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RESEARCH ARTICLE

Odor identification and progression to dementia: The role of odor characteristics and set size

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Abstract

INTRODUCTION: We evaluated short versions of a 16-item odor identification (OID) test, with regard to their ability to identify individuals at high dementia risk.

METHODS: Participants from the population-based SNAC-K study ($n = 2418$) were followed across 12 years. We formed 13 abbreviated clusters based on the identifiability and perceptual characteristics of the Sniffin' Sticks Test (SST) items, and pre-existing test versions. Dementia hazard was estimated with Cox regressions.

RESULTS: Lower OID scores were associated with an increased dementia hazard across all odor clusters. Lower performance in the high identifiability cluster showed the strongest association with dementia (hazard ratio = 1.39, 95% confidence interval [1.28–1.51]). Moreover, the high-intensity odor cluster showed a stronger association with dementia than the low-intensity cluster ($P = 0.02$).

DISCUSSION: The findings suggest that the SST items differ with regard to their association with dementia and support using a reduced set size for clinical practice.

KEYWORDS
dementia, olfaction, perceptual characteristics, Sniffin' Sticks Test

Highlights

- Odor identification (OID) items differ in their association with future dementia.
- Reduced OID set sizes render hazard ratios comparable to larger set sizes.
- Identifiability and perceptual characteristics of odors should be considered when designing dementia screening instruments.

1 | INTRODUCTION

Olfactory impairment is a well-established early marker for dementia and Alzheimer's disease (AD).[1,2] This association is further substantiated by neurological findings showing that brain structures critical for olfactory functioning are selectively affected early in the disease process.[3,4]

In addition to the basic sensory acuity required for detecting a smell, odor identification (OID) puts demands on cognitive abilities.[5,6] This cognitive load is further exacerbated in free OID, in which odors are

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identified without verbal cues. The OID task is thus dependent on both intact peripheral olfactory structures and central brain regions used for odor interpretation and verbal labeling.

Olfactory decline is believed to occur at an early stage in dementia progression.[7,8] It was previously shown that poor OID performance predicts dementia development across 10 years,[9] and we have demonstrated that olfactory dysfunction is associated with incident dementia in the subsequent 12 years.[10]

To date, researchers have predominantly used standardized OID tests, for example, the 16-item Sniffin' Sticks Test (SST),[11] which were not initially designed for detecting dementia. There is a need to identify odors that best discriminate between individuals with high versus low risk of future dementia.[12,13]

Importantly, smaller set sizes, comprising fewer odor items, can increase clinical relevance as they reduce the test burden for the clinician and the patient. Abbreviated versions have been derived from the SST, such as the 12-item[14] and 5-item[15] tests. The 5-item test effectively predicted dementia over a 5-year follow-up period.[2] Although shorter tests may compromise reliability, this could be compensated for by the higher discriminative ability of the included odor items.

It is well established that the sense of smell declines with increasing age.[16,17] We have further shown that perceptual characteristics of the odor affect identifiability and the size of the age-related impairment for that odor. For instance, intense odors are more easily identified irrespective of age[18] and a study by Konstantinidis et al.[19] suggested that the identification of unpleasant odors is less affected by increasing age.

We aimed to examine the role of perceptual and phenomenological odor characteristics in the association with future dementia. The importance of odor intensity, pleasantness, familiarity, and identifiability was explored by considering specific clusters of the SST. As intense and unpleasant odors are better identified among cognitively healthy individuals, we hypothesized that these odors would be more suitable for detecting individuals with an increased risk of dementia. In contrast, all older individuals may have difficulties identifying pleasant odors with low intensity. Identifying familiar odors is typically found easier compared to less familiar odors, which is assumed to be due to elevated past exposure;[20] thus, we also considered this dimension. We further formed clusters based on how easily identifiable the odors were. Here, we expected individuals approaching a dementia diagnosis to have more pronounced difficulties with free OID, given the increased cognitive demands of that task.

As a second aim, we evaluated differences between the 16-item SST and existing reduced versions in their association with future dementia, as well as a cluster consisting of odors that showed the strongest association with dementia in the present sample.

This study offers a novel perspective on the olfaction and dementia link by considering odor characteristics and different odor set sizes, while drawing on a large longitudinal sample with 12 years of follow-up.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors searched the literature using traditional sources (e.g., PubMed). Limitations identified with previous research included a lack of evaluations of the role of odor characteristics and comparisons across different odor set sizes in the association with future dementia.
2. **Interpretation**: Odor identification (OID) items differ in their association with future dementia. Reduced OID set sizes render hazard ratios comparable to larger set sizes and contribute clinically relevant information with regard to future dementia risk.
3. **Future directions**: Identifiability and perceptual characteristics of odors should be considered when designing dementia screening instruments based on OID tasks.

2 | METHODS

We preregistered the study on Open Science Framework (https://osf.io/xwup6/).

2.1 | Participants

We used data from the population-based Swedish National Study on Aging and Care-Kungsholmen (SNAC-K: https://www.snac-k.se). Participants were ≥ 60 years of age and lived in Kungsholmen in central Stockholm, either home dwelling or in an institution. A random sample was drawn from 11 age cohorts ranging from 60 to 99+ years. Of the eligible study population ($N = 4590$), 3363 individuals participated in the baseline assessment (2001–2004), which encompassed comprehensive social, medical, and cognitive assessments. Follow-up assessments were performed every 3 (< 78 years) or 6 (≥ 78 years) years. Participants were followed for up to 12 years.

We excluded 417 individuals with dementia, Parkinson's disease, schizophrenia, developmental disorder, or a Mini-Mental State Examination (MMSE) score < 24 at baseline. An additional 279 individuals did not take part in the cognitive assessment and 194 individuals did not perform the olfaction test due to self-reported anosmia ($n = 68$), asthma or allergies ($n = 44$), olfactory oversensitivity ($n = 18$), refusal ($n = 23$), or other reason ($n = 41$).[10] Furthermore, 55 individuals had missing data on one or several odor items and could not be used to form the odor clusters. OID scores were available for all odors for 2418 individuals, which constituted the final sample, of which 86 participants had missing data on the free OID task.

All parts of SNAC-K were approved by the Karolinska Institute Ethical Committee or Stockholm Regional Ethical Review Board. The ethical standards of the Declaration of Helsinki from 1964 were followed.

2.2 | Olfactory assessment

Olfactory function was assessed with the revised 16-item SST OID test battery.[21] The odor items (apple, banana, clove, coffee, cinnamon, fish, garlic, lemon, leather, licorice, peppermint, pineapple, rose, turpentine,

mushroom, and gasoline) were stored in felt-tip pens and presented individually for 5 seconds by the test leader in conjunction with an odor recognition test.[22] First, the participants were asked to identify the items freely, without any verbal cues. If correctly identified, the next odor item was presented, otherwise the correct verbal descriptor was provided among three incorrect alternatives in a forced choice format. Correct identification with either free or cued identification was awarded 1 point, with a maximum total score of 16.[17] In the rare cases in which an item was skipped, for instance, due to test implementation errors, 0.25 points were given, equivalent to chance level.[23]

2.3 | Dementia diagnosis

The outcome of interest was the incidence of all-cause dementia over the 12-year follow-up. Dementia was assessed at baseline and during subsequent assessments according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.[24] The examining physician and a physician reviewing the information collected during the medical examination independently made a diagnosis. In cases of disagreement, a senior neurologist gave the final diagnosis. Additional dementia cases were identified through medical records and death registers among participants who died between assessments. Here, the date of death served as the date of dementia diagnosis.

2.4 | Covariates

Information on covariates was collected through a nurse interview, medical assessment, medication lists, laboratory tests, and the National Patient Register. Age was measured in years since birth, education as years of formal schooling, and sex was dichotomized. Additionally, we considered smoking status, depression, hypertension, diabetes, and history of cardiovascular disease (CVD: atrial fibrillation, heart failure, ischemic heart disease) and stroke. Genotyping was performed for apolipoprotein E (*APOE*; rs429358), with participants categorized as ε4 allele carriers or non-carriers. Semantic memory performance was assessed with SRB:1, a forced-choice vocabulary task comprising 30 items.[25]

2.5 | Clustering of the odor items

In total, 13 odor clusters were formed that were based on different subsets of the 16-item SST (see Table 1). "Identifiability" was calculated as the percentage of individuals (see Table SA in supporting information) who were able to identify the odor in our sample, with either free or cued identification. These data form the basis of the low and high identifiability, and the high free identifiability odor clusters. Due to the high difficulty of the free OID task, a low free identifiability odor cluster was not formed, as floor effects were already expected for the high free identifiability cluster.

For estimations of the odor perceptual dimensions (intensity, pleasantness, and familiarity) the ratings from Lindroos et al. were used.[18] They calculated weighted means for these dimensions for all 16 odor items using three different samples, consisting of primarily young adults < age 30 from Western Europe or New Zealand.[11,18,26] These ratings were used to create clusters of high and low intensity, pleasant and unpleasant, and high- and low-familiarity odors. It should be noted that all odors showed relatively high ratings on these dimensions (see Table SA), as they were considered when selecting the odor items to be included in the SST.[11]

Two existing shorter versions of the SST, the 12-item[14] and the 5-item test[15] built the base for two additional reduced odor clusters. As the revised SST version[21] does not comprise the odor item orange, which was used in both the 12- and 5-item tests, we substituted it with the odor item apple due to similar perceptual odor features.[27]

Last, the "hazard of future dementia" of each odor item was estimated and served as the basis for the high- and low-hazard clusters.

All clusters based on the odor characteristics and the individual items´ association with dementia had a set size of 6 items to enable statistical comparison across clusters. For example, the six odors rated as most intense formed the high-intensity odor cluster and the six odors rated least intense formed the low-intensity cluster. The procedure entailed that four odors with middle-range values are not represented in any cluster for that dimension. This rendered clusters that were clearly separated, while keeping the clusters as large as possible to enhance reliability.

2.6 | Statistical analysis

OID, age, years of education, and semantic memory were treated as continuous measures. The OID scores were reversed to represent the higher risk of dementia when scoring low. The continuous covariates were centered at the sample's mean, and health and behavioral data were dichotomized.

To estimate the risk of incident dementia based on baseline OID scores in the different odor clusters, we conducted Cox proportional hazard regression analyses with Stata (StataCorp, version 17). Follow-up time was measured in years from the baseline assessment to dementia diagnosis, death, or drop-out. Model 1 adjusted for age, sex, and years of education, while model 2 additionally controlled for semantic memory, depression, stroke, CVD, diabetes, hypertension, current smoking, and *APOE*. Due to missing data, model 2 analyses were run with a subset of 2251 individuals.

The proportional hazards assumption was tested with the Schoenfeld test and confirmed with corresponding plots of residuals, indicating only minor deviations for two of the clusters. To compare hazard estimates between clusters, Wald hypothesis tests were conducted. Last, we performed stratified analyses for young-old (< 78) and old-old (≥ 78) age groups for all odor clusters.

TABLE 1 Odor items included in the respective odor clusters.

Odor item	Odor cluster													
	16-item	12-item	5-item	High identifiability	Low identifiability	High free identifiability	High intensity	Low intensity	Unpleasant	Pleasant	High familiarity	Low familiarity	High HR	Low HR
Apple														
Banana														
Cinnamon														
Cloves														
Coffee														
Fish														
Garlic														
Gasoline														
Leather														
Lemon														
Licorice														
Mushroom														
Peppermint														
Pineapple														
Rose														
Turpentine														

Abbreviation: HR, hazard ratio.

TABLE 2 Baseline sample characteristics in the total sample and stratified by future dementia status.

Variable	Total sample ($n = 2418$)	No dementia ($n = 2080$)	Incident dementia ($n = 338$)	p value
Age (years)[a]	72.18 (9.88)	70.90 (9.60)	80.04 (7.73)	<0.001
Sex[b]				0.01
Female	1479 (61.17%)	1251 (60.14%)	228 (67.46%)	
Male	939 (38.83%)	829 (39.86%)	110 (32.54%)	
Education (years)[a]	12.21 (4.23)	12.45 (4.25)	10.74 (3.81)	<0.001
MMSE[a]	28.92 (1.29)	29.05 (1.19)	28.15 (1.58)	<0.001
OID[a]	11.72 (2.99)	12.04 (2.79)	9.71 (3.42)	<0.001
Vocabulary[a]	22.86 (5.04)	23.19 (4.90)	20.82 (5.42)	<0.001
Depression[c]	94 (3.89%)	71 (3.41%)	23 (6.80%)	<0.01
Stroke[b]	117 (4.84%)	82 (3.94%)	35 (10.36%)	<0.001
Heart disease[b]	496 (20.51%)	382 (18.37%)	114 (33.73%)	<0.001
Diabetes[b]	219 (9.06%)	184 (8.85%)	35 (10.36%)	0.37
Hypertension[b]	1237 (51.24%)	1045 (50.34%)	192 (56.80%)	0.03
Current smoking[b]	359 (14.93%)	316 (15.29%)	43 (12.72%)	0.22
Any *APOE* ε4 allele[b]	672 (29.45%)	549 (28.00%)	123 (38.32%)	<0.001

Notes: OID, olfactory identification score in the 16-item cluster; missing data: vocabulary $n = 20$, hypertension $n = 4$, current smoking $n = 13$, *APOE* ε4 $n = 136$.
Abbreviations: *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; OID, odor identification.
[a]Mean with standard deviations.
[b]Number and percentage of participants.

3 | RESULTS

Baseline characteristics for the sample are shown in Table 2. During the 12 years of follow-up, 338 individuals received a dementia diagnosis. These participants were more likely to be female, older, and have fewer years of education compared to the individuals without incident dementia. Furthermore, they scored lower on the OID and semantic memory tasks at baseline. Additionally, future dementia was associated with baseline depression, a history of stroke, CVD, hypertension, and the presence of the *APOE* ε4 allele (*Ps* < 0.05).

The hazard ratio (HR) associated with the performance in each of the odor clusters is displayed in Figure 1. Full results from models 1 and 2 are shown in Table SB in supporting information. Cox regression does not account for the number of odors included in the cluster when calculating the HR. This restricts the comparability of odor clusters with unequal size, as larger odor clusters yield a lower hazard estimate. As reported previously, a significant association was observed between a lower performance in the 16-item cluster and higher dementia hazard (HR = 1.14, 95% confidence interval [CI; 0.10–1.19], $p < 0.001$).[10] The hazard for dementia rose by 14% with each odor item that was not identified. Likewise, lower OID performances on the 12-item (HR = 1.15, 95% CI [1.10–1.21], $p < 0.001$) and the 5-item odor cluster (HR = 1.29, 95% CI [1.18–1.42], $p < 0.001$) were associated with future dementia.

The performance in the high identifiability odor cluster showed the strongest association with dementia (HR = 1.39, 95% CI [1.28–1.51], $p < 0.001$), although the performance in the low identifiability item cluster also yielded a significant association with future dementia. The two dementia hazard estimates differed significantly ($\chi^2[1] = 18.96$, $p < 0.001$), following the Wald hypothesis test. A lower score in the high free identifiability cluster was significantly associated with an increased hazard for dementia (HR = 1.34, 95% CI [1.21–1.48], $p < 0.001$).

The high-intensity cluster rendered a significantly higher hazard of dementia (HR = 1.34, 95% CI [1.24–1.45], $p < 0.001$) compared to the low-intensity cluster (HR = 1.22, 95% CI [1.13–1.32], $P < 0.001$: χ^2 [1] = 5.42, $p = 0.02$). Further, both pleasant and unpleasant odor cluster performance was significantly associated with future dementia, although the estimates did not differ ($\chi^2[1] = 3.15$, $p = 0.08$). Both the performance in the high familiarity and low familiarity clusters showed significant associations with future dementia, with similar HRs ($\chi^2[1] = 0.1$, $p = 0.75$).

Additionally, Cox proportional hazard models for each odor item were performed separately (model 1). The failed identification of 13 of the 16 odor items was individually associated with an increased hazard for incident dementia during follow-up (see Table SC in supporting information). The performance associated with a cluster of six items with the individually highest hazard for future dementia (high HR cluster) yielded an HR of 1.41 (95% CI [1.30–1.53], $p < 0.001$). This estimate was significantly different ($\chi^2 = 24.99[1]$, $p < 0.001$) from the item cluster based on the six items with the weakest association with dementia (low HR cluster, HR = 1.14, 95% CI [1.06–1.24], $p < 0.001$).

The dementia hazard estimates obtained in the age-stratified analyses (young-old vs. old-old) yielded similar patterns as for the total sam-

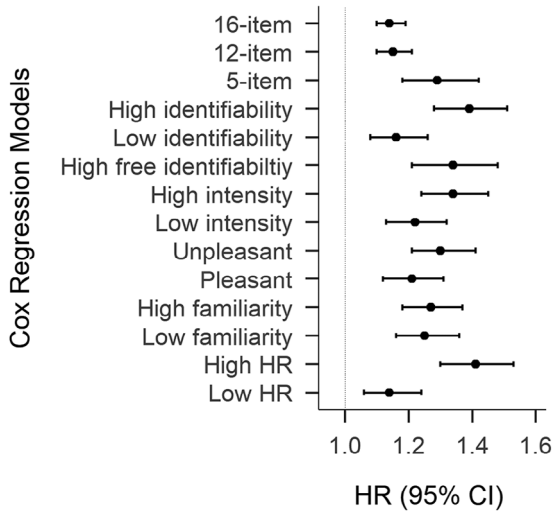

FIGURE 1 Hazards ratios and 95% confidence intervals of Cox regression analyses for the respective odor item clusters and incident dementia across the 12-year follow-up interval. *Note*: $n = 2251$. The dashed line indicates the HR of 1, which would imply no effect of OID performance on dementia. All item clusters without specified item number contained six items. All HR estimates were calculated with model 2 covariates (age, sex, years of education, semantic memory score, depression diagnosis, stroke, cardiovascular diseases, diabetes, hypertension, current smoking, and *APOE ε4*). APOE, apolipoprotein E; CI, confidence interval; HR, hazard ratio; OID, odor identification.

ple (see Table SD in supporting information). However, in the young-old cohort, a lower performance in the low identifiability odor cluster was not associated with future dementia. Moreover, the dementia hazard estimates for almost all odor clusters were slightly higher for the young-old age cohort, except for the high free identifiability item cluster (young-old: HR = 1.28, 95% CI [1.08–1.51], $p < 0.01$; old-old: HR = 1.37, 95% CI [1.21–1.56], $P < 0.001$). Significant differences between the hazard estimates were only evident within the old-old age cohort. Here, a significant difference between the HR of the high intensity (HR = 1.32, 95% CI [1.20–1.45], $P < 0.001$) and the low intensity (HR = 1.19, 95% CI [1.09–1.31], $P < 0.001$) odor clusters was found ($\chi^2[1] = 4.49$, $p = 0.034$). Likewise, the hazard estimates of the unpleasant (HR = 1.29, 95% CI [1.18–1.41], $p < 0.001$) and the pleasant (HR = 1.17, 95% CI [1.07–1.29], $p < 0.01$) odor clusters differed significantly ($\chi^2[1] = 3.95$, $p = 0.047$).

4 | DISCUSSION

We investigated characteristics that may distinguish the association between OID performance and future dementia. The results showed that the estimation of HR for those who will progress to dementia can be improved by selecting certain odor items over others. Also, we examined several abbreviated OID tests, validating the usefulness of smaller set sizes.

4.1 | Cluster-specific OID performances and future dementia

As expected, the high HR cluster showed a strong association with incident dementia. A similar HR was observed for the high identifiability cluster. A participant who identified one odor item less was 1.39 times more likely to receive a dementia diagnosis during follow-up compared to someone who correctly identified one odor item more. In comparison, the low identifiability cluster was likely very challenging across all participants. This highlights that odor items should be tailored to the average olfactory capabilities of older individuals.

Free OID is particularly difficult for individuals in the preclinical phase of dementia.[10] We found that the dementia hazard for the free high identifiability cluster was slightly lower than for the high identifiability cluster. This might be attributed to the overall very high difficulty of free OID, even for cognitively intact participants. However, cued OID and free OID performance were assessed simultaneously, and there were differences in sample size due to missing data for the free ID score. These conditions prohibit strong conclusions regarding why this pattern was observed.

Further, performance in the high-intensity odor cluster resulted in a significantly higher dementia hazard compared to the low-intensity odors. In contrast, no significant difference was observed for the pleasantness- and familiarity-based odor cluster comparisons. However, the age-stratified analyses yielded further insights. A higher dementia sensitivity of the high intensity (vs. low intensity) and unpleasant (vs. pleasant) odors was found in the old-old age cohort (but not in the young-old cohort), which may be explained by previous work. First, the high-intensity odors might have compensated for the sensory decline common in old age,[28] allowing for more efficient differentiation between those with and without increased dementia risk. Second, the identification advantage associated with unpleasant odors, possibly explained by increased survival from an evolutionary perspective,[19] might have been more apparent in old-old participants. In contrast, better retained olfactory perceptual abilities of the younger participants might have enabled the identification of all odors to a similar degree. Thus, the challenges in identifying pleasant and less intense odors may begin to manifest in individuals at increased dementia risk only in advanced old age.

The low variability of the odors´ familiarity ratings in the SST might explain why there were no differences observed for this dimension. Notably, past research suggests that highly familiar odors could prove useful as they are often easier to describe for everyone.[20] In the realm of smell, it's essential to acknowledge the significant impact of subjective perceptual differences. Factors such as age, sex, hormonal status, culture, and frequency of exposure can influence the perceived pleasantness and familiarity.[29,30] Notably, within the SST battery there appears to be substantial agreement regarding which odors are generally considered pleasant.[18,31] Looking into culturally familiar odors might be a starting point to tackle the subjective component of odor perception.[32]

4.2 | Other abbreviated SST versions

The 16-item cluster showed the weakest association with future dementia per point interval, most likely due to the larger cluster size. The dementia hazard associated with a lower score in the 12-item cluster did not differ from the 16-item cluster. In line with this, the individual odor items' HRs showed that odor items with weak dementia associations are not part of the 12-item screening test.[14] The 5-item cluster was associated with a considerably higher dementia hazard for each item not correctly identified, corroborating previous research.[2] Notably, there is some overlap between the high identifiability odors determined in our sample and the odor ratings from Hummel et al.,[14] which were used for the 5-item test.[15] The heightened effectiveness of these abbreviated tests imparts substantial clinical value, potentially streamlining the integration of OID assessments as valuable adjuncts in preclinical dementia screenings.

We found garlic, gasoline, and mushroom to be part of the clusters showing the highest HRs (i.e., high identifiability, high intensity, high HR) in our sample. Based on our and previous findings, we could recommend the use of the odor items apple, banana, cloves, fish, garlic, gasoline, mushroom, peppermint, and rose when the aim of the olfactory assessment is predementia screening. However, the differences in the association between lower OID performance in different item clusters and future dementia were relatively small. Note that some of these odors (rose, apple, banana) also appear in subsets of the University of Pennsylvania Smell Identification Test and the Odor Stick Identification Test for the Japanese, showing the best separation between individuals across different cognitive statuses (i.e., normal, mild cognitive impairment, AD).[33,34,35]

4.3 | Strengths and limitations

While the longitudinal design with 12 years of follow-up and a large sample size offered a strong foundation for addressing the research question, several limitations should be noted. First, the study's sample is relatively homogeneous in terms of ethnicity, education level, and socioeconomic status. Furthermore, individuals with self-reported anosmia, for example, due to short- or long-term illness or injury, could not be tested. Attrition bias is a common challenge in longitudinal studies. In this study, it was mitigated by using complementary data from medical records and death registers for the dementia diagnoses. Our outcome variable was all-cause dementia, yet olfactory functioning can differ among various dementia types.[36] It should also be noted that the ratings of the odor perceptual dimensions were not obtained from the current study sample and were primarily based on younger individuals. However, this may be considered a benefit because older adults are worse at differentiating odors based on perceptual attributes and this might have introduced substantial noise in the perceptual dimension ratings. It is possible that odor tasks measuring OID in a different way compared to the SST would render different results compared to the present study. Last, some odor clusters overlapped significantly, suggesting that a specific dimension of olfactory perception could play a role in more than one cluster.

In conclusion, this study suggests that certain odor items, particularly those easier to identify and of higher intensity, would be most relevant to include in OID tests designed to identify individuals with increased dementia hazard. Additionally, unpleasant odors may exhibit enhanced sensitivity, especially among people of advanced old age. Last, the findings support the use of a reduced number of odor items for clinical practice and further substantiate the robust link between poor olfactory function and an increased dementia risk.

AUTHOR CONTRIBUTIONS

Study conception and design: E.D., M.L., I.E., and E.L. Data collection: G.G. and E.L. Data analysis: E.D., I.E., D.R., and E.L. Writing the first draft of the manuscript: E.D. Interpretation of the results and critically revising the manuscript for important intellectual content: all authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants in SNAC-K provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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