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Diabetes mellitus and oral lichen planus: A systematic review and meta-analysis

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Abstract

Objective: To undertake a meta-analysis of the association of Oral Lichen Planus (OLP) with diabetes, two diseases with an important impact on public health and the economy, but the evidence of which about their association is inconsistent.

Methods: Relevant studies were localized by searching MEDLINE, EMBASE, Conference Proceedings, and other databases from inception to October 2020, without restrictions. The reference lists of included studies and of related reviews were also inspected. Global pooled odds ratios were calculated, and predefined subgroup analyses were performed. The heterogeneity between studies and publication bias was assessed and sensitivity analysis was carried out.

Results: Thirty-two studies were included in the meta-analysis. Pooled ORs showed a moderate association between diabetes and OLP [OR: 1.87 (95%CI: 1.57, 2.34)]. The association is limited to studies carried out on adults only [OR: 2.12 (95%CI: 1.75, 2.57)] and is observed in all study designs. Globally, the heterogeneity was low to moderate. Studies carried out in European populations show a stronger association of diabetes and OLP than Asiatic studies [OR: 2.49 (95%CI: 1.87, 3.32) and 1.60 (95%CI: 1.25, 2.03), respectively].

Conclusions: Diabetes and OLP are moderately associated. Systematic diagnosis of diabetes in OLP patients could prove useful.

KEYWORDS
diabetes mellitus, meta-analysis, Oral lichen planus

1 | INTRODUCTION

Lichen planus (LP) is a chronic, inflammatory mucocutaneous disease that affects the skin, nails, scalp, and mucous membranes, especially the oral and the genital mucosa (Katta, 2000). The global prevalence of oral lichen planus (OLP) among clinical patients is around 1%, with a higher prevalence in African (1.43%) and South American (3.18%) populations (Li et al., 2020), while the prevalence of Diabetes Mellitus (DM) among OLP patients sways between 1.6% and 37.7% (Otero Rey et al., 2019).

OLP prevalence increases progressively with age and is three times higher after the age of 40 years (Gonzalez-Moles et al., 2020). OLP is associated with poorer quality of life and higher levels of anxiety and perceived stress (Daume et al., 2020; Radwan-Oczko et al., 2018; Zucoloto et al., 2019).

OLP imposes a heavy burden on health costs (Ni Riordain et al., 2016), and transforms to a malignant disease at a rate that varies between 1.09% (Fitzpatrick et al., 2014) and 2.28% (González-Moles et al., 2020). This malignant transformation rate is underestimated

(González-Moles et al., 2019). Indeed, 250 per 100,000 patients with DM have oral cancer (Ramos-Garcia et al., 2020). Experts call for the establishment of multi-center longitudinal studies with uniform diagnostic criteria to improve the identification of patients with oral premalignant diseases, including OLP (Warnakulasuriya et al.,2020).

The development of OLP has also been associated with several comorbidities including hepatitis B and C infections, thyroid diseases, bowel diseases, metabolic syndromes like hypertension, dyslipidemia, and certain immunological disorders (DeAngelis et al., 2019; Hasan et al., 2019; Nosratzehi, 2018).

The results of studies on the relation between DM and OLP are conflicting. While some studies suggested an increased risk of OLP in patients with DM, with a magnitude of association that varies considerably between studies (Arduino et al., 2017; Nagao et al., 2005), others did not find any association between these diseases (Gerayli et al., 2015; Xue et al., 2005).

A meta-analysis was recently carried out on the relation of diabetes and oral potentially malignant disorders, including OLP (Ramos-Garcia et al., 2020). We aimed at completing and updating this meta-analysis.

2 | MATERIALS AND METHODS

2.1 | Search strategy

Prisma guidelines were followed to retrieve relevant studies. Electronic search was carried out in the following databases: Medline, EMBASE, Conference Proceedings Citation Index-Science, the Open Access Theses and Dissertations, and the five regional bibliographic databases of the World Health Organization (WHO): African Index Medicus, Latin American and Caribbean Health Science Literature Database, Index Medicus for the Eastern Mediterranean Region, Index Medicus for South-East Asia Region and Western Pacific Region Index Medicus. The databases were searched from their inception until October 2020. The following search terms were used in Medline without any language restriction: "(Oral Lichen Planus) AND (Diabetes)", both in MeSH terms and free-text words. The search syntax was adapted for other databases and was completed by checking manually the reference lists of related reviews as well as those of studies retrieved electronically.

2.2 | Studies selection

Retrieved titles and abstracts were scanned independently by two authors (NM and JS) for their potential inclusion in the meta-analysis. Potentially eligible studies were then selected, and their text was thoroughly reviewed to decide about their inclusion in the study. Discrepancies between reviewers were resolved by consensus.

Studies that met the following criteria were included: (1) observational epidemiological studies measuring the association between DM and OLP and reporting crude or adjusted Odds Ratio (OR), Relative Risk (RR) or Incidence Rate Ratio (IRR) and their 95% Confidence Interval (CI), or providing sufficient data for their calculation, (2) studies that identified OLP cases following established clinical and/or histological criteria, (3) studies that presented a control or comparison group.

The exclusion criteria were studies (1) examining cutaneous LP or other extraoral locations that do not involve OLP, (2) not reporting sufficient data to calculate effect measures, 3) not reporting data on a comparison group.

The study protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42020219080).

2.3 | Data extraction

NM and PIV independently extracted the relevant data following a questionnaire that was designed for the purpose of the present meta-analysis. The extracted data encompassed: (1) study source: first author and year of publication; (2) setting: country, source of population (convenience sampling or well-defined source population); (3) exposure ascertainment: method of DM determination (questionnaire, blood test, medical records); (4) type of DM (any type, type 1 or type 2); (5) outcome ascertainment: method of OLP diagnosis (clinical, histopathological); (6) study design: cohort, case-control or cross-sectional; (7) Adjustment for age and sex; and (8) measure of effect: reported OR, RR, IRR and their 95% CI or number of diabetic and non-diabetic OLP subjects and OLP-free comparison subjects to calculate these estimates.

2.4 | Quality assessment

We used the Newcastle-Ottawa quality scale (NOS) in its original version for cohort and case-control studies (Wells et al., 2000), as well as in its version adapted to cross-sectional studies (Modesti et al., 2016). We assessed the risk of bias using the following sections: selection, comparability, exposure, and outcome. We scored each criterion 1 point or 0 points. The NOS appraisal of cohort and case-control studies is based on 8 items, while the version corresponding to cross-sectional studies uses 7 items. We, therefore, computed a weighted total score to compare the quality of studies independently of their design, dividing the total score by the number of items of the scale. Studies with a weighted score >0.50 were considered as of higher quality, and those with a score ≤0.50 were deemed of lower quality. Details on the scoring system are available in Supplemental fileS1.

2.5 | Data synthesis and statistical analysis

Pooled OR was obtained by using the inverse of variance of each study as a weight. ORs were considered unbiased estimates of the rate ratio (Rothman et al., 2008). When effect measures were

reported for type 1 and type 2 DM, they were pooled together to obtain an overall effect per study. Both fixed and random effects models were computed, but the random effects model estimates were used when heterogeneity was present. The heterogeneity between studies was evaluated by calculating R_i, the proportion of total variance due to between-study variance (Takkouche et al., 1999). R_i values were interpreted as follows: low heterogeneity when Ri <0.4, moderate heterogeneity when Ri ranges between 0.4 and 0.75, and high heterogeneity when Ri exceeds 0.75. Subgroup analyses were designed a priori. They involved study design, quality score, geographical location, exposure and outcome ascertainment, type of diabetes, and control for confounding variables.

The presence of publication bias was explored visually using a funnel plot, and, more formally, using Egger´s regression test (Egger et al., 1997), and the Trim and Fill analysis (Duval & Tweedie, 2000).

As studies with a cross-sectional design are the most likely to be rejected if they present no association, sensitivity analysis was undertaken by considering that: (1) the published cross-sectional studies represent only half of the studies ever carried out and the other half was rejected, (2) the unpublished studies obtained a null association (OR = 1), and (3) the prevalence of OLP in the unpublished studies was equal to the average prevalence of the published studies.

All analyses were carried out using HEpiMa version 2.1.3 (Costa-Bouzas et al., 2001), and Stata v 12 (Stata Corp).

3 | RESULTS

3.1 | Literature search and study characteristics

The literature search yielded 937 unique studies, 880 of which were excluded after the revision of titles and abstracts. Out of the 57 publications selected for full-text review, 32 fulfilled the inclusion criteria and were included in the meta-analysis. Figure 1 represents the screening process and the motives of exclusion. The general characteristics and the identification of the included studies are presented in Table 1. The 32 included publications encompassed 21 case-control studies, 10 cross-sectional studies, and one cohort study. One study was published in Croatian (Roguljić, 2017), one in German (Hornstein et al., 1984), and one in Persian (Mojabi et al., 2009). The remainder were published in English.

3.2 | Association between diabetes and OLP

Pooled OR from all studies revealed a moderate association between DM and OLP [OR: 1.87 (95%CI: 1.57, 2.22)], and a low degree of heterogeneity between studies was observed (R_i = 0.26) (Figure 2, Table 2).

The magnitude of association between DM and OLP was higher among cross-sectional studies [OR: 2.37 (95%CI: 1.60, 3.50)]

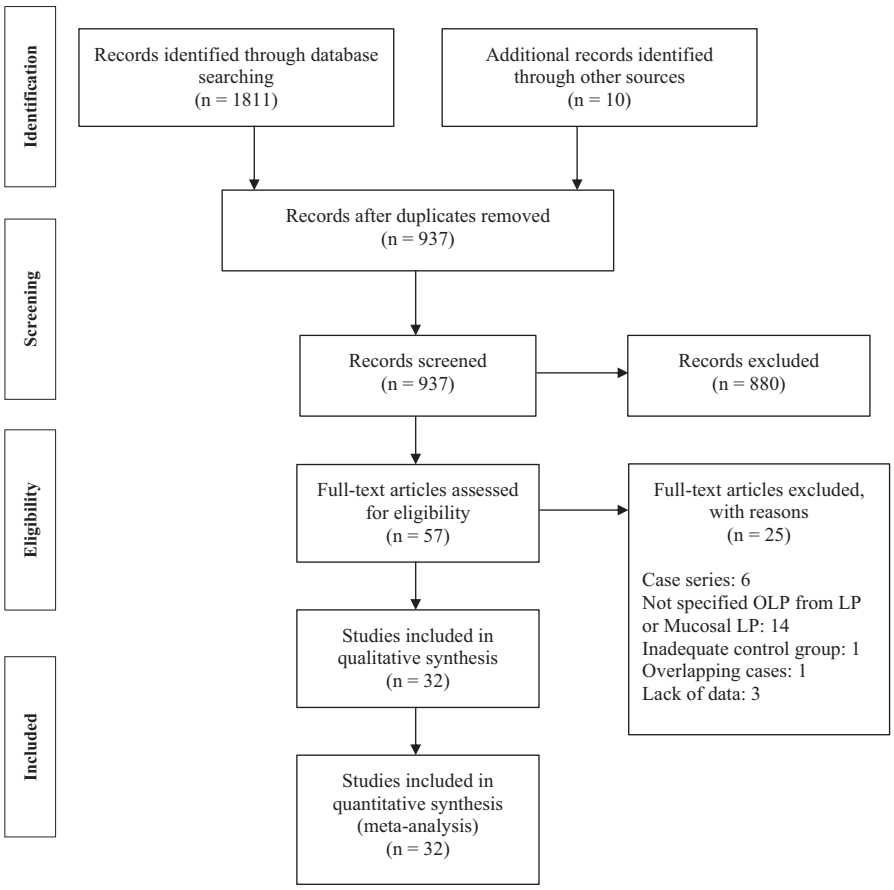

FIGURE 1 Flow diagram of the selection of studies about diabetes and oral lichen planus

TABLE 1 Characteristics of studies included in the meta-analysis of oral lichen planus and diabetes mellitus

Source	Country	Age category	Diabetes type	Diabetes ascertainment
Cohort				
Nagao et al., 2005	Japan	Adults	Any DM	Questionnaire/ Interview
Case-control				
Dave et al., 2020	United States	Adults	Type 2 DM	Blood test/ medical records
Kats et al., 2019	Israel	Adults	Any DM	Blood test/ medical records
Zhou et al., 2018	China	Adults	Unspecified	Unspecified
Arduino et al., 2017	Italy	Adults	Unspecified	Questionnaire/ Interview
Roguljić, 2017	Croatia	Adults	Any DM	Blood test/ medical records
Bhattacharjee et al., 2016	India	Adults	Type 2 DM	Questionnaire
Gerayli et al., 2015	Iran	Adults	Unspecified	Blood test/ medical records
Nagao & Sata, 2012	Japan	Adults	Any DM	Questionnaire/ Interview
Canjuga et al., 2010	Croatia	Adults	Any DM	Blood test/ medical records
Chalkoo, 2010	India	Adults	Any DM	Blood test/ medical records
Ali & Suresh, 2007	Saudi Arabia	Adults	Any DM	Blood test/ medical records
Seyhan et al., 2007	Turkey	Children and adults	Any DM	Blood test/ medical records
Xue et al., 2005	China	Children and adults	Unspecified	Blood test/ medical records
Denli et al., 2004	Turkey	Children and adults	Any DM	Blood test/ medical records
Machado et al., 2003	Brazil	Adults	Unspecified	Unspecified
Petrou-Amerikanou et al., 1998	Greece	Adults	Any DM	Blood test/ Medical records
			Type 1 DM	
			Type 2 DM	
Gorsky et al., 1996	Israel	Adults	Unspecified	Blood test/ medical records
Van Dis et al., 1995	USA	Adults	Type 1 DM	Medical records
Borghelli et al., 1993	Argentine	Children and adults	Unspecified	Unspecified
Hornstein et al., 1984	Germany	Adults	Unspecified	Blood test/ medical records
Lundström, 1983	Sweden	Adults	Any DM	Blood test/ medical records
Cross-sectional				
Mohsin et al., 2014	Pakistan	Unspecified	Type 2 DM	Unspecified
Al-Maweri et al., 2013	Malaysia	Adults	Type 2 DM	Blood test/ medical records
López-Jornet et al., 2012	Spain	Adults	Unspecified	Blood test/ medical records
Saini et al., 2010	Malaysia	Adults	Any DM	Blood test/ medical records
Mojabi et al., 2009	Iran	Adults	Any DM	Questionnaire/ Interview
			Type 1 DM	
			Type 2 DM	
Lundström, 2009	Sweden	Children and adults	Unspecified	Medical records
Chung et al., 2004	Taiwan	Adults	Any DM	Blood test/ medical records
Guggenheimer et al., 2000	USA	Adults	Type I DM	Questionnaire
Zareei & Shirei, 2000	Iran	Adults	Any DM	Unspecified
Sallay et al., 1989	Hungary	Adults	Type 2 DM	Blood test/ medical records

Abbreviations: CI, confidence interval; DM, diabetes mellitus; DM-, subjects free from diabetes mellitus; DM+, subjects with diabetes mellitus; OLP, oral lichen planus; OLP-, subjects free from oral lichen planus; OLP+, subjects with oral lichen planus; OR, odds ratio.

[a]reported OR and 95%CI. All OR and 95%CI were calculated in this meta-analysis except those marked with superscript lower-case letter a ([a]) that were extracted from the corresponding publication; and ---: unavailable information.

than among case-control studies [OR: 1.68 (95%CI: 1.38, 2.01)]. Heterogeneity was absent in cross-sectional studies (R_i = 0.001), and moderate in case-control studies (R_i = 0.34). The only cohort study, with a follow-up of 4 years, also reported a strong association between DM and OLP [OR: 6.40 (95%CI: 2.40, 17.60)] (Table 2).

OLP ascertainment	Sex and age matching or adjustment	OLP+, DM+	OLP+, DM-	OLP-, DM+	OLP-, DM-	OR (95%CI)
Clinical & histological	Yes	---	---	---	---	6.40 (2.4, 17.6)[a]
Clinical & histological	Yes	35	26	15	46	2.80 (1.20, 6.30)[a]
Clinical & histological	Yes	4	98	5	97	0.79 (0.21, 3.04)
Clinical & histological	Yes	6	186	6	156	0.84 (0.27, 2.65)
Clinical & histological	Yes	36	271	14	228	2.16 (1.14, 4.11)
Clinical & histological	No	4	3	59	60	1.36 (0.29, 6.32)
Clinical	No	11	2	489	498	5.60 (1.24, 25.40)
Clinical & histological	No	29	105	27	107	1.09 (0.61, 1.97)
Clinical & histological	Yes	6	53	8	77	1.09 (0.36, 3.32)
Clinical & histological	No	22	160	9	171	2.61 (1.17, 5.84)
Clinical & histological	Yes	7	13	3	17	3.05 (0.66, 14.14)
Clinical & histological	Yes	14	26	6	34	3.05 (1.03, 9.02)
Clinical & histological	Yes	8	22	1	29	10.55 (1.23, 90.66)
Clinical & histological	No	78	596	10	68	0.89 (0.44, 1.80)
Clinical & histological	No	22	238	20	260	1.20 (0.64, 2.26)
Clinical & histological	Yes	7	47	7	57	1.27 (0.41, 3.88)
Clinical & histological	No	18	5	474	269	2.04 (0.75, 5.56)
		8	5	131	269	3.29 (1.05, 10.24)
		10	5	131	269	1.57 (0.53, 4.64)
Clinical & histological	No	21	136	10	80	1.24 (0.55, 2.75)
Clinical	Yes	11	8	262	265	1.39 (0.55, 3.51)
Clinical	No	4	6	725	670	0.62 (0.17, 2.19)
Clinical & histological	Yes	53	124	21	156	3.18 (1.82, 5.55)
Clinical & histological	Yes	6	1	34	39	6.88 (0.79, 60.06)
Clinical & histological	No	7	14	388	401	1.81 (0.53, 6.23)
Clinical & histological	No	3	1	390	392	3.02 (0.31, 29.11)
Clinical & histological	Yes	25	175	8	192	3.43 (1.51, 7.80)
Clinical & histological	No	3	1	418	421	3.02 (0.31, 29.17)
Clinical	No	12	3	260	153	2.35 (0.65, 8.47)
		7	3	141	153	2.53 (0.64, 9.98)
		5	3	119	153	2.14 (0.50, 9.15)
Clinical	Yes	48	755	3	47	1.00 (0.30, 3.32)
Clinical	No	5	27	59	984	3.09 (1.15, 8.31)[a]
Clinical	No	2	2	403	266	1.52 (0.21, 10.82)
Clinical & histological	Yes	5	2	96	101	2.63 (0.50, 13.88)
Clinical & histological	No	23	119	6	70	2.25 (0.88, 5.81)

Eighteen studies were conducted in Asia, nine in Europe, three in North America, and two in South America. Stratifying the analysis by geographic location showed that the association between DM and OLP is stronger in the European studies [OR: 2.49 (95%CI: 1.87, 3.32)] than in the Asian studies [1.60 (95%CI: 1.25, 2.03)]. The heterogeneity between studies was absent in the European studies

category (R_i = 0.001) and moderate in the Asian ones (R_i = 0.36) (Table 2).

Twenty-six studies were carried out in adults exclusively, and five studies involved a mixed population of children and adults. A strong association between DM and OLP was observed in the population of adults [OR: 2.12 (95%CI: 1.75, 2.57), while no association was observed in the subgroup of studies that involved a mixed population of children and adults [OR: 1.07 (95%CI: 0.71, 1.61)] (Table 2).

Most of the included studies (N = 23) did not specify the type of DM. The pooled OR estimate of these studies was similar to that obtained in the general analysis [OR: 1.81 (95% CI: 1.38, 2.38)]. Furthermore, a strong association was detected for type 2 DM studies [OR: 2.50 (95% CI: 1.63, 3.82)].

The majority of the studies (N = 22) ascertained the presence of diabetes using medical records and/or blood tests, whereas only five studies used questionnaires for this purpose. The remaining five studies did not report the method of diabetes ascertainment. Studies that relied on questionnaires showed a stronger association between DM and OLP [OR: 2.56 (95%CI: 1.63, 4.03)] than those that used medical records or blood tests [OR: 1.87 (95%CI: 1.53, 2.28].

Stratifying the analysis by quality score revealed a substantially stronger association between DM and OLP among studies of higher quality [OR: 2.99 (95%CI: 2.24, 4.00)] than among studies of lower quality [OR: 1.44 (95%CI: 1.16, 1.79)]. No heterogeneity was observed in both subgroups of studies.

Half of the studies (N = 16) controlled for confounding from sex and age while the other half did not adjust for these factors. Studies adjusting for sex and age indicated a strong association between DM and OLP [OR: 2.32 (95% CI: 1.82, 2.97)]. The subgroup of studies that did not control for sex and age showed a weaker association between DM and OLP [OR: 1.52 (95%CI: 1.19, 1.93)].

3.3 | Publication bias and sensitivity analysis

The visual examination of the funnel plot showed that the graph is slightly skewed to the right in the direction that favors the presence of association (Figure 3). Nonetheless, the Egger´s regression test did not confirm the presence of publication bias (p = 0.352).

The trim and fill analysis suggested the addition of two studies, but the corrected OR = 1.83 (95%CI: 1.54, 2.18), very close to our estimate, confirmed the presence of an association between DM and OLP. This association also withstood when pooled OR was recalculated under the extreme assumptions [OR: 1.14 (95%CI: 1.05, 1.24)], confirming further the existence of an association between DM and OLP.

4 | DISCUSSION

This meta-analysis shows that there is a moderate association between DM and OLP. This association was limited to adult patients, and it was observed in numerous study groups. A stronger association was detected in the European populations than in the Asian populations. In general, there was a low to moderate heterogeneity of effect between studies included in this meta-analysis. Our findings are not

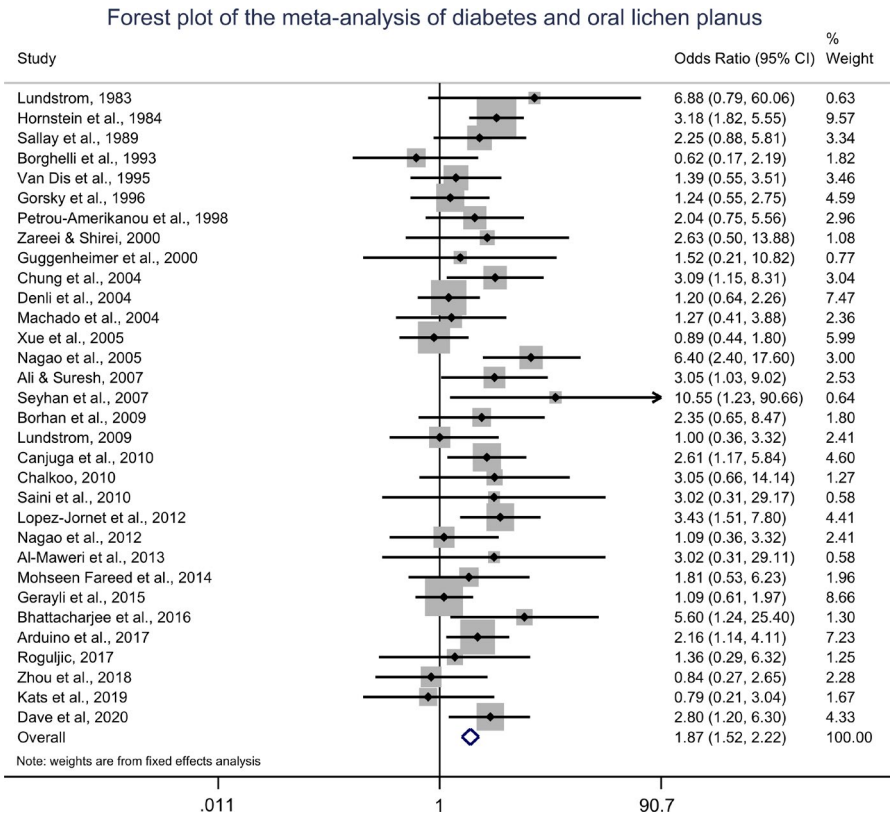

FIGURE 2 Forest plot of the meta-analysis of diabetes and oral lichen planus

TABLE 2 Fixed and random effects pooled odds ratios (ORs) and 95% confidence interval (CIs) of diabetes mellitus and oral lichen planus (OLP)

Subgroup	Number of Studies	OR (95% CI) Fixed effects	OR (95% CI) Random effects	R_I[a]	Q test *p*-value
All studies	32	1.87 (1.57, 2.22)	1.89 (1.53, 2.34)	0.26	0.10
Study design					
Case-control	21	1.68 (1.38, 2.01)	1.68 (1.30, 2.17)	0.34	0.07
Cross-sectional	10	2.37 (1.60, 3.50)	2.37 (1.60, 3.50)	0.001	0.94
Cohort	1	6.40 (2.40, 17.60)	---	---	---
Location					
Asia	18	1.60 (1.25, 2.03)	1.77 (1.28, 2.45)	0.36	0.07
Europe	9	2.49 (1.87, 3.32)	2.49 (1.87, 3.32)	0.001	0.72
Age category					
Adults only	26	2.12 (1.75, 2.57)	2.12 (1.73, 2.61)	0.09	0.33
Adults and children	5	1.07 (0.71, 1.61)	1.09 (0.65, 1.82)	0.30	0.24
Type of diabetes					
Unspecified/any	23	1.79 (1.47, 2.17)	1.81 (1.38, 2.38)	0.42	0.02
Type 1	4	1.77 (0.99, 3.14)	1.77 (0.99, 3.14)	0.001	0.91
Type 2	7	2.50 (1.63, 3.82)	2.50 (1.63, 3.82)	0.001	0.95
Diabetes ascertainment					
Blood test/ medical records	22	1.87 (1.53, 2.28)	1.90 (1.50, 2.42)	0.24	0.16
Questionnaire	5	2.56 (1.63, 4.03)	2.66 (1.37, 5.15)	0.47	0.14
OLP ascertainment					
Clinical and histological	26	1.85 (1.53, 2.22)	1.87 (1.47, 2.38)	0.33	0.06
Clinical only	6	2.02 (1.27, 3.21)	2.02 (1.27, 3.21)	0.001	0.48
Target population					
Defined	5	2.90 (1.90, 4.44)	2.90 (1.90, 4.44)	0.001	0.46
Convenience sample	27	1.71 (1.42, 2.07)	1.72 (1.38, 2.16)	0.22	0.16
Quality score					
Lower	22	1.44 (1.16, 1.79)	1.44 (1.16, 1.79)	0.001	0.70
Higher	10	2.99 (2.24, 4.00)	2.99 (2.24, 4.00)	0.001	0.44
Sex and age adjustment					
Yes	16	2.32 (1.82, 2.97)	2.25 (1.65, 3.06)	0.29	0.14
No	16	1.52 (1.19, 1.93)	1.52 (1.19, 1.93)	0.001	0.45

[a]Ri: Proportion of total variance due to between-study variance.

easily ascribed to publication bias as shown in the analysis, and the association between the two diseases was robust even under extreme assumptions. Also, the association was of larger magnitude among studies with high quality than among studies with lower quality.

Our meta-analysis was updated and completed that carried out by Ramos-Garcia et al., (2020). We incorporated seventeen new studies, while 15 were already included in Ramos-Garcia's work. Some studies were excluded from our meta-analysis due to the lack of a control group or the presence of zero cell counts (e.g., zero unexposed cases) that yield undefined relative risk estimates. In spite of these large differences in the studies included, the global result is very similar in both meta-analyses. This demonstrates that the analysis of the relation of DM and OLP was robust to methodologic decisions.

The majority of the studies adequately ascertained the exposure (DM) and the outcome (OLP) using medical records and histopathological tests, respectively. Therefore, misclassification of the exposure or the outcome is unlikely to happen. In those studies in which diabetes antecedents are assessed through questionnaires, misclassification cannot be ruled out. However, this misclassification is probably non-differential regarding OLP, that is, an erroneous diagnosis of diabetes occurs independently of the subsequent diagnosis of OLP. In a similar fashion, misclassification of OLP diagnosis may have occurred in those studies that lack histologic confirmation of this diagnosis. Again, had this error in the diagnosis of OLP occurred, it would have been independent of whether the subject is diabetic or not. In both cases of misclassification, the bias introduced, if any, is toward the null value. The true but

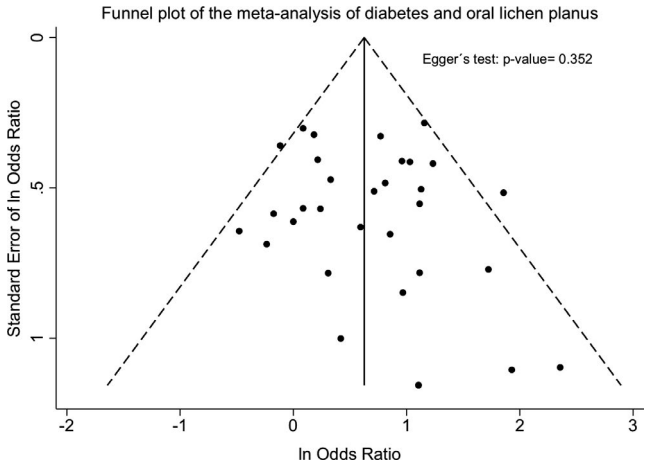

FIGURE 3 Funnel plot of the meta-analysis of diabetes and oral lichen planus

unobserved association is then stronger than the one we observed in our results.

In spite of the strong association observed, so far, the biological mechanism implied in the relation between DM and OLP is still unknown. A possible link between intake of hypoglycemic medicines in diabetic patients and occurrence of OLP has been hypothesized but was not confirmed further (Kaomongkolgit, 2010). Also, an increase in the development of autoimmune diseases in patients with diabetes has been observed, which seems to indicate the existence of a general autoimmune disorder in these patients (Ramos-Garcia et al., 2020).

Worldwide, 9.3% of the population suffers from diabetes (Saeedi et al., 2019). Based on this prevalence and on our results, and assuming that the relation between both diseases is of causal nature, we estimate that more than 7% of OLP cases may be attributable to diabetes among people with this disease (Rothman, 1986).

Our meta-analysis has some limitations. The studies included in our meta-analysis were not adjusted for factors other than age and sex. Residual confounding may then have theoretically distorted our results, as occurs frequently in meta-analyses of observational studies. Although no factor, such as a genetic polymorphism, has been found to be a confounder of the relation between diabetes and OLP, we cannot rule out the existence of such a factor. However, the existence of an unidentified factor, of genetic nature or else, associated with both diabetes and OLP, which could explain a high proportion of the observed effect, is highly unlikely. Even if this potential factor could double the risk of OLP among subjects exposed to it (OR confounder–disease =2) and, simultaneously, this factor happened to be twice more prevalent among diabetics than among non-diabetics (OR confounder–exposure =2), the adjusted OR of the relation diabetes-OLP would still be 1.66 (assuming one-third of people are exposed to this unknown factor) (Greenland, 1996). In line with this argument, it is worth mentioning that studies with age-and-sex adjustment yielded a stronger association than studies with no adjustment.

Furthermore, only one of the studies included in this meta-analysis used a cohort design. The large majority were assimilated to case-control studies but lacked the sophistication inherent to this design. In particular, the overwhelming majority used prevalent controls instead of incident ones. Furthermore, 27 out of 32 studies relied on convenience sampling (e.g., patients of a single consultation) and did not provide any target population to which the results could be generalized. Also, no lag time between diabetes onset and OLP occurrence was assessed. Therefore, we cannot rule out simultaneity between diabetes and OLP occurrence or reverse causation (i.e., OLP preceding diabetes). Indeed, recent reports indicate that the relation between DM and OLP may be reciprocal, that is, that one disease may be causally related with the other (Zhao et al., 2019).

In conclusion, this meta-analysis shows that a moderate association exists between DM and OLP. Future research should be based on prospective studies in which latency time between diagnosis of diabetes and occurrence of OLP is carefully assessed. Assessing DM among OLP patients could prove useful.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Narmeen Mallah: Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Writing-original draft; Writing-review & editing. **Pablo Ignacio Varela-Centelles:** Conceptualization; Data curation; Formal analysis; Investigation; Writing-review & editing. **Javier Seoane-Romero:** Data curation; Formal analysis; Investigation; Writing-review & editing. **Bahi Takkouche:** Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing-review & editing.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/odi.13927.

DATA AVAILABILITY STATEMENT

The data set of this meta-analysis is available in FigShare at https://figshare.com/s/e52102983f1b47806e25. [reserved https://doi.org/10.6084/m9.figshare.13554152].

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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