Evidence for a role of metformin in preventing olfactory dysfunction among older adults*

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Abstract

Background: Olfactory dysfunction (OD) is increasingly recognized as a hallmark of unhealthy aging and is intimately associated with mortality, but therapies remain elusive. Recognizing the increased prevalence of OD in individuals with diabetes, and the potential anti-aging effects of metformin, we studied the association of metformin use with OD.

Methods: Cross-temporal study of participants from Waves 2 (2010-11) and 3 (2015-16) of the National Social Life, Health, and Aging Project (NSHAP), a nationally representative cohort study of community-dwelling older adults. We included participants with diabetes who had complete data on olfaction and relevant covariates at Wave 2 and were not lost to follow-up at Wave 3. Olfactory identification (OI), the ability to identify the odorant, and olfactory sensitivity (OS), the ability to detect the presence of an odorant, were tested. Weighted multivariable logistic regression was used to study the association between metformin use at Wave 2 (baseline) and odds of having impaired OI/OS at Wave 3, adjusted for age, sex, race/ethnicity, education, smoking, BMI, HbA1c, years since diabetes diagnosis, and insulin use.

Results: Among 228 participants with diabetes (mean age=70 years, 53% female, 21% Black), 112 (49%) used metformin at baseline. Relative to nonusers, users had 58% lower odds of impaired OI and 67% lower odds of impaired OS at Wave 3. Among participants with normal baseline OS (N=62), users had 97% lower odds of impaired OS at Wave 3.

Conclusion: Metformin use is associated with lower odds of OD among individuals with diabetes, suggesting a potential protective effect on olfaction. Future work including a larger sample and additional information on metformin use is needed to establish whether these findings are independent of diabetic control.

Key words: olfaction, olfactory dysfunction, metformin, aging, diabetes

Introduction

An increasing body of evidence has established that olfactory dysfunction (OD) is a unique and independent predictor of overall mortality [1–4]. In an ever more aged global population, OD is a highly common condition affecting approximately 40% of adults aged 65 years and older [5]. Although the exact causal relationship is not fully understood, studies have linked OD with various conditions, including neurodegenerative diseases, nutritional inadequacies, impaired detection of hazardous stimuli, social isolation, and accelerated brain aging [6,7]. In neurodegenerative conditions such as Alzheimer's and Parkinson's diseases, olfactory dysfunction is commonly observed before cognitive decline [8]. Moreover, a substantial link between OD and mortality is evident even in individuals who do not develop dementia, suggesting that OD may reflect pathophysiological changes linked with an overall decrease in physiological reserve [9]. Though longitudinal studies are lacking, there is a growing body of evidence supporting the association between OD and the dyshomeostatic syndrome of frailty in older adults [10–12]. Despite the well-recognized significance of olfaction and the

adverse outcomes associated with its dysfunction, the management of OD among older adults remains limited and therapeutic strategies are still relatively scarce. In contrast, interventions addressing other sensory impairments, such as vision and hearing loss, have demonstrated substantial health benefits, including improved cognition and a lower incidence of dementia in the setting of hearing amplification and eyeglasses [13–16]. Although approaches such as olfactory training may help to mitigate olfactory loss and improve health span in older adults, the potential benefits of OD-targeted therapies remain largely unexplored [17–22].

As researchers continue to uncover insights into the complex workings of aging and the olfactory system, a concurrent trend focused on the development of geroprotective therapies is rapidly emerging, seeking to identify interventions to slow down the aging process and increase healthy lifespan. One promising avenue in this field is the potential anti-aging effect of metformin, a medication commonly prescribed to treat type 2 diabetes. Recent studies have shed light on its additional benefits in extending lifespan and reducing age-related diseases via reduced oxidative stress and chronic inflammation, independent of diabetic control [23–25]. Among patients with diabetes, metformin use has shown to be associated with improved cognitive function and reduced incidence of cardiovascular disease, cancer, and dementia [26,27]. In addition, a study by Bannister et al. demonstrated that the increased longevity among metformin-treated patients with diabetes was even greater than that of healthy controls without diabetes [28]. In a preclinical study, metformin usage is associated with olfactory recovery when given as pre-treatment in a cranial irradiation mouse model, suggesting a neurogenic potential [29].

Recognizing the role of OD as a marker of unhealthy aging and mortality, the emerging evidence on the anti-aging effects of metformin, and the increased prevalence of OD among individuals with diabetes [30,31], our objective was to investigate the potential impact of metformin on olfaction. Using data from the National Social Life, Health, and Aging Project (NSHAP), a nationally representative cohort study of older adults in the United States (U.S.), we hypothesized that among adults with diabetes, metformin users had lower odds of having impaired olfactory function over time compared to nonusers.

Materials and methods

Study population

The National Social Life, Health, and Aging Project (NSHAP) is a longitudinal, nationally representative study of community-dwelling older adults in the U.S since 2005. Three rounds of data from in-home visits by interviewers from the National Opinion Research Center (NORC) have been completed and released. Our cross-temporal study uses Wave 2 (2010-2011) and Wave 3 (2015-2016) of NSHAP, which included the same olfaction assessments. In this study, we included participants who reported having diabetes and had complete olfactory function testing at Wave 2 (N=422), considered the baseline visit in this study. Among those, we excluded 60 participants for missing data on covariates at Wave 2 (race/ethnicity=2, BMI=18, HbA1c=30, years since diabetes diagnosis=10), 109 participants who were lost to follow-up at Wave 3, and 25 participants with missing data on olfactory function at Wave 3. Our primary analytic sample consisted of 228 participants. NSHAP was approved by the Institutional Review Board at the University of Chicago and NORC. All participants provided written, informed consent. This current study was approved by the Johns Hopkins IRB (IRB00297556).

Diabetes mellitus and metformin use

Participants were considered as having diabetes if they answered yes to the following question: "Has a doctor ever told you that you have diabetes or high blood sugar?" Additionally, all participants were asked to report all their medications. Those who reported metformin were considered users while those who did not were considered nonusers at baseline (Wave 2).

Olfactory assessment

Two aspects of olfactory function, olfactory identification (OI) and sensitivity (OS), were assessed in NSHAP using commercially available Sniffin' Sticks pens (Burghart Medical Technology, Wedel, Germany) at Waves 2 and 3. OI was measured using the five-item Sniffin' Sticks test [32,33]. Participants were asked to identify each odor from a set of four word/picture options on a card in a forced-choice protocol [33]. Those who refused to answer were considered as having an incorrect response, consistent with published studies using this data [34–36]. The odorants were rose, leather, orange, fish, and peppermint. Participants who correctly identified <4 odorants were considered as having impaired OI. Additionally, OS was measured using smell pens with ascending concentrations of n-butanol (0.13%, 0.25%, 0.5%, 2.0%, 4.0%, and 8.0%). Participants were first presented with 8.0% n-butanol scented pen to introduce the smell they would subsequently identify in the test. A total of 6 trials were conducted, with the strength of the scented pen varying in each trial. In each trial, participants were presented with 3 pens and were asked to identify the pen with n-butanol scent. Participants who responded correctly in <5 trials were considered as having impaired OS consistent with prior studies [11,37]. In our analyses, participants' OI and OS scores were treated as two independent outcomes.

Covariates

We accounted for sociodemographic factors collected at Wave 2 including age (continuous), gender (male, female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and other), education (less than high school, high school or equivalent, vocational/some college/associate degree, and bachelor's degree

Table 1. Characteristics of National Social Life, Health, and Aging Project (NSHAP) Wave 2 (2010-2011) participants with diabetes mellitus by metformin use status.

		Metformin Use	
	Total	**Users**	**Nonusers**
Number of participants, n (%)	228	112 (49)	116 (51)
Age (years), mean (SD)	70 (6)	69 (6)	71 (7)
Male, n (%)	96 (47)	45 (43)	51 (50)
Race/ethnicity, n (%)			
Non-Hispanic White	135 (70)	62 (68)	73 (71)
Non-Hispanic Black	56 (21)	28 (19)	28 (22)
Hispanic	34 (8)	19 (10)	15 (7)
Other	3 (1)	3 (3)	0 (0)
Educational attainment, n (%)			
Less than high school	62 (21)	33 (23)	29 (19)
High school or equivalent	58 (26)	32 (32)	26 (20)
Some college/associate degree	74 (34)	35 (34)	39 (33)
Bachelor's degree or higher	34 (20)	12 (11)	22 (29)
Smoking status, n (%)			
Never smoker	90 (37)	42 (37)	48 (37)
Ex-smoker	106 (50)	53 (48)	53 (52)
Current smoker	32 (13)	17 (15)	15 (11)
BMI (kg/m^2), mean (SD)	33 (9)	35 (10)	32 (8)
HbA1c (%), mean (SD)	7 (1)	7 (1)	7 (2)
Years since diabetes diagnosis, mean (SD)	11 (9)	10 (8)	11 (10)
Insulin use, n (%)	39 (15)	16 (13)	23 (16)
Olfactory identification at Wave 2 (2010-2011), n (%)			
Normal	196 (91)	96 (90)	100 (91)
Impaired	32 (9)	16 (10)	16 (9)
Olfactory sensitivity at Wave 2 (2010-2011)			
Average value, mean (SD)	3.6 (1.4)	4.0 (1.3)	3.3 (1.5)
Normal, n (%)	62 (27)	36 (37)	26 (19)
Impaired, n (%)	166 (73)	76 (64)	90 (81)
Olfactory identification at Wave 3 (2015-2016), n (%)			
Normal	186 (83)	95 (89)	91 (77)
Impaired	42 (17)	17 (11)	25 (23)
Olfactory sensitivity at Wave 3 (2015-2016)			
Average value, mean (SD)	3.4 (1.4)	3.6 (1.3)	3.2 (1.4)
Normal, n (%)	44 (20)	25 (26)	19 (14)
Impaired, n (%)	184 (80)	87 (74)	97 (86)

NSHAP Wave 2 analytical weights were applied to account for differing probabilities of selection as well as differential non-response. Unweighted counts and weighted proportions are displayed for categorical variables and weighted means and standard deviations (SD) are displayed for continuous variables.

or more). We also accounted for health-related factors including smoking status (never, previous, current smoker) and body mass index (continuous in kg/m^2, calculated based on height and weight at Wave 2). Lastly, we included diabetic factors including HbA1c (continuous, measured in whole blood), years since diagnosis of diabetes, and insulin use (binary, based on self-reported use).

Statistical analysis

Participants' characteristics were summarized in the total analytic sample as well as stratified by metformin use status (users and nonusers). We presented unweighted counts and weighted percentages for categorical variables and weighted means and standard deviations (SD) for continuous variables. We compared characteristics between metformin users and nonusers with one-way ANOVA for continuous variables and chi-squared tests for categorical variables.

We used weighted logistic regression models to examine the association of metformin use at baseline (Wave 2) with the odds of having impaired OI and OS at Wave 3. A model-building approach was adopted whereby we present estimates 1) from the unadjusted model and 2) from the model adjusted for sociodemographic (age, sex, race/ethnicity, educational attainment), health-related (smoking status, BMI), and diabetic factors (HbA1c, years since diagnosis of diabetes, and insulin use) collected at Wave 2. Additionally, we explored the associations by stratification of baseline OI and OS function. In a secondary analysis, we explored the associations by stratification of diabetes control (controlled, HbA1c < 6.5% vs. uncontrolled, HbA1c >= 6.5%).

We applied NSHAP sampling weights to descriptive analysis to account for the complex sampling design and differential probabilities of non-response, and to reflect the nationally representativeness of the survey. We used inverse probability weighting (IPW) to account for differential attrition at Wave 3. Described elsewhere, IPW has been suggested as a robust approach to handle emigrant selection bias in cohort studies (38). Stabilized attrition weights were calculated based on predicted probabilities derived from probit regression (with the exposure variable and all variables that independently predict both attrition and outcome) of loss to follow-up due to study withdrawal between Wave 2 and 3 (See Supplemental Material for detail). Combined analytical weights were created by multiplying the stabilized attrition weights and complex sampling weights and were applied to all regression analyses. Results are presented as odds ratios (OR) with 95% Confidence Intervals (CI). All analyses were conducted using Stata version 17.0 (StataCorp, TX, USA).

Results

Study population

Our analytic sample consisted of 228 participants with diabetes mellitus. Their baseline characteristics at Wave 2 are detailed in Table 1. The average age was 70 years (range 52 to 88 years) and 53% were female, 21% were non-Hispanic Black, and 8% were Hispanic. Among the included participants, 112 (49%) reported metformin use while 116 (51%) did not. Compared to nonusers, metformin users tended to be younger on average (69 vs. 71 years) and more likely to be female (57% vs. 50%). Additionally, users and nonusers had similar average HbA1c levels (6.8%), duration since diabetes diagnosis (11 and 10 years, respectively), and proportion of insulin users (13% and 16%). On olfactory testing at baseline (Wave 2), a similar proportion of metformin users and nonusers had normal OI (90% vs. 91%) while a larger proportion of users had normal OS (37% vs. 19%). At Wave 3, a larger proportion of metformin users had normal OI (89% vs. 77%) and OS (26% vs. 14%). The proportion of metformin users and nonusers with impaired OI and OS is displayed in Figure 1.

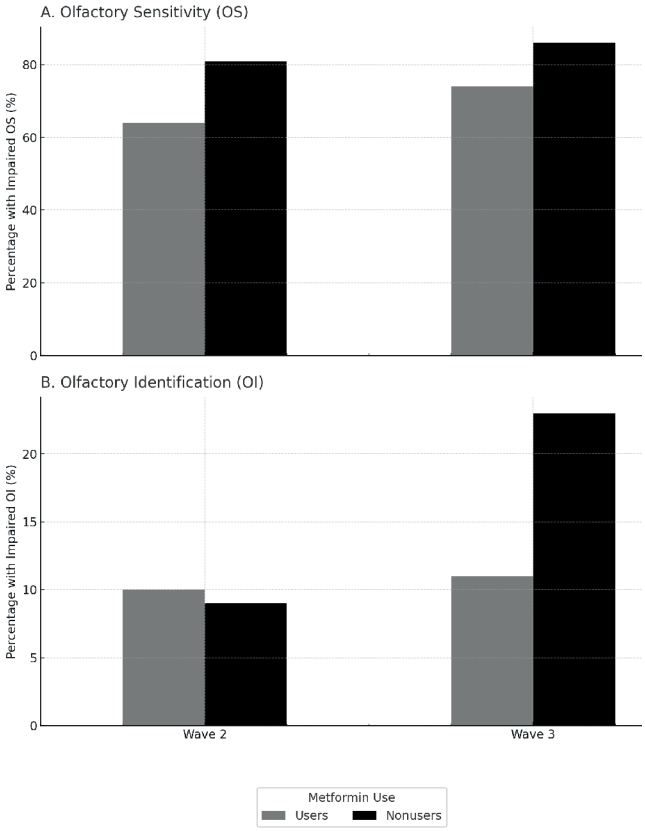

Figure 1. Proportion of participants with impaired OS and OI at Wave 2 and Wave 3 stratified by metformin use.

Change in olfactory identification

In the unadjusted logistic regression model, we found that metformin use at baseline was associated with 65% lower odds of having impaired OI at Wave 3 relative to nonusers (OR=0.35; 95% CI [0.17, 0.72]) (Table 2). In the model adjusted for sociodemographic, health, and diabetic covariates, the odds of having impaired OI were 58% lower for metformin users compared to nonusers (OR=0.42 [0.19, 0.96]).

In stratified analyses, among participants with normal baseline OI, estimates from the unadjusted model were of greater magnitude whereby metformin use was associated with 76% lower odds of impaired OI at Wave 3 (OR=0.26 [0.12, 0.55]). In the adjusted model, findings were in the same direction but no longer statistically significant (OR=0.37 [0.13, 1.07]).

Table 2. Association between Wave 2 (2010-2011) metformin use and Wave 3 (2015-2016) olfactory identification (OI) among NSHAP participants with diabetes mellitus.

	Odds of Impaired Olfactory Identification at Wave 3			
	Unadjusted model		Adjusted model*	
Metformin use at Wave 2	**OR**	**95% CI**	**OR**	**95% CI**
Analytical sample (N=228)				
Nonusers (n=116)	REF		REF	
Metformin users (n=112)	**0.35**	**(0.17, 0.72)**	**0.42**	**(0.19, 0.96)**
Subgroup with Normal OI Function (N=196)				
Nonusers (n=100)	REF		REF	
Metformin users (n=96)	**0.25**	**(0.12, 0.55)**	0.37	(0.13, 1.07)
Subgroup with OI Dysfunction (N=32)				
Nonusers (n=16)	REF		REF	
Metformin users (n=16)	Underpowered		Underpowered	

Abbreviations: OI = olfactory identification; OR = odds ratio; CI = confidence interval. Combined analytical weights (product of attrition weights and NSHAP Wave 2 analytical weights) were applied to account for complex survey design and differential attrition. * Logistic regression model adjusted for participants' age, sex, race/ethnicity, education attainment, smoking status, BMI, glycosylated hemoglobin level, years since diabetes diagnosis, and insulin use were included.

Table 3. Association between Wave 2 (2010-2011) metformin use and Wave 3 (2015-2016) olfactory sensitivity (OS) among NSHAP participants with diabetes mellitus.

	Odds of Impaired Olfactory Identification at Wave 3			
	Unadjusted model		Adjusted model*	
Metformin use at Wave 2	**OR**	**95% CI**	**OR**	**95% CI**
Analytical sample (N=228)				
Nonusers (n=116)	REF		REF	
Metformin users (n=112)	**0.39**	**(0.19, 0.80)**	**0.33**	**(0.14, 0.79)**
Subgroup with Normal OS Function (N=62)				
Nonusers (n=26)	REF		REF	
Metformin users (n=36)	0.21	(0.04, 1.07)	**0.03**	**(0.004, 0.17)**
Subgroup with OS Dysfunction (N=166)				
Nonusers (n=90)	REF		REF	
Metformin users (n=76)	0.63	(0.22, 1.83)	0.60	(0.20, 1.84)

Abbreviations: OR = odds ratio; OS = olfactory sensitivity; CI = confidence interval. Combined analytical weights (product of attrition weights and NSHAP Wave 2 analytical weights) were applied to account for complex survey design and differential attrition. * Logistic regression model adjusted for participants' age, sex, race/ethnicity, education attainment, smoking status, BMI, glycosylated hemoglobin level, years since diabetes diagnosis, and insulin use were included.

Change in olfactory sensitivity

We found that in the unadjusted model, metformin use at baseline was associated with 61% lower odds of having impaired OS at Wave 3 (OR=0.39 [0.19, 0.80]) (Table 3). In the adjusted model, this change was of greater magnitude, with 67% lower odds of having impaired OS among metformin users compared to nonusers (OR=0.33 [0.14, 0.79]).

In stratified analyses, we found that among participants with normal baseline OS, metformin use was associated with 97% lower odds of impaired OS at Wave 3 (OR=0.03 [0.004, 0.17]) in the adjusted model, while the association among those with baseline impaired OS was not statistically significant (OR=0.60 [0.20, 1.84]).

Change in olfactory function stratified by control of diabetes

In a secondary analysis stratified by baseline diabetic disease control, metformin users consisted of 43% of those with controlled diabetes and 51% of those with uncontrolled diabetes. All findings were in the direction of lower odds of impaired OI and

Table 4. Association between Wave 2 (2010-2011) metformin use and Wave 3 (2015-2016) olfactory identification (OI) and sensitivity (OS) among NSHAP participants with diabetes mellitus, stratified by control of diabetes mellitus.

	Odds of Impaired Olfactory Identification at Wave 3			
	Unadjusted model		Adjusted model*	
Metformin use at Wave 2	**OR**	**95% CI**	**OR**	**95% CI**
Subgroup with controlled diabetes** (N=94)				
Nonusers (n=51)	REF		REF	
Metformin users (n=43)	**0.30**	**(0.12, 0.75)**	0.81	(0.30, 2.18)
Subgroup with uncontrolled diabetes** (N=134)				
Nonusers (n=65)	REF		REF	
Metformin users (n=69)	0.45	(0.17, 1.20)	0.63	(0.28, 1.41)
	Odds of Impaired Olfactory Sensitivity at Wave 3			
	Unadjusted model		**Adjusted model***	
Metformin use at Wave 2	**OR**	**95% CI**	**OR**	**95% CI**
Subgroup with controlled diabetes** (N=94)				
Nonusers (n=51)	REF		REF	
Metformin users (n=65)	0.35	(0.13, 1.00)	**0.25**	**(0.08, 0.82)**
Subgroup with uncontrolled diabetes** (N=134)				
Nonusers (n=65)	REF		REF	
Metformin users (n=69)	0.41	(0.13, 1.29)	0.37	(0.09, 1.51)

Abbreviations: OR = odds ratio; OS = olfactory sensitivity; CI = confidence interval. Combined analytical weights (product of attrition weights and NSHAP Wave 2 analytical weights) were applied to account for complex survey design and differential attrition. * Logistic regression model adjusted for participants' age, sex, race/ethnicity, education attainment, smoking status, BMI, glycosylated hemoglobin level, years since diabetes diagnosis, and insulin use were included. ** Controlled diabetes defined as HbA1c<6.5% whereas uncontrolled diabetes defined as HbA1c>= 6.5%.

OS at Wave 3 among metformin users (Table 4). Only the association of metformin use at baseline with lower odds of impaired OS at Wave 3 was statistically significant (OR=0.25 [0.08, 0.82]).

Discussion

Using data from a nationally representative cohort of community-dwelling older adults in the U.S., we demonstrate that among individuals with diabetes, metformin use was associated with lower odds of OD over time after controlling for sociodemographic, health, and diabetes-related covariates. Specifically, metformin users were 58% and 67% less likely to have impaired OI and OS, respectively, compared to nonusers. Strikingly, in the subgroup with normal OS at baseline, metformin users were 97% less likely to have impaired OS at follow-up. Our findings shed light on the potential protective effect of metformin on olfactory function and the differential impact on olfactory subdomains among adults with diabetes.

To our knowledge, this is the first study to examine the association between metformin use and change in OD longitudinally. One previous study with a cross-sectional study design found that among 238 diabetic patients, metformin users had 74% lower odds of having OD compared to nonusers [39]. Current evidence supports that OD and metformin use are both independently associated with mortality and aging-related diseases, but whether the two are linked is still unknown. Recently, OD has been associated with increased risk of age-related morbidity, frailty, and all-cause mortality [1–4,11,12]. On the other hand, a compelling systematic review by Campbell et al. found that metformin use among persons with diabetes reduced all-cause mortality and cancer incidence when compared to persons receiving non-metformin therapies and those without diabetes [24], as well as the incidence of cardiovascular disease and dementia [26,27]. This growing evidence prompted the ongoing clinical trial TAME (Targeting Aging by Metformin) to investigate the efficacy of metformin in promoting healthier aging [40]. These findings, combined with those of the current study, suggest that metformin's diabetes-independent healthy aging effects may play a role in mitigation of age-associated OD.

Currently, observational studies investigating metformin use are limited to samples of adults with diabetes. Because the control group in the current study consists of adults with diabetes who are not on metformin, it is challenging to determine whether the observed effects of metformin on OD are truly independent of diabetic disease control and are secondary to anti-aging properties including reduced oxidative stress and inflammation [23,25]. Several studies have noted that OD prevalence is increased in populations with diabetes, and OD has been posited as a potential microvascular complication of diabetes similar to peripheral neuropathy [31,41–43], which could explain the strong association found between metformin use and OS. While this

remains a strong possibility that will require future exploration, we attempted to account for disease control by including diabetic metrics in our analysis, specifically HbA1c, years since diagnosis, and insulin use. In addition, we stratified by diabetic disease control to further disentangle the mechanisms underlying the studied associations and to potentially isolate two groups of participants that may differ in additional characteristics (e.g., diet, exercise, health-seeking behaviors) that were not picked up among covariates. Generally, we found that the direction of the associations was consistent among those with controlled and uncontrolled diabetes, suggesting that our findings may not be driven by diabetic disease control. However, these were limited by the sample sizes and will need to be explored in larger groups to generate robust and reliable conclusions. Furthermore, future investigation on the generalizability of our results to non-diabetic populations is needed to provide additional validation of both the health-promoting effects of metformin and the value of OD as a health marker.

Interestingly, the association between metformin use and decreased odds of OD was markedly stronger when examining OS as opposed to OI. This distinction may provide insight into the mechanisms underlying the association, as these two olfactory components involve different processes. OS refers to the minimum concentration of a substance that can be detected. This function is primarily dependent on peripheral sensory processing and is closely related to the number and functional status of olfactory receptor neurons, their synaptic connections in the olfactory bulb, and the signal transduction to higher cortical centers. In contrast, OI represents a more complex mechanism that involves functional detection of odorants as well as the cognitive interpretation and recognition of these odors, implicating higher brain functions such as memory and attention. Although our results suggest an association between metformin use and OI, estimates were no longer statistically significant after adjusting for covariates, suggesting that metformin may exert protective effects on primarily on lower-level, peripheral mechanisms of olfaction. This may be due to the drug's known systemic effects on metabolic regulation [44], which may have indirect effects on the health and function of olfactory neurons. However, it is possible that these findings were influenced by the low statistical power secondary to sample size. Additionally, the prevalence of impaired OI in our study sample (9% at Wave 2 and 17% at Wave 3) was lower than what would be expected among older adults, while the prevalence of impaired OS was high, consistent with the known association of OD and diabetes [31]. This suggests that the test used for OI may be underestimating the true prevalence of OD and consequently the studied associations.

An important strength in this study is the use of a weighted sample from a robust and diverse nationally representative cohort of older adults in the U.S. However, one limitation intrinsic to the nature of our research question is the inclusion of the subset of individuals with diabetes only. This also led to a small sample size that limited the statistical power of our findings. Additionally, we were limited by the number of confounders we could include given the large proportion of missing data for important covariates (e.g., history of nasal surgery or head injury) and in our ability to stratify the outcome of by degree of impairment (i.e., hyposmia and anosmia) which would provide a more granular understanding of the studied association. Further investigation in larger populations is necessary to generate statistically stronger estimates for the association between metformin usage with OS and OI. Another limitation is the cross-temporal study design. Although it allowed the investigation of change in olfactory function over time, future longitudinal studies will be better suited to establish whether metformin use truly affects olfactory function. Lastly, lack of data on the duration and dosage of metformin treatment may be a source of unmeasured confounding.

Conclusion

We found that metformin use is associated with reduced OD over time in a sample of community-dwelling adults with diabetes in the U.S. This association was more strongly related to OS, suggesting that this potential protective effect is mediated through peripheral mechanisms of olfaction. Given prior reports on the cognitive and health benefits of the treatment of OD, longitudinal characterization of olfactory function during metformin treatment may provide vital information about the mechanistic underpinnings of both metformin and OD, as they relate to aging and mortality.

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Authorship contribution

Concept and design: SA, VV, NRR; Acquisition, analysis, or interpretation of data: SA, VV, WZ, NSR, APL, MR, NRR; Drafting and revision of the manuscript: SA, VV, WZ, NSR, APL, MR, NRR; Final approval before submission: SA, VV, WZ, NSR, APL, MR, NRR; Supervision: NRR.

Conflict of interest

The authors declare no conflicts of interest.

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Availability of data and materials

The datasets analyzed during the current study are available at https://www.icpsr.umich.edu/web/NACDA/studies/34921 and https://www.icpsr.umich.edu/web/NACDA/studies/36873.

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SUPPLEMENTARY MATERIAL

Summary of inverse probability weighting

Diabetes mellitus has been associated with increased morbidity, mortality, and disability in the older adult population [40]. The choice of different treatment regimens (metformin versus other medication) may depend on various factors (disease severity and control, side-effects to treatment, insurance coverage, etc.). As is illustrated in Supplemental Table 1, participants who were lost to follow-up differed from their counterparts who remained in the study at Wave 3 in terms of certain characteristics. To account for differential attrition and the subsequent emigrant selection bias that may influence the study results, we adopted inverse probability weighting (IPW), an approach that has been described in detail previously [33]. Inverse probability weighting is a weighting procedure which accounts for differential attrition by assigning greater weights to participants included in the final analytical sample who exhibited greater risk of study drop out based on a set of pre-identified factors (demographic, socioeconomic, and health characteristics that are more strongly associated with attrition). To obtain estimates that were adjusted for possible selection bias due to study dropout at Wave 3, IPW weights were calculated from predicted probabilities derived using probit regression models the examined the association between attrition and a set of patient characteristics. Based on existing literature [41], the following covariates were included in the IPW model: age, sex, race/ethnicity, educational attainment, smoking status, BMI, HbA1c, years since diagnosis of diabetes, insulin use, and metformin use. After obtaining the IPW weights (by deriving the inverse of each participant's predicted probability of study dropout), we further calculated the stabilized IPW weights (by multiplying the conditional probability of study dropout given exposure status), these weights, along with NSHAP survey weights, were later applied in the primary analyses of the association between metformin use and olfactory impairments. The mean and standard deviation of the stabilized weights were 1.17 and 0.67, respectively, and the range of the weights was [0.66, 6.46], indicating the appropriateness of the IPW approach in this research setting.

Supplemental Table 1. Characteristics of National Social Life, Health, and Aging Project (NSHAP) Wave 2 (2010-2011) participants with diabetes mellitus by Wave 3 attrition status.

	Lost to follow-up	Analytic sample	Total
Number of participants, n (%)	109 (28.2)	228 (71.8)	337 (100.0)
Metformin use, n (%)			
No	65 (55.7)	116 (52.5)	181 (53.4)
Yes	44 (44.3)	112 (47.5)	156 (46.6)
Age (years), mean (SD)	75 (7)	69 (6)	71 (7)
Male, n (%)	59 (48.4)	96 (46.8)	155 (47.2)
Race/ethnicity, n (%)			
Non-Hispanic White	63 (68.5)	135 (69.7)	198 (69.4)
Non-Hispanic Black	30 (18.2)	56 (20.8)	86 (20.1)
Hispanic	13 (9.0)	34 (8.3)	47 (8.5)
Other	3 (4.3)	3 (1.2)	6 (2.0)
Educational attainment, n (%)			
Less than high school	39 (30.4)	62 (20.7)	101 (23.4)
High school or equivalent	23 (22.1)	58 (25.5)	81 (24.6)
Some college/associate degree	26 (25.6)	74 (33.7)	100 (31.4)
Bachelor's degree or higher	21 (22.0)	34 (20.1)	55 (20.6)
Smoking status, n (%)			
Never smoker	43 (42.3)	90 (36.9)	133 (38.5)
Ex-smoker	56 (49.3)	106 (49.8)	162 (49.6)
Current smoker	10 (8.3)	32 (13.3)	42 (11.9)
BMI (kg/m^2), mean (SD)	30 (6)	33 (9)	32 (8)
HbA1c (%), mean (SD)	7 (1)	7 (1)	7 (1)
Years since diabetes diagnosis, mean (SD)	15 (12)	11 (9)	12 (10)
Insulin use, n (%)	24 (19.0)	39 (14.5)	63 (15.8)

NSHAP Wave 2 analytical weights were applied to account for differing probabilities of selection as well as differential non-response. Unweighted counts and weighted proportions are displayed for categorical variables and weighted means and standard deviations (SD) are displayed for continuous variables.