



# Association of Odor Identification Ability With Amyloid- $\beta$ and Tau Burden: A Systematic Review and Meta-Analysis

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**Background:** The associations between olfactory identification (OI) ability and the Alzheimer's disease biomarkers were not clear.

**Objective:** This meta-analysis aimed to examine the associations between OI and A $\beta$  and tau burden.

**Methods:** Electronic databases (PubMed, Embase, PsycINFO, and Google Scholar) were searched until June 2019 to identify studies that reported correlation coefficients or regression coefficients between OI and A $\beta$  or tau levels measured by positron emission tomography (PET) or cerebrospinal fluid (CSF). Pooled Pearson correlation coefficients were computed for the PET imaging and CSF biomarkers, with subgroup analysis for subjects classified into different groups.

**Results:** Nine studies met the inclusion criteria. Of these, five studies ( $N = 494$ ) involved A $\beta$  PET, one involved tau PET ( $N = 26$ ), and four involved CSF A $\beta$  or tau ( $N = 345$ ). OI was negatively associated with A $\beta$  PET in the mixed ( $r = -0.25$ ,  $P = 0.008$ ) and cognitively normal groups ( $r = -0.15$ ,  $P = 0.004$ ) but not in the mild cognitive impairment group. A similar association with CSF total tau in the mixed group was also observed. No association was found between OI and CSF phosphorylated tau or A $\beta_{42}$  in the subgroup analysis of the CSF biomarkers. Due to a lack of data, no pooled  $r$  value could be computed for the association between the OI and tau PET.

**Conclusion:** The associations between OI ability and A $\beta$  and CSF tau burden in older adults are negligible. While current evidence does not support the association, further studies using PET tau imaging are warranted.

**Keywords:** olfaction, Alzheimer's disease, amyloid- $\beta$ , tau, positron emission tomography, cerebrospinal fluid

## INTRODUCTION

Amyloid- $\beta$  (A $\beta$ ) aggregates and tau neurofibrillary tangles are known as the two neuropathological hallmarks of Alzheimer's disease (AD) (Villemagne et al., 2018). The importance of the two biomarkers, whether for clinical or research use, is obvious in the biologically oriented effort to tackle the worldwide AD issue (Jansen et al., 2015; Alzheimer's Association, 2020). This is especially true when the National Institute on Aging and Alzheimer's Association (NIA-AA) proposed the A $\beta$ /tau/neurodegeneration (AT(N)) classification system to update the diagnostic criteria for AD recommended in 2011 (Jack et al., 2018). This biomarker-driven research framework has shown potential to improve the predictive accuracy for memory decline among non-demented elderly individuals and thereby provide prognostic values for clinical change and progression (Jack et al., 2019; Yu et al., 2019).

In the evolving biomarker research field of AD, olfactory function has been frequently seen in studies related to neurodegenerative diseases (Marin et al., 2018; Dintica et al., 2019; Tu et al., 2020) since its first association with dementia was claimed in 1974 (Waldton, 1974). Impaired olfaction, olfactory identification (OI) ability in particular, has been reported in AD and prodromal AD ailments, such as mild cognitive impairment (MCI) (Roalf et al., 2017; Marin et al., 2018; Jung et al., 2019). Moreover, several lines of evidence have indicated that OI impairment is valuable in predicting cognitive decline in cognitively intact participants and progression from MCI to AD dementia, and it might suggest neurodegeneration in the brain among non-demented older adults (Devanand et al., 2015; Roberts et al., 2016; Dintica et al., 2019). OI, the ability to identify and name specific odorants, is therefore considered a potential early biomarker of cognitive decline and AD dementia.

Due to the well-known disadvantages of current standard measures of AD biomarkers, namely, their expensive cost and invasiveness, a convenient, inexpensive, and easily accessible test that predicts amyloid and tau status would therefore reduce the burden and cost of clinical AD trials. Studies have attempted to identify correlations of OI ability with amyloid and tau burden both *in vitro* and *in vivo*. Postmortem studies (Kovacs et al., 1999; Attems et al., 2005; Attems and Jellinger, 2006; Wilson et al., 2007, 2009; Franks et al., 2015) have linked OI ability with the pathologic manifestations of AD, A $\beta$ , and neurofibrillary tangles. Studies involving *in vivo* positron emission tomography (PET) imaging scans or cerebrospinal fluid (CSF) measures also showed interesting results. But the results are inconsistent and inconclusive; the aim of this systematic review was therefore to provide a comprehensive overview of OI ability associated with the A $\beta$  and tau burden in older adults.

## METHODS

### Selection Criteria

This systematic review was conducted according to the PRISMA guidelines (Moher et al., 2015) and followed a predetermined protocol (PROSPERO No. CRD42019138642). The selection criteria of the studies were as follows: (1) reported associations

between OI test scores and A $\beta$  or tau levels (measured via PET imaging or CSF); (2) evaluated OI by common smell tests, such as the University of Pennsylvania Smell Identification Test (UPSIT), the "Sniffin' Sticks" OI test, and the Odor Stick Identification Test for Japanese (OSIT-J); (3) included older adults (mean age of sample  $\geq$  60 years); and (4) made data available in the publication or via contact with the authors to allow computation of correlation coefficients.

### Search Strategy

Systematic electronic databases (PubMed, Embase, PsycINFO, and Google Scholar) were searched for articles published in English from their inception until June 2019 with the following search items: "olfaction" OR "smell" OR "odor" OR "olfactory" AND "amyloid" OR "tau" OR "cerebrospinal fluid" OR "positron emission tomography." Filters were applied to limit searches to human studies in the English language. The reference lists and similar articles of the eligible publications were searched manually for additional studies.

### Amyloid and Tau Assessment

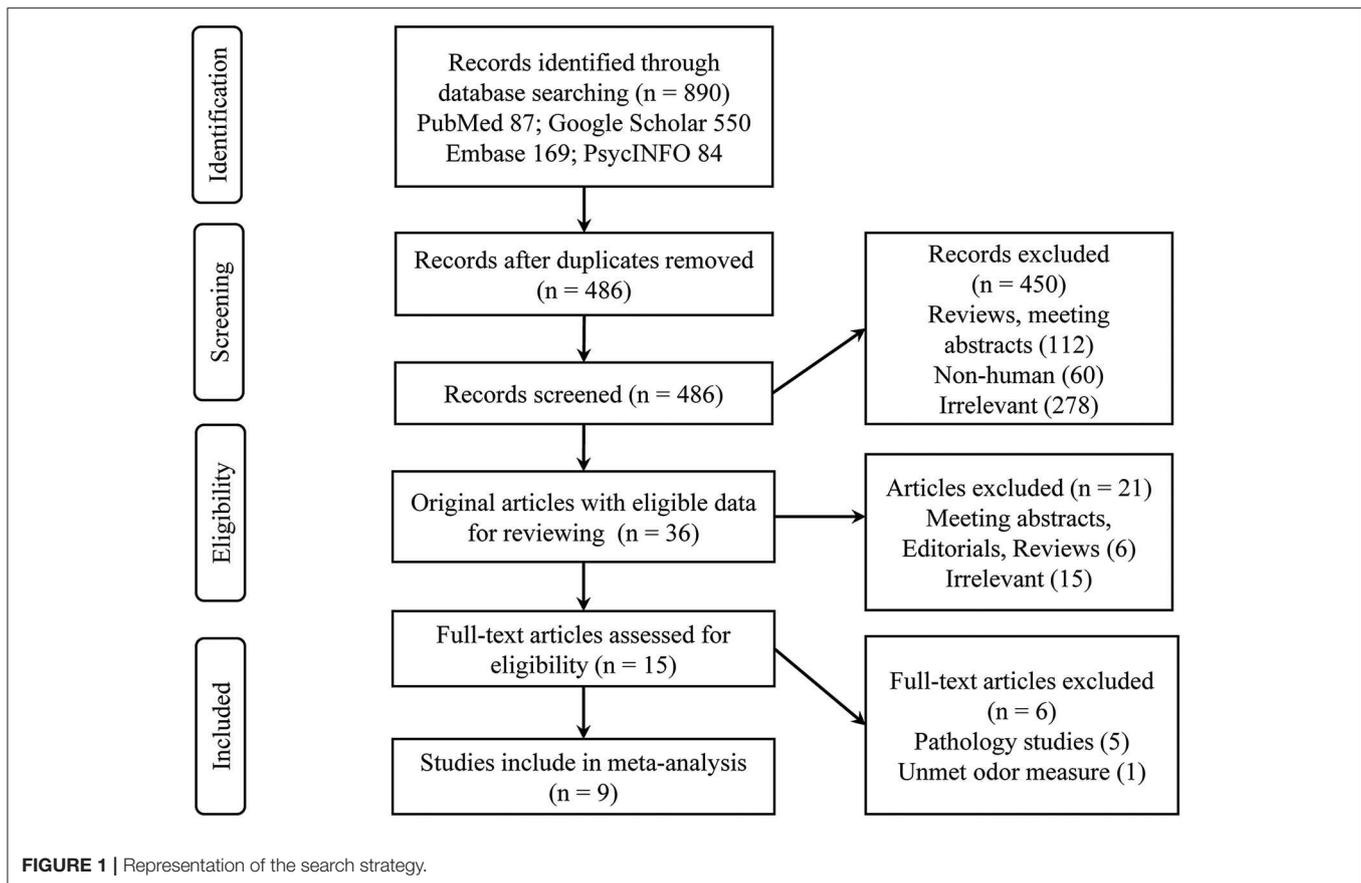
PET amyloid imaging agents included Pittsburgh Compound B (PIB), florbetapir, and florbetaben. PET tau imaging agents included tau-specific ligands, such as flortaucipir. Estimates of amyloid and tau binding in PET studies were used from the global cortex or cortical regions via standardized uptake value ratios (SUVRs) or distribution volume ratios (DVRs). The CSF method included measurement of A $\beta$  1-42 (A $\beta$ <sub>42</sub>), *p*-tau<sub>181</sub>, and *t*-tau levels.

### Odor Identification Test

OI was tested with the UPSIT, Sniffin' Sticks, OSIT-J, or other commercially available tests. The shorter versions of the UPSIT and Sniffin' Sticks test were also eligible. Homemade tests and tests that also assessed other olfactory functions (e.g., olfactory threshold or discrimination) were excluded.

### Data Extraction and Study Quality Assessment

Data were independently extracted by two investigators (LT and XL) from cross-sectional cohort studies and baseline measurements of longitudinal studies with clinical follow-up. For the studies with different groups of subjects, i.e., cognitively normal (CN), MCI, AD, and mixed (whole sample) groups, the correlation coefficient values were extracted separately for the subgroup comparisons when data were available. The following information was extracted from each included study: the sample size, the study design, the country and cohort name, the methodology used to measure AD biomarkers, the odor tests, the sample demographic characteristics, and the bivariate correlations (or related statistical information) between the AD biomarkers and the OI score. The methodologic quality of each included study was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Whiting et al., 2011).



## Effect Size Computation and Statistical Analysis

The cross-sectional associations between OI test scores and A $\beta$  or tau levels were evaluated using Pearson correlation coefficients ( $r$ ). A preadjusted  $r$  was used in all studies when available. In cases where  $r$  values were not reported, they were calculated from the scatter plot graph of the OI score vs. A $\beta$  or tau levels. Two studies (Körtvélyessy et al., 2015; Risacher et al., 2017) reported a non-significant association between the OI score and A $\beta$  or tau levels, but no data were available. In this case,  $z = 0.00$  was assigned as a conservative estimate. The other three studies reported an unstandardized regression coefficient ( $b$ ) (Growdon et al., 2015; Reijts et al., 2017; Vassilaki et al., 2017), with which we calculated  $r$  according to previous methods (Kim et al., 2019). Specifically, the following formulas were used:

$$(\text{Estimated } r)^2 = t^2 / (t^2 + n - 2)$$

$$t = b / \text{the standard error of } b$$

$$\text{Estimated } r \times b \geq 0.$$

We used the Comprehensive Meta-Analysis (CMA), version 3 software (Biostat, NJ) to compute the  $r$  values and calculate the pooled mean  $r$  values for the PET imaging and CSF biomarkers, with subgroup analysis for subjects classified into different groups. As random-effects models incorporate between-study heterogeneity and give wider (i.e., more conservative) confidence

intervals (CIs) when heterogeneity is suspected, all analyses and plots were reported using a random-effects model. The presence of publication bias with a funnel plot was not assessed because very few studies were included in our meta-analysis (Sterne et al., 2011). To examine between-study heterogeneity, in addition to Cochran's  $Q$  (to determine whether the between-study variability was greater than the sampling error) and  $\tau$  (to quantify the between-study variance of the true effect sizes), the  $I^2$  statistic was also used.

*Post hoc* subgroup analyses were conducted to determine the source of the heterogeneity when statistically significant heterogeneity was identified. The analyses examined the degree to which heterogeneity resulted from variance due to moderators such as (a) the type of OI test (e.g., UPSIT edition), (b) the PET imaging method (PIB or non-PIB) and the measurements (SUVR or DVR), (c) the code of the SUVR/DVR (continuous or categorical), (d) adjustments for covariates (e.g., age, sex) or lack thereof, (e) the sample size, and (f) the method  $r$  was obtained.

## RESULTS

### Description of Studies

A total of nine eligible studies were included in the final systematic review and meta-analysis (see **Figure 1** for flowchart),

with five studies pertaining to A $\beta$  PET and four about CSF A $\beta$  or tau. The characteristics of the included studies are shown in **Table 1**. The selected studies were published between 2010 and 2018. Seven studies were cross-sectional, and two were longitudinal. The median number of subjects per study was 93 (range, 22–215), with a total number of 839 (56% female) subjects. Three studies with a relatively large sample (over 100) focused on CN older adults, two of which utilized the PET imaging method (Growdon et al., 2015; Vassilaki et al., 2017). For the PET method, the included total sample sizes of CN, MCI, and AD individuals were 392, 75, and 20, respectively, with seven subjective cognitive decline (regarded as CN in our analysis) individuals. The sample sizes for the studies using the CSF method were 161, 63, and 95 individuals, respectively, with 26 non-AD dementia patients. The mean sample age was 71.8 years (SD = 6.8).

Demographic variables such as age, sex, and education were adjusted statistically in a few studies. The inclusion criteria for individuals with MCI were mostly according to Petersen's criteria, while for AD, it was the NINCDS-ADRDA criteria. The methodologic quality assessment showed that only the patient selection domain had the high risk of bias, mostly due to inappropriate exclusions (**Table 2**).

## AD Biomarkers

Five studies applied A $\beta$  PET imaging [four used  $^{11}\text{C}$  PIB (Bahar-Fuchs et al., 2010; Growdon et al., 2015; Vassilaki et al., 2017; Kreisl et al., 2018); one used  $^{18}\text{F}$ -florbetapir/florbetaben (Risacher et al., 2017)], and only one study utilized tau PET imaging [ $^{18}\text{F}$ -florbetapir (Risacher et al., 2017)]. For the majority of studies, the PET SUVR was used as a continuous variable to explore the association between the A $\beta$  burden and OI score. Four studies measured CSF levels, two of which examined A $\beta_{42}$ , *p*-tau, and *t*-tau (Körtvélyessy et al., 2015; Lafaille-Magnan et al., 2017), whereas one study measured A $\beta_{42}$  and *p*-tau (Kouzuki et al., 2018), and the other one measured A $\beta_{42}$  and *t*-tau (Reijs et al., 2017).

## Odor Identification Score

The OI score was obtained mostly (seven studies) from the UPSIT, with 40 odors used by four studies and a short edition (6–12 odors) used by three studies. The other two studies used either Sniffin' Sticks (Körtvélyessy et al., 2015) or the OSIT-J (Kouzuki et al., 2018). The raw OI scores were reported by all studies except one (Lafaille-Magnan et al., 2017), which used a transformed UPSIT error score. In this case, the raw score was calculated from the scatter plot graph. One study (Dhilla Albers et al., 2016) was excluded because a homemade olfactory screening with mixed evaluation was adopted.

## Correlation Between the Odor Identification Score and PET Imaging

Meta-analyses were based on the correlation between the OI score and the PET SUVR or DVR. For two studies (Growdon et al., 2015; Vassilaki et al., 2017), the *r* values were calculated based on the regression coefficients. For correlations of subgroup subjects (CN, MCI, and AD), the *r* values were obtained via the

authors for one study (Kreisl et al., 2018) and calculated from the scatter plot graph for another study (Bahar-Fuchs et al., 2010). One study (Risacher et al., 2017) reported a non-significant association without available data, in which  $z = 0.00$  was assigned accordingly. Our results showed that the OI score was negatively associated with A $\beta$  PET SUVR or DVR in the mixed group ( $r = -0.25$ , 95% CI  $[-0.42, -0.07]$ ,  $P = 0.008$ ; **Figure 2**).

Subgroup analysis also showed a negative association in the CN group ( $r = -0.15$ , 95% CI  $[-0.24, -0.05]$ ,  $P = 0.004$ ). However, the MCI group showed no correlation ( $r = -0.2$ , 95% CI  $[-0.72, 0.46]$ ,  $P = 0.568$ ). Only one study had an AD group, which also showed no correlation. The combination of MCI and AD together did not change the result (data not shown). The association between the OI score and tau PET imaging was reported by one study (Risacher et al., 2017), showing that the tau level in the mean temporal lobe was negatively associated with the preadjusted UPSIT total score ( $r = -0.45$ ,  $P < 0.05$ ).

## Correlation Between the Odor Identification Score and CSF Biomarkers

Meta-analyses were based on the correlation between the OI score and CSF biomarker levels. For two studies, the *r* values were calculated based on the regression coefficients (Reijs et al., 2017) or from the scatter plot graph (Lafaille-Magnan et al., 2017). One study (Körtvélyessy et al., 2015) reported a non-significant association without available data, in which  $z = 0.00$  was assigned accordingly. MCI and AD were analyzed together given the limited data.

Our analysis showed that the OI score was negatively associated with CSF *t*-tau in the mixed group ( $r = -0.17$ , 95% CI  $[-0.28, -0.05]$ ,  $P = 0.006$ ; **Figure 3**). The same was true for CSF *p*-tau ( $r = -0.14$ , 95% CI  $[-0.28, 0.001]$ ,  $P = 0.052$ ) and A $\beta_{42}$  ( $r = 0.14$ , 95% CI  $[-0.01, 0.28]$ ,  $P = 0.069$ ) in the mixed group but only with a marginal association. Subgroup analysis showed no association in the CN or MCI/AD group for CSF A $\beta_{42}$  or *t*-tau (data not shown).

## Moderator Effects

The present data showed a statistically significant heterogeneous between-study variability for the PET imaging method in the mix ( $Q = 15.2$ ,  $P < 0.01$ ,  $\tau^2 = 0.033$ ,  $I^2 = 73.68\%$ ) and MCI groups ( $Q = 10.3$ ,  $P < 0.01$ ,  $\tau^2 = 0.267$ ,  $I^2 = 80.64\%$ ). *Post hoc* subgroup analyses indicated that the pooled *r* values in the mixed group remained statistically significant when the moderator variables were adjusted (**Table 3**).

A significant negative correlation ( $r = -0.55$ , 95% CI  $[-0.72, -0.32]$ ,  $P < 0.001$ ) for the MCI group was observed when these accounted for data from studies that had utilized the 40-item UPSIT, although this only pertained to two studies. **Table 3** provides a summary of the meta-analysis by potential moderator variables of the association between the OI score and PET imaging.

## DISCUSSION

This meta-analysis explored the relationships between OI ability and the cerebral measures of amyloid and tau deposition via

**TABLE 1** | Characteristics of the included studies.

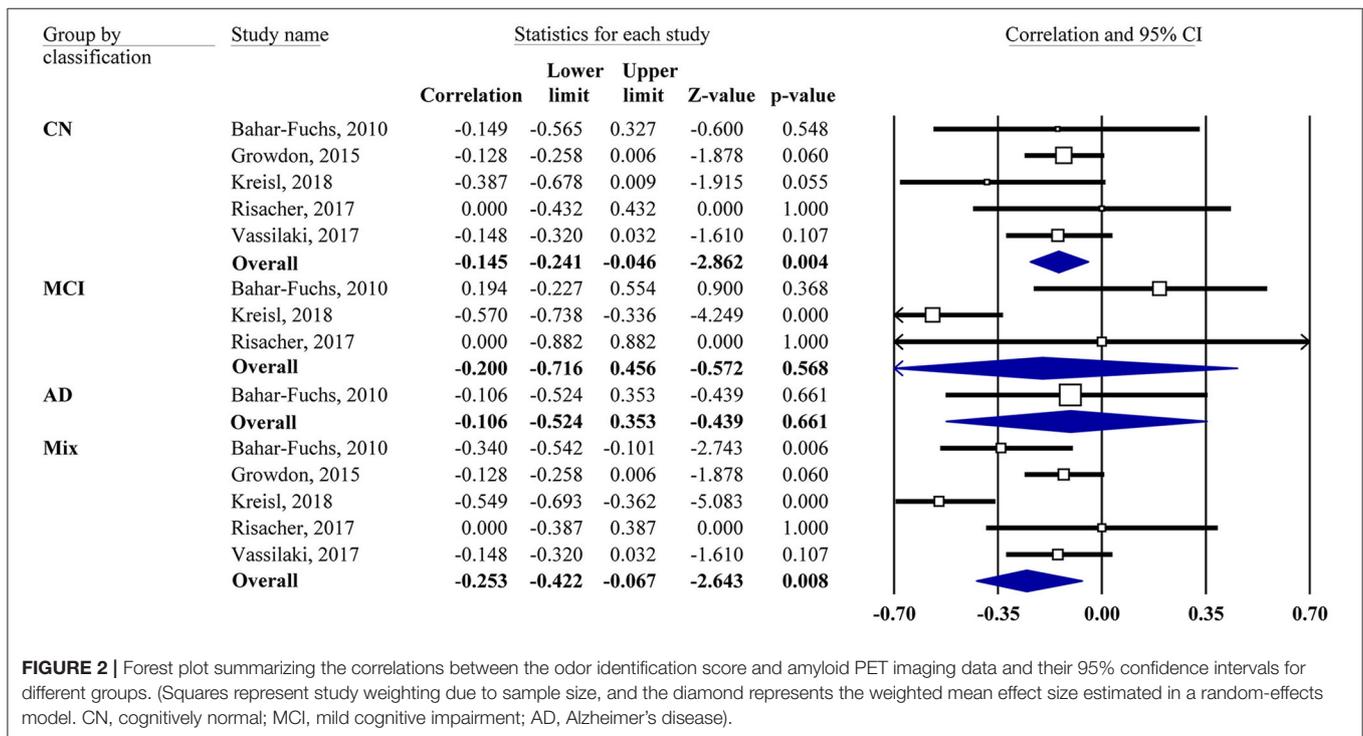
References	Design (follow-up)	Country	N	Cohort	Mean age [year (SD)]	Sex, female (%)	Olfactory test	AD biomarker	Classification	Statistical analysis
Bahar-Fuchs et al. (2010)	XS	Australia	63	Longitudinal PIB PET project at Austin Health	73.6 (8.2)	58.6	UPSIT (6-item)	PET: A $\beta$ ( $^{11}$ C PIB)	CN, MCI, AD	Pearson correlation
Growdon et al. (2015)	XS	USA	215	Harvard Aging Brain Study	73.9 (5.9)	59.1	UPSIT	PET: A $\beta$ ( $^{11}$ C PIB)	CN	Multiple linear regression
Kreisl et al. (2018)	LT (1 year)	USA	71	Longitudinal observational study of AD biomarkers	68.5 (7.6)	49.0	UPSIT	PET: A $\beta$ ( $^{11}$ C PIB)	CN, MCI	Pearson correlation
Risacher et al. (2017)	XS	USA	26	Indiana Alzheimer Disease Center	70.4 (8.8)	63.4	UPSIT	PET: A $\beta$ ( $^{18}$ F-florbetapir/florbetaben); Tau ( $^{18}$ F-flortaucipir)	CN, SCD, MCI	Pearson correlation
Vassilaki et al. (2017)	XS	USA	119	Mayo Clinic Study of Aging	79.2 (-)	48.5	UPSIT (12-item)	PET: A $\beta$ ( $^{11}$ C PIB), $^{18}$ F-FDG-PET	CN	Multiple linear regression
Körtvélyessy et al. (2015)	XS	Germany	22	Memory Clinic, University of Magdeburg	72.7 (6.9)	66.7	Sniffin (12-item)	CSF: A $\beta_{42}$ , <i>p</i> -tau, <i>t</i> -tau	AD	Pearson correlation
Kouzuki et al. (2018)	XS	Japan	71	Faculty of Medicine, Tottori University	78.3 (1.1)	43.8	OSIT-J	CSF: A $\beta_{42}$ , <i>p</i> -tau	CN, MCI, AD	Pearson correlation
Lafaille-Magnan et al. (2017)	XS	Canada	100	The PREVENT-AD cohort	62 (6)	70.0	UPSIT	CSF: A $\beta_{42}$ , <i>p</i> -tau, <i>t</i> -tau	CN	Multiple linear regression
Reijs et al. (2017)	LT (3 years)	Netherlands	152	The EDAR study	67.4 (9.5)	47.2	UPSIT (12-item)	CSF: A $\beta_{42}$ , <i>t</i> -tau	CN, MCI, AD, non-AD dementia	Multiple linear regression

XS, cross sectional; LT, longitudinal; UPSIT, University of Pennsylvania Smell Identification Test; OSIT-J, Odor Stick Identification Test for Japanese; PET, positron emission tomography;  $^{11}$ C PIB,  $^{11}$ C-Pittsburgh compound B; A $\beta$ , amyloid  $\beta$ ; CSF, cerebrospinal fluid; A $\beta_{42}$ , amyloid- $\beta_{42}$ ; *t*-tau, total tau; *p*-tau, phosphorylated tau;  $^{18}$ F-FDG,  $^{18}$ F-fluorodeoxyglucose; CN, cognitively normal; SCD, subjective cognitive decline; MCI, mild cognitive impairment; AD, Alzheimer's disease.

**TABLE 2** | Risk of bias and applicability concern summary: review authors' judgements about each domain for included studies, individually.

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
1. Bahar-Fuchs	😊	😊	😊	😊	😊	😊	😊
2. Growdon	😊	😊	😊	😊	😊	😊	😞
3. Kreisl	😊	😊	😊	😊	😊	😊	😊
4. Risacher	😊	😊	😊	😊	😊	😊	😊
5. Vassilaki	😊	😊	😊	😊	😞	😊	😞
6. Körtvélyessy	?	😊	😊	?	😊	😊	😊
7. Kouzuki	😞	😊	😊	😊	😞	😊	😊
8. Lafaille-Magnan	😞	😊	😊	😊	😞	😞	😊
9. Reijs	😊	😊	😊	😊	😞	😊	😊

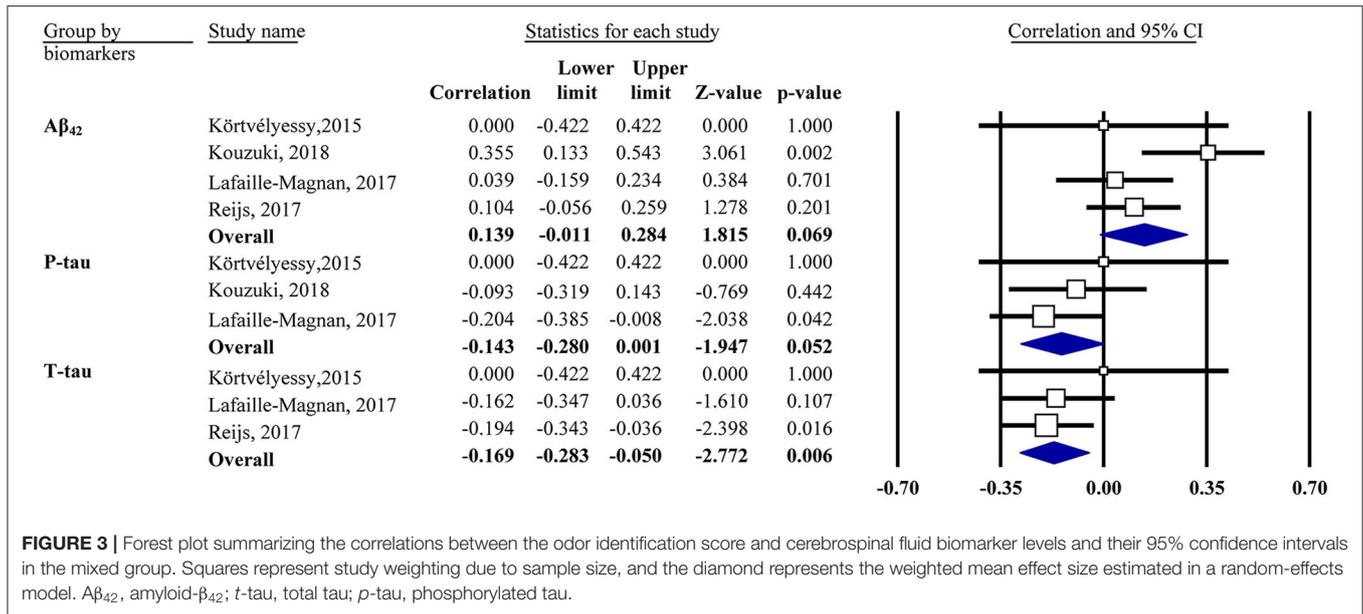
😊, low risk; 😞, high risk; ?, unclear risk.



**FIGURE 2** | Forest plot summarizing the correlations between the odor identification score and amyloid PET imaging data and their 95% confidence intervals for different groups. (Squares represent study weighting due to sample size, and the diamond represents the weighted mean effect size estimated in a random-effects model. CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease).

PET imaging or CSF evaluation. Our main finding was that A $\beta$  (measured by PET) and *t*-tau (measured by CSF evaluation) depositions were only weakly associated with OI scores across a mixed population (CN, MCI, and AD) of older adults. A weak association was also observed in the CN group between the A $\beta$  deposition (measured by PET) and OI score. As all the pooled absolute *r* values were <0.3, the correlation could be considered negligible. There were no associations between the MCI and AD groups or between CSF A $\beta$ <sub>42</sub> and *t*-tau. In addition, no pooled *r* value could be computed for the association between the OI score

and tau PET due to the lack of data. These findings suggest that the associations between OI ability and A $\beta$  and CSF tau burden in older adults are negligible. OI ability is believed to be linked with the pathologic manifestations of AD in postmortem studies (Kovacs et al., 1999; Attems et al., 2005; Attems and Jellinger, 2006; Wilson et al., 2007, 2009; Franks et al., 2015). Among the AD pathologic changes associated with OI, neurofibrillary tangles were particularly noted, especially in olfactory bulb (OB) (Kovacs et al., 1999; Attems et al., 2005; Attems and Jellinger, 2006) and central olfactory regions (entorhinal cortex and CA1/subiculum



**FIGURE 3 |** Forest plot summarizing the correlations between the odor identification score and cerebrospinal fluid biomarker levels and their 95% confidence intervals in the mixed group. Squares represent study weighting due to sample size, and the diamond represents the weighted mean effect size estimated in a random-effects model. A $\beta$ <sub>42</sub>, amyloid- $\beta$ <sub>42</sub>; t-tau, total tau; p-tau, phosphorylated tau.

**TABLE 3 |** Pooled Pearson's *r* values and 95% confidence intervals (CIs) adjusted for moderator variables (for A $\beta$  PET only).

Moderator variables		MCI		Mix	
		<i>r</i> [95% CI]	<i>f</i> <sup>2</sup>	<i>r</i> [95% CI]	<i>f</i> <sup>2</sup>
Odor test	UPSIT-L	-0.55 [-0.72, -0.32]***	0	-0.26 [-0.56, 0.1]	85
	UPSIT-S	Bahar-Fuchs et al. (2010)+		-0.23 [-0.4, -0.04]*	40
PET method	PIB	-0.24 [-0.79, 0.53]	90	-0.29 [-0.47, -0.09]**	79
	Non-PIB	Risacher et al. (2017)		Risacher et al. (2017)	
PET measure	SUVR	-0.2 [-0.72, 0.46]	81	-0.35 [-0.57, -0.09]*	79
	DVR	-		Growdon et al. (2015)	
Amyloid analysis	Continuous	-0.2 [-0.72, 0.46]	81	-0.35 [-0.59, -0.05]*	71
	Categorical	-		-0.14 [-0.24, -0.03]*	0
Sample size	>100	-		-0.14 [-0.24, -0.03]*	0
	<100	-0.2 [-0.72, 0.46]	81	-0.35 [-0.59, -0.05]*	71
Method of obtaining <i>r</i>	Reported	Kreisl et al. (2018)		-0.45 [-0.63, -0.23]***	54
	Estimated	0.18 [-0.23, 0.53]	0	-0.13 [-0.23, -0.02]*	0

The results for adjusted covariates equaled those of the odor test.

PET, positron emission tomography; UPSIT, University of Pennsylvania Smell Identification Test, -L = 40 items, -S = 6~12 items; PIB, Pittsburgh Compound B; SUVR, standardized uptake value ratio; DVR, distribution volume ratio; MCI, mild cognitive impairment.

“+” references.

\**P* < 0.05; \*\**P* < 0.01; \*\*\**P* < 0.001.

area of the hippocampus) (Wilson et al., 2007). This was in line with the tau PET imaging study (Risacher et al., 2017) included in our analysis, which indicated a low negative correlation between the tau and OI score in the mean temporal lobe. Of note, this was in response to the idea endorsed by Kametani et al. suggesting that it is tau contributed to the development and progression of AD, not A $\beta$  (Kametani and Hasegawa, 2018). Nevertheless, the meta-analysis of *in vivo* CSF t-tau, not p-tau, yielded only a very weak association, which was considered negligible. The inconsistency of the two findings might be explained by the following aspects: the histopathological study contained a relatively small sample size with advanced age and a

span of several years between olfactory testing and death. More importantly, *in vitro* neuropathological studies focused mainly on specific olfactory-related regions, while *in vivo* CSF studies could not take the same approach. However, the association with OI for the A $\beta$  burden on autopsy appeared non-significant, which supported our meta-analysis findings, particularly the results regarding CSF A $\beta$ , despite a low negative correlation that could be observed in the mixed group with moderator variables adjusted for the A $\beta$  PET imaging.

The mixed group, in general, showed a negligible correlation between OI ability and the A $\beta$  and CSF tau burden. However, the MCI and AD groups, both of which are associated with OI

impairment and inclined to be associated with A $\beta$  or tau burden (Jansen et al., 2015; Roalf et al., 2017; Villemagne et al., 2018; Jung et al., 2019), showed no correlation between the two at all among the different biomarker classifications. The correlation was observed in the MCI group for A $\beta$  PET when only the studies that applied the 40-item UPSIT were included, which was largely due to one study alone (Kreisl et al., 2018). Although part of the irrelevant finding may be related to the relatively small size of the sample within the included studies, especially for the AD group with A $\beta$  PET imaging ( $n = 20$ ), we speculate that OI ability is not specific to the underlying AD pathophysiology, especially A $\beta$ . On the other hand, the CN group is usually characterized by intact OI ability and a lack of A $\beta$  or tau burden, making the correlation between the two likely. In fact, Kreisl et al. (2018) attributed the correlation between OI ability and PIB SUVR largely to the subjects with high OI scores and low PIB binding in their study. Nevertheless, our results did not show any correlations in the CN group, with a negligible association for A $\beta$  PET imaging. This result again suggests that OI ability is non-specific for the underlying A $\beta$  burden.

The weak association between OI ability and the cerebral measures of amyloid and CSF tau levels might be explained by several possibilities. First, like the notion mentioned above, OI impairment may not be specific to AD. It is known that impaired OI is associated with normal aging, and some age-related changes in olfactory function may relate to factors irrelevant to AD pathophysiology (e.g., deterioration of the olfactory epithelium and ossification of the cribriform plate) (Doty et al., 1984; Doty and Kamath, 2014). In addition, many neuropsychiatric disorders, such as Parkinson's disease (Hoyles and Sharma, 2013), dementia with Lewy bodies (Mahlknecht et al., 2015), and schizophrenia (Kamath et al., 2019), are reported to be associated with OI impairment. In addition to AD pathologic alterations, alpha-synucleinopathy of Parkinson's disease and dementia with Lewy bodies in the cortical brain and olfactory-related regions are also observed and are supported by convincing evidence (Wilson et al., 2007; Arnold et al., 2010; Nag et al., 2019).

Second, the limitations of the A $\beta$  burden itself and its current measures are worth noting. The A $\beta$  burden is not conclusive in determining the risk of AD or cognitive impairment. The prevalence of incidental A $\beta$  positivity increases with age, and approximately a quarter of CN elders are amyloid-positive on PET scans or CSF evaluations (Jansen et al., 2015); the so-called asymptomatic cerebral amyloidosis stage may make the correlation between cerebral amyloid and OI impairment fruitless because the latter occurs predominantly in MCI and AD but not CN (Jansen et al., 2015; Jung et al., 2019). It is also worth noting that A $\beta$  burden reaches a plateau early in the disease process or even in the preclinical phase of the AD (Ingelsson et al., 2004; Serrano-Pozo et al., 2011); hence, it is not the most appropriate to correlate OI with A $\beta$  in AD, especially in late stage. Furthermore, a more toxic soluble or oligomeric form of A $\beta$  (Walsh et al., 2002; Shankar et al., 2008), which is considered critical in the AD pathological cascade but has not been measured in the included studies, may potentially correlate with OI ability more directly (Bahar-Fuchs et al., 2010).

Third, the same concept may apply to CSF *t*-tau and *p*-tau, which are often used to stage preclinical AD and are viewed as biomarkers of a "disease state," despite potentially correlating with OI ability (Mattsson et al., 2017; Lian et al., 2019). It was suggested that CSF P-tau levels might vary among AD and occur before measurable cognitive decline, which also makes the correlation difficult (Leuzy et al., 2019; Meyer et al., 2020). However, there are advantages to associating PET tau, viewed as a biomarker of a "disease stage," with dementia status and cognitive decline (Brier et al., 2016; Mattsson et al., 2017). Risacher et al. (2017) stated that tau deposition significantly correlated with OI ability, on the condition that A $\beta$  was positive. This, to a certain extent, corresponds with the definition of AD under the AT(N) scheme (Jack et al., 2018), which requires that both A $\beta$  and tau are positive. Therefore, correlating OI ability with PET tau will be promising and plausible, especially when focusing on A $\beta$ -positive individuals.

Finally, the included PET studies focused mainly on composite gray matter from frontal, parietal, lateral temporal cortex, and other regions of interest (Growdon et al., 2015; Vassilaki et al., 2017; Kreisl et al., 2018) but olfactory structure, while an olfactory region-targeted evaluation approach may strengthen the exploratory association. A number of neuroimaging studies indicate the association between structural and functional degeneration of distinct brain regions and olfactory impairment, mainly to the hippocampus and the primary olfactory cortex (Thomann et al., 2009; Growdon et al., 2015; Vasavada et al., 2015, 2017; Risacher et al., 2017; Vassilaki et al., 2017; Wu et al., 2019). In addition, postmortem studies mentioned above (Kovacs et al., 1999; Attems et al., 2005; Attems and Jellinger, 2006; Wilson et al., 2007, 2009) also state that the association between AD pathologic changes and OI largely reflects in the OB. Thus, it might be wiser to adopt a strategic regional analysis, rather than averaging the biomarker levels for the whole brain. Nevertheless, PET has so far not provided sufficient resolution measuring A $\beta$  and/or tau deposition in the OB in humans, as stated by Risacher et al. (2017).

Furthermore, the prion-like hypothesis in AD is also worth noting concerning the olfactory impairment. Like the prion detected in olfactory epithelium of sporadic Creutzfeldt-Jakob disease (Tabaton et al., 2004), A $\beta$  and tau also appeared in olfactory structures in AD and healthy subjects, including olfactory epithelium and OB (Kovacs et al., 1999; Wilson et al., 2007; Arnold et al., 2010; Brozzetti et al., 2020), both are susceptible to protein and enzyme modifications involved in AD pathogenesis (Dibattista et al., 2020). It was hypothesized that pathological modifications lead to the activation of protein accumulation in the OB after environmental insults, and then induces the propagation of the disease within the brain in a prion-like fashion by a templating process (Rey et al., 2018). Thus, OB was considered the entry site for this prion-like spreading in AD. Here, A $\beta$  was proposed as an initiator for AD pathogenesis, while prion-like propagation of tauopathy dominated the process and might even independent of A $\beta$  (Walker, 2018). Taken together, we believe these underlying pathologic development starting from olfactory neurons may contribute to the OI impairment, as memory dysfunction in AD and/or MCI was not enough

to explain this deficit (Wilson et al., 2007; Reijs et al., 2017). Hence, the olfactory region-based association, again, between OI ability and A $\beta$ , tau particularly is important. Recently, a non-invasive nasal brushing technique was used to collect the olfactory neuroepithelium (Brozzetti et al., 2020), from which neurodegeneration-associated proteins were detected, making correlating OI ability with A $\beta$  and tau levels in peripheral olfactory system *in vivo* possible. This, certainly, may help clarify the relationship between the olfactory function and biomarkers of interest. A comprehensive search, a detailed subgroup analysis, and the appraisal of potential moderators for heterogeneity are the strengths of the study. In addition, active communication with the authors of the included studies and the comprehensive extraction of additional data provided our analysis with more power than the original publications offered.

However, several limitations of our study should also be noted. First, the available data did not allow us to correlate PET tau with OI ability or to identify associations within the AD group. In addition, other olfactory functions (olfactory threshold and discrimination) were not considered in this study. Thus, the inferences in the study cannot be extended to the above situation. Second, the sample sizes in general were modest but relatively small in the AD group and the CSF analysis, which reflects the limited amount of available data in the associated field and limits the power of detecting associations. Third, it was shown that the association was greater if the OI was defined by suggested cutoffs of abnormality, such as anosmia and normosmia (Vassilaki et al., 2017). Unfortunately, no such data could be obtained because only one study took the approach. Fourth, *t*-tau/A $\beta$ <sub>42</sub> or *p*-tau/A $\beta$ <sub>42</sub> might correlate with odor identification better than single CSF measures due to their improved ability for defining biomarker positivity, but the data was limited. Two studies reported *p*-tau/A $\beta$ <sub>42</sub>, and the pooled results indicated a weak association ( $r = -0.17$ ,  $P = 0.03$ ). Fifth, it is advisable to take APOE  $\epsilon$ 4 allele into account when analyzing the associations between OI ability and amyloid- $\beta$  and tau burden as the latter interacts with APOE  $\epsilon$ 4 allele. This has not been done as only a few studies adjusted APOE  $\epsilon$ 4 allele. Finally, the comprehensive data extraction was a double-edged sword, as it may have yielded results that deviate from the original results due to the recalculation and estimation of the data.

Future studies using PET tau imaging with larger sample sizes may help further clarify this issue. Concerning other olfactory functions, a recently published study (Lian et al., 2019) investigated the relationship between the threshold discrimination identification score and CSF A $\beta$  and tau levels in AD patients with or without olfactory dysfunction (OD), finding that only *t*-tau levels were significantly lower in the AD-OD group, but the significant correlation disappeared after adjusting for age, sex, education, and disease duration. The same was true for the study by Doorduijn et al. (2020), which found no associations between AD biomarker levels and threshold discrimination identification. Another excluded study using odor percept identification performance with a homemade test to correlate with A $\beta$  PET data also yielded a negative result (Dhillal Albers et al., 2016). These findings appear to be consistent with our meta-analysis results. Additionally, the *p*-tau/*t*-tau ratio has recently been shown to be related to olfaction in peripheral

olfactory systems (Liu et al., 2018); thus, it might be interesting to examine the association between the *p*-tau/*t*-tau ratio and OI ability.

Here, we provide a thorough analysis on the negligible association between OI ability and A $\beta$  and CSF tau burden, from the limitation of the OI test and A $\beta$  measures themselves (both are lack of specificity) and the drawbacks of currently averaging the A $\beta$  levels for the whole brain, to the possible association between the pathologic development (amyloid plaques and tauopathy) and OI impairment based on the prion-like hypothesis in AD. Specifically, we point out that the prion-like spreading A $\beta$ , especially tau along the olfactory pathway (starting from OB) may contribute to the OI impairment, in parallel of memory dysfunction to some extent. This highlights a strategic regional analysis in the future, and a handful of other ideas, such as treating OI as a categorical variable (e.g., anosmia, normosmia), using *t*-tau/A $\beta$ <sub>42</sub> or *p*-tau/A $\beta$ <sub>42</sub>, focusing on the APOE  $\epsilon$ 4 allele carriers, and most importantly measuring by PET tau imaging.

In summary, our meta-analysis suggests that OI impairment correlates marginally with A $\beta$  PET data but not CSF A $\beta$  and more weakly correlates with CSF *t*-tau but not *p*-tau. These findings may disappoint those who intend to use OI ability alone for the early detection of AD. Nevertheless, PET tau might be more strongly associated with OI impairment; however, more studies are needed to clarify this association. Importantly, our results should not be regarded as a rationale for denying the value of olfactory testing in AD research. OI test may have limited value predicting amyloid and tau status when used alone, yet it is possible that an enhanced association between the two may be yielded when combined with other biologic markers discussed above (e.g., focusing on APOE  $\epsilon$ 4 carriers using tau PET imaging with olfactory region-based analysis), and it is still valuable in predicting cognitive decline and progression from MCI to AD dementia. In fact, as a low-cost, non-invasive method of evaluating olfactory function, the assessment of OI ability, combined with global cognitive testing, has the potential to help clinicians identify persons who rarely transition to dementia (Devanand et al., 2019), thus helping practitioners decide whether to apply further diagnostic investigations, such as PET scans, which help reduce the burden and cost of clinical AD trials and as the first diagnostic tau radiotracer for use with PET was approved by the US Food and Drug Administration, further research is possible and warranted.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

LT contributed to the study design, data analysis, and interpretation and drafted the manuscript. XL contributed to data analysis and interpretation and critical revision of the manuscript. ZF and MZ contributed to data analysis and revision of the manuscript. XY and HW contributed to the design

of this study, interpretation of data, and critical revision of the manuscript and had primary responsibility for the final content. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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