ISSN: 2583-5386
DOI: doi.org/10.51219/JIH/atoosa-h-bigvand/54

URF PUBLISHERS
connect with research world

Journal of Integrated Health

https://urfpublishers.com/journal/integrated-health

Vol: 3 & Iss: 4

Review

Olfactory and Gustatory Dysfunction in Patients with Multiple Sclerosis: A Meta-Analysis

Atoosa H Bigvand*, Ab.Akber.T.K and Jillian Popiovic

Citation: Bigva AH, Ab Akber TK, Popiovic J. Olfactory and Gustatory Dysfunction in Patients with Multiple Sclerosis: A Meta-Analysis. *J Integrated Health* 2024;3(4): 301-310. DOI: doi.org/10.51219/JIH/atoosa-h-bigvand/54

Received: 03 September, 2024; **Accepted:** 30 October, 2024; **Published:** 01 November, 2024

***Corresponding author:** Atoosa H Bigvand, USA, E-mail: aheidari@health.ucsd.edu

Terminologies:

- Olfactory Dysfunction
- Gustatory Dysfunction
- Multiple Sclerosis
- Sniffin Stick Test
- Taste strip test (TST)
- UPSIT (University of Pennsylvania Smell Identification Test)
- TDIS core (Threshold, Discrimination, and Identification)
- Anosmia, Normosmia, Ageusia, Hypogeusia
- Demyelinating Disease
- Autoimmune Disease
- EDSS score (Expanded Disability Status Scale)

Table of contents:

Abbreviations:

- MS : Multiple Sclerosis
- OD : Olfactory dysfunction
- GD : Gustatory dysfunction
- PPMS : Primary Progressive Multiple Sclerosis
- RRMS : Relapse Remitting Multiple Sclerosis
- SPMS : Secondary Progressive Multiple Sclerosis
- TDI : Threshold, discrimination, identification
- TST : Taste strip test.
- EDSS : Expanded Disability Status Scale

Research question: How does olfactory and gustatory dysfunction in Multiple Sclerosis patients compare to normal controls as assessed by TDI and TST scores?

ABSTRACT

Importance: These studies can provide us with the importance of routine and systemic checkups, and to track clinical manifestations like olfactory, gustatory dysfunction and progression in Multiple Sclerosis (MS) patients. It can also give insight into the olfactory and gustatory changes in MS progression.

Study Objectives:

1. Compare the TDI score among MS patients and healthy controls.
2. Compare the TST score among MS patients and healthy controls.
3. How is OD and GD in progression of the disease?

Method: We conducted a systematic article search using three data sources Pub Med (Medline), Scopus and Pro Quest. We also searched the snowballing technique to include references. Studies report olfactory dysfunction based on Thresholds, Discrimination and Identification (TDI) scores, among MS participants regardless of the diagnostic method. The Gustatory dysfunction associated with MS has a smaller number of studies and we integrated data from the studies with the TST score assessment. 8 studies were included for OD/MS. 2 studies for GD/MS we real so included based on the inclusion criteria. The quality assessment was done using NIH tools and the R studio was used for the statistical assessment.

Results: We can observe alteration of the scores (T, D and I) in patients with MS compared with the healthy controls. The overall TDI score in MS patients shows a lower value than that of the control group (SMD= -0.93; 95% CI: [-1.12, -0.73]) (SMD=-1.19 CI 95% [- 1.74, -0.65] P value<0.01). In two of the studies, the TST score shows decreased value in the MS group compared with the control and in one of the studies it is significantly lower (SMD= [-0.76 CI95% -1.20, -0.32]).

Conclusion: Overall, the collective TDI score in MS patients is lower than that in the control group and the level of Identification score is lower in MS compared with control. The result of this meta-analysis from two gustatory dysfunction studies shows slower TST scores in MS cases compared with the healthy controls.

1. Introduction

Olfaction (sense of smell) and gustation (sense of taste) are referred to as chemical senses because they respond to chemicals in the environment. The olfactory receptor neurons are in a small region located in the superior nasal cavity within the olfactory epithelium. The exact mechanism by which olfaction is mediated is still not completely clear to this date, so far, it has been revealed that an interaction between odor neuron receptors and odor molecules initiate the process, leading to the production of olfactory signals which travel through the olfactory nerves to the Central Nervous System (CNS). It is the means to the perception of smell, recognizing imminent dangers, and even storing memories and emotions. Gustation is the chemical sense associated with the tongue. The surface of the tongue, along with the rest of the oral cavity, is lined by a stratified squamous epithelium. Only four tastes are recognized: sweet, salty, sour and bitter. Recent research suggests that there may also be a sixth taste for fats or lipids. In the orbit of Frontal cortex, olfactory inputs converge onto neurons with taste inputs, forming representations of flavor. The sense of olfaction and gestation are important not only for the detection of potential dangers such as fire or spoilt food, but also for the quality of life of human beings[1,2].

Multiple sclerosis is an autoimmune disease that results in demyelination. Multiple sclerosis is the most common progressive neurologic disease of young adults worldwide. A total of 2.8 million people is estimated to live with MS worldwide[3]. MS prevalence has increased. The pooled incidence rate across 75 reporting countries is 2.1 per 100,000 persons/year, and the mean age of diagnosis is 32 years of age. Females are twice as likely to live with MS as males[3]. Current estimates suggest that 300,000 to 400,000 individuals are affected in the United States, but this is based large revisions of estimates from older data sets. Ethnicity is one of the risk factors introduced for this disease. These estimates do not reflect the changing demographics of the United States or potential changes in the ascertainment of MS due to modifications in the diagnostic criteria and new treatment options. Studies have reported steep increases in the prevalence of MS over the past few decades across several provinces. Olfaction is shown to be prone to impairment in three main aspects, including threshold discrimination, and identification. Olfactory dysfunctions are reported as one of the most common manifestations in the initial stages of certain CNS diseases, including Alzheimer's disease and Parkinson's disease.

MS can have various clinical manifestations, one of which is olfactory dysfunction. So far, this manifestation is less focused in clinical practice. The association of changes in olfactory-related structures with olfactory function, as well as taste sense functioning in patients with multiple sclerosis, is not well understood[4]. The main and accessory olfactory systems have received considerable attention from scientists and clinicians during the last decade. Although smell and taste changes are rarely reported, the olfactory and gustatory functions are impaired in a considerable number of patients with MS. Also, there is growing evidence that the degree to which MS patients present with olfactory problems can be used as a potential prognostic factor.

Previous studies have provided conflicting evidence on determining the specific aspect of olfaction that suffers the most among MS patients. Such aspects include Threshold, Discrimination and Identification (TDI) dysfunction. Previous investigation has shown that MS patients frequently suffer from a loss of smell and taste. The psychophysical testing of Ortho-nasal and retro-nasal and gustatory function is an effective and inexpensive method to establish chemosensory function in MS

patients. Although we have few studies with quantitative data that can be included in our study, we aim to work on integrating the of possible quantitative results.

2. Method

A comprehensive search was performed using three data sources Pub Med (Med Line), Scopus, and Pro Quest which included published manuscripts and abstracts. The search included the following terms: multiple sclerosis [MeSH], multiple sclerosis and Olfactory Dysfunction [MeSH], and Olfactory Dysfunction. Other terms included Multiple sclerosis [MeSH terms], Multiple Sclerosis and Gustatory Dysfunction [MeSH term], and Gustatory Dysfunction. The Boolean search term used was 'and', and no filters or limits were applied. We also searched the snowballing technique to include references, reviews studies published up to March 2022. Studies report olfactory dysfunction based on Thresholds, Discrimination and Identification (TDI) scores, among MS participants regardless of the diagnostic method. Case reports and case series articles, articles that were written in any language other than English and any older published studies before 1990 were excluded due to the differences in clinical terms. Articles published up to March 2022 are included. studies were found on Olfactory Dysfunction (OD)/Multiple Sclerosis and Gustatory Dysfunction (GD)/MS, "Olfaction Disorder", "Smell Disorder", "smell dysfunction", "taste dysfunction", taste disorder", "taste loss", "smell loss" mesh terms. Boolean "and" was used. Three researchers (AB, AATK and JP) independently screened the articles. One of the researchers defended this in front of the committee of three members of experts in the topic and research, as the thesis project.

After checking for inclusion and exclusion criteria, and the availability of the quantitative result, 8 studies were included in the meta- analysis for OD and MS. From the second search, 2 applicable studies were included based on the same criteria and availability of quantitative data **(Table 1, Table 2 and Table 3).**

Other variables that we collected in our table included the exact name of the olfaction screening test, MS subtype, disease duration, EDSS score, number of hyposmia and anosmia in both case and control, plus the mean and standard deviation of the Threshold, Discrimination and Identification (TDI) scores if applicable. Had any of the included articles used over one diagnostic method, each different method would have been mentioned in a separate row of the table with its respective data. We used the Systematic Review and Meta-Analysis statement (PRISMA) guideline. In case necessary data were missing from the eligible studies, emails were sent to the first and corresponding authors to be able to get the needed data. The literature search found 1630 articles for OD/MS and 761 articles were found for the GD/MS. Based on inclusion criteria, 8 studies were included for the olfactory function and 2 studies for Gustatory dysfunction. This was based on inclusion criteria and the availability of the needed quantitative data.

Table 1: Inclusion and exclusion criteria for studies included in this meta- analysis.

Inclusion Criteria	Exclusion Criteria
- Primary research studies - Publication in a peer reviewed journal - Written in the English Language - TDI and TST score measurement. - Outcomes that include the association between GD and MS and OD and MS	- Studies without the necessary quantitative data - Studies that use score measurements other than TDI and TST scores

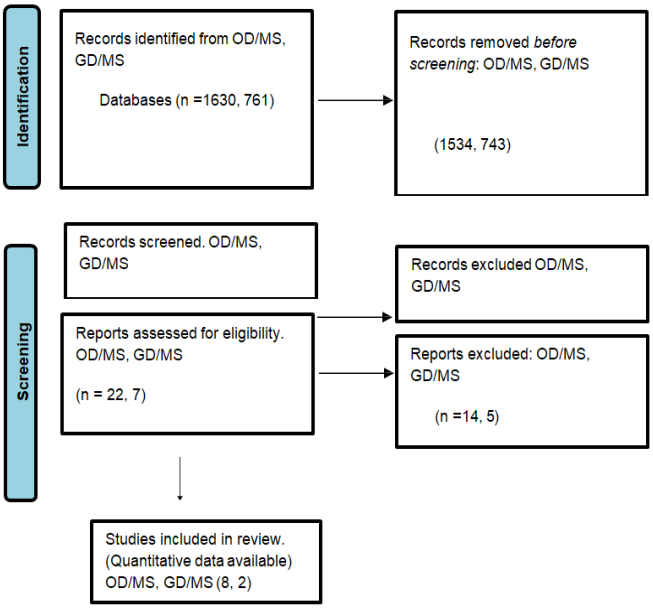


Figure 1: PRISMA guidelines followed for articles included in this meta-analysis**.**

3. Participants

Patients with Multiple Sclerosis are compared with the matched healthy controls. In some of the studies, the phenotype of MS cases mentioned are Primary Progressive Multiple Sclerosis (PPMS) and Relapsing-Remitting MS (RRMS).

4. Outcome

The outcomes of these studies included Olfactory dysfunction in MS based on TDI score measurement and Gustatory Dysfunction in MS based on TST score measurement. The Sniffin Sticks test is comprised of 3 subtests, resulting in 4 scores: T threshold score, D discrimination score, I identification score, and TDI global olfactory score. This is a psychophysical test developed by Hummel in 1997. It allows a semi-objective assessment of the patient's olfactory performance using the 3 subtests. Test instructions must be strictly observed to ensure reliable results and they must be performed in a quiet, well-ventilated room to avoid the presence of any residual odors. Ideally, the examiner also wears odorless cotton gloves or must wash his/her hands in water without using soap.

The scores are measured and recorded by two or more investigators to reduce the chances of bias. The test participants must not smoke, eaten or drank anything other than water for fifteen minutes before the test. Each pen must be presented only once, for 3 to 4 seconds, about 2 cm from the edge of the external nares.

The taste test was performed on filter paper strips. ("Taste Strips", Burghart, Wedel, Germany), with a length of 8 cm and a tip area of 2 cm^2 being impregnated with the taste (4 concentrations of each of the 4 basic taste qualities). The following concentrations were used for the taste strips: sweet: 0.4, 0.2, 0.1, 0.05 g/ mL of sucrose; sour: 0.3, 0.165, 0.09, 0.05g/ mL of citric acid; salty:0.25, 0.1, 0.04, 0.016g/mL of sodium chloride; bitter: 0.006, 0.0024, 0.0009, 0.0004g/mL of quinine hydrochloride. Distilled water was used as a solvent and taste solutions were prepared freshly in regular intervals**.**

The TDI score Threshold-Discrimination-Identification test, which is a global olfactory score consisting of the sum of the three

scores. The initial classification of TDI scores defined functional anosmia, complete loss of the sense of smell, as a TDI score ≤16.5, normosmia, normal sense of smell, as a TDI score>30.5, and hyposmia, reduced sense of smell, as any score between these two values.

For the gustatory testing, there are different taste tests such as the Taste Identification Test and Taste Strip Test. A taste score of 10 in the TST is selected as a cut-off value to distinguish normageusia, a normal sense of taste, from hypogeusia, a reduced sense of taste. Scores less than 10 indicate hypogeusia. There are many studies based on TDI scores that have available quantitative data which makes them suitable for being included in a meta-analysis. The number of studies for GD and MS is limited and only two studies were found with the necessary data based on TST measurement.

5. Eligibility Criteria

All published studies relevant to the topic, regardless of the year of publishing, were included in this paper. Primary research studies that are published in a peer-reviewed journal and written in the English language were sought. Lastly, studies with data on TST and TDI scores as outcomes were included (Table 1).

The research question, framing criteria, search strategy, databases, required data for the analysis, integrated statistical analysis, importation of all results to an excel sheet, protocol writing, registration, abstract and manuscript were the steps taken to complete this meta-analysis. Key elements of the study design were assessed and reported for each study.

6. Coding Process

Each article was independently coded for the relevant information, which included: sample size, sample selection, duration of the disease, EDSS score, phenotypes, TDI and TST score, and participants' mean age in the MS and the control groups.

7. Statistical Analyses and Methods

R studio software was used for this meta-analysis (meta for) to assess the mean difference (MD) of TDI and TST scores between the MS patients and those in the control group. A statistical test for the study heterogeneity was performed by I-square (I^2) in R Studio software.

8. Data Extraction

Tables 3 and 4 include information such as first author, region of study, date of publication, the sample size of the case (MS) and the control group and the demographic variables for case and control such as gender (n) and mean age of participants. Other variables in the tables included MS phenotype, disease duration, and EDSS score.

Identification, total TDI scores, TST score (mean/SD), the author's name, and the year of publication, plus the number of MS and control groups participants were tracked in 5 different Excel sheets and imported into R studio. The mean values and standard deviations are extracted for both the case and control groups. Most of the included studies reported EDSS score at or around 3[5,6].

Table 2: Overview of studies included in the meta-analysis that pertain to OD in MS patients.

Study	Year	MSn/control n	Mean age MS/control	EDSS	Phenotype	Disease Duration (years)	Female/Male
HZB Caglayan et al.	2016	30/30	34.3 ±9.8/35.8 ±9.2	1.91±1.57	N/A	47.7 ±48	N/A
Schmidt et al.	2017	32/32	53.4±9.3/51.9±17.6	4.9 ±2.1	PPMS	11.3	N/A
Schmidt et al.	2017	32/32	35.5 ±9.3/51.9±17.6	2.6 ±1.8	RRMS	5.6	N/A
AriciDuzO et al.	2021	10/10	33.2±7.5	N/A	RIS	٣.٢ ٢,١٤±	7/3
AriciDuzO et al.	2021	10/10	37±9.5	٦.٩ ٤,٧±	RRMS	٦.٩ ٤,٧±	8/2
Erbet al.	2012	30/30	39.7/41	3	N/A	N/A	N/A
Dahlslett et al.	2012	30/30	42.6±12.1/42.4±12.5	3	N/A	4.2	20/10
Lutterotti et al.	2011	50/30	37.35	3	RRMS, SPMS, PPMS	N/A	35/15
Marini Katerin a	2019	59	N/A	N/A	N/A	N/A	N/A
Parma et al.[21]	2010	25/30	45	1.8	RRMS	9.2	N/A

One limitation is that the female /male ratio is not reported in most of the studies **(Tables 3 and Table 4).** The mean age of participants in all studies is from 35 to 42 years of age and only a slight difference has been seen in some studies[7]. It was found that most of the studies focus on the RRMS subgroup, though some have PPMS participants.

Table 3: Overview of studies included in the meta-analysis that pertain to GD in MS patients[20].

Study	Year	MS n/control	Mean age MS/control	EDSS	Phenotyp e	Disease Duration (years)	Female/Male
Dahlslett et al.	2012	30/30	42.6±12.1/42.4±12.5	3	N/A	4.2	20/10
Fleiner et al.	2012	16/16	43.2	3	PPMS	N/A	N/A

9. Result

Eight studies reported TDI scores (563 controls and 249 cases) and, the overall TDI score in MS patients was lower than that in the control group (SMD=-1.00;95%CI: [- 1.44,-0.56]). Also, the overall level of Threshold (SMD= -0.47; 95% CI: [-0.75, -0.19]), Discrimination (SMD=-0.53;95% CI:[-0.96, - 0.10]) and Identification (SMD=-1.02;95% CI:[-1.36, 0.68])were lower in MS compared with control, **respectively (Figure 1, Figure 2, Figure 3).**

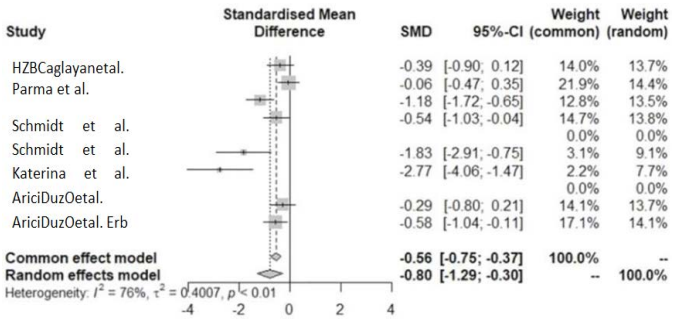
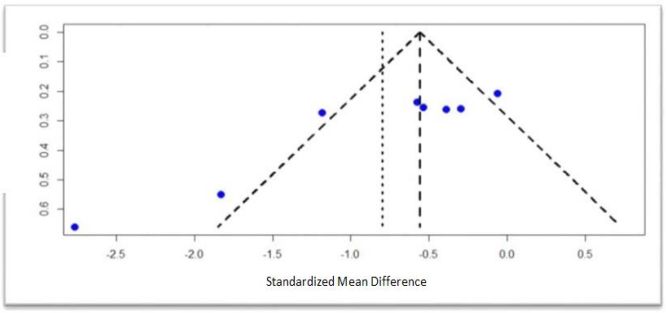
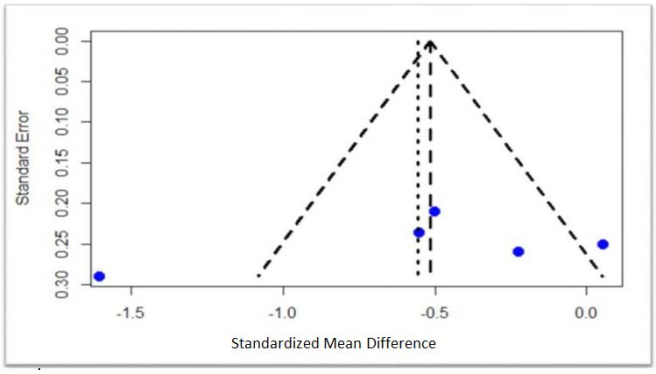


Figure 2: PRISMA guidelines followed for article included in this meta-analysis[18,19].





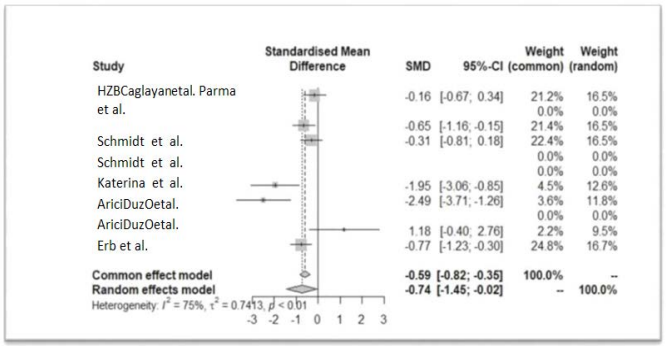
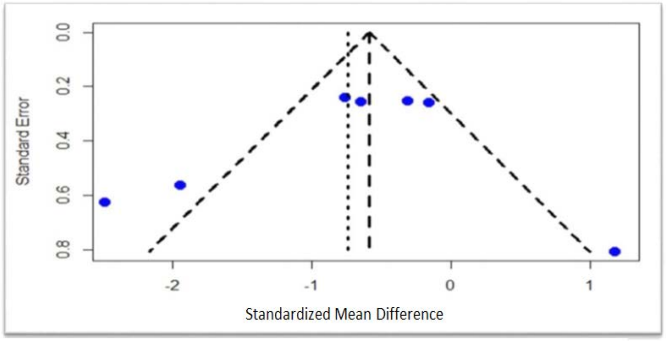
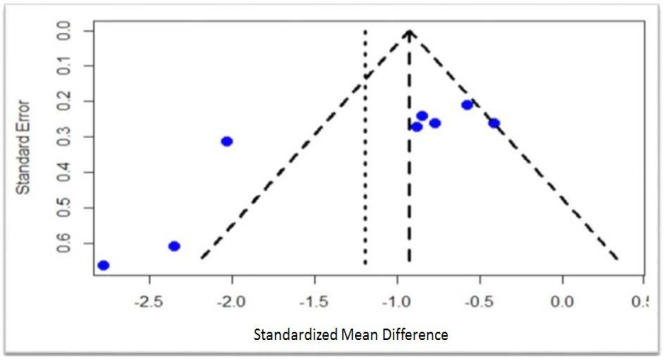


Figure 3: Discrimination.





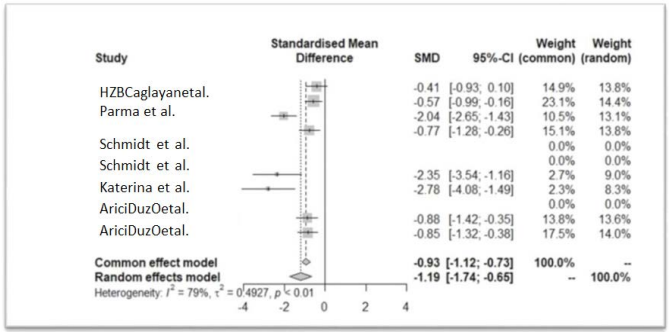


Figure 4: Identification.

Study heterogeneity was observed inall4 indices; however, we did not find any evidence of publication bias. Eight studies went into detail and categorized the dysfunction as TDI score, Threshold, Discrimination, and Identification scores. The score is generally reported as in Mean (±SD) and is utilized to report the findings of the Sniffin' Sticks Test and the TDI test. Here, we chose the TDI score as an independent screening test and reported the three major aspects of olfaction. The overall TDI score in MS patients was lower than that in the control group (Figure 4, Tables 6,7,8).

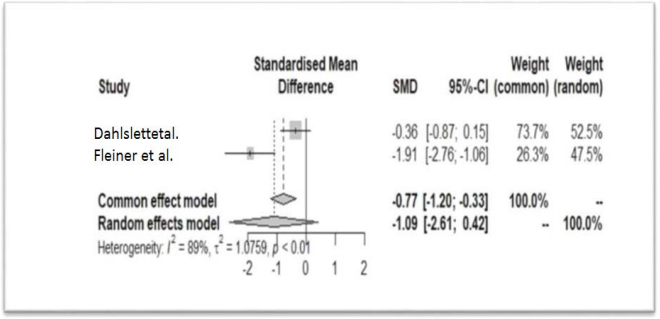


Figure 5: TDI Score.

Two studies on Gustatory Dysfunction are included in the meta-analysis, and the other 6 are explained qualitatively in the review section. In these two studies included in quantitative analyses, we observed that the TST score was lower in MS cases compared with the control group (72 MS cases and 72 healthy controls). The heterogeneity (I^2) as well as the publication bias by the funnel plot were both assessed (Figure 5).

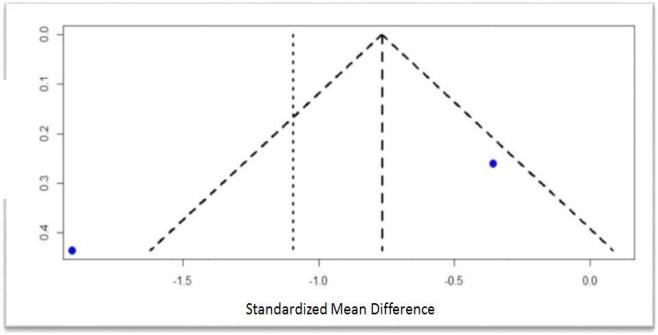


Figure 6: TST Score.

Table 4: Summary of mathematical analysis of individual Threshold (T), Discrimination (D), and Identification (I)scores using both the Common Effect Model and Random Effect Model.

	Standard Mean Difference	CI95%	P-value
Common Effect Model T Score	-0.56	[-0.75, -0.37]	<0.0001
Random Effect Mode lT Score	-0.80	[-1.29, -0.80]	0.001
Common Effect Mode lD Score	-0.52	[-0.73, -0.30]	<0.0001
Random Effect Mode lD Score	-0.56	[-1.09, -0.03]	0.001
Common Effect Model I Score	-0.93	[-1.12, -0.73]	<0.0001
Random Effect Model I Score	-1.19	[-1.74, -0.65]	<0.0001

Table 5: Summary of mathematical analysis of the overall Threshold, Discrimination, and Identification (TDI) Score using both the Common Effect Model and Random Effect Model.

TDI Score	Standard Mean Difference	CI95%	P-Value
Common Effect Model Score	[-1.12, -0.73]	-0.93	<0.0001
Random Effect Model Score	[-1.74, -0.65]	-1.19	<0.0001

Table 6: Summary of mathematical analysis of the results of the Taste Strip Test using both the Common Effect Model and Random Effect Model.

TST Score	Standard Mean Difference	CI95%	P-Value
Common Effect Model Score	[-1.20, -0.32]	-0.76	0.00
Random Effect Model Score	[-2.61, -0.42]	-1.19	0.15

10. Clinical Relevance

The standard mean difference shows that the overall mean value of individual T, D and I score, as well as the collective TDI and TST scores are lesser in MS patients than in the healthy control group. We consider the 'small'effectsizelessthan0.5, 'medium' effect size equal to 0.5, and 'large' more than 0.5 effect size, with a smaller effect size indicating less significance. For the threshold score, the SMDs are 0.5 and 0.8, which are considered medium and large effect size respectively. The effect size for Discrimination(D) is medium and the common effect size of the Identification (I) score is large. The overall effect sizes for the total TDI and TST scores are high. This result provides us within sight into the importance of routine and systemic.

Checkup sin MS patients in an effort for the progression of the disease. MS patients show higher levels of olfactory impairment, but they also forfeit this ability as their disease progresses, which might be due to a lot of underlying factors such as extensive demyelination.

11. Interpretation

Figure 1 and Figure 2, and 3are the forest plots that show the SMD (Standard Mean Difference) and 95% confidence intervals resulting from the meta-analysis. On the left side, studies included in the analysis with the authors and the year of publication can be seen. Next, there is the plot with each of the studies' SMD and CI 95% in front of the it. The square represents the SMD as a dot at the center and the CI 95% for the lower and upper limits as two side aspects of it. Each square size is representative of the sample size.

The diamonds represent the common and random effect model which identifies the CI 95% limit points. Very roughly, it shows the difference between the average score of participants with Multiple Sclerosis and the average score of participants in the control group. The range of the confidence intervals for each study is small and on the right side, the weight of each study is shown. There is no prominent weight in any of the studies and they are generally equal, along with the random effects. The heterogeneity is 76% and the effect shows that there are differences in the Threshold score of MS cases compared with matched healthy controls. The result of each study falling on one side of the vertical line or the other depends on the statistics being used.

12. Interpretation

Figure 1, Figure 2 and Figure 3 are the forest plots that show the SMD (Standard Mean Difference) and 95% confidence intervals resulting from the meta-analysis. On the left side, studies included in the analysis with the authors and the year of publication can be seen. Next, there is the plot with each

of the studies' SMD and CI 95% in front of the it. The square represents the SMD as ado that the center and the CI 95% for the lower and upper limits as two side aspects of it. Each square size is representative of the sample size.

The diamonds represent the common and random effect model which identifies the CI 95% limit points. Very roughly, it shows the difference between the average score of participants with Multiple Sclerosis and the average score of participants in the control group. The range of the confidence intervals for each study is small and on the right side, the weight of each study is shown. There is no prominent weight in any of the studies and they are generally equal, along with the and on effects. The heterogeneity is 76% and the effect shows that there are differences in the Threshold score of MS cases compared with matched healthy controls. The result of each study falling on one side of the vertical line or the other depends on the statistics being used.

This forest plot shows that the random effect model and common effect model are almost falling on the same line after running the meta-analysis. A study by Schmidt et al. for one of the phenotypes shows almost no difference. The random effect model has a larger gap between the lower and upper limits. The I^2 indicates the level of heterogeneity and can take values from 0% to 100%. If $I^2 \leq 50\%$, studies are considered homogeneous. Here it is 80% so we use the random effect model, as it is larger than 50%. The discrimination score shows a difference between the two groups (Figure 2). The SMD in this plot for Identification score shows the difference in both groups, which is lower in MS cases compared with the control group (Figure 3). We assessed the difference between the total TDI score in MS cases and the healthy control participants and it is observed to be lower in the MS group (Figure 4).

The meta-analysis for the two studies based on TST score for the gustatory assessment shows89%of heterogeneity (I^2). More weights are observed for a study by[7] in both random and common effects. The TST score in MS patients is lower compared with the control group (Figure 5) and a study by on the plot shows a significantly lower mean value in MS patients compared with the control group[8].

13. Publication Bias

To examine whether the obtained effect sizes were influenced by publication bias, a funnel plot was used to estimate the possible bias. The funnel plot was run for all the individual scores (T, D and I) and both total scores (TDI and TST) and each of the dots represents a study in the funnel plot. Each dot is placed based on the X-axis (Standard Error) and the Y-axis (Standard Mean Difference). The side aspects of the pyramid are representing the CI 95%. Here we have some of the studies falling out of these lines but with most studies in the pyramid, there is no indication of any significant publication bias. This is a suitable tool for the bias assessment but not the correction of it[9]. The two vertical lines represent no effect and the common effect. Based on the scoring, the results from the review are fair. We need more studies to be available quantitatively for the TST score in MS cases compare with control.

14. Quality Assessments

Study quality assessment tools from NIH were utilized to assess the study quality and identify possible sources of bias for each of those included in the analysis. "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" was used to assess quality according to the design of the studies (Table 5,Table 5 cont.)

Table 7: Quality Assessment of studies included in the meta-analysis Y: Yes. N:No CD: Cannot be determined N/A: Not Applicable.

	Lutter otti et al. 2011	Dahlslett et al. 2011	Fleiner et al. 2010	HZB Caglayan et al. 2016
1. Was there search question or objective in this paper clearly stated?	Y	Y	Y	Y
2.Was the study population clearly specified and defined?	Y	Y	CD	Y
3.Was the participation rate of eligible persons at least 50%?	Y	Y	Y	Y
4. Were all the subjects selected or recruited from the same or similar population (including the same time period)? Were inclusion and exclusion criteria for being in the study pre specified and applied uniformly to all participants?	Y	Y	Y	Y
5.Was a sample size justification, power description, or variance and effect estimates provided?	CD	CD	CD	Y
6.Forth analyses in this paper, were the exposure(s)of interest measured prior to the outcome(s) being measured?	Y	Y	CD	Y
7.Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y	Y	Y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measure discontinuous variable)?	Y	Y	CD	Y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented constantly a cross all study participants?	Y	Y	Y	Y
10.Wasthe exposure(s)assessed more than once overtime?	N	CD	CD	CD
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented constantly cross all study participants?	Y	CD	CD	Y
12.Were the outcome assessors blinded to the exposure status of participants?	N/A	N/A	CD	N/A
13.Wasloss of follow-up after baseline 20%orless?	N/A	N/A	N/A	N/A
14.Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposures and outcomes?	Y	Y	CD	Y
Overall quality of the study	FAIR	FAIR	FAIR	GOOD

Table 8: Continued. Quality Assessment of studies included in the meta-analysis Y: Yes N: No CD: Cannot be determined N/A: Not Applicable.

	Standard Mean Difference	CI95%	P-value
Common Effect Model T Score	-0.56	[-0.75, -0.37]	<0.0001
Random Effect Mode lT Score	-0.80	[-1.29, -0.80]	0.001
Common Effect Mode lD Score	-0.52	[-0.73, -0.30]	<0.0001
Random Effect Mode lD Score	-0.56	[-1.09, -0.03]	0.001
Common Effect Model I Score	-0.93	[-1.12, -0.73]	<0.0001
Random Effect Model I Score	-1.19	[-1.74, -0.65]	<0.0001

All studies containing TDI and TST scores were included in this assessment. This assessment indicates the strength of the evidence on which conclusions are based and allows comparisons between studies based on risk of bias[9]. All the included studies had a partial bias in at least one assessment question, but based on what we got after the scoring shows that our result from the review is fair.

15. Discussion

Eight studies went into detail and categorized the dysfunction as TDI score, Threshold, Discrimination and Identification scores. The score is generally reported as the Mean.

Value and in the same way, we analyzed the gustatory dysfunction IN MS population. The overall TDI and TST score sin MS patients were lower than the scores in the control group. For assessing the gustatory dysfunction there were only 2 studies containing the needed quantitative data and there are few other studies that are discussing the same results such as in Gustatory Dysfunction in Multiple Sclerosis[10]. Here we discuss each one of the scores individually and we observe that Discrimination and Threshold scores show changes, as well as the Identification score difference, between the MS patients and healthy controls.

There is longitude in all studies about MS and OD/GD which discuss the changes in the MS patients from the baseline depending on the time variable[11,12].

It is recognized that olfactory dysfunction may be an early symptom in MS, and it has been reported that olfactory dysfunction may be considered a marker of disability progression in MS, and longer disease duration (DD) in MS patients[12]. This highlights the potential role of smell assessment in the monitoring of MS evolution. Olfactory detection and recognition were significantly higher in the MS group according to previous studies[4] and, in some of the studies, olfactory recognition threshold positively correlated with expanded disability status scale scores(EDSS)[12,4]. Also, inot her studies, the olfactory bulb(OB)volume reduced was in patients with olfactory dysfunction[12,4].

A study conducted in 2012 with a sample size of 153 participantsreportedthat11% of MS patients had olfactory dysfunction. This article is unique as it is one of the few studies that reported olfactory dysfunction in the control group as well, at 3%, which is significantly less than that of the MS group. In a 2020-published Austrian study[13] evaluated 260 MS patients and found that 27.3% had hyposmia, which is much higher than the general population. This study also reported that 110 MS patients (42%) were smokers which might be used for future research into the presumably confounding association between smoking and olfactory dysfunction among MS patients.[11] examined 64 MS patients in 2017 and revealed that57.8% had olfactory dysfunction. It is no table to mention that this was one of the few studies where the Threshold, Discrimination, and Identification (TDI) test was performed as the screening tool of demyelination and MS- plaque formation with in the olfactory-related CNS regions, and how these are thought to disturb normal olfaction in the same way they affect other sensory pathways affected by MS.

In the olfactory dysfunction is compared in PPMS and RRMS cases as well as with the control group[6]. Olfactory dysfunction was more frequent and severe in PPMS compared with RRMS, independent of disease duration and overall disability status. Here neither age, sex, EDSS, nor disease duration was significantly associated with the composite TDI score. A study done by Ozge et al shows the RIS compared with RRMS and both with the healthy controls. All the scores individually and the total TDI score shows lower levels in MS participants and in the RIS cases have more scores compared with RRMS.

In the olfactory threshold correlated significantly with the number of relapses in the year prior to assessment and shorter disease duration[13]. Odor discrimination, identification, and their sum score were significantly correlated with longer disease duration and a higher EDSS. Here the regression models show a negative correlation between the average Discrimination score with EDSS as well as the duration of the disease in years.

Based on the previous investigations and this meta-analysis is we observe are duction in TDI, TST, and individual scores in MS patients. A possible explanation for this is that the inflammation within the CNS[14], demyelination of olfactory bulbs (which is observed in different studies;)[15], and the burden of plaque in brain areas associated with the olfactory system contribute to the disturbances seen in the olfaction of MS patients. Further biological and pathological studies, such as[16], may show exact changes in the epithelium surrounding neurons causing the disruption and/or the neuron's degeneration and demyelination. There should be more investigation into the progression of gustatory dysfunction in MS as the neurons are correlating with the ones responsible for the sense of smell in the frontal lobe. The neurons and the papillae on the tongue can be the focus of study in different phenotypes. According to Thomas Hummel

There is a clear difference in the perception of ortho- and retro nasal stimuli, suggesting a "duality of the sense of smell", due to the direction of the airflow towards the olfactory epithelium. This could explain the higher prevalence of the ortho nasal of compared to the retro nasal OF in MS patients. MS-related plaques and demyelinating processes vary in number, volume, and location. Therefore, olfactory, and gustatory function differs from patient to patient.

Gustatory dysfunction is a known and common element during multiple sclerosis progression[17]. Gustatory dysfunction has been described during the chronic progressive phase and during the relapse phase of MS. In one study, five patients with clinically definite multiple sclerosis developed transient gustatory disorders during the relapse phase of their disease. Ageusia occurred as one of the first symptoms in three patients, revealing the disease. Symptoms generally improved with remission or corticosteroid administration. These disorders are due to demyelinating lesions of the gustatory pathways in the thalamus or brainstem. Pertaining to GD in MS, we have limited number of studies available for the meta-analysis, however, we included 2 studies with the quantitative data. A qualitative review of other available germane studies could help with better understanding. The TST score shows reduction in MS cases as discussed previously.

16. Conclusion

Overall collective TDI score in MS patients is lower than that in the control group and the individual levels of Threshold, Discrimination, and Identification scores are lower in MS compared with the control group. Also, seeing the result from this meta- analysis applied to gustatory dysfunction studies shows lower TST score in MS cases compared with the healthy controls. Although, the number of studies available with quantitative data for GD and MS are limited It also provides us with the importance of routine and systemic checkups in MS patients to prevent progression.

17. Strengths

To our knowledge, this is the first meta-analysis that assesses the TDI score, individual Threshold, Discrimination and Identification scores, other meta-analysis focuses more on the prevalence. This is the first time that the results of studies on taste loss (GD) in MS cases are integrated.

18. Limitations

In most of the studies, the association between the type of medication patients receive and the olfactory dysfunction are not mentioned. This could be a confounder for the result. Also, in some of the studies there is incomplete information about the demographics, and limited data about the other confounders like smoking. We couldn't have the consistency on risk factors.

e.g. (Caglayanet al.) Most of the studies have the matching ratio for gender (male / female) however, not all of them do. Moreover, for female participants there are no details about the eligibility criteria such as pregnancy, lactation and menopausal status in any the studies.

For gustatory dysfunction in MS, it was difficult to find a larger number of eligible studies to be included in a meta-analysis, which limits the bias assessment and the overall conclusion.

The studies show different duration of the disease and the phenotypes, but it should also be mentioned that there are limited numbers of studies conducted around topics related to the olfactory and gustatory dysfunction in MS.

19. Funding

This research is not funded, and, it is a Non-financial support review.

20. Competing interest

N/A

21. Protocol

No protocol was prepared for this study.

22. Recommendations

For all the studies germane to the topic but with other measurement methods, a systematic article view is recommended to support the result and to give a qualitative conclusion on more numbers of studies, especially in case of GD and MS.

There can be further meta-analysis to pool data from the studies of the MRI results of MS patients[17] to look for changes in the olfactory bulb and sulcus for better clarification through the OD manifestation in Multiple Sclerosis (MS).

23. Acknowledgments

I wish to sincerely thank Dr. Raphael Cuomo, the chair of the project and his through out guidance and time.

I also thank Dr. Florin Vaida, Chair of the Biostatistics Department at UCSD, Dr. Linda Ngyun, one of the Neuroscience lab members, and the committee members including Dr. Graves.

24. References

1. Qualityof Life: A Rochet M, El-Hage W, Richa S, Kazour F, Atanasova B. Depression, Olfaction, and Mutual Relationship. Brain Sci. 2018 May 4;8(5):80. doi: 10.3390/brainsci8050080. PMID: 29734670; PMCID: PMC5977071.
2. Pozharskaya T, Liang J, Lane AP. Regulation of inflammation-associated olfactory neuronal death and regeneration by the type II tumor necrosis factor receptor. Int Forum Allergy Rhinol. 2013 Sep;3(9):740-7. doi: 10.1002/alr.21187. Epub 2013 Jun 3. PMID: 23733314; PMCID: PMC3784625.
3. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, Robertson N, La Rocca N, UitdehaagB,vanderMeil,WallinM, HelmeA,AngoodNapierC,RijkeN,B anekeP.Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler. 2020 Dec;26(14):1816-1821. doi: 10.1177/1352458520970841. Epub 2020 Nov 11. PMID: 33174475; PMCID: PMC7720355.
4. LiL M, YangLN, Zhang LJ, Fu Y, Li T, Qi Y, Wang J, Zhang DQ, Zhang N, Liu J, Yang L. Olfactory dysfunction in patients with multiple sclerosis. J Neurol Sci. 2016 Jun 15;365:34-9. doi: 10.1016/j.jns.2016.03.045. Epub 2016 Apr 6. PMID: 27206870.
5. Batur Caglayan HZ, Irkec C, Nazliel B, Akyol Gurses A, Capraz Olfactory functioning in early multiple sclerosis: Sniffin' Sticks Test study. Neuropsychiatr Dis Treat. 2016 Aug 26;12:2143-7. doi: 10.2147/NDT.S116195. PMID: 27621629; PMCID: PMC5012609.*
6. Schmidt FA, MaasMB, GeranR, Schmidt c , kunteH, Ruprechtk, PaulF, Goktaso, Harmsl, Olfactory dysfunction in partients with primary progressive MS. Neurol Neuroimmunol Neuro in flamm. 2017 jun 14:4(4):e369.doi: 10.1212/NXI.0000000000000369. PMID:28638852; PMCID: PMC5471346. *
7. Dahlslett SB, Goektas O, Schmidt F, Harms L, Olze H, Fleiner
8. Erb K, Bohner G, Harms L, Goektas O, Fleiner F, Dommes E, Schmidt FA, Dahlslett B, LüdemannL
9. .Olfactory function in patients with multiples clerosis : adi fusion tensor imaging study. J Neurol Sci. 2012 May 15;316(1- 2):56-60. doi: 10.1016/j.jns.2012.01.031. Epub 2012 Feb PMID: 22341621. *

10. Ma, LL, Wang, YY,Yang, Zh Et Al Methodological quality (risk of bais) assessment tools For Primary and secondary mediacal studies: what are they and which is better? Military Med Res 7,7 (2020). https://doi.org/10.1186/s40779-020-00238-8

11. Doty RL, Tourbier IA, Pham DL, Cuzzocreo JL, Udupa JK, Karacali B, Beals E, Fabius L, Leon-Sarmiento FE, Moonis G, Kim T, Mihama T, Geckle RJ, Yousem DM. Taste dysfunction in multiple sclerosis. J Neurol. 2016 Apr;263(4):677-88. doi: 10.1007/s00415- 016-8030-6. Epub 2016 Jan 25. PMID: 26810729; PMCID: PMC5399510.

12. Uecker FC, Olze H, Kunte H, Gerz C, Göktas Ö, Harms L, Schmidt FA. Longitudinal Testing of Olfactory and Gustatory Function in Patients with Multiple Sclerosis. PLoS One.2017 Jan 20;12(1):e0170492. doi: 10.1371/journal.pone.0170492. PMID:28107525; PMCID: PMC5249198*

13. Ciurleo R, Bonanno L, De Salvo S, Romeo L, Rifici C, Sessa E, D'Aleo G, Russo M, Bramanti P, Marino S, Caminiti F. Olfactory dysfunction as a prognostic marker for disability progression in Multiple Sclerosis: An olfactory event related potential study. PLoS One. 2018 Apr 17;13(4):e0196006. doi: 10.1371/journal.pone.0196006. PMID: 29664936; PMCID: PMC5903665.

14. Bsteh G, Steiger R, Tuovinen N, Hegen H, Berek K, Wurth S, Auer M, Di Pauli F, Gizewski ER, Deisenhammer F, Berger T, Scherfler C. Impairment of odor discrimination and identification is associated with disability progression and gray matter atrophy of the olfactory system in MS. Mult Scler. 2020 May;26(6):706-715. doi: 10.1177/1352458519838205. Epub 2019 Mar 21. PMID: 30895860; PMCID: PMC7232781

15. Yue Y, Stone S, Lin W. Role of nuclear factor κB in multiple sclerosis and experimental autoimmune encephalomyelitis. Neural Regen Res. 2018 Sep;13(9):1507-1515. doi: 10.4103/1673- 5374.237109. PMID: 30127103; PMCID: PMC6126134.

16. Chen M, Reed RR, Lane AP. Acute inflammation regulates neurore generation through the NF-κB pathway in olfactory epithelium. Proc Natl Acad Sci U S A. 2017 Jul 25;114(30):8089-8094. doi: 10.1073/pnas.1620664114. Epub 2017 Jul 10. PMID: 28696292; PMCID: PMC5544262

17. ChenM,ReedRR,LaneAP.Chronic In flammation Lutterotti A, Vedovello M, Reindl M, Ehling R, DiPauli F, Kuenz B, Gneiss C, Deisenhammer F, Berger T. Olfactory threshold is impaired in early, active multiple sclerosis. Mult Scler. 2011 Aug;17(8):964-9. doi: 10.1177/1352458511399798. Epub 2011 Mar 3. PMID: 21372115

18. Ou Yang Q, Wang Y, Zhang YW, Yu M, Wang X. Change in Functional Brain Activation Patterns Induced by Olfactory Stimulation in Multiple Sclerosis. Neuropsychiatr Dis Treat. 2020 Jun 9;16:1451- 1458. doi: 10.2147/NDT.S252933. PMID: 32606698; PMCID: PMC7294099.

19. Arici Duz O, Saatci O, Karakulak EZ, Birday E, Hanoglu L. Olfactory Dysfunction and Cognition in Radiologically Isolated Syndrome and Relapsing-Remitting Multiple Sclerosis. Eur Neurol. 2021;84(3):175-182. doi: 10.1159/000514433. Epub 2021 Apr 8.

20. KateriniM, Olfactory and Gustatory Function in Multiple Sclerosis Patients.Aristotle University of Thessaloniki. 2019. *

21. FleinerF,DahlslettSB,SchmidtF,HarmsL,GoektasO.Olfactory and gustatory function in patients with multiple sclerosis. Am J Rhinol Allergy. 2010 Sep-Oct;24(5):e93-7. doi: 10.2500/ajra.2010.24.3506. PMID: 21244723.

22. Parma,V.,Tornasi,C.,Grossi,P.,Atzori,M.,Perini,P.,Calabrese,M.,Tirind elli,M., Gallo.