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The Association Between Diabetes and Olfactory Impairment in Adults: A Systematic Review and Meta-Analysis

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Background: Evidence suggests that olfactory impairment (OI) may be a degenerative neurologic complication of diabetes; however, the association is not yet well established. The objective of this work was to systematically review existing literature on the association between diabetes and OI in adults, with meta-analysis of evaluable studies.

Methods: A literature search encompassing 358 abstracts from the last 75 years in PubMed, EMBASE, and Cochrane was performed. English-language articles investigating adults with diabetes and OI in comparison to control groups with original data and ≥7 subjects were included. The Newcastle-Ottawa scale was applied for quality assessment. Two investigators independently reviewed all articles. For meta-analysis, the odds ratio of OI in diabetes compared with control groups was calculated using the fixed effects model.

Results: The initial search yielded 358 abstracts, from which 21 articles were reviewed and 11 articles (n = 6,747) were included. Studies included were case-control (64%) or cross-sectional (36%) with evidence level 3b. On the Newcastle-Ottawa scale, the mean quality assessment score for case-control and cross-sectional studies was 7.4 (maximum of 9) and 7.0 (maximum of 10), respectively. A statistically significant association between diabetes and olfaction compared with controls was found in 6 (55%) of the 11 articles. Four studies were eligible for meta-analysis, which yielded an overall odds of having OI with diabetes as 1.58 times more likely than in control groups (95% CI [1.16, 2.16]; I^2 = 10.3%).

Conclusions: The reviewed studies support a significant association between diabetes and OI. Further studies are warranted to characterize this association.

Key Words: Anosmia, dysosmia, hyposmia, smell disorder, olfactory nerve diseases.

Level of Evidence: 3a

INTRODUCTION

Diabetes mellitus (DM) presents an increasingly significant health challenge in the United States, affecting over 30 million adults.[1] For individuals with type I (T1D) and type II (T2D) diabetes, microvascular complications, such as peripheral neuropathy and retinopathy, contribute to increased morbidity and health care costs.[2] Although visual impairment resulting from microvascular complications in diabetes has been well studied,[3] the association between olfactory impairment (OI) and diabetes is not well understood.

Olfaction is an underappreciated sense that is often overlooked in clinical practice in comparison to vision and hearing. However, olfaction plays a critical role in everyday functioning—impacting food intake, safety, survival, and social communication.[4] Previous studies have highlighted the importance of olfaction in maintaining health, as OI is associated with decreased quality of life and depressive symptoms.[5,6] Furthermore, OI is an increasingly relevant health concern in an aging population, with estimates of greater than 60% of individuals above 80 years of age experiencing OI.[7] Although an epidemiologic study reported 18% prevalence in the general population,[8] this is likely an underestimate as many individuals remain undiagnosed and often overestimate their subjective sense of smell.[9]

Although olfaction is not routinely assessed in the clinical setting, its application in diabetes management may be warranted, as previous studies have suggested an association between OI and diabetes-related cognitive impairment.[10] Moreover, the current availability of low-cost, validated tools[11] for olfactory assessment lends further support for potential utility in clinical practice.

To examine the association between diabetes and OI in adults, we performed a systematic review and meta-analysis of the existing literature.

METHODS

Information Searches and Sources

A systematic review of published English literature was conducted to investigate the association between diabetes and OI in adults. The systematic review was conducted with adherence to the Preferred Reporting Items

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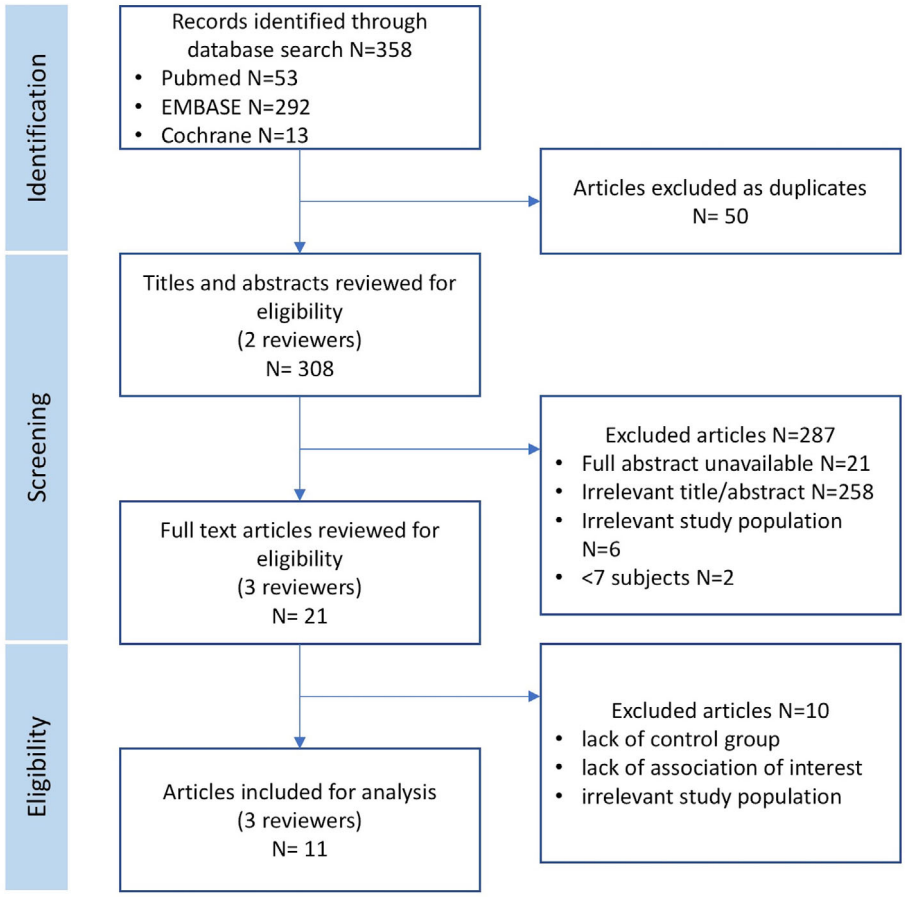

Fig. 1. PRISMA flowchart of study selection for systematic review, article review, and selection.

for Systematic Reviews and Meta-Analysis (PRISMA) guidelines as shown in Figure 1.[12]

A medical librarian (SS) with expertise in systematic reviews was consulted to develop comprehensive search strategies. PubMed, Cochrane Library, and EMBASE were queried for relevant publications. Date filters were not applied with the intention of generating a broad list of potential studies. A principal electronic search strategy was developed for PubMed and then applied to the other databases. The electronic search incorporated the following Medical Subject Headings (MeSH): olfaction disorders, olfactory nerve diseases, diabetes mellitus, and diabetes insipidus. The following key words were also included: smell disorder, cacosmia, dysosmia, paraosmia, anosmia, and cranial nerve disease (Table I).

In addition to the electronic search strategy, relevant review articles and references were examined for thorough assessment of the existing literature (Supporting Information Appendix).

Study Selection and Eligibility Criteria

Two investigators (SJK, MJW, or SYL) independently reviewed abstracts and selected studies for inclusion based on prespecified criteria. Where inclusion decisions differed, full articles were discussed to reach consensus. English-language articles investigating adults with diabetes and OI in comparison to control groups with original data and ≥7 subjects were included. Exclusion criteria were studies with no abstract present; written in a language besides English; not relevant to the study question; duplicate articles; case report/small case series; secondary research (review article, position paper); pediatric population; population with congenital abnormalities (cystic fibrosis, Kallmann syndrome), no outcome of interest; incomplete data; lack of a nondiabetic control group. Accompanying full-text publications were reviewed by two investigators to confirm that all criteria were met. In cases of disagreement, discussion including a third investigator (SL) was used to reach consensus.

TABLE I.
Search Strategy.

Major MeSH Terms	Major Text Terms
Olfaction disorders	Smell disorder
Olfactory nerve disease	Cacosmia
Diabetes mellitus	Dysosmia
Diabetes insipidus	Paraosmia
	Anosmia
	Cranial nerve disease

MeSH = medical subject headings.

Data Extraction and Quality Assessment

Data were extracted and reviewed independently by two investigators using a predesigned form. Disagreement was addressed through a review of the full-text article and input from a third investigator (SL). Extracted data included study design, patient demographics, T1D and/or T2D prevalence, method of olfactory testing, method of diabetes diagnosis, estimates of association between prevalent diabetes and OI, and other clinical characteristics. Level of evidence was determined based on published guidelines by the Oxford Centre for Evidence-Based Medicine, Levels of Evidence (OCEBM Levels of Evidence 2009).[13] A modified Newcastle-Ottawa Assessment Scale[14] for assessing nonrandomized studies in systematic reviews was applied for quality assessment. This scale uses the following domains to assess the quality of the study: representativeness and selection of cases and controls, comparability of controls on basis of design/analysis, and ascertainment of exposure/outcome. No studies were excluded based on quality assessment.

Summary Measures and Meta-Analysis

Articles were categorized based on olfactory test method, diabetes diagnostic criteria, and primary findings (significant association; positive, negative) regarding the relationship between olfaction and diabetes. Meta-analytic methods that accounted for between-study heterogeneity were used to estimate pooled effect sizes from the systematic review. Only studies with odds ratios (ORs) describing the odds of OI in participants with diabetes against the odds of OI in the control group were included in the meta-analysis. Heterogeneity across studies was assessed using the I^2 statistic. If the heterogeneity test was significant, the random effects model was used. If the heterogeneity test was nonsignificant, the fixed effects model was used. Analysis of publication bias was performed using funnel plot techniques in the Egger weighted-linear regression method. Analyses were performed using Stata 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

RESULTS

Search Characteristics

The initial search yielded 358 abstracts (PubMed 53, EMBASE 292, and Cochrane 13), from which 21 articles were reviewed and 11 articles were included. The 11 publications selected in this review included a total of 6,747 subjects. Included articles were case-control (7, 64%) or cross-sectional (4, 36%) with evidence level 3b. No randomized controlled trials met inclusion criteria. Study population sizes ranged widely from N = 60–3,151. A summary of all included articles is shown in Table II.

Associations by Diabetes Subtype

A statistically significant association between prevalent diabetes (T1D and/or T2D) and olfactory function compared with nondiabetic controls was found in 6 (55%) of the 11 articles. The association between olfactory function and diabetes did not vary by diabetes subtype. Among the six articles that demonstrated a statistically significant association between diabetes and OI, three studies[15–17] specifically evaluated participants with T2D, while two studies[18,19] did not distinguish diabetes subtype, and a single study[20] characterized both T1D and T2D patients. Among the five articles that did not find a statistically significant association between diabetes and olfactory function, a single study[21] evaluated T1D and T2D, two studies[22,23] did not specify subtype, one study[24] examined T1D only, and one study[25] examined T2D only. Studies that demonstrated a statistically significant association recruited participants from a wide range of geographies (Canada, Sweden, Greece, France, Iran, and Turkey) with variations in baseline characteristics (Table II).

Olfactory Testing

Multiple components of olfactory function were assessed including odor threshold, discrimination, identification, pleasantness, intensity, and familiarity. Olfactory threshold testing measures the minimum stimulus required to detect odors, while identification and discrimination, which requires the patient to detect, recognize, and name an odor, reflects higher order processing.[26] Among the studies included in this review, odor identification was the most commonly tested component of olfaction (10, 91%). Due to differences in the components of olfaction tested, studies did not align on the scoring system used to quantify OI. Sniffin' Sticks was the most common method for assessment of olfactory function (6, 55%), wherein odors are presented as felt-tipped pens with multiple choice answer options, with extended versions providing measures for odor threshold, discrimination, and identification. Additional validated measures of olfaction included the Scandinavian Odor Identification Test,[18] Brief Smell Identification Test,[25] and the butanol threshold test.[17]

The majority of studies (6, 55%) performed a complete otolaryngologic exam or nasal endoscopy to exclude other factors contributing to OI including, for example, acute or chronic rhinosinusitis, nasal polyps, or septal deviation.[16–19,21,24] Among studies that included a complete otolarynglogic exam or nasal endoscopy, four out of six found a significant association between OI and diabetes.[16–19] In addition to olfactory testing, a minority of studies (4, 27%) evaluated other sensory functions including auditory, visual, or gustatory impairment.[17,20–22] Two studies found that the loss of olfactory and gustatory function is not correlated with the duration of diabetes.[17,21] One study found that diabetes was related to an increased odds of multisensory impairment (OR, 1.75; 95% CI [1.16–2.63]).[22]

Diabetes Diagnosis

Method of diabetes diagnosis ranged from validated clinical measures to self-reports and physician diagnoses (Table II). A minority of studies (3, 27%) used fasting serum glucose measures, oral glucose tolerance tests, or HbA1c measures to verify diabetes diagnosis.[15,22,23]

TABLE II.
Articles included in systematic review.

#	Author	Study Type	Year	N Total (Case, Control)	Population Studied	Age (years)*	Diabetes Subtype	Olfactory Test (Tool, *Component)*	OI Definition	ENT Exam	Diabetes Diagnosis	Main Findings	Adjustments
1	Brady et al	Case-control	2013	70 (51, 19)	Patients from University of Calgary in Canada	Mean, 57.9 (DM), 52.9 (control)	T2D	Sniffin' Sticks *TDI, subjective odor ratings (pleasantness, intensity, familiarity)*	No standard definition	No	FSG > 126 mg/dL, OGTT > 200 mg/dL	DM patients showed significant reduction in olfactory function compared with control group (F[6, 63] = 2.68, P = .02)	—
2	Bramerson et al†	Cross-sectional	2004	1,387 (not reported)	Swedish population	20–80+ (stratified)	Not specified	SOIT *Identification*	Hyposmia if 10–12, anosmia if <9 on a 16-point scale	Yes	Self-report	Risk for anosmia increased with DM (OR = 2.6, 95% CI [1.3–5.5])	—
3	Chan et al†	Cross-sectional	2017	3,151 (657, 2,494)	US nationally representative sample (NHANES)	≥40	Not specified	Self-report 8-item Pocket Smell Test *Identification*	Severe hyposmia or anosmia if <5 correct answers on 8-item pocket smell test	No	FSG > 126 mg/dL, OGTT > 200 mg/dL, HbA1c ≥ 6.5%, self-report, use of DM drugs or insulin	Diabetics under insulin treatment showed a higher prevalence of severe hyposmia/ anosmia (OR = 1.57, 95% CI [0.89–2.78])	Age, gender, race, education, smoking, sinonasal symptoms, xerostomia, head injury, hypertension, obesity, cardiovascular disease
4	Duda-Sobczak et al†	Case-control	2017	136 (106, 30)	Patients from Poznan University in Poland	Mean, 35 (DM), 40 (control)	T1D	Sniffin' Sticks *Identification*	OI if 0–10 on a 12-point scale	Yes	Patients recruited from outpatient clinic (HbA1c measured)	No significant difference in hyposmia prevalence in T1D (67.9%) vs. control (53.3%)	—
5	Gouveri et al	Case-control	2014	154 (119, 35)	Patients from Democritus University of Thrace in Greece	Mean, 63.6 (DM), 51.5 (control)	T2D	Sniffin' Sticks *TDI*	Anosmia if ≤15, hyposmia if 16–34.5 on a 48-point scale	Yes	Patients recruited from outpatient clinic (plasma glucose, HbA1c measured)	Patients with T2DM had lower TDI scores (29.29 ± 5.24 vs. 34.86 ± 3.72, P < .001) compared to controls	—

6	Hawkins et al	Cross-sectional	2011	288 (63, 225)	African Americans living independently in the community	Mean 64.2, range, 55–87	T2D	BSIT *Identification*	No standard definition	No	Self-report	Patients with and without diabetes performed at near identical levels on BSIT (9.89 ± 1.7 vs. 9.82 ± 2.0, $t = 0.26$, $P = .8$)	—
7	Khil et al[†]	Cross-sectional	2015	1,208 (not reported)	Inhabitants of Dortmund, Germany	Mean, 51.9, range, 25–74	Not specified	Sniffin' Sticks *Identification*	OI if <10 on a 12-point scale	No	Physician diagnosis or blood glucose ≥ 200 mg/dL	No significant relationship between olfaction and diabetes (OR = 1.16, 95% CI [0.69–1.94])	Age, sex
8	Le Floch et al	Case-control	1993	98 (68, 30)	Patients recruited from outpatient clinic in Creteil, France	Mean, 55.6 (T2D insulin), 52.8 (T2D non-insulin), 36.6, (T1D), 52.5 (control)	T1D, T2D	Smell recognition score *Identification*	No standard definition	No	Patients recruited from outpatient clinic (plasma glucose, HbA1c measured)	Smell recognition score was significantly lower in diabetic patients (12.4 ± 0.5 vs. 15.1 ± 0.5, $P < .001$)	—
9	Naka et al	Case-control	2010	105 (76, 29)	Patients recruited from Medical University of Vienna, Austria	Mean, 52.5 (DM), 45.6 (control)	T1D, T2D	Sniffin' Sticks *Identification*	No standard definition	Yes	Self-report (not clearly stated)	Patients with uncomplicated DM showed no clinically significant loss of smell function	—
10	Seraj et al	Case-control	2015	60 (30, 30)	Patients recruited from diabetes clinic in Iran	Mean, 47 (DM), 42 (control)	Not specified	Absorbent Perfumer's Paper Strips *Threshold*	OI if <median of olfactory threshold in the control group	Yes	Patients recruited from outpatient clinic	Significant difference ($P < .01$) between the median of olfactory threshold in diabetic patients and control group	—

(Continues)

TABLE II.
Continued

#	Author	Study Type	Year	N Total (Case, Control)	Population Studied	Age (years)*	Diabetes Subtype	Olfactory Test (Tool, *Component*)	OI Definition	ENT Exam	Diabetes Diagnosis	Main Findings	Adjustments
11	Yazla et al	Case-control	2018	90 (60, 30)	Patients recruited from outpatient clinic in Turkey	Mean, 55.4 (T2D, w/o DPN), 60.3 (T2D w/DPN) 55.5 (control)	T2D	Butanol Threshold Test Sniffin' Sticks *Threshold, Identification*	Hyposmic if 7–9, anosmic if ≤6 on 12-point scale	Yes	Patients recruited from outpatient clinic (HbA1c measured)	Control subjects showed significantly higher Sniffin' sticks and butanol threshold scores than the diabetic patients without DPN (P = .001, P = .009)	—

*Studies varied in how they reported age.
†Included in meta-analysis.
BSIT = brief smell identification test; DM = diabetes mellitus; DPN = diabetic peripheral neuropathy; FSG = fasting serum glucose (mg/dL); OGTT = oral glucose tolerance test (mg/dL); OI = olfactory impairment; OR = odds ratio; SOIT = Scandinavian odor identification test; T1D = type I diabetes; T2D = type II diabetes; TDI = threshold discrimination identification.

Otherwise, most studies relied on participant self-reports (3, 27%)[18,21,25] or recruited participants directly from outpatient diabetes clinics (5, 46%).[16,17,19,20,24] Among studies that used validated clinical measures to diagnose diabetes, only Brady et al found that DM patients demonstrated a general significant reduction in olfactory function when compared with controls.[15] Among studies using participant self-reports,[18,21,25] Brämerson et al found that the risk of anosmia increased with DM (OR, 2.6; 95% CI [1.3–5.5]), whereas the other studies did not find a significant association between olfaction and diabetes.[21,25] Interestingly, four out of five studies with participants recruited from outpatient clinics found a significant association between diabetes and olfaction (Table II).[16,17,19,20]

Other Findings

In addition to examining the relationship between OI and diabetes, the majority of studies (7, 64%) also investigated the association between diabetic peripheral neuropathy and olfaction. While two studies[19,21] found no significant association, the majority of studies[16,17,20,24] found that peripheral neuropathy is associated with lower olfactory scores. Brady et al further reported OI particularly among diabetics with neuropathic pain, suggesting that OI may be partially explained by limited attention and concentration due to pain.[15] Additional associations of OI with retinopathy, diabetes duration, treatment (oral, insulin), hypertension, and body mass index (BMI) were explored with results summarized in Table III.

Meta-Analysis

Four studies were evaluable for meta-analysis. We only considered studies with a threshold defining OI that either provided an OR or specified the number of participants with OI in the diabetes and control group from which ORs were computed (Fig. 2). Given that the heterogeneity test was nonsignificant, the fixed effects model was used. Overall, the pooled data demonstrated that the odds of having OI with diabetes was 1.58 times more likely than without diabetes (95% CI [1.16–2.16], I^2 = 10.3%) (Fig. 2). Publication bias was assessed using a standard error funnel plot (Fig. 3). There is symmetry of the effect sizes around the pooled overall effect, suggesting limited publication bias related to this association.

Quality Assessment

The mean modified Newcastle-Ottawa Quality Assessment scores for case-control and cross-sectional studies were 7.4 (maximum of 9) and 7.0 (maximum of 10), respectively (Table IV).

DISCUSSION

To our knowledge, this is the first systematic review examining the association between diabetes and OI. The results from the 11 studies included in this review support an association between diabetes and OI, highlighting several mechanisms including olfactory nerve impairment

TABLE III.
Additional Findings on the Association Between Olfaction and Other Participant Characteristics.

Article #	Author	DPN	Retinopathy	Diabetes Duration	Treatment	Hypertension	BMI	Other Sensory Impairment
1	Brady et al	OI partially attributed to NeP, but pain severity not associated with OI	Assessed, but association with olfaction not reported	No association with olfaction	Assessed, but association with olfaction not reported	Assessed, but association with olfaction not reported	—	—
2	Bramerson et al	—	—	—	—	—	—	—
3	Chan et al	—	—	No association with olfaction	Among DM participants, significant trend to hyposmia/anosmia for those on aggressive treatment (oral and insulin) compared to those with no drug treatment (OR = 1.33, 95% CI [0.60–2.96] and OR = 2.86, 95% CI [1.28–6.40]; *P*-trend .01)	Increased prevalence of hyposmia/anosmia in DM not explained by increased prevalence of hypertension among those on aggressive treatment	Positive association between self-reported olfactory dysfunction but not objective olfactory dysfunction	—
4	Duda-Sobczak et al	Lower olfactory identification scores in neuropathy group (8 points [IQR, 7–9] vs. 10 points [IQR, 9–11]; *P* = .005)	Lower olfactory identification scores in retinopathy group (9 points [IQR, 8–11] vs. 10 points [IQR, 9–11]; *P* = .03)	Diabetes duration was an independent predictor of neuropathy and retinopathy	—	—	Negative correlation between olfactory identification score and BMI	—
5	Gouveri et al	TDI scores lower in the presence of DPN (28.23 ± 4.85 vs. 31.15 ± 5.28, *P* = .017)	TDI scores lower in the presence of retinopathy (27.63 ± 4.58 vs. 30.65 ± 5.78, *P* = .047)	No association with olfaction	No association with olfaction	Hypertension associated with lower olfactory scores (29.03 ± 4.92 vs. 33.61 ± 5.54, *P* < .001)	No association with olfaction	—
6	Hawkins et al	—	—	—	—	Patients with and without hypertension performed at near identical levels on BSIT (9.88 ± 1.91 vs. 9.75 ± 2.0, *t* = 0.55, *P* = .59)	—	—
7	Khil et al	—	—	—	—	Assessed, but association with olfaction not reported	Assessed, but association with olfaction not reported	Auditory, gustatory, visual impairment assessed. Diabetes was related to an elevated odds of multisensory impairment (OR = 1.75, 95% CI [1.16, 2.63])

(Continues)

TABLE III.
Continued

Article #	Author	DPN	Retinopathy	Diabetes Duration	Treatment	Hypertension	BMI	Other Sensory Impairment
8	Le Floch et al	SRS was associated with DPN (10.3 ± 1.0 vs. 14.1 ± 0.9, $P < .01$)	In diabetes patients, SRS was not significantly associated with retinopathy (11.2 ± 1.1 vs. 13.7 ± 0.8)	SRS was associated with diabetes duration ($r = 0.27$, $P < .05$)	SRS did not differ significantly in diabetes patients with or without antihypertensive drugs (12.2 ± 0.6 vs. 12.5 ± 0.5)	—	In diabetes patients, BMI ($r = 0.03$) was not significantly associated with SRS	In diabetes patients, SRS was associated with electrogustometric threshold ($r = 0.39$, $P < .001$)
9	Naka et al	DM patients with microangiopathy exhibited unchanged chemosensory function	DM patients with microangiopathy exhibited unchanged chemosensory function	Diabetes duration did not correlate with the degree of chemosensory function	—	—	Assessed, but association with olfaction not reported	Participants with lower BMI exhibited higher taste sensitivity ($r = -0.27$, $P = .019$)
10	Seraj et al	No association with olfaction	No association with olfaction	No association with olfaction	No association with olfaction	—	—	—
11	Yazla et al	DPN patients had lower Sniffin' Sticks scores ($P < .001$) and butanol threshold scores ($P < .001$) compared to controls	—	No correlation between duration of diabetes and Sniffin' sticks scores and butanol threshold scores	Assessed, but association with olfaction not reported	—	No correlation between BMI and Sniffin' sticks scores and butanol threshold scores	DPN participants had higher sucrose thresholds ($P = .002$). Gustatory function was better in control subjects compared to DPN participants.

BMI = body mass index (kg/m^2); BSIT = brief smell identification test; DM = diabetes mellitus; DPN = diabetic peripheral neuropathy; IQR = interquartile range; NeP = neuropathic pain; OI = olfactory impairment; OR = odds ratio; SRS = smell recognition score; TDI = threshold, discrimination, and identification.

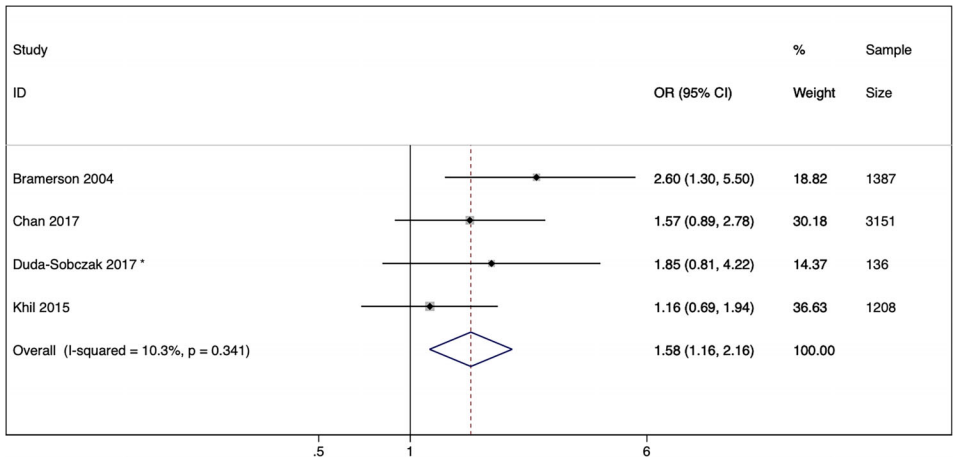

Fig. 2. Forest plot of ORs of olfactory impairment (OI) and diabetes. The square is a measure of effect for each study, and its corresponding horizontal line represents 95% confidence intervals. The blue diamond summarizes the average effect size of the four included studies. *OR was calculated from prevalent OI in diabetes and control group provided in article. OR = odds ratio.

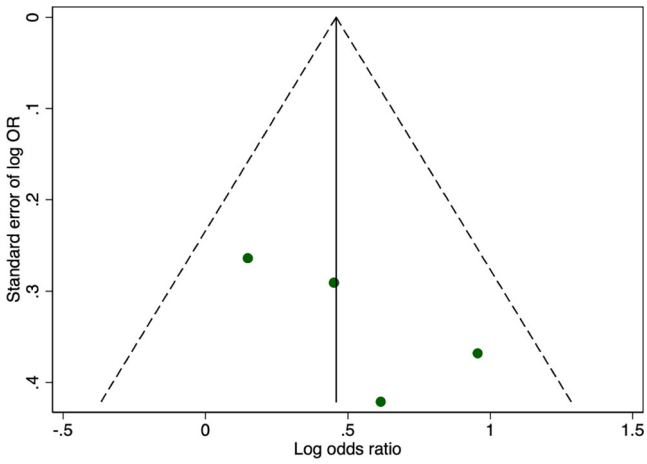

Fig. 3. Precision funnel plot illustrating potential for publication bias. Each circle represents one of the four eligible articles included in the systematic review.

related to neurodeneration[15] and microvascular disease.[16] In a meta-analysis of four eligible studies included in this review, the odds of having OI with diabetes were 1.58 times more likely than in the control group, and this was statistically significant. Although causal relationship and pathophysiology is not clearly demonstrated in these studies, the majority of studies found significant associations, pointing to the need for larger prospective studies on this topic.

Although not conducted in a systematic fashion, prior review articles have highlighted the potential utility of olfactory testing for early detection of central diabetic neuropathy and diabetes-related cognitive impairment.[27] In fact, OI has been implicated in Alzheimer's dementia, with support for its use as a predictive marker of cognitive decline.[28] Given that validated measures of olfactory testing are readily available as a quick and inexpensive clinical tool, a better understanding of the pathophysiology of OI in diabetes could foreseeably translate into clinical application and patient benefit.

TABLE IV.
Quality Assessment of Included Articles (Modified Newcastle-Ottawa Quality Assessment Scale Case-Control and Cross-Sectional Studies).

Article	Selection Grade	Comparability Grade	Exposure/Outcome Grade	Total Score
Case-control	Max 4	Max 2	Max 3	Max 9
Brady et al	3	2	3	8
Duda-Sobczak et al	3	2	3	8
Gouveri et al	3	1		7
Le Floch et al	4	2	3	9
Naka et al	2	2	3	7
Seraj et al	1	2	3	6
Yazla et al	4	0	3	7
Cross-sectional	Max 5	Max 2	Max 3	Max 10
Bramerson et al	3	2	3	8
Chan et al	2	2	3	7
Hawkins et al	3	1	3	7
Khil et al	1	2	3	6

The majority of studies included in this review examined OI in participants with T2D, while several studies did not stratify by diabetes subtype, and others exclusively studied participants with T1D (Table II). An association between OI and diabetes was found in both subtypes, precluding overarching conclusions on whether the association varied by subtype. The lack of stratification in some studies presents a limitation, as the pathophysiologic differences in subtype may play a role in the potential mechanism or baseline characteristics that explain the association between OI and diabetes. In T2D, hyperglycemia can result in increased cortical thinning of the orbitofrontal cortex, contributing to accelerated cognitive decline.[27] Central manifestations of diabetic neuropathy affecting the olfactory nerve has also been proposed as a mechanism.[16] Other factors may also contribute to differences in subtype, including the prevalence of comorbidities, medication intake, BMI, and age of participants. Participant characteristics across studies also varied widely in sample size (n = 60–3,151) and population of interest (US population-based to Iranian diabetic hospital-based), all likely contributing to the differences in outcome and limited generalizability of findings.

Currently, many validated tools are available for accurate assessment of olfactory function (threshold, discrimination, and identification [TDI]) including Sniffin' Sticks[11] and the University of Pennsylvania Smell Identification Test (UPSIT).[29] Despite the wide availability of these validated tools, the studies included in this review did not adhere to the same method of assessment. Sniffin' Sticks was the most common tool used in olfactory assessment; however, the definition of OI varied among the studies. While some studies tested all components of OI and calculated TDI scores, others only tested identification (Table II). If olfactory testing has potential clinical utility in predicting diabetes complications, assessments that include fewer odors with a limited range in scores may not adequately measure the degree of OI among patients in the early stages of olfactory decline where detection may be most useful.

The majority of studies included in this review conducted additional analyses, ranging from the association between OI and diabetes complications, subtype, duration of disease, treatment, hypertension, BMI, and multisensory impairment (Table III). Among diabetic comorbidities, peripheral neuropathy was the most investigated topic. Interestingly, Brady et al further subcategorized participants with diabetes on the basis of neuropathic pain, since chronic pain can be a potential confounder in olfactory testing due to its influence on attention and concentration.[15] Although OI was partially attributed to the presence of neuropathic pain on subcategory assessment, pain severity was not associated with olfactory dysfunction.[15] Whether neuropathy contributes to or explains OI is inconclusive at best from current evidence.

This evaluation of the current literature points to a need for large, prospective, high-quality studies that adhere to a standardized definition of OI to define its association with diabetes and it is time to develop relative to other microvascular complications. Study methodologies should adhere to a single, easily administered method of olfactory assessment that incorporates odor threshold, discrimination, and identification with a unified scoring system that allows for comparison of results across multiple studies. A common language is needed to improve methodolic quality and generalizability in this field.[30] Studies would benefit from eligibility criteria including no evidence of structural pathology on nasal endoscopy and objective testing for diabetic staging and comorbidities. To guide future investigation into the underlying mechanism of OI in diabetes, participants should ideally be stratified according to diabetes subtype, presence and severity of microvascular complications, presence of multisensory impairment, and type and duration of treatment.

The current evidence supports an association between OI and diabetes, with a potential link to microvascular complications including peripheral neuropathy. Findings from this systematic review must be considered in light of the heterogeneity in participant characteristics, methodological differences, and study designs outlined above. In addition, we only included articles published in English, which may be a potential source of language and publication bias. As studies included do not examine temporality, we caution against drawing conclusions on the predictive value of OI in diabetes and diabetes microvascular complications until large prospective studies are available.

CONCLUSION

This review supports an association between diabetes and OI. However, all of the studies included in this review were case-control or cross-sectional studies, with heterogenous methodologies in selection criteria, method of olfactory assessment, and evaluation of diabetic comorbidities. Further high-quality studies are needed to confirm the association of OI and diabetes, establish temporality, and elucidate underlying pathologic mechanisms. Expanding the body of literature on this topic may provide support for implementing olfactory evaluation as a low-cost and widely available clinical tool for early detection of diabetic complications and diabetes management.

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