PREDICTORS OF OLFACTORY DYSFUNCTION AND ITS SEVERITY AMONG ADULTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: *Olfactory function of patients with chronic kidney disease (CKD) is often affected by the disease. This predisposes them to malnutrition, poor quality of life and worsens disease prognoses. It is therefore imperative that factors that predict olfactory dysfunction and its severity are identified for prompt treatment.*

Aim: *To identify factors associated with olfactory dysfunction and its severity among adults with CKD.*

Materials and methods: *This was a prospective, hospital-based case-control study of adult patients with CKD at the University College Hospital, Ibadan, Nigeria. The control groups were age and gender matched healthy volunteers without CKD. Interviewer-assisted questionnaires were administered to participants to obtain biodata, relevant clinical data, and renal disease information. Olfactory Threshold (OT), Odour Discrimination (OD) and Odour Identification (OI) tests were carried out on participants using the "Sniffin sticks test". Factors that predict olfactory dysfunction were identified among the spectrum of the disease severity.*

Results: *There were 100 patients with CKD and 100 healthy controls, age ranges between 19 and 86 years (mean ± SD=46.3±13.9 years) for the cases and between 20 and 85 years (mean ± SD=43.4±14.9 years) for the control, respectively. The mean Total Threshold Discrimination and Identification (TDI) scores were 26.0 ± 6.4 and 33.8 ± 3.3 in cases and controls, respectively, p - 0.01.*
The prevalence of olfactory dysfunction among patients with CKD was 77% (hyposmia 72%, anosmia 5%), while the control population had a prevalence of 16% and all were hyposmia.
Increasing age was associated olfactory dysfunction [OR 2.71, 95% CI (1.5344 – 7.0611), p - 0.01] while the sub-analysis also showed that increasing age was also associated with the scores in all the three olfactory tasks; OI(p=0.014), OD(p=0.001), OT(p=0.040) and TDI(p=0.001), but only affected the OD (0.002) among the controls. Other factors independently associated with olfactory dysfunction were duration of CKD [OR 1.84 (1.3502 – 9.3692), p - 0.02] and dialysis status [OR 0.65, 95% CI (0.2405 – 0.8366), p - 0.01] while the stages of CKD had no association with olfactory dysfunction [OR 1.1, 95% CI (0.8514 – 1.3315), p - 0.58].

Conclusion: *There was high prevalence of olfactory dysfunction among adults with CKD. Increasing age, duration of CKD and dialysis status were identified as predictors of olfactory dysfunction while there was no association between severity of CKD and olfactory dysfunction.*

Key words: *Olfactory function, Chronic kidney disease, Severity, Sniffing sticks test.*

INTRODUCTION

Olfactory dysfunction is one of the complications of chronic kidney disease (CKD) and it is highly prevalent.[1-3]However, the associated factors that determine the occurrence and severity of the olfactory dysfunction among patients with CKD have not been extensively examined. Thus, these unidentified factors are not often considered in the management of the primary disease. The impact of disordered olfaction may be contributing to the reduced quality of life that has been reported, by several studies among individuals with CKD. Hence, the need for olfactory assessment, identification, and treatment of the risk factors for olfactory disorders and its severity among patients with CKD, as this will improve the quality of their care and total quality of life. Information on the management of olfactory dysfunction in patients with CKD is sparse in the literature and the factors associated with olfactory loss among patients with CKD need to be explored to manage them effectively.
The severity of olfactory loss among healthy population has been shown to be worse in the aged and among males,[4,5] these findings have not been confirmed or refuted among patients with CKD, who often suffer from olfactory disorder. There have been conflicting reports on the impact of stages of CKD on the severity of olfactory disorders, while some studies have reported association between severity of kidney disease and that of olfactory disorders, others found no such association.[4,6]. Other factors that is being putatively considered to be associated with development of olfactory disorders include primary causes of CKD, treatment modalities, duration of CKD, being on dialysis, duration of dialysis and last dialysis episode.
The aetiology of olfactory dysfunction is yet to be completely unraveled, however, accumulation of uraemic toxins and malnutrition have been suggested as the major underlying factors for the abnormal olfaction in patients with kidney disease.[7-9]

Determining the relationship between olfactory disorders and its severity with the putative risk factors will provide more insight into the pathophysiology of olfactory disorder in CKD. This information will guide in designing appropriate strategies for prevention and treatment of olfactory disorders among patients with CKD. This study, therefore, aims to identify the predictors of olfactory disorder and its severity among patients with CKD.

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METHOD

Study population: It was a hospital-based prospective case-control study conducted at the Medical Outpatient (MOP) clinic, medical wards and Ear Nose and Throat (ENT) clinic of the University College Hospital, Ibadan. Consenting adult patients (≥ 18years) with clinical and laboratory diagnosis of CKD at MOP clinic and medical wards, were enrolled as subjects and the controls were age and gender matched healthy volunteers. CKD was defined as estimated Glomerular Filtration Rate (eGFR) of less than 60mls/min/1.73m^2 and/or a urine albumin-to-creatinine ratio (ACR) of 30 mg/g or higher in at least one clinical test or two, within three-month interval.[10] Effort was made to recruit almost equal proportion participants into all stages of CKD. Excluded from participating in the study were individuals suffering from upper respiratory tract infection, symptoms of nasal allergy, congenital olfactory dysfunction, previous nasal

surgery/trauma, previous head injury, smokers or those that smoked and stopped and those that sniff tobacco.

Informed consent: Written informed consent was obtained from all participants after the study and its purpose have been fully explained to them.

Ethical approval: Ethical approval was sought and obtained from the Joint University of Ibadan/University College Hospital ethics committee with the approval number UI/EC/18/0035.

Study procedure: Interviewer's assisted questionnaire was administered on all participants to obtain relevant data including participants' socio-demographic data, duration of ailment, medical history, symptoms of CKD, the worst ever recorded eGFR value of the subject, primary cause of CKD, treatment modalities for CKD, duration of CKD, dialysis status, duration of dialysis and last dialysis episode. The nasal examination findings of the participants were also documented, and olfactory function test was carried out with the pen-like odour dispensing devices "sniffing sticks". The sniffing sticks contain three test kits for odour identification (OI), odour discrimination (OD) and odour threshold (OT), three minutes breaks were observed in-between the three test components.[11] Each of these 3 different tests allows for a maximum score of 16 points and together, a total maximum score of 48 points. The sum of olfactory identification (OI), odour discrimination (OD) and odour threshold (OT) values was referred to as Threshold Discrimination and Identification (TDI) score. It ranges from 1- 48.[11]

Blood samples were collected to determine serum creatinine, which was used to calculate the eGFR of each participants using chronic kidney disease-Epidemiology Collaboration equation (CKD-EPI).[12]

Statistical analysis: Data obtained were analysed using statistical package (IBM-SPSS statistic, version 20). Demographic variables were represented using tables while summary statistics were carried out using means and proportions. The eGFR were graded as stage 1 CKD ≥ 90, stage 2 CKD 60–89, stage 3 CKD 30–59, stage 4 CKD 15–29, stage 5 CKD [End Stage Kidney Disease (ESKD)] <15.[11] While Olfaction was graded as TDI score >30 normosmia, 16-30 hyposmia and ≤ 15 anosmia, odour identification ≥12, odour discrimination ≥11 and odour threshold >6 were normal values.[13,14]Abnormal TDI was determined for each age categories using the normative scores derived by Oleszkiewicz et et al. (15)

Association between eGFR (stages of CKD) and severity of olfactory dysfunction were determined using Chi-square tests. Factors associated with olfactory dysfunction were determined using ANOVA for categorical variables or correlation for continuous variables. Factors independently predicting olfactory dysfunction were identified with multivariate analysis. Correction for alpha error inflation for multiple comparisons was carried out using Bonferroni correction. Level of statistical significance was set at p value of <0.05.

RESULTS

There were 100 subjects with CKD and 100 age and gender matched healthy controls. The age ranges were 19 - 86 and 20 – 85 years, respectively while the mean ages (SD) were 46.3±13.9 and 43.4±14.9 years, respectively, Table 1. There were 56 males 44 females among the cases, while the control had 52 males and 48 females. The distribution of cases based on CKD stages were;stage 1-4(4%), stage 2 – 8(8%), stage 3-19 (19%), stage 4 – 22 (22%) stage 5–47 (47%). The mean OI, OD, OT and TDI were significantly lower in the cases compared to the controls, while the mean serum creatinine and urinary albumin creatinine ratio were significantly higher in the cases relative to the controls (Table1).

There were 77 (77.0%) of cases with olfactory dysfunction (TDI score ≤ 30) and of this,72.0% of them had hyposmia (TDI score16-30) while 5.0% had anosmia (TDI score ≤ 15). The prevalence of olfactory dysfunction among the control was 16.0% and all were hyposmic, (Table 1). The three components of the olfactory score i.e., OI, OD and OT were separately analysed to determine the pattern of olfactory dysfunction in the participants. The score of OI was below normal range (<12) in 49.0%, OD was below normal range (<11) in 82.0% and OT was below normal (≤ 6) in 50.0% of the cases as shown in Figure 1. The pattern of individual components of the olfactory test among control shows the score of OI was below normal range in 9.0%, OD was below normal rang in 42.0% and OT in 8.0% as in Figure 2.

On univariate analysis, age > 45 years [Odd Ratio (OR) 3.25, 95% Confidence Interval (CI) (1.2189 – 8.6550, p - 0.014], duration of dialysis [OR 2.6, 95% CI (1.0532 – 6.7115), p - 0.041] and dialysis status [OR 0.29, 95% CI (0.1084 – 0.7654), p -0.01] were factors identified to be associated with olfactory dysfunction, (Table 2). With multivariate analysis, the 3 factors were independently associated with olfactory dysfunction; increasing age [OR 2.71, 95% CI (1.5344 – 7.0611), p - 0.01], duration of CKD [OR 1.84 (1.3502 – 9.3692), p - 0.02] and dialysis status [OR 0.65, 95% CI (0.2405 – 0.8366), p - 0.01] while the stages of CKD had no association with olfactory dysfunction [OR 1.1, 95% CI (0.8514 – 1.3315), p - 0.58], Table 3.

Sub-analysis of the components of TDI showed that increasing age was associated with the scores in all the three olfactory tasks; OI(p=0.014), OD(p=0.001), OT(p=0.040) and TDI(p=0.001), Table 4, but only affected the OD (0.002) among the controls.

The stages of CKD have no significant relationship with the severity of olfactory dysfunction (χ- 3.350, p=0.911). The CKD patients were also categorized into 3 based on the urinary albumin creatinine ratio (UACR) and there was no association between UACR and severity of olfactory dysfunction (χ- 6.475, p=0.166).

Primary causes of CKD have been shown to have no association with olfactory dysfunction [OR 1.1, 95% CI (0.8514 – 1.3315), p - 0.58, although the sub – analysis of TDI score showed association with only odour discrimination (p=0.037).

DISCUSSION

There was high prevalence (77%) of olfactory dysfunction among patients with CKD with the majority (93.5%) having hyposmia and some (6.5%) having anosmia. This shows that CKD had effect on their olfaction when compared to the prevalence of olfactory dysfunction among the controls in this study. The high prevalence of olfactory dysfunction among patients with CKD in this study is similar to findings from other previous studies.[4,16,17]

Age was an important factor associated with olfactory dysfunction among the participants. The older the patients, the more likely they are to develop olfactory dysfunction and they are at a higher risk of having the severe form. This was similar to the findings from the studies on healthy population by, Murphy *et al*[4], Bramerson *et al.*[18] and Orhan *et al.*[19] where age was found to be inversely correlated with the olfactory function. However, Neuland *et al.*[20]and Nordin *et al.*[21] reported no association between age and olfaction.

Gender of the participants was not associated with olfactory dysfunction in this study, although the mean olfactory scores in males were slightly higher than females, but was not statistically significant. The mean score of OT was also slightly higher in females than in males among the study group. OT is thought to reflect peripheral olfactory events, which may not really be influenced by the participants' state of mind, unlike the OI and OD that are reflections of central olfactory processing pathways which are more affected in CKD patients. This assumption may strongly hold to be true as the emotional state of the individuals may affect their olfaction.[22]

The finding in this study can be compared to the report by Veronika *et al*.[23] where the proportion of females with olfactory dysfunction (hyposmic 66.7%, anosmic 6.7%)was higher than that of the males (hyposmic 56.7%, anosmic 3.3%) among patients with CKD. However, the male to female ratio in population studied was skewed towards the male at 2:1.[24]

The stages of CKD of the patients were not associated with olfactory dysfunction. This finding seems to suggest that the chronic exposure to uraemic toxins determines olfactory dysfunction in CKD. Moreso that olfactory dysfunction was associated with duration of CKD. Uraemia has been reported by studies[7-9] to be responsible for the disordered olfactory function among the patients with CKD. This is because of the effects of uraemia on olfactory epithelia, olfactory receptor cells, olfactory bulb, and the olfactory center. Their affectation results in olfactory dysfunction by

reducing sensitivity of the mucosa and impaired regeneration of olfactory receptor cells. In addition, the chronic malnutrition which is common among patients with CKD and the repeated removal of amino acids and other nutrients by dialysis, may limit the regeneration and continuous renewal of cells in the olfactory epithelium, and thus contribute to olfactory dysfunction[8,9]

The modalities of treatment received by the CKD patients showed no association with the olfactory dysfunction, even though renal transplantation and dialysis have been shown to reverse or reduce olfactory dysfunction.[25,26] The distribution of cases based on the treatment modality was not even, while most of them were on haemodialysis (50.0%), only a few (4.0%) had failed kidney transplant and none was on peritoneal dialysis. This may be because most of the patients with CKD present late in the hospital when the disease is advanced. This study observed that patients with CKD who are on haemodialysis were more likely to have olfactory dysfunction compared to those who were only on conservative management. The loss of nutrients during haemodialysis may explain this association. Haemodialysis is responsible for removal of toxic metabolites in patients with CKD and should help preserve the olfactory receptors and mucosal. However, when this is being done for a long duration, the stress and cost implication of haemodialysis might make patients prone to some neuropsychological and cognitive disorders, which might manifest as reduced OI and OD that are central olfactory pathways dependent.[25,26] Similarly, Raff *et al.*[2] found the use of medication as a possible cofounder for olfactory dysfunction, but this present study did not find any association with medication use.

The duration of CKD correlates inversely with odour threshold i.e., the longer the duration of the disease the lower the odour threshold score, but have no association with OI and OD components. This suggests that the duration of CKD affects the peripheral olfactory functions which may be due to problems with regeneration of olfactory receptors or toxic effect of accumulated metabolites on the olfactory mucosal.[26,27]

There was a significant association between duration of dialysis and odour discrimination as well as odour identification suggesting that the longer the duration of dialysis the lower the mean score of OI and OD.

In this study, the primary cause of CKD in the patients did not show any statistically significant association with OD. However, all aetiologies had a significant number of patients with abnormal odour discrimination score. The distribution of primary cause of CKD in this study shows that hypertension was the leading cause of CKD (48.1%). Hypertension has been reported to have some link to the central olfactory pathway. However, we did not observe any association and this may be because, the major determinant of olfactory dysfunction among patients with CKD is exposure to uraemic toxins. Our finding is similar to the observation by Koseoglu*et al*[1]who also found hypertension (39.8%) to be the leading cause of CKD, also found no association between the aetiologies of CKD and TDI score.

The haemoglobin concentration of CKD patients which is usually lower compared to healthy subjects was also analysed to determine any correlation between the haemoglobin level and olfactory dysfunction among the CKD patients. We found no association despite ~~anaemia~~ being a universal finding among patients with CKD.

The limitation of this study was the inability to recruit equal proportion of participants in various stages of CKD. This was because most of patients seen at the hospital were those in advanced stages of CKD. Additionally, the non-assessment of cognitive function and non-use of nasal endoscopy may have contributed to overestimation of the effects of CKD on olfactory dysfunction. However, other secondary causes of olfactory dysfunction were included in the exclusion criteria, in addition to the use of anterior rhinoscopy.

CONCLUSION

The prevalence of olfactory dysfunction among adults with CKD in this study was high. Increase age, duration of CKD and dialysis status were factors identified to be predictors of olfactory dysfunction among patients with CKD in this study. Surprisingly, the study observed no association between the severity of CKD and the severity of olfactory dysfunction among the study population.

Table 1: Baseline characteristics cases and controls

Variable	Chronic kidney disease n = 100 Mean/frequency/ percentage	Healthy controls n = 100 Mean/frequency/ percentage	p – value
Age (years)	46.3±13.9	43.4±14.9	0.23
Gender (Female)	44 (44%)	51 (51%)	0.76
Educational status Tertiary Below tertiary	 34 (34%) 66 (66%)	 41 (41%) 59 (59%)	0.31
BMI (kg/m^2)	23.4 ± 6.0	24.9 ± 4.4	0.06
um creatinine (mg)	6.7 ± 3.3	0.9 ± 0.5	0.01
eGFR (ml/min/1.73m^2	30.2 ± 15.6	119.7 ± 43.8	0.01
Urinary Albumin Creatinine Ratio (mg/g)	534.7 ± 365.1	10.8 ± 4.8	0.01
TDI	26.0 ± 6.4	33.8 ± 3.3	0.01
OD	9.8 ± 3.7	12.4 ± 5.6	0.01
OI	8.7 ± 4.2	11.3 ± 4.9	0.01
OT	6.5 ± 3.5	9.7 ± 5.8	0.01
Olfactory dysfunction	77 (77%)	16 (16%)	0.01
Spectrum of olfactory dysfunction Hyposmia Anosmia	 72 (72%) 5 (5%)	 16 (16%) 0	0.26
PCV (%)	25.8 + 7.2	38.8 ± 8.4	0.01
Nasal congestion	15 (15%)	12 (12%)	0.53
Nose bleed	3 (3%)	1 (1%)	0.61
Recurrent sneezing	9 (9%)	10 (10%)	0.81
Tinnitus	8 (8%)	7 (7%)	0.79
Vertigo	6 (6%)	11 (11%)	0.31
Hearing problem	5 (5%)	6 (6%)	0.75

BMI – Body Mass Index, eGFR – estimated Glomerular Filtration Rate, OI - Odour Identification, OD - Odour discrimination and Odour Threshold (OT), PCV – Packed Cell Volume, TDI – Threshold Discrimination and Identification

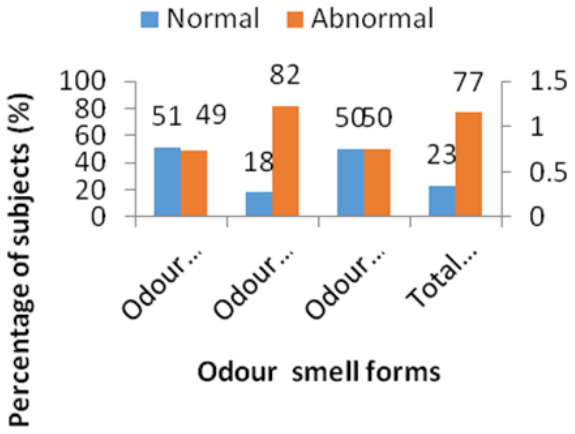

Figure 1: Pattern of olfactory test components among cases

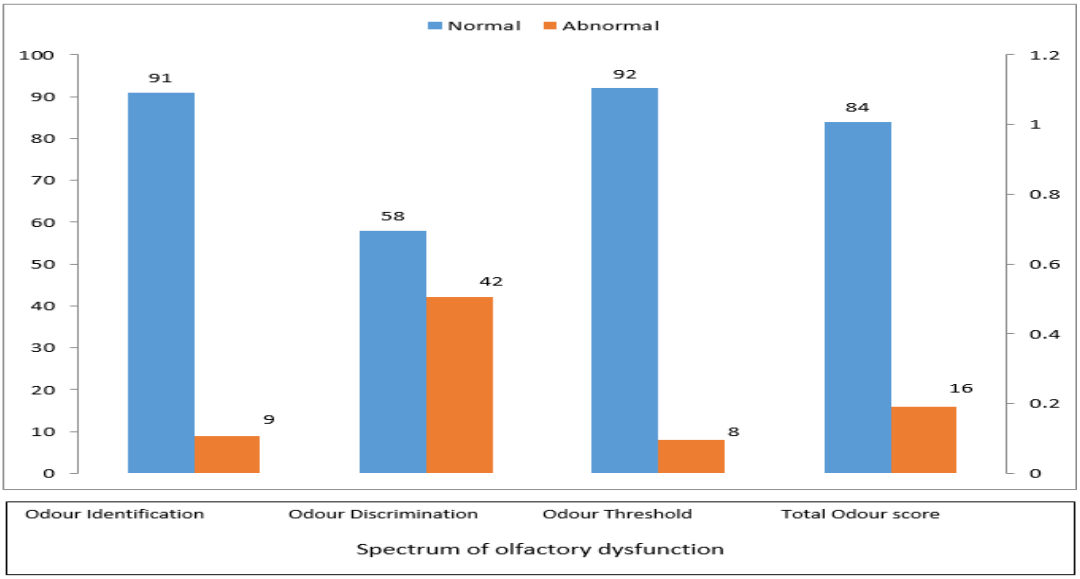

Figure 2: Pattern of olfactory test components among control

Table 2: Univariate analyses of factors associated with olfactory dysfunction among cases

Variable	Olfactory dysfunction (TDI score < 30) n = 77 Mean/frequency/ percentage	Normal olfactory function (TDI score ≥ 30) n = 23 Mean/frequency/ percentage	95% Confidence interval	p - value
Age > 45 years				
Yes	55 (71.4%)	10 (43.5%)	3.25 (1.2189 – 8.6550	0.014
No	22 (28.6%)	13 (56.5%)		
Gender				
Female	38 (49.4%)	13 (56.5%)	0.75 (0.2936 – 1.9143)	0.55
Male	39 (50.6%)	10 (43.5%)		
Stage of CKD				
Stage III	22 (28.6%)	8 (34.8%)	1.1 (0.8514 – 1.3315)	0.58
Stage IV	25 (32.5%)	7 (30.4%)		
Stage V	30 (39.0%)	8 (34.8%)		
Aetiology of CKD				
Hypertension				
CGN	37 (48.1%)	8 (34.8%)	1.73 (0.6591 – 4.5640)	0.26
Other	16 (20.8%)	6 (26.1%)		
	14(51.918.1%)	9 (39/1%)		
Duration of CKD				
Less than 12 months			2.6 (1.0532 – 6.7115)	0.041
≥ 12 months	59 (76.6%)	12 (52.2%)		
	18 (23.4%)	11 (47.8%)		
Dialysis status				
Yes	27 (35.1%)	15 (65.2%)	0.29 (0.1084 – 0.7654)	0.01
No	50 (64.9%)	8 (34.8%)		
BMI ≥ 30kg/m^2				
Yes	14 (18.2%)	2 (8.7%)	2.53 (0.5308 – 12.1028)	0.23
No	58 (81.8%)	21 (91.3%)		
Proteinuria				
Yes	65 (84.4%)	16 (69.6%)	2.36 (0.8041 – 6.9839)	0.11
No	12 (15.6%)	7 (30.4%)		
Anaemia				
Yes	61 (79.2%)	17 (73.9%)	1.79 (0.6570 – 4.8995)	0.25
No	16 (20.8%)	6 (26.1%)		

BMI – Body Mass Index, CKD – Chronic Kidney Disease, TDI – Threshold Discrimination and Identification

Table: 3 Multivariate analyses of factors associated with olfactory dysfunction among cases

Variable	95% Confidence interval	p - value
Age > 45 years	2.71 (1.5344 – 7.0611)	0.01
Gender	1.32 (0.7125 – 3.3073	0.74
Aetiology of CKD	1.73 (0.6591 – 4.5640)	0.26
Duration of CKD	1.84 (1.3502 – 9.3692)	0.02
Dialysis status	0.65 (0.2405 – 0.8366)	0.01
Anaemia	1.67 (0.7480 – 6.8535)	0.53

BMI – Body Mass Index, CKD – Chronic Kidney Disease, TDI – Threshold Discrimination and Identification

Table 4: Effect of age on olfaction among the CKD patients N=100

olfactory dysfunction	Age category	Number	Mean ±SD	95%CI	f-test	p-value
Odour identification	18-35	25	11.4±1.7	10.7-12.1	4.436	0.014
	36-55	51	11.6±2.0	11.0-12.1		
	>55	24	10.0±2.9	8.8-11.2		
	Total	100	11.2±2.3	10.7-11.6		
odour discrimination	18-35	25	10.1±1.9	9.2-10.7	12.388	0.001
	36-55	51	8.5±2.3	7.8-9.1		
	>55	24	6.9±2.2	5.9-7.8		
	Total	100	8.5±2.4	8.0-8.9		
odour threshold	18-35	25	6.8±2.6	5.8-7.9	3.324	0.040
	36-55	51	6.7±2.5	6.1-7.4		
	>55	24	5.3±2.0	4.5-6.2		
	Total	100	6.4±2.4	5.9-6.9		
total odour score	18-35	25	28.2±4.1	26.5-29.9	8.488	0.001
	36-55	51	26.8±5.6	25.2-28.4		
	>55	24	22.2±6.1	19.6-24.8		
	Total	100	26.0±5.8	24.9-27.2		

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