1 # Lower Odor Identification in Subjective Cognitive

2 # Decline: A Meta-analysis

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LOWER ODOR IDENTIFICATION IN SUBJECTIVE COGNITIVE DECLINE

26   **Abstract**

27   **Introduction:** Odor identification correlates with Alzheimer's disease (AD) biomarkers, and its

28   decline may emerge before measurable cognitive deficits—as early as the subjective cognitive

29   decline (SCD) stage. We aimed to compare odor identification between SCD and cognitively

30   normal (CN) stages and investigate whether cognitive differences moderate olfactory deficits.

31   **Methods:** A systematic search of four databases identified studies assessing olfactory

32   identification and cognitive screening in individuals aged 50+. A random-effects meta-analysis

33   was performed on 11 studies (660 SCD, 574 CN).

34   **Results:** Individuals with SCD exhibited lower olfactory identification scores compared to CN

35   participants (SMD = -0.67, 95%CI [-1.31, -0.03], p = .04). Meta-regression revealed a negative

36   association ($\beta = -1.79$, p = .02) between cognitive and olfactory differences, indicating that

37   greater cognitive decline was not consistently associated with greater olfactory deficits, lower

38   odor identification scores in SCD occurred despite minimal cognitive differences across groups.

39   **Discussion:** Odor identification is lower in pre-MCI individuals reporting SCD. Olfactory

40   decline may emerge independently prior to measurable cognitive decline, supporting the role of

41   odor identification as a screen for AD.

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1. Background

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the accumulation of amyloid-β plaques and tau neurofibrillary tangles, followed by widespread neurodegeneration and cognitive decline, culminating in dementia.[1] Early identification of individuals at risk for AD is critical for timely intervention, particularly as the disease progresses over decades before the occurrence of first cognitive deficits,[2] and as therapies targeting amyloid pathology and other early pathological stages become available. Subjective cognitive decline (SCD) refers to self-reported cognitive decline in the absence of measurable deficits on neuropsychological tests.[3] SCD is considered the first symptom of AD, appearing at stage 2 of the disease,[1,4] and has been associated with an increased risk for the development of mild cognitive impairment (MCI) and progression to the dementia stages of the disease.[5,6]

While SCD is associated with an increased risk of cognitive decline, not all individuals reporting SCD will decline.[6] Furthermore, the presence of AD biomarkers among individuals with SCD varies considerably, ranging from 10% to 76%.[5,7,8] This broad variability suggests a lack of diagnostic precision and highlights the heterogeneity of SCD as a clinical entity. Therefore, SCD alone is not sufficient to predict cognitive decline, necessitating the identification of additional reliable, and easily accessible markers that can improve the specificity of early risk assessment.

One promising candidate for preclinical AD detection is odor identification impairment. Multiple studies have demonstrated that odor identification is impaired at the dementia[9] and MCI[10] stages and is thought to emerge even before measurable episodic memory deficits.[11] The primary olfactory cortex morphometry is damaged in MCI[12] and olfactory identification is

73 associated with hippocampal volume and entorhinal cortex thickness in patients with MCI[13–15]

74 and individuals with SCD.[16] Olfactory identification is also associated with longitudinal tau

75 pathology accumulation within the central olfactory system in cognitively normal individuals.[17]

76 Several longitudinal studies have demonstrated that olfactory identification scores are associated

77 with cognitive decline in cognitively normal individuals[18–20] and conversion from MCI to

78 dementia stage.[21,22] Taken together, these findings suggest that olfactory impairment may

79 represent a subtle, early marker of neurodegeneration, and could have predictive value in the

80 detection of preclinical AD.

81 A prior meta-analysis[23] suggested a trend toward lower olfactory identification scores in

82 individuals with SCD compared to cognitively normal (CN) older adults. The number of

83 included studies was small (k = 5), limiting the analysis of potential moderators and the

84 interpretation of the conclusions. Since its publication, several new studies have examined

85 olfactory function in SCD. With the advent of treatments that mitigate the burden of amyloid

86 pathology at the MCI and early dementia stages, it is crucial to identify low-cost, non-invasive,

87 and accessible signs and markers for AD that manifest prior to the onset of measurable cognitive

88 deficits, particularly before the progression to MCI. Olfactory testing may thus offer a valuable

89 complement to existing cognitive screening tools and could aid in stratifying risk in clinically

90 normal individuals reporting cognitive concerns. The aim of the meta-analysis was (1) to

91 compare odor identification between older adults with SCD and CN older adults without

92 cognitive complaint, and (2) to evaluate the magnitude of olfactory identification impairment in

93 SCD by comparing the effect sizes of olfactory differences with those observed in general

94 cognitive screening measures (e.g., Montreal Cognitive Assessment - MoCA,[24] Mini-Mental

95 State Examination - MMSE[25]).

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2. Methods

98 The protocol of this meta-analysis was not registered.

99

2.1 Study Eligibility Criteria

101   Eligible studies included a direct comparison of odor identification scores between

102 individuals with SCD and CN participants without cognitive impairment or cognitive complaint,

103 with both groups including men and women aged 50 years and older. The definition of SCD was

104 based on two core criteria: (1) self-reported cognitive decline relative to a previous performance

105 level and (2) normal cognitive performance on standardized cognitive tests, such as the MMSE

106 or the MoCA to exclude MCI. CN participants were required to be CN without objective

107 cognitive impairment (i.e., scoring > -1.5 standard deviations on cognitive tests) and without

108 self-reported complaints of cognitive decline. Studies were excluded if participants were younger

109 than 50 years of age, had a diagnosed cognitive impairment, or had a psychiatric or neurological

110 condition that could affect cognitive or olfactory function.

111   **Outcome.** Eligible studies had to assess olfactory identification using a validated

112 olfactory identification test to be included in the meta-analysis. The eligible tests included the

113 Sniffin' Sticks Identification Test (SSIT),[26] the Odor Perception Identification Test (OPID)[13]/ the

114 AROMHA Brain Health Test,[27] the University of Pennsylvania Smell Identification Test

115 (UPSIT),[28] or the Cross-Cultural Smell Identification Test (CC-SIT).[29] Similarly, eligible studies

116 were required to include a measure of general cognition functioning using a standard screening

117 test (MoCA or MMSE)[24,25] to allow for effect size comparisons across cognitive and olfactory

118 measures.

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120   *2.2 Search Strategy and Information Source.*

121   A systematic literature search was conducted to identify relevant studies published up to

122 February 1st, 2025. The search was conducted in the PsycNET, PubMed, Academic Search

123 Complete (EBSCO), and Scopus databases. The following keywords and Boolean operators were

124 used: ("SCD" OR "subjective cognitive decline" OR "subjective cognitive impairment" OR

125 "subjective memory impairment" OR "subjective memory decline" OR "cognitive complaint*"

126 OR "memory complaint*" OR "cognitive concerns" OR "memory concerns") AND ("olfac*" OR

127 "smell" OR "olfactory dysfunction" OR "olfactory impairment"). Studies had to be published in

128 English.

129   After the removal of 106 duplicates, 113 titles and abstracts were screened for eligibility.

130 We excluded studies that were unrelated to the research question, review articles, case studies,

131 qualitative studies, or the absence of a control group. After the initial screening, 40 studies were

132 identified as potentially eligible and were further assessed for inclusion. After reviewing full-text

133   articles, 11 studies and 13 reports met the inclusion criteria (Figure 1). The list of included

134   studies is reported in Supplementary material.

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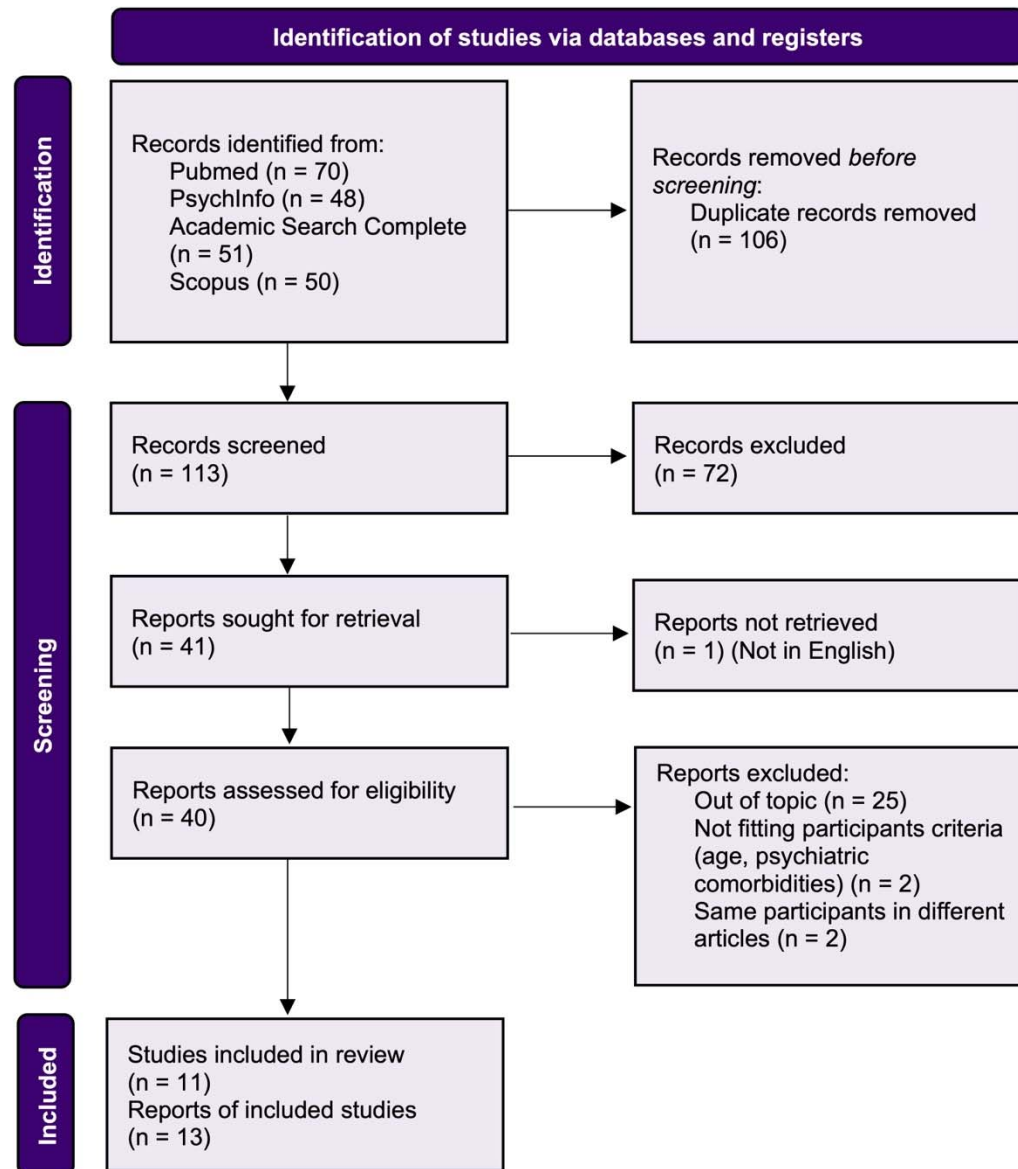
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137   Figure 1. PRISMA Flow Diagram of Study Selection.

138   The figure illustrates the study selection process based on PRISMA (Preferred Reporting Items

139   for Systematic Reviews and Meta-Analyses) guidelines.

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2.3 Risk of Bias Assessment

142   The methodological quality of each included study was assessed using the Newcastle-

143 Ottawa Scale (NOS)**,** as recommended.[30] The NOS[31] is a tool designed to evaluate the quality of

144 non-randomized case-control studies in meta-analyses, assessing three key domains: participant

145 selection, comparability between groups, and outcome ascertainment. The scoring system ranges

146 from 0 to 9 points, with higher scores indicating higher study quality. Studies scoring 0–3 were

147 considered at high risk of bias, 4–6 at moderate risk, and 7–9 at low risk. The risk of bias for

148 each study was independently evaluated by two reviewers (BJ and CZ). If disagreement emerged,

149 the most conservative score was assigned. No major disagreements occurred during this process,

150 and no studies were excluded based on quality assessment. The final risk of bias scores for each

151 included study are summarized in Supplementary Table 1.

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2.4. Statistical Analyses

154   We conducted random-effects meta-analyses using the *meta* package in R. We

155 standardized mean differences (SMD, Hedges' *g*) for each study by comparing the mean scores

156 of SCD and CN groups. To improve variance estimation, we performed random-effects model

157 using the Hartung-Knapp adjustment, with effect sizes weighted by the inverse variance of their

158 standard errors. This approach provides robust confidence intervals and improves statistical

159 inference, especially in meta-analyses with small numbers of studies or high heterogeneity.[32–34]

160 We assessed heterogeneity using Cochran's Q statistic, Higgins' I^2 index, and τ^2 to quantify

161 between-study variability. High heterogeneity ($I^2 > 75\%$) prompted further investigation through

162 meta-regression. We conducted meta-regression analyses to examine the potential moderating

163   effects of *age*, *sex proportion* (female), *educational level* (years), and *test modality* on effect

164   sizes.

165   We assessed potential publication bias using visual inspection of funnel plots, Egger's

166   regression test, and the trim-and-fill method. Funnel plot asymmetry and Egger's test *p*-values <

167   .05 were considered indicative of potential bias. We used the trim-and-fill method to impute

168   missing studies and adjust the pooled effect size under the assumption of publication bias.

169   Statistical significance was set at *p* < .05 for all analyses.

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171   **3. Results**

172   *3.1 Study selection and characteristics*

173   A total of 11 studies met the inclusion criteria, combining 660 individuals with SCD and 574 CN

174   participants (see Figure 1 & Table 1). Two reports/articles used the same sample, therefore this

175   dataset counted as a single study to avoid duplication.[35,36] According to the study quality

176   assessment, no studies were excluded for a high risk of bias (i.e., NOS scale ≤3) (Supplementary

177   Table 1).

178

179   Table 1. Characteristics of included studies.

Authors (Year)	n (SCD/CN)	Women % (SCD/CN)	SCD Age	CN Age	SCD Education	CN Education
Bouhaben et al. (2024)	47/101	70%/61%	69.74 (6.83)	69.0 (7.98)	na (na)	na (na)
Chen et al. (2021)	70/50	67%/64%	67.3 (5.7)	64.5 (4.4)	11.5 (3.3)	11.8 (2.9)
Dhilla Albers et al. (2016)	74/70	23%/71%	77.0 (8.16)	75.0 (8.75)	16.0 (2.9)	17.0 (2.6)
Jobin et al. (2024)	31/73	62% /63%	75.48 (9.22)	72.25 (9.13)	16.25 (2.5)	16.42 (3.62)
Papadatos et al. (2023)	55/55	78%/81%	70.08 (7.0)	69.07 (5.56)	16.97 (3.1)	15.77 (3.24)
Risacher et al. (2017)	10/10	60%/79%	72.2 (6.4)	68.5 (6.9)	17.5 (2.0)	17.6 (2.0)
Schmicker et al. (2023)	17/18	47%/55%	71.7 (7.0)	73.5 (0.48)	13.8 (2.7)	14.3 (2.2)
Sohrabi et al. (2009)	81/63	na / na	65.53 (7.3)	64.66 (7.73)	na (na)	na (na)
Tahmasebi et al. (2019)	161/69	51%/63%	66.93 (10.32)	65.5 (10.4)	12.45 (3.55)	12.12 (4.01)
Wang et al. (2021)	84/35	62%/49%	67.0 (5.6)	67.5 (5.3)	11.5 (3.3)	11.8 (2.9)
Weber et al. (2004)	30/30	63%/43%	66.0 (8.9)	65.9 (9.7)	13.9 (3.5)	16.0 (3.0)
Authors (Year)	n (SCD/CN)	Olfactory/ Cognitive Test	SCD Olfactory	CN Olfactory	SCD Cognitive	CN Cognitive

			Score	Score	Score	Score
Bouhaben et al. (2024)	47/101	SSIT/MoCA	11.23 (3.74)	13.18 (1.61)	28.67 (1.12)	28.96 (1.10)
Chen et al. (2021)	70/50	SSITMMSE	10.8 (2.3)	12.8 (2.0)	27.30 (2.00)	27.20 (1.80)
Dhilla Albers et al. (2016)	74/70	OPID/MMSE	0.67 (0.17)	0.69 (0.17)	28.95 (1.38)	29.45 (0.84)
Jobin et al. (2024)	31/73	OPID/MoCA	10.68 (2.95)	10.79 (2.74)	-0.24 (1.17)	0.29 (0.84)
Papadatos et al. (2023)	55/55	BSIT/MoCA	10.33 (1.69)	10.6 (1.41)	27.22 (1.84)	27.93 (1.50)
Risacher et al. (2017)	10/10	UPSIT/MoCA	35.7 (3.3)	34.5 (2.3)	26.10 (2.30)	26.80 (2.5)
Schmicker et al. (2023)	17/18	SSIT/MMSE	9.41 (1.51)	9.06 (1.47)	28.10 (1.50)	29.10 (1.00)
Sohrabi et al. (2009)	81/63	SSIT/MMSE	12.38 (2.18)	13.12 (1.49)	28.98 (1.06)	29.11 (1.07)
Tahmasebi et al. (2019)	161/69	SSIT/MMSE	12.16 (2.57)	12.83 (2.16)	28.84 (1.22)	28.71 (1.00)
Wang et al. (2021)	84/35	SSIT/MMSE	11.1 (2.2)	12.9 (2.0)	26.80 (2.00)	27.00 (1.50)
Weber et al. (2004)	30/30	CC-SIT/MMSE	9.7 (1.7)	10.3 (1.3)	28.50 (1.5)	29.1 (1.00)

180   Note*:* CC-SIT: Cross-Cultural Smell Identification Test. MoCA: Montreal Cognitive Assessment.

181   MMSE: Mini-Mental State Examination. OPID: Odor Percept Identification. SSIT: Sniffin'

182   Sticks Identification Test. UPSIT: University of Pennsylvania Smell Identification Test. Some

183   studies did not report data on educational level or sex proportion (indicated as 'na'). Additionally,

184   data from Tahmasebi et al. (2019) were provided by the authors and have been used in multiple

185   publications. MoCA score was available for only a subsample of participants (SCD n = 18, CN n

186   = 28 included in Jobin et al., 2024.

187

188   *3.2 Main Effect (Olfactory Identification)*

189   Meta-analysis of the pooled SMD revealed that SCD groups exhibited significantly lower

190   olfactory identification scores compared to CN groups (SMD= -0.67, 95% CI [-1.31, -0.03], *p*

191   = .04). Variability in effect sizes across studies was observed (I^2 = 92.1%, τ^2 = .73) and

192   statistically significant (Q(10) = 125.84, *p* < .001) (Figure 2).
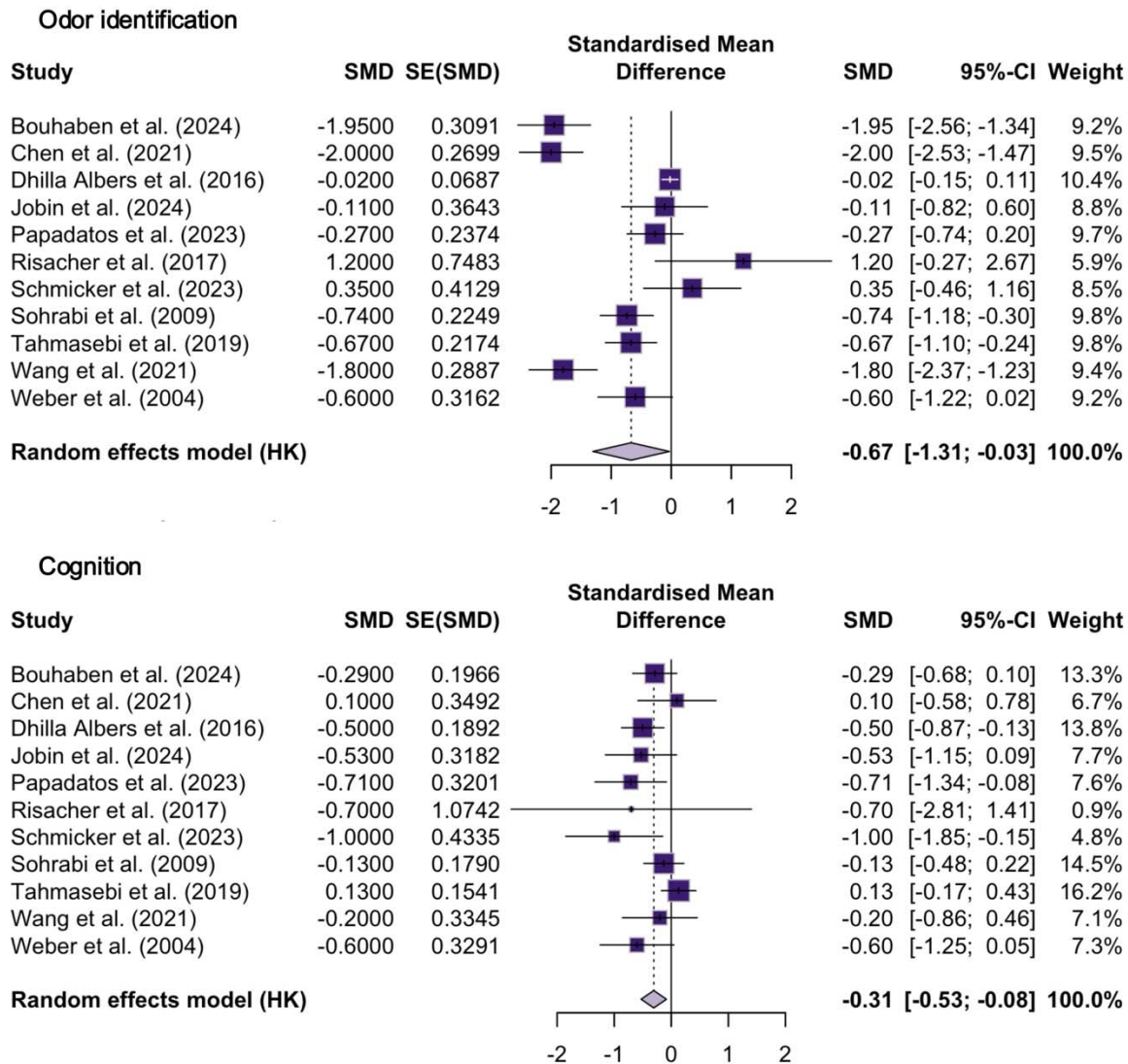
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Figure 2: Forest plots of standardized mean differences (SMD) of odor identification and

cognitive performances in individuals with SCD vs. CN participants.

Each horizontal line represents the 95% confidence interval (CI) for an individual study, with the

square indicating the SMD estimate. The size of the square reflects the weight of the study in the

meta-analysis. The diamond at the bottom represents the overall pooled SMD and its 95% CI,

estimated using a random-effects model.

203   ***3.2.1. Moderator Analysis***

204   Meta-regression analyses were performed to identify potential sources of heterogeneity.

205   *Age* differences between SCD and CN groups did not significantly moderate the observed

206   differences in odor identification performance (β = 0.09, SE = 0.20, 95% CI [-0.36, 0.54], *p* = .67,

207   $R^2 = 0\%$), suggesting that age alone does not account for the variability in effect sizes across

208   studies (Figure 3). Neither *sex proportion (female %)* (β = -2.72, SE = 1.49, 95% CI [-6.14, 0.70],

209   *p* = .10, $R^2 = 23.52\%$), *educational level* (years) (β = 0.03, SE = 0.39, 95% CI [-0.90, 0.95], *p*

210   = .94, $R^2 = 0\%$), or *test modality* ($F(4,6) = 1.56$, *p* = .30) significantly moderated the differences

211   observed in odor identification between SCD and CN groups. However, cognitive score on

212   screening measures was a significant moderator (β = -1.79, SE = 0.64, 95% CI [-3.24, -0.34], *p*

213   = .02, $R^2 = 46.47\%$), indicating that larger odor identification differences were observed in

214   studies where cognitive differences between SCD and CN groups were smaller or minimal
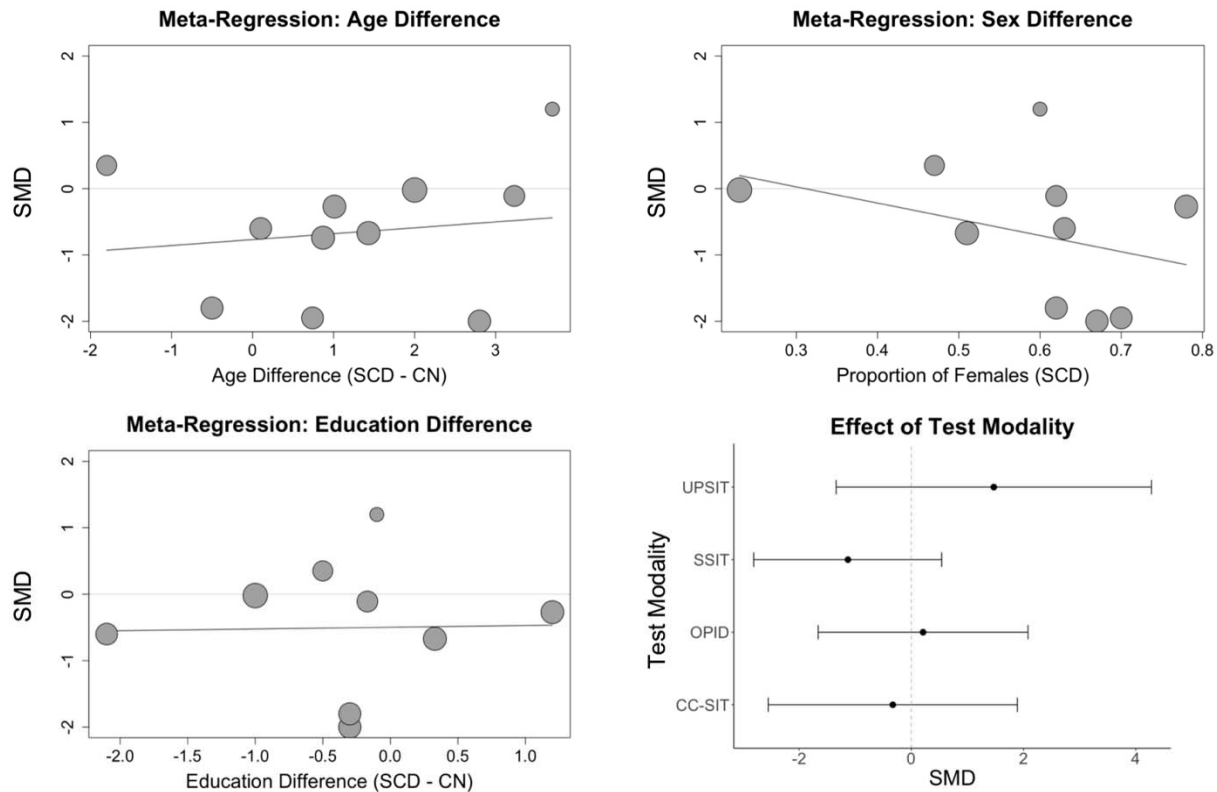
215   (Figure 4).

216

Figure 3. Meta-regression and Test Modality Effects on Standardized Mean Difference (SMD) in

odor identification across SCD and CN groups.

The four panels depict meta-regression analyses evaluating the impact of age difference (top-left),

sex difference (top-right), and education difference (bottom-left). The bottom-right panel shows

the effect of test modality on SMD, with different olfactory identification tests (UPSIT, SSIT,

OPID, CC-SIT) represented as separate estimates with corresponding 95% confidence intervals.

Negative SMD values indicate poorer olfactory performance in the SCD group compared to the

CN group. Overall, none of these potential moderators reached statistical significance. Two

studies did not provide information regarding sex distribution, [49] and one did not report

educational level; [49,50] these studies were excluded from the respective moderator analyses.
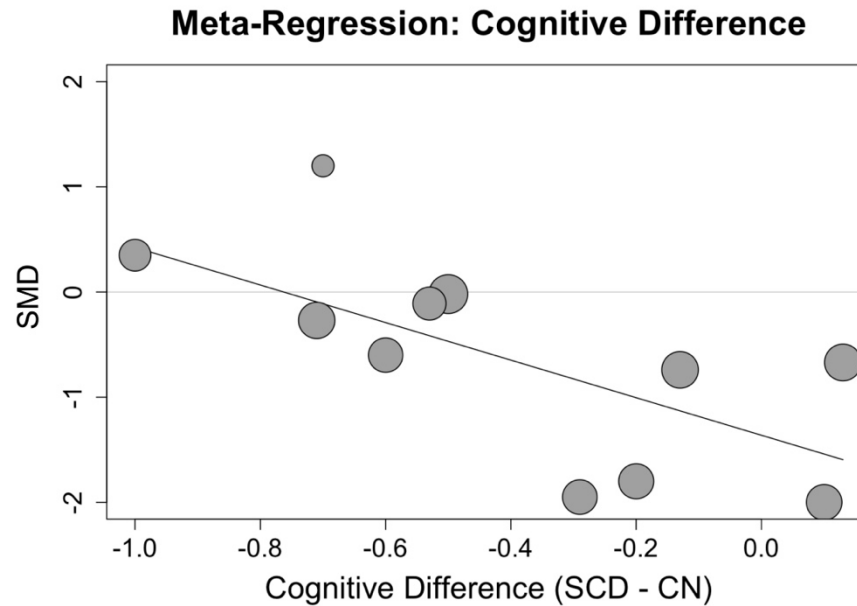
Figure 4. Meta-regression Effect of Cognition on Standardized Mean Difference (SMD) in odor identification across SCD and CN groups.

Negative SMD values suggest poorer olfactory performance in SCD compared to CN. The meta-regression analysis identified cognitive scores on screening tests as a significant moderator (β = -1.79, p = .02), indicating that larger olfactory differences were observed in studies with smaller cognitive differences between groups.
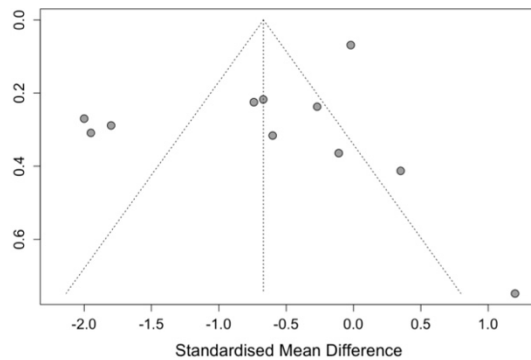
3.2.2. Publication Bias

Publication bias was assessed using funnel plot inspection, Egger's test, and the trim-and-fill method. Funnel plot symmetry indicated a low likelihood of substantial small-study effects or selective reporting, which was further supported by a non-significant result from Egger's test (t = -1.79, p = .11). The trim-and-fill analysis imputed two additional studies, resulting in an adjusted pooled standardized mean difference of -0.30 (95% CI [-1.03, 0.44], p = .39), which was substantially weaker and statistically non-significant compared tothe original estimate (SMD = -
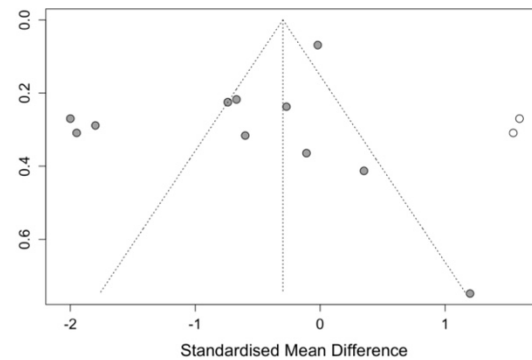
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244   0.67, 95% CI [-1.31, -0.03], p = .04). This adjustment suggests that the observed effect size

245   might have been overestimated in the presence of publication bias, and raises caution regarding

246   the robustness of the original effect (Figure 5).

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248
249   Figure 5. Funnel Plots Assessing Publication Bias.

250   For each comparison (olfactory identification and cognition), the left panel displays the funnel

251   plot for publication bias, where each point represents an individual study's SMD plotted against

252   its standard error. The dotted lines indicate the expected distribution of studies in the absence of

253   bias. Symmetry suggests minimal small-study effects or selective reporting. The right panel
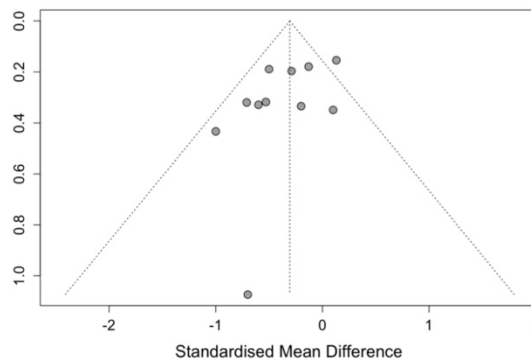
254   shows the trim-and-fill-adjusted funnel plot, with open circles representing imputed studies

255   added to correct for potential asymmetry. The adjusted pooled effect size was smaller than the

256   original estimate, suggesting possible overestimation due to publication bias. The wide

257   confidence interval of the adjusted estimate includes zero, indicating that the association may not

258   be significant after accounting for missing studies.

259

260

261   *3.3. Main Effect (Cognitive Score on Screening Tests)*

262   The meta-analysis of cognitive differences between SCD and CN also revealed a

263   significant effect (SMD = -0.31, 95% CI [-0.53, -0.08], p = .01). Heterogeneity was moderate (I^2

264   = 39.3%, τ^2 = .05, p = .21) but not statistically significant (Q(10) = 16.48, p = 0.09), indicating

265   that cognitive differences between SCD and CN are consistent across studies (Figure 2). As

266   heterogeneity remained below the critical threshold (I^2 < 75%), no moderator analysis was

267   deemed necessary. Overall, the odor identification differences (SMD = -0.67) show a larger

268   effect size than cognitive differences (SMD = -0.31).

269

270   *3.3.1. Publication Bias*

271   Funnel plot inspection showed no strong evidence of asymmetry, and Egger's test was

272   again non-significant (t = -1.88 p = .09), indicating a low likelihood of publication bias (Figure

273   4). The trim-and-fill analysis imputed four additional studies, resulting in an adjusted pooled

274   SMD of -0.19 (95% CI [-0.42, 0.05], p = .11), which, although weaker and non-significant,

275   remained in the same direction.

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278   **4. Discussion**

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279   Here we report that individuals with SCD exhibited lower odor identification scores

280   compared to CN participants, extending the hypothesis that olfactory deficits may serve as an

281   early marker of the presence of AD pathology and future cognitive decline during Stage 2

282   (Subjective Cognitive Decline). The effect size for group differences in odor identification (SMD

283   = -0.67) was larger than that observed for general cognitive screening tests (SMD = -0.31),

284   suggesting that olfactory impairment may be a more sensitive measure of subtle

285   neurodegenerative changes in individuals with SCD. Heterogeneity was observed across studies

286   in odor identification differences, which could not be explained by age, sex proportion, education,

287   or test modality. Cognitive performance significantly moderated olfactory scores, however, the

288   direction of this association indicated that larger olfactory deficits were observed in studies

289   where cognitive differences between SCD and CN groups were smaller. This finding suggests a

290   distinct pattern between cognitive performance on screening tests and olfactory function in SCD,

291   supporting the potential of odor identification as a marker for neurodegenerative changes not

292   captured by standard cognitive screening tools. Although publication bias did not appear to have

293   strongly influenced the results, the high level of heterogeneity highlights the need for further

294   investigation into additional contributing factors, including genetic predispositions and fluid

295   and/or imaging biomarkers of neurodegeneration, which may account for the variability in

296   olfactory identification deficits in SCD populations.

297   This meta-analysis confirmed that odor identification is reduced in SCD compared to CN

298   participants, confirming a trend observed in an initial meta-analysis published in 2021.[23] In the

299   context of the AD continuum, this finding suggests that odor identification is impaired prior to

300   the onset of cognitive deficits associated with MCI. This result aligns with studies demonstrating

301   associations between olfactory scores and AD tau or amyloid pathology biomarkers measured in

302   cognitively unimpaired,[17,37] and non-demented individuals.[38,39] A longitudinal study showed that

303   lower olfactory identification score correlates with baseline tau accumulation in primary

304   olfactory region and predicted accelerated progression of tau pathology in these regions ~2.5

305   years after.[17] Similarly, olfactory identification has been associated with hippocampal volume

306   and entorhinal cortex thickness in patients with MCI[13–15] and individuals with SCD without

307   cognitive impairment.[16] These findings suggest that odor identification tests could be among the

308   earliest objective measurements of AD-related damage to brain regions involved in olfactory

309   processing, occurring before the observable cognitive deficits.

310   Moderator analyses revealed that age, sex, education, and olfactory test modality did not

311   significantly moderate the effect size. Cognitive performance on screening tests emerged as a

312   significant moderator, although the direction of the association indicated that larger differences in

313   odor identification performance were observed in studies where cognitive differences between

314   SCD and CN groups were smaller. This finding reflects that olfactory identification deficits are

315   detectable when cognitive decline is absent and that cognitive performance remains within the

316   normal range on standard screening tests. While odor identification is not positively correlated

317   with cognitive scores on general screening tests in this meta-analysis, prior research has shown

318   significant positive associations between odor identification and declarative memory, which is

319   typically the first cognitive domain affected in the course of AD.[40] Longitudinal studies have

320   demonstrated that lower odor identification scores predict future cognitive decline[18,41,42] and

321   conversion to MCI.[19,43] Taken together, these findings support the potential role of odor

322   identification as an early marker of neurodegenerative changes that may precede the onset of

323   cognitive decline and MCI in at-risk individuals.

324   Another potential explanation for this inverse association is the differential influence of

325   cultural bias on cognitive versus olfactory measures.[44] While odor identification can be affected

326   by prior sensory experience and familiarity with specific odors, cognitive screening tests might

327   be influenced by language, educational background, cultural knowledge, and test-taking

328   conventions. These factors may reduce the sensitivity and variability of cognitive scores across

329   diverse populations, attenuating group differences. In contrast, olfactory tests may preserve

330   greater discriminatory power despite cultural variation, contributing to the larger effect sizes

331   observed in odor identification. Future studies should continue to explore how olfactory

332   measures can be optimized for diverse populations and validated as early, culturally robust

333   biomarkers of neurodegeneration.

334   It is important to note that reduced odor identification function is not specific to AD and

335   should not be used as a stand-alone diagnostic tool. Several other conditions can impair olfaction,

336   including neurological disorders such as Parkinson's disease, and traumatic brain injury; as well

337   as non-neurological conditions like chronic rhinosinusitis, among others.[45] Therefore,

338   interpretation of olfactory testing in the context of early AD detection must be approached with

339   caution. Two meta-analyses demonstrated that among olfactory functions, olfactory identification

340   is more specifically damaged in AD[9] and MCI[10] compared to a broader loss of smell observed in

341   conditions affecting the peripherical olfactory system[45] or in Parkinson's disease.[9] Furthermore, a

342   recent study showed that while a higher odor identification score was associated with a higher

343   probability of not having MCI (79%), lower score has limited sensitivity (58%) in distinguishing

344   MCI from SCD.[46] This suggests that the absence of an olfactory identification deficit lowers the

345   likelihood of AD, whereas a reduced score should lead to further investigation. In such cases,

346   more invasive and expensive diagnostic tools—such as, blood-based or CSF biomarkers,

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347   structural MRI, PET scans, comprehensive neuropsychological testing, and

348   otorhinolaryngological examination—should be considered. Odor identification might serve as a

349   low-cost, non-invasive first-line screening tool for brain health, and low score should trigger

350   more in-depth evaluation to rule out other modifiable causes of olfactory dysfunction that may

351   benefit from early intervention addressing social isolation, auditive and visual impairments,

352   cardiovascular risk factors, depression, physical inactivity, among others.[47]

353   Our findings support the inclusion of an odor identification testing as an additional risk

354   factor in the SCD+ framework, which aims to refine the identification of individuals at elevated

355   risk of AD. This framework also includes criteria such as memory-specific complaints, onset of

356   SCD within the past five years, age over 60, external confirmation of cognitive decline, and

357   clinical help-seeking.[3] Given the associations between olfactory deficits and AD biomarkers,[17,48]

358   medial temporal atrophy,[13–15] and longitudinal cognitive decline,[18–20,42] integrating odor

359   identification into the SCD+ criteria could enhance the stratification of risk for preclinical AD.

360   Future studies should investigate whether combining olfactory testing with the SCD+ framework

361   improves the prediction of progression to MCI and AD dementia.

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363   **4.1 Limitations**

364   The main limitation of this meta-analysis is that while meta-regression identified

365   cognitive performance as a significant moderator, other potential contributors to heterogeneity

366   such as genetic risk (e.g., APOE-ε4 status), neuropathological burden, or environmental factors

367   were not assessed due to limited available data. These potential variables could have enhanced

368   the comprehension of the significant heterogeneity observed in odor identification differences

369   between groups ($I^2 = 92.1\%$). Future research should incorporate these variables, particularly

370   amyloid and tau biomarkers, to strengthen the specificity of olfactory impairment as a preclinical

371   marker AD.[1]

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373   **4.2 Conclusion**

374   The presence of odor identification impairments, observed alongside normal-range of

375   cognitive performance in individuals with SCD, reinforces the hypothesis that olfactory

376   impairment may constitute an early marker of AD preceding MCI. These findings align with

377   previous research associating odor identification impairment with AD biomarkers and

378   longitudinal cognitive decline. Future longitudinal research should explore whether combining

379   odor identification testing with the SCD+ criteria improves the accuracy and precision of

380   predicting AD pathology, future cognitive decline, and progression to MCI or AD dementia.

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Conflict of Interest Statement

Albers is a co-founder and shareholder of Aromha, Inc. He consults for Sudo Biosciences, Merck,

and Bristol Myers Squibb; has been sponsored for research presentations to Incyte; and has

received in-kind support from Eli Lilly and International Fragrances and Flavors. Jobin, Zigrand,

Frasnelli, and Boller do not report any conflict of interest.

Consent Statement

559   Consent was not necessary as this study in a meta-analysis. All primary studies included

560   in this meta-analysis obtained informed consent from their participants and reported this in their

561   respective publications.

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563   **Keywords**

564   Subjective cognitive decline, Alzheimer's disease, Biomarker, Olfaction, Smell,

565   Olfactory identification, Meta-Analysis.

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