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Running title:
Olfactory training in individuals with normosmia

ORIGINAL CONTRIBUTION

Olfactory training in normosmic individuals: a randomised controlled trial

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SUMMARY

Background: *Even if olfactory training (OT) is a well-established treatment for individuals with olfactory dysfunction, the effect on individuals with normosmia remains uncertain. In this randomised controlled trial, we explore how OT with different exposure lengths affect olfactory function in individuals with normosmia.*

Methodology*: Two hundred normosmic individuals were randomly assigned to one of two intervention groups performing OT with different exposure lengths or to a control group. The OT groups did OT twice daily for three months, sniffing four different odours (eucalyptus, lavender, mint, and lemon) for 10 seconds per bottle during either a total of 40 seconds (standard OT) or 4 minutes (extended OT), while the control group did not perform any OT. Olfactory function was assessed using a 48-item Sniffin Sticks test at baseline, after the intervention, and after one year.*

Results: *We found no significant effect of OT in either of the intervention groups on any aspect of olfaction after intervention or at follow-up. There was no association between sex, age, allergic rhinitis, education or olfactory scores at baseline, and changes in olfactory function after OT. The extended OT group performed significantly fewer training sessions compared to those in the standard OT group (p=0.03).*

Conclusions: *OT had a limited effect on olfactory function in individuals with normosmia. Further, the superiority of a more extended OT is not supported by this study, and shorter training sessions seem to improve compliance with OT.*

(Word count: 235)

Keywords: smell, olfactory receptor neurons, olfactory mucosa, olfaction disorders, nose

INTRODUCTION

Olfaction is a sense that, to date, is not completely understood. Many actions and decisions in our daily life may be driven by certain odours, and olfaction is of crucial importance in human interaction, nutrition and the ability to avoid environmental hazards [1]. An impaired olfactory function may enhance depression and anxiety symptoms [2]. Furthermore, olfaction is of physiological importance being associated with major health outcomes, including neurodegenerative diseases and mortality [3, 4]. Olfactory function diminishes with age, and some studies indicate a possible olfactory superiority of women over men [4-11]. Depending on definitions and investigated populations, olfactory dysfunction (OD) affects more than a quarter of the population [10], possibly more after the Covid-19 pandemic [12], and olfactory training (OT) has been regarded as a good treatment option due to the unique neural plasticity of the olfactory mucosa and pathway, both through bottom-up and top-down processes [13-16].

The efficacy of OT is mostly documented in individuals with OD, as in a 2017 meta-analysis which reported an improvement of olfactory function after OT, with a large effect on the global olfactory score (TDI), discrimination (D) and identification (I) for patients with OD of different etiologies and a small to moderate effect on the threshold (T) [17]. A recent review suggests that OT may have several benefits both in those with and without OD since, in addition to enhancing olfactory function, it may improve cognitive performance and increase volume in several brain regions as well as increase neural connectivity [18]. This may have implications for diminishing the negative consequences of olfactory loss and might even prevent age- or disease-related olfactory loss. However, the effectiveness of OT on olfactory performance in normosmic individuals is poorly studied, and the results are heterogeneous. While some studies reported improved olfactory sensitivity after repeated exposure to odours [19, 20], other studies found no increase [21, 22]. Negoias et al. [13] even found decreased olfactory sensitivity after OT in normosmic individuals. The same study found no change in I scores after OT [13], while OT resulted in significantly better I score in other studies [22, 23]. In children and sommeliers, OT is reported to improve olfactory sensitivity [24-26]. However, in an older population, the efficacy of OT is controversial as one study found no significant increase in olfactory function after OT [27], while another reported a significant improvement of olfactory function and improved verbal function, subjective well-being and decreased depressive symptoms in the OT group [28].

Although OT is a well-established treatment for OD, questions regarding the efficacy and

mechanism of OT persist [29]. The most efficient way to perform OT and the long-term effect of OT remains uncertain. In patients with OD, increasing the concentration of the odours [30], adding more odours [31] and longer duration of OT [32] is suggested to increase OT's efficacy. In individuals with normosmia, more complex training tasks may be advantageous [22, 33]. To our knowledge, how OT with different exposure lengths influences olfactory function in individuals with normosmia is not explored.

In summary, OT does not seem to improve olfactory function in all circumstances, and more research is needed to understand the effects of OT, identify the population most likely to benefit from the treatment and establish optimal training protocols. This motivated the present randomised trial, where the primary aim was to explore how OT with different exposure lengths influences different aspects of olfaction and the long-term effect of OT in a normosmic population. The secondary aim was to identify factors associated with changes in olfactory function after OT.

MATERIALS AND METHODS

Study design

In this randomised controlled trial, the participants were randomly assigned to one of two intervention groups to perform OT with different exposure lengths or to a control group. They did not receive any financial compensation for participation. The randomization was performed using a web-based program provided by the Clinical research unit at the Norwegian University of Science and Technology. The participants were evaluated at baseline, after three months of intervention and after one year. The power calculation was based on a difference in change in TDI of 2 between the two intervention groups, a standard deviation of 4.0 and a power of 90%, indicating a sample size of 84 in each group. The clinical trial's number was NCT02980718.

Participants

A total of 200 participants were recruited via public advertisement between 2016 and 2019 [9]: 90 participants to perform extended OT, 90 participants to perform standard OT [34] and 20 participants as controls with no OT or any other intervention/instruction (figure 1). The inclusion criteria were adults aged 18-65 with normosmia (TDI score > 30.5). Exclusion criteria were diseases affecting olfaction, such as chronic rhinosinusitis with or without nasal polyps, severe symptoms of allergic rhinitis, sinonasal surgery within the last three years

before inclusion, recent or ongoing upper respiratory tract infection, Alzheimer's disease, Parkinson's disease, multiple sclerosis and chronic obstructive pulmonary disease. Additionally, individuals who were not able to participate due to limitations in language, practical implementation or mental condition were excluded from the study. All participants signed an informed consent form. The study was approved by The Regional Committee for Medical Research Ethics in Mid-Norway (reference number 2016/837), and investigations were performed in accordance with the principles of the Declaration of Helsinki/Hong Kong.

Variables

Background variables, such as age, sex, symptoms of allergy, smoking and level of education, were assessed using a questionnaire [35]. Self-reported olfactory function was assessed on a 100 mm Visual Analogue Scale (VAS), with 0 mm as "the worst possible sense of smell" and 100 mm as "the best possible sense of smell" [36]. The participants noted the subjective change in olfactory function after the intervention period and after one year. Allergy status was assessed using a skin prick test with an allergy panel consisting of birch, grass and mugwort pollen, Cladosporium, house dust mite and dog, cat and horse epithelia, together with positive and negative controls. A positive test was defined as a wheal diameter >3 mm [37]. Participants with a positive test and typical symptoms of hypersensitivity were classified as having allergic rhinitis. Nasal endoscopy (2.7 mm, 0° True View II endoscope, Olympus, Japan) was performed by an otolaryngologist after olfactory testing. The findings were scored using the modified Lund-Kennedy scoring system based on polyp extend (none with polyps were included in this study), oedema (0: absent; 1: mild; 2: severe), and discharge (0: none; 1: clear; 2: thick and purulent) [38]. For statistical purposes, the results were dichotomized to "no mucus or oedema" and "presence of mucus and/or oedema".

Olfactory training

Participants in the two intervention groups were instructed to perform OT for three months with twice daily sessions of four bottles containing oils from eucalyptus, lavender, mint and lemon plants. They were instructed to do OT according to the assigned OT intervention group. Those undergoing standard OT [34] were instructed to sniff 10 seconds per bottle for a total of 40 seconds. Those undergoing extended OT were instructed to continuously sniff each bottle for 10 seconds and then without a delay rotate them for a total of 4 minutes. To focus the attention on the OT, the participants in the intervention groups were asked to log the training session twice daily in a diary.

Olfactory outcome

The main outcome of the RCT was the olfactory function scores, evaluated using the Sniffin' Sticks test (Burghart Messtechnik, Wedel, Germany) [39]. The test consists of three subtests, T, D and I, which form the composite global olfactory score (TDI). T was determined when the odorized pen (n-butanol) was identified among three samples, with the other two pens containing the solvent propylene glycol, which has little or no odour. Concentration was increased if one of the odourless pens was selected and decreased if the correct pen was identified twice in a row. The T score was the mean of the last four reversal points, ranging from 1 to 16. In the D test, the participant was encouraged to discriminate one different odour from two identical odours. This was performed for 16 triplets of pens. In the I test, the participant was presented with single pens and asked to identify each of the 16 odours from a list of four descriptors. The summated TDI score from the T, D and I subtests, with a maximum of 48 points (each subtest with 16 points), were used to categorize patients in terms of normosmia (score≥30.75), hyposmia (score 16.25–30.5) and functional anosmia (referred to as anosmia) (score≤16) [6]. Clinically significantly improved olfaction was defined as an increase in TDI score by 5.5 [40].

Statistical analysis

SPSS version 27 (SPSS Inc., Chicago, IL, USA) and Stata version 17.0 was used for statistical analysis. Comparisons between the three groups were performed using one-way ANOVA and Chi^2 tests (Fisher's Exact test if expected value < 5). The assumption of normality was satisfied for all continuous variables, based on a test of normality (Shapiro-Wilk), histogram and Q-Q plot and according to the central limit theorem. Linear mixed models were estimated to compare the change in olfactory function after intervention and at follow-up between the two intervention groups and the control group. Models that were fitted included study arm, follow-up time, age group (18-30 years, 31-40 years, 41-50 years, 51-60 years, 61-65 years), sex, allergic rhinitis, smoking, education and endoscopic findings of mucus or oedema. We assessed the interaction effects between the measurement time (baseline vs post-OT vs follow-up) and training regimen (extended vs standard vs control group). To study the effect of intervention in subgroups, three-way interaction effects between the study arm, follow-up time and the covariate of interest (age group, sex, allergic rhinitis, education and endoscopic findings of mucus or oedema) were estimated. Similarly, the interaction effects between measurement time, training regimen and T, D, I and TDI

below/above the median at baseline were explored. To further examine the potential impact of age, sex and baseline TDI on the effects of OT within each intervention group, we compared the youngest and oldest one-third of participants, men vs women and those with the lowest and highest one-third baseline TDI scores. The alpha level was set at 0.05.

RESULTS

There were no significant differences in characteristics or olfactory function between the three groups at baseline (table 1). The OT diary was submitted by 97% (151/156). Of 186 possible sessions per participant, the mean (SD) number of training sessions for both training groups was 160.7 (23.9) per participant. Subjects in the extended OT group performed significantly fewer training sessions compared to those in the standard OT group (156.0 (26.6) vs 164.7 (20.7), p=0.03).

A linear mixed model comparing the change in T, D, I and TDI after intervention (3 months) and follow-up (1 year) between the two intervention groups and controls revealed no significant effect of the intervention at any of the endpoints (figure 2 and supplementary table). For all outcomes, we tested for potential three-way interaction effects between the randomization arm, follow-up time and each of the following covariates: sex, age group, education, allergic rhinitis and endoscopic findings of mucus or oedema. Due to the low number of smokers in the intervention and control groups, we did not proceed with further analysis of this group. The only statistically significant interaction effect was the endoscopic finding of mucus or oedema for outcome TDI (table 2). Participants in the extended OT group with normal endoscopic findings had significantly higher TDI scores at follow-up compared to the standard OT group (between-group differences 1.29, 95% confidence interval 0.36, 2.22, p-value 0.007). Other comparisons were not statistically significant. Further, to consider a potential ceiling effect, we tested if there were any three-way interaction effects between the randomization arm, follow-up time and olfactory function scores (T, D, I and TDI) below or above median values at baseline. None of these were significant (table 2).

Comparing the effect of OT in the one-third youngest and oldest revealed no significant differences within the two intervention groups (table 3). Considering the baseline TDI score, participants with the highest one-third TDI score at baseline, both in the standard and extended OT group, had a significantly greater increase in TDI after intervention and at follow-up,

compared to those with the lowest one-third baseline TDI score. The same applied to T and I in the extended OT group after intervention (table 3). Women had significantly higher D after extended OT than men, but there were no differences between sexes at follow-up (table 3).

DISCUSSION

This study aimed to explore how OT with different exposure lengths influences olfaction in a normosmic population. We found no significant effect of OT in either of the intervention groups on any aspect of olfaction (T, D, I, or TDI) after intervention (3 months) or at follow-up (1 year). There were similar findings regardless of sex, age group, allergy status, education, or if the olfactory function was below or above the median at baseline. The extended OT group performed significantly fewer training sessions compared to those in the standard OT group.

Although OT is a promising approach to improve olfactory function in individuals with OD [17], the results from this study indicate that OT has little influence on olfactory function in individuals with normosmia. Conversely, two studies found OT to be effective both in individuals with normosmia and OD [19, 41]. Consistent with our results, prior studies have demonstrated unsuccessful attempts to improve olfactory function in normosmic individuals [13, 21]. One explanation for this outcome is that OT may have limited effectiveness in individuals with high olfactory scores at baseline due to a ceiling effect. However, even in those with baseline olfactory function scores below the median, we did not observe a significant effect of OT, unlike results from another study on normosmic individuals [41]. Additionally, when comparing individuals with the one-third lowest and highest baseline TDI scores in each intervention group, we found a statistically significant, but not clinically significant [40], greater effect of both training regimens in the group with the highest baseline TDI scores, which challenges the notion of a ceiling effect. Another explanation for the lack of effect of OT in normosmic individuals could be that repeated odour exposure in individuals with normosmia might lead to diminished interest in the task, although our participants reported high adherence to the training.

However, the most effective OT regimen is yet to be established. Different approaches have been suggested to provide a greater training effect, such as a longer duration of OT [32], adding more odours to the training regimen [31], and the use of odours at higher concentrations [30]. In individuals with normosmia, more complex training features have been

suggested as beneficial [22, 33]. In our study, the lack of difference in olfactory function after intervention and at follow-up between the two intervention groups suggests that extended OT is not superior to standard OT. This is supported by another study that found no benefit from a more intense OT regimen [19]. This finding can have implications for the future standardization of recommended training regimens. Four minutes of OT is more exhausting than 40 seconds of OT, and a shorter training regimen probably improves compliance. This claim is supported by our finding of significantly better compliance in the standard OT group compared to the extended OT group.

We found no influence of sex on the effect of OT in individuals with normosmia, consistent with findings in other studies [13, 41]. Furthermore, there were no clinically significant differences between men and women within the intervention groups [40]. Moreover, we found no differences in the changes in olfactory function after OT between age groups. Increasing age is considered to be the most common cause of OD [9, 10], and some studies have demonstrated OT to be more effective in younger individuals [41, 42], but this is not confirmed in other studies [13, 32], nor in our study, as we found no difference in olfactory outcome after OT comparing the youngest and oldest one-third in each intervention group. Allergy, considered to affect olfactory function dependent on disease severity and duration [43], also did not affect OT in our study. Neither did education level, which in some studies is associated with olfactory function [9, 44]. However, those with normal endoscopy in the extended OT group showed slightly higher TDI at follow-up compared to the standard OT group, but the difference was not clinically significant [40].

Several studies have shown a correlation between changes in olfactory function and structural changes in olfactory processing areas of the brain after OT, with a better olfactory function being related to increased cortical thickness and density in several brain regions [22, 45, 46]. Interestingly, structural changes can be observed even when the olfactory function appears unchanged [13]. The functional implication of these morphologic changes without a measurable change in olfactory function remains unclear. One can speculate if these volume changes reflect other functional effects of OT, which extend beyond its impact on olfactory function, such as improved cognitive function, particularly verbal fluency and learning/memory [18], and preventive effect on age- or disease-related olfactory decline [27, 28, 47]. Hence, although we did not find any significant change in olfactory function after OT in normosmic individuals, the training may have had other beneficial effects. To explore this,

magnetic resonance imaging, cognitive assessment and longitudinal study design are required.

The present study is unique in that it uses a randomised controlled trial study design with a large sample size and three comparative groups to study the effect of OT on olfactory function in individuals with normosmia. The use of comprehensive and validated tests for olfactory assessment, follow-up measurements to explore how training effects persisted following OT cessation, and OT registration to observe training compliance further strengthens the study. Among limitations, OT compliance was based on self-reports, and whether the participants performed OT accordingly to the regimen is difficult to verify. Further, the basis for comparison would have been more reliable if the extended OT group had similar compliance to those in the standard OT group. Moreover, other potential effects of OT, like cognitive function or structural changes in the brain, were not investigated [18]. Neither was comorbidity [44], psychological health [48, 49] nor medication [4], which might influence the potential effect of OT. The study might be biased in terms of sex. Further, the allergy classification was uncertain, as the diagnosis solely relied on a positive skin prick test and typical symptoms of hypersensitivity without specifying the symptomatic allergen. Next, due to the dropout frequency, our negative findings may be caused by type II errors, but we were close to the number of participants we needed in the two intervention groups. Finally, although there is a risk of reaching a ceiling effect in a study on OT in normosmic individuals, our findings of greatest improvement in those with the highest baseline TDI suggest that further enhancement of olfactory function may still be possible, dependent on the individual's capacity for olfactory regeneration [16, 50].

In conclusion, our findings confirm that OT has a limited effect on olfactory function in individuals with normosmia. Further, the superiority of a more extended OT is not supported by this study, and shorter training sessions seem to improve compliance with OT. Neither sex, age, allergic rhinitis, education, nor olfactory scores at baseline were associated with changes in olfactory function after OT.

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AUTHORSHIP CONTRIBUTION

ITH: Study design, data collection, statistical analysis, paper drafting

WMT: Study design, data collection, statistical analysis, paper drafting

TAM: Statistical analysis, paper drafting

TH: Study design, statistical analysis, paper drafting

SN: Study design, paper drafting

MB: Study design, data collection

ASH: Study design, statistical analysis, paper drafting

CONFLICT OF INTEREST

None declared

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FIGURES
Legends for illustration

Figure 1. Inclusion and exclusion flowchart of the study population

Figure 2. Figure derived from a linear mixed model illustrating mean and confidence interval for A. Threshold, B. Discrimination, C. Identification and D. TDI: sum of the T, D and I scores at baseline, after three months and one year for intervention and control groups.

TABLES
Legends for table

Table 1. Demographics and descriptive statistics of the three study groups at baseline. P-values compare baseline means in the three groups. VAS: visual analogue scale; MLK: modified Lund Kennedy endoscopy score; TDI: sum of the T, D and I scores; T: threshold; D: discrimination; I: identification.
Note. [a] vs men, [b] vs non-smoker, [c] vs no allergic rhinitis, [d] vs no oedema/mucus.

Table 2. Table showing p-values for potential three-way interaction effects between randomisation arm, follow-up time and each of the following covariates: sex, age group, education, allergic rhinitis, endoscopic findings of mucus or oedema and olfactory function values below/above median at baseline. TDI: sum of the T, D and I scores; T: threshold; D: discrimination; I: identification. *$p<0.05$.

Table 3. Estimated differences in olfactory function after standard or extended OT between the one-third youngest and oldest (adjusted for baseline olfactory score), those with the one-third lowest and highest baseline TDI scores and men vs women, after intervention (1) and at follow-up (2). Estimates are derived from a linear mixed model. TDI= sum of the T, D and I scores; T= threshold; D= discrimination; I= identification; CI= confidence interval. *p<0.05.

Supplementary table. Estimated changes in olfactory function by intervention groups and controls. Estimates are derived from a linear mixed model estimating differences in olfactory function after intervention (1) and at follow-up (2) between each intervention group. TDI: sum of the T, D and I scores; T: threshold; D: discrimination; I: identification; CI: confidence interval.

Table 1.

	Total	Extended OT	Standard OT	Control group	p-value
Age mean (SD)	40.0 (11.6)	38.8 (10.7)	41.3 (12.4)	39.3 (11.3)	0.3
Women [a] n (%)	151 (75.5)	66 (73.3)	68 (75.6)	17 (85.0)	0.5
Smoker [b] n (%)	8 (4.0)	4 (4.4)	3 (3.3)	1 (5.0)	0.9
Allergic rhinitis [c] n (%)	56 (28.0)	27 (30.0)	23 (25.6)	6 (30.0)	0.8
Education: n (%)					0.5
High school	26 (13.0)	9 (10.0)	15 (16.7)	2 (10.0)	
College/University	173 (86.5)	80 (88.9)	75 (83.3)	18 (90.0)	
MLK mean (SD)	0.4 (1.0)	0.5 (1.1)	0.3 (0.8)	0.4 (1.0)	0.4
Oedema/mucus [d] n (%)	34 (17.0)	18 (20.0)	13 (14.4)	3 (15.0)	0.6
VAS, olfactory function mean (SD)	69.0 (16.9)	70.8 (14.8)	67.2 (17.8)	68.8 (21.0)	0.4
TDI mean (SD)	34.3 (2.3)	34.5 (2.2)	34.1 (2.3)	34.4 (2.3)	0.2
T mean (SD)	7.2 (1.6)	7.4 (1.5)	7.0 (1.6)	7.4 (1.7)	0.2
D mean (SD)	13.5 (1.5)	13.5 (1.5)	13.5 (1.5)	13.6 (1.7)	0.8
I mean (SD)	13.6 (1.2)	13.6 (1.3)	13.6 (1.2)	13.4 (1.1)	0.9

Table 1. Demographics and descriptive statistics of the three study groups at baseline. P-values compare baseline means in the three groups. VAS: visual analogue scale; MLK: modified Lund Kennedy endoscopy score; TDI: sum of the T, D and I scores; T: threshold; D: discrimination; I: identification.

Note. [a] vs men, [b] vs non-smoker, [c] vs no allergic rhinitis, [d] vs no oedema/mucus.

Table 2.

	Sex	Age group	Education	Allergic rhinitis	Mucus/oedema	Baseline values
T	0.20	0.85	0.83	0.59	0.09	0.46
D	0.13	0.17	0.50	0.67	0.16	0.19
I	0.86	0.54	0.22	0.14	0.99	0.24
TDI	0.12	0.23	0.44	0.60	0.02*	0.70

Table 2. Table showing p-values for potential three-way interaction effects between randomisation arm, follow-up time and each of the following covariates: sex, age group, education, allergic rhinitis, endoscopic findings of mucus or oedema and olfactory function values below/above median at baseline. TDI: sum of the T, D and I scores; T: threshold; D: discrimination; I: identification. *$p<0.05$.

Table 3.

Olfactory function Standard OT	1/3 youngest vs 1/3 oldest Mean difference (95% CI)	p-value	1/3 lowest vs 1/3 highest baseline TDI Mean difference (95% CI)	p-value	Men vs women Mean difference (95% CI)	p-value
TDI1	1.15 (-0.28, 2.58)	0.12	-1.05 (-1.96, -0.14)	0.02*	-1.21 (-2.60, 0.17)	0.09
T1	-0.03 (-0.81, 0.76)	0.95	-0.24 (-0.79, 0.30)	0.38	-0.69 (-1.44, 0.05)	0.07
D1	0.70 (-0.08, 1.50)	0.08	-0.03 (-0.57, 0.51)	0.91	-0.42 (-1.18, 0.35)	0.29
I1	0.40 (-0.27, 1.08)	0.24	-0.02 (-0.45, 0.42)	0.94	-0.22 (-0.87, 0.43)	0.50
TDI2	1.08 (-0.38, 2.54)	0.15	-1.97 (-2.89, -1.04)	<0.001*	0.05 (-1.36, 1.46)	0.94
T2	0.07 (-0.73, 0.87)	0.86	-0.27 (-0.78, 0.25)	0.31	-0.31 (-1.07, 0.45)	0.43
D2	0.37 (-0.44, 1.18)	0.37	-0.42 (-1.00, 0.16)	0.16	0.69 (-0.09, 1.47)	0.08
I2	0.57 (-0.12, 1.26)	0.10	-0.29 (-0.72, 0.13)	0.18	-0.48 (-1.14, 0.19)	0.16
Olfactory function Extended OT						
TDI1	-0.64 (-2.18, 0.89)	0.41	-1.56 (-2.55, -0.58)	0.002*	-0.27 (-1.69, 1.15)	0.70
T1	-0.39 (-1.24, 0.44)	0.36	-0.74 (-1.26, -2.11)	0.01*	0.32 (-0.46, 1.09)	0.42
D1	-0.71 (-1.57, 0.14)	0.10	-0.36 (-0.92, 0.21)	0.22	-0.86 (-1.65, -0.06)	0.03*
I1	0.60 (-0.13, 1.33)	0.11	-0.43 (-0.84, -0.01)	0.04*	0.18 (-0.49, 0.85)	0.60
TDI2	-0.75 (-2.31, 0.81)	0.34	-1.44 (-2.33, -0.54)	0.002*	1.06 (-0.37, 2.48)	0.15
T2	-0.78 (-1.64, 0.07)	0.07	-0.43 (-0.96, 0.10)	0.11	0.65 (-0.12, 1.42)	0.10
D2	0.04 (-0.83, 0.90)	0.94	-0.24 (-0.82, 0.34)	0.42	0.08 (-0.72, 0.88)	0.84
I2	0.12 (-0.62, 0.86)	0.75	-0.39 (-0.82, 0.03)	0.07	0.27 (-0.41, 0.94)	0.43

Table 3. Estimated differences in olfactory function after standard or extended OT between the one-third youngest and oldest (adjusted for baseline olfactory score), those with the one-third lowest and highest baseline TDI scores and men vs women, after intervention (1) and at follow-up (2). Estimates are derived from a linear mixed model. TDI= sum of the T, D and I scores; T= threshold; D= discrimination; I= identification; CI= confidence interval. *p<0.05.

641 Supplementary table.

Olfactory function	Between-Group Differences in changes Mean (95% CI)	p-value
TDI1/extended-standard	-0.02 (-0.86, 0.82)	0.97
T1	0.35 (-0.16, 0.87)	0.18
D1	-0.30 (-0.79, 0.19)	0.24
I1	-0.06 (-0.47, 0.36)	0.78
TDI1/extended-control	0.33 (-0.99, 1.65)	0.63
T1	0.11 (-0.70, 0.93)	0.78
D1	0.19 (-0.58, 0.96)	0.63
I1	0.06 (-0.59, 0.71)	0.86
TDI1/standard-control	0.35 (-0.96, 1.65)	0.60
T1	-0.24 (-1.05, 0.57)	0.56
D1	0.49 (-0.27, 1.25)	0.21
I1	0.12 (-0.53, 0.76)	0.72
TDI2/extended-standard	0.76 (-0.09, 1.61)	0.08
T2	0.19 (-0.33, 0.71)	0.48
D2	0.45 (-0.05, 0.94)	0.08
I2	0.15 (-0.27, 0.57)	0.49
TDI2/extended-control	0.14 (-0.18, 1.47)	0.84
T2	-0.33 (-1.15, 0.49)	0.43
D2	0.71 (-0.06, 1.48)	0.07
I2	-0.20 (-0.85, 0.45)	0.55
TDI2/standard-control	-0.62 (-1.93, 0.69)	0.36
T2	-0.52 (-1.33, 0.29)	0.21
D2	0.26 (-0.50, 1.03)	0.49
I2	-0.35 (-1.00, 0.30)	0.29

643 Supplementary table. Estimated changes in olfactory function by intervention groups and
644 controls. Estimates are derived from a linear mixed model estimating differences in olfactory
645 function after intervention (1) and at follow-up (2) between each intervention group. TDI:
646 sum of the T, D and I scores; T: threshold; D: discrimination; I: identification; CI: confidence
647 interval.
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