Relationship Between Poor Olfaction and Mortality Among Community-Dwelling Older Adults: A Cohort Study

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Relationship Between Poor Olfaction and Mortality Among Community-Dwelling Older Adults

A Cohort Study

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Background: Poor olfaction is common among older adults and has been linked to higher mortality. However, most studies have had a relatively short follow-up and have not explored potential explanations.

Objective: To assess poor olfaction in relation to mortality in older adults and to investigate potential explanations.

Design: Community-based prospective cohort study.

Setting: 2 U.S. communities.

Participants: 2289 adults aged 71 to 82 years at baseline (37.7% black persons and 51.9% women).

Measurements: Brief Smell Identification Test in 1999 or 2000 (baseline) and all-cause and cause-specific mortality at 3, 5, 10, and 13 years after baseline.

Results: During follow-up, 1211 participants died by year 13. Compared with participants with good olfaction, those with poor olfaction had a 46% higher cumulative risk for death at year 10 (risk ratio, 1.46 [95% CI, 1.27 to 1.67]) and a 30% higher risk at year 13 (risk ratio, 1.30 [CI, 1.18 to 1.42]). Similar associations were found in men and women and in white and black persons. However, the association was evident among participants who reported excellent to good health at baseline (for example, 10-year mortality risk ratio, 1.62 [CI, 1.37 to 1.90]) but not among those who reported fair to poor health (10-year mortality risk ratio, 1.06 [CI, 0.82 to 1.37]). In analyses of cause-specific mortality, poor olfaction was associated with higher mortality from neurodegenerative and cardiovascular diseases. Mediation analyses showed that neurodegenerative diseases explained 22% and weight loss explained 6% of the higher 10-year mortality among participants with poor olfaction.

Limitation: No data were collected on change in olfaction and its relationship to mortality.

Conclusion: Poor olfaction is associated with higher long-term mortality among older adults, particularly those with excellent to good health at baseline. Neurodegenerative diseases and weight loss explain only part of the increased mortality.

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The human sense of smell gradually decreases with age. Olfactory impairment or poor sense of smell affects up to 25% of U.S. older adults and, unlike hearing or vision impairment, often goes unrecognized (1, 2). Poor sense of smell may adversely affect safety (3), nutrition (4), and quality of life in older adults (5). Furthermore, accumulating evidence suggests that olfactory impairment is among the earliest symptoms of major neurodegenerative diseases, such as Alzheimer disease (6–8) and Parkinson disease (9–11).

Several studies, typically with a median follow-up of 5 years or less, have shown an "independent" association between olfactory impairment and increased all-cause mortality among older adults (12–17). However, poor olfaction may reflect a person's deteriorating health in the years before death. Further, few studies have examined the association by sex (13, 16, 17) or race (13) despite reports of sex-based and racial differences in both the prevalence of olfactory impairment (1, 2) and its relationship to neurodegenerative diseases (9, 18). Finally, little is known about why poor olfaction predicts higher mortality among older adults. Although contributions from neurodegenerative diseases (12–15, 17), poor nutrition (12, 13, 17), food or gas poisoning (12, 13), and fire or hazardous environment (19) have been speculated, few empirical data exist.

Therefore, we examined olfaction in relation to all-cause mortality at various lengths of follow-up in a biracial, community-based cohort of older adults in the United States. We further examined this association by sex, race, and general health status, and investigated potential explanations through analyses of mediators and cause-specific deaths.

Methods

Study Population

The Health ABC (Health, Aging, and Body Composition) Study was designed to investigate whether changes in body composition act as a common pathway by which multiple diseases affect illness, disability,

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Table 1. Baseline Population Characteristics, by Tertile of BSIT Score (*N* = 2289)*

Characteristic	Olfaction, by Tertile of BSIT Score			*P* Value†
	Poor (Score, 0–8) (*n* = 727)	Moderate (Score, 9–10) (*n* = 785)	Good (Score, 11–12) (*n* = 777)	
Mean age (SD), *y*	76.1 (2.9)	75.6 (2.9)	75.2 (2.7)	<0.001‡
Male sex	426 (58.6)	375 (47.8)	299 (38.5)	<0.001
White race	404 (55.6)	487 (62.0)	536 (69.0)	<0.001
Education				<0.001
Less than high school	225 (30.9)	167 (21.3)	114 (14.7)	
High school	220 (30.3)	269 (34.3)	261 (33.6)	
Postsecondary	282 (38.8)	349 (44.5)	402 (51.7)	
Body mass index				0.078
<25 kg/m^2	267 (36.7)	246 (31.3)	248 (31.9)	
25–30 kg/m^2	298 (41.0)	328 (41.8)	344 (44.3)	
>30 kg/m^2	162 (22.3)	211 (26.9)	185 (23.8)	
Brisk walking				0.056
≥90 min/wk	64 (8.8)	73 (9.3)	95 (12.2)	
<90 min/wk	663 (91.2)	712 (90.7)	682 (87.8)	
Alcohol drinking				<0.001
Never	197 (27.1)	219 (27.9)	226 (29.1)	
Current	341 (46.9)	396 (50.4)	427 (55.0)	
Former	189 (26.0)	170 (21.7)	124 (16.0)	
Cigarette smoking				0.002
Never	310 (42.6)	341 (43.4)	388 (49.9)	
Current	68 (9.4)	57 (7.3)	39 (5.0)	
Former	349 (48.0)	387 (49.3)	350 (45.0)	
General health status				<0.001
Excellent to good	564 (77.6)	670 (85.4)	667 (85.8)	
Fair to poor	163 (22.4)	115 (14.6)	110 (14.2)	
Dementia	184 (25.3)	93 (11.8)	57 (7.3)	<0.001
Parkinson disease	13 (1.8)	3 (0.4)	1 (0.1)	<0.001§
Chronic kidney disease	210 (28.9)	169 (21.5)	155 (19.9)	<0.001
Cardiovascular disease	205 (28.2)	225 (28.7)	222 (28.6)	0.98
Cancer	139 (19.1)	160 (20.4)	151 (19.4)	0.81
Diabetes	185 (25.4)	187 (23.8)	159 (20.5)	0.064
Hypertension	531 (73.0)	589 (75.0)	559 (71.9)	0.38
Depressive symptoms	122 (16.8)	118 (15.0)	86 (11.1)	0.005

BSIT = Brief Smell Identification Test.
* Values are numbers (percentages) unless otherwise indicated.
† Calculated using the χ^2 test for categorical variables unless otherwise indicated.
‡ Calculated using the *t* test for continuous variables.
§ Calculated using the Fisher exact test.

and mortality in older adults (20). Briefly, in 1997 and 1998, the study enrolled 3075 well-functioning, community-dwelling persons (48.4% men and 41.6% black persons) aged 70 to 79 years in the metropolitan areas of Pittsburgh, Pennsylvania, and Memphis, Tennessee (20). Eligibility criteria were no difficulty in walking a quarter mile, climbing 10 steps, or performing activities of daily living; no active cancer treatment in the previous 3 years; and no plan to move away from the study area in the next 3 years. Participants were followed through 2014 with annual clinic or home visits and semiannual or quarterly telephone interviews. For participants who were not able to attend clinic visits, the study team visited them at home (taking fewer measurements) or interviewed them or their proxies by telephone (21).

The 12-item Brief Smell Identification Test (BSIT) was administered to 2544 participants who attended the year 3 clinic visit in 1999 or 2000 (hereafter called baseline) (22). After exclusion of participants who were missing the BSIT score (*n* = 7), covariates (*n* = 32), or mediators (*n* = 149) or were lost to follow-up (*n* = 67), the final analytic sample included 2289 participants (**Appendix Figure 1**, available at Annals.org). We followed participants for survival analyses at years 3, 5, 10, and 13 after baseline.

The study protocol was approved by all relevant institutional review boards. All study participants gave informed consent at enrollment.

The BSIT

The BSIT is a simple and cost-effective smell identification test to screen for olfactory impairment; it has been validated and widely used in clinical and epidemiologic studies (22, 23). Participants were asked to smell 12 odorants that are common in daily life, 1 at a time, and then identify the odor from 4 possible answers in a forced-choice format (22). One point was given for each correct answer, such that the total score ranged from 0 to 12 (22). We categorized total BSIT scores into poor, moderate, and good sense of smell using tertile ranges of 0 to 8, 9 to 10, and 11 to 12 points, respectively, consistent with both population norms (22) and conventional uses of the score in other epidemiologic studies (8, 24).

Outcomes

Health ABC closely monitored the health and survival of study participants with comprehensive hospitalization and death surveillance. For each hospitalization, up to 20 diagnoses were recorded at discharge using codes from the International Classification of Diseases, Ninth Revision, Clinical Modification. This discharge summary, along with medical history records and physical examination results, was subsequently reviewed and adjudicated by a local medical event adjudicator. For each death, study investigators had an exit interview with a knowledgeable proxy who provided detailed information on the death event and the participant's physical functioning before death. A central team of medical experts reviewed these data, together with hospitalization records, death certificates, and autopsy data, and adjudicated the underlying cause of death by consensus.

Our outcomes of interest were cumulative all-cause mortality at 3, 5, 10, and 13 years of follow-up; cause-specific mortality from dementia or Parkinson disease; cardiovascular disease (that is, fatal myocardial infarction, fatal coronary heart disease, cerebrovascular disease, atherosclerotic disease other than coronary or cardiovascular, or other cardiovascular disease) (25); cancer; and respiratory disease, including chronic obstructive pulmonary disease and pneumonia. Analyses on other specific causes of death were precluded by small numbers.

Baseline Covariates

In the analyses, we considered the following covariates at baseline: sociodemographic characteristics (age, sex, race, and education), anthropometric indicators (weight and height), lifestyle (smoking, alcohol drinking, and physical activity), self-reported health status (excellent, very good, good, fair, and poor), and health conditions (Table 1).

We defined baseline health conditions using previously published criteria. Briefly, chronic kidney disease was defined as a glomerular filtration rate less than 60 mL/min/1.73 m^2 (26). Cardiovascular disease included adjudicated diagnoses of coronary heart disease (myocardial infarction or angina), congestive heart failure, cerebrovascular disease (stroke, transient ischemic attack, or carotid artery disease), and peripheral vascular disease (27, 28). Cancer diagnoses, except for melanoma, were adjudicated by a panel of physicians after review of hospital records, death certificates, and annual interview data (29). Diabetes was defined as a patient-reported diagnosis by a physician, antidiabetic medication use, a fasting blood glucose level of at least 6.99 mmol/L (126 mg/dL), or an oral glucose tolerance test result of at least 11.10 mmol/L (200 mg/dL) (30). Hypertension was defined as a patient-reported diagnosis by a physician, use of antihypertensive medications, or either systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg (31). Depressive symptoms were defined as a score of 10 or greater on the 10-item Center for Epidemiologic Studies Depression Short Form (32).

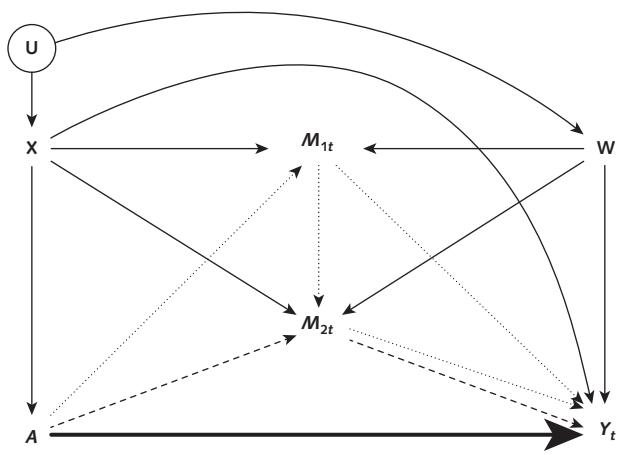
Potential Mediators

In mediation analyses, we focused on neurodegenerative diseases and weight loss (as a surrogate for malnutrition) because existing literature speculates that they may partly explain the relationship between poor olfaction and higher mortality (12–17) (Supplement, available at Annals.org). Although contributions from hazardous events (such as food or gas poisoning and fires) are also suspected, we could not examine these contributions because of lack of data.

We used previously published definitions of dementia and Parkinson disease (9, 18). Briefly, study participants' cognitive status was evaluated at clinic visits 1, 3, 5, 8, 10, 11, and 16 using the Modified Mini-Mental State examination (score range, 0 to 100) (33). We defined dementia as a score less than 80 at clinic visit 1, a race-stratified decline in score of at least 1.5 SD from clinic visit 1, or an adjudicated diagnosis of dementia by the study team based on hospitalization and medication data. Two movement disorder specialists adjudicated the diagnosis of Parkinson disease by consensus after comprehensive review of patient-reported Parkinson diagnosis by a physician, medication use, hospitalization surveillance, and adjudicated cause of death (9). Because poor olfaction is a well-established prodromal symptom for both Parkinson disease (9, 11, 34–36) and dementia (7, 37–39), we assume that it might have developed before clinical diagnosis, even for patients with prevalent dementia or Parkinson disease at baseline. We therefore included both prevalent and incident cases of dementia or Parkinson disease in defining mediation pathways involving these diseases.

We defined weight loss as a binary variable that indicated average annual weight loss of at least 2%,

Figure 1. Directed acyclic graph for the mediation analysis.



The bold arrow represents the direct effect of olfaction, the dotted arrows represent the natural indirect effect through M_{1t}, and the dashed arrows represent the partial indirect effect through M_{2t}. A = olfaction; M_{1t} = dementia or Parkinson disease; M_{2t} = average annual weight loss ≥2%; *t* = year (3, 5, 10, or 13); U = unmeasured confounding; X and W = baseline confounders; Y_t = all-cause mortality for year *t*.

Table 2. Estimated Average Risk for All-Cause Mortality and RRs, by Olfaction (*N* = 2289)

Years of Follow-up	Estimated Average Risk						Total Effect	
	Poor		Moderate		Good		Poor vs. Good	Moderate vs. Good
	Deaths, *n*	Estimated Average Risk (95% CI)*	Deaths, *n*	Estimated Average Risk (95% CI)*	Deaths, *n*	Estimated Average Risk (95% CI)*	RR (95% CI)*	RR (95% CI)*
3	48	0.05 (0.04–0.07)	39	0.05 (0.04–0.06)	30	0.05 (0.03–0.07)	1.15 (0.69–1.86)	1.04 (0.65–1.73)
5	123	0.14 (0.12–0.17)	90	0.12 (0.09–0.14)	78	0.13 (0.10–0.16)	1.14 (0.86–1.50)	0.92 (0.68–1.22)
10	351	0.44 (0.40–0.48)	279	0.35 (0.32–0.39)	206	0.30 (0.27–0.34)	1.46 (1.27–1.67)	1.17 (1.01–1.33)
13	473	0.61 (0.57–0.65)	408	0.52 (0.49–0.55)	330	0.47 (0.44–0.50)	1.30 (1.18–1.42)	1.11 (1.01–1.22)

RR = risk ratio.
* Model was adjusted for age, sex, race, education, body mass index, drinking, brisk walking, smoking, self-reported general health status, cardiovascular diseases, cancer, diabetes, hypertension, depressive symptoms, and chronic kidney disease. See the second footnote to Table 3 for the definition of the total effect.

using body weights measured at visits 3, 4, 5, 6, 8, 10, 11, and 16. We first calculated the percentage of annual weight change between the 2 closest clinic visits (for example, [weight at visit 4 − weight at visit 3] ÷ [weight at visit 3]) and then averaged the percentages over the visits between baseline and any given year of follow-up. We defined weight loss as "yes" if the average annual weight loss was at least 2% and "no" if not. A cutoff of 2% is beyond the annual weight loss of 0.5% that is reported to be normal in older adults (40), and this cutoff corresponded to approximately the first quintile of weight change in our study population.

Because weight loss and malnutrition are common in Parkinson disease (41–43) and dementia (44–46), a sequential relationship between these diseases and subsequent weight loss was 1 of 2 pathways whereby dementia or Parkinson disease mediated the relationship between poor olfaction and higher mortality. Consistent with our analysis of all-cause mortality, we did mediation analyses in a time-dependent manner at follow-up years 3, 5, 10, and 13.

Statistical Analysis

Figure 1 presents a potential directed acyclic graph, a common approach to depicting, encoding, and modeling causal pathways, in this case among olfaction; dementia or Parkinson disease; weight loss; and cumulative mortality rates at years 3, 5, 10, and 13. In this graph, we defined the total effect of olfaction on all-cause cumulative mortality at a given year as the combination of its natural direct effect (*bold arrow*), the natural indirect effect mediated through all pathways involving dementia or Parkinson disease (*dotted arrows* from olfaction to dementia or Parkinson disease to weight loss to death and from olfaction to dementia or Parkinson disease to death), and the partial indirect effect mediated through the pathway involving only weight loss (*dashed arrows* from olfaction to weight loss to death). The Supplement presents modeling details, assumptions, and programs. Briefly, the key assumptions encoded in Figure 1 are no unmeasured confounding between olfaction–mediator and olfaction–outcome relationships, no unmeasured confounding between mediator–outcome relationships, and no mediator–outcome confounders affected by olfaction. The estimation procedure is the weighting and imputation approach described by Steen and colleagues (47). We presented the aforementioned causal effects on a risk ratio scale and calculated percentile-based 95% CIs using 1000 bootstrap replications (48). We calculated the proportion mediated (that is, the ratio of an indirect effect to the total effect on the risk difference scale) for each mediator (the Supplement shows conversion from the risk difference to risk ratio scale).

Baseline potential confounders included age, sex, race, education level, body mass index categories, smoking history, drinking history, brisk walking, dichotomized self-reported health status (that is, excellent to good vs. fair to poor), and baseline chronic diseases (that is, chronic kidney disease, cardiovascular disease, cancer, diabetes, hypertension, and depressive symptoms). We further examined potential effect modifications by sex, race, and self-reported health status by including multiplicative interaction terms in the natural-effects regression models (47).

For cause-specific mortality, we did flexible parametric survival analyses (49, 50) and estimated the standardized survival and 95% CIs, adjusting for potential confounders. We further calculated the difference in standardized survival for each cause of death comparing good versus poor or moderate olfaction groups.

To evaluate the robustness of results, we did sensitivity analyses using the alternative weighting scheme (47) and calculated E-values (51) for each of the aforementioned causal effects or mediation pathways. E-values can be interpreted as the minimum strength of association that an unmeasured confounder needs to have with both olfaction and all-cause mortality (or mediators), given adjusted covariates, to explain away the estimated causal effects; larger E-values indicate more robust results (51).

We used R, version 3.4.1 (R Foundation), and Stata, version 15 (StataCorp), for mediation analysis of all-cause mortality (see codes in the Supplement); we used Stata, version 15 (user-written command stpm2 [49]), for standardized survival of cause-specific mortality, with a 2-sided α of 0.05.

Role of the Funding Source

Study sponsors had no role in the study design, data analyses, interpretation of results, manuscript preparation, or decision to submit the manuscript for publication.

RESULTS

The mean age of study participants at baseline was 75.6 years (SD, 2.9; range, 71 to 82). Poor olfaction was associated with older age, male sex, black race, lower education level, alcohol drinking, smoking, and fair to poor health status (Table 1). Of the chronic diseases examined, poor olfaction was strongly associated with prevalent dementia, Parkinson disease, and chronic kidney disease; modestly associated with depressive symptoms; and not associated with cardiovascular disease, cancer, diabetes, or hypertension.

During 13 years of follow-up, 1211 participants died (Table 2). Poor olfaction was significantly associated with higher all-cause mortality at years 10 and 13. Compared with participants with good olfaction, those with poor olfaction had a 46% higher cumulative risk for death at year 10 and a 30% higher risk at year 13. Participants with moderate olfaction also had an increase in mortality (17% at year 10 and 11% at year 13) that was small but statistically significant. Similar associations were found in both sexes and both races (Appendix Tables 1 and 2, available at Annals.org). However, the association seems to be driven by participants who reported excellent to good health at baseline (Appendix Table 3, available at Annals.org). Among these participants, poor olfaction was associated with 62% higher all-cause mortality at year 10 and 40% higher all-cause mortality at year 13, whereas we did not note any association among participants with fair to poor health.

Figure 2 shows differences in standardized survival for 4 major causes of death between participants with good olfaction and those with poor or moderate olfaction. Poor olfaction was strongly associated with death from dementia or Parkinson disease and modestly associated with death from cardiovascular disease. Poor olfaction, however, was not associated with death from cancer or respiratory disease. Appendix Figure 2, available at Annals.org, shows standardized survival curves.

In the mediation analysis, we estimated how much of the total effect of olfaction on all-cause mortality could be explained by various mediation pathways hypothesized in the directed acyclic graph (Figure 1). Compared with good olfaction, the natural direct effect of poor olfaction on mortality was statistically significant at years 10 and 13 (Table 3). The natural indirect effect mediated through pathways involving dementia or Parkinson disease was statistically significant for the poor and moderate olfaction groups at years 10 and 13. The partial indirect effect mediated through the pathway involving only weight loss was statistically significant for the poor and moderate olfaction groups at year 13.

Figure 2. Difference in standardized survival of cause-specific death comparing good versus poor or moderate olfaction groups (N = 2289).

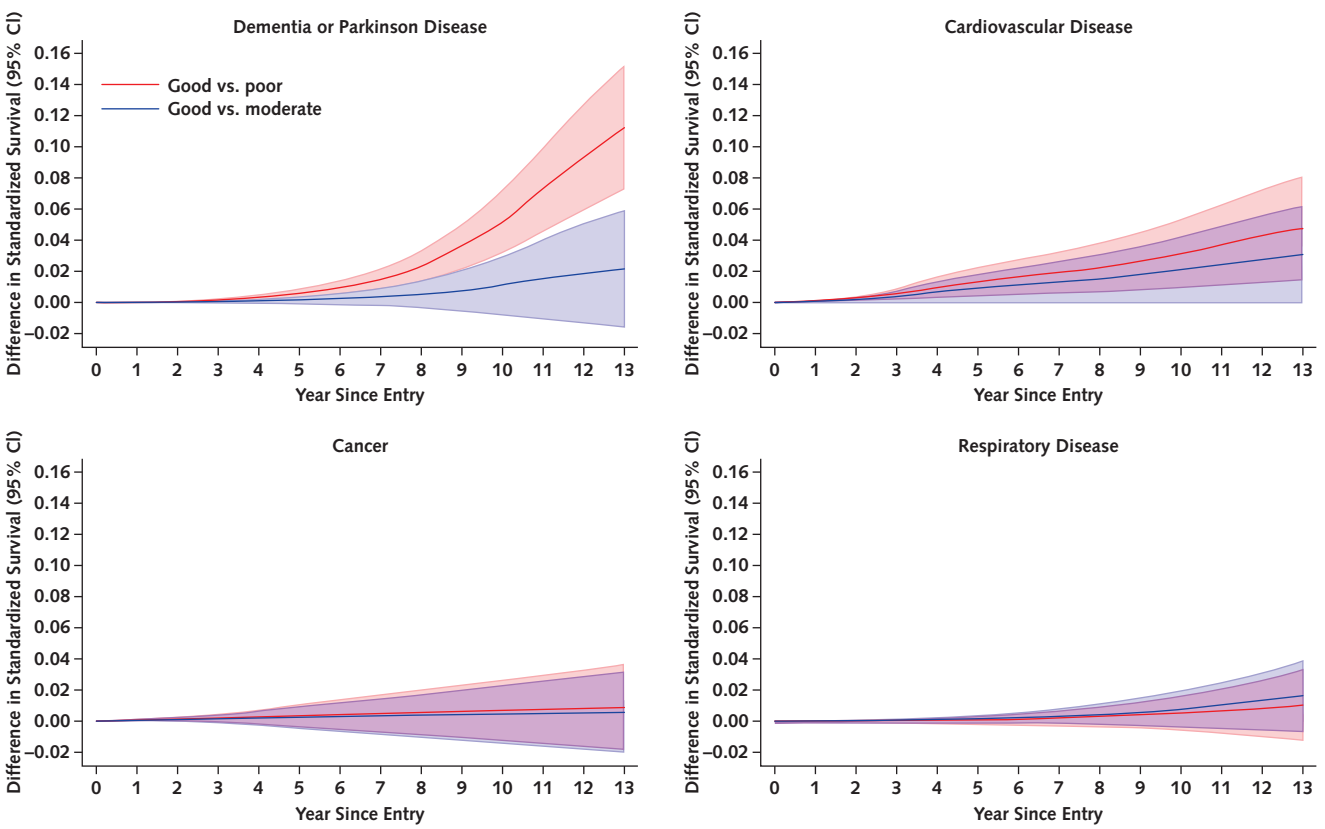


Table 3. Mediation Analysis for the Association Between Olfaction and All-Cause Mortality (*N* = 2289)

Years of Follow-up	RR (95% CI) for Natural Direct Effect*†		Natural Indirect Effect Mediated by All Pathways Through Dementia or Parkinson Disease†				Partial Indirect Effect Mediated by Pathway Through Only Weight Loss†			
	Poor vs. Good	Moderate vs. Good	Poor vs. Good		Moderate vs. Good		Poor vs. Good		Moderate vs. Good	
			RR (95% CI)*	Proportion Mediated	RR (95% CI)*	Proportion Mediated	RR (95% CI)*	Proportion Mediated	RR (95% CI)*	Proportion Mediated
3	1.02 (0.64–1.64)	1.06 (0.67–1.80)	1.15 (1.05–1.28)	NA‡	1.04 (1.00–1.11)	NA‡	0.98 (0.85–1.12)	NA‡	0.94 (0.80–1.07)	NA‡
5	1.05 (0.81–1.37)	0.91 (0.69–1.22)	1.08 (1.02–1.15)	NA‡	1.04 (1.01–1.08)	NA‡	1.00 (0.89–1.10)	NA‡	0.97 (0.86–1.07)	NA‡
10	1.33 (1.15–1.52)	1.13 (0.98–1.29)	1.08 (1.05–1.11)	22	1.02 (1.00–1.04)	13	1.02 (0.98–1.06)	6	1.01 (0.98–1.05)	9
13	1.20 (1.09–1.30)	1.08 (0.97–1.18)	1.06 (1.04–1.08)	23	1.01 (1.00–1.02)	9	1.03 (1.00–1.06)	11	1.02 (1.00–1.05)	22

NA = not applicable; RR = risk ratio.
* Model was adjusted for age, sex, race, education, body mass index, drinking, brisk walking, smoking, self-reported general health status, cardiovascular disease, cancer, diabetes, hypertension, depressive symptoms, and chronic kidney disease.
† Natural direct effect is *olfaction → all-cause mortality*. Natural indirect effect through dementia/Parkinson disease is the combined paths of *olfaction → dementia/Parkinson disease → weight loss → all-cause mortality* and *olfaction → dementia/Parkinson disease → all-cause mortality*. Partial indirect effect through weight loss is *olfaction → weight loss → all-cause mortality*. The total effect is the sum of the natural direct effect, the natural indirect effect through dementia/Parkinson disease, and the partial indirect effect through only weight loss in the risk difference scale and product of component effects in the RR scale (see **Supplement** for details).
‡ The total effect was not statistically significant or direct and indirect effects were of opposite signs.

Together, dementia or Parkinson disease and weight loss potentially explained 28% of the higher mortality associated with poor olfaction at year 10 and 34% of that at year 13. For moderate olfaction, the corresponding proportions were 22% at year 10 and 31% at year 13. Appendix Table 4 (available at Annals.org) shows the distributions of mediators during follow-up. We found similar results in the sensitivity analysis that used the alternative weighting scheme (Appendix Table 5, available at Annals.org). The E-values (Appendix Table 6, available at Annals.org) for effects of poor olfaction ranged from 1.54 to 2.28 for the total effect, 1.16 to 1.99 for the natural direct effect, 1.31 to 1.57 for the natural indirect effect through pathways involving dementia or Parkinson disease, and 1.00 to 1.21 for the partial indirect effect through the pathway involving only weight loss.

DISCUSSION

In this community-based, prospective cohort of older U.S. adults, we found that poor olfaction was associated with 46% higher mortality at year 10 and 30% higher mortality at year 13 compared with good olfaction. The association was robust and could not be explained by measured confounders, such as demographic characteristics, lifestyle, and comorbid conditions. Furthermore, the association was present in both men and women and in both black and white participants, suggesting broad generalizability. Of note, the association was driven by participants who reported excellent to good health at the time of the BSIT, which highlights the fact that impaired olfaction is more than a marker of poor overall health. As expected, poor olfaction was strongly associated with deaths due to dementia or Parkinson disease, consistent with its known links to neurodegenerative diseases (52, 53). Mediation analyses further suggested that about 30% of the higher mortality associated with poor olfaction could be explained by dementia or Parkinson disease and weight loss. This study represents an important step toward a better understanding of the connections between olfaction and health among older adults.

Several studies have examined whether poor olfaction is independently associated with the survival of older adults, often with a median follow-up of 5 years or less (12–17). These studies used a screening test similar to the BSIT to assess sense of smell. With 1 exception (17), they reported that poor olfaction was associated with higher mortality after adjustment for demographic characteristics, lifestyle, and major chronic diseases (12–16). Few studies reported a follow-up beyond 5 years. Schubert and colleagues (16) followed 2418 U.S. adults aged 53 to 97 years for a maximum of 17 years, and olfactory impairment was associated with 28% higher mortality on the hazard ratio scale. Ekström and colleagues (15) reported that each 1-point increase in smell identification score was associated with 8% lower 10-year mortality among adults aged 40 to 90 years. None of the studies, however, explored potential explanations for this relationship.

Our analyses in this large, community-based, biracial cohort confirmed that poor olfaction was independently associated with long-term mortality. A novel observation is that the association was driven by participants who reported excellent to good health at baseline. We speculate that older adults with fair to poor heath had multiple medical conditions increasing their risk for death and that the cumulative effect of these conditions on mortality outweighed the effect of poor olfaction. On the other hand, poor olfaction among older adults with excellent to good health may be an early warning sign for insidious adverse health conditions that eventually lead to death. Of note, we also observed a slightly stronger association with 10-year mortality than 13-year mortality. We suspect that this may be related to our participants' ages, which averaged 75.6 years (range, 71 to 82 years) at baseline: People are dying at the end of their life span regardless of their sense of smell. Consistent with this possibility, Ekström and colleagues (15) noted a stronger association between olfaction and mortality among younger participants. Further examination of the role of olfaction

among younger elderly populations is therefore of great interest.

In this study, we attempted to analytically address the complex question of why older adults with poor olfaction are at higher risk for death. As expected, poor olfaction was strongly associated with death due to dementia or Parkinson disease, and we further quantified the potential contribution of these diseases to all-cause mortality in the long term. This finding fits well with the growing body of literature indicating that poor olfaction is an early but nonspecific warning for several major neurodegenerative diseases (52, 53). Our mediation analyses also suggest a moderate contribution from weight loss, consistent with the known contributions of unintentional weight loss to mortality (54) and with established connections between poor olfaction and malnutrition (55). Olfactory impairment may first lead to decreased appetite or poor food choices that may in turn contribute to malnutrition and weight loss (56–58).

Nevertheless, it is interesting to note that dementia or Parkinson disease and weight loss together explained only about 30% of the higher long-term mortality associated with poor olfaction. Although we could not examine contributions from other potential explanations, such as spoiled food, gas poisoning, or fires, we do not believe that these events contributed substantially to the observed higher mortality. These events are rare among older Americans and are associated with a mortality rate of 2.8 to 3.0 deaths per 100 000 persons (59). Therefore, a large proportion of the higher mortality associated with poor olfaction remains unexplained. Future studies should investigate the connections between olfactory impairment and the health of older adults beyond the nervous system.

Our study was done in a large, well-established cohort of older adults with 13 years of meticulous follow-up. Extensive data collection enabled us to control for a broad range of covariates and to conduct mediation analyses to explore potential clinical explanations of the association between olfaction and mortality.

Despite many strengths, the current study has notable limitations. First, our participants were aged 71 to 82 years at baseline and were old but reasonably functional, which may limit the generalizability of the study results to younger or less functional older adults. Second, we tested olfaction only once at baseline and could not examine changes in olfaction or their effect on mortality. Furthermore, the BSIT does not differentiate potential causes of olfactory impairment, which could be unrelated to aging (for example, due to nasal surgery or chronic rhinosinusitis). Therefore, future studies with repeated measurements of olfaction and careful assessment of causes of impairment will help better determine the role of poor olfaction in aging, chronic diseases, and survival of older adults. Finally, like all observational studies, our analyses are subject to bias due to potential unobserved confounding. Although our results are robust to changes in some model specification and weighting schemes, the E-values for estimated effects were relatively small, indicating that the findings could be confounded by unobserved confounders of moderate strength given the covariates controlled in analyses.

In conclusion, this study provides clear evidence of an association between poor olfaction and long-term mortality among older adults, independent of commonly suspected confounders. This elevated risk can be only partially explained by dementia or Parkinson disease and weight loss, indicating that some health consequences of poor olfaction in the context of aging are unknown. Future studies should investigate olfactory impairment as a general marker of aging to better understand its health implications and associated mechanisms in the broadest sense.

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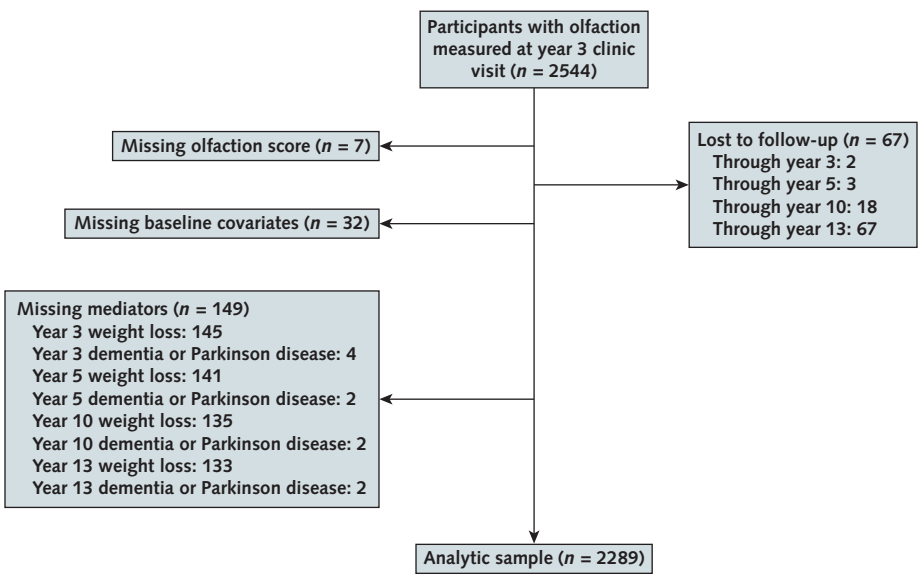
Appendix Figure 1. Flow chart of analytic sample.



Appendix Table 1. Total Effect of Olfaction on All-Cause Mortality, by Sex (*N* = 2289)

Years of Follow-up	Men (*n* = 1100)					Women (*n* = 1189)				
	Deaths, *n*			RR (95% CI)*		Deaths, *n*			RR (95% CI)*	
	Poor	Moderate	Good	Poor vs. Good	Moderate vs. Good	Poor	Moderate	Good	Poor vs. Good	Moderate vs. Good
3	36	27	13	1.46 (0.77–3.19)	1.38 (0.72–2.99)	12	12	17	0.88 (0.39–1.85)	0.77 (0.33–1.56)
5	85	61	35	1.26 (0.90–1.91)	1.16 (0.78–1.73)	38	29	43	1.09 (0.70–1.66)	0.70 (0.44–1.14)
10	218	152	87	1.44 (1.17–1.77)	1.23 (1.00–1.50)	133	127	119	1.51 (1.24–1.85)	1.15 (0.93–1.41)
13	295	215	137	1.30 (1.14–1.49)	1.14 (1.00–1.30)	178	193	193	1.31 (1.14–1.50)	1.11 (0.96–1.28)

RR = risk ratio.
* Model was adjusted for age, sex, race, education, body mass index, drinking, brisk walking, smoking, self-reported general health status, cardiovascular disease, cancer, diabetes, hypertension, depressive symptoms, and chronic kidney disease.

Appendix Table 2. Total Effect of Olfaction on All-Cause Mortality, by Race (*N* = 2289)

Years of Follow-up	White (*n* = 1427)					Black (*n* = 862)				
	Deaths, *n*			RR (95% CI)*		Deaths, *n*			RR (95% CI)*	
	Poor	Moderate	Good	Poor vs. Good	Moderate vs. Good	Poor	Moderate	Good	Poor vs. Good	Moderate vs. Good
3	25	19	15	1.60 (0.82–3.29)	1.21 (0.61–2.56)	23	20	15	0.83 (0.41–1.75)	0.90 (0.45–1.91)
5	58	46	43	1.36 (0.94–1.98)	1.02 (0.69–1.52)	65	44	35	0.97 (0.64–1.47)	0.84 (0.55–1.31)
10	182	162	130	1.56 (1.28–1.85)	1.24 (1.03–1.51)	169	117	76	1.35 (1.09–1.66)	1.10 (0.88–1.39)
13	256	246	214	1.38 (1.21–1.56)	1.17 (1.03–1.33)	217	162	116	1.18 (1.01–1.36)	1.03 (0.88–1.20)

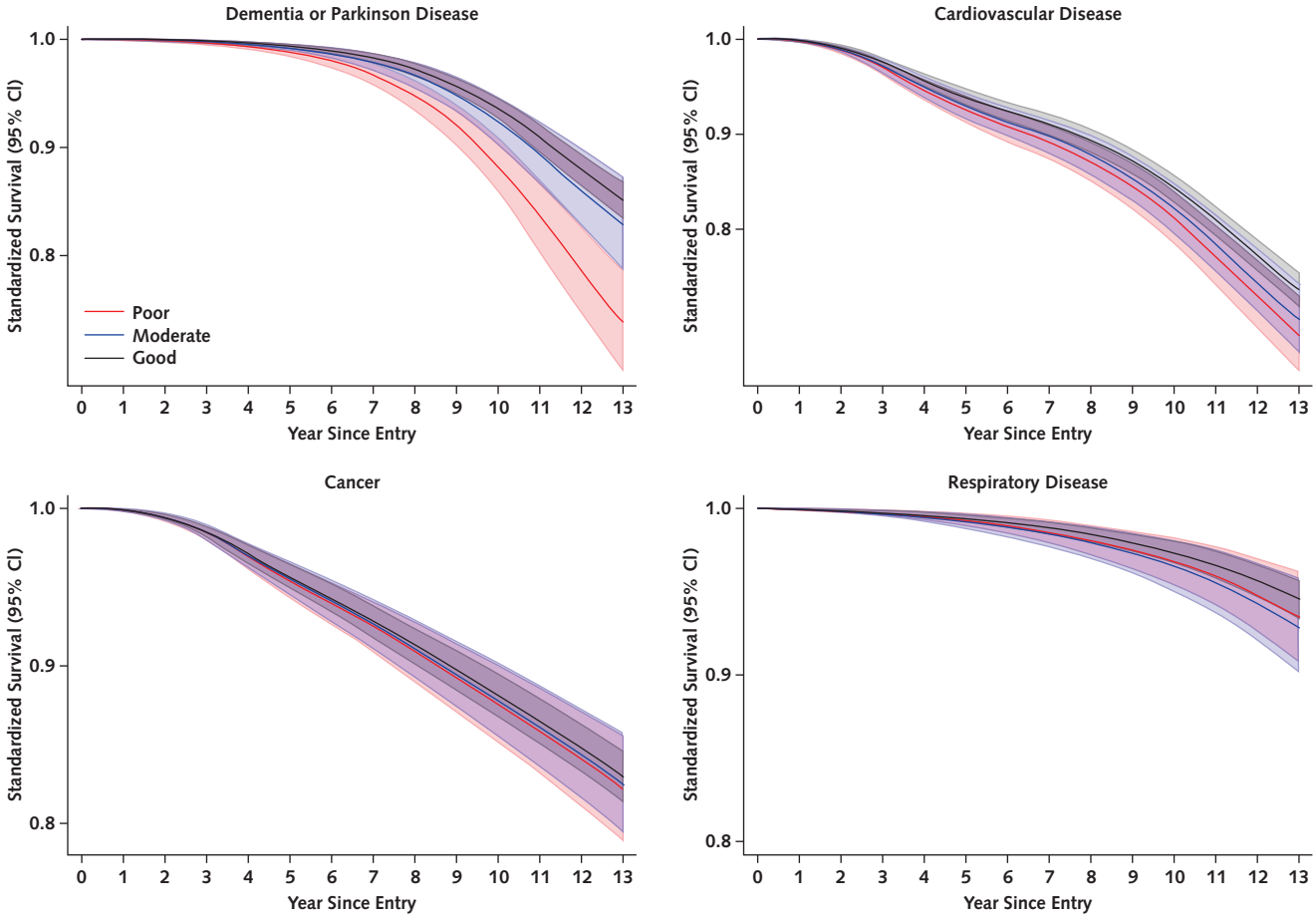
RR = risk ratio.
* Model was adjusted for age, sex, race, education, body mass index, drinking, brisk walking, smoking, self-reported general health status, cardiovascular disease, cancer, diabetes, hypertension, depressive symptoms, and chronic kidney disease.

Appendix Table 3. Total Effect of Olfaction on All-Cause Mortality, by Self-reported Heath Status (*N* = 2289)

Years of Follow-up	Excellent to Good Health (*n* = 1901)					Fair to Poor Health (*n* = 388)				
	Deaths, *n*			RR (95% CI)*		Deaths, *n*			RR (95% CI)*	
	Poor	Moderate	Good	Poor vs. Good	Moderate vs. Good	Poor	Moderate	Good	Poor vs. Good	Moderate vs. Good
3	34	32	24	1.15 (0.66–2.01)	1.09 (0.66–1.90)	14	7	6	1.16 (0.43–5.31)	0.91 (0.25–3.69)
5	84	71	61	1.19 (0.87–1.63)	0.97 (0.70–1.38)	39	19	17	1.04 (0.61–1.87)	0.82 (0.46–1.46)
10	265	226	160	1.62 (1.37–1.90)	1.24 (1.05–1.48)	86	53	46	1.06 (0.82–1.37)	0.97 (0.73–1.29)
13	360	331	262	1.40 (1.25–1.57)	1.15 (1.02–1.28)	113	77	68	1.00 (0.84–1.19)	1.01 (0.83–1.22)

RR = risk ratio.
* Model was adjusted for age, sex, race, education, body mass index, drinking, brisk walking, smoking, self-reported general health status, cardiovascular disease, cancer, diabetes, hypertension, depressive symptoms, and chronic kidney disease.

Appendix Figure 2. Standardized survival of cause-specific death among different olfactory function groups (*N* = 2289).



Appendix Table 4. Distribution of Mediators Over Follow-up (*N* = 2289)

Years of Follow-up	Dementia or Parkinson Disease, *n (%)*	Average Annual Weight Loss ≥2%, *n (%)*
3	452 (19.7)	474 (20.7)
5	563 (24.6)	408 (17.8)
10	744 (32.5)	443 (19.4)
13	854 (37.3)	437 (19.1)

Appendix Table 5. Sensitivity Analysis: Mediation Analysis for the Association Between Olfaction and All-Cause Mortality Using the Alternative Weighting Scheme Modeling on Weight Loss (*N* = 2289)

Years of Follow-up	RR (95% CI) for Total Effect*		RR (95% CI) for Natural Direct Effect*		RR (95% CI) for Natural Indirect Effect Mediated by All Pathways Through Dementia/Parkinson Disease*		RR (95% CI) for Partial Indirect Effect Mediated by Pathway Through Only Weight Loss*	
	Poor vs. Good	Moderate vs. Good	Poor vs. Good	Moderate vs. Good	Poor vs. Good	Moderate vs. Good	Poor vs. Good	Moderate vs. Good
3	1.16 (0.70–1.88)	1.07 (0.67–1.79)	1.02 (0.63–1.63)	1.06 (0.67–1.80)	1.08 (0.95–1.26)	0.99 (0.87–1.11)	1.05 (0.99–1.11)	1.02 (0.97–1.09)
5	1.15 (0.86–1.51)	0.94 (0.70–1.26)	1.05 (0.81–1.37)	0.91 (0.69–1.22)	1.02 (0.93–1.12)	0.97 (0.89–1.05)	1.07 (1.01–1.13)	1.06 (1.00–1.13)
10	1.47 (1.27–1.68)	1.18 (1.02–1.35)	1.33 (1.15–1.52)	1.13 (0.98–1.29)	1.06 (1.02–1.10)	1.00 (0.97–1.03)	1.04 (1.02–1.07)	1.04 (1.02–1.07)
13	1.30 (1.19–1.42)	1.11 (1.01–1.22)	1.20 (1.09–1.30)	1.08 (0.97–1.18)	1.05 (1.02–1.08)	1.00 (0.98–1.02)	1.04 (1.02–1.06)	1.04 (1.02–1.06)

RR = risk ratio.
* Model was adjusted for age, sex, race, education, body mass index, drinking, brisk walking, smoking, self-reported general health status, cardiovascular disease, cancer, diabetes, hypertension, depressive symptoms, and chronic kidney disease. Natural direct effect is *olfaction → all-cause mortality*. Natural indirect effect through dementia/Parkinson disease is the combined paths of *olfaction → dementia/Parkinson disease → weight loss → all-cause mortality* and *olfaction → dementia/Parkinson disease → all-cause mortality*. Partial indirect effect through weight loss is *olfaction → weight loss → all-cause mortality*.

Appendix Table 6. Sensitivity Analysis: Olfaction and All-Cause Mortality Total Effect and Mediation Analysis (*N* = 2289)

Years of Follow-up	Total Effect				Natural Direct Effect				Natural Indirect Effect Mediated by All Pathways Through Dementia/Parkinson Disease				Partial Indirect Effect Mediated by Pathway Through Only Weight Loss			
	Poor vs. Good		Moderate vs. Good		Poor vs. Good		Moderate vs. Good		Poor vs. Good		Moderate vs. Good		Poor vs. Good		Moderate vs. Good	
	RR*	E-Value	RR*	E-Value	RR*	E-Value	RR*	E-Value	RR*	E-Value	RR*	E-Value	RR*	E-Value	RR*	E-Value
3	1.15	1.57	1.04	1.24	1.02	1.16	1.06	1.31	1.15	1.57	1.04	1.24	0.98	1.16	0.94	1.32
5	1.14	1.54	0.92	1.39	1.05	1.28	0.91	1.43	1.08	1.37	1.04	1.24	1.00	1.00	0.97	1.21
10	1.46	2.28	1.17	1.62	1.33	1.99	1.13	1.51	1.08	1.37	1.02	1.16	1.02	1.16	1.01	1.11
13	1.30	1.92	1.11	1.46	1.20	1.69	1.08	1.37	1.06	1.31	1.01	1.11	1.03	1.21	1.02	1.16

RR = risk ratio.
* RRs of the total effect are from Table 2; RRs of the natural direct effect, natural indirect effect though dementia/Parkinson disease, and partial indirect effect through only weight loss are from Table 3.