Association of gustatory dysfunction and Alzheimer's disease: a systematic review and meta-analysis*

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Abstract

Background: Chemosensory dysfunction has been reported to be involved in the pathogenesis of Alzheimer's disease (AD). Compared with olfaction, gustatory dysfunction in AD has not been evaluated in depth. We reviewed previously published studies regarding gustatory dysfunction in patients with AD compared with healthy controls.

Methods: A systematic review was conducted by searching the MEDLINE, Cochrane Library, Embase, and PubMed databases covering publications from January 2000 to February 2023. The search was performed using the keyword "Alzheimer* AND (gustatory OR taste OR gustation)." Only studies that performed gustatory function testing and compared the results between patients with AD and healthy controls were included. A random-effects meta-analysis was performed.

Results: Twelve articles were finally included, and various gustatory tests including taste strips, the taste disk test, taste solutions, and subjective questionnaires were applied. Overall gustatory function based on the taste strip test was significantly decreased in patients with AD compared with controls in two out of three papers. The overall gustatory function of patients with AD was significantly decreased in all studies based on the taste disk and taste solution tests. We also found that the sweet taste test showed low heterogeneity across all the included studies, and there was low publication bias. In studies using subjective questionnaires, gustatory function was not significantly different between patients with AD and healthy controls in the meta-analysis.

Conclusions: Based on these studies, gustatory dysfunction diagnosed by gustatory function testing was closely related to AD. However, the results of subjective questionnaires were not significantly different between patients with AD and healthy controls in the current meta-analysis. As the number of studies and enrolled subjects was limited and unified gustatory function testing was lacking, further studies are needed to confirm this relationship.

Key words: gustatory dysfunction, taste, Alzheimer's disease, systematic, meta-analysis

Introduction

Chemosensory functions including smell and taste are important in the maintenance of life. They alert us to danger (e.g., gas, fire), prevent ingestion of toxins, and support oral nutrition, and impairments in chemosensory function may result in an increased risk of malnutrition, mood disorders, diminished social interactions, and reduced quality of life [1–3]. Various conditions such as natural aging, neurodegenerative diseases, mood disorders, and chronic medical diseases have been reported to be associated with impaired olfactory and/or gustatory function [4]. Alzheimer's disease (AD) is the most frequent type of dementia, accounting for 70% of dementia cases [5]. Neurodegenerative symptoms such as episodic memory loss, progressive loss of autonomy in the usual activities, and chemosensory dysfunction have been demonstrated to be symptoms of AD [5-7]. Olfactory dysfunction is associated with memory and cognitive dysfunction and is known to be early symptom of AD [8]. Amyloid-β production and neuroinflammation, which are typical pathologic characteristics of AD, are related to the underlying causes of impaired olfaction [8].Furthermore, in a recent study, differential expression of disease-associated genes between patients with AD and healthy controls has been reported, suggesting potential molecular mechanisms of olfactory dysfunction in AD [9]. Gustatory function in AD is less commonly evaluated than ol-

factory function. There was a previous report that the total taste scores in patients with AD was lower than that in controls [10]. Gustatory dysfunction has been suggested to be a sensitive marker for detecting preclinical AD in patients with subjective cognitive decline [11]. However, it has also been reported that there was no significant difference in taste sensitivities between wild-type mice and an AD mouse model, and no apparent difference was observed in the expression of taste markers in their taste bud cells [12].

Gustation and olfaction affect each other and are interrelated [11]. In some cases, it is difficult to distinguish gustatory dysfunction from olfactory dysfunction in patients complaining of chemosensory dysfunction. Subjective recognition of gustatory dysfunction is not always correlated with objective measurement outcomes [13]. Therefore, we hypothesized that gustatory function measured through validated gustatory function testing should be reviewed between patients with AD and healthy control subjects to suggest the potential involvement of gustatory dysfunction in the pathogenesis of AD. This study sought to systematically review and summarize the literature regarding gustatory function in patients with AD.

Materials and methods

A systematic review was conducted using the meta-analysis protocol (PRISMA-P) and Preferred Reporting Items for Systematic Reviews (PROSPERO CRD42021243325) [14,15].

Search strategy

We conducted a comprehensive search of the MEDLINE, Cochrane Library, Embase, and PubMed databases covering publications from January 2000 to February 2023. The search was performed using the keywords "Alzheimer* AND (gustatory OR taste OR gustation)." The reference lists of the identified studies and eligible articles were searched manually.

Inclusion and exclusion criteria

All studies reporting gustatory function in patients with AD were included. We included studies that performed validated gustatory function tests in patients with AD and compared the results with those from healthy control subjects. The exclusion criteria were as follows: 1) review articles, case reports, commentaries, proceedings, laboratory studies, and other irrelevant studies; 2) studies that did not demonstrate the results of gustatory function tests; 3) animal studies; and 4) studies that results could not be extracted due to language limitations.

Study selection

The titles and abstracts of the studies collected through the search strategies were independently reviewed by two authors (HJM and KSK). The full text of each paper was retrieved upon determining the eligibility of the study. Potentially relevant studies chosen by at least one author were selected, and the full texts of these articles were reviewed by two authors (HJM and KSK). A third investigator (IYK) participated in settlement of disagreements if the two authors' (HJM and KSK) opinions were different. There were no objections by the three authors to the final included studies.

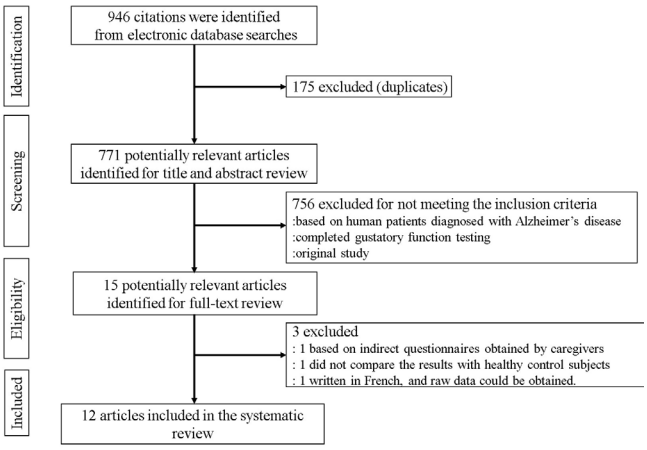

Figure 1. Flow diagram of the study selection process.

Data extraction and quality assessment

All interrelated data were independently extracted from the included studies through a standardized form by two authors (HJM and KSK). During the process of reviewing the full-text papers, relevant information such as article identifiers (including authors, publication year, and journal), study identifiers (such as sample size, study design, country, inclusion criteria, and criteria used for assessing gustatory function), population details (age, sex), and outcome measures (such as taste strip test scores, taste disk test results, and questionnaire responses) were extracted. The risk of bias was evaluated via Newcastle-Ottawa Quality Assessment Scale for case-control studies [16].

Outcome measurements of gustatory function testing

Psychophysical gustatory function tests evaluated in the current analysis were the taste strip, taste disk, and taste solution tests. Subjective self-assessment of gustatory function using questionnaires were also evaluated (Table 1).

The raw data of the detection threshold test and recognition threshold are continuous variables; the higher the score is, the worse the gustatory function. The raw data of identification and subjective questionnaire tests are also continuous variables; the higher the score is, the better the gustatory function. If the raw data were presented by the left and right sides, we used the raw data from the left side [10]. In cases in which patients with AD were divided by severity, we used the raw data from the severe group [16].

Statistical analysis

A frequency analysis was conducted on the various methods employed to measure gustatory function. Taste strip test scores, taste disk test findings, taste solution test results, and questionnaire findings were reported in more than three studies, and each meta-analysis was performed according to these tests. In the cases of taste strip and taste solution tests, the detection threshold score for total gustatory function and specific taste categories such as sweet, salty, sour, and bitter were subjected to meta-analysis. The taste strip and taste disk tests were followed by standardized protocols in all reviewed studies, and the raw data were obtained for statistical analysis. For the taste disk test, both the detection and recognition thresholds for total gustatory function and specific taste categories were reviewed. For the taste solution test, each score for the threshold concentration was adjusted and standardized to between 1 and 5 points for the meta-analysis. For questionnaire outcomes, a scaling adjustment was made to ensure a maximum score of 5; then, a meta-analysis was conducted. The standardized mean difference (SMD) and its corresponding 95% confidence interval (CI) were used as the effect analysis indices. Statistical heterogeneity was visually assessed using forest plots and formally using Cochran's Q and the I^2 statistic; heterogeneity was considered high for I2 values greater than 75% [17]. Due to the limited number of studies, we were unable to perform Egger's test. Instead, publication bias was assessed by funnel plots. All analyses were performed using the metafor and meta packages in R version 4.2.1 [19].

Table 1. Population, intervention, comparator, outcome, and study design (PICOS).

Author	Design	Location	Gustatory function test	Study characteristics and raw data	Number enrolled subjects
Martin et al., 2018	Cross-sectional, descriptive, comparative cohort study	Spain	Taste solution test normative value is not presented	The detection threshold concentration scores salty taste 2.28±0.64 in AD sweet taste 2.32±1.14 in AD salty taste 1.96±0.62 in Control sweet taste 2.06±0.94 in Control	71 in AD 252 in control
			Triangle test	Triangle test for different taste discrimination	
Kouzuki et al., 2018	Prospective comparative cohort study	Japan	Taste solution test normative value is not presented each taste score ranges from 1 to 6	The recognition threshold concentration scores Sweet taste 2.22±0.1 in AD Salty taste 2.7±0.2 in AD Sour taste 3.0±0.2 in AD Bitter taste 2.3±0.2 in AD Sweet taste 2.2±0.1 in Control Salty taste 2.2±0.1 in Control Sour taste 2.5±0.1 in Control Bitter taste 2.1±0.1 in Control	40 in AD 40 in control
			Questionnaire from 1 to 5 1 indicating the worst, 5 indicating the best	Questionnaires: self-rated gustatory function 4.6±0.1 in AD, 4.6±0.2 in Control	
Sakai et al., 2016	Prospective comparative cohort study	Japan	Taste disk test normal: total average value<3.0 boundary: 3.0≤total average value<3.5 mild: 3.5≤total average value<4.5 moderate: 4.5≤total average value<5.5 severe: total average value≥5.5 no sensitivity: no response	Detection threshold concentration score Sweet taste 2.0±1.1 in AD Salty taste 1.6±0.9 in AD Sour taste 1.7±0.9 in AD Bitter taste 2.2±0.7 in AD Sweet taste 1.4±0.7 in Control Salty taste 1.1±0.3 in Control Sour taste 1.4±0.6 in Control Bitter taste 1.6±0.9 in Control Recognition threshold concentration score Sweet taste 3.0±1.2 in AD Salty taste 2.9±2.1 in AD Sour taste 4.3±1.7 in AD Bitter taste 3.3±1.5 in AD Sweet taste 2.3±0.8 in Control Salty taste 2.1±1.0 in Control Sour taste 3.0±1.2 in Control Bitter taste 2.5±1.0 in Control	32 in AD 22 in control

Table continues on next page

Author	Design	Location	Gustatory function test	Study characteristics and raw data	Number enrolled subjects
Kouzuki et al., 2020	Prospective comparative cohort study	Japan	Taste solution test each tastant score ranges from 1 to 14 normative values for detection are Sweet taste 6.008±1.914 Salty taste 4.959±1.581 Sour taste 4.959±1.606 Bitter taste 5.585±1.792	Detection threshold concentration score Sweet taste 5 (4–7) in AD Salty taste 4 (2–5) in AD Sour taste 4 (2–6) in AD Bitter taste 5 (3–8) in AD Umami taste 9 (6–11) in AD Sweet taste 3 (2–4.8) in Control Salty taste 2 (1–2) in Control Sour taste 1.5 (1–4) in Control Bitter taste 3.5 (1.3–5) in Control Umami taste 4 (1–7.8) in Control	29 in AD 14 in control
			normative values for recognition are Sweet taste 6.854±1.711 Salty taste 6.244±1.456 Sour taste 5.821±1.584 Bitter taste 6.333±1.551	Recognition threshold concentration score Sweet taste 8 (7–10) in AD Salty taste 7 (6–9) in AD Sour taste 7 (6–10) in AD Bitter taste 8 (6–10) in AD Umami taste 14 (12–14) in AD Sweet taste 7.5 (6–8) in Control Salty taste 6 (6–7) in Control Sour taste 6 (5.3–7.8) in Control Bitter taste 6 (5.7.8) in Control Umami taste 10.5 (9.3–12) in Control	
			Questionnaire from 0 to 4, 0 indicating the worst, 4 indicating the best	Questionnaires: self-rated gustatory function 4.0 (4-4) in AD 4.0 (4-4) in Control	
Suto et al., 2014	Prospective comparative cohort study	Japan	Food cognition test Filter disc test	Food naming and food-taste matching test. Number of correctly identifying taste :raw data are not demonstrated	30 in AD 15 in control
Doorduijn et al., 2020	Prospective comparative cohort study	Netherlands	Taste strip test normative values are Sweet taste 2.0 Salty taste 2.0 Sour taste 2.0 Bitter taste 1.0 Total score 9.0	Recognition threshold concentration score Sweet taste 2.9±0.2 in AD Salty taste 2.5±0.2 in AD Sour taste 1.7±0.2 in AD Bitter taste 1.9±0.2 in AD Sweet taste 3.0±0.2 in Control Salty taste 2.2±0.2 in Control Sour taste 2.2±0.1 in Control Bitter taste 2.0±0.2 in Control	40 in AD 30 in control
Petekkaya et al., 2022	Prospective comparative cohort study	Turkey	Taste strip test Questionnaire	(AD-control) values are demonstrated Developed questionnaire score raw data are not demonstrated	15 in AD 15 in control
Ogawa et al., 2017	Prospective comparative cohort study	Japan	Taste disk test	Detection threshold concentration score Sweet taste 2.7±0.9 in AD Salty taste 2.6±0.9 in AD Sour taste 3.2±0.9 in AD Bitter taste 3.2±1.2 in AD Sweet taste 1.8±0.6 in Control Salty taste 1.5±0.4 in Control Sour taste 2.0±0.5 in Control Bitter taste 2.0±0.6 in Control	22 in AD 21 in older control
				Recognition threshold concentration score Sweet taste 3.3±1.3 in AD Salty taste 3.5±1.3 in AD Sour taste 4.2±1.4 in AD Bitter taste 4.2±1.4 in AD Sweet taste 2.4±1.0 in Control Salty taste 1.9±0.7 in Control Sour taste 2.9±0.9 in Control Bitter taste 2.5±0.6 in Control	
			Electrogustometry	Electrogustometry was additionally performed.	

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Author	Design	Location	Gustatory function test	Study characteristics and raw data	Number enrolled subjects
Naudin et al., 2015	Prospective comparative cohort study	France	Taste solution test normative data is not presented	Number of correctly identifying taste Sweet 15 in AD Salty 5 in AD Sour 9 in AD Bitter 7 in AD Sweet 24 in Control Salty 21 in Control Sour 10 in Control Bitter 18 in Control	20 in AD 24 in control
Steinbach et al., 2010	Prospective comparative cohort study	Germany	Taste strip test	The left and right side were separately tested. Recognition threshold concentration scores Sweet taste 2.0±1.1 in AD Salty taste 1.6±1.1 in AD Sour taste 1.2±1.0 in AD Bitter taste 1.4±1.3 in AD Sweet taste 3.0±1.0 in Control Salty taste 2.8±1.0 in Control Sour taste 2.1±1.0 in Control Bitter taste 2.4±1.2 in Control	30 in AD 29 in older control
			Questionnaire score on a visual analog scale	Questionnaires for subjective gustatory function 71.5±21.0 in AD 85.0±20.6 in Control	
Contri-Degiovanni et al., 2020	Cross-sectional, descriptive, Comparative cohort study	Brazil	Taste strip test	Taste strip test modified by Vieira et al. Patients with AD were divided into mild and moderate. Recognition threshold concentration scores Sweet taste 2.9±1.2 in AD Salty taste 1.7±1.5 in AD Sour taste 3.3±0.9 in AD Bitter taste 2.6±0.9 in AD Sweet taste 3.2±0.8 in Control Salty taste 3.2±0.9 in Control Sour taste 3.6±0.7 in Control Bitter taste 3.4±0.9 in Control	23 in moderate AD 30 in older control
Sakai et al., 2017	Prospective Comparative cohort study	Japan	Taste disk test	Detection threshold concentration score Sweet taste 2.1±1.3 in AD Salty taste 1.4±0.9 in AD Sour taste 1.6±0.8 in AD Bitter taste 2.1±0.6 in AD Sweet taste 1.4±0.7 in Control Salty taste 1.1±0.3 in Control Sour taste 1.4±0.6 in Control Bitter taste 1.6±0.8 in Control	18 in AD, 22 in control
			Judgement of tastes Taste-picture matching test	Recognition threshold concentration score Sweet taste 2.9±1.2 in AD Salty taste 3.3±1.9 in AD Sour taste 4.3±1.8 in AD Bitter taste 3.4±1.5 in AD Sweet taste 2.3±0.8 in Control Salty taste 2.1±1.0 in Control Sour taste 2.9±1.0 in Control Bitter taste 2.5±0.9 in Control	

Data are presented as the mean ± standard deviation or median (interquartile range).

Results

Search results

We identified 946 potentially relevant studies from the database search. After excluding 175 duplicates, 771 records were screened based on their titles and abstracts. Of these, 756 studies were excluded because they did not meet the inclusion criteria. A full-text review of the remaining 15 studies was performed. Three studies were excluded for the following reasons: 1) one

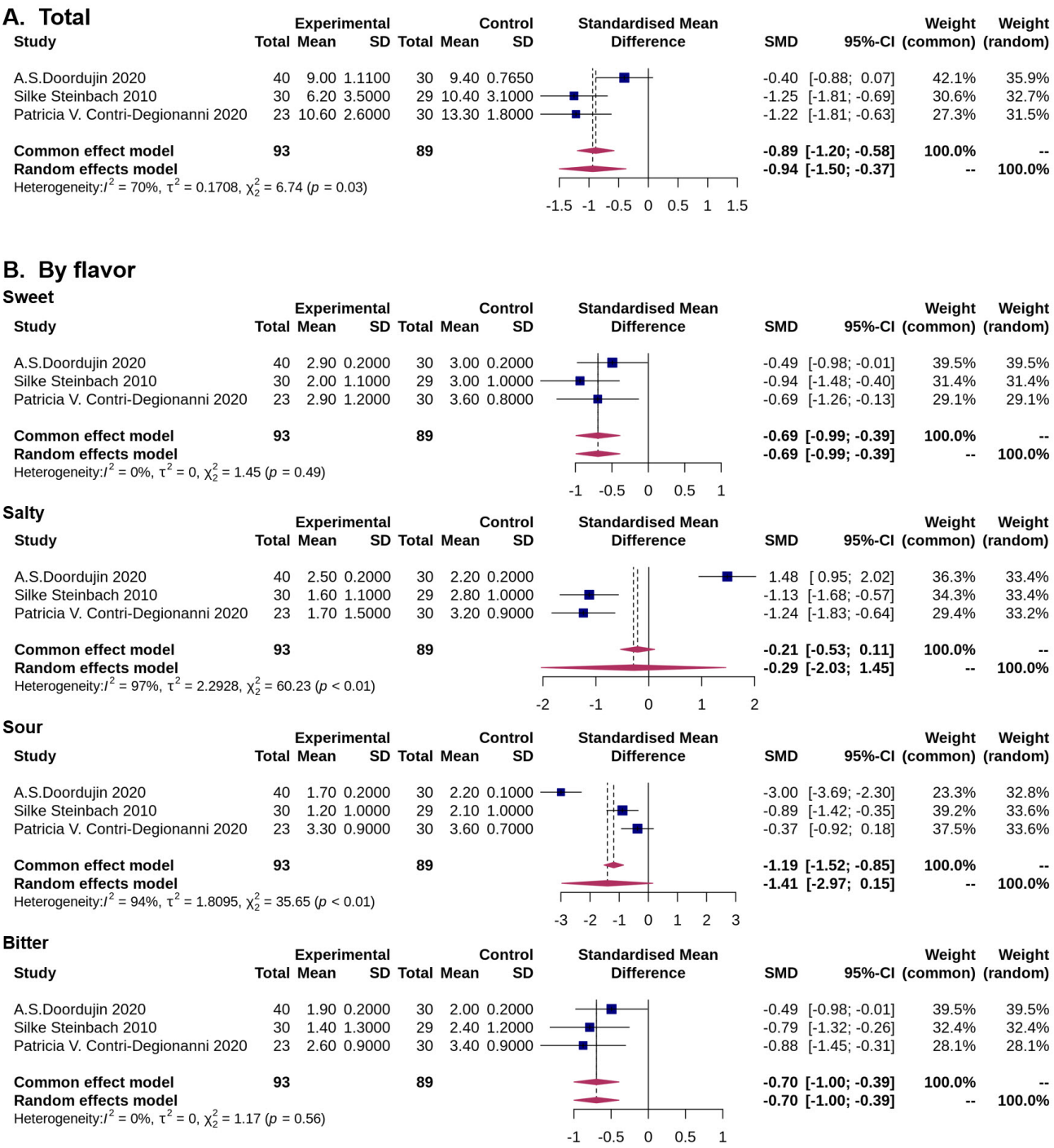

Figure 2. Forest plot of the standardized mean difference (SMD) using taste strip test scores. (A) The common- and random-effects models showed that taste ability was reduced in patients with AD compared with control subjects. (B) Forest plot of the SMD using the taste strip test scores for four specific taste criteria (sweet, salty, sour, and bitter).

study was based on indirect questionnaires obtained by caregivers; 2) the results of one study did not include a comparison with healthy control subjects; and 3) one study was written in French, and the raw data could not be obtained. Finally, 12 studies were included in this systematic review and meta-analysis (Figure 1, Table 1) [5,10,16,18–26]. No studies were found to have a high risk of bias after performing a quality assessment using the Newcastle-Ottawa Quality Assessment Scale (Supplementary Table 1). Most of the studies used more than one method to evaluate gustatory function. Among the various methods, the taste strip, taste solution, and taste disk tests as well as questionnaires were the most commonly performed (Supplementary Figure 1).

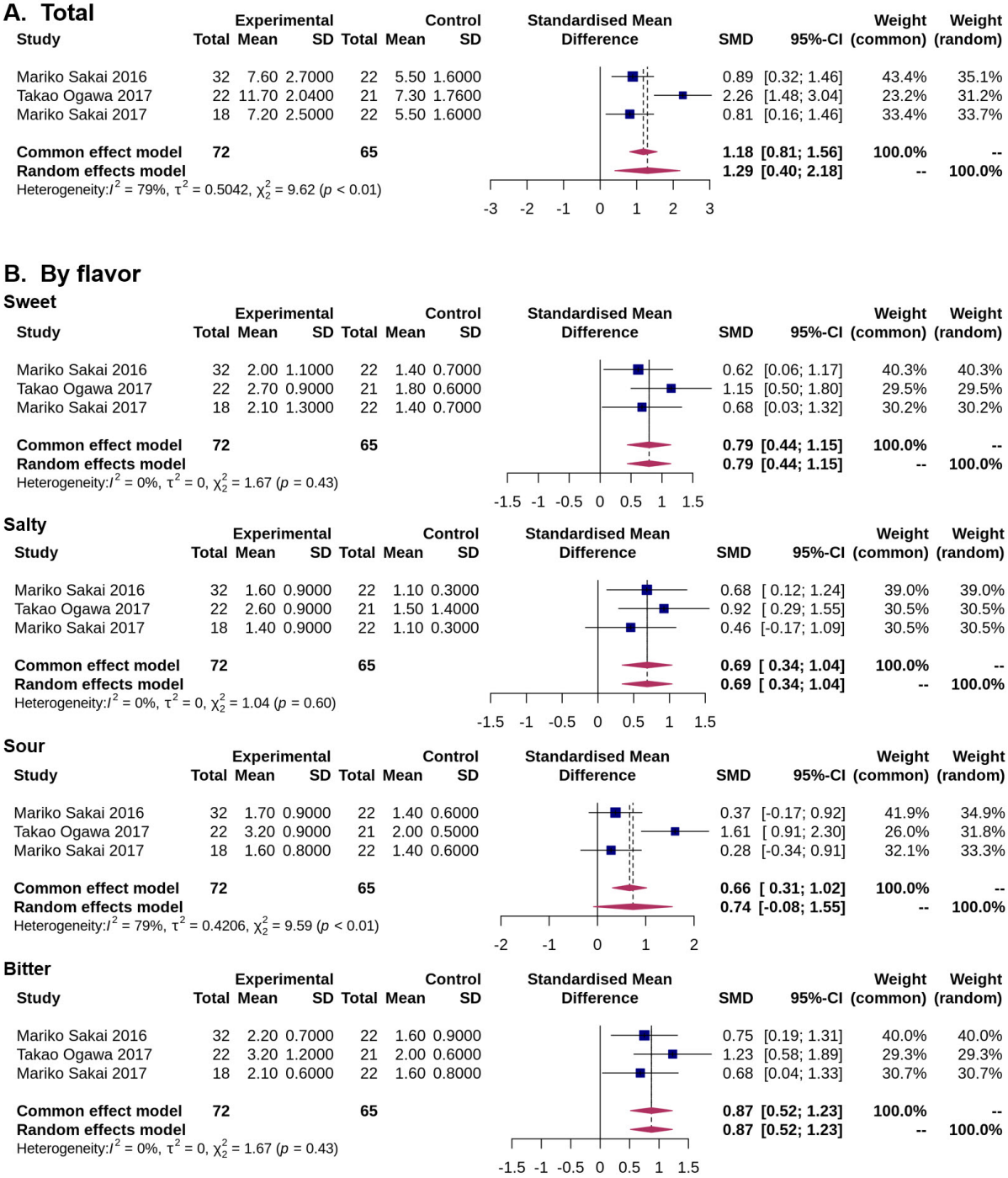

Figure 3. Forest plot of the SMD using taste disk test scores (detection threshold). (A) The common- and random-effect models showed that taste ability was reduced in patients with AD compared with control subjects. (B) Forest plot of the SMD using taste disk test scores (detection threshold) for four specific taste criteria (sweet, salty, sour, and bitter).

Gustatory dysfunction in AD using the taste strip test

A meta-analysis of three papers using the taste strip test was performed [10,16,22]; one study in which the only different values between patients with AD and control subjects was excluded [10,16,22,23,27]. The total population across these three studies was 182 subjects (89 in the control group and 93 in the AD group). Figure 2A shows a forest plot of these three papers using the taste strip test score. In two of three papers, the gustatory function of the AD group was significantly lower than that in the healthy control group. Figure 2B shows a forest plot of the three papers that used the taste strip test scores for four specific taste criteria (sweet, salty, sour, and bitter). Regarding sweet and bitter tastes, the gustatory function of the AD group was significantly decreased in all three papers. For salty taste, in two

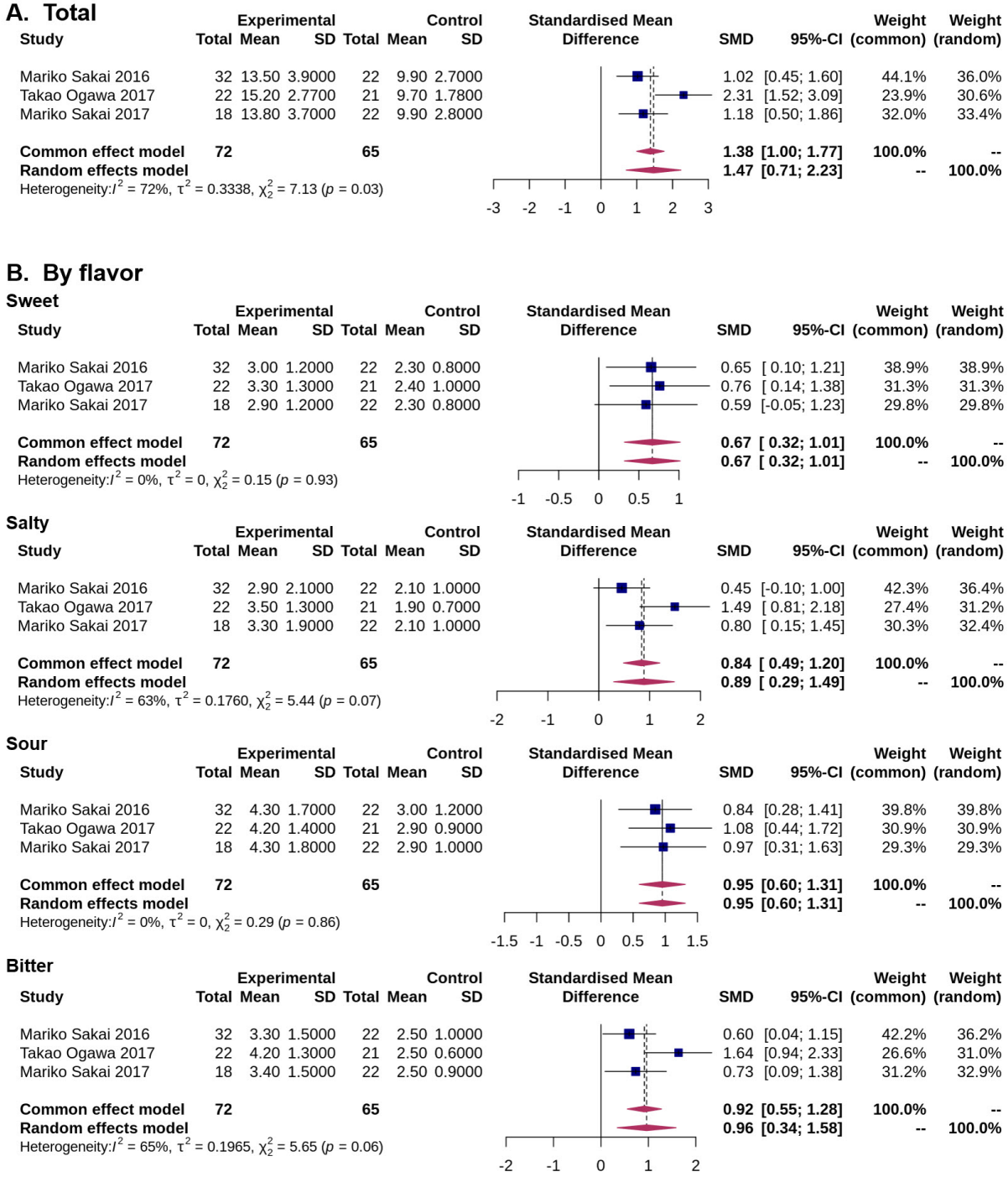

Figure 4. Forest plot of the SMD using taste disk test scores (recognition threshold). (A) The common- and random-effect models showed that taste ability was reduced in patients with AD compared with control subjects. (B) Forest plot of the SMD using taste disk test scores (recognition threshold) for four specific taste criteria (sweet, salty, sour, and bitter).

studies, there was a significant decrease in gustatory function in the AD group compared with the control group. However, in one study, there was a significant opposite result. Regarding sour taste, in two studies, there was a significant decrease in gustatory function in the AD group compared with the control group.

Supplementary Figure 2 shows a funnel plot of three papers that used the taste strip test score (Supplementary Figure 2A) for four specific taste criteria (sweet, salty, sour, and bitter) (Supplementary Figure 2B). For sweet and bitter tastes, which showed low heterogeneity, there was low publication bias (low asymmetry). One study that was excluded from the current meta-analysis due to the absence of raw data also described that the results of the taste strip test and showed that gustatory function was

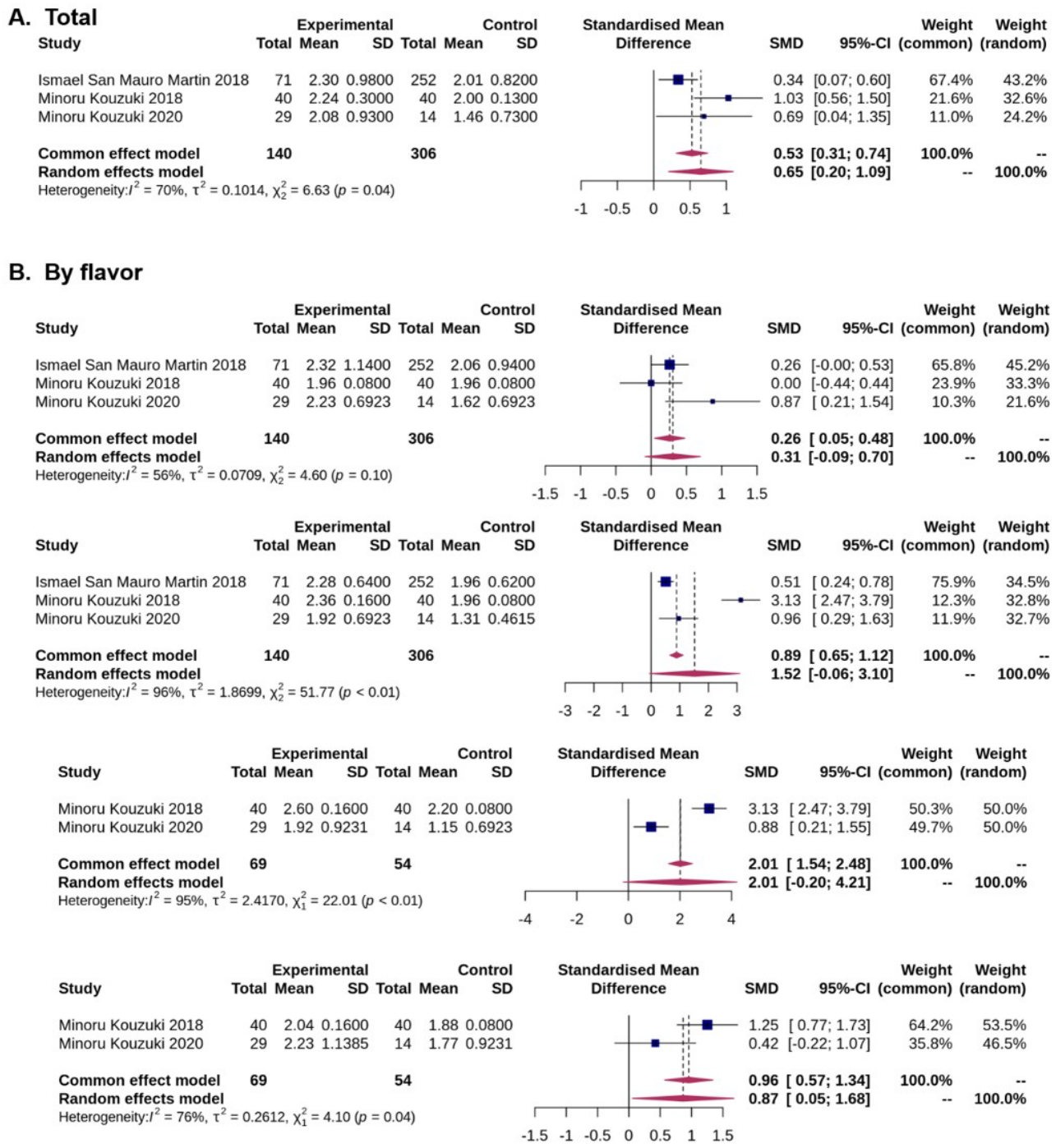

Figure 5. Forest plot of the SMD using the taste solution test. (A) The common- and random-effect models showed that taste ability was reduced in patients with AD compared with control subjects. (B) Forest plot of the SMD using the taste solution test for four specific taste criteria (sweet, salty, sour, and bitter).

significantly decreased in patients with AD compared with controls [23].

Gustatory dysfunction in AD using the taste disk test (detection threshold)

A meta-analysis was performed using three papers that used the taste disk test method (Sanwa Kagaku Kenkyusho Co., Ltd., Nagoya, Japan) for the detection threshold [19,24,26]. The total population across these three studies was 137 subjects (65 in the control group and 72 in the AD group). Figure 3A shows a forest plot of three papers that used the taste disk test score for the detection threshold. In each study, the gustatory function of the AD group was significantly decreased compared with that of the control group.

Figure 3B shows a forest plot of three papers using the taste disk test method to detect four specific taste criteria (sweet, salty, sour, and bitter). For sweet and bitter tastes, the gustatory function of the AD group was significantly decreased in all three papers. Regarding salty taste, in two studies, the detection function was significantly decreased in the AD group compared with the control group. Regarding sour taste, in one study, the detection function was significantly decreased in the AD group compared with the control group. Supplementary Figure 3 shows a funnel plot of three papers that used the taste disk test score (detection threshold) (Supplementary Figure 3A) for four specific taste criteria (sweet, salty, sour, and bitter) (Supplementary Figure 3B). For sweet, salty, and bitter tastes, which showed low heterogeneity, there was low publication bias (low asymmetry).

Gustatory dysfunction in AD using the taste disk test (recognition threshold)

A meta-analysis was performed using three papers that used the taste disk test method for the recognition threshold [19,24,26]. The total population across these three studies was 137 subjects (65 in the control group and 72 in the AD group). Figure 4A shows a forest plot of three papers that used the taste disk test score for the recognition threshold, and the gustatory function of the AD group was significantly decreased compared with that in the control group.

Figure 4B shows a forest plot of three papers that used the taste disk test for the recognition threshold for four specific taste criteria (sweet, salty, sour, and bitter). Regarding sweet taste, the recognition function of the AD group was significantly decreased in two out of three papers. Regarding salty taste, in two studies, there was a significant decrease in the AD group compared with the control group. Regarding sour and bitter tastes, the recognition function of the AD group was significantly decreased in all three papers.

Supplementary Figure 4 shows a funnel plot of three papers that used the taste disk test for the recognition threshold (Supplementary Figure 4A) for four specific taste criteria (sweet, salty, sour, and bitter) (Supplementary Figure 4B). For sweet and sour tastes, which showed low heterogeneity, there was low publication bias (low asymmetry).

Gustatory dysfunction in AD using the taste solution test

A meta-analysis was performed using three papers that used the taste solution test method [5,18,20], and one study that only described the identification test score was excluded [25]. The total population across these three studies was 446 subjects (306 in the control group and 140 in the AD group). Figure 5A shows a forest plot of three papers using the taste solution test score. In all three studies, the gustatory function of the AD group was significantly decreased. Figure 5B shows a forest plot of three papers using the taste solution test scores for four specific taste criteria (sweet, salty, sour, and bitter). In the study by Martin et al. [5], there were no results available for sour and bitter tastes; thus, the meta-analysis on sour and bitter tastes only considered two papers. Regarding sweet taste, the gustatory function of the AD group was significantly decreased in one out of three papers. Regarding salty taste, the taste ability of the AD group was significantly decreased in all three papers. Regarding sour taste, the taste ability of the AD group was significantly decreased in two of two papers. Regarding bitter taste, the taste ability of the AD group was significantly decreased in one of two papers.

Supplementary Figure 5 shows a funnel plot of three papers that used the taste solution test score (Supplementary Figure 5A) for four specific taste criteria (sweet, salty, sour, and bitter) (Supplementary Figure 5B). For sweet taste, which showed low heterogeneity, there was low publication bias (low asymmetry).

One study that was excluded from the current meta-analysis also reported that patients with AD performed worse than healthy controls in the identification test [25].

Gustatory dysfunction in AD using questionnaires

A meta-analysis of three papers using the questionnaire method was performed [10,18,20], and one paper in which only different values between patients with AD and control subjects were demonstrated was excluded [10,18,20,23]. The total population across these three studies was 153 subjects (69 in the control group and 84 in the AD group). Figure 6 shows a forest plot of three papers that used the questionnaire score. In each study, the subjective gustatory function of the AD group was not statistically significantly decreased compared with that in the control group. Supplementary Figure 6 shows a funnel plot.

One study that was excluded from the current meta-analysis due to the absence of raw data described that subjective gustatory function was decreased in patients with AD compared with controls [23].

Gustatory dysfunction in AD using other gustatory function tests

Suto et al. reported the results of the filter disc method as an identification test and found that the test score was not significantly different between patients with AD and healthy controls [21]. They also performed the food cognition test, which consisted of food naming, matching, and taste matching using culture-friendly common foods. Martin et al. applied the triangle test and found that recognition of sweet and salty flavors was reduced in patients with AD compared with controls [5]. Ogawa et al. demonstrated the results of electrogustometry along with the taste disc test; regarding electrogustometry, there were no significant differences between the AD and control groups [24]. Sakai et al. performed a taste discrimination and identification test along with the taste disk test using six pairs of different

tastes and four pairs of the same tastes, and a taste-picture matching test was applied to evaluate the identification function [26]. They reported that taste discrimination was preserved and that taste identification was disturbed in patients with AD compared with control subjects.

Discussion

Based on the current study, we found that in most studies, the overall gustatory function evaluated by validated tests was decreased in patients with AD compared with healthy control subjects. Psychophysical tests such as the taste strip, taste disk, and taste solution tests were frequently applied, and a combination of more than two tests were also commonly applied. However, patients' subjective recognition of their gustatory function through questionnaires was not significantly different from that of healthy control subjects.

The study of olfactory ability and its role in neurodegenerative diseases has aroused considerable interest, and it is currently believed that olfactory impairment is a potential early marker for the onset of neurodegenerative diseases [28]. Although the mechanisms have not been clearly identified, pathological protein aggregation in olfactory regions before other regions [29], abnormal neural networks in the olfactory bulb and piriform cortex [30], and dysbiosis in the nasal mucosal microbiota [31] have been suggested as underlying mechanisms. As olfactory functions are strongly connected with gustatory functions and because similar brain regions are involved in both smell and taste, more recent studies have tried to evaluate gustatory function in neurodegenerative diseases such as Parkinson's disease and AD [32]. Through our meta-analysis, we suggest that gustatory function measured through validated tests might be decreased in patients with AD, while subjective dysfunction may not.

There are five basic tastes in the detection of taste: sweet, salty, sour, bitter, and umami (more recently, it has been suggested that fat may also be another basic taste) [33]. In the current study, we found that in most studies, the perceptive function of four tastes (sweet, salty, sour, and bitter) was measured. When we further evaluated the relationship between gustatory function to each tastant and AD, the gustatory function of each taste in AD was heterogeneously reported according to the applied test. In the taste strip test, the gustatory functions for sweet and bitter tastes were significantly decreased in patients with AD compared with control subjects. In the taste disk test, the detection function for sweet and bitter tastes was decreased in patients with AD; however, the recognition function was not. In the taste solution test, the gustatory functions for salty and sour tastes were reduced in patients with AD. Although the presented data are heterogenous, we found that the sweet taste test showed low heterogeneity in all the included studies, and there seemed to be low publication bias (low asymmetry). Therefore, we hypothesized that the sweet taste test could be a more reliable taste than other tastes. Further studies regarding the relationship between each taste and AD could be important to identify the pathogenic mechanism.

Measured gustatory function through validated tests could be different from patients' subjectively recognized gustatory function [34,35]. The gustatory pathway has been shown to be modulated by sensory input from cranial nerves I and V, and olfaction is an important part of taste [33]. It also has been reported that the retronasal olfactory system is involved in the discrepancy between self-perception of taste and assessed gustatory function testing [36]. In addition, it has been suggested that patients may have mistaken an actual olfactory deficit for a subjective loss of taste since olfaction and gustation are interrelated and both are vital for the perception of flavor [35]. All these mechanisms could be considered potential mechanisms of our result demonstrating a discrepancy between subjectively recognized and test-based gustatory function.

In the current study, we found that subjective gustatory dysfunction based on questionnaires was not significantly different between patients with AD and healthy control subjects. Furthermore, while there are validated questionnaires used in practice to assess olfactory disorders, there are no such validated questionnaires to evaluate gustatory function [37]. Therefore, we suggest that clinicians carefully evaluate gustatory function and consider performing validated gustatory function testing in patients with AD even in those without subjective recognition of dysfunction. As the mechanisms regarding gustatory dysfunction in AD have not been well identified, future mechanism studies need to be performed to support our hypothesis.

Regarding gustatory function testing, standardized gustatory function tests are lacking. Chemical tests such as the taste disk test, the taste strip test, electrogustometry, and gustatory evoked potential testing have been introduced for clinical application. Combining gustatory function testing with testing of other functions such as food cognition testing and food naming tests has also been applied in evaluating gustatory function in patients with AD. During our meta-analysis, we found that the taste strip and taste disk tests are standardized tests for determining the taste detection threshold, and the taste disk test also has been applied to evaluate the recognition threshold. Although the taste solution test also enables the acquisition of the detection threshold, various concentrations of taste solutions (not unified) were applied, which was not optimal for meta-analysis. In addition, we found that culture-specific taste identification tests using various tastants were applied. Therefore, we suggest that standardized gustatory function testing using unified concentrations of tastants be applied in a future study to further enable large population-based meta-analysis regarding gustatory dysfunction.

Our study has several limitations. First, our analysis was based on studies with relatively small sample sizes. Studies containing

the results of validated gustatory function tests are limited and could not support our results as confirmative findings. More evidence is needed to draw a definitive conclusion about the clinical relevance of gustatory dysfunction in patients with AD. Second, we did not evaluate the specific symptoms of gustatory dysfunction. Gustatory disorders are classified clinically as either quantitative or qualitative. Quantitative dysfunction can be classified as ageusia, hypogeusia, and hypergeusia. Qualitative dysfunction can be classified as parageusia and phantogeusia. However, we could not subtype the specific type of gustatory dysfunction, and if there was any discomfort related to gustation, it was described as gustatory dysfunction.

Conclusion

We found that gustatory function test-based gustatory dysfunction is frequently reported in patients with AD compared with the healthy controls, suggesting a high possibility of a close relationship between gustatory dysfunction and AD. In addition, we found that subjective patient recognition of gustatory dysfunction was not different between patients with AD and healthy control subjects. We suggest that further study of standardized gustatory function testing be performed to support our findings.

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Authorship contribution

IYK performed the statistical analysis, initial drafting, and revision of the manuscript. KSK collected the data and reviewed the data and manuscript. HJM participated in study conceptualization, data collection, initial writing of the manuscript, and final submission.

Availability of data and materials

This study's data are available from the corresponding author upon reasonable request. The data are not publicly available.

Conflict of interest

The authors declare no conflicts of interest.

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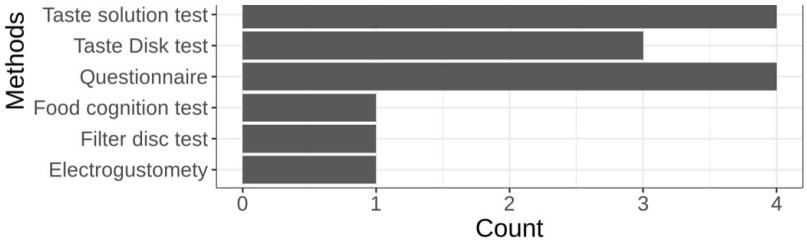
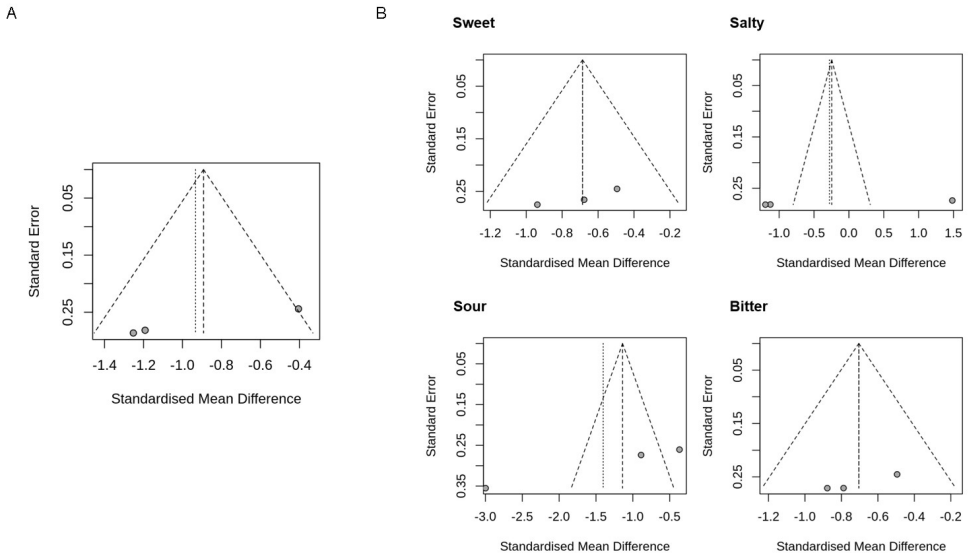
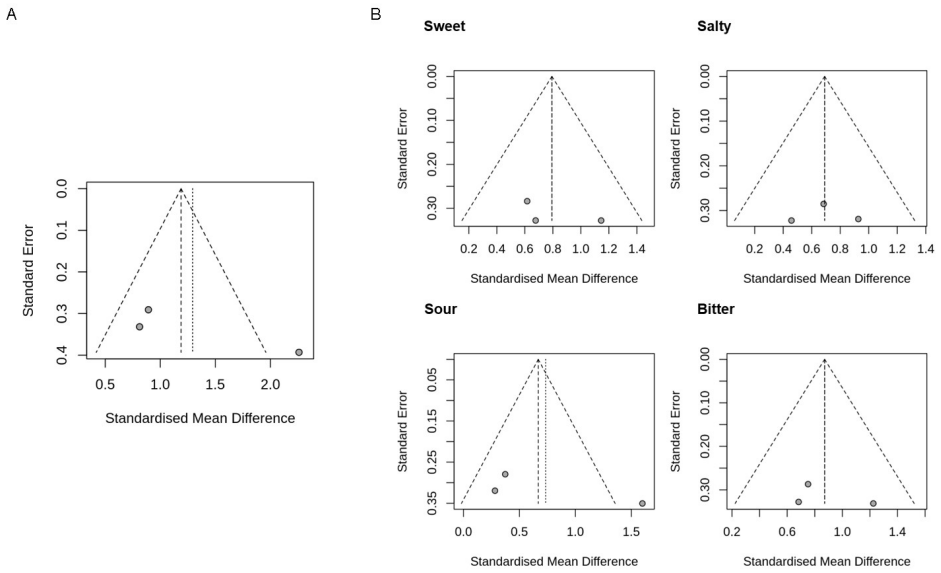
SUPPLEMENTARY MATERIAL



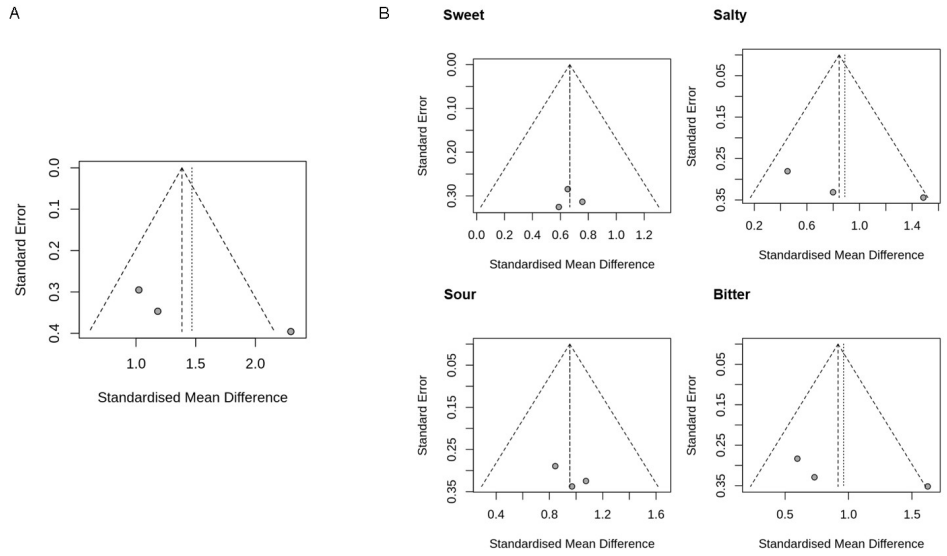
Supplementary Figure 1. Number of different taste testing methods applied in the included studies.



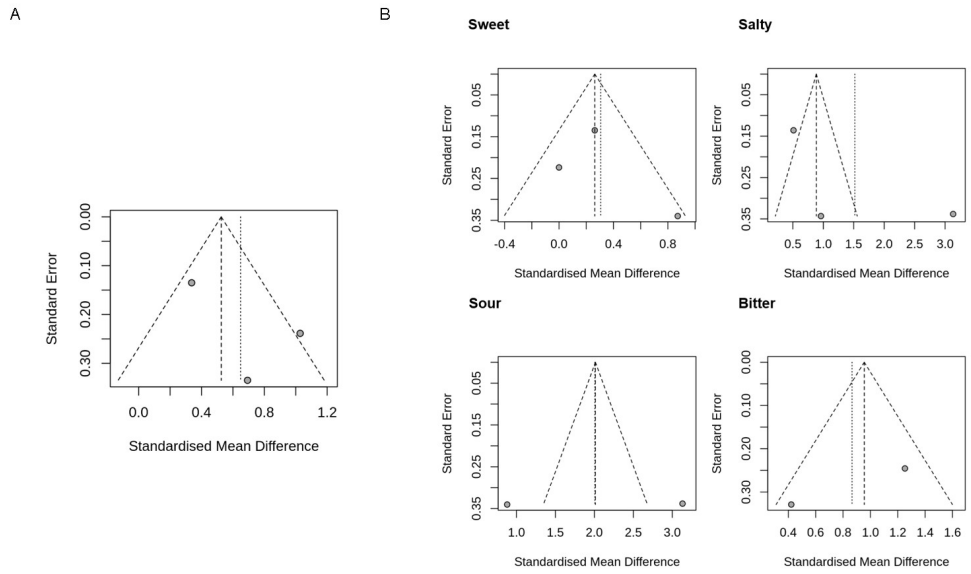
Supplementary Figure 2. Funnel plots of the results of taste strip tests. (A) Funnel plot of three papers using the taste strip test. (B) Funnel plot of three papers using the taste strip test score for four specific taste criteria (sweet, salty, sour, and bitter).



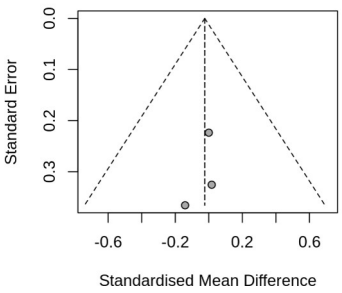
Supplementary Figure 3. Funnel plots of the results of taste disk tests (detection threshold). (A) Funnel plot of three papers using the taste disk test. (B) Funnel plot of three papers using the taste disk test score for four specific taste criteria (sweet, salty, sour, and bitter).



Supplementary Figure 4. Funnel plots of the results of taste disk tests (recognition threshold). (A) Funnel plot of three papers using the taste disk test. (B) Funnel plot of three papers using the taste disk test score for four specific taste criteria (sweet, salty, sour, and bitter).



Supplementary Figure 5. Funnel plots of the results of taste solution test. (A) Funnel plot of three papers using the taste solution test. (B) Funnel plot of three papers using the taste solution test score for four specific taste criteria (sweet, salty, sour, and bitter).



Supplementary Figure 6. Funnel plots of questionnaire results.