Association of olfactory impairment and short telomere length: the smell of biological aging?

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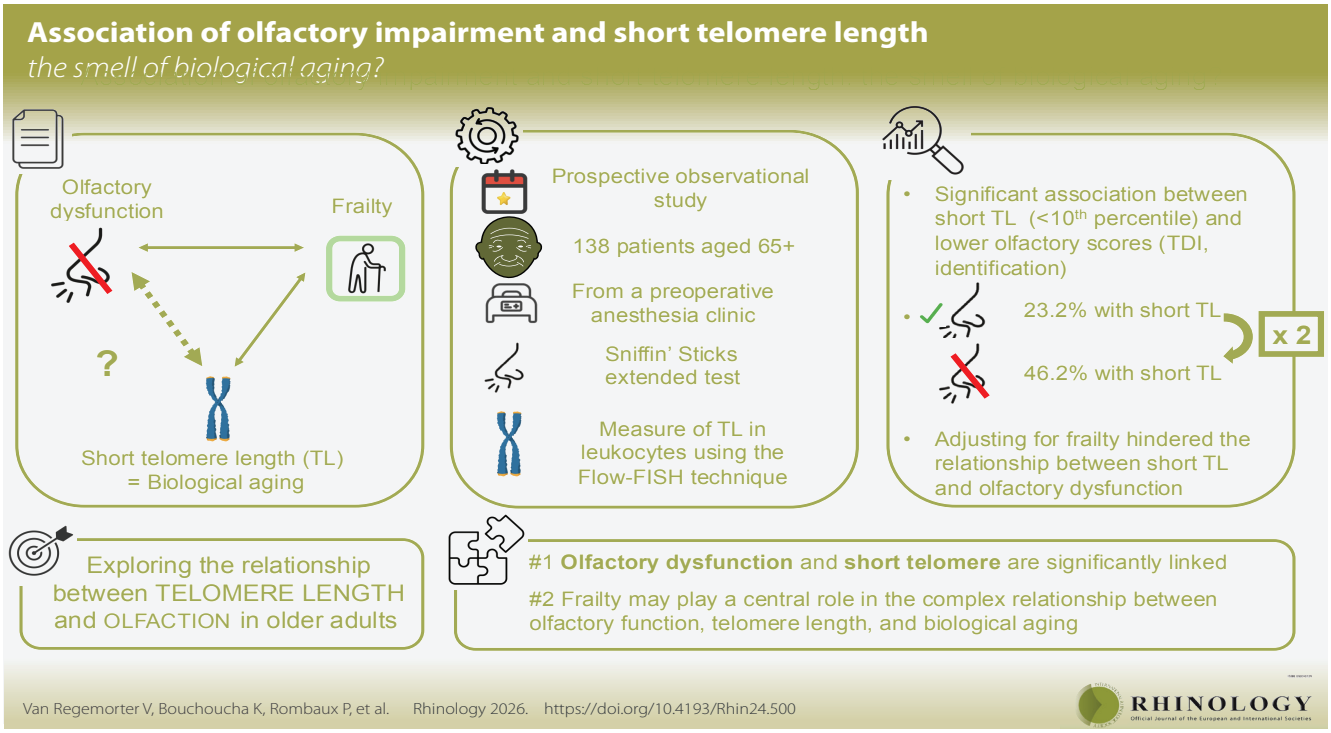

Abstract

Background: Olfactory dysfunction is a common issue among the older population and has been associated with both frailty and increased mortality risk. Telomere length (TL), a marker of biological aging, may provide insights into these associations. This study investigates the relationship between TL and olfactory function in older adults.

Methodology: We conducted a prospective observational study involving 138 participants aged 65 and above, recruited from a preoperative anesthesia clinic. Olfactory function was assessed using the Sniffin' Sticks test, and TL was measured in leukocytes using the Flow-FISH technique. Data analysis included comparisons between short TL (<10th percentile) and normal TL (≥10th percentile) groups, considering factors like age, sex, and frailty.

Results: Short TL was found in 27.5% of participants. Those with short TL had significantly lower TDI (threshold, discrimination, identification) scores. Specifically, 46.2% of participants with a TDI score ≤10th percentile had short TL compared to 23.2% with higher TDI scores. Adjusting for frailty attenuated this relationship, indicating a shared biological component between olfactory function and TL.

Conclusions: Our study reveals a significant association between lower olfactory function and shorter TL in older adults, suggesting that olfactory impairment may reflect underlying biological aging. Further research is needed to elucidate the complex interactions between olfactory function, TL, and frailty.

Key words: olfaction, frailty, telomere shortening, aging

Introduction

Humans are not all equal when it comes to aging. Many 80-year-old individuals are still active and in good health, while others are bedridden. A clinical indicator of biological aging is the concept of frailty, corresponding to a decreased physiological reserve and, therefore, to a reduced capacity to respond to a physical challenge [1]. Frailty status is considered more relevant than chronological age and medical comorbidities when evaluating the risk in older adults [2]. Therefore, when studying the effect of age on the development of diseases or mortality, speaking in terms of biological age and frailty is more accurate than chronological age.

Olfactory impairment is a frequent complaint among the general population. Age is well established as the prime determinant of olfactory decline [3,4], but notable variation in olfactory performance still exists among older adults. This raises the important question of whether olfactory function may serve as a sensitive marker of physiological (rather than simply chronological) aging. In the last decades, many studies have reported on the intriguing fact that olfactory dysfunction in older individuals is an independent predictor of mortality risk [5–10]. Anosmic people are at higher risk of death than normosmic individuals [11] and a recent meta-analysis concluded that olfactory impairment was associated with a 52% higher risk of all-cause mortality [12]. Despite the apparent robustness of the link, the causes remain largely unanswered. In a previous review [13], we summarized the putative underlying mechanisms, notably a more advanced physiological age leading to accelerated brain aging.

According to the WHO definition [14], aging is the consequence of the accumulation of a wide variety of molecular and cellular damages over time. Several hallmarks contributing to the aging process and phenotype have been described [15]. Among them, telomere shortening has been recognized for several years as a contributor to cellular senescence and aging [16]. Telomeres consist of repeated TTAGGG sequences located at the end of chromosomes, playing an essential role in chromosomal integrity. In the absence of telomerase, each cell division shortens telomeres, and aging is therefore associated with a progressive shortening of telomeres in somatic cells. Long telomeres are usually considered a sign of good cellular health and better regenerative potential of the tissues, while, in contrast, abnormally short telomeres are responsible for premature aging syndromes [17].

Based on these considerations, we aimed in this study to examine whether olfactory dysfunction serves as a marker of accelerated biological aging, as measured by leukocyte telomere length. In a recent cohort of older surgical patients, we found that olfactory dysfunction was significantly associated with preoperative frailty and increased postoperative complications [18]. Similar findings have been seen in patients undergoing head and neck surgery, where olfactory dysfunction was independently linked to increased frailty and adverse postoperative outcomes, such as longer hospital stays [19]. Our results further revealed that frailty – reflecting advanced aging – might largely underlie this association between olfactory impairment and poor outcome. We hypothesized that olfactory dysfunction could also be related to shorter telomere length, possibly providing a biological explanation for why some adults preserve good chemosensory function while others do not. To test this, we investigated the relationship between telomere length, measured in leukocytes using a Flow-FISH technique, and olfactory function in older people.

Materials and methods

Study population and design

A prospective observational study was conducted at the Cliniques universitaires Saint-Luc (Brussels, Belgium) between March 2021 and December 2022. The institutional Ethics Committee of Cliniques universitaires Saint-Luc, Université catholique de Louvain (Brussels, Belgium) approved the study protocol on March 3rd, 2020 (2020/22JAN/050). We recruited volunteers aged ≥ 65 from our hospital's preoperative anesthesia clinic who were enrolled after receiving an explanation. The participants were scheduled for either vascular surgery, including aortic or lower limb interventions, or orthopedic procedures, specifically total hip replacement surgery and lumbar spinal stenosis surgery. They all gave written informed consent and were tested before their programmed surgery. Exclusion criteria were the following: a history of neurologic disease (including any type of diagnosed dementia or cognitive impairment), psychiatric disorder, severe head trauma, sino-nasal illness or surgery, and any diagnosed olfactory loss. We did not consider the history of COVID-19 as an exclusion criterion per se and considered it as a covariate in our analyses. However, we did not include subjects who reported a recent COVID-19 infection (< 3 months) or complained of a subjective residual olfactory dysfunction.

Olfactory function testing

Each participant underwent the Sniffin' Sticks extended test (Burghart Messtechnik GmbH, Wedel, Germany). We used the n-butanol threshold subtest. Threshold (T), discrimination (D), and identification (I) were scored separately on 16 points. We also calculated the global TDI score by adding the results of the three olfactory modalities subtests for a total of 48 points.

We classified these olfactory scores into seven percentiles (p) categories according to the recently updated age- and sex-adjusted norms of the Sniffin' Sticks tests [3]. The categories were the following: 1) ≤ p5 (5th percentile or below), 2) > p5 to ≤ p10 (above 5th percentile to 10th percentile and below), 3) > p10 to ≤ p25 (above 10th percentile to 25th percentile and below), 4) > p25 to ≤ p50 (above 25th percentile to 50th percentile and below), 5) > p50 to v p75 (above 50th percentile to 75th percentile and below), 6) > p75 to≤ p90 (above 75th percentile to 90th

percentile and below), and (7) > p90 (above 90th percentile). We defined olfactory dysfunction as a TDI, threshold, discrimination, or identification score below or equal to the 10th percentile (≤p10) for age and sex.

Leukocyte telomere length measurement

All participants had a blood sample taken the same day they were tested for their olfactory function. Telomere length (TL) was measured by Flow-FISH (Fluorescence In Situ Hybridization), which is currently considered the gold standard technique for TL measurement [20]. TL was measured, in duplicate, in granulocytes and lymphocytes in the Cliniques universitaires Saint-Luc as described previously, using the FITC-labelled *(CCCTAA)*3 PNA probe (Panagene) and calf thymus cells as internal controls [21]. Fluorescence was measured with a Navios EX flow cytometer (Beckman Coulter).

We then compared lymphocyte TL measurements to those of a reference cohort of 491 healthy individuals (0 to 99 years) obtained in the Cliniques universitaires Saint-Luc (ISO15189). Short TL was defined as below the 10th percentile for age (< p10). Long TL was defined as equal to or above the 90th percentile for age (≥ p90). Average TL comprised measures equal to or above the 10th percentile (≥ p10) but below the 90th percentile (< p90). Normal TL was described as all measures equal or above the 10th percentile (≥ p10) (i.e., including individuals with long TL).

Covariables

We registered demographic (age, sex, body mass index (BMI)) and olfactory-related (smoking status) characteristics. Three age categories were defined: 65 to 69, 70 to 79, 80, and more. Moreover, we collected medical data known to influence TL, such as arterial hypertension, hypercholesterolemia, obesity (BMI ≥ 30), ischemic cardiopathy, and diabetes. We calculated a depression score with the Hospital Anxiety and Depression Scale (HADS) [22]. All the cohort took the Edmonton Frail Scale (EFS), a validated screening tool for frailty ranging from 0 to 17 points [23]. An individual was defined as frail when scoring ≥ 6/17. This test evaluates nine domains of frailty: functional performance, cognitive function, general health, functional independence, social support, used medications, nutrition, mood, and continence [24].

Statistical analyses

This study aimed at evaluating the association between olfactory function and leukocyte TL. We ran data analyses with SPSS version 28.0. The Kolmogorov-Smirnov test was used to assess the normality of the data. Ordinal and continuous variables were not normally distributed and were expressed as medians ± standard deviation. We analyzed olfactory scores (TDI, threshold, discrimination, and identification) according to age categories, sex, and smoking status using a Kruskal-Wallis or Mann-Whitney U-test. We realized comparisons between subjects with short TL and normal TL using a Pearson χ^2 for nominal variables and a Mann-Whitney U-test or a Kruskal-Wallis test for ordinal and continuous variables. We performed Pearson χ^2 or Fisher's Exact tests to analyze the association between short TL and olfactory dysfunction. We used multivariable linear regression analyses to assess the association between short TL and the TDI score while adjusting for potential confounding variables. We tested covariables related to TL that were associated with short TL at a threshold P-value < 0.2 in our first analysis (obesity, frailty) and covariables usually associated with the TDI score (age and sex). Using a Kruskal-Wallis test, we compared olfactory score percentiles categories between short, average, and long TL. A P-value < 0.05 was considered statistically significant.

Table 1. Olfactory TDI scores depending on baseline characteristics.

Characteristics	TDI score (Median ± SD)	P-value
Age, year		
65-69	29.25 ± 6.50	
70-79	28.00 ± 6.00	0.037
≥ 80	24.25 ± 5.00	
Sex		
Female	28.50 ± 5.50	0.068
Male	26.50 ± 6.50	
Smoking status		
Present smoker	28.50 ± 6.00	
Former smoker	26.50 ± 6.00	0.41
Non-smoker	26.50 ± 7.50	

TDI: Threshold, Discrimination and Identification

Results

Study population general and olfactory characteristics

We first characterized our study cohort, including their olfactory and telomere profiles. The cohort consisted of 138 participants with a median age of 73.5 years (69-78), including 73 female subjects (52.9%) and 67 past or active smokers (48.6%). Olfaction tests, using Sniffin' sticks, gave olfactory scores for threshold (T), discrimination (D), and identification (I) of, respectively, 4.4 ± 2.0, 10.3 ± 2.6, and 11.6 ± 2.8. Median TDI score was 26.3 ± 6.2 and, as expected, significantly decreased with increasing age categories (P = 0.037) (Table 1).

Male subjects tended to have a lower TDI score than females, but the difference was not statistically significant. Smoking status had no significant impact on TDI scores. According to original TDI scores cut-offs, most subjects (94/138, 68.1%) were classified as hyposmic (TDI score ≥ 16.5 and ≤ 30.5) while 10 participants (7.2%) were anosmic (< 16.5) and 34 (24.6%) were normosmic (> 30.5). When comparing to normative data for age and sex, 26 subjects (18.8%) had a TDI score below or at the 10th percentile (≤ p10), 32 (23.2%) had a threshold score ≤ p10, 20

Table 2. Characteristics of the cohort population depending on leukocyte telomere length.

Characteristics	Short TL (< p10) n = 38	Normal TL (≥ p10) n = 100	P-value
Age, year	73 ± 5	74 ± 6	0.36
Female, n (%)	20 (52.6)	53 (53.0)	0.97
Active or past smoker, n (%)	21 (55.3)	46 (46.0)	0.33
History of COVID-19, n (%)	6 (15.8)	18 (18.0)	0.76
Arterial hypertension, n (%)	28 (73.7)	76 (76.0)	0.78
Hypercholesterolemia, n (%)	20 (52.6)	57 (57.0)	0.64
Obesity (BMI ≥ 30), n (%)	16 (42.1)	26 (26.0)	0.066
Ischemic cardiopathy, n (%)	10 (26.3)	21 (21.0)	0.50
Diabetes, n (%)	7 (18.4)	19 (19.0)	0.94
HADS - depression score	4 ± 3	4 ± 3	0.57
Frailty (EFS ± 6/17), n (%)	13 (34.2)	22 (22.0)	0.141

TL: telomere length, BMI: body mass index, HADS: Hospital Anxiety and Depression Scale, EFS: Edmonton Frail Scale

Table 3. Univariable linear regression analysis associating short telomere length and covariables with the TDI score.

Variable	Standardized regression coefficient	P-value
Short TL	- 0.174	0.041
Age	- 0.145	0.090
Sex	- 0.178	0.036
BMI	-0.021	0.80
EFS score	- 0.317	< 0.001

TL: telomere length, BMI: body mass index, EFS: Edmonton Frail Scale

Table 4. Multivariable linear regression models associating short TL and covariables with the TDI score.

Variable	Standardized regression coefficient	P-value
Short TL	- 0.191	0.022
Age	- 0.183	0.029
Sex	- 0.197	0.019
Short TL	-0.191	0.024
Age	-0.183	0.031
Sex	-0.197	0.020
BMI	-0.001	0.99
Short TL	-0.138	0.089
Age	- 0.108	0.19
Sex	- 0.215	0.008
EFS score	- 0.287	< 0.001

TL: telomere length, BMI: body mass index, EFS: Edmonton Frail Scale

(14.5%) had a discrimination score ≤ p10, and 14 (10.1%) had an identification score ≤ p10.

Telomere length (TL) data

TL data were obtained using Flow-FISH on lymphocytes isolated from the 138 participants of our study. We found 38 subjects (27.5%) with TL below the 10th percentile (< p10), thus referred to as short TL, and 100 (72.5%) with normal TL (≥ p10, 10th percentile or above). The group with normal TL included 17 subjects with long TL (≥ p90, 90th percentile or above), representing 12.3% of the whole cohort. The high percentage of volunteers with short TL in our cohort may be related to the fact that participants were enrolled among patients in the process of undergoing surgery. Alternatively, divergence from our results may be partially explained by the fact that the reference cohort used to build the Flow-FISH curves did not include many older people. Nevertheless, the group with short TL did not particularly suffer more from cardiovascular diseases or diabetes, known to be related to telomere length, than the rest of the cohort [16].
We compared the participants' characteristics according to their leukocyte TL (short or normal) (Table 2). Obesity and frailty status were more frequent in the group with short TL (42.1% vs. 26.0% and 34.2% vs. 22.0%, respectively), but differences were not statistically significant.

Influence of short telomere length (TL) on olfactory function

To investigate the relationship between short TL and olfactory function, we compared the distribution of TL status across different olfactory performance groups. Among the subjects with a TDI score ≤ p10, 46.2% (12/26) had short TL compared to 23.2% of those with a TDI score > p10 (P = 0.018) (Figure 1). Similarly,

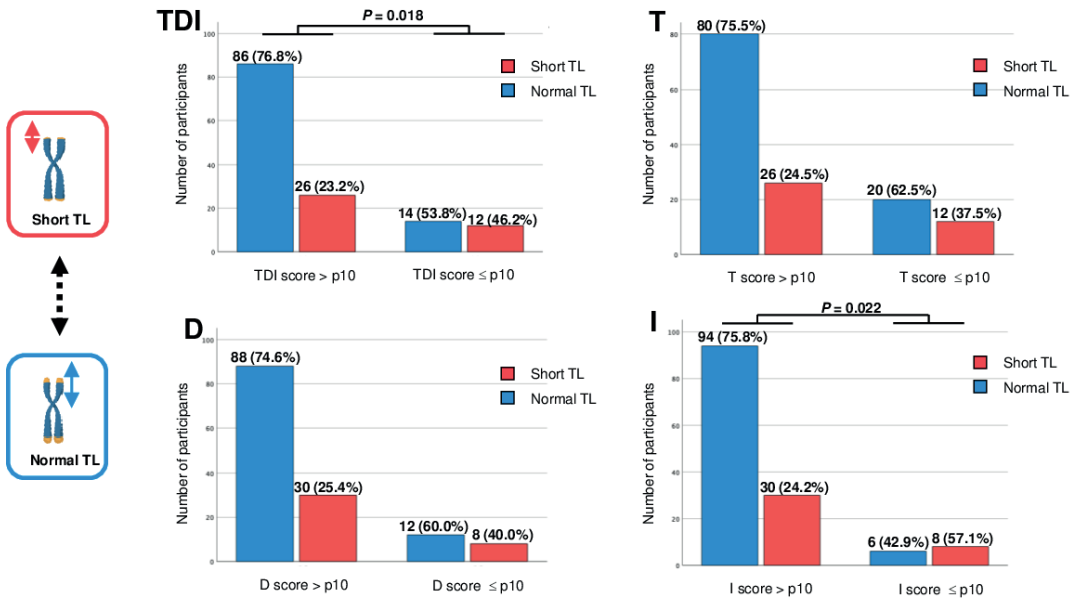

Figure 1. Comparison of telomere length according to olfactory scores. (TDI) TDI total score. T: Threshold score. D: Discrimination score. I: Identification score. TL: telomere length. > p10: above the 10th percentile. ≤ p10 : 10th percentile or below.

when looking at the identification subscore, 57.1% (8/14) of those with an identification score ≤ p10 had short TL, versus only 24.2% (30/124) with higher identification scores (P = 0.022) (Figure 1). While showing a comparable pattern, the differences regarding discrimination and threshold scores did not reach statistical significance (Figure 1).

Furthermore, when olfactory score percentile categories were compared between participants with short and normal TL, significant differences emerged for the TDI (P = 0.036), the threshold (P = 0.030), and the discrimination (P = 0.010) modalities, but not for the identification score.

To better characterize these associations, we performed linear regression analyses. In univariable analyses, short TL was significantly associated with the TDI score (P = 0.041), while sex was also a significant covariate (Tables 3 and 4). Adjusting for the BMI had no effect. However, when frailty (as measured by the EFS score) was included in the model, the relationship between short TL and the TDI score was attenuated and lost statistical significance. In contrast, none of the individual threshold, discrimination, or identification subscores showed significant associations with short TL in regression analyses (all P > 0.05).

Olfactory function scores across different telomere length groups

To further examine how telomere length relates to olfactory performance, we compared the olfactory score percentiles categories for the TDI, the threshold, the discrimination and the identification across three TL-defined groups: short TL (< p10), average TL (≥ p10 to < p90), and long TL (≥ p90). Statistically significant differences were observed for the TDI, the threshold, and the discrimination scores, all of which showed higher values in groups with increasing TL (Figure 2). Although the identification subscore exhibited a similar trend, the differences were not statistically significant (Figure 2). Notably, only 1 participant (5.9%) with long TL had a TDI score ≤ p10, compared to 15.7% (13/83) in the average TL group and 31.6% (12/38) in the short TL group.

Discussion

Our study unveiled a significant association between low olfactory scores and short TL in older individuals. This correlation was present for the composite TDI score and the odor identification component of the test battery. The correlation was not statistically significant for odor thresholds and odor discrimination, although the changes went in the same direction as seen for odor identification. These differences may be attributed to a lack of power or a larger variance for odor discrimination and odor thresholds. Vohra and colleagues recently reported that lower scores at the 12-item Brief Smell Identification Test were associated with short TL – the lowest quartile of their samples, measured with quantitative polymerase chain reaction (qPCR) – in a large cohort of 1603 older individuals [25]. Our study, albeit smaller, strengthens these data with extended olfactory testing and measurement of TL with the gold-standard Flow-FISH technique [20,21]. One of the major drawbacks of the qPCR technique lies in its inability to discriminate between the TL of lymphocytes and granulocytes [26], which is a major issue since aging or diseases affect lymphocytes and granulocytes TL differently [27]. Furthermore, the Flow-FISH technique demonstrates far more accuracy and reliability than qPCR, subject to significant variabi-

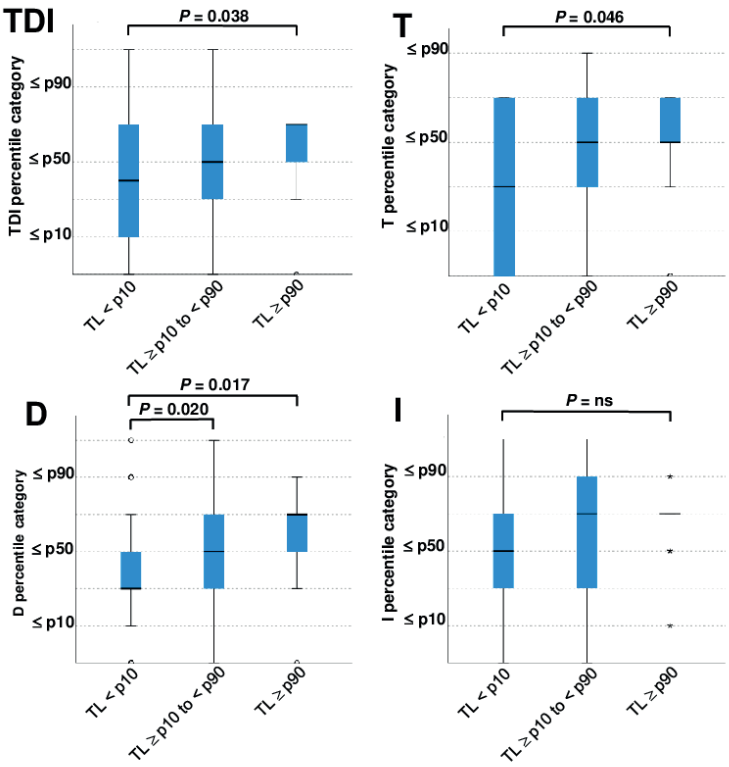

Figure 2. Olfactory scores percentile category according to short, average, and long telomere length. TDI: TDI total score. T: Threshold score. D: Discrimination score. I: Identification score. TL: telomere length. TL < p10: telomere length below the 10th percentile. TL ≥ p10 to < p90: telomere length equal to or above the 10th percentile and below the 90th percentile. TL ≥ p90: telomere length equal to or above the 90th percentile. Ns: not significant.

lity [28]. Besides, here, olfactory function and TL assessments were realized simultaneously, as opposed to their asynchronous data collection over a 5-year period [25].

Contrary to previous evidence [16,29], cardiovascular diseases and diabetes were not more common in people with short TL. Although we found a trend towards higher obesity rates, adjusting for BMI did not affect our results. In the study by Vohra et al. [25], data were adjusted for several related illnesses, including diabetes and arterial hypertension. This suggests that these conditions – specifically obesity and diabetes, which have been related to olfactory impairment – may not be responsible for the connection between olfactory dysfunction and short TL.

While individual olfactory subtests did not reach statistical significance, we found a significant association between short TL and the TDI score, indicating a relationship with global olfactory performance. The fact that only the aggregated TDI score could capture a significant relationship with short TL is likely attributable to limited statistical power. Interestingly, consideration of frailty hindered the relationship between olfaction and short TL. Although the lack of statistical significance may reflect, once again, an insufficient sample size, these findings may also support the idea that they share a common biological component.

While there is clear evidence that frailty is linked to olfactory dysfunction [30], contradictory results have been reported for TL [31,32]. These studies, however, used qPCR to measure TL and suffered from heterogeneity, especially in frailty assessments. A recent study on Chinese participants aged 75 years and older found no correlation between Fried's frailty criteria and TL [33]. On the contrary, a significant relationship was reported in a younger cohort (40-69 years) [34]. In the present study, frailty tended to be more frequent in older persons with short TL, although this was not statistically significant. Therefore, it seems difficult to associate short TL with frailty [35]. Conclusions may, nonetheless, be difficult to draw because, in cohorts of older individuals, there might be a survival bias towards an enrichment of people with reduced frailty. This is in line with a recent meta-analysis, which showed an increased risk of all-cause mortality in people with short TL but with a weaker link in the oldest part of the sample [36]. Altogether, and despite missing a clear-cut answer concerning frailty, these results suggest complex and intricate links between olfaction, TL, frailty, and mortality in older individuals.

To account for the discrepancies between studies, Sanders and colleagues suggested that TL could be a biomarker of aging in specific tissues rather than at the level of the whole organism [37]. Yet, the olfactory system relies on continuous cellular neurogenesis, and alteration of these processes may account for olfactory decline [38]. A study performed on mice with short TL showed impaired cellular regeneration of the olfactory epitheli-

um when subjected to induced damage compared to wild-type mice with long TL [39]. The olfactory system may thus be more sensitive to short TL than other tissues, which may account for the strong association between olfactory function and TL. Nevertheless, differences in olfactory function were not observed between the two groups of mice in the absence of induced damages, suggesting that, in humans, the link between short TL and impaired olfactory function may only appear with age, when the regenerative potential of the olfactory system may be exhausted by cumulative damages to the olfactory epithelium. It will also be interesting to test whether the protective effects of long TL on olfactory function are mediated through an impact on the nasal epithelium or on neurons within the brain regions linked to olfaction.

We showed that olfactory scores improved with TL in a dose-dependent fashion. The TDI, the threshold, and the discrimination scores were all higher in people with long TL than the participants with short TL. It is interesting to note that there are still debates about whether longer TL predicts prolonged lifespan [17]. Along this line, long TL could favor certain cancer types [40]. In humans, long TL was more frequent in the oldest old, probably reflecting a survivor effect [41]. Furthermore, "healthy" centenarians tend to have longer TL than "unhealthy" ones [42]. Nevertheless, the fact that a better sense of smell and longer TL are related provides mutual evidence for both being indicators of aging.

Limits

This study has several limitations. As discussed earlier, some results probably suffered from a small sample size. Besides, our cohort was composed of preoperative patients scheduled to undergo vascular or orthopedic interventions, which may have influenced our results. In our analyses, we used only one screening tool, the EFS, to evaluate frailty status, and no additional biological aging markers were included beyond telomere length. Consequently, this may limit the interpretation and broader applicability of our findings.

Conclusion

We found a positive correlation between global olfactory function and telomere length in older individuals; however, this association was no longer significant after adjusting for frailty. These findings suggest that frailty may play a central role in the complex relationship between sense of smell, telomere length and biological aging. Our results provide further evidence for the intricate, yet still not fully elucidated, links among these markers. Additional larger studies, with expanded covariate assessment, are essential to fully understand the significance of these markers as hallmarks of biological aging, with a particular focus on determining the causal relationships between them.

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Authors' contributions

VV contributed to conducting the study, collecting and analyzing the data, and writing the draft manuscript. KB helped collect the data and revise the draft manuscript. PR contributed to writing the draft manuscript. MAV helped analyze the data and revise the draft manuscript. TH contributed to writing the draft manuscript. AD contributed to conducting the study, analyzing the data, and revising the draft manuscript. CH helped conduct the study, analyze the data and revise the draft manuscript.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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