Quality of Life, Depression, Sexual Dysfunction and Work Absenteeism in Relapsing-Remitting Multiple Sclerosis Patients Starting Glatiramer Acetate as First-Line Treatment: A Prospective Cohort Study

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Abstract

Introduction: Quality of life (QoL) has gained increasing importance in multiple sclerosis (MS). We aimed to assess QoL and potentially associated factors such as depression, sexual dysfunction and work absenteeism in patients starting glatiramer acetate (GA) in clinical practice.

Methods: A prospective cohort study carried out in relapsing-remitting MS patients starting GA as first-line treatment. Patient information on QoL (Multiple Sclerosis Quality of Life-54 [MSQoL-54]), depression (Beck Depression Inventory), sexual dysfunction (Multiple Sclerosis Intimacy and Sexuality Questionnaire-19) and work absenteeism was assessed from starting GA to week 96.

Results: Ninety-eight evaluable patients were enrolled in the study (mean age, 38.0 ± 8.4 years; female, 69.4%; mean MS duration, 42.6 ± 62.9 months; annual relapse rate since MS diagnosis, 0.4), and followed up at weeks 24 (n=96), 48 (n=94), 72 (n=89) and 96 (n=80). Patient QoL was preserved during the study, with improvements on the MSQoL-54 subscales of change in health (p<0.05) and health distress (p<0.05). Depression, primary and secondary sexual dysfunction remained stable, but the number of patients with tertiary sexual dysfunction decreased at week 96 (p<0.05). Work absenteeism also decreased over the study (p<0.01). Depression, sexual dysfunction and work absenteeism affected MSQoL-54 physical and mental health composites (p<0.05).

Conclusion: QoL of our patients was preserved during the 96-week administration of GA. Though depression, sexual dysfunction and work absenteeism impair patient QoL, they remained stable or even improved during the study.

Keywords: Absenteeism; Depression; Glatiramer acetate; Quality of life; Multiple sclerosis; Sexual dysfunction

Introduction

Quality of life assessment in patients with multiple sclerosis has gained increasing importance as it encompasses all aspects of patients’ lives that may be affected by the disease. Though patients’ quality of life worsens as multiple sclerosis progresses and physical function deteriorates, it depends not only on the disability caused by physical limitations but also on their emotional status, which may also affect the perception of wellbeing and quality of life [1-3]. In this scenario, depression has been shown to have a notable impact on quality of life, and is considered a significant and independent predictor of impaired quality of life [4-10]. Sexual dysfunction is another common and often underestimated clinical symptom of multiple sclerosis that, along with its emotional repercussions, has been shown to affect patients’ quality of life [11,12]. The information available on the impact of sexual dysfunction on quality of life, however, is still limited. The consequences of multiple sclerosis often negatively affect patients’
Materials and Methods

First-line disease-modifying drugs for relapsing-remitting multiple sclerosis including interferon-beta (INFb)-1a, INFb-1b and glatiramer acetate have been shown to improve the course of the disease. However, their effect on patients' quality of life has not yet been fully clarified. Indeed, the information available on INFb's effect on quality of life is controversial, ranging from some benefit [15] to absence of effect [16-19] or even to quality of life detriment [20]. The effect of glatiramer acetate treatment on quality of life has not been well assessed, and improvements in quality of life have been reported in treatment-naïve patients with relapsing-remitting multiple sclerosis six months after starting GA treatment that were sustained for another six months [21].

In light of the above, this study aimed to expand the information available on quality of life and potentially associated factors such as depression, sexual dysfunction and work absenteeism in patients with relapsing-remitting multiple sclerosis starting glatiramer acetate as first-line treatment in clinical practice.

Materials and Methods

This study was conducted in the Departments of Neurology at 37 Spanish hospitals in accordance with the World Medical Association Declaration of Helsinki, all its amendments and national regulations. The study was approved by the ethic committee of Hospital Donostia (San Sebastián, Spain) and all patients gave their written informed consent.

Patient population

Between November 2009 and November 2010, all patients meeting selection criteria who agreed to participate in the study were consecutively recruited into the study. Inclusion criteria were patients aged 18 to 60 years, with a diagnosis of relapsing-remitting multiple sclerosis, no previous treatment for multiple sclerosis and a score of 5.5 or less on the Expanded Disability Status Scale (EDSS). Patients must not have had any cognitive impairment that precluded informed consent.

Study design

This was a prospective cohort study conducted in patients with relapsing-remitting multiple sclerosis receiving glatiramer acetate treatment for multiple sclerosis and followed-up for two years according to clinical practice.

All treatments were administered from commercial sources and according to routine clinical practice. No restrictions regarding patients’ treatment were specified in the study protocol.

Assessments

Patients’ information was retrieved from their medical charts at the start of glatiramer acetate treatment (baseline) and at weeks 24, 48, 72 and 96. The data retrieved at these visits included demographics, medical history of multiple sclerosis, patients’ disability according to the EDSS [22], quality of life measured according to scores on the Multiple Sclerosis Quality of Life-54 (MSQoL-54) questionnaire [23,24], depression according to scores on the 21-item Beck Depression Inventory (BDI) [25,26], sexual dysfunction according to the Multiple Sclerosis Intimacy and Sexuality Questionnaire-19 (MSISQ-19), [27,28] and work absenteeism related to multiple sclerosis according to the occurrence of work absenteeism, the number of working days missed and the causes of work absenteeism.

EDSS scores, which range from 0 (normal neurological status) to 10 (death from multiple sclerosis), were obtained by the same researcher in a given patient. The MSQoL-54 questionnaire consists of 54 items distributed in 12 multiple-item scales and two single-item scales, including questions from the Short Form 36-Item Health Survey as a generic core measure and 18 additional items specific for multiple sclerosis that assess health distress, sexual function, overall quality of life, cognitive function and energy. Physical and mental health composite scores are calculated as a simplified two-dimension solution to MSQoL-54 questionnaire. The composites scores range from 0 (poor health) to 100 (optimal health). The BDI is composed of 21 categories of symptoms and attitudes which describe a specific behavioral manifestation of depression and consist of a graded series of four to five self-evaluative statements. Numerical values are assigned for each statement from 0 (neutral) to 3 (maximal severity) indicating the degree of severity of the manifestations of depression. Total scores range from 0 to 63, where higher scores indicate worse depressive states. Patients may also be categorized as having ups and downs considered normal if their BDI scores were 10 or less, as having mild mood disturbance if their BDI scores were between 11 and 16, as having borderline clinical depression if their BDI scores were between 17 and 20, as having moderate depression if their BDI scores were between 21 and 30, as having severe depression if their BDI scores were between 31 and 40 and as having extreme depression if their BDI scores were higher than 40. The cut-off value of at least 17 points was established as suggestive of the presence of depression. The MSISQ-19 consists of 19 items assessing the perceived influence of multiple sclerosis symptoms on sexual activity and satisfaction. Scores on the MSISQ-19 show the presence of primary, secondary and tertiary sexual dysfunction. Primary sexual dysfunction occurs as a result of neurologic changes related to multiple sclerosis that directly affect sexual feelings and/or sexual response, secondary sexual dysfunction refers to physical changes related to multiple sclerosis that affect the sexual response indirectly and tertiary sexual dysfunction refers to psychological, emotional, social and cultural aspects of multiple sclerosis that impact upon sexuality.

Statistical considerations

The primary efficacy endpoint was the change in patients’ quality of life during the 96-week study period, measured according to the scores on the physical and mental health composites of the MSQoL-54 questionnaire. Sample size was calculated to fulfill the primary objective of the study. At the time of study design, the only data available on the impact of multiple sclerosis therapy on quality of life measured by the MSQoL-54 questionnaire was reported by Simone et al., who found that multiple sclerosis patients followed up for two
years experienced a decrease of six or more points in 80% of MSQoL-45 measurements (dimensions and summary composite scores), with an standard deviation of approximately 20 points [20]. Taking into account these data, an alpha risk of 0.05 and a beta risk of 0.20 in a two-sided analysis, the number of evaluable patients needed to be enrolled into the study to detect a difference of six or more points in MSQoL-54 scores would be of 92 patients; considering a percentage of missing data of 20% or lower, e.g. due to non-evaluable patients, the total sample size would be of 110 patients. Analysis of the primary endpoint included the calculation of mean scores and standard deviations (SD) of both physical and mental health composites of MSQoL-54 questionnaire throughout the study. Comparison of these scores during the study was performed using the repeated measures general linear model. Comparison of scores on the MSQoL-54 questionnaire at baseline with those reported at week 24, 48, 72 and 96 were also performed using paired t-tests.

The secondary endpoints included assessment of depression, sexual dysfunction and work absenteeism at baseline. Other secondary endpoints were the change in depression, sexual dysfunction and work absenteeism during the study and their impact on patients’ quality of life.

The distribution of patients according to the following categories of the BDI was calculated as the frequency and valid percentage in each study visit: ups and downs considered normal (BDI scores ≤10), mild mood disturbance (BDI scores, 11-16), borderline clinical depression (BDI scores, 17-20), moderate depression (BDI scores, 21-30), severe depression (BDI scores, 31-40) and extreme depression (BDI scores, >40). The overall frequency of patients with depression, which was defined as a BDI score ≥17, was also calculated. Comparison of mean BDI scores and the proportion of patients within the above categories during the study was performed using paired t-tests and McNemar’s tests, respectively. The impact of depression on patients’ quality of life was assessed comparing the scores on the physical and mental health composites of MSQoL-54 questionnaire reported by patients with those without depression using t-tests or Mann-Whitney tests.

The frequencies and valid percentages of patients with primary, secondary and tertiary sexual dysfunction according to MSISQ-19 scores were calculated in each study visit. The overall frequency of sexual dysfunction in each study visit was also assessed according to patients with at least one of these categories (primary, secondary or tertiary sexual dysfunction). Changes during the study were assessed using McNemar’s tests. The impact of sexual dysfunction on patients’ quality of life was assessed comparing the scores on the physical and mental health composites of MSQoL-54 questionnaire between patients without sexual dysfunction and those with any kind of sexual dysfunction by using Mann-Whitney tests.

Work absenteeism related to multiple sclerosis was assessed according to the frequency and valid percentage of patients missing at least one day from work, the mean (SD) number of working days missed and the causes for work absenteeism. Changes in the frequency of patients absent from work and the number of working days missed during the study were assessed using McNemar’s tests and Wilcoxon tests, respectively. The impact of work absenteeism on patients’ quality of life was assessed by comparing the scores on the physical and mental health composites of the MSQoL-54 questionnaire in patients at least one day absent from work versus those with no day absent from work using Mann-Whitney tests.

A correction method for multiple testing was not performed in the statistical analysis for the present study due to the controversy about its use in observational studies leading to potential risks and errors [29,30]. Further information on this subject is provided in Appendix 1.

Missing data were not considered in the analyses and a significance level of 0.05 was used for statistical testing. The statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, Illinois, USA).

### Results

#### Patient characteristics

A total of 101 patients agreed to participate in the study, three of whom were excluded from the analysis due to insufficient available data. Therefore, the evaluable population comprised a total of 98 patients, whose characteristics are described in Table 1. Patients’ disposition during the study is shown in Figure 1.

| Patient characteristics | Value |
|-------------------------|-------|
| At baseline             | At first relapse* | 32.2 (8.0) |
| Female, n (%)           | 68 (69.4) |
| Ethnicity, n (%):       | Caucasian 96 (98.0) |
| Family history of multiple sclerosis, n (%) | 10 (10.4) |
| Mean duration of multiple sclerosis, months (SD) | 42.6 (62.9) |
| Mean number of relapses since multiple sclerosis diagnosis (SD) | 1.3 (1.3) |
| Annual relapse rate since multiple sclerosis diagnosis | 0.4 |
| Mean time from last relapse to baseline, months (SD) | 14.8 (23.8) |

*Missing data, n=3; †Missing data, n=2; ‡Missing data, n=5; §Missing data, n=29; SD: Standard Deviation

Table 1: Baseline patient characteristics (N=98).

#### Expanded disability status scale

Patients showed a mean (SD) EDSS score of 1.8 (1.0) at baseline, with 88 (89.8%) patients showing minimal disability (EDSS 0-2.5) and 10 (10.2%) patients showing moderate disability (EDSS 3-5) without technical aid. EDSS scores during the study period are described in Figure 2.
When paired comparisons were performed to assess differences in EDSS scores from baseline, it was shown that the mean EDSS scores remained stable throughout the study period but with a slight tendency to improvement at week 96 (mean [SD], 1.1 [0.3] versus 1.0 [0.2], p=0.058). In addition, the proportion of patients with minimal disability slightly increased and the proportion of patients with moderate disability that did not need any technical aid slightly decreased, though not significantly, reaching 95.0% (n=76) and 5.0% (n=4) of patients, respectively, at week 96.
Multiple sclerosis quality of life-54

Even though scores on the MSQoL-54 questionnaire improved slightly during the 96-week study period, the results obtained from the repeated measures general linear model showed that statistically significant differences were not attained in either the physical or mental health composites (Figure 3). Similarly, comparison of scores on the physical and mental health composites between baseline and weeks 24, 48, 72 and 96 only showed statistically significant differences in the mental health composite at week 72, in which the scores were significantly higher than baseline (mean [SD], 70.6 [15.3] versus 73.9 [15.9], p<0.05; Figure 4). In addition, consistent statistically significant improvements from baseline to weeks 24, 48, 72 and 96 were observed in the MSQoL-54 subscales of change in health and health distress (Figure 4).

Depression

A total of 65 (66.3%) patients reported experiencing ups and downs considered normal according to the BDI at baseline, while 20 (20.4%) patients showed mild mood disturbance, 10 (10.2%) borderline clinical depression and 3 (3.1%) patients moderate depression. Therefore, a total of 13 (13.3%) patients showed overall depression (Table 2). No significant differences were found in either the mean BDI scores or the distribution of patients among the BDI categories throughout the study.

| Depression (BDI)§<sup>1</sup> | Baseline | Week 24 | Week 48 | Week 72 | Week 96 |
|-------------------------------|----------|---------|---------|---------|---------|
| (N=98)                        | (N=96)   | (N=94)  | (N=89)  | (N=80)  |
| Depression categories, n (%): |          |         |         |         |         |
| Ups and downs considered normal (BDI scores 1-10) | 85 (66.3) | 64 (66.7) | 61 (67.0) | 70 (80.5) | 63 (78.8) |
| Mild mood disturbance (BDI scores 11-16) | 20 (20.4) | 19 (19.8) | 18 (19.8) | 6 (6.9) | 7 (8.8) |
| Borderline clinical depression (BDI scores 17-20) | 10 (10.2) | 6 (6.3) | 5 (5.5) | 4 (4.6) | 7 (8.8) |
| Moderate depression (BDI scores 21-30) | 3 (3.1) | 6 (6.3) | 5 (5.5) | 7 (8.0) | 3 (3.8) |
| Severe depression (BDI scores 31-40) | 0 (0.0) | 1 (1.0) | 2 (2.2) | 0 (0.0) | 0 (0.0) |
| Extreme depression (BDI scores >40) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Overall depression (BDI scores ≥17), n (%) | 13 (13.3) | 13 (13.5) | 12 (13.2) | 11 (12.6) | 10 (12.5) |
| Mean BDI scores (SD) | 8.8 (6.3) | 8.5 (7.1) | 8.5 (7.4) | 7.6 (6.7) | 7.4 (6.1) |
| Sexual dysfunction (MSISQ-19), n (%)<sup>§</sup><sup>1</sup> |          |         |         |         |         |

Table 2: Patients’ depression, sexual dysfunction and work absenteeism throughout the 96-week study period.

- *Missing data at week 48, n=3; †Missing data at week 72, n=2; ††Missing data at baseline and week 24, n=3; †††Missing data at weeks 48 and 72, n=6; †‡Missing data at week 96, n=5; ‡‡‘One patient may be included in more than one of the following categories: primary sexual dysfunction, secondary sexual dysfunction and tertiary sexual dysfunction; ‡‡‡Missing data at baseline and week 48, n=11; ‡‡‡‡Missing data at week 24, n=7; ‡¶Missing data at week 72, n=6; ‡¶¶Missing data at week 96, n=9; ‡¶¶¶Missing data at baseline, n=3; ‡¶¶¶¶Missing data at week 24, n=4; ‡¶¶¶¶¶Multiresponse variable over patients missing at least one day from work.

BDI: Beck’s Depression Inventory; MSISQ-19: Multiple Sclerosis Intimacy and Sexuality Questionnaire-19; SD: standard deviation.

The analysis of the impact of depression on patients’ quality of life showed that patients with depression reported worse scores on both physical and mental health composites of the MSQoL-54 questionnaire throughout the study period (Figure 5a).

Multiple sclerosis intimacy and sexuality questionnaire-19

The overall frequency of patients with baseline sexual dysfunction according to MSISQ-19 scores reached 43 (45.3%) patients, and remained stable throughout the 96-week study period.

When the type of sexual dysfunction according to MSISQ-19 was analyzed at baseline, primary sexual dysfunction was found in 31 (32.6%) patients, secondary sexual dysfunction in 21 (22.1%) patients and tertiary sexual dysfunction in 17 (17.9%) patients (Table 2). Distribution of patients with primary and secondary sexual dysfunction...
dysfunction did not significantly change from baseline to weeks 24, 48, 72 or 96. However, the proportion of patients with tertiary sexual dysfunction tended to decrease from baseline to week 72 (p=0.057), reaching statistically significance at week 96 (p<0.05).

The presence of sexual dysfunction was shown to worsen patients’ quality of life, as patients with sexual dysfunction reported lower scores on the physical and mental health composites of the MSQoL-54 questionnaire during the whole study period (Figure 5b).

Work absenteeism was associated with patients’ quality of life during the 96-week study period, as patients absent from work reported worse scores on both the physical and mental health composites of the MSQoL-54 questionnaire at baseline, week 24, week 48, week 72 and week 96 (Figure 5c).

Discussion

This prospective cohort study showed that the quality of life of our population of patients with relapsing-remitting multiple sclerosis was preserved during the 96-week administration of glatiramer acetate under clinical practice conditions. Although glatiramer acetate treatment may have played a role in slowing down worsening of multiple sclerosis, this finding must be considered with caution since our patient population had intrinsically low disease activity in terms of EDSS scores and annual relapse rate. However, other studies also showed low disease activity in patients treated under clinical practice conditions [31,32], and another reported early gain in quality of life measured by the Leeds Multiple Sclerosis Quality of Life scale in patients receiving glatiramer acetate in daily practice [21].

A protective effect on quality of life of other first-line treatments for multiple sclerosis such as IFNb has also been previously suggested in patients with relapsing-remitting multiple sclerosis[18], whose quality of life measured by the MSQoL-54, Short Form 36-Item Health Survey and Functional Assessment of Multiple Sclerosis questionnaires remained stable for up to three years [16-18]. However, though some improvements in the physical health composite of the MSQoL-54 questionnaire have been reported during the same duration of IFNb treatment, mainly as a result of worsening of the mental health composite [20].

In our study, disability, depression, primary sexual dysfunction and secondary sexual dysfunction were observed to remain stable during the study period, while tertiary sexual dysfunction and work absenteeism due to multiple sclerosis were significantly improved at week 96. Maintenance of disability even during 15 years of glatiramer acetate administration has been previously reported, showing a mean EDSS change of 0.6 points from the start of treatment [33]. However, since the EDSS is highly dependent on ambulation and does not provide information on parameters associated with patients’ wellbeing [34], other parameters that might be potentially associated with patients’ wellbeing needed to be assessed. Indeed, our results support the influence of depression, sexual dysfunction and work absenteeism on the quality of life of patients with relapsing remitting-multiple sclerosis. These results are in line with previous studies reporting that multiple sclerosis patients with lifetime major depression show lower quality of life measured by the MSQoL-54 questionnaire, mainly in terms of energy, mental health, cognitive function, general quality of life, sexual function and emotional role limitations [9]. Depression measured according to the BDI or the Hamilton Rating Scale for Depression has been reported to be associated with both physical and mental health composites of the MSQoL-54 questionnaire [4-7], regardless of the disease-related physical disability and disease type [7]. Depression has been claimed to be a significant independent predictor of impaired patient quality of life measured using the MSQoL-54 and

Work absenteeism

At baseline, 46 (52.9%) patients reported having missed at least one day from work in the previous six months due to multiple sclerosis. The mean (SD) number of working days missed was 45.8 (56.5) days and the main reasons for work absenteeism were clinical signs of multiple sclerosis and disease relapses (Table 2). When work absenteeism was analyzed over the whole study, statistically significant decreases from baseline were observed in the proportion of patients missing at least one day from work at week 24 (p<0.01), week 48 (p<0.001), week 72 (p<0.01) and week 96 (p<0.01). Even though the number of working days missed from work decreased from baseline, statistically significant differences were only reached at week 48 (p<0.05).

Work absenteeism was associated with patients’ quality of life during the 96-week study period, as patients absent from work reported worse scores on both the physical and mental health composites of the MSQoL-54 questionnaire at baseline, week 24, week 48, week 72 and week 96 (Figure 5c).
Functional Assessment of Multiple Sclerosis questionnaires [4-10]. Patients with sexual dysfunction have also been shown to have poorer quality of life, with significantly lower scores on all scales of the Short Form 36-Item Health Survey [11] and on all of scales of the MSQoL-54 questionnaire except for pain and cognitive function [12]. Similar detriments in quality of life were observed in unemployed versus unemployed patients, who had lower scores on most dimensions of the MSQoL-54 questionnaire [13,14], suggesting the importance of sustained employment after the diagnosis of multiple sclerosis [14].

Though the low disease activity of our study patient population does not allow conclusions to be drawn about the effect of glatiramer acetate, decreased work absenteeism has previously been reported in patients receiving this agent [35,36]. In addition, there is no evidence that glatiramer acetate aggravates depression and it might even induce an antidepressant effect through its neuroprotective and anti-inflammatory activity [37]. Indeed, switching to glatiramer acetate has been recommended when a depressive episode is confirmed in patients receiving IFNβ [38]. Moreover, recently published data on patients switching from IFNb to glatiramer acetate [39], and preliminary results from ongoing studies in patients switching to glatiramer acetate [40,41] showed patients’ quality of life remained stable or even improved.

The authors acknowledge that although observational studies provide valuable information on treatments administered in clinical practice, their limitations should be considered when interpreting the results. The open-label study design, the absence of a comparator group and the potential regression to the mean effect should also be taken into account. In addition, data on other factors that might have influenced patients’ quality of life such as relapses, fatigue and treatment-related adverse events were not retrieved, and longer follow-up might have been needed for potential differences to become evident. The low disease activity of the study patient population precluded drawing conclusions about the effect of glatiramer acetate and may limit the representativeness of the study findings. Though caution is advisable when interpreting the study results, we consider that they still provide helpful information to physicians when treating multiple sclerosis in clinical practice.

In conclusion, the study results show that the quality of life of our population of patients with relapsing-remitting multiple sclerosis was preserved during the 96-week administration of glatiramer acetate in clinical practice conditions. Depression, sexual dysfunction and work absenteeism due to multiple sclerosis are factors that significantly impair patients’ quality of life. However, our study shows stable disability, depression and primary/secondary sexual dysfunction as well as improved tertiary sexual dysfunction and work absenteeism. The study findings should be interpreted with caution based on the low disease activity of the patient population. Further research is still needed to confirm the effect of glatiramer acetate, and to increase knowledge of other potentially associated factors, the long-term effect of multiple sclerosis therapies and the impact of the switch to glatiramer acetate on patients’ quality of life.

Appendix 1

There is currently no unanimity about the use of multiple test corrections (methods such as those of Bonferroni, Holm, Benjamini, etc.). In general, these methods reduce the probability of making type I errors, but they increase the probability of making type II errors. It seems cautious to prioritize minimizing the probability of type I errors over type II errors in studies where several treatments are compared, probabilistic independence is expected between analysis groups and/or variables that would give rise to multiple tests, results have confirmatory implications for practical use.

Methods of correcting for multiple testing provide solutions for these situations. However, if any of the above conditions are not a priority or are not applicable to the study, it would be cautious to minimize the probability of making a type II error rather than a type I error.

Using multiple test corrections would minimize type I errors, but it would also increase the probability of type II errors, which would imply that differences that are really related to the phenomena under study would not be detected.

In the present study, the effect of only one treatment was assessed during the study follow-up, and its use was supported by certain evidence of effectiveness. Therefore, it appears reasonable to assume the overall absence of probabilistic independence in the measurements of variables of patients included in the study. Consequently, the authors decided to prioritize the avoidance of increasing the probability of committing type II errors.

For readers who may be interested in the effect of multiple test corrections, Bonferroni correction would result in a p-value that was estimated to be of 0.0003 for the analyses carried out in this study. The authors would also like to explain that significant p-values of the study analyses were classified to be shown in the article as p<0.05, p<0.01, p<0.005 or p<0.001. The data included in this appendix is intended to provide the reader interested in knowing more about multiple test corrections with some information to interpret the study results based on the multiple test correction approach used.

Finally, the authors would like to advise the reader that the study conclusions should not be considered as definitive. As mentioned in the article, the study findings should be interpreted with caution and further research is still needed to confirm them.

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