Bloody olfaction? Confounding associations of sex and age on the influence of blood parameters and body weight on odor identification performance in healthy adults

Doris Schicker [a,b,*], Brid Karacan [a], Beate Brandl [c,d], Thomas Skurk [c,d], Dorothee Volkert [e], Hans Hauner [c,d,f], Jessica Freiherr [a,b,**]

[a] Sensory Analytics & Technologies, Fraunhofer Institute for Process Engineering and Packaging IVV, Freising, Germany
[b] Department of Psychiatry and Psychotherapy, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[c] Core Facility Human Studies, ZIEL Institute for Food and Health, Technical University of Munich, Freising, Germany
[d] Else Kröner-Fresenius-Center of Nutritional Medicine, TUM School of Life Sciences, Technical University of Munich, Freising, Germany
[e] Institute for Biomedicine of Aging, Friedrich-Alexander-University Erlangen-Nürnberg, Nuremberg, Germany
[f] School of Medicine, Institute of Nutritional Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

ARTICLE INFO

ABSTRACT

Olfactory function and nutrition are closely related and may influence each other via metabolic parameters. However, the relationship between nutritional blood parameters and olfactory performance is still unclear. Inconclusive findings exist for specific blood parameters. In this extensive analysis, we examined the relationship between olfactory performance, measured with MONEX-40, as well as intensity and pleasantness ratings with 38 metabolic blood parameters, age, sex, and the anthropometric measurements body mass index (BMI) and body fat percentage (BFP). Therefore, we included data of 418 healthy, well-phenotyped Caucasians of the *Enable* cohort. We replicated age-dependent olfactory identification scores ($p < 0.001$) and found slight evidence for a body fat dependence measured with BFP ($BF_{10} = 10.466$). We further identified a sex difference only in middle-aged adults ($p < 0.001$) that could be explained by environmental factors. Several blood parameters correlated significantly with the MONEX-40 score ($p < 0.05 – p < 0.001$). However, these effects diminished after adjusting for sex and age ($p > 0.9$) that were identified as confounders. The same applies for BFP. In addition, no parameters were identified to correlate significantly with perceived olfactory intensity or pleasantness score if controlled for sex and age ($p > 0.08$). Our results suggest that metabolic blood parameters are not related to olfactory identification performance in a relevant manner and highlight the importance of controlling for sex and age in chemosensory research.

1. Introduction

Olfactory perception is responsible for preferences in everyday life, especially with respect to food choice, nutritional habits, and appetite. The human sense of smell develops already prenatally and odors perceived by the fetus influence liking and attention towards aromas after birth [1]. Associated with this is the acceptance and pleasantness of corresponding food items. However, humans do not only prefer food due to the odor but can also smell if food is rotten or poisonous. Therefore, the sense of smell is essential for safe nutrition and influences eating behavior [2–4]. Food consumption, in turn, is reflected in metabolic parameters as well as anthropometric measures.

On the other hand, evidence exists that fasting enhances olfactory perception, whereas in a satiated state, odor sensitivity decreases. Therefore, various metabolic processes seem to regulate olfactory perception [5], resulting in a complex interaction. This leads to the research question, whether correlations between metabolic parameters and olfactory performance exist.

1.1. Bodyweight and the relation to smelling ability

One anthropometric measure closely related to nutrition is the body
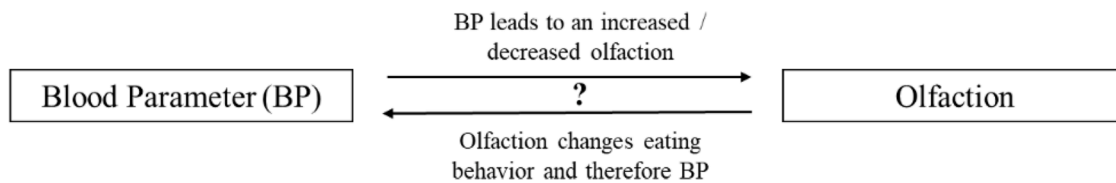

Fig. 1. Proposed hypothesis that metabolic blood parameters could correlate with olfactory performance.

mass index (BMI) that is often used to classify participants of studies in an obese and non-obese group. Several studies found a negative association between olfactory function and BMI [6–10]. However, other studies established that BMI is not related to olfactory dysfunction overall [11,12] or among healthy people [13] or that the relationship is age- and sex-dependent [14]. In some studies, olfactory function was measured only with identification tests; here, it is not clear whether associations with the BMI exist. Whereas in one study, a correlation was established, other studies did not support this [15] or only supported this finding for smokers [16]. As the BMI is a measure of a person's relative weight, it is closely related to metabolic parameters and nutrition. A more valid predictor for excessive body fat, especially for active people, is body fat percentage (BFP), as this also takes into account muscle mass [17]. Neither BMI nor BFP are sex- or age-independent [14, 18–21]. However, using BFP instead of the BMI could provide a more stable outcome if associations between body weight and smelling ability are examined.

1.2. Sex and age and the relation to smelling ability

Sex and age, on the other hand, have been broadly shown to correlate with olfactory performance. A decreased olfactory function can be found in older adults [2,7,11,22–26]. That can be led back to structural changes in the nose and an aging olfactory system as well as a decline in cognitive abilities and memory function [27,28]. Most studies suggest a gender effect: women outperform men with regards to smelling abilities [25,26,29–32].

1.3. Metabolic parameters and the relation to smelling ability

Several metabolic parameters have already been examined for a relationship with our sense of smell. A high odor identification score was found to be significantly associated with high levels of free triiodothyronine (FT$_3$), however not with thyroid-stimulating hormone (TSH) or free thyroxine (FT$_4$) [33]. Also, in other studies, a diminished olfactory function for adults with hypothyroidism has been established [34,35]. However, a significant association was reported not in all studies [36]. Cholesterol was also in the interest of several studies. Reduced HDL cholesterol and elevated triglycerides, but not LDL or total cholesterol, were significantly associated with olfactory dysfunction in Korean women [37]. However, neither HDL nor LDL cholesterol or triglycerides individually were found in another study to be significantly associated with smell dysfunction or thresholds [2]. Nevertheless, in one of these studies, a significant association with higher blood concentrations of total cholesterol was established [38]. Yet other studies proved different outcomes based on age and sex [14], the use of adjustment [11] or between healthy people and patients with type 2 diabetes mellitus [39], which in turn is associated with olfactory performance [39,40], but not in others [36,41]. However, diabetes mellitus type 1 or HbA1c were not found to be related to olfactory function [42]. Another blood parameter related to nutrition and sensory perception is the blood concentration of insulin. Higher blood levels of insulin and poor insulin sensitivity were shown to decrease olfactory performance and mediate the effect of body weight on olfactory performance [43,44]. However, no association between blood insulin and self-reported olfactory dysfunction was reported [11]. The effect of intranasal insulin was found to decrease

[45–47] as well as enhance [43,48,49] olfactory performance in different studies. Glucose levels were established to be associated with olfactory performance in older people dependent on age and sex [14].

In addition to the above-mentioned metabolic parameters, creatinine, urea, and phosphorus but not albumin – molecules that are related to renal function – were found to be associated with odor threshold [50]. Albumin, though, was associated with odor identification [51]. This study also established associations with total cholesterol and LDL cholesterol for a study cohort, in which patients with chronic kidney disease and kidney failure were included. In addition, patients with liver cirrhosis report olfactory loss, although, neither serum levels of bilirubin nor zinc were shown to correlate with olfactory function [52].

As stated above, former research provides first evidence that metabolic parameters might affect olfactory performance. Inversely, olfaction might influence metabolic parameters via changes of eating behavior (see Fig. 1). Due to several interventions, cross-sectional or patient studies, several nutrition-related parameters have been identified. The results of the studies often differ, partly depending on the sex, age, or diseases of participants or other confounders. In large studies in the US (NHANES), Korea (KNHANES), and China, representative population samples were investigated [11,14,37,38]. In these studies, the examined blood values were limited or no objective olfactory tests were conducted. Therefore, we performed a broad analysis for well-phenotyped healthy Caucasians from 18 to 85 years of the E*nable* cohort [20]. We did not focus on special parameters but explored 38 blood parameters in addition to sex, age, and body weight. We aimed to establish whether and which metabolic parameters correlate with olfactory identification performance, more accurately the 40-item Monell Extended Sniffin' Sticks Identification Test (MONEX-40) score [53]. We hypothesized that age and sex are important confounders of potential relationships. In addition, we hypothesized that BFP instead of BMI provides a better measurement for the evaluation of the relation between body weight and olfactory performance.

2. Materials and methods

2.1. Ethics statement

We used data of the E*nable* study [20] The study protocol for this study was approved by the ethical committee of the Faculty of Medicine of the Technical University of Munich (approval no. 452/15) and Friedrich-Alexander-Universität Erlangen-Nürnberg (approval no. 291/15B). The guidelines of the International Conference on Harmonization of Good Clinical Practice and the World Medical Association Declaration of Helsinki (in the revised version of Seoul, South Korea 2008) were considered. All study participants had provided written informed consent.

2.2. Database

2.2.1. Participants

To address our research question, we used data of the well-phenotyped E*nable* cohort that was described in detail elsewhere [20]. This cohort covers healthy participants (but partially with overweight) out of four age groups (children, young adults, middle agers, older adults). For our analysis, we included participants from the young (18 –

Table 1

Overview of participants' descriptives. We present the number of participants divided into age and sex groups as well as the median, mean and standard deviation (SD) of the age groups.

Sex	Age group Young	Middle	Old	Total
Male	42	84	79	205
Female	45	94	74	213
Total	87	178	153	418
Median	22.0	52.5	77.0	56.0
Mean	22.0	52.7	78.1	55.6
SD	2.0	6.9	2.7	21.2

Young: age 18 – 25 years; middle: age 40 – 65 years, old: age 75 – 85 years.

25 years, n = 87), middle-aged (40 – 65 years, n= 178), and older adults (75 – 85 years, n= 153) groups who conducted the MONEX-40 test. To get valid smelling scores, we excluded participants reporting respiratory illnesses, acute allergic reactions or blocked noses ($n = 28$). In total, we included 418 participants in our analysis (see Table 1). Participants' BMI was between 18.6 and 34.9 kg/m2 (mean 25.6, SD 4.2, 49.3% had a BMI of < 25). BFP was in the range of 3.0 to 53.5 (mean 31.6, SD 10.0) (measured with Seca mBCA 515 device (Seca GmbH & Co KG, Hamburg, Germany)).

2.2.2. Blood parameters

Participants' blood samples were collected in the fasting state and analyzed by a certified laboratory (SynLab; Munich, Germany). The validity of the data was approved by experts. We used the following blood parameters: erythrocytes, hemoglobin, thrombocytes, leukocytes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γGT), lactate dehydrogenase (LDH), sodium, potassium, calcium, phosphorus, magnesium, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, albumin, creatinine, urea, uric acid, iron, ferritin, transthyretin (prealbumin), c-reactive protein (CRP), total protein, insulin, thyroid-stimulating hormone (TSH), free thyroxine (FT3), and free triiodothyronine (FT4). In addition, we also calculated some commonly used ratios and indices such as LDL/HDL ratio, ferritin index, glomerular filtration rate (GFR) calculated with the Chronic Disease Epidemiology Collaboration (CKD-EPI) equation [54], hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red blood cell distribution width (RDW). In total, we considered 38 different parameters.

2.2.3. Olfactory performance

Participants' olfactory performance was tested using the 40-item Monell Extended Sniffin' Sticks Identification Test (MONEX-40) [53]. Participants were presented 40 odors with the help of Sniffin' Sticks and were asked to identify each odor based on 4 descriptors (3 wrong, 1 correct) that were provided per odor. Therefore, participants could achieve a score from 0 (all sticks were identified false) to 40 (all sticks were identified correctly). In addition, participants rated the perceived intensity and pleasantness of each odor on Likert scales ranging from 0 to 10 or -5 to 5, respectively. We calculated the average intensity and pleasantness scores for each participant by taking the means of the 40 respective participant's ratings.

2.2.4. Statistical data analysis

Using a Chi-square test, we examined the association between age and sex with the MONEX-40 score. To account for equality of variances, we squared the MONEX-40 score. A two-way ANOVA with the factors age (young, middle-aged, and old adults) and sex (female, male) on the dependent variable of the squared MONEX-40 score was used to detect effects of sex and age group on the ability to smell. The Shapiro-Wilk test revealed that not all blood parameters were normally distributed. Therefore, we performed a non-parametric correlation using Kendall's tau-b. In addition to the 38 blood parameters, we added BMI, BFP, sex, and age as variables. To detect nutritional parameters that correlate with the MONEX-40 score after controlling for sex and age effects, we additionally performed partial correlations with sex and age as covariates. All reported p-values were adjusted using Holm correction [55].

In addition to the above-mentioned statistical methods, we used Bayesian non-parametric correlation with non-informative prior to gain more information about the relation between the MONEX-40 score and blood parameters. This approach focuses on both the null and the alternative hypothesis at the same time and therefore can quantify evidence for the null hypothesis [56], in our case that there exists no linear correlation. To control for sex and age, we separated the participants into groups based on age and sex in accordance with the results of the ANOVA. As the Bayesian statistics are not affected by multiple comparisons, we do not have to adjust for multiple comparisons [57]. To simplify the language, we used in the following the word "significant" not only for frequentist correlations with Holm corrected significance levels below 0.05 but also if the Bayes factor BF_{10} was above 10,
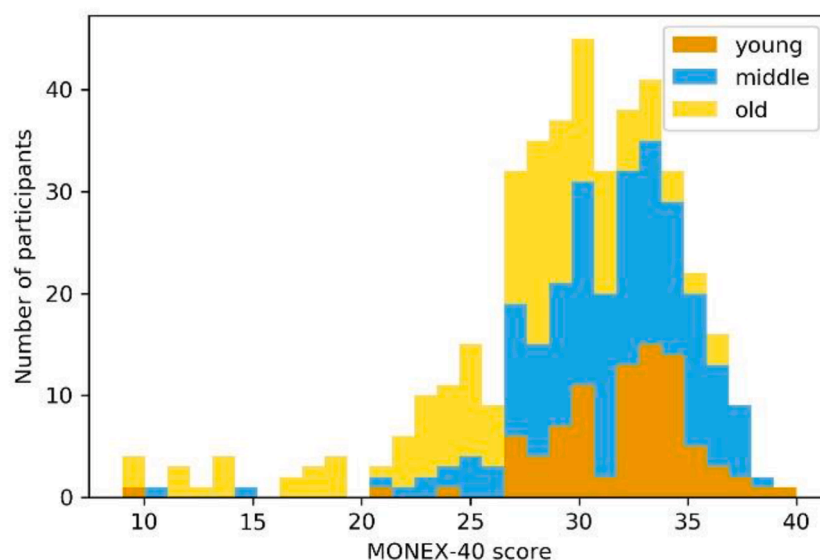

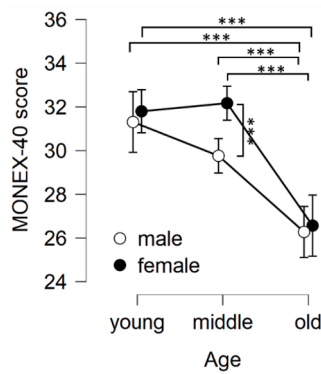**Fig. 2.** Distribution of participants' MONEX-40 scores grouped by age.

Fig. 3. Descriptive plot of MONEX-40 score grouped by sex and age. Dots display means, error bars the 95% confidence interval. For respective n of groups, see Table 1. For understanding that is more intuitive the unsquared MONEX-40 scores are shown.
***: $p < 0.001$ in post-hoc comparisons of sex and age group in two-way ANOVA with factors age and sex on squared MONEX-40 score (see Table 2).

Table 2
Post-hoc comparisons of sex and age group on squared MONEX-40 score.

		Mean difference	SE	t	p-value	
male, young	female, young	-22.160	50.253	-0.441	1.000	
	male, middle	100.833	44.264	2.278	0.116	
	male, old	282.178	44.729	6.309	< 0.001	***
female, young	female, middle	−27.436	42.459	−0.646	1.000	
	female, old	280.080	44.278	6.326	< 0.001	***
male, middle	female, middle	−150.430	35.167	−4.278	< 0.001	***
	male, old	181.344	36.709	4.940	< 0.001	***
female, middle	female, old	307.516	36.400	8.448	< 0.001	***
male, old	female, old	−24.258	37.892	−0.640	1.000	

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, Holm adjusted for comparing a family of 6.

indicating strong evidence for a non-zero correlation.

To examine if sex and age are confounding factors, we performed confounding analysis [58] (that is statistically the same as mediation analysis based on [59]) for blood parameters for which the significant relationship disappeared after controlling for sex and age. The blood parameter of interest was the independent variable; the MONEX-40 score was the dependent variable, and sex and age were considered as potential confounders. We performed separate analyses for each blood parameter. We used bias-corrected bootstrap with 1000 replications to calculate confidence intervals and account for non-parametric data [60]. According to Rucker and Zhao [61,62], we interpreted the indirect effect as a requirement for a confounding effect. Hypotheses were confirmed if the 95% confidence interval (CI) did not include zero.

To investigate other olfactory performance characteristics, we also analyzed the relationship between intensity and pleasantness scores of odors with age, sex, and nutritional parameters using partial Kendall's tau correlation analysis with conditions on sex and age. Results are presented in the supplementary material.

Statistical analysis was conducted using JASP 0.16 [63,64]. Holm adjusted p-values for correlations were computed using RStudio Cloud (R version 4.1.0).

3. Results

3.1. Influence of sex and age group on MONEX-40 score

A Chi-square test showed that there was no significant association between age and sex with the MONEX-40 score (X^2 (2, $N = 418$) = 0.676, $p = 0.713$). Out of 418 participants, 77 (18.4%) reached a MONEX-40 score lower than 27 that is often used as a cut-off value to identify normosmic subjects (Fig. 2) [47,65]. 76.6% of the hyposmic subjects belonged to the older age group, 19,5% to the middle-agers, and only 3.9% were young adults (percentage of hyposmic subjects per age group: young 3.4%, middle-aged 8.4%, old 38.6%).

A two-way ANOVA with the factors age (young, middle-agers and older adults) and sex (female, male) on the dependent variable of the squared MONEX-40 score revealed a significant interaction effect (F(2, 412) = 3.744, $p = 0.024$, $\eta^2 = 0.014$, Levene's test for equality of variances: F(5, 412) = 1.786, $p = 0.115$). Post-hoc analyses revealed a significant decrease of the smelling ability from young or middle-agers to older adults for both sexes. A significant sex difference was only found for middle-agers with a better score for females (Fig. 3, Table 2).

3.2. Correlation between blood parameters and MONEX-40 score

Next, we examined the associations between the blood parameters as well as BMI and BFP on the MONEX-40 score. As sex and age were found to have a significant influence on the MONEX-40 score, we conducted in addition to zero-order correlations partial correlations, either by conditioning on these factors (frequentist) or by building subgroups (frequentist and Bayesian). As sex was not found to have a significant effect for young and old adults, we did not split these cohorts based on sex. This resulted in four different subgroups (young adults, female middle-agers, male middle-agers, and older adults). Coefficients, p-values, and BF_{10} values for all correlations are shown in the supplementary material.

The frequentist zero-order correlation between each blood parameter and the MONEX-40 score revealed weak ($|\tau| < 0.2$) negative correlations for RDW, γGT, LDH, urea, uric acid, and ferritin as well as a weak positive correlation for phosphorus and moderate ($|\tau| < 0.3$) positive for GFR. In addition, the correlations of the MONEX-40 score with sex and age were statistically significant. All parameters showing a significant correlation with smell ability were also significantly associated with sex and/or age. A partial correlation for age and sex revealed no significant factors (see Table 3), indicating a confounding effect of sex and/or age (see Fig. 4).

Bayesian zero-order correlation provides evidence that in addition to the above-mentioned parameters, creatinine ($\tau = -0.105$, $BF_{10} = 10.677$) and BFP ($\tau = -0.105$, $BF_{10} = 10.466$) correlated negatively with the MONEX-40 score. However, the significant variables again showed a significant relationship with sex or age (see supplementary material).

3.2.1. Young adults

Neither age nor sex correlated significantly with the MONEX-40 score in the group of young adults. That resembles the results of the ANOVA. Therefore, we did not control for sex and age. Regarding blood parameters, there was a weak negative correlation between TSH and MONEX-40 score that was statistically significant ($\tau = -0.288$, $p = 0.006$, $BF_{10} = 302.008$). No other variables reached significance (see supplementary material).

3.2.2. Middle-agers

In the group of middle-agers, sex correlated significantly with the MONEX-40 score ($\tau = 0.309$, $p < 0.001$, $BF_{10} = 1.159e+7$) but not with age. This fits with the results of the ANOVA. Therefore, we controlled for sex. No blood parameters reached significant correlations with the MONEX-40 score, neither using frequentist nor Bayesian correlation (see supplementary material).

Table 3

Kendall's tau correlation between selected parameters[1] and MONEX-40 score, sex, and age. Results of zero-order correlation as well as partial correlation with condition on sex and age are illustrated.

Variable[1]		Zero-order correlations MONEX-40 score		Sex		Age		Partial correlations MONEX-40 score	
Sex	Kendall's Tau B	0.156	***	—		—		—	
	p-value	5.415e −03		—		—		—	
Age	Kendall's Tau B	−0.322	***	−0.053	ns	—		—	
	p-value	2.814e −19		1.000		—		—	
RDW	Kendall's Tau B	−0.121	*	0.082	ns	0.256	***	−0.059	ns
	p-value	0.015		1.000		1.933e −12		1.00	
γGT	Kendall's Tau B	−0.127	**	−0.343	***	0.160	***	−0.033	ns
	p-value	6.990e −03		8.910e −16		6.718e −05		1.00	
LDH	Kendall's Tau B	−0.144	***	0.051	ns	0.278	***	−0.071	ns
	p-value	8.740e −04		1.000		2.628e −05		1.00	
Phosphorus	Kendall's Tau B	0.162	***	0.369	***	−0.215	***	0.050	ns
	p-value	1.171e −04		1.010e −17		9.576e −09		1.00	
Creatinine	Kendall's Tau B	−0.105	ns	−0.476	***	0.073	ns	−0.018	ns
	p-value	0.064		2.092e −30		0.896		1.00	
GFR	Kendall's Tau B	0.242	***	−0.023	ns	−0.610	***	0.072	ns
	p-value	3.752e −11		1.000		1.671e −73		1.00	
Urea	Kendall's Tau B	−0.195	***	−0.254	***	0.307	***	−0.073	ns
	p-value	5.636e −07		1.489e −08		4.625e −18		0.988	
Uric acid	Kendall's Tau B	−0.141	**	−0.457	***	0.128	**	−0.044	ns
	p-value	1.434e −03		4.808e −28		4.369e −03		1.00	
Ferritin	Kendall's Tau B	−0.137	**	−0.360	***	0.256	***	−0.008	ns
	p-value	1.788e −03		1.143e −17		5.335e −13		1.00	
BFP	Kendall's Tau B	−0.105	ns	0.384	***	0.349	***	−0.062	ns
	p-value	0.064		3.377e −20		3.766e −24		1.00	

$* \ p < 0.05$, $** \ p < 0.01$, $*** \ p < 0.001$, ns: non-significant; Holm adjusted for comparing a family of 42, 41, 41 and 40 respectively.
1 For all these variables, Bayesian zero-order correlation provides strong evidence for a non-zero correlation with the MONEX-40 score.
RDW: red blood cell distribution width, γGT: gamma-glutamyltransferase, LDH: lactate dehydrogenase, GFR: glomerular filtration rate.
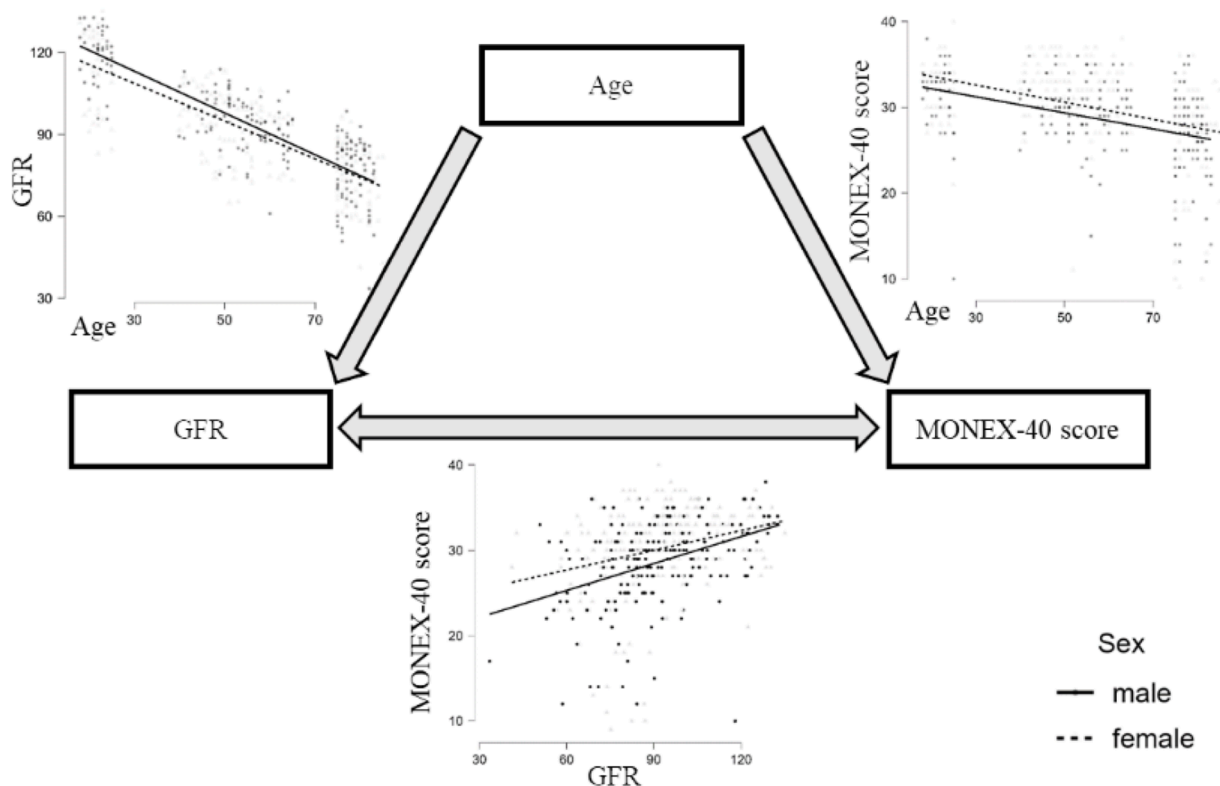

Fig. 4. Example for a confounding effect of age on metabolic blood parameters: Age, GFR, and MONEX-40 score correlated with each other. However, the correlation between GFR and MONEX-40 score became insignificant after controlling for age, indicating a confounding effect of age. In this case, sex did not correlate significantly with GFR.

3.2.3. Older adults

In the group of older adults, neither sex nor age correlated significantly with MONEX-40 score in accordance with the ANOVA results. Therefore, we did not separate the senior cohort. No blood parameters correlated significantly with the MONEX-40 score in frequentist or Bayesian correlation (see supplementary material).

Table 4

Total indirect and direct effects of given blood parameters and BFP on MONEX-40 score through age and sex.

Variable	N	Total indirect effects Estimate	95% CI Lower	Upper	Direct effects Estimate	95% CI Lower	Upper	Interpretation according to [60]
RDW	416	−0.717	−1.184	−0.340	−0.522	−1.193	0.073	Indirect-only
γGT	418	−0.023	−0.034	−0.012	0.006	−0.016	0.020	Indirect-only
LDH	418	−0.018	−0.024	−0.012	−0.008	−0.020	0.003	Indirect-only
Phosphorus	418	1.866	1.266	2.560	−0.198	−1.211	0.832	Indirect-only
Creatinine	418	−3.018	−4.878	−1.064	−2.740	−5.961	0.707	Indirect-only
GFR	417	0.082	0.051	0.117	0.008	−0.029	0.048	Indirect-only
Urea	418	−0.106	−0.144	−0.074	−0.054	−0.119	0.008	Indirect-only
Uric acid	418	−0.443	−0.661	−0.239	−0.276	−0.614	0.067	Indirect-only
Ferritin	418	−0.006	−0.009	−0.004	−5.865e −4	−0.004	0.003	Indirect-only
TSH	418	0.347	0.095	0.768	−0.207	−0.713	0.211	Indirect-only
BFP	418	0.071	−0.126	−0.024	−0.023	−0.086	0.043	Indirect-only

Bias-corrected percentile bootstrap confidence intervals (CI) based on 1000 samples.
RDW: red blood cell distribution width, γGT: gamma-glutamyltransferase, LDH: lactate dehydrogenase, GFR: glomerular filtration rate, TSH: thyroid-stimulating hormone, BFP: body fat percentage.

3.3. Confounding analysis of nutritional parameters on MONEX-40 score through age and sex

Several blood parameters showed significant zero-order correlations with the MONEX-40 score; however, all partial correlations became insignificant. To provide evidence for a confounding effect of age and sex on these relationships, we conducted confounding analyses for the blood parameters RDW, γGT, LDH, phosphorus, creatinine, GFR, urea, uric acid, ferritin, TSH as well as BFP.

Table 4 summarizes the results necessary to detect confounders, further statistics can be found in the supplementary material. Our data indicated indirect-only confounding [62].

4. Discussion

Whether and which blood parameters may be associated with olfactory performance is still unclear, as several studies lead to different outcomes (e.g. hypothyroidism [34–36], cholesterol [2,11,14,37,38], type 2 diabetes mellitus [36,39–41], insulin [11,43,44], see Introduction). In this broad study, we examined the relationship between olfactory performance and 38 blood parameters as well as sex, age, and the anthropometric measurements BMI and BFP of 418 healthy, well-phenotyped Caucasians. Therefore, we did not focus – as other studies – on olfactory performance effects for patients suffering from illnesses like diabetes [37,38,40,43,47], thyroid [31–33], or kidney [48–50,62] diseases but examined a whole bandwidth of metabolic parameters equally for healthy participants (including overweight subjects). By using the MONEX-40 test (51), we were able to objectively examine participants' olfactory identification scores. Within a total of 18.4% of subjects that can be classified as hyposmic subjects using a typical cut-off value of 27, we have a representative sample if it is taken into account that over one-third of our participants were older than 75 years (63, 64).

4.1. Age and sex

It is well established that olfactory performance is age- and sex-dependent. From youth to adulthood, olfactory performance typically increases greatly. Around the retirement age, a pronounced decline can be observed [25]. Whereas the increase can be explained by learning effects, the later decrease is most likely due to age-related structural changes in the nose and an aging olfactory system. In addition, a decrease in cognitive abilities and memory decline can contribute to the performance decline [27,28]. We were able to replicate these results, as there were significant negative differences between our young and middle-aged participants compared to older subjects. No significant differences were established between the young and middle-aged

subjects in accordance with the flatting olfactory performance curve for subjects within these age range [25]. Within our three pre-defined age groups, age did not correlate significantly with olfactory performance. This indicates that within an age group, individual differences are more important than a smaller age difference.

In addition to age effects, previous studies reported a sex difference with better olfactory performances for women versus men. Whereas some studies found such effects over a broad age range [25,26,31], some only found these effects for young adults [22,32]. Interestingly, our female participants outperformed the male participants only in the middle-aged cohort, whereas no differences were established for young and old participants. Similarly, only in the middle-aged cohort sex correlated significantly with the MONEX-40 score. This could be due to the larger sample size of the middle-aged compared to the young and old age groups as sex-related differences were shown to be relatively small and therefore need a larger sample size to become significant [25,31]. However, the difference in mean MONEX-40 scores was 2.4 for our middle-aged participants and less than half a point if males and females in the young and older age group were compared. This reveals a sample-size independent effect of a more enhanced sex difference in middle-aged adults. According to our results, discussed explanations based on hormones [32] also seem insufficient as they cannot explain the non-significant sex difference in our young cohort. In addition to anatomical and/or physiological as well as higher-level cognitive differences between males and females, a difference in odor experience or learning was discussed to cause the differences [31,66]. It was shown that women are more likely to take main responsibility for meal planning or preparing and that older men are more likely to take no responsibility for these activities [67]. That corresponds to the trend of an increasing proportion of men, especially men of younger age, that are cooking [68]. Therefore, the differences in exposure to and sensibilization for odors due to cooking and meal preparation could be one explanation that differences were only found in middle-aged adults. With a diminished sense of smell for older people, this possible effect seems to lose its importance. Further research should investigate this potential relationship.

4.2. BMI and BFP

We did not find a significant correlation between olfactory identification performance and BMI. However, we established evidence in favor of a negative correlation between BFP and the MONEX-40 score. As several studies suggest a significant relationship between body weight or obesity and olfactory performance [9], we recommend using BFP instead of BMI as a measure of overweight. An explanation could be that BFP in contrast to BMI can better differentiate between muscle and fat mass [17]. Stratified analysis of our data did not establish significant
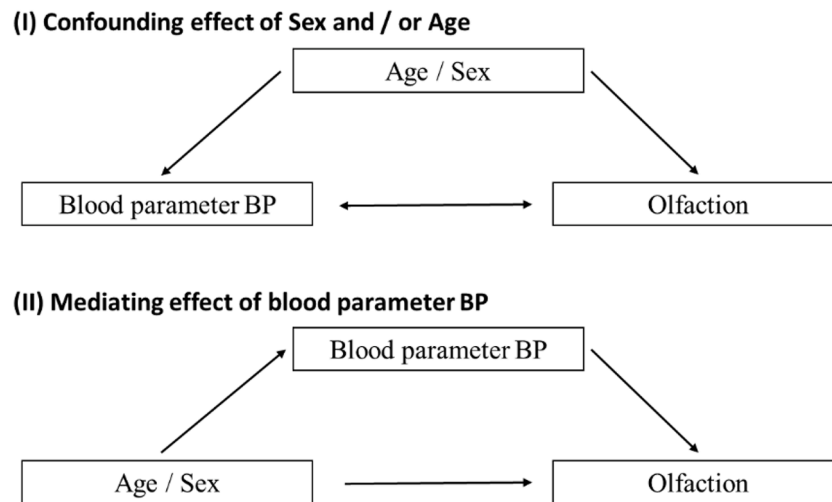
(I) Confounding effect of Sex and / or Age

(II) Mediating effect of blood parameter BP

Fig. 5. Two possible explanations for the significant zero-order but non-significant correlation if a blood parameter BP is controlled for sex and / or age.

BMI or BFP correlations with the MONEX-40 score. In addition, the effect of BFP lost significance if controlled for sex and age, both variables were identified as confounders. That corresponds with previous literature showing that BMI and BFP are sex- and age-dependent [14,18–20].

4.3. Blood parameters

There are already existing large-scale studies in Korean, Chinese, and US populations. KNHANES (Korea) data revealed that blood parameters were not associated with olfactory self-reported dysfunction if the effects were adjusted, although t-tests revealed some significant blood parameters [11]. Among the Chinese population, only significant associations after adjusting for total cholesterol were reported [38]. In the NHANES study (US), however, it was revealed that the direction is opposite for men and women and no blood parameters were found with not varying association by sex and age group [14]. Both latter studies also relied on self-reported olfactory function. Our study adds to these previous ones for a Caucasian population with the advantage that we objectively assessed olfactory ability using the MONEX-40 test.

We were able to show that several blood parameters relevant in metabolism (namely RDW, γGT, LDH, phosphorus, creatinine, GFR, urea, uric acid, and ferritin) correlated significantly with odor identification ability. All these parameters also correlated significantly with sex and/or age in accordance with the literature [69–74]. Controlling for these effects diminished the correlations with the MONEX-40 score. In addition, no parameters were identified to correlate significantly with perceived olfactory intensity or pleasantness score if controlled for sex and age (see supplementary material). We confirmed the non-correlation using Bayesian hypothesis testing, in fact, for nearly all blood parameters evidence favored a zero-correlation (see supplementary material). This indicates that age and sex should be of particular interest if examining relationships between blood parameters and olfactory function.

However, not all effects disappeared after controlling for sex and/or age. In stratified correlation analysis, we identified that TSH correlated negatively with the MONEX-40 score for young adults. That fits to other studies that found a diminished olfactory function for adults with hypothyroidism and therefore with low levels of FT3 and FT4 and high levels of TSH [34,35]. Similarly, the authors of another study found that a high odor identification score is significantly associated with high levels of FT3. However, in this study, no significant associations with TSH or FT4 were established [33]. Whereas in these studies, young adults or subjects over a broad age range were investigated, in a study with subjects older than 55 years no significant association between odor identification and thyroid disorder was found [36]. This corresponds to our result that the relation between TSH and MONEX-40 is age-dependent.

Besides TSH, if removing sex and age effects, we were not able to find evidence for a relationship between metabolic parameters - partially resulting from eating behavior - and odor identification performance. In fact, we were able to show evidence in favor of a zero-correlation for cholesterol (HDL, LDL, or total) or triglycerides. These parameters were identified in some studies to be related to olfactory function [11,37,44, 50]; however, in other studies no significant associations were reported [2,11,38]. Serum insulin also did not affect olfactory identification performance in our study as found in a previous study [11], even if intranasal insulin levels seem to affect olfactory performance, either negatively [45–47] or positively [43,48,49]. Phosphorus, urea, and creatinine were also shown previously to be related to olfactory function, more specifically to olfactory thresholds [50]. This study cohort included patients with renal insufficiency and in the analysis, authors did not control for sex and age. We did establish significant associations for zero-order correlations, too, but for creatinine and phosphorus in other directions than the previous paper. We found negative correlations for creatinine and positive correlations for phosphorus while they established the complete opposite effects. In addition, we showed that no direct but only indirect effects existed if sex and age were considered. Taken together, the discrepancy in the directionality could be explained by differences in study populations. Our broad analysis, therefore, highlights the importance of controlling for sex, age, and health status of the study population.

Nevertheless, we identified blood parameters of which the correlating effect with the odor identification ability could be explained through (I) a confounding effect by sex and/or age. Another possible explanation could be that (II) these blood parameters mediate the age and sex effect on odor identification (see Fig. 5). Explanation I entails that the significant correlation is due to the fact that people within a given age range or with a given sex (a) have a special level of a blood parameter and (b) have a special prevalence of smell ability, but that (a) and (b) do not (totally) influence each other. Explanation II claims that age and sex do influence the smelling ability via blood parameters as mediators. That means that special blood parameters that change during aging or that are different between males and females influence olfaction and, therefore, can partially explain possible sex and age differences.

As we were interested in the correlation between blood parameters reflecting nutritional behavior and the metabolic state, we performed confounding analysis to test explanation I. Indeed, age and sex were identified as confounders. However, although we provided evidence for a confounding effect, a mediating effect could also occur. Mediation

analysis to clarify this question should be based on thorough literature research to justify the underlying theory and precisely include relevant blood parameters in the model. In addition, targeted studies should be performed, for example through interventions (compare [44] that showed a mediating effect of insulin on the relationship between BMI and olfactory sensitivity).

5. Conclusion

Nutrition and olfaction are closely related and may influence each other via metabolic parameters. Using data of the well-phenotyped *Enable* cohort, we examined the relationship between 38 blood parameters as well as age, sex, and body weight/composition on olfactory identification performance measured with MONEX-40. We replicated age-dependent olfactory identification scores and found slight evidence for a body fat dependence measured with BFP. Our data suggest a sex difference only in middle-aged adults that could be explained by environmental factors. In addition, we were able to show that several blood parameters relevant to metabolism correlate significantly with odor identification ability. However, removing the effects of sex and age diminished these correlations, and sex and age seem to confound the correlations in healthy participants. To summarize, our results suggest that metabolic parameters resulting from nutrition are not related to olfactory identification performance in a relevant manner and highlight the importance of controlling for sex, age, and health status of study population in chemosensory research.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

Data will be made available upon request.

Author contributions

BB, TS, DV, HH, JF provided data of *E*nable cohort. DS performed statistical analysis and wrote the manuscript. BK and JF revised the manuscript. All authors critically read the manuscript and approved the final version. The present work was performed in partial fulfillment of the requirements for obtaining the degree "Dr. rer. biol. hum.".

Data availability statement

All analyzed data is part of the *Enable* dataset [20].

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.physbeh.2022.113907.

References

[1] B. Schaal, L. Marlier, R. Soussignan, Human foetuses learn odours from their pregnant mother's diet, Chem. Senses 25 (2000) 729–737.

[2] W.Y. Kim, M. Hur, M.S. Cho, H.S. Lee, Effect of olfactory function on nutritional status of Korean elderly women, Nutr. Res. 23 (2003) 723–734.

[3] S. Boesveldt, K. de Graaf, The differential role of smell and taste for eating behavior, Perception 46 (2017) 307–319.

[4] E.P. Köster, R. Haller, C. Rummel, S. Henneberg, U. Pollmer, E.P. Köster, The influence of early experience with vanillin on food preference later in life, Chem. Senses 24 (1999) 465–467.

[5] B. Palouzier-Paulignan, M.-.C. Lacroix, P. Aimé, C. Baly, M. Caillol, P. Congar, A. K. Julliard, K. Tucker, D.A. Fadool, Olfaction under metabolic influences, Chem. Senses 37 (2012) 769–797.

[6] J.C. Fernandez-Garcia, J. Alcaide, C. Santiago-Fernandez, M.M. Roca-Rodriguez, Z. Aguera, R. Baños, C. Botella, R. de La Torre, J.M. Fernandez-Real, G. Fruhbeck, An increase in visceral fat is associated with a decrease in the taste and olfactory capacity, PLoS ONE 12 (2017), e0171204.

[7] M.J. Karpa, B. Gopinath, E. Rochtchina, J.J. Wang, R.G. Cumming, C.M. Sue, P. Mitchell, Prevalence and neurodegenerative or other associations with olfactory impairment in an older community, J. Aging Health 22 (2010) 154–168.

[8] A. Pastor, F. Fernández-Aranda, M. Fitó, S. Jiménez-Murcia, C. Botella, J. M. Fernández-Real, G. Frühbeck, F.J. Tinahones, A.B. Fagundo, J. Rodriguez, A lower olfactory capacity is related to higher circulating concentrations of endocannabinoid 2-arachidonoylglycerol and higher body mass index in women, PLoS ONE 11 (2016), e0148734.

[9] M. Peng, D. Coutts, T. Wang, Y.O. Cakmak, Systematic review of olfactory shifts related to obesity, Obes. Rev. 20 (2019) 325–338.

[10] B. Chen, C. Masala, A. Oleszkiewicz, V. Englmaier, N. Gunder, S. Menzel, A. Haehner, T. Hummel, Nonlinear association between chemosensory dysfunction and body mass index, J. Sens. Stud. 37 (2022) e12715.

[11] W.H. Lee, J.H. Wee, D.-.K. Kim, C.-.S. Rhee, C.H. Lee, S. Ahn, J.H. Lee, Y.-.S. Cho, K.H. Lee, K.S. Kim, Prevalence of subjective olfactory dysfunction and its risk factors: Korean National Health and Nutrition Examination Survey, PLoS ONE 8 (2013) e62725.

[12] G. Liu, G. Zong, R.L. Doty, Q. Sun, Prevalence and risk factors of taste and smell impairment in a nationwide representative sample of the US population: a cross-sectional study, BMJ Open 6 (2016), e013246.

[13] M. Poessel, N. Breuer, A. Joshi, A. Pampel, A. Villringer, T. Hummel, A. Horstmann, Reduced olfactory bulb volume in obesity and its relation to metabolic health status, Front. Hum. Neurosci. 14 (2020) 515.

[14] S. Gallo, L. Byham-Gray, V.B. Duffy, H.J. Hoffman, J.E. Hayes, S. Rawal, Associations of olfactory dysfunction with anthropometric and cardiometabolic measures: findings from the 2013–2014 national health and nutrition examination survey (NHANES), Physiol. Behav. 215 (2020), 112702.

[15] W. Skrandies, R. Zschieschang, Olfactory and gustatory functions and its relation to body weight, Physiol. Behav. 142 (2015) 1–4.

[16] K.S. Fluitman, H.J. Nadar, D.S. Roos, H.W. Berendse, B.J. Keijser, M. Nieuwdorp, R. G. Ijzerman, M. Visser, The association of olfactory function with BMI, appetite, and prospective weight change in Dutch community-dwelling older adults, J. Nutr., Health Aging 23 (2019) 746–752.

[17] S. Mazic, M. Djelic, J. Suzic, S. Suzic, M. Dekleva, D. Radovanovic, L. Scepanovic, V. Starcevic, Overweight in trained subjects-are we looking at wrong numbers? (Body mass index compared with body fat percentage in estimating overweight in athletes, Gen. Physiol. Biophys. 28 (2009) 200–204.

[18] A.S. Jackson, P.R. Stanforth, J. Gagnon, T. Rankinen, A.S. Leon, D.C. Rao, J. S. Skinner, C. Bouchard, J.H. Wilmore, The effect of sex, age and race on estimating percentage body fat from body mass index: the heritage family study, Int. J. Obes. 26 (2002) 789–796.

[19] U. Simchen, C. Koebnick, S. Hoyer, S. Issanchou, H.-.J. Zunft, Odour and taste sensitivity is associated with body weight and extent of misreporting of body weight, Eur. J. Clin. Nutr. 60 (2006) 698–705.

[20] B. Brandl, T. Skurk, R. Rennekamp, A. Hannink, E. Kiesswetter, J. Freiherr, S. Ihsen, J. Roosen, M. Klingenspor, D. Haller, A phenotyping platform to characterize healthy individuals across four stages of life-the enable study, Front. Nutr. 7 (2020).

[21] A. Rosa, I. Pinna, C. Masala, Role of body weight and sex in the olfactory and gustatory pleasantness, intensity, and familiarity of a lipid-rich food, J. Sens. Stud. (2022) e12739.

[22] T. Hummel, G. Kobal, H. Gudziol, A. Mackay-Sim, Normative data for the "Sniffin'Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects, Eur. Arch. Oto-Rhino-Laryngol. 264 (2007) 237–243.

[23] H. Kaneda, K. Maeshima, N. Goto, T. Kobayakawa, S. Ayabe-Kanamura, S. Saito, Decline in taste and odor discrimination abilities with age, and relationship between gustation and olfaction, Chem. Senses 25 (2000) 331–337.

[24] A. Keller, M. Hempstead, I.A. Gomez, A.N. Gilbert, L.B. Vosshall, An olfactory demography of a diverse metropolitan population, BMC Neurosci. 13 (2012) 1–17.

[25] A. Oleszkiewicz, V.A. Schriever, I. Croy, A. Hähner, T. Hummel, Updated sniffin'sticks normative data based on an extended sample of 9139 subjects, Eur. Arch. Oto-Rhino-Laryngol. 276 (2019) 719–728.

[26] J. Mullol, I. Alobid, F. Mariño-Sánchez, L. Quintó, J. de Haro, M. Bernal-Sprekelsen, A. Valero, C. Picado, C. Marin, Furthering the understanding of olfaction, prevalence of loss of smell and risk factors: a population-based survey (OLFACAT study), BMJ Open 2 (2012), e001256.

[27] J. Attems, L. Walker, K.A. Jellinger, Olfaction and aging: a mini-review, Gerontology 61 (2015) 485–490.

[28] R.L. Doty, V. Kamath, The influences of age on olfaction: a review, Front. Psychol. 5 (2014) 20.

[29] R.L. Doty, S. Applebaum, H. Zusho, R.G. Settle, Sex differences in odor identification ability: a cross-cultural analysis, Neuropsychologia 23 (1985) 667–672.

[30] R.L. Doty, E.L. Cameron, Sex differences and reproductive hormone influences on human odor perception, Physiol. Behav. 97 (2009) 213–228.

[31] P. Sorokowski, M. Karwowski, M. Misiak, M.K. Marczak, M. Dziekan, T. Hummel, A. Sorokowska, Sex differences in human olfaction: a meta-analysis, Front. Psychol. 10 (2019) 242.

[32] X. Wang, C. Zhang, X. Xia, Y. Yang, C. Zhou, Effect of gender on odor identification at different life stages: a meta-analysis, Rhinology 57 (2019) 322–330.

[33] E. Günbey, R. Karlı, F. Gökosmanoğlu, B. Düzgün, E. Ayhan, H. Atmaca, R. Ünal, Evaluation of olfactory function in adults with primary hypothyroidism, Int. Forum Allergy Rhinol. 5 (2015) 919–922.

[34] F. Deniz, S.A. Ay, M. Salihoglu, O. Kurt, K. Baskoy, A. Altundag, H. Tekeli, A. Yonem, T. Hummel, Thyroid hormone replacement therapy improves olfaction and taste sensitivity in primary hypothyroid patients: a prospective randomised clinical trial, Exp. Clin. Endocrinol. Diabetes 124 (2016) 562–567.

[35] K. Baskoy, S.A. Ay, A. Altundag, O. Kurt, M. Salihoglu, F. Deniz, H. Tekeli, A. Yonem, T. Hummel, Is there any effect on smell and taste functions with levothyroxine treatment in subclinical hypothyroidism? PLoS ONE 11 (2016), e0149979.

[36] K.A. Hawkins, G.D. Pearlson, Age and gender but not common chronic illnesses predict odor identification in older African Americans, Am. J. Geriatric Psychiatry 19 (2011) 777–782.

[37] S.-.H. Hwang, J.-.M. Kang, J.-.H. Seo, K. Han, Y.-.H. Joo, Gender difference in the epidemiological association between metabolic syndrome and olfactory dysfunction: the Korea National Health and Nutrition Examination Survey, PLoS ONE 11 (2016), e0148813.

[38] Z. Huang, S. Huang, H. Cong, Z. Li, J. Li, K.L. Keller, G.C. Shearer, P.M. Kris-Etherton, S. Wu, X. Gao, Smell and taste dysfunction is associated with higher serum total cholesterol concentrations in Chinese adults, J. Nutr. 147 (2017) 1546–1551.

[39] E. Gouveri, M. Katotomichelakis, H. Gouveris, V. Danielides, E. Maltezos, N. Papanas, Olfactory dysfunction in type 2 diabetes mellitus: an additional manifestation of microvascular disease? Angiology 65 (2014) 869–876.

[40] E. Catamo, G. Tornese, M.P. Concas, P. Gasparini, A. Robino, Differences in taste and smell perception between type 2 diabetes mellitus patients and healthy controls, Nutr., Metabol. Cardiovasc. Dis. 31 (2021) 193–200.

[41] A. Naka, M. Riedl, A. Luger, T. Hummel, C.A. Mueller, Clinical significance of smell and taste disorders in patients with diabetes mellitus, Eur. Arch. Oto-Rhino-Laryngol. 267 (2010) 547–550.

[42] A. Altundag, S.A. Ay, S. Hira, M. Salıhoglu, K. Baskoy, F. Denız, H. Tekelı, O. Kurt, A. Yonem, T. Hummel, Olfactory and gustatory functions in patients with non-complicated type 1 diabetes mellitus, Eur. Arch. Oto-Rhino-Laryngol. 274 (2017) 2621–2627.

[43] S.E. Thanarajah, V. Hoffstall, L. Rigoux, R. Hanssen, J.C. Brüning, M. Tittgemeyer, The role of insulin sensitivity and intranasally applied insulin on olfactory perception, Sci. Rep. 9 (2019) 1–8.

[44] M. Poessel, J. Freiherr, K. Wiencke, A. Villringer, A. Horstmann, Insulin resistance is associated with reduced food odor sensitivity across a wide range of body weights, Nutrients 12 (2020) 2201.

[45] C. Ketterer, M. Heni, C. Thamer, S.A. Herzberg-Schäfer, H.U. Häring, A. Fritsche, Acute, short-term hyperinsulinemia increases olfactory threshold in healthy subjects, Int. J. Obes. 35 (2011) 1135–1138.

[46] Y.F. Brünner, C. Benedict, J. Freiherr, Intranasal insulin reduces olfactory sensitivity in normosmic humans, J. Clin. Endocrinol. Metabol. 98 (2013) E1626–E1630.

[47] R. Rodriguez-Raecke, Y.F. Brünner, A. Kofoet, S. Mutic, C. Benedict, J. Freiherr, Odor sensitivity after intranasal insulin application is modulated by gender, Front. Endocrinol. (Lausanne) 9 (2018) 580.

[48] V. Schöpf, K. Kollndorfer, M. Pollak, C.A. Mueller, J. Freiherr, Intranasal insulin influences the olfactory performance of patients with smell loss, dependent on the body mass index: a pilot study, Rhinology 53 (2015) 371–378.

[49] A. Rezaeian, Effect of intranasal insulin on olfactory recovery in patients with hyposmia: a randomized clinical trial, Otolaryngol.–Head Neck Surg. 158 (2018) 1134–1139.

[50] M.I. Griep, P. van der Niepen, J.J. Sennesael, T.F. Mets, D.L. Massart, D.L. Verbeelen, Odour perception in chronic renal disease, nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association-European Renal Association 12 (1997) 2093–2098.

[51] S.U. Nigwekar, J.M. Weiser, S. Kalim, D. Xu, J.L. Wibecan, S.M. Dougherty, L. Mercier-Lafond, K.M. Corapi, N.D. Eneanya, E.H. Holbrook, Characterization and correction of olfactory deficits in kidney disease, J. Am. Soc. Nephrol. 28 (2017) 3395–3403.

[52] A.F.P. Temmel, S. Pabinger, C. Quint, P. Munda, P. Ferenci, T. Hummel, Dysfunction of the liver affects the sense of smell, Wien. Klin. Wochenschr. 117 (2005) 26–30.

[53] J. Freiherr, A.R. Gordon, E.C. Alden, A.L. Ponting, M.F. Hernandez, S. Boesveldt, J. N. Lundström, The 40-item Monell extended sniffin'sticks identification test (MONEX-40), J. Neurosci. Methods 205 (2012) 10–16.

[54] A.S. Levey, L.A. Stevens, C.H. Schmid, Y. Zhang, A.F. Castro III, H.I. Feldman, J. W. Kusek, P. Eggers, F. van Lente, T. Greene, A new equation to estimate glomerular filtration rate, Ann. Intern. Med. 150 (2009) 604–612.

[55] S. Holm, A simple sequentially rejective multiple test procedure, Scand. J. Stat. (1979) 65–70.

[56] E.-.J. Wagenmakers, J. Verhagen, A. Ly, How to quantify the evidence for the absence of a correlation, Behav. Res. Methods 48 (2016) 413–426.

[57] A. Sjölander, S. Vansteelandt, Frequentist versus Bayesian approaches to multiple testing, Eur. J. Epidemiol. 34 (2019) 809–821.

[58] L.A. Gelfand, J.L. Mensinger, T. Tenhave, Mediation analysis: a retrospective snapshot of practice and more recent directions, J Gen Psychol 136 (2009) 153–178.

[59] R.M. Baron, D.A. Kenny, The moderator–mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations, J. Pers. Soc. Psychol. 51 (1986) 1173.

[60] K.J. Preacher, D.D. Rucker, A.F. Hayes, Addressing moderated mediation hypotheses: theory, methods, and prescriptions, Multivariate Behav. Res. 42 (2007) 185–227.

[61] D.D. Rucker, K.J. Preacher, Z.L. Tormala, R.E. Petty, Mediation analysis in social psychology: current practices and new recommendations, Soc. Personal. Psychol. Compass 5 (2011) 359–371.

[62] X. Zhao, J.G. Lynch Jr, Q. Chen, Reconsidering Baron and Kenny: myths and truths about mediation analysis, J. Consum. Res. 37 (2010) 197–206.

[63] JASP Team, JASP (Version 0.16.3)[Computer software], 2022. https://jasp-stats. org/.

[64] J. Love, R. Selker, M. Marsman, T. Jamil, D. Dropmann, J. Verhagen, A. Ly, Q. F. Gronau, M. Šmíra, S. Epskamp, D. Matzke, A. Wild, P. Knight, J.N. Rouder, R. D. Morey, E.-.J. Wagenmakers, JASP: graphical statistical software for common statistical designs, J. Stat. Soft. 88 (2019) 1–17, https://doi.org/10.18637/jss. v088.i02.

[65] S.M. Hoffmann-Hensel, R. Sijben, R. Rodriguez-Raecke, J. Freiherr, Cognitive load alters neuronal processing of food odors, Chem. Senses 42 (2017) 723–736.

[66] G. Brand, J.-.L. Millot, Sex differences in human olfaction: between evidence and enigma, Q. J. Exp. Psychol. B 54 (2001) 259–270.

[67] L.A. Flagg, B. Sen, M. Kilgore, J.L. Locher, The influence of gender, age, education and household size on meal preparation and food shopping responsibilities, Public Health Nutr. 17 (2014) 2061–2070.

[68] L.P. Smith, S.W. Ng, B.M. Popkin, Trends in US home food preparation and consumption: analysis of national nutrition surveys and time use studies from 1965 to 1966 to 2007–2008, Nutr. J. 12 (2013) 1–10.

[69] J.J. Hoffmann, K.C. Nabbe, N.M.A. van den Broek, Effect of age and gender on reference intervals of red blood cell distribution width (RDW) and mean red cell volume (MCV), Clin. Chem. Lab. Med. (CCLM) (2015) 53.

[70] N. Bohnen, C.P. Degenaar, J. Jolles, Influence of age and sex on 19 blood variables in healthy subjects, Z. Gerontol. 24 (1991) 339–345.

[71] J. Fang, M.H. Alderman, Serum uric acid and cardiovascular mortality: the NHANES I epidemiologic follow-up study, 1971-1992, JAMA 283 (2000) 2404–2410.

[72] L.A. Inker, T. Shafi, A. Okparavero, H. Tighiouart, J.H. Eckfeldt, R. Katz, W. C. Johnson, N. Dermond, Z. Tariq, I. Benayache, Effects of race and sex on measured GFR: the multi-ethnic study of atherosclerosis, Am. J. Kidney Dis. 68 (2016) 743–751.

[73] G. Röhrig, I. Becker, A. Hagemeier, K. Gutensohn, T. Nebe, White blood cell counts, CRP, GGT and LDH in the elderly German population, J. Lab. Med. 43 (2019) 57–65.

[74] D.H. Rushton, J.H. Barth, What is the evidence for gender differences in ferritin and haemoglobin? Crit. Rev. Oncol. Hematol. 73 (2010) 1–9.