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Research Article

# Transitions Between Mild Cognitive Impairment, Dementia, and Mortality: The Importance of Olfaction

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## Abstract

**Background:** The existing literature suggests that impaired olfaction may be an early marker for cognitive decline. Tracking the earliest stages of the progression to dementia is paramount, and yet the importance of olfactory ability throughout cognitive states and death remains unclear.
**Methods:** Drawing data from the Rush Memory and Aging Project ($N$ = 1 501; 74% female), olfactory ability was assessed using the Brief Smell Identification Test (range = 0–16), while cognitive states (unimpaired, mild cognitive impairment [MCI], and dementia) were determined using a 3-step neuropsychological diagnostic protocol at up to 15 annual occasions. Multistate survival models simultaneously estimated the association of olfactory ability on transitions through cognitive states and death, while multinomial regression models estimated cognitively unimpaired and total life expectancies.
**Results:** Higher olfactory scores were associated with a reduced risk of transitioning from unimpaired cognition to MCI (hazard ratio [HR] = 0.86, 95% confidence interval [CI] = 0.82–0.88) and from MCI to dementia (HR = 0.89, 95% CI = 0.86–0.93), indicating that 1-unit increase in olfactory scores was associated with an approximate 14% and 11% reduction in risk, respectively. Additionally, higher olfactory scores were associated with a greater likelihood of transitioning backward from MCI to unimpaired cognition (HR = 1.07, 95% CI = 1.02–1.12). Furthermore, higher baseline olfactory scores were associated with more years of longevity without cognitive impairment. However, olfaction was not associated with the transition to death when accounting for transitions through cognitive states.
**Conclusions:** Findings suggest that higher olfactory identification scores are associated with a decreased risk of transitioning to impaired cognitive states and that associations between olfaction and mortality may occur primarily through the pathway of neurodegeneration.

**Keywords:** Alzheimer's, Dementia, Life expectancy, Multistate survival modeling

Existing research indicates that the link between olfactory ability and cognition is useful for the prediction of future cognitive impairment (1), neurodegenerative disease (2), and mortality (3–11); however, the extent to which olfaction is associated with cognitively unimpaired life span is unclear. Likewise, previous research has not systematically investigated whether olfactory test scores are sensitive enough to predict intraindividual progression through different cognitive states over time. Previous research using Cox regression models to estimate the role of olfactory identification scores in predicting different cognitive outcomes (3–11) has been constrained by its ability to estimate progression to only a single cognitive state (eg, mild cognitive impairment [MCI] *or* dementia), and has not accounted for changes in cognitive states, transitions, during study follow-up occasions. An extension of traditional survival analysis, multistate survival models, can elucidate the relationship between covariates, intermediate outcomes (eg, MCI *and* dementia), and death (12) and address this gap in the literature.

Olfactory processing areas in the brain, such as the olfactory bulb and the entorhinal cortex, are some of the earliest areas affected by neurodegenerative pathology (13,14). Further, the amount of pathology has been shown to be related to the degree of olfactory impairment (15), suggesting that the underlying mechanism for both

cognitive and olfactory decline may be irreparable damage to the brain regions supporting these functions, which might be easily identified through declining olfactory scores (16). Therefore, olfactory testing could be an excellent addition to routine clinical testing as an early marker of cognitive decline.

This study extends prior work with the Rush Memory and Aging Project (MAP) (7) to examine associations with olfaction and transitions between clinically diagnosed cognitive states (unimpaired, MCI, and dementia) and death using multistate survival modeling (MSM). This approach permits simultaneous estimation of transitions through multiple cognitive states while also accounting for death as a competing risk factor. Further, using the transition probabilities estimated by the MSM, we estimated nonimpaired and total life expectancies (LEs). In this paper, we investigate *(a) the association of olfactory deficits and transitions between different cognitive states and death; and (b) whether individuals who have higher olfactory identification scores at baseline have longer cognitively unimpaired and total LEs*. Based on previous research examining olfactory ability as an early indicator of cognitive functioning in older adulthood (7,15), and the hypothesis that olfactory impairment reflects neuropathology in brain areas that support both olfactory and cognitive ability, we predict that individuals who have lower scores on olfactory identification tests at baseline may be more likely to transition to impaired cognitive states and death, and may have shorter LEs than individuals who have higher olfactory scores at baseline.

## Method

### Participants

The current analysis is based on data from 1 501 individuals assessed annually from MAP (17), a longitudinal study of older adults with ongoing recruitment from retirement communities in northeastern Illinois between 1997 and 2019. Although cognitive functioning was assessed annually from study inception in 1997, olfactory testing first occurred in 2000. As such, 2000 was treated (and will be referred to) as baseline in the present study for participants recruited before 2000.

Participants met eligibility criteria for the present analysis if they completed an olfactory identification assessment, demographic information, and had at least 2 states (ie, at least 2 cognitive states or 1 cognitive state plus death). These criteria resulted in excluding a total of 683 participants from the full sample ($N$ = 2 184), resulting in an analytic sample of 1 501 (Figure 1).

### Standard Protocol Approvals, Registrations, and Patient Consents

The study was reviewed by the Institutional Review Board of Rush University Medical Center. All participants signed an informed consent and a repository consent that allows their data to be repurposed.

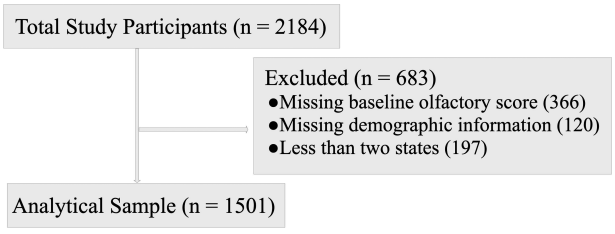


**Figure 1.** Flow chart of study participants.

### Measures

#### Olfactory assessment

Olfaction was assessed at baseline using the 12-item Brief Smell Identification Test (B-SIT) (18). During the test, a microencapsulated patch containing an odorant is scratched with a pencil and placed under the nose of the participant. Response options on the B-SIT are forced-choice: participants choose which out of 4 presented words best represent the smell. Consistent with previous research (7), up to 2 missing responses are allowed (missing items assigned a score of 0.25). If more than 2 items are not answered, the entire test is treated as missing and participants not included in the analysis. Summed scores are computed based on the number of correct responses. Continuous olfactory scores were centered on 11 (score—11), which represents the minimum score for normal olfactory ability (18,19). For estimation of LEs, the multinomial regression model requires ordered categories. Therefore, specific numbers aligning with previous literature (18,19) were chosen and olfactory ability was classified as low (score of 5), moderate (10), and normal (12).

#### Cognitive assessment

The cognitive states used in the MSM were obtained from a 3-step diagnostic protocol used in the Rush MAP, which included an annual clinical diagnosis based on computer scoring of 11 cognitive tests, clinical judgment by a neuropsychologist, and diagnostic classification by a clinician (neurologist, geriatrician, nurse practitioner, or second neuropsychologist) (20). Adjudication was employed when there was a disagreement between the 2 clinicians and a neurologist was asked to provide a third opinion. The resulting clinical diagnoses were used in this study to operationally define the clinical cognitive states: (i) No cognitive impairment (NCI), which refers to those individuals with neither dementia nor MCI; (ii) MCI which represents individuals with cognitive impairment but who did not meet criteria for dementia; and (iii) dementia which indicates evidence of a meaningful decline in cognitive function relative to a previous level of performance including impairment in at least 2 domains of cognition. There was a mean of 7.37 waves of cognitive data for each participant, with up to 15 years of follow-up.

#### Apolipoprotein E

Apolipoprotein E (*APOE*) allele status was included as a dichotomous variable, in which individuals with 1 or more ε4 alleles were coded as 1, and individuals without an ε4 allele were coded as 0 (21).

#### Chronic conditions

To control for the potential impact of chronic diseases and associated medications on both cognition and olfaction (22), we created a chronic conditions variable. The overall burden of chronic diseases was operationalized as a count of the total number of self-reported chronic conditions at baseline: hypertension, diabetes, heart disease, cancer, thyroid disease, head injury with concussion, and stroke (23).

#### Education

Education was measured as years of education reported at baseline, and centered at 12 (number of years of education—12) to represent high school education in the United States.

### Smoking

Self-reported smoking status was measured at baseline. Current smokers were coded as 1 and (current) nonsmokers were coded as 0.

## Statistical Analysis

All analyses were conducted in R (24). The MSM package (25) was used to estimate the multistate survival models, while the elect package (estimating life expectancies in continuous time) (26) was used to estimate LEs. MSM (27) was used to assess individual transitions through different cognitive states (NCI, MCI, dementia), and death as well as backward transitions from MCI to NCI and dementia to MCI, as shown in Figure 2. MSM is an extension of traditional survival modeling that allows investigation of the association of olfactory ability with transitions to more than 1 cognitive state within a single model, while also accounting for death as a competing risk factor (Figure 2). Interval censoring was used in cases where participants had missing data between 2 states, where state transitions were known to have occurred within this interval, but the exact timing of the transition was unknown (26). This allows the estimation of transition probabilities even in cases with missing cognitive state data. Further, MSM utilizes maximum likelihood estimation, which is robust to data missingness and provides estimates for all participants, even those with missing outcome data. The cognitive states were based on all available longitudinal cognitive assessment data for each participant. Age, sex, education, *APOE* ε4 allele, baseline olfactory score, smoking status, and chronic conditions were included as covariates on all transitions and were selected based on previous literature (3–11) and available data. Models that included interaction terms between olfactory scores and each of the other key covariates (age, sex, APOE) were additionally fitted to determine whether these covariates moderated the association of olfactory scores with the transition probabilities. Further, we completed 3 follow-up analyses: first, additional MSM models were conducted to assess whether smoking in the past affected results. Our data could not account for improvements in olfactory functioning after quitting smoking; as such, we conducted a sensitivity analysis to examine whether past smoking affected results in our particular sample. Second, a Cox survival analysis estimated the association between olfaction and mortality to improve comparability of the current analysis to the existing literature and to clarify the importance of accounting for cognition when examining olfaction and death. Lastly, as in previous work (28), we included backward transitions from dementia to MCI. To examine whether individuals with backward transitions affected results, we ran a sensitivity analysis, excluding all participants with a transition from dementia to MCI or NCI.

Finally, we fit a multinomial regression model using the elect package and the hazard ratios (HRs) estimated by the MSM to predict years spent in NCI and impaired states, as well as total years of LE. We define LE as the estimated number of years of life remaining at a given age, such that the calculated LEs estimate the average number of years for an average individual at various levels of each covariate (eg, for a nonsmoker at 80 years old). Each of the LE estimates is conditional on specified values drawn from the parameters in the MSM model (26). For example, olfactory identification was treated as a continuous variable in the MSM model, but for the LE analyses we specified a particular score (eg, a score of 5 on the olfactory identification test). Similarly, each covariate included in the LE analysis was conditional on specified options (eg, age, smoking status, years of education, APOE allele status), which are detailed in the Results section.

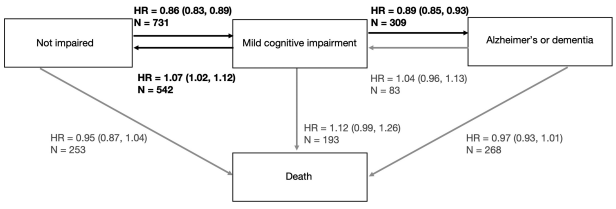


**Figure 2.** Four-state model illustrating the effect of 1 additional correct item on the Brief Smell Identification Test on transitioning between states. *Note*: The figure includes the total number of individual transitions between states, as well as pooled hazard ratios (HRs) and 95% confidence intervals.

## Data Availability

MAP data are available via the Rush Alzheimer's Disease Center Research Resource Sharing Hub and can be requested at https://www.radc.rush.edu. Qualified investigators can submit requests for deidentified data.

# Results

The total number of individual transitions between cognitive states during the study is reported in Figure 2 as a state map, with significant transitions for olfaction indicated in bold. Table 2 depicts the HRs and 95% confidence intervals (CIs) for all included transitions (eg, NCI to MCI) and covariates.

Participants had a mean age at baseline of 80 years (*SD* = 88) and had completed an average of 15 years of education. Of these participants, 21% were APOE ε4 carriers, 93% were White, 58% had never smoked, and 74% were female (Table 1). Participants had an average of 7 years of follow-up (*SD* = 4; range = 2–18), and 23% (*n* = 347) received a diagnosis of dementia at some point during the study; the average age at dementia diagnosis was 88 years (*SD* = 7; range = 64–106).

## Association Between Baseline Olfaction and Transitions Between Cognitive States

Higher baseline olfactory identification was associated with a lower risk of transitioning from NCI to MCI (Table 2) and from MCI to dementia. Interpretation of the HR for clinical utility indicates that

**Table 1.** Baseline Descriptive Statistics for the Sample

| Variable | Mean (*SD*) *N* (%) | Range |
|---|---|---|
| Olfactory score | 8.88 (2.33) | 0–12 |
| MMSE | 27.71 (2.67) | 9–30 |
| MCI (baseline), *n* (%) | 372 (24.8%) | |
| Dementia diagnosis, *n* (%) | 56 (3.7%) | |
| APOE ε4 | 311 (20.7%) | |
| Age | 79.65 (7.73) | 53–100 |
| Female, *n* (%) | 1 117 (74.4%) | |
| White, *n* (%) | 1 388 (92.5%) | |
| Chronic conditions | 1.44 (1.06) | 0–6 |
| Education (years) | 14.72 (3.33) | 0–29 |
| Smoking | 40 (2.7%) | |

*Notes*: APOE = apolipoprotein E; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination. Chronic conditions include a count of hypertension, diabetes, heart disease, cancer, thyroid disease, head injury with concussion, and stroke.

**Table 2.** Hazard Ratios and 95% Confidence Intervals (CIs) for the Effect of Olfaction and Covariates on the Transitions Through Different States of Cognitive Functioning

| | **MAP** (*N* = **1 501**) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Olfaction | Age | Sex | Education | Chronic Conditions | APOE ε4 | Smoking |
| Transition | **Hazard Ratios (95% CI)** | | | | | | |
| N to MCI | **0.86 (0.83, 0.89)** | **1.06 (1.05, 1.07)** | 1.13 (0.95, 1.35) | 1.00 (0.97, 1.02) | 1.02 (0.94, 1.1) | **1.25 (1.04, 1.51)** | **1.82 (1.17, 2.84)** |
| N to Death | 0.95 (0.87, 1.04) | **1.10 (1.07, 1.14)** | 1.37 (0.89, 2.11) | **0.93 (0.88, 0.99)** | **1.30 (1.09, 1.55)** | 0.96 (0.55, 1.65) | **2.62 (1.03, 6.63)** |
| MCI to N | **1.07 (1.02, 1.12)** | **0.97 (0.96, 0.98)** | 0.98 (0.79, 1.22) | **1.05 (1.02, 1.08)** | **1.10 (1.01, 1.21)** | **0.66 (0.52, 0.84)** | 1.18 (0.70, 2.00) |
| MCI to Dem | **0.89 (0.85, 0.93)** | **1.06 (1.05, 1.08)** | 0.93 (0.72, 1.19) | 0.98 (0.94, 1.01) | **1.12 (1.01, 1.25)** | **1.48 (1.17, 1.88)** | 1.12 (0.52, 2.4) |
| MCI to Death | 1.12 (0.99, 1.26) | **1.08 (1.02, 1.14)** | 1.67 (0.91, 3.06) | 1.02 (0.94, 1.12) | 1.11 (0.81, 1.52) | 0.57 (0.23, 1.45) | 1.15 (0.21, 6.38) |
| Dem to MCI | 1.04 (0.96, 1.13) | 0.98 (0.95, 1.01) | **1.74 (1.09, 2.79)** | 1.00 (0.94, 1.07) | **1.26 (1.04, 1.53)** | 0.70 (0.42, 1.17) | 3.08 (0.79, 12.10) |
| Dem to Death | 0.97 (0.93, 1.01) | **1.07 (1.04, 1.09)** | **1.50 (1.13, 1.99)** | 0.97 (0.93, 1.00) | 1.07 (0.96, 1.20) | 0.88 (0.67, 1.17) | 1.00 (0.39, 2.55) |

*Notes*: The hazard ratios indicate the increased or decreased risk of the corresponding transition based on a 1-unit change in the predictor. APOE = apolipoprotein E; Dem = dementia; MAP = Memory and Aging Project; MCI = mild cognitive impairment; N = unimpaired cognition. Bold values indicate statistically significant results.

for each 1-unit increase in olfactory score there was a 14% reduction in risk of transitioning to MCI from NCI (HR = 0.86, 95% CI = 0.82–0.88), meaning that an individual with an olfactory identification score of 12 (high) would be 65% less likely to transition to MCI from NCI compared to an individual with a score of 5 (low). Higher smell scores were associated with a greater likelihood of backward transition from MCI to NCI, indicating that an individual with a score of 12 would be 60% more likely to transition back to NCI from MCI compared to an individual scoring 5 on the olfactory test. Baseline olfactory scores were not associated with the transition to death from any of the cognitive states.

## Association Between Covariates and Transitions Between Cognitive States

### Age

As expected, older age was associated with a greater risk of transitioning from NCI to MCI (HR = 1.06, 95% CI = 1.05, 1.07) and from MCI to dementia (HR = 1.06, 95% CI = 1.05, 1.08). Further, older age was associated with a greater risk of transitioning to death from NCI (HR = 1.1, 95% CI = 1.07, 1.3), MCI (HR = 1.07, 95% CI = 1.02, 1.13), and from dementia (HR = 1.07, 95% CI = 1.05, 1.09), as well as lower likelihood of transitioning backward from MCI to NCI (HR = 0.97, 95% CI = 0.96, 0.98).

### Sex

Male participants had a greater likelihood of transitioning backward from dementia to MCI (HR = 1.14, 95% CI = 1.12, 2.87) and were more likely to transition from dementia to death (HR = 1.5, 95% CI = 1.61, 2.0).

### Education

Higher education at baseline was associated with a lower risk of transitioning to death from NCI (HR = 0.93, 95% CI = 0.88, 0.99), and a greater likelihood of the backward transition from MCI to NCI (HR = 1.05, 95% CI = 1.02, 1.08).

### APOE ε4

Having an ε4 allele was associated with a greater risk of transitioning to MCI from NCI (HR = 1.24, 95% CI = 1.03, 1.50) and from MCI to dementia (HR = 1.50, 95% CI = 1.17, 1.89), as well as a lower likelihood of transitioning backward from MCI to NCI (HR = 0.66, 95% CI = 0.52, 0.84).

### Chronic conditions and smoking

Having more chronic conditions was associated with a greater risk of transitioning from MCI to dementia (HR = 1.12, 95% CI = 1.01, 1.25), and a greater risk of transitioning from NCI to death (HR = 1.3, 95% CI = 1.11, 1.54). Likewise, more chronic conditions were associated with a greater likelihood of transitioning backward from MCI to NCI (HR = 1.14, 95% CI = 1.04, 1.25), and from dementia to MCI (HR = 1.24, 95% CI = 1.06, 1.54). Smokers had a greater risk of transitioning to MCI from unimpaired cognition and a greater risk of transitioning from NCI to death (HR = 2.62, 95% CI = 1.03, 6.63).

### Interaction terms and sensitivity analyses

None of the interaction terms were significant. The sensitivity analysis including previous smoking status suggests that smoking in the past did not affect results. As such, neither the interaction terms nor past smoking were included in the final MSM model.

Cox survival modeling of the estimated risk of all-cause mortality using a method comparable to previous studies (3–11) (ie, not accounting for transitions through cognitive states, in contrast to MSM) produced results that were similar to previous studies (3–8,10,11), suggesting that higher olfactory scores significantly predicted reduced risk of death across the full follow-up period (HR = 0.825, 95% CI = 0.80, 0.85).

Excluding individuals who transitioned from dementia to MCI or dementia to NCI did not affect olfactory results. In this sensitivity analysis, having more medical conditions was no longer associated with the transition from MCI to dementia; however, more chronic conditions were still associated with an increased likelihood of transitioning back to NCI from MCI (HR = 1.12; 95% CI = 1.02, 1.23). Therefore, while more chronic conditions may increase risk of death, more chronic conditions do not necessarily increase the risk of transitioning to MCI or dementia, and may actually increase likelihood of returning to NCI from MCI. This may be due to effective management of the underlying conditions, which could present as an initial decrease in cognitive ability due to the development of additional chronic conditions, but once conditions are medicated or managed effectively, individuals may return to NCI.

### Life Expectancy

Cognitively unimpaired and total LEs showed increasing trends with higher olfactory identification scores for both female and male participants (Figure 3). Significant differences in LE estimates (indicated by CIs that do not overlap) were found for females without an *APOE* ε4 allele across all olfactory levels (ie, from a score of 5 to 10 and from 10 to 12) in unimpaired LEs. While there were no significant differences in the LE estimates between the sexes (ie, female participants with an olfactory score of 5 vs male participants with a score of 5), the trend was that females had longer estimated LE (Figure 3). For all other estimates, LEs for both males and females were significant between low (5) and moderate (10) olfactory levels. Interpretation of these estimates for clinical utility indicates that an average nonsmoking 80-year-old female with a high school education, no chronic health conditions, without an *APOE* ε4 allele, and with a low smell score at baseline was estimated to live approximately 4 additional years (to 84) without cognitive impairment and 9.5 years overall (Table 3). In comparison, an average female participant with all the above characteristics but with moderate olfactory scores was estimated to have 8 years of LE without cognitive impairment and 13 total years of LE, while those with high olfactory scores had 10 years of LE without cognitive impairment and 14 years overall. Both male and female participants without an *APOE* ε4 allele demonstrated a trend of longer LEs compared to individuals with an *APOE* ε4 allele across all olfactory levels (Figure 3). Compared to those without an *APOE* ε4 allele, females with 1 or more *APOE* ε4 allele(s) and with high smell scores were expected to live an additional 2 years free of cognitive impairment.

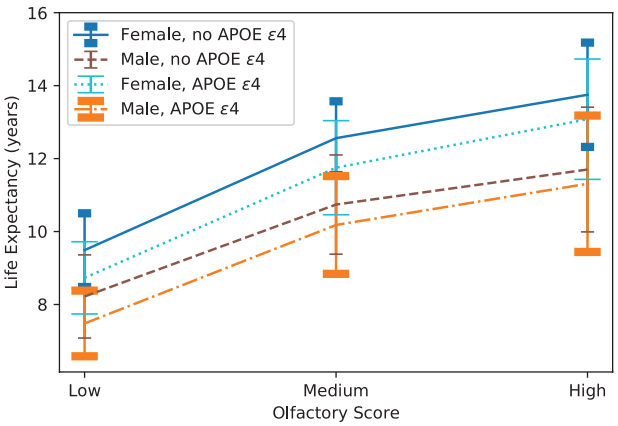


**Figure 3.** Cognitively unimpaired and overall life expectancies for female and male apolipoprotein E (*APOE*) ε4 allele carriers and noncarriers for low (5), medium (10), and high (12) olfactory scores.

## Discussion

The current study found that higher baseline olfactory identification scores were associated with a lower risk of transitioning to MCI and dementia as well as with an increased likelihood of returning to NCI from MCI. While the MSM results did not provide evidence for an association between olfactory scores and death, the LE estimates based on the MSM HRs suggest that individuals with baseline olfactory identification scores of 10 would live significantly longer than those with a score of 5. While these results may seem contradictory, together they demonstrate that olfactory scores can indicate longevity and that associations between olfaction and mortality are likely a function of underlying pathology rather than causal. Results provide support for the clinical value of olfactory testing.

### Olfactory Identification Ability Predicts Transition Between Cognitive States

Our findings indicate that higher baseline olfactory identification scores are associated with a lower risk of transitioning from NCI to MCI and dementia, adjusting for age, sex, education, smoking, *APOE* ε4 allele status, and chronic conditions (Table 2). Higher baseline olfactory scores also had a protective effect, such that those with higher scores on the olfactory identification test were more likely to return to NCI from MCI, as well as have a greater number of years of life without diagnosed cognitive impairment. Healthy individuals with high olfactory scores lived free of diagnosed cognitive impairment for up to 6 years longer, on average, than those who had low olfactory scores (Table 3).

### Olfactory Identification and Mortality, Accounting for Cognitive States

In this analysis, the multistate survival model accounts for cognitive impairment across an average of 7.37 years of follow-up (up to

**Table 3.** Life Expectancies for Nonsmoking Male and Female Participants at Age 80 With a High School Education, and No Chronic Conditions for Low, Medium, and High Olfactory Scores by *APOE* ε4 Status

| | Overall Life Expectancies in Years (95% CIs) | Life Expectancies Without Cognitive Impairment in Years (95% CIs) |
|---|---|---|
| Without *APOE* ε4 | | |
| Female, olfaction (5) | 9.49 (8.48, 10.33) | 4.265 (3.65, 4.84) |
| Female, olfaction (10) | 12.56 (11.55, 13.34) | 8.20, (7.36, 8.65) |
| Female, olfaction (12) | 13.75 (12.32, 14.69) | 10.03 (8.93, 10.82) |
| Male, olfaction (5) | 8.22 (7.08, 9.24) | 3.83 (3.27, 4.64) |
| Male, olfaction (10) | 10.74 (9.38, 12.10) | 7.25 (6.48, 8.26) |
| Male, olfaction (12) | 11.70 (9.99, 13.11) | 8.79 (7.59, 10.08) |
| *APOE* ε4 carrier | | |
| Female, olfaction (5) | 8.73 (7.74, 9.53) | 3.05 (2.48, 3.64) |
| Female, olfaction (10) | 11.75 (10.46, 12.62) | 6.30 (5.44, 7.08) |
| Female, olfaction (12) | 13.08 (11.43, 14.14) | 8.04 (6.87, 9.09) |
| Male, olfaction (5) | 7.48 (6.58, 8.53) | 2.75 (2.18, 3.40) |
| Male, olfaction (10) | 10.18 (8.84, 11.18) | 5.67 (4.73, 6.62) |
| Male, olfaction (12) | 11.31 (9.44, 12.75) | 7.21 (5.84, 8.52) |

*Notes*: APOE = apolipoprotein E; CIs = confidence intervals.

15 years follow-up). While existing literature shows that lower olfactory scores are associated with mortality (3–11,29,30), our findings suggest that, once cognitive status is accounted for, olfactory ability does not directly predict the transition to death from any state. This finding helps to elucidate potential underlying mechanisms for the link between olfaction and death, which are currently unclear in the literature (29,30). Specifically, our findings suggest that olfaction may not predict mortality above and beyond the competing risk of cognitive decline. Importantly, research suggests that MCI (31,32) and dementia (33) substantially increase risk of death; as such, associations previously reported between olfaction and mortality that do not account for cognition may be partially or largely accounted for by the pathway through cognitive decline. Our findings, that higher olfaction is associated with a substantially decreased risk of transitioning forward through cognitive states (14% per unit increase in olfactory score for NCI to MCI, and 10% per unit increase in olfactory score for MCI to dementia), are consistent with this explanation. Indeed, prior work in MAP applying Cox regression models suggested that low olfactory scores at baseline were associated with increased risk of mortality. That is, in an analysis that did not account for multiple cognitive states, increased risk of mortality was observed in the same data set (ie, MAP) (7). Although low olfactory ability appears to be associated with increased risk of mortality (7) and increased neuropathology in other studies using MAP data (15,34,35), previous work examining risk of death had not simultaneously accounted for the competing risk of transitions through cognitive states. As a sensitivity analysis, we ran a similar Cox survival model, but including the additional years of follow-up available now compared to the previous study (7). When the transitions through cognitive states were not accounted for (and instead the models were only adjusted for baseline cognition), we similarly found that olfaction was a significant predictor of death. As in the previous findings (7), our Cox analysis also indicated that higher olfactory scores were associated with a 17.5% decrease in mortality risk across the full follow-up period (HR = 0.825; 95% CI = 0.80, 0.85). While our sensitivity analyses modeling the risk of all-cause mortality showed that better olfaction predicted reduced risk of death, the more comprehensive MSM analyses that account for occasion-specific cognition reveal that olfactory impairment was not a significant direct predictor of mortality. When the time-varying transitions were accounted for (via multistate modeling), our results showed that baseline olfactory identification score alone did not directly predict death (as suggested by previous research). The MSM approach suggests that the association between olfactory impairment and mortality shares variance with the increased risk of mortality associated with cognitive impairment. That is, the association between olfaction and death is primarily accounted for by the pathway through cognitive decline.

In addition, some research suggests that the association between olfactory ability and mortality may require a substantial period of time to develop. Previous work using proportional hazards models to examine the association between low olfactory scores and death differentiated between prevalent and incident forms of sensory impairment in an examination of risk of mortality over 10 and 15 years (5). Their results indicated that prevalent low olfactory scores were associated with a higher risk for 15-year mortality (5), consistent with most previous studies (3,4,6–8,10,11). However, when they examined the risk of mortality in a subsample of individuals without prevalent olfactory deficits (ie, all participants had high olfactory ability at baseline), but including individuals with incident olfactory deficits (ie, some participants had decreased olfaction at follow-up occasions), results indicated that low olfactory ability was not associated with mortality in the following 10 years. These results suggest that more than 10 years of olfactory impairment may be required in the prediction of mortality rates. Importantly, these findings suggest that olfaction may be a particularly sensitive marker of neural integrity.

Alternatively, mortality may be partly or fully accounted for by cognitive decline prior to death. That is, rather than causing death, the mechanisms linking olfactory performance to risk of mortality may be more related to the aging central nervous system or underlying pathology buildup (29,30). This postulation is further substantiated by the estimated LEs for individuals with better olfaction (ie, individuals with higher olfactory ability were estimated to have longer cognitively unimpaired and total years of LE relative to individuals with lower olfactory ability). While this may seem counterintuitive, given that we did not find a direct association between olfaction and mortality, these findings actually further substantiate our explanation that the association between olfaction and mortality may be accounted for by the pathway through cognitive decline. As higher olfactory ability is associated with longer cognitively unimpaired LEs, the olfactory system may be a more sensitive indicator of overall brain health (eg, brain aging and neuropathology). In other words, individuals with higher olfaction at baseline are less likely to transition to MCI or dementia, which is reflected in their total estimated LE, in addition to their cognitively healthy LE. Together, these results suggest that olfactory testing, although not disease-specific, may be a useful and cost-effective approach for the preclinical assessment of brain health.

### Covariates

It is well known that age is a risk factor for cognitive decline (36). As expected, older age was associated with a greater risk of transitioning forward through cognitive states, as well as death. Male participants with a dementia diagnosis had a greater likelihood of returning to MCI, as well as a higher risk of death. These findings may be due to the small percentage of men in the sample (26%), sex differences in medication efficacy or adherence, depression, amount of social or cognitive engagement, hospital stays, or lifestyle and hormonal differences (37,38).

Education is often included as a component of socioeconomic status (SES), as a proxy for cognitive reserve in late-life cognition (39), and is a reliable predictor of an array of outcomes across the life span (40,41). In this study, although more education was associated with a lower risk of death, it was not significantly associated with transitions between cognitive states. This may be due to the high average education in this cohort. Future studies including participants with more variability in education and SES may provide additional insights.

Having more chronic conditions was associated with a greater likelihood of cognitive improvement, indicated by the significant backward transitions from MCI to NCI and from dementia to MCI. While these results are not intuitive, it is possible that lifestyle changes and medications prescribed in the management of chronic conditions may result in improvements in cognitive performance or mitigate the symptoms of cognitive impairment that ensue from unmanaged chronic conditions and hospital stays. For example, better management of chronic conditions could simultaneously lead to better cognitive outcomes. However, interpretation is difficult due to the complexity of interactions between health conditions, medications, and cognition (42) and by research suggesting that some medications also affect olfaction (43).

*APOE* ε4 has been shown to adversely affect both memory (44,45) and olfactory functioning (46,47). The current analysis suggests that having 1 or more *APOE* ε4 allele(s) increases the likelihood of transitioning to MCI and dementia, and decreases the likelihood of returning to NCI from MCI, indicating a deleterious effect on cognitive health. LEs were also detrimentally affected by the presence of 1 or more ε4 allele(s), with carriers had lower LEs across all olfactory ability levels. For example, an average 80-year-old nonsmoking male participant with a high school education, no chronic conditions, a high olfactory score, and no *APOE* ε4 allele had 1.6 years of additional cognitively unimpaired LE and 0.4 years of additional overall LE compared to those with an *APOE* ε4 allele (Table 2), indicating that the *APOE* allele may not substantially influence total LE, but does influence cognitively unimpaired life span. In female participants, there appeared to be a slight upwards trend in cognitively unimpaired LE as smell ability increased in those with an *APOE* ε4 allele. For example, 80-year-old females without an *APOE* ε4 allele had 1.3 years (low olfactory score), 1.9 years (moderate), and 2 years (high) of additional cognitively unimpaired LEcompared to those with an *APOE* ε4 allele (Table 2). Although the difference is not large, further investigation is warranted to determine the extent of sex differences in the effects of *APOE* ε4 on olfactory ability and LE.

### Limitations

Our findings are based on a fairly homogenous sample of highly educated, mainly white, individuals with a mean age of 80 years who agreed to brain donation after death. Future studies examining multiethnic and mid-life cohorts would benefit this literature. As with most olfactory identification tests, the B-SIT is a forced-choice test where scoring may overestimate olfactory ability. For example, imputing results for up to 2 missing olfactory items on the test may potentially skew results higher for individuals who may be skipping questions due to not knowing the answers. Some items on the B-SIT have been found to have low reliability and may not be assessing participant ability as accurately as other items on the test (19). Although the B-SIT is a shorter version of the University of Pennsylvania Smell Identification Test (UPSIT), which means that the degrees of olfactory dysfunction may not be as clearly delineated, and errors or missing answers have a greater effect on scores, the B-SIT was found to be comparable to the UPSIT for predicting conversion to dementia (48). In addition, an objective scale for chronic conditions, as opposed to self-report, would provide a better measure of health. Exclusion criteria for the analytical sample were based on the requirements for analysis. However, potential selection bias may be present due to survival effects and attrition, as those with missing data or fewer follow ups were not included. Finally, future research conceptually replicating these MSM analyses, or adding in gait speed (49), in additional longitudinal studies of aging would improve our understanding of the importance of accounting for cognition when examining the association between olfactory ability and mortality.

## Conclusion

This study provides evidence that higher olfactory identification ability decreases the likelihood of transitioning to cognitive impairment and increases the likelihood of returning to an unimpaired state. It also suggests that associations between olfaction and mortality are likely to occur primarily through the pathway of neurodegeneration. Results support the notion that olfactory testing may be a useful tool in assessing and monitoring brain health and that implementation of regular olfactory testing as part of general health checkups may improve understanding of cognitive health.

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## Conflict of Interest

None declared.

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## Author Contributions

J.E.K., G.M.-T., A.M.P., T.Y., and N.A.L. contributed to conception and study design. J.E.K. and T.Y. created an initial manuscript draft and J.E.K., T.Y., N.A.L., G.M.-T., A.M.P., and D.A.B. contributed to the text. N.A.L. prepared the data and N.A.L. and J.E.K. contributed to the analysis of data. J.E.K. prepared the figures. J.E.K. and N.A.L. prepared the tables. D.A.B. is part of the RUSH working group and contributed to acquisition of data. G.M.-T. supervised data analysis and A.M.P. and G.M.-T. supervised methodology.

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