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Featured Article

Intact global cognitive and olfactory ability predicts lack of transition to dementia

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Abstract

Introduction: Odor identification deficits characterize Alzheimer's disease and other dementias. We examined if intact performance on brief cognitive and odor identification tests predicts lack of transition to dementia.

Methods: In an urban community, 1037 older adults without dementia completed the 40-item University of Pennsylvania Smell Identification Test, which includes the 12-item Brief Smell Identification Test (B-SIT). Data from 749 participants followed up for 4 years were analyzed.

Results: In covariate-adjusted survival analyses, impairment on the Blessed Orientation Memory Concentration Test and B-SIT each predicted dementia (n = 109), primarily Alzheimer's disease (n = 101). Among participants with intact olfactory (B-SIT $\geq$ 11/12 correct) and cognitive (Blessed Orientation Memory Concentration Test $\leq$ 5/28 incorrect) ability, 3.4% (4/117) transitioned to dementia during follow-up with no transitions in the 70–75 and 81–83 years age group quartiles.

Discussion: Odor identification testing adds value to global cognitive testing, and together can identify individuals who rarely transition to dementia, thereby avoiding unnecessary diagnostic investigation.

Keywords: Olfaction; Cognition; Dementia; Diagnosis; Investigation

1. Introduction

In the early pathological stages of Alzheimer's disease (AD), neurofibrillary tangles develop in the olfactory bulb and central odor processing regions including the entorhinal, piriform, hippocampal, and orbitofrontal cortices [1]. Clinically, this neuropathology manifests as impairment on olfactory tests, particularly tests of odor identification [1,2]. In cross-sectional studies, impairment in odor identification distinguishes cognitively intact older adults from patients with mild cognitive impairment (MCI) and AD, and combining a brief cognitive test with an odor identification test can improve diagnostic classification among AD, MCI, and controls [2]. In longitudinal studies, impaired

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odor identification has predictive utility for future dementia that is comparable with episodic memory impairment, and appears to be superior to episodic verbal memory tests in predicting cognitive decline [3–6].

The utility of intact performance on brief odor identification and global cognitive tests in predicting lack of cognitive decline or conversion to AD has not been examined explicitly. The ability to identify individuals who will not decline cognitively can reduce the need for unnecessary diagnostic investigation, and improve selection of patients for clinical trials, including prevention trials.

In a community cohort of older adults, we reported that the 40-item University of Pennsylvania Smell Identification Test (UPSIT) predicted dementia and cognitive decline, whereas the Selective Reminding Test (SRT) of episodic verbal memory predicted dementia but not cognitive decline [6]. In the same cohort, the Blessed Orientation Memory Concentration Test (BOMC), which is a brief, global cognitive assessment, was administered [7–9]. We now compare the predictive utility of the Brief Smell Identification Test (B-SIT), a 12-item component of the UPSIT, and the BOMC, which each require approximately 5 minutes to administer, for the outcomes of cognitive decline and dementia. Based on our reported finding of olfactory but not episodic memory impairment predicting cognitive decline, we hypothesized that the B-SIT but not the BOMC would predict cognitive decline.

Furthermore, in the context of brief instruments to assess global cognition, when used alone, showing poor predictive accuracy for dementia and Alzheimer's disease (AD), we assessed the predictive utility of the combination of the B-SIT and BOMC [10,11]. In particular, as a potential approach to detecting individuals unlikely to decline cognitively and therefore not require further diagnostic investigation for dementia, we tested if intact performance on both the B-SIT and BOMC was associated with lack of transition to dementia during follow-up.

2. Methods

2.1. Participants

A stratified random sample of 50% of all Medicare beneficiaries aged 65 years and older, obtained from the Health Care Finance Administration, was recruited from a specific region of North Manhattan, New York [12]. This Washington Heights/Inwood Columbia Aging Project cohort includes participants recruited originally in 1992 (approximately 25% of subjects) and a new cohort recruited between 1999 and 2001 (approximately 75% of subjects) [12]. Follow-up evaluations were completed every 2 years. At each evaluation, all participants received a standardized neuropsychological test battery that included measures of learning and memory, orientation, abstract reasoning, executive function, language, and visuospatial ability. A standardized neurological examination included a 10-item version of the Unified Parkinson's Disease Rating Scale [13]. The BOMC (scoring range 0–28; higher scores indicate worse cognition), the primary global cognitive measure in this cohort, is a six-item derivative of the Blessed Memory Concentration Test [14,15]. It takes 5 minutes to administer, correlates very closely with the MMSE, and is effective in discriminating AD from controls and evaluating cognitive change over time [7–9]. The BOMC was administered to all participants at the 1992 baseline evaluation and subsequently at all follow-up evaluations, including when a new cohort wave was recruited between 1999 and 2001 [12].

2.2. Olfactory testing

Odor identification testing was performed with the UPSIT, a highly reliable, sensitive, and extensively validated test [16]. The research technician administered the UPSIT and neuropsychological tests in English or Spanish based on the participant's language ability. In the UPSIT, each of 40 common odorants is embedded in microcapsules located on separate pages in four booklets, each with 10 pages. The participant scratches an odorant strip containing the microcapsule, sniffs the emanated odor, and identifies the odor from 4 choices. The total score ranges from 0 (no odors correctly identified) to 40 (all odors correctly identified).

The 12-item B-SIT is a subset of the 40-item UPSIT and may have similar accuracy for the prediction of dementia [3,16–18]. For this report, B-SIT scores were computed from the twelve B-SIT items within the UPSIT. The B-SIT score ranges from 0 to 12 with 0 indicating all odors incorrectly identified and 12 indicating all 12 odors correctly identified. For study inclusion, the participant needed to complete a minimum 11 of 12 B-SIT items. For participants who completed only 11 items, a score of 0.25 (1 of 4 choices per multiple choice item) was imputed for the missing item.

The study sample comprised all participants without dementia who received the UPSIT and BOMC and met study inclusion/exclusion criteria as reported previously; clinical stroke and Parkinson's disease were excluded specifically in the Washington Heights/Inwood Columbia Aging Project cohort [6,12]. Anosmia was defined in this study as a B-SIT score $\leq$3 of 12 because a score of 3 of 12 is obtained by chance in this multiple choice test. Evaluations were completed between 2004 and 2006, identified as "baseline" for this report. Follow-up evaluations occurred during 2006 – 2008 (first follow-up) and 2008 – 2010 (second follow-up).

2.3. Cognitive composite scores and diagnosis

Based on a previously published factor analysis from the neuropsychological test battery, composite cognitive domain scores were derived for memory, language, and

visual-spatial ability, utilizing norms adjusted for language of administration and demographic variables [12]. The memory composite comprised three 12-item 6-trial SRT measures (total immediate recall or SRT TR, delayed recall, and delayed recognition); the language composite comprised measures of naming, letter and category fluency, verbal abstract reasoning, repetition and comprehension; the visual-spatial ability composite comprised the Benton Visual Retention Test recognition and matching variables, the Rosen Drawing Test, and the Identities and Oddities subtest. A consensus conference was used to diagnose participants based on available clinical and neuropsychological test information without access to UPSIT or other biomarker data [12]. As previously published, cognitive decline was defined a priori as a decline in the average of the three cognitive composite scores (memory, executive, visuospatial) of 0.5 SD or greater decline by 2-year follow-up, and as 1 SD or greater decline by 4-year follow-up [6]. Diagnostic outcomes at the last available follow-up time-point were used.

2.4. Apolipoprotein E genotyping

DNA was amplified by polymerase chain reaction and genotypes assessed by sizes of DNA fragments. Apolipoprotein E genotypes were determined blind to participant status.

2.5. Standard protocol approvals, registrations, and patient consents

The Columbia University Institutional Review Board approved the study protocol and informed consent forms. Written informed consent was obtained from all participants in the study.

2.6. Statistical analyses

Distributions and group differences in demographic and clinical variables were examined by χ^2, t-test, and general linear models as appropriate. B-SIT score of 11 or 12 of 12 indicates no odor identification deficit in a broad range of individuals and BOMC score $\leq$5 of 28 is in the normative range for middle-aged to older adults [7–9,18]. Therefore, these cutoff points, which represent stringent criteria, were used in the main analyses. Broader normative criteria of B-SIT $\geq$ 9 and BOMC $\leq$6, which may be more applicable to older age cohorts, were also examined [19].

The definition of cognitive decline was based on the change in composite cognitive domain scores from the baseline to last available follow-up. Therefore, logistic regression analyses were used for the outcome of cognitive decline. For the dichotomous outcome of dementia or AD, discrete time survival models were used to evaluate the associations between baseline B-SIT scores and the time for transition to dementia or AD. For each outcome, we examined four models: B-SIT only; BOMC only; B-SIT and BOMC together; B-SIT, BOMC, and their interaction. All analyses were conducted with age, gender, education in years, and language of test administration as covariates.

To evaluate predictive ability between the UPSIT and its component B-SIT, the concordance index (C-index) was computed, based on 10-fold cross-validation [20]. The C-index is a measure of goodness of fit for binary outcomes. In survival analysis, the C-index is the fraction of all pairs of subjects whose predicted survival times are correctly ordered among all subjects that can be ordered, that is, it is the probability of concordance between the predicted and the observed survival, and it is less affected by censoring time [21,22]. In logistic regression, the C-index is numerically the same as the area under the curve of the receiver operating characteristic curve. The sample was randomly partitioned into 10 subsamples. Of the 10 subsamples, a single subsample was retained as the validation data for testing the model and the remaining subsamples were used as training data. We repeated this procedure for each of 9 subsamples and the AUC was averaged. To evaluate predictive ability between UPSIT and B-SIT, the C-index was computed based on 10-fold cross-validation as described. The C-indices were compared across different models using the bootstrapping method with 5000 resamples. Analyses were conducted in SAS 9.4 and R (v.3.0.1) package survcomp.

3. Results

3.1. Baseline demographic and clinical measures

Of the 1037 participants without dementia who completed the UPSIT and BOMC at initial evaluation, 749 participants were followed up. Demographic and clinical characteristics by age quartile are described in Table 1. English and Spanish B-SIT scores did not differ in the total sample (P = .86) or in the follow-up sample (P = .37) after adjusting for age and education. Of 749 participants, 748 completed all 12 B-SIT items and one participant completed 11 of 12 items.

Compared with the rest of the sample, participants with anosmia (n = 38) were older (mean 82.5 SD 6.5 years vs. mean 80.1 SD 5.4 years, P = .03), more likely to be male (47% vs. 72%, P < .001), have lower education (mean 8.7 SD 4.9 years vs. mean 10.8 SD 4.8 years, P < .02), and have lower SRT total and delayed recall scores (P's < .01). Anosmic participants, who were included in all analyses, did not differ significantly from the rest of the sample in race/ethnic distribution, Center for Epidemiological Studies Depression Scale scores, and apolipoprotein E ε4 genotype.

3.2. Follow-up

Of the 1037 participants, 273 were not followed for the following reasons: death n = 65, refused n = 60, did not return for scheduled appointment n = 55, unable to locate

Table 1
Participant characteristics by age quartile at baseline

	Age 70–75, n = 187		Age 76–80, n = 205		Age 81–83, n = 160		Age 84–101, n = 197		Total N = 749	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	73.48	1.37	78.11	1.39	81.86	0.85	87.35	3.27	80.18	5.52
Education in years	11.66	4.72	11.58	4.7	9.89	5.18	9.49	4.54	10.69	4.86
BOMC cognition (0-28)	1.97	3.14	2.81	4.12	3.53	3.83	3.76	4.47	3	3.99
B-SIT (0-12)	8.77	2.13	8.34	2.5	7.79	2.38	7.59	2.56	8.13	2.44
CES-D	1.20	1.38	1.30	1.46	1.37	1.56	1.26	1.37	1.28	1.44
	n	%	n	%	n	%	n	%	n	%
Female	125	66.84	133	64.88	122	76.25	151	76.65	531	70.89
Race/ethnicity										
White	59	31.55	85	41.46	35	21.88	54	27.41	233	31.11
African-American	61	32.62	49	23.9	50	31.25	59	29.95	219	29.24
Hispanic	67	35.83	71	34.63	75	46.88	84	42.64	297	39.65
Transition to dementia	16	8.56	24	11.71	25	15.63	44	22.34	109	14.55
Cognitive decline*	25	13.59	33	16.34	39	26	50	26.60	147	20.3
APOE e4 positive†	50	27.32	47	24.1	33	20.75	43	22.16	173	23.67
Smoking‡										
Current	19	10.22	11	5.39	9	5.66	4	2.04	43	5.77
Past	52	27.96	63	30.88	50	31.45	57	29.08	222	29.80
Never	115	61.83	130	63.73	100	62.89	135	68.88	480	64.43

Abbreviations: B-SIT, Brief Smell Identification Test, range 0–12, higher scores indicate better odor identification test performance, 0-10 impaired, 11-12 intact; BOMC, Blessed Orientation Memory Concentration Test, range 0–28, higher scores indicate worse cognitive performance, ≥ 6 impaired, 0-5 intact; CES-D, Center for Epidemiological Studies Depression Scale. Scoring range 0-60, with higher scores indicating greater depressive symptomatology.

*25 participants had missing data.

†18 participants had missing data.

‡4 participants had missing data.

n = 73, moved n = 20. There were no significant differences in sex, education, BOMC, and APOE4 status between participants who were and were not followed. Participants who were not followed were 1.23 years older ($P = .0025$) and had lower B-SIT (mean .89 lower, $P < .0001$), SRT total recall (mean 3.41 lower, $P < .0001$) and delayed recall (mean 0.84 lower, $P < .0001$) scores. More African-American participants were not followed in comparison to other ethnic/racial groups ($P = .0082$). In another 15 participants, incomplete baseline evaluation with missing data for either BOMC or B-SIT led to exclusion from the study sample.

In the 749 participants who completed at least one follow-up, 109 (14.55%) transitioned to dementia, of which 101 transitioned to AD dementia. Two participants transitioned to vascular dementia, 3 participants to Lewy body dementia, 3 participants to dementia of other causes. These 109 participants transitioned to dementia on average 4.98 (SD = 1.73) years from the baseline. Forty-two (38.53%) transitioned to dementia at the first follow up, and 67 (61.47%) participants transitioned to dementia at the second follow up.

3.3. Comparability of B-SIT to UPSIT

The predictive utility for the 40-item UPSIT was compared to that of the 12-item B-SIT subset for three outcomes: dementia, AD dementia, and cognitive decline. The UPSIT and B-SIT were similar in their C indices for the prediction of dementia (UPSIT C-index = 0.743, B-SIT C-index = 0.745; $P = .84$), AD (UPSIT C-index = 0.727, B-SIT C-index = 0.757; $P = .78$), and cognitive decline (UPSIT C-index = 0.646, B-SIT C-index = 0.646; $P = .81$). These P values are bootstrapped P values.

3.4. Transition to dementia and AD

Participants who transitioned to a diagnosis of dementia during follow-up (n = 109) had a mean baseline B-SIT score of 6.77 (SD 2.59) compared to a mean baseline B-SIT score of 8.37 (SD 2.34) in the rest of the sample (n = 640). In discrete time survival analyses that included age, sex, language, and education in years as covariates, lower baseline B-SIT was significant for the outcome of transition to dementia with a hazards ratio HR of 2.25, 95% CI: 1.12–4.49, $P = .02$. In similar survival analyses that included the same covariates, worse BOMC performance was significant with HR 5.64, 95% CI: 3.49–9.12, $P < .0001$. In a similar model that included both B-SIT and BOMC, worse BOMC performance was significant with HR 5.60, 95% CI: 3.47–9.05, $P < .0001$, and B-SIT was also significant with HR 2.25, 95% CI: 1.10–4.60, $P = .03$. There was no significant interaction between the two predictors ($P = .45$).

Participants who transitioned to a diagnosis of AD during follow-up (n = 101) had a mean baseline B-SIT score of 6.90 (AD 2.53) compared with a mean baseline B-SIT score of 8.33 (SD 2.37) in participants who did not transition to AD. For the prediction of AD, very similar results were found to those for dementia: lower baseline B-SIT was associated with transition to AD with an HR of 2.25, 95% CI 1.12–4.50, $P = .02$. In similar survival analyses that included the same covariates, worse BOMC performance was significant for the outcome of transition to AD with HR 5.57, 95% CI 3.44–9.01, $P < .0001$. In a similar model that included both B-SIT and BOMC, worse BOMC performance was significant with HR 5.52, 95% CI 3.41–8.94, $P < .0001$, and B-SIT was also significant with HR 2.25, 95% CI 1.10–4.59, $P = .03$. There was no significant interaction between the two predictors ($P = .43$).

Apolipoprotein E ε4 genotype, which was available in 731 participants, did not show any significant interactions with BOMC or B-SIT (P's $> .36$). Apolipoprotein E ε4 genotype was associated with incident dementia ($\chi^2 = 4.02$, $P = .045$), but this effect was not significant after including B-SIT and BOMC and demographic covariates in the Cox regression model (HR: 1.49, 95% CI: 0.93–2.40, $P = .10$) in which the effects of BOMC and B-SIT were essentially unchanged. Smoking (current or past smoker, yes/no items) and Center for Epidemiological Studies Depression Scale scores were not significant covariates in any of the analyses of cognitive decline or AD dementia as outcomes (P's $> .91$).

3.5. Prediction of cognitive decline

In logistic regression analyses for the outcome of cognitive decline that included age, sex, language, and education as covariates, lower B-SIT was associated with cognitive decline with odds ratio (OR) 2.48 (95% CI: 1.34–4.58, $P = .004$). In logistic regression for the outcome of cognitive decline that included the same covariates, worse BOMC performance was not significant (OR = 1.36, 95% CI: 0.86–2.16, $P = .19$). In a similar model with the same covariates that included both B-SIT and BOMC, BOMC was not significant with OR 1.34 (95% CI: 0.84–2.12, $P = .22$), but B-SIT remained significant with OR 2.37 (95% CI: 1.33–4.55, $P = .004$). There was no significant interaction between the two predictors ($P = .68$).

3.6. Proportion transitioning to dementia

Table 2 shows the proportions transitioning to dementia during follow-up. Participants who were unimpaired on both B-SIT and BOMC using the stringent criteria had a low likelihood (4/117 or 3.4%) of being diagnosed with dementia during 4 years of follow-up. For participants who were unimpaired on both B-SIT and BOMC, there were no transitions (0 of 37 participants) to dementia in the youngest 70–75 years age quartile, and no transitions in the 81–83 years age quartile (0 of 21 participants). When broader cutoff criteria were used for the B-SIT and BOMC, similar results were obtained (Table 2). In each age quartile, the number of transitions to AD essentially was identical to the number of transitions to dementia.

3.7. Proportion showing cognitive decline

Participants who were unimpaired on both B-SIT and BOMC using the stringent criteria had a low likelihood (10 of 115 or 8.7% in the total sample) of cognitive decline during 4 years of follow-up. For participants who were unimpaired on both B-SIT and BOMC, 5.4% and 5% showed cognitive decline in the 70–75 and 76–80 years age groups, respectively, whereas 15% and 16.7% showed cognitive decline in the two oldest age groups, respectively (Table 3).

4. Discussion

Intact performance on both the B-SIT and BOMC was associated with a low 3.5% rate of transition to dementia, with no transitions in the 70–75 and 81–83 years old age quartiles. In an earlier, separate clinical cohort of 144 patients with MCI who were followed up for 3 years, no patient younger than 70 years with high UPSIT scores transitioned to dementia [4]. These findings address the novel and unique aim of the present study, and suggest that for older adults up to their mid 80s who are unimpaired on both a brief odor identification test and a brief global cognitive test, transition to dementia in the next few years is very unlikely and further investigative evaluation for dementia typically is not needed. The need to assess both olfaction and global cognition is highlighted by the weaker predictions for only one of these two measures (Tables 2 and 3).

High olfactory ability likely indicates "non-transition" to dementia because while most individuals with AD dementia have olfactory deficits, many people without dementia may have olfactory deficits due to other causes, often age-associated. Overall, olfactory deficits have high sensitivity but lower specificity in distinguishing AD from other dementias and controls [23]. From prior work, one might then conclude that an older person with intact olfaction is less likely to show cognitive decline. Nonetheless, the present results do provide strong evidence that there is an olfactory performance threshold above which the risk of dementia is very low, particularly when combined with a global cognitive assessment.

Using stringent cutoff criteria, the B-SIT and BOMC were each significant for the prediction of dementia and retained significance when both measures were included in the same model. Similar results were obtained for AD, which comprised most dementia diagnoses because clinical stroke and Parkinson's disease were study exclusion criteria. In this report, the B-SIT but not the BOMC predicted cognitive decline. The BOMC may be insensitive to subtle changes in cognition, including memory, that can be better detected

Table 2
Baseline olfactory and cognitive scores in the prediction of transition to dementia in 749 community-dwelling WHICAP study participants

		B-SIT 0-10 impaired, 11-12 intact BOMC ≥ 6 impaired, 0-5 intact		B-SIT 0-8 impaired, 9-12 intact BOMC ≥ 7 impaired, 0-6 intact	
		Transition to dementia		Transition to dementia	
		No	Yes	No	Yes
Age quartile (years)	Baseline measure impaired/intact	n (%)	n (%)	N (%)	n (%)
All	BOMC impaired	12 (66.7)	6 (33.3)	25 (75.8)	8 (24.2)
	B-SIT impaired	428 (90.7)	44 (9.3)	258 (85.2)	45 (14.9)
	Both impaired	87 (61.3)	55 (38.7)	40 (50.6)	39 (49.4)
	Both intact	113 (96.6)	4 (3.4)	317 (94.9)	17 (5.1)
	All	640 (85.5)	109 (14.6)	640 (85.5)	109 (14.6)
70–75	BOMC impaired	3 (75.0)	1 (25)	3 (75.0)	1 (25)
	B-SIT impaired	119 (93.0)	9 (7.0)	57 (89.1)	7 (10.9)
	Both impaired	12 (66.7)	6 (33.3)	7 (63.6)	4 (36.4)
	Both intact	37 (100.0)	0 (0)	104 (96.3)	4 (3.7)
	All	171 (91.4)	16 (8.6)	171 (91.4)	16 (8.6)
76–80	BOMC impaired	5 (83.3)	1 (16.7)	8 (88.9)	1 (11.1)
	B-SIT impaired	117 (92.1)	10 (7.9)	65 (84.4)	12 (15.6)
	Both impaired	21 (65.6)	11 (34.4)	10 (55.6)	8 (44.4)
	Both intact	38 (95)	2 (5)	98 (97.0)	3 (3.0)
	All	181 (88.3)	24 (11.7)	181 (88.3)	24 (11.7)
81–83	BOMC impaired	3 (100.0)	0 (0.0)	8 (100.0)	0 (0.0)
	B-SIT impaired	80 (88.9)	10 (11.1)	55 (82.1)	12 (17.9)
	Both impaired	31 (67.4)	15 (32.6)	17 (63.0)	10 (37.0)
	Both intact	21 (100.0)	0 (0)	55 (94.8)	3 (5.2)
	All	135 (84.4)	25 (15.6)	135 (84.4)	25 (15.6)
84–101	BOMC impaired	1 (20.0)	4 (80.0)	6 (50.0)	6 (50.0)
	B-SIT impaired	112 (88.2)	15 (11.8)	81 (85.3)	14 (14.7)
	Both impaired	23 (50)	23 (50.0)	6 (26.1)	17 (73.9)
	Both intact	17 (89.5)	2 (10.5)	60 (89.6)	7 (10.5)
	All	153 (77.7)	44 (22.3)	153 (77.7)	44 (22.3)

Abbreviations: B-SIT, Brief Smell Identification Test, range 0–12, higher scores indicate better odor identification test performance, 0-10 impaired, 11-12 intact; BOMC, Blessed Orientation Memory Concentration Test, range 0–28, higher scores indicate worse cognitive performance, ≥ 6 impaired, 0-5 intact; WHICAP, Washington Heights/Inwood Columbia Aging Project.

by more in depth neuropsychological assessment. The consistent findings with the SRT in relation to the UPSIT in our prior report [5], and the BOMC in relation to the B-SIT, suggest that odor identification impairment is superior to episodic verbal memory impairment in identifying individuals who are likely to decline cognitively over time [24–26].

The predictive utility of odor identification impairment, by itself, for dementia or AD is established [5,27–31]. Of 30 published studies, all showed odor identification deficits in AD compared with healthy comparison subjects [32]. The 40-item UPSIT was used in 14 studies and its component 12-item B-SIT in 5 studies [18]. In a meta-analysis of AD versus controls, odor identification impairment showed an effect size averaging 2.05 with a range from 1 to 5 across studies [33]. By contrast, effect sizes for the MMSE and Montreal Cognitive Assessment (MoCA) ranged from 1.6 to 1.9 in differentiating dementia from controls in 5 published studies of clinical samples ranging from 150 to 225 patients, which is consistent with other reports [34,35]. In our cohort, 89% of participants with olfactory impairment, either by itself or in addition cognitive impairment on BOMC, transitioned to dementia. By contrast, impairment on the BOMC alone was less predictive (55%) and BOMC impairment was accompanied by B-SIT impairment in most participants (Table 2). These findings confirm that olfactory sensory impairment, particularly early in the course of dementia, is a salient marker of cognitive decline and future dementia.

The relatively stringent B-SIT cutoff score of greater than 10 of 12 to identify intact odor identification ability was based on a mean B-SIT score of 10.63 reported in a cognitively intact sample with a mean age of 58.92 years [18]. In the Health ABC epidemiological study, among 2462 participants with a mean age of 75.6 years, approximately one-third (n = 764) scored 0-8, one-third (n = 863) scored 9-10, and one-third (n = 835) scored 11-12 on the B-SIT [19]. In our cohort, 38% of participants showed impaired performance with the B-SIT cutoff >8 of 12 (Table 2). The lower B-SIT scores in older age groups are consistent with the reported decline in odor identification ability from the seventh to ninth decades of life [36]. Anosmic participants were older and had greater memory impairment, and both age and incipient AD pathology may contribute to this finding.

Table 3
Baseline olfactory and cognitive scores in the prediction of cognitive decline in 724 community-dwelling WHICAP study participants

		B-SIT 0-10 impaired, 11-12 intact BOMC ≥ 6 impaired, 0-5 intact		B-SIT 0-8 impaired, 9-12 intact BOMC ≥ 7 impaired, 0-6 intact	
		Cognitive decline		Cognitive decline	
		No	Yes	No	Yes
Age quartile (years)	Measure impaired/intact	N (%)	n (%)	N (%)	n (%)
All	BOMC impaired	15 (83.3)	3 (16.7)	27 (81.8)	6 (18.2)
	B-SIT only	365 (79.0)	97 (21.0)	221 (75.7)	71 (24.3)
	Both Impaired	92 (71.3)	37 (28.7)	46 (66.7)	23 (33.3)
	Both Intact	105 (91.3)	10 (8.7)	283 (85.8)	47 (14.2)
	All	577 (79.7)	147 (20.3)	577 (79.7)	147 (20.3)
70–75	BOMC impaired	4 (100.0)	0 (0)	4 (100.0)	0 (0.0)
	B-SIT impaired	112 (88.2)	15 (11.8)	54 (85.7)	9 (14.3)
	Both impaired	8 (50.0)	8 (50.0)	4 (40.0)	6 (60.0)
	Both intact	35 (94.6)	2 (5.4)	97 (90.7)	10 (9.4)
	All	159 (86.4)	25 (13.6)	159 (86.4)	25 (13.6)
76–80	BOMC impaired	5 (83.3)	1 (16.7)	7 (77.8)	2 (22.2)
	B-SIT impaired	100 (80.0)	25 (20.0)	55 (73.3)	20 (26.7)
	Both impaired	26 (83.9)	5 (16.1)	16 (94.1)	1 (5.9)
	Both intact	38 (95.0)	2 (5.0)	91 (90.1)	10 (9.9)
	All	169 (83.7)	33 (16.3)	169 (83.7)	33 (16.3)
81–83	BOMC impaired	3 (100.0)	0(0.0)	7 (87.5)	1 (12.5)
	B-SIT impaired	60 (69.0)	27 (31.0)	44 (68.8)	20 (31.3)
	Both impaired	31 (77.5)	9 (22.5)	16 (72.7)	6 (27.3)
	Both intact	17 (85.0)	3 (15.0)	44 (78.6)	12 (21.4)
	All	111 (74.0)	39 (26.0)	111 (74.0)	39 (26.0)
84–101	BOMC impaired	3 (60.0)	2 (40.0)	9 (75.0)	3 (25.0)
	B-SIT impaired	93 (75.6)	30 (24.4)	68 (75.6)	22 (24.4)
	Both impaired	27 (64.3)	15 (35.7)	10 (50.0)	10 (50.0)
	Both intact	15 (83.3)	3 (16.7)	51 (77.3)	15 (22.7)
	All	138 (73.4)	50 (26.6)	138 (73.4)	50 (26.6)

Abbreviations: B-SIT, Brief Smell Identification Test, range 0–12, higher scores indicate better odor identification test performance, 0-10 impaired, 11-12 intact; BOMC, Blessed Orientation Memory Concentration Test, range 0–28, higher scores indicate worse cognitive performance, ≥ 6 impaired, 0-5 intact.

Other biomarkers have been studied in relation to olfaction. In a cross-sectional study, impaired odor identification was associated with increased CSF t-tau and p-tau$_{181}$ to A$\beta_{1\text{-}42}$ ratio, which is the CSF signature of AD brain pathology [37]. In another cross-sectional study, cognitively normal older adults with elevated brain amyloid on positron emission tomography (PET) and thinner entorhinal cortices on magnetic resonance imaging had lower odor identification test scores [38]. We have reported that both Pittsburgh Compound B PET amyloid abnormalities and lower UPSIT scores predicted cognitive decline longitudinally in a clinical MCI sample with independent effects for the two measures in this prediction [39]. In that study, high UPSIT scores were associated with negative amyloid PET scans, supporting the notion that intact odor identification ability may obviate the need for further workup.

We show here that normative performance on a brief cognitive test (BOMC) is not, by itself, sufficiently accurate to predict diagnostic outcome, and this finding is consistent with evidence that the MMSE or MoCA by itself does not have high predictive accuracy, but this can be improved by in-depth neuropsychological testing when available [4,34,35,40,41]. Our findings suggest that if an individual shows lack of impairment on both a global cognitive and brief odor identification test, the likelihood of transition to dementia is very low and further investigation may not be needed. Identification of this profile may provide a screening tool to exclude patients in treatment trials of cognitively impaired or at-risk patients, or prevention trials in cognitively intact individuals, while avoiding the extra burden and expense of brain imaging or CSF procedures. Blood-based biomarkers are in development, and may represent another avenue for screening purposes [42].

There were limitations to this study. Participants who were not followed up were more likely to be male, have lower education, and have lower olfaction and cognition scores. Odor identification testing may not give accurate results in the presence of significant nasal disease including active upper respiratory infection, and currently active smokers. Odor identification deficits can occur in individuals with several subtypes of dementia, including AD, Lewy body dementia, and possibly vascular dementia, as well as Parkinson's disease [43–45]. Odor identification test performance declines with age in the general population, particularly after the 7th decade of life, and women score

3-5% better than men on average [36]. Age-adjusted norms are available with the B-SIT test, which has been cross-culturally validated [17]. Age-related changes also occur with other markers of MCI and AD dementia: cognitive test performance, indices of magnetic resonance imaging–defined brain atrophy, FDG and amyloid PET abnormalities, as well as a decrease in amyloid $\beta_{1\text{-}42}$ levels with increased tau and phospho tau protein levels in CSF [46,47]. For the B-SIT by itself, predictive accuracy for cognitive decline was moderate in this community cohort, and it needs to be supplemented with neuropsychological testing if used for diagnostic purposes. The BOMC is no longer widely used, but it is a brief global cognitive test that is very similar to the MMSE and MoCA that are used in primary care and other settings where time is limited, and it is likely that similar results would have been obtained with the MMSE or MoCA [40,41].

The cutoff scores for B-SIT chosen for this study were based on normative performance on this test; the cutoffs for the BOMC were also based on normative performance but the published data on this instrument are more limited [8,9,18]. The findings from this community cohort need to be examined in clinical settings where patients present with cognitive complaints. Brief cognitive tests need to be compared with brief odor identification tests in large primary care samples to determine their comparative and added utility for both diagnosis and estimation of prognosis for cognitive decline and dementia in older adults.

RESEARCH IN CONTEXT

1 Systematic review: Prior research consistently demonstrates that odor identification impairment occurs in dementia and predicts the transition from mild cognitive impairment to dementia, primarily Alzheimer's disease, but whether intact performance on both brief cognitive and odor identification tests is associated with lack of transition to dementia is not known.

2 Interpretation: Our findings provide empirical evidence that intact performance on both the Brief Smell Identification Test and Blessed Orientation Memory Concentration Test predicts a low likelihood of future dementia.

3 Future directions: The article proposes a framework for the generation of new hypotheses and the conduct of additional studies on the application of our findings from this community cohort to clinical settings, particularly primary care, and their potential utility in the decision to include or exclude cognitively impaired or at-risk patients in prevention and treatment trials of cognitive enhancers.

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