings point to the necessity for future research with more detailed clinical and demographic data in order to fully understand the association between mean BMI in MS patients and healthy controls.

Acknowledgements:

This work was developed with the help of Dra. Joana Novo from the Neurology Department, Centro Hospitalar de vila Nova de Gaia/ Espinho, Vila Nova de Gaia, Portugal and Dra. Vera Afreixo, Assistant Professor at the Department of Mathematics of the University of Aveiro, Researcher at the Institute for Biomedicine –Aveiro (iBi-MED), CIDMA and IEETA.

References:

1. A. Jamali, E. Sadeghi-Demneh, N. Fereshtenajad, and S. Hillier, “Somatosensory impairment and its association with balance limitation in people with multiple sclerosis,” Gait Posture, vol. 57, no. 320, pp. 224–229, 2017, https://doi.org/10.1016/j.gaitpost.2017.06.020
2. R. M. Ransohoff, D. A. Hafler, and C. F. Lucchinetti, “Multiple sclerosis - A quiet revolution,” Nat. Rev. Neurol., vol. 11, no. 3, pp. 134–142, 2015, https://doi.org/10.1038/nrneurol.2015.14
3. N. E. J. Med, P. M. C. May, P. Health, S. Room, and L. T. Schulz, “Association Between Change in Body Mass Index, Unified Parkinson’s Disease Rating Scale Scores, and Survival Among Persons With Parkinson Disease,” vol. 379, no. 20, pp. 1971–1972, 2020, https://doi.org/10.1001/jamaneurol.2015.4265.Association
4. P. Zeng, X. Yu, and H. Xu, “Association between premorbid body mass index and amyotrophic lateral sclerosis: Causal inference through genetic approaches,” Front. Neurol., vol. 10, no. MAY, pp. 1–10, 2019, https://doi.org/10.3389/fneur.2019.00543
5. A. K. Hedström, T. Olsson, and L. Alfredsson, “High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women,” Mult. Scler. J., vol. 18, no. 9, pp. 1334–1336, 2012, https://doi.org/10.1177/1352458512436596

6. K. L. Munger, T. Chitnis, and A. Ascherio, “Body size and risk of MS in two cohorts of US women,” Neurology, vol. 73, no. 19, pp. 1543–1550, 2009, https://doi.org/10.1212/WNL.0b013e3181c0d6e0
7. P. Tettey et al., “An adverse lipid profile and increased levels of adiposity significantly predict clinical course after a first demyelinating event,” J. Neurol. Neurosurg. Psychiatry, vol. 88, no. 5, pp. 395–401, 2017, https://doi.org/10.1136/jnnp-2016-315037
8. S. S. Kvistad et al., “Body mass index influence interferon-beta treatment response in multiple sclerosis,” J. Neuroimmunol., vol. 288, pp. 92–97, 2015, https://doi.org/10.1016/j.jneuroim.2015.09.008
9. P. Tettey et al., “An adverse lipid profile is associated with disability and progression in disability, in people with MS,” Mult. Scler. J., vol. 20, no. 13, pp. 1737–1744, 2014, https://doi.org/10.1177/1352458514533162
10. M. A. Gianfrancesco et al., “Obesity during childhood and adolescence increases susceptibility to multiple sclerosis after accounting for established genetic and environmental risk factors,” vol. 8, no. 5, pp. 1–20, 2015, https://doi.org/10.1016/j.orcp.2014.01.002.Obesity
11. E. À. Barr, “Obesity interacts with infectious mononucleosis in risk of multiple sclerosis,” pp. 578–585, 2014, https://doi.org/10.1111/ene.12620
12. C. Valburg, A. Sonti, J. N. H. Stern, S. Najjar, and A. Harel, “Dietary factors in experimental autoimmune encephalomyelitis and multiple sclerosis : A comprehensive review,” pp. 1–9, 2020, https://doi.org/10.1177/1352458520923955
13. E. Dardiotis et al., “Body mass index in patients with Multiple Sclerosis : a meta-analysis Body mass index in patients with Multiple Sclerosis : a meta-analysis,” Neurol. Res., vol. 41, no. 9, pp. 836–846, 2019, https://doi.org/10.1080/01616412.2019.1622873
14. A. K. Hedström, T. Olsson, and L. Alfredsson, “Body mass index during adolescence, rather than childhood, is critical in determining MS risk,” Mult. Scler., vol. 22, no. 7, pp. 878–883, 2016, https://doi.org/10.1177/1352458515603798
15. M. Versini, P. Y. Jeandel, E. Rosenthal, and Y. Shoenfeld, “Obesity in autoimmune diseases: Not a passive bystander,” Autoimmun. Rev., vol. 13, no. 9, pp. 981–1000, 2014, https://doi.org/10.1016/j.autrev.2014.07.001
16. K. Wesnes et al., “Body size and the risk of multiple sclerosis in Norway and Italy: The EnvIMS study,” Mult. Scler. J., vol. 21, no. 4, pp. 388–395, 2015, https://doi.org/10.1177/1352458514546785
17. L. E. Mokry, S. Ross, N. J. Timpson, S. Sawcer, G. Davey Smith, and J. B. Richards, “Obesity and Multiple Sclerosis: A Mendelian Randomization Study,” PLoS Med., vol. 13, no. 6, pp. 1– 16, 2016, https://doi.org/10.1371/journal.pmed.1002053
18. I. Katz Sand, “The Role of Diet in Multiple Sclerosis: Mechanistic Connections and Current Evidence,” Curr. Nutr. Rep., vol. 7, no. 3, pp. 150–160, 2018, https://doi.org/10.1007/s13668-018-0236z
19. T. Uher et al., “Serum lipid profile changes predict neurodegeneration in interferon-β1a-treated multiple sclerosis patients,” J. Lipid Res., vol. 58, no. 2, pp. 403–411, 2017, https://doi.org/10.1194/jlr.M072751