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# The Association Between Olfactory Impairment and Total Mortality in Older Adults

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***Background.*** Population-based data on the relationship between impaired olfaction and risk of mortality among older adults are lacking. We used a representative cohort of adults aged 60 years or older to assess whether olfactory loss is a predictor of mortality, independent of potential confounders.

***Methods.*** Olfaction was measured by the San Diego Odor Identification Test (SDOIT) among 1,636 participants enrolled in the Blue Mountains Eye Study (2002–2004). Five-year all-cause mortality was confirmed using the Australian National Death Index.

***Results.*** More than one in five participants (21.8%) with olfactory impairment had died over the 5 years compared with less than 10% of participants without olfactory loss. Moderate olfactory loss (SDOIT score ≤3) was associated with a 68% increased risk of all-cause mortality (multivariable-adjusted hazard ratio, 1.68; 95% confidence interval, 1.10–2.56). This association did not persist after further adjustment for cognitive impairment. The association between olfactory loss and all-cause mortality was more marked among older participants (≥70 years) than younger participants (<70 years) with olfactory impairment (multivariable-adjusted hazard ratio, 1.48; 95% confidence interval, 1.02–2.15). However, adjusting for cognitive impairment diminished this association.

***Conclusions.*** Older adults with moderately impaired olfaction compared with those with normal olfaction had a higher risk of dying 5 years later. The relationship between olfaction and mortality, however, may be largely mediated by cognitive impairment in these older adults. Our findings highlight the value of identifying olfactory loss in the preclinical stage in the older patient before the development of related comorbidities.

***Key Words:*** Olfactory impairment—Mortality—Cognitive impairment—Older adults—Blue Mountains Eye Study.

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A decrease in olfactory function with increasing age has been well reported (1,2). We previously reported a 27.0% (3) prevalence of olfactory impairment among Blue Mountains Eye Study (BMES) participants aged 60 years or older. This rate was comparable to the 24.5% rate observed in the Wisconsin Epidemiology of Hearing Loss Study for persons aged 43–86 years (2), and the 32.9% prevalence in persons aged 53 years or older in the Skövde study (4).

In spite of this relatively high prevalence, olfactory impairment appears to have been overlooked compared with dysfunction of other senses, such as vision and hearing. Although hearing and seeing are obviously of greater interest to humans, the sense of smell encompasses a wide range of functions (5). Decreased smell results in appetite suppression, leading to weight loss and malnutrition (6). Olfactory impairment is a contributory factor in the age-related increases in accidental gas poisonings and explosions that can endanger public safety (6). In the presence of impaired olfaction, disability and diminished quality of life are observed (7–9).

Olfactory dysfunction may also contribute to a high degree of anxiety and depression in older adults. Anxiety due to the inability to enjoy food and drinks and to socialize together with fears that the symptoms are indicative of an underlying disorder (6). There are also published reports showing a significant relationship between olfactory dysfunction and depressive symptoms (8,10,11). Recently, there is growing interest in the link between impaired olfaction and neurodegenerative disorders (12). Olfactory impairment predicts future cognitive decline (13–15) and predates Parkinson's disease by 4 or more years (16,17). Finally, olfactory dysfunction is also linked to numerous other disorders, including diabetes (18), renal disease (19), and epilepsy (20). Only one population-based study (21) of 1,162 adults (mean age 79.7 years) to date has assessed the link between olfaction and mortality risk. After adjusting for age, sex, and education, the authors showed that persons with versus those without olfactory impairment had a 36% increased risk of dying. However, this cohort study did not examine the relationship between severity of olfactory impairment and risk of mortality.

Population-based data on whether olfactory deficit is an independent predictor of mortality to date are lacking. In the current study, we used a large population-based data set of adults aged 60 years and older to determine the association between the presence of olfactory impairment (including severity) and risk of all-cause mortality 5 years later.

## Methods

### *Study Population*

The BMES is a population-based cohort study of common eye diseases and other health outcomes in a suburban Australian population located west of Sydney. Study methods and procedures have been described elsewhere (22). Baseline examinations of 3,654 residents aged older than 49 years were conducted during 1992–1994 (BMES-1, 82.4% participation rate). Of the baseline participants, 2,335 (75.1% of survivors) returned for 5-year follow-up examinations during 1997–1999 (BMES-2), and 1,952 participants (53.4% of the original cohort or 76.6% of survivors) returned for 10-year follow-up examinations during 2002–2004 (BMES-3). For the current study, we use data from BMES-3 only as olfactory function was only assessed at this examination. The University of Sydney and the Western Sydney Area Human Ethics Committees approved the study, and written informed consent was obtained from all participants at each examination.

### *Questionnaire and Physical Examination*

A face-to-face interview with trained interviewers was conducted, and comprehensive data, including information about medical history, hearing, demographic factors, socioeconomic characteristics, lifestyle, and health risk behavior such as exercise and smoking, were obtained from all participants. The medical history included cardiovascular or other systemic disease and associated risk factors and medications used. A past history of angina, diabetes, myocardial infarction, and stroke was determined by responses to a question: "Has a doctor advised you that you have any of the following conditions?" Cognitive decline was assessed using the Mini-Mental State Examination questionnaire (23). Participants with scores less than 24 were considered cognitively impaired.

Classification of hypertension was based on the 2003 World Health Organization/International Society of Hypertension guidelines (24). Participants were classified as having hypertension stage 1 if systolic blood pressure was 140–159 mm Hg or if diastolic blood pressure was 90–99 mm Hg. Participants were classified as having hypertension stage 2 if they were previously diagnosed with hypertension and were using antihypertensive medications, if systolic blood pressure was 160 mm Hg or greater, or if diastolic blood pressure was 100 mm Hg or greater at examination. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, with less than 20 defined as low. Disability in walking at baseline was assessed as present if the participant was observed by a trained examiner to have walking difficulties or used walking aids or a wheelchair.

### *Olfaction Examination*

The San Diego Odor Identification Test (SDOIT) (25) and related olfactory and taste questions were a component of the BMES III examination, and complete olfaction and taste data were obtained from 1,636 of 1,952 (83.8%) BMES-3 participants. Participants were tested individually with the SDOIT, an 8-item odor identification test with a test-retest reliability relatively similar to that for the 40-item University of Pennsylvania Smell Identification Test (UPSIT; $r = 0.86$ SDOIT; $r = 0.94$ UPSIT) (26). Odorants were presented to participants in random order in an opaque container covered with gauze. An interstimulus pause of 45 seconds was used to prevent adaptation (27). A picture board illustrating the odorants as well as distracters was used for participants to identify each odorant. Scores were calculated by the number of odorants identified correctly. We defined mild olfactory impairment as less than six but greater than three correct responses and moderate as three or less correct responses out of a total of eight possible responses.

### *Assessment of Mortality*

To identify and confirm persons who died after BMES-3, demographic information including surname, first and second names, gender, and date of birth of the 1,636 participants was cross-matched with Australian National Death Index data for deaths to the end of 2007. A probabilistic record linkage package was used, adopting a multiple-pass procedure in which both data sets were grouped based on different characteristics (eg, date of birth, name, sex) each time. Matches were divided into exact and nonexact. All nonexact matched records were examined manually and accepted if there was only one nonexact matched characteristic that was not critical. Information provided by family members during follow-up was also included if the participant was reported to have died on or before December 2007. The *International Classification of Diseases, Ninth Revision* (28) and *International Statistical Classification of Diseases, 10th Revision* (29) cause of death codes were also obtained. The primary cause of death (ie, death from any cause) was used in statistical modeling. The validity of Australian National Death Index data has been reported to have high sensitivity and specificity for cardiovascular mortality (92.5% and 89.6%, respectively) (30). The census cutoff point for all-cause death was December 2007 (5-year follow-up).

### *Statistical Analysis*

SAS statistical software (SAS Institute, Cary NC) version 9.1 was used for analyses. The association between olfactory

Table 1. Baseline Characteristics of Study Participants

| Characteristics | Olfactory Impairment, $N = 441$ | No Impairment, $N = 1,195$ | $p$ Value |
|---|---|---|---|
| Age, y, *M* (*SD*) | 77.2 (7.5) | 72.1 (7.2) | <.0001 |
| Men, *n* (%) | 238 (54.0) | 447 (37.4) | <.0001 |
| Current smoker, *n* (%) | 33 (7.5) | 68 (5.7) | .19 |
| Body mass index, kg/m$^2$, *M* (*SD*) | 26.0 (4.4) | 27.6 (4.7) | <.0001 |
| Alcohol consumption, *n* (%) | | | |
| Never | 85 (19.5) | 217 (18.3) | .69 |
| Light | 191 (43.7) | 555 (46.8) | |
| Moderate | 153 (35.0) | 396 (33.4) | |
| Heavy | 8 (1.8) | 17 (1.4) | |
| Poor self-rated health, *n* (%) | 106 (24.2) | 217 (18.2) | .01 |
| Visual impairment, *n* (%) | 79 (18.0) | 103 (8.6) | <.0001 |
| Presence of hypertension, *n* (%) | 248 (56.8) | 692 (58.2) | .60 |
| Systolic blood pressure, mm Hg, *M* (*SD*) | 141.5 (21.4) | 142.4 (21.5) | .46 |
| Serum total cholesterol, mmol/L, *M* (*SD*) | 5.3 (1.0) | 5.5 (1.1) | <.0001 |
| Mini-Mental State Examination score, *M* (*SD*) | 27.9 (3.0) | 28.9 (1.7) | <.0001 |
| Stroke, *n* (%) | 37 (8.5) | 57 (4.8) | .005 |
| History of diabetes, *n* (%) | 71 (18.9) | 155 (14.4) | .04 |
| History of cancer, *n* (%) | 60 (13.7) | 213 (17.9) | .04 |
| History of angina, *n* (%) | 79 (18.2) | 159 (13.4) | .02 |
| History of acute myocardial infarction, *n* (%) | 50 (11.6) | 112 (9.5) | .22 |

impairment and mortality was examined using Cox regression models to estimate hazard ratios and 95% confidence intervals. Multivariable regression models were first adjusted for age and sex (Model 1) and then further adjusted for confounders that were found to be significantly associated with mortality, that is, BMI, current smoking status, alcohol consumption, poor self-rated health, presence of hypertension and/or diabetes, history of cancer, angina, stroke, and/or acute myocardial infarction (Model 2), serum total cholesterol (Model 3), and cognitive impairment (Model 4). We estimated the proportion surviving using the Kaplan–Meier method.

## Results

Table 1 compares the baseline characteristics of participants with (27.0%) and those without (73.0%) olfactory impairment. Persons with olfactory loss were more likely to be older and male and to have visual impairment, cognitive impairment, diabetes, angina, stroke, lower BMI, and poor self-rated health but higher serum total cholesterol.

More than one in five participants with olfactory impairment had died over the 5-year period compared with less than 10% of participants with normal olfaction (Table 2). This proportion increased with the severity of impairment, that is, more than one in four participants (27.4%) with moderate impairment died during the 5-year period. Figure 1 shows the 5-year survival of BMES participants with differing severity of olfactory loss. Older persons with moderate olfactory impairment had lower survival than those with mild or no impairment. Participants with any level of olfactory dysfunction had a 67% higher risk of all-cause mortality than those without olfactory impairment (Table 2). However, after further adjustment for total serum cholesterol (Model 3), this association became nonsignificant. Similarly, moderate olfactory loss was associated with a 68% increased risk of total mortality, but in Model 4 after further adjustment for cognitive impairment, this association did not persist (Table 2).

We previously showed that olfactory impairment is strongly age and sex related (3). Hence, we stratified our analyses by age and sex (Table 3). The association between olfactory loss and all-cause mortality was more marked among participants aged 70 years or older (multivariable-adjusted hazard ratio, 1.48; 95% confidence interval, 1.02–2.15). Again, after adjusting for cognitive impairment, however, this association became nonsignificant. A slightly higher proportion of men than women with olfactory dysfunction had died over the 5 years, 17.4% versus 11.4%. However, in Model 4, a significant association between olfactory loss and mortality was not observed among either men or women considered separately (Table 3).

## Discussion

In this large cohort study of adults aged more than 60 years, more than one in five participants (21.8%) with olfactory impairment had died during the 5-year follow-up compared with less than 10% of participants without olfactory

Table 2. All-Cause Mortality (over 5 years) by Severity of Olfactory Impairment

| Olfactory Impairment | No. of Deaths (%) | Hazard Ratio (95% confidence interval) | | | |
|---|---|---|---|---|---|
| | | Model 1* | Model 2† | Model 3‡ | Model 4§ |
| None | 99 (8.3) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Any | 96 (21.8) | 1.69 (1.26–2.27) | 1.67 (1.22–2.30) | 1.40 (0.98–1.99) | 1.24 (0.85–1.81) |
| Mild | 37 (16.4) | 1.39 (0.95–2.04) | 1.33 (0.88–2.01) | 1.15 (0.72–1.82) | 1.01 (0.62–1.64) |
| Moderate | 59 (27.4) | 1.99 (1.42–2.80) | 2.04 (1.41–2.95) | 1.68 (1.10–2.56) | 1.51 (0.96–2.38) |

*Notes*: *Adjusted for age and sex.

†Further adjusted for body mass index, systolic blood pressure, current smoking status, alcohol consumption, poor self-rated health, visual impairment, presence of hypertension and/or diabetes, and history of cancer, angina, stroke, and/or acute myocardial infarction.

‡Further adjusted for serum total cholesterol.

§Further adjusted for cognitive impairment.

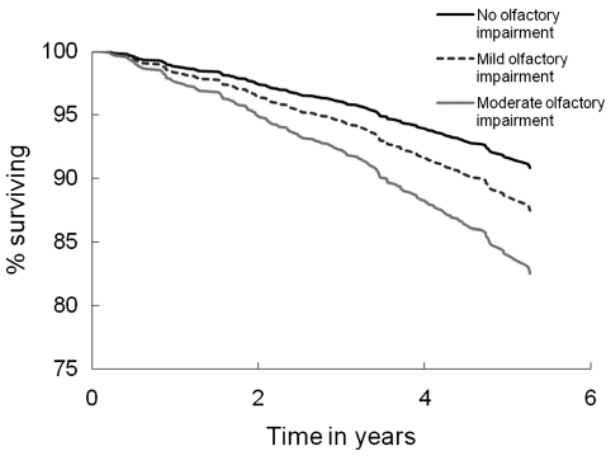


Figure 1. Age-sex adjusted Kaplan–Meier survival curves by severity of olfactory impairment among Blue Mountains Eye Study participants aged 60 years and older.

loss. This proportion increased with the severity of impairment, that is, more than one in four participants (27.4%) with moderate impairment died over 5 years. Older adults with moderately impaired olfaction had a 68% greater risk of dying compared with those with normal olfaction over a 5-year period. The association between olfactory impairment and all-cause mortality was particularly marked among participants aged 70 years or older. However, these observed associations with mortality did not persist after further adjustment for cognitive impairment.

A U.S. study of older adults showed that persons with impaired olfactory function were around 36% more likely to die than those with normal olfaction (21). However, in the analysis, only age, sex, and education were adjusted for in the multivariate model. We observed that persons with any olfactory impairment had a 67% increased risk of dying 5 years later after multivariate adjustment. This association, however, did not persist after adjusting for either total serum cholesterol and/or cognitive impairment. This could have been partly due to reduced statistical power as 217 participants did not have serum cholesterol measures and Mini-Mental State Examination scores and so were excluded from the multivariate analyses. The association between moderate olfactory impairment and mortality was strong after adjusting for all covariates, including serum total cholesterol, that is, a 68% higher risk of mortality, but subsequent adjustment for cognitive impairment diminished this association.

Olfactory impairment could be a predictor of mortality as it is a marker of neurodegenerative diseases that are known to contribute to mortality (21). We and others previously showed that olfactory impairment is significantly associated with cognitive impairment and Parkinson's disease (3,13–17). Olfactory impairment is an early marker of Parkinson's disease (16), most likely due to Lewy body inclusions in olfactory bulb and primary olfactory cortex (31). Moreover, the level of olfactory performance is related to postmortem extent of Alzheimer's disease pathology, even in individuals who died without evidence of mild cognitive impairment or dementia (32). This could explain why most of our observed associations between olfaction and mortality became nonsignificant after including cognitive impairment in the final multivariate model. Alternatively, as discussed, we may not have been able to detect modest associations due to the lack of statistical power caused by excluding participants from analyses who did not have Mini-Mental State Examination measures.

Olfaction also plays an important role in eating habits and nutritional intake (33). Thus, it is not surprising that weight loss is more frequent in individuals with olfactory dysfunction (34). Indeed in our cohort, BMI was significantly lower in participants with than without olfactory

Table 3. Association Between Olfactory Impairment and All-Cause Mortality (over 5 years), Stratified by Age and Sex

| | | Hazard Ratio (95% confidence interval) | | | |
|---|---|---|---|---|---|
| | No. of Deaths (%) | Model 1* | Model 2† | Model 3‡ | Model 4§ |
| Age <70 y | | | | | |
| No olfactory impairment | 595 (94.9) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Olfactory impairment | 32 (5.1) | 0.80 (0.23–2.77) | 1.35 (0.37–4.98) | 1.26 (0.26–6.15) | 1.14 (0.22–5.92) |
| Age ≥70 y | | | | | |
| No olfactory impairment | 1087 (82.0) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Olfactory impairment | 238 (18.0) | 1.81 (1.32–2.46) | 1.76 (1.26–2.47) | 1.48 (1.02–2.15) | 1.30 (0.87–1.93) |
| Men | | | | | |
| No olfactory impairment | 655 (82.6) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Olfactory impairment | 138 (17.4) | 1.85 (1.25–2.73) | 1.67 (1.09–2.54) | 1.40 (0.87–2.26) | 1.33 (0.81–2.20) |
| Women | | | | | |
| No olfactory impairment | 1027 (88.6) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Olfactory impairment | 132 (11.4) | 1.49 (0.94–2.36) | 1.77 (1.07–2.92) | 1.49 (0.85–2.61) | 1.50 (0.88–2.56) |

*Notes*: *Adjusted for age and sex.

†Further adjusted for body mass index, systolic blood pressure, current smoking status, alcohol consumption, poor self-rated health, visual impairment, presence of hypertension and/or diabetes, and history of cancer, angina, stroke, and/or acute myocardial infarction.

‡Further adjusted for serum total cholesterol.

§Further adjusted for cognitive impairment.

impairment. Patients with olfactory impairment are also shown to exhibit specific dislikes toward certain foods (33,35). For instance, older women with olfactory loss were found to have a reduced preference for fruits and vegetables while consuming larger amounts of sweets and fats (36). This, however, was not shown to lead to systemic changes in BMI or energy intake (33). The higher risk of mortality observed among persons with olfactory loss could also be mediated by poor nutritional status. Additional longitudinal studies with adequate study power will be needed to assess this relationship.

We observed stronger associations among the older subgroup (in persons aged 70 years or older); this could primarily be due to the significant age-associated increase in the prevalence of olfactory impairment observed in the BMES and other adult studies (2,3,37). Hence, the greater number of persons with olfactory deficits in this age group could have allowed us to detect modest associations between olfactory impairment and all-cause mortality.

Although the prevalence of impaired olfaction in the "healthy" aging population could be greater than previously thought (3), many older people may not raise the issue of a smell impairment themselves because they are not always aware of it (9) or do not understand its potential importance. Our findings could have relevant public health implications as they emphasize to clinicians the finding that olfactory loss and reduced cognitive function are likely to coexist in older patients and could potentially reduce their survival. Hence, odor identification tests, combined with neuropsychological tests, could be useful in identifying this group of older adults so as to prevent their likely rapid decline in health.

Strengths of this study include its prospective design, reasonable follow-up rate, and ascertainment of mortality by validated National Death Index data. There are also a number of limitations of this study. First, the SDOIT tests only a limited number of stimulants, possibly leading to an underestimation of deficits in the rare spectrum of olfaction (3), although it is more reliable than self-reported olfactory loss. Second, although we collected information on and controlled for important confounders, other unmeasured factors (eg, lifestyle or societal factors) could have influenced our study findings. Finally, the number of persons with olfactory impairment was relatively small (27.0%), which could have led to insufficient power to detect some modest associations.

In summary, we observed significant associations between olfactory loss and mortality, particularly in persons aged more than 70 years and among those with moderately impaired olfaction. These associations, however, were not independent of cognitive impairment. Our findings suggest that the association between olfaction and mortality risk could be mediated, at least in part, by the presence of impaired cognition in this group of older adults. Further large cohort studies with adequate adjustment of potential confounders are required to examine the relationship between olfactory impairment and mortality risk.

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Conflict of Interest

All authors have no conflict of interest and declare no financial interest.

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