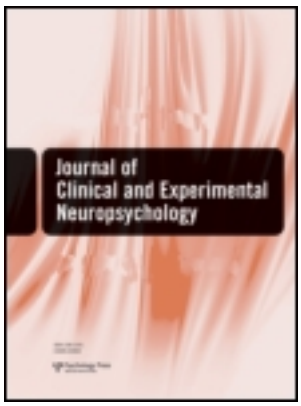

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Odor identification and cognitive function in the Beaver Dam Offspring Study

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Olfactory impairment is associated with cognitive impairment in older adults but less is known about the association of olfactory impairment and cognitive function in middle-aged adults. The association between olfactory impairment and cognitive function tests of attention, processing speed, and executive and psychomotor function was explored in 2837 participants (21–84 years; mean age 49 years) in the Beaver Dam Offspring Study. Among middle-aged participants (aged 35–64 years), those with impairment on an odor identification test took significantly longer to complete the Trail Making Test (TMT-A and TMT-B) and the Grooved Peg Board (GPB) test, than those without olfactory impairment in regression models adjusted for multiple factors. Similar results were found for the TMT-A and TMT-B, but not the GPB, in the whole cohort. Olfactory impairment was associated with poorer performance on cognitive function tests in a primarily middle-aged cohort.

Keywords: Olfaction; Odor identification; Cognitive function; Executive function; Epidemiology.

Proficiency in odor identification has been found to decrease with age, and among those over 80 years of age the prevalence of olfactory impairment is high (Doty et al., 1984; Murphy et al., 2002; Schubert et al., 2012; Schubert, Cruickshanks, Klein, Klein, & Nondahl, 2011). Olfactory impairment is common in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD; Mesholam, Moberg, Mahr, & Doty, 1998; Rahayel, Frasnelli, & Joubert, 2012; Serby, Larson, & Kalkstein, 1991), and studies have found that declines in olfactory function precede the onset of cognitive impairment or the clinical signs of AD or PD (Devanand et al., 2000; Ponsen et al., 2004; Ross et al., 2008). A population-based study of older adults found that those with impairment on an odor identification test had a threefold higher risk of developing cognitive impairment five years later (Schubert et al., 2008). Other longitudinal studies have found that lower scores or impairment on odor identification tests were associated with the incidence of mild cognitive impairment or cognitive decline in older adults (Graves et al., 1999; Olofsson et al., 2009; Royall, Chiodo, Polk, & Jaramillo, 2002; Swan & Carmelli, 2002; Wilson, Arnold, Tang, & Bennett, 2006; Wilson, Schneider, et al., 2007).

Less is known about the association between olfaction and cognitive function in younger (i.e., middle-aged) adults. As more has been learned

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about aging and the long period of subclinical changes that may precede some age-related conditions, it has become clear that factors in midlife may be important markers for health later in life. Evaluating the association between olfactory impairment and cognitive function in middle age has the potential to improve our understanding of the associations seen with cognitive impairment at older ages.

Odor identification may be influenced by cognitive function as it requires not only a patent pathway for sensing an odor, but also higher order cognitive abilities to identify and name an odor (Hedner, Larsson, Arnold, Zucco, & Hummel, 2010). A high genetic correlation between odor identification and cognitive function has also been reported (Doty, Petersen, Mensah, & Christensen, 2011), and the presence of the apolipoprotein E epsilon 4 (ApoE ε4) gene has been reported to modify the association between odor identification and cognitive decline in older adults (Olofsson et al., 2009). Several aspects of cognitive function have been reported to be associated with successful performance on odor identification tests, including verbal ability, semantic and episodic memory, processing speed, and executive function, though the results have not been consistent across studies (Finkel, Reynolds, Larsson, Gatz, & Pedersen, 2011; Hedner et al., 2010; Larsson, Nilsson, Olofsson, & Nordin, 2004; Larsson, Oberg, & Backman, 2005; Wehling, Nordin, Espeseth, Reinvang, & Lundervold, 2010). If the cognitive domains of processing speed and executive function contribute to odor identification performance, then impairment in odor identification may be indicative of poorer cognitive function in these domains.

The aim of the present study was to determine whether there is an association between olfactory impairment and performance on cognitive function tests of attention, executive and psychomotor function, and processing speed in the Beaver Dam Offspring Study. This large cohort has the advantage of including a substantial number of middle-aged adults and extensive covariate data that allow for adjustment of other health, behavioral, and socioeconomic factors that may be common to both olfaction and cognitive function.

METHOD

The Beaver Dam Offspring Study (BOSS) is a study of sensory disorders and aging in the adult children (aged 21–84 years) of participants in the population-based Epidemiology of Hearing Loss Study (1993–present; Cruickshanks et al., 2003; Cruickshanks et al., 1998; Nash et al., 2011). The BOSS examinations were conducted in 2005–2008 and included measures of hearing, vision, olfaction, cognitive function, and cardiovascular health and an extensive health and lifestyle questionnaire. Study examiners were trained and certified in the data collection protocols. These analyses include 2837 participants with olfactory and cognitive function test data. Written informed consent was obtained from participants prior to examination, and the study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin.

Cognitive function measures

The tests of cognitive function included the Trail Making Test Part A (TMT-A) and Part B (TMT-B), and Grooved Peg Board (GPB).The TMT is a test of attention, processing speed, and executive function (Arbuthnott & Frank, 2000; Reitan, 1992; Strauss, Sherman, & Spreen, 2006). The GPB (Lafayette Instruments, Lafayette, IN, USA) is a test of attention, executive and psychomotor function, and manual dexterity (Ashendorf, Vanderslice-Barr, & McCaffrey, 2009; Strauss et al., 2006). For these three tests (TMT-A, TMT-B, GPB), participants used their dominant hand, and the score was the number of seconds (s) it took to successfully complete each test with a longer time indicating poorer performance. Participants were given five minutes (300 s) to complete each test, and, if unable to complete the test in the allotted time, they were assigned a score of 301 s.

Measure of olfaction

The San Diego Odor Identification Test (SDOIT) was used to measure olfaction (Murphy et al., 2002; Raynor et al., 2010; Schubert et al., 2012). The SDOIT is a standardized odor identification test with a test–retest agreement of 96%; it has been shown to be comparable to the Brief Smell Identification Test (B-SIT) for classifying olfactory impairment ($\kappa = .81$, 95% confidence interval [0.63, 0.99]; Krantz et al., 2009) and has been used previously in a large epidemiological study (Murphy et al., 2002; Schubert et al., 2011). The SDOIT score is the number of odors correctly identified after two trials. Olfactory impairment was defined as identifying fewer than six of the eight odorants correctly (Murphy et al., 2002; Schubert et al., 2012).

Additional covariates

There are many factors (e.g., demographic, health, behavioral) that have been associated with olfaction and cognition in the literature that have the potential to confound or modify the association between olfactory impairment and cognitive function scores (Bendlin et al., 2010; Murphy et al., 2002; Schubert et al., 2008; Schubert et al., 2011). Covariates available in the BOSS were tested in analyses to determine their effect on the association between olfactory impairment and cognitive function test scores. Pertinent covariates obtained by interview included years of education, household income, occupation, smoking history, exercise, alcohol consumption, history of Alzheimer's disease, Parkinson's disease, head injury (skull fracture, broken nose, concussion), epilepsy, cardiovascular disease, nasal problems (nasal polyps, deviated septum), allergies, recent sinus problems, upper respiratory infection or stuffy nose on day of examination, and dominant hand. Participants completed the Centers for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977). Height and weight (for body mass index, BMI; kg/m^2), seated blood pressure, hearing level, and visual acuity were measured at examination (Nash et al., 2011). A carotid artery ultrasound scan was done for measurement of intima media thickness (IMT) and plaque assessment (Nash et al., 2011). The Mini-Mental State Exam (MMSE) was administered to participants who were 50 years of age or older at examination (Folstein, Folstein, & McHugh, 1975). Cognitive impairment was defined as a MMSE score less than 24 (out of 30) or a diagnosis of dementia. Blood samples were collected and tested for hemoglobin A1C, and participants were classified as having diabetes mellitus if they reported a doctor diagnosis or had a measured hemoglobin A1C $\geq$ 6.5%. Samples on participants 45 years and older were also genotyped for ApoE ε4 carrier status, and those with at least one allele were classified as an ApoE ε4 carrier.

Statistical analyses

Statistical analyses were conducted using SAS (SAS System Inc., Cary, NC, USA). Cognitive function test scores by olfactory status were analyzed using the Student's t test. Ordinary least squares linear regression models were used to evaluate the association between olfactory impairment and cognitive function score. To begin, individual base models including age, sex, education, and olfactory impairment were run with TMT-A, TMT-B, and GPB as the outcome. Covariates that were potential confounders or effect modifiers of the association between olfactory impairment and each cognitive function test were added individually to each base model. To ensure that confounders were adequately considered, covariates with a $p < .20$ or that changed the olfactory impairment estimate by 10% (defined a priori) when added to the base models were investigated further. Only covariates that were determined to be confounders or effect modifiers of the association between olfactory impairment and cognitive function score were retained in the final multivariable model for each cognitive function test. The base and multivariable models were repeated restricting the analyses to participants aged 35–64 years. To evaluate the relationship between SDOIT score and cognitive function, the multivariable models were repeated using the SDOIT score as a continuous variable. In addition, generalized estimating equation models were used to adjust for familial correlations.

To ensure that associations were not only due to participants with cognitive impairment or who were unable to complete the tests in the allotted time, sensitivity analyses were done on the final multivariable models for each cognitive function test excluding those participants who were unable to complete the TMT-A, TMT-B, or GPB in the allotted time (score = 301 s) and those with cognitive impairment (MMSE score <24). To address the effects of including participants who may have had a severe head injury on the association of olfactory impairment with cognitive test score, additional sensitivity analyses were done excluding those reporting a loss of consciousness of five minutes or more from a head injury. A principal component analysis (PCA) was performed for the TMT-A, TMT-B, and GPB to reduce the number of cognitive function measures to create a summary score representing the variance in cognitive function measured by the three tests. The association between olfactory impairment and this measure of cognitive function was assessed for the whole cohort and among those aged 35–64 years.

RESULTS

The descriptive characteristics of the study cohort are shown in Table 1. Participants were 21–84 years (mean age 49 years), and 88% were between the ages of 35 and 64 years. One hundred and nine (3.8%) participants had olfactory impairment, more than one third had 16 or more years of education, and more than half reported a yearly household

TABLE 1
Characteristics of participants with olfactory and cognitive function data

Characteristic	*n (%)*
N	2837
Women	1545 (54.5)
Men	1292 (45.5)
Age group (years)	
21–34	169 (6.0)
35–44	827 (29.2)
45–54	1057 (37.3)
55–64	604 (21.3)
65–84	180 (6.3)
Education, years completed	
<12	72 (2.6)
12	834 (29.6)
13–15	958 (34.0)
≥16	958 (34.0)
Household income ≥$50,000/year	1843 (67.0)
Smoking history	
Never	1523 (53.7)
Past, stopped ≥5 years	687 (24.3)
Past, stopped <5 years	114 (4.0)
Current smoker	508 (17.9)
Dominant hand right	2504 (88.3)
Olfactory impairment	109 (3.8)
Exercise at least once/week	1720 (60.7)
BMI ≥30 kg/m^2	1254 (44.7)
Depressive symptoms (CES-D ≥16)	405 (14.5)
ApoE ε4 carrier[a]	171 (10.7)
History of:	
Nasal polyps/deviated septum	299 (10.6)
Recent nasal congestion/sinus problems	1022 (36.0)
Head injury	824 (29.0)
Cardiovascular disease	91 (3.2)
Diabetes mellitus	174 (6.1)
Statin use	429 (15.1)

Notes. MMSE = Mini-Mental State Exam; BMI = body mass index; CES-D = Center for Epidemiological Studies Depression Scale; ApoE ε4 = apolipoprotein E epsilon 4 allele.
[a]Only available on 1594 participants over 45 years.

income of $50,000 or more. Those with olfactory impairment took significantly longer to perform the TMT-A, TMT-B, and GPB than those without impairment ($p < .0001$, Table 2).

In ordinary linear regression base models adjusted for age, sex, and education level, those with olfactory impairment took approximately 7 s longer to complete the TMT-A ($\beta = 6.9$, 95% CI [5.1, 8.7], $p < .0001$), 15 s longer to complete the TMT-B ($\beta = 14.7$, 95% CI [9.0, 20.4], $p < .0001$), and 4 s longer ($\beta = 4.4$, 95% CI [1.2, 7.6], $p = .007$) to complete the GPB than those without olfactory impairment (Table 3). In the final multivariable model, the association between olfactory impairment and performance on the TMT-A and TMT-B remained significant, though the olfactory impairment estimated coefficient for TMT-B was slightly attenuated ($\beta = 12.5$, 95% CI [6.9, 18.0], $p < .0001$) after further adjusting for income. While there were many covariates that were independent predictors of performance on TMT-A and TMT-B, only income had a modest effect on the olfactory impairment estimate and was retained in the fully adjusted models for TMT-A and TMT-B. The estimated coefficient for olfactory impairment was slightly attenuated and no longer statistically significant ($\beta = 3.0$, 95% CI [–0.1, 6.2], $p = .06$) for the GPB when income, mean IMT, BMI, and diabetes were included in the model (Table 3). ApoE ε4 carrier status, smoking history, history of head injury, depressive symptoms, hearing impairment, and vision impairment did not modify the association between olfactory impairment and TMT-A, TMT-B, or GPB and were not retained in the final models. There were too few cases of AD or PD in this cohort to support analyses with those variables. The multivariable models for TMT and GPB were repeated adjusting for familial correlation, and the results were similar (data not shown).

The SDOIT score was also significantly associated with each of the cognitive function tests. Each one unit decrease in SDOIT score was associated with a 1 s increase in TMT-A ($\beta = 1.3$, 95% CI [1.0, 1.6], $p < .0001$) and GPB ($\beta = 1.2$, 95% CI [0.7, 1.8], $p < .0001$) completion times and a 3 s increase in TMT-B ($\beta = 3.3$, 95% CI [2.3, 4.3], $p < .0001$) completion time in the multivariable models in the whole cohort.

TABLE 2
Cognitive function test scores by olfactory impairment

Olfaction status	*TMT-A (s) Mean (SD) (range)*	*TMT-B (s) Mean (SD) (range)*	*GPB (s) Mean (SD) (range)*
n	2837	2832	2832
All	28.0 (10.4) (9–151)	67.6 (32.7) (23–301)	72.7 (18.3) (35–301)
Not impaired	27.5 (9.4) (9–111)	66.5 (30.7) (23–301)	72.2 (17.8) (35–301)
Impaired	39.5 (21.1) (14–151)*	95.4 (59.5) (30–301)*	85.1 (24.8) (54–197)*

Notes. TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; GPB = Grooved Peg Board.
*$p < .0001$ for difference between impaired and not impaired.

TABLE 3
Association between olfactory impairment and cognitive function test score

	TMT-A					*TMT-B*					*GPB*				
Model	*n*	β^a	*SE*	*95% CI (p)*	R^2	*n*	β^a	*SE*	*95% CI (p)*	R^2	*n*	β^a	*SE*	*95% CI (p)*	R^2
All															
Base model	2822	6.9	0.92	[5.1, 8.7] (<.0001)	.20	2818	14.7	2.93	[9.0, 20.4] (<.0001)	.22	2818	4.4	1.63	[1.2, 7.6] (.007)	.23
Multivariable model	2735	6.4	0.92	[4.6, 8.2] (<.0001)	.21	2731	12.5	2.84	[6.9, 18.0] (<.0001)	.23	2663	3.0	1.62	[–0.1, 6.2] (.06)	.27
35–64 years															
Base model	2473	6.9	1.05	[4.9, 9.0] (<.0001)	.17	2470	15.0	3.32	[8.5, 21.5] (<.0001)	.19	2469	5.4	1.75	[1.9, 8.8] (.002)	.19
Multivariable model	2403	6.5	1.05	[4.5, 8.6] (<.0001)	.18	2400	12.2	3.21	[5.9, 18.5] (.0002)	.20	2345	4.3	1.73	[0.9, 7.7] (.01)	.24

Notes. TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; GPB = Grooved Peg Board; CI = confidence interval. Base models include: age, sex, education; Multivariable models include: TMT-A and TMT-B—age, sex, education, income; GPB—age, sex, education, income, mean intima media thickness (IMT), body mass index (BMI), diabetes.
[a]Estimated β coefficient for olfactory impairment.

The base and multivariable models for TMT-A, TMT-B, and GPB were repeated restricting the analyses to participants 35–64 years. The estimated coefficients for olfactory impairment were similar to those in the whole cohort for TMT-A and TMT-B in the base and multivariable models. However, unlike the results in the full cohort, the olfactory impairment estimated coefficient remained statistically significant ($\beta = 4.3$, 95% CI [0.9, 7.7], $p = .01$) in the multivariable model for GPB among those 35–64 years (Table 3). SDOIT score also was significantly associated with TMT-A ($\beta = 1.3$, 95% CI [0.9, 1.6], $p < .0001$), TMT-B ($\beta = 3.2$, 95% CI [2.1, 4.2], $p < .0001$, and GPB ($\beta = 1.4$, 95% CI [0.8, 2.0], $p < .0001$) in the multivariable models. The lower the SDOIT score, the longer the time to complete the task.

In sensitivity analyses excluding participants ($n = 21$) with cognitive impairment or who were unable to complete the cognitive function tests in the allotted time, the results were similar for the whole cohort and the middle-aged group although the effect sizes were slightly attenuated. Multivariable sensitivity analyses excluding participants with a history of loss of consciousness due to a head injury ($n = 138 + 62$ missing) also showed small significant associations between olfactory impairment and TMT-A ($\beta = 4.5$, 95% CI [2.6, 6.5], $p < .0001$) and TMT-B ($\beta = 8.6$, 95% CI [2.7, 14.6], $p = .005$) but not GPB in the whole cohort, although effects were slightly attenuated. Among the middle-aged group, results were similar for TMT-A ($\beta = 3.9$, 95% CI [1.7, 6.2], $p = .0006$) but the association was no longer statistically significant for TMT-B ($\beta = 6.7$, 95% CI [−0.1, 13.6], $p = .05$) or GPB.

PCA was used to compute a summary score based on the three cognitive function tests. The PCA yielded one component with an eigenvalue >1 which accounted for 67% of the variance; this component was retained as the summary score. The TMT-A, TMT-B, and GPB coefficients from the first principal component's eigenvector were 0.60, 0.59, and 0.54, respectively. In a model adjusted for age, sex, education, income, mean IMT, BMI, and diabetes, olfactory impairment was associated with the summary score (estimated β coefficient = 0.72, $SE = 0.12$, $p < .0001$). PCA results were similar among those 35–64 years (estimated β coefficient = 0.78, $SE = 0.14$, $p < .0001$). These associations remained significant in multivariable sensitivity analyses excluding participants with a severe head injury.

DISCUSSION

In this large study composed primarily of middle-aged adults, olfactory impairment was associated with poorer performance on three tests of cognitive function and the total variance captured by the summary score. These differences were small, an average of 4–12 s, but statistically significant in this well-educated, high-functioning cohort with a mean age of 49 years. Despite the fact these differences were small, they remained significant after adjustment for additional covariates and in sensitivity analyses excluding those with cognitive impairment or unable to complete the tests. Furthermore, the findings were similar after restricting the analyses to those 35–64 years. These results suggest that impairment in odor identification in midlife is

associated with slightly poorer performance on cognitive function tests of attention, processing speed, and executive function.

The findings of the present study are consistent with previous studies that have reported that processing speed is associated with odor identification (Dulay, Gesteland, Shear, Ritchey, & Frank, 2008; Finkel et al., 2011; Larsson et al., 2004; Larsson et al., 2005) though results specific to the TMT-A have been inconsistent in previous studies (Dulay et al., 2008; Larsson et al., 2005; Wehling et al., 2010). One study found no correlation between the TMT-A and performance on a cued odor identification test (Wehling et al., 2010), and another study found that TMT-A was significantly correlated with odor identification but was not significant in regression models (Larsson et al., 2005). However, both studies only included healthy participants who were not hyposmic or anosmic. Another study that did not restrict participation with regards to olfactory function found a significant correlation between TMT-A and odor identification and when combined into a cognitive speed latent construct with two other measures of cognitive speed had a direct effect on odor identification performance (Dulay et al., 2008). In the current study, the effect size for olfactory impairment and the TMT-A was only a few seconds but it was robust and remained significant in multivariable and sensitivity analyses.

Olfactory impairment was associated with poorer performance on the executive function measures of TMT-B and GPB in this study. Previous studies on the cognitive correlates of odor identification performance have been inconsistent with regards to executive function. While one study found executive function to be a reliable predictor of odor identification performance (Hedner et al., 2010), another found executive function to be correlated but not significant in regression analyses (Westervelt, Ruffolo, & Tremont, 2005), and other studies found no association (Larsson et al., 2004; Larsson et al., 2005; Wehling et al., 2010). Although two of these negative studies also used the TMT-B as a measure of executive function, the smaller size ($n < 150$ each), older mean age (mean age 75 years and 62 years, respectively), and exclusion criteria of these studies may have limited their ability to find an association (Larsson et al., 2005; Wehling et al., 2010).

Although usually employed as a test of psychomotor function, the GPB also measures attention, speed, and executive function (Ashendorf et al., 2009; Strauss et al., 2006). We found that odor identification impairment was significantly associated with GPB score in middle-aged adults though the effect size of four seconds longer is small in comparison to the average time to complete the test (72 s) for the cohort as a whole. This finding is consistent with Westervelt et al. (2005) who reported a modest correlation ($r = .37$, $p < .01$) between performance on the GPB and that on an odor identification test in a small study of older adults with a mean age of 70 years. In a study of PD evaluating clinical motor and nonmotor tests, odor identification (86.7%) had the best diagnostic accuracy for PD followed by the GPB (80.0%), suggesting that these two tests may be affected similarly by pathological processes (Bonen, Studenski, Constantine, & Moore, 2008). The association between olfactory impairment and the GPB was more robust among those 35–64 years than in the whole cohort, possibly indicating that small differences in function were more detectable in this age range. The olfactory impairment association with GPB was not significant in the sensitivity analyses excluding participants with a history of a loss of consciousness due to a head injury. It is possible the significant association seen with GPB in this study was unique to participants with this head injury history, which would suggest that either odor identification impairment and lower GPB performance may share a common etiology or the exclusion of these data from the analyses limited our power to detect an association.

ApoE ε4 carrier status did not affect the relationship between olfactory impairment and cognitive function. Our ability to detect an association with ApoE ε4 may have been limited by the younger age of the cohort and the low percentage of participants with an ApoE ε4 allele, though findings in other studies have been mixed (Doty et al., 2011; Finkel et al., 2011; Graves et al., 1999; Olofsson et al., 2009).

The differences in cognitive function test performance by olfactory impairment status found in the current study could be due to (a) the common innate cognitive abilities required to do both the odor identification and cognitive function tests (as discussed), or (b) a reflection of aging or pathological changes in the brain that affect both olfactory and cognitive processes, or a combination of the two. Pathological changes that occur in the brain with aging or disease are reported to start early in areas important for olfactory processing (Braak & Braak, 1997a; Kovacs, Cairns, & Lantos, 2001; Wilson, Arnold, Schneider, Tang, & Bennett, 2007). There is evidence that AD-type pathological changes, amyloid deposits and neurofibrillary tangles, may be present as early as the late 20s or early 30s in a small proportion of individuals (Braak & Braak, 1997b). In older adults, the density and distribution of neurofibrillary tangles in

the entorhinal cortex and hippocampus on autopsy was related to performance on an odor identification test proximal to death (Wilson, Arnold, et al., 2007). However, it is not known whether, or how, these types of changes may affect olfactory or cognitive function in younger and middle-aged adults. Differences seen in the current study were small (average of a few seconds).

The limitations of this study include the cross-sectional design, which prohibits determining causality or direction of the associations seen and the lack of an olfactory threshold test. Whereas odor identification may be more closely linked to cognitive function, a threshold test would provide additional information on olfactory function that may allow for more precise categorization of olfactory status (Lötsch, Reichmann, & Hummel, 2008). In addition, only three cognitive function tests that measured similar domains were administered to the whole cohort, and a larger battery of tests that included verbal ability and memory measures would allow for a more comprehensive assessment of the association between olfactory impairment and cognitive function. The strengths of this study include the large, well-defined cohort and the use of standardized measures of odor identification and cognitive function that were administered by highly trained examiners. In addition, detailed demographic, health, and behavioral data were available.

In conclusion, olfactory impairment on an odor identification test was associated with poorer performance on cognitive function tests of attention, speed, and executive and psychomotor function in a primarily middle-aged cohort. Similar associations with olfactory impairment have been reported previously in older adults and among those at risk for cognitive impairment but the present findings are from a younger cohort with an overall low risk of cognitive impairment, which adds to the evidence that olfactory impairment may be an early indicator of cognitive dysfunction. The differences found here were small, an average of 4–12 s, and are unlikely to affect day-to-day functioning in this middle-aged cohort. However, olfactory impairment may be a marker of increased risk of greater decline in cognitive function with aging and be an important indicator of cognitive impairment later in life. Additional research is needed to confirm these findings, and longitudinal data are needed to determine whether olfactory impairment predicts decline in cognitive function in middle-aged adults.

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REFERENCES

Arbuthnott, K., & Frank, J. (2000). Trail Making Test, Part B as a measure of executive control: Validation using a set-switching paradigm. *Journal of Clinical and Experimental Neuropsychology*, *22*, 518–528.

Ashendorf, L., Vanderslice-Barr, J. L., & McCaffrey, R. J. (2009). Motor tests and cognition in healthy older adults. *Applied Neuropsychology*, *16*, 171–176.

Bendlin, B. B., Carlsson, C. M., Gleason, C. E., Johnson, S. C., Sodhi, A., Gallagher, C. L., . . . Asthana, S. (2010). Midlife predictors of Alzheimer's disease. *Maturitas*, *65*, 131–137.

Bonen, N. I., Studenski, S. A., Constantine, G. M., & Moore, R. Y. (2008). Diagnostic performance of clinical motor and non-motor tests of Parkinson disease: A matched case-control study. *European Journal of Neurology*, *15*, 685–691.

Braak, H., & Braak, E. (1997a). Diagnostic criteria for neuropathologic assessment of Alzheimer's disease. *Neurobiology of Aging*, *18*, S85–S88.

Braak, H., & Braak, E. (1997b). Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiology of Aging*, *18*, 351–357.

Cruickshanks, K. J., Tweed, T. S., Wiley, T. L., Klein, B. E., Klein, R., Chappell, R., . . . Dalton, D. S. (2003). The 5-year incidence and progression of hearing loss. The Epidemiology of Hearing Loss Study. *Archives of Otolaryngology–Head and Neck Surgery*, *129*, 1041–1046.

Cruickshanks, K. J., Wiley, T. L., Tweed, T. S., Klein, B. E., Klein, R., Mares-Perlman, J. A., & Nondahl, D. M. (1998). Prevalence of hearing loss in older adults in Beaver Dam, Wisconsin. The Epidemiology of Hearing Loss Study. *American Journal of Epidemiology*, *148*, 879–886.

Devanand, D. P., Michaels-Marston, K. S., Liu, X., Pelton, G. H., Padilla, M., Marder, K., . . . Mayeux, R. (2000). Olfactory deficits in patients with mild cognitive impairment predicts Alzheimer's disease at follow-up. *American Journal of Psychiatry*, *157*, 1399–1405.

Doty, R. L., Petersen, I., Mensah, N., & Christensen, K. (2011). Genetic and environmental influences on odor identification ability in the very old. *Psychology and Aging*, *26*, 864–871.

Doty, R. L., Shaman, P., Applebaum, S. L., Giberson, R., Sikorski, L., & Rosenberg, L. (1984). Smell identification ability: Changes with age. *Science*, *226*, 1441–1443.

Dulay, M., Gesteland, R. C., Shear, P. K., Ritchey, P. N., & Frank, R. A. (2008). Assessment of the influence of cognition and cognitive processing speed on three tests of olfaction. *Journal of Clinical and Experimental Neuropsychology*, *30*, 327–337.

Finkel, D., Reynolds, C. A., Larsson, M., Gatz, M., & Pedersen, N. L. (2011). Both odor identification and ApoE-ε4 contribute to normative cognitive aging. *Psychology and Aging*, *26*, 872–883.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189–198.

Graves, A. B., Bowen, J. D., Rajaram, L., McCormick, W. C., McCurry, S. M., Schellenberg, G. D., & Larson, E. B. (1999). Impaired olfaction as a marker for

cognitive decline: Interaction with apolipoprotein E epsilon 4 status. *Neurology*, *53*, 1480–1487.

Hedner, M., Larsson, M., Arnold, N., Zucco, G. M., & Hummel, T. (2010). Cognitive factors in odor detection, odor discrimination, and odor identification tasks. *Journal of Clinical and Experimental Neuropsychology*, *32*, 1062–1067.

Kovacs, T., Cairns, N. J., & Lantos, P. L. (2001). Olfactory centres in Alzheimer's disease: Olfactory bulb is involved in early Braak's stages. *Neuroreport*, *12*, 285–288.

Krantz, E. M., Schubert, C. R., Dalton, D. S., Zhong, W., Huang, G. H., Klein, B. E., . . . Cruickshanks, K. J. (2009). Test–retest reliability of the San Diego Odor Identification Test and comparison with the Brief Smell Identification Test. *Chemical Senses*, *34*, 435–440.

Larsson, M., Nilsson, L. G., Olofsson, J. K., & Nordin, S. (2004). Demographic and cognitive predictors of cued odor identification: Evidence from a population-based study. *Chemical Senses*, *29*, 547–554.

Larsson, M., Oberg, C., & Backman, L. (2005). Odor identification in old age: Demographic, sensory and cognitive correlates. *Aging, Neuropsychology, and Cognition*, *12*, 231–244.

Lötsch, J., Reichmann, H., & Hummel, T. (2008). Different odor tests contribute differently to the evaluation of olfactory loss. *Chemical Senses*, *33*, 17–21.

Mesholam, R. I., Moberg, P. J., Mahr, R. N., & Doty, R. L. (1998). Olfaction in neurodegenerative disease. A meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. *Archives of Neurology*, *55*, 84–90.

Murphy, C., Schubert, C. R., Cruickshanks, K. J., Klein, B. E. K., Klein, R., & Nondahl, D. M. (2002). Prevalence of olfactory impairment in older adults. *Journal of the American Medical Association*, *288*, 2307–2312.

Nash, S. D., Cruickshanks, K. J., Klein, R., Klein, B. E., Nieto, F. J., Huang, G. H., . . . Tweed, T. S. (2011). The prevalence of hearing impairment and associated risk factors: The Beaver Dam Offspring Study. *Archives of Otolaryngology–Head & Neck Surgery*, *137*, 432–439.

Olofsson, J. K., Ronnlund, M., Nordin, S., Nyberg, L., Nilsson, L. G., & Larsson, M. (2009). Odor identification deficit as a predictor of five-year global cognitive change: Interactive effects with age and ApoE-ε4. *Behavioral Genetics*, *39*, 496–503.

Ponsen, M. M., Stoffers, D., Booij, J., van Eck-Smit, B. L., Wolters, E. C., & Berendse, H. W. (2004). Idiopathic hyposmia as a preclinical sign of Parkinson's disease. *Annals of Neurology*, *56*, 173–181.

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measures*, *1*, 385–401.

Rahayel, S., Frasnelli, J., & Joubert, S. (2012). The effect of Alzheimer's disease and Parkinson's disease on olfaction: A meta-analysis. *Behavioral Brain Research*, *231*, 60–74.

Raynor, L. A., Pankow, J. S., Cruickshanks, K. J., Schubert, C. R., Miller, M. B., Klein, R., & Huang, G. H. (2010). Familial aggregation of olfactory impairment and odor identification in older adults. *Laryngoscope*, *120*, 1614–1618.

Reitan, R. M. (1992). *Trail Making Test manual for administration and scoring*. Tucson, AZ: Reitan Neuropsychology Laboratory.

Ross, G. W., Petrovitch, H., Abbott, R. D., Tanner, C. M., Popper, J., Masaki, K., . . . White, L. R. (2008). Association of olfactory dysfunction with risk for future Parkinson's disease. *Annals of Neurology*, *63*, 167–173.

Royall, D. R., Chiodo, L. K., Polk, M., & Jaramillo, C. J. (2002). Severe dysosmia is specifically associated with Alzheimer-like memory deficits in non-demented elderly retirees. *Neuroepidemiology*, *21*, 68–73.

Schubert, C. R., Carmichael, L. L., Murphy, C., Klein, B. E. K., Klein, R., & Cruickshanks, K. J. (2008). Olfaction and the 5-year incidence of cognitive impairment in an epidemiological study of older adults. *Journal of the American Geriatrics Society*, *56*, 1517–1521.

Schubert, C. R., Cruickshanks, K. J., Fischer, M. E., Huang, G. H., Klein, B. E. K., Kleins, R., . . . Nondahl, D. M. (2012). Olfactory impairment in an adult population: The Beaver Dam Offspring Study. *Chemical Senses*, *37*, 325–334.

Schubert, C. R., Cruickshanks, K. J., Klein, B. E. K., Klein, R., & Nondahl, D. M. (2011). Olfactory impairment in older adults: Five-year incidence and risk factors. *Laryngoscope*, *121*, 873–878.

Serby, M., Larson, P., & Kalkstein, D. (1991). The nature and course of olfactory deficits in Alzheimer's disease. *American Journal of Psychiatry*, *148*, 357–360.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3rd ed.). New York, NY: Oxford University Press.

Swan, G. E., & Carmelli, D. (2002). Impaired olfaction predicts cognitive decline in nondemented older adults. *Neuroepidemiology*, *21*, 58–67.

Wehling, E. I., Nordin, S., Espeseth, T., Reinvang, I., & Lundervold, A. J. (2010). Familiarity, cued and free odor identification and their association with cognitive functioning in middle-aged and older adults. *Aging, Neuropsychology, and Cognition*, *17*, 205–219.

Westervelt, H. J., Ruffolo, J. S., & Tremont, G. (2005). Assessing olfaction in the neuropsychological exam: The relationship between odor identification and cognition in older adults. *Archives of Clinical Neuropsychology*, *20*, 761–769.

Wilson, R. S., Arnold, S. E., Schneider, J. A., Tang, Y., & Bennett, D. A. (2007). The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. *Journal of Neurology, Neurosurgery & Psychiatry*, *78*, 30–35.

Wilson, R. S., Arnold, S. E., Tang, Y., & Bennett, D. A. (2006). Odor identification and decline in different cognitive domains in old age. *Neuroepidemiology*, *26*, 61–67.

Wilson, R. S., Schneider, J. A., Arnold, S. E., Tang, Y., Boyle, P. A., & Bennett, D. A. (2007). Olfactory identification and incidence of mild cognitive impairment in older age. *Archives of General Psychiatry*, *64*, 802–808.