Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Exclusion Criteria for Magnetic Resonance Imaging (MRI) in the Rhineland Study

Absolute contraindications Participants with the following conditions are ineligible for MRI: ・ Pregnancy ・ Active implant ・ Mechanical contraceptives ・ Undetachable metal or foreign bodies in the body ・ Work- or hobby-related metal processing
Relative contraindications[a] ・ Artificial joints, vascular prostheses, stents or metal clips, and the like, in the body ・ Heart or head surgery (mainly concerning those with implants) In cases where the participant has a relative contraindication, further steps are taken to clarify whether/ what foreign material has been inserted into the body. For this purpose, documentation of foreign material, or doctor's letters and/or information about the clinic and year of implantation is obtained and assessed by the study physician.
Refusal to undergo MR imaging

[a] Tattoos were initially considered as contraindication in the beginning of the Rhineland Study but removed later.

eTable 2. The Association of Determinants With Olfactory Function Using Multivariable Linear Regression (n=1915)

	Difference (95% CI) in SIT-12 score			
	With SIT-12 and MRI-derived measures	With SIT-12, MRI-derived measures and smoking	With SIT-12	With SIT-12 and smoking
No. of participants	541	454	1915	1724
Age, year	-0.04 (-0.05, -0.03)	-0.04 (-0.06, -0.03)	-0.04 (-0.05, -0.04)	-0.04 (-0.05, -0.04)
Sex: men vs. women	-0.26 (-0.54, 0.02)	-0.24 (-0.55, 0.07)	-0.20 (-0.34, -0.05)	-0.17 (-0.32, -0.02)
Nasal patency: blocked vs. free	-0.28 (-0.66, 0.09)	-0.30 (-0.71, 0.12)	-0.21 (-0.41, -0.02)	-0.18 (-0.39, 0.02)
Smoking status:				
former vs. never	n/a	0.18 (-0.16, 0.51)	n/a	0.04 (-0.12, 0.20)
current vs. never	n/a	0.06 (-0.41, 0.53)	n/a	0.01 (-0.22, 0.24)

Abbreviations: SIT-12, 12-item “Sniffin’ Sticks” odor identification test; OBV, olfactory bulb volume; n/a, not applicable.

eTable 3. Relation Between Volumes of Olfactory Brain Structures and Olfactory Function

	Difference (95% CI) in SIT-12 score[b]				
Olfactory brain structures[a]	**volume**	**age**	**sex**	**volume×age**	**volume×sex**
Olfactory bulb					
Model 1	0.51 (0.38, 0.65)	-0.46 (-0.60, -0.33)	-0.29 (-0.55, -0.02)		
Model 2	0.54 (0.41, 0.68)	-0.44 (-0.58, -0.30)	-0.29 (-0.56, -0.03)	0.17 (0.03, 0.31)	
Model 3	0.46 (0.29, 0.64)	-0.44 (-0.58, -0.30)	-0.29 (-0.56, -0.03)	0.17 (0.03, 0.30)	0.19 (-0.07, 0.46)
Entorhinal cortex					
Model 1	-0.03 (-0.17, 0.11)	-0.58 (-0.71, -0.44)	-0.26 (-0.54, 0.02)		
Model 2	-0.03 (-0.17, 0.11)	-0.57 (-0.71, -0.43)	-0.26 (-0.54, 0.02)	0.04 (-0.12, 0.19)	
Model 3	-0.12 (-0.31, 0.07)	-0.57 (-0.71, -0.44)	-0.26 (-0.54, 0.02)	0.02 (-0.14, 0.18)	0.20 (-0.08, 0.48)
Amygdala					
Model 1	0.09 (-0.06, 0.24)	-0.54 (-0.69, -0.39)	-0.27 (-0.55, 0.01)		
Model 2	0.06 (-0.09, 0.21)	-0.52 (-0.67, -0.37)	-0.26 (-0.54, 0.02)	0.16 (0.03, 0.29)	
Model 3	-0.01 (-0.20, 0.19)	-0.52 (-0.67, -0.36)	-0.26 (-0.54, 0.02)	0.17 (0.03, 0.30)	0.15 (-0.13, 0.44)
Parahippocampal cortex					
Model 1	-0.02 (-0.17, 0.12)	-0.58 (-0.72, -0.44)	-0.27 (-0.55, 0.02)		
Model 2	-0.04 (-0.18, 0.11)	-0.56 (-0.70, -0.41)	-0.25 (-0.54, 0.03)	0.17 (0.03, 0.31)	
Model 3	0.05 (-0.14, 0.24)	-0.56 (-0.70, -0.42)	-0.27 (-0.55, 0.02)	0.17 (0.03, 0.31)	-0.20 (-0.49, 0.08)
Hippocampus					
Model 1	0.04 (-0.12, 0.19)	-0.56 (-0.71, -0.41)	-0.25 (-0.53, 0.04)		
Model 2	0.01 (-0.14, 0.16)	-0.51 (-0.67, -0.36)	-0.24 (-0.52, 0.04)	0.22 (0.08, 0.35)	
Model 3	-0.03 (-0.22, 0.17)	-0.51 (-0.67, -0.36)	-0.23 (-0.52, 0.05)	0.21 (0.08, 0.35)	0.09 (-0.20, 0.37)
Insular cortex					
Model 1	-0.05 (-0.19, 0.09)	-0.58 (-0.72, -0.44)	-0.26 (-0.54, 0.02)		
Model 2	-0.05 (-0.19, 0.09)	-0.58 (-0.72, -0.44)	-0.26 (-0.55, 0.02)	-0.01 (-0.14, 0.12)	
Model 3	-0.02 (-0.21, 0.18)	-0.58 (-0.72, -0.44)	-0.27 (-0.55, 0.02)	-0.01 (-0.14, 0.13)	-0.07 (-0.34, 0.21)
Lateral orbitofrontal cortex					
Model 1	-0.04 (-0.18, 0.10)	-0.58 (-0.72, -0.44)	-0.27 (-0.55, 0.01)		
Model 2	-0.04 (-0.18, 0.10)	-0.58 (-0.72, -0.44)	-0.26 (-0.55, 0.02)	0.02 (-0.12, 0.16)	
Model 3	0.12 (-0.07, 0.31)	-0.59 (-0.73, -0.45)	-0.27 (-0.56, 0.01)	0.01 (-0.13, 0.15)	-0.35 (-0.63,-0.07)

(continued)

	Difference (95% CI) in SIT-12 score[b]				
Olfactory brain structures[a]	**volume**	**age**	**sex**	**volume×age**	**volume×sex**
Medial orbitofrontal cortex					
Model 1	0.03 (-0.11, 0.17)	-0.57 (-0.71, -0.44)	-0.25 (-0.53, 0.03)		
Model 2	0.04 (-0.10, 0.18)	-0.57 (-0.71, -0.43)	-0.26 (-0.54, 0.02)	-0.08 (-0.21, 0.05)	
Model 3	0.04 (-0.13, 0.21)	-0.57 (-0.71, -0.43)	-0.26 (-0.54, 0.02)	-0.08 (-0.21, 0.05)	0.00 (-0.29, 0.30)

Abbreviation: SIT-12, 12-item "Sniffin' Sticks" odor identification test.
[a] Volumetric measures (including OBV) from the right and left side were averaged, head-size adjusted, and normalized.
[b] Separate multivariable linear regressions were performed for each regional brain volumes with adjustment for age, sex, and nasal patency:
Model 1: SIT-12 ~ volume + age + sex + nasal patency
Model 2: SIT-12 ~ volume + age + sex + nasal patency + volume × age
Model 3: SIT-12 ~ volume + age + sex + nasal patency + volume × age + volume × sex

eTable 4. Relation Between Volumes of Central Olfactory Structures and Olfactory Bulb Volume

	Difference (95% CI) in OBV [b]				
Central olfactory structures[a]	**volume**	**age**	**sex**	**volume×age**	**volume×sex**
Entorhinal cortex					
Model 1	0.00 (-0.08, 0.09)	-0.22 (-0.31, -0.14)	0.06 (-0.11, 0.22)		
Model 2	0.00 (-0.08, 0.09)	-0.23 (-0.31, -0.14)	0.06 (-0.11, 0.22)	-0.03 (-0.13, 0.06)	
Model 3	0.01 (-0.11, 0.12)	-0.23 (-0.31, -0.14)	0.06 (-0.11, 0.22)	-0.03 (-0.13, 0.06)	-0.01 (-0.18, 0.16)
Amygdala					
Model 1	0.08 (-0.01, 0.17)	-0.19 (-0.28, -0.10)	0.05 (-0.12, 0.22)		
Model 2	0.08 (-0.01, 0.17)	-0.19 (-0.29, -0.10)	0.05 (-0.12, 0.22)	-0.02 (-0.10, 0.06)	
Model 3	0.12 (0.01, 0.24)	-0.20 (-0.29, -0.11)	0.05 (-0.12, 0.22)	-0.02 (-0.10, 0.06)	-0.10 (-0.26, 0.07)
Parahippocampal cortex					
Model 1	-0.06 (-0.15, 0.03)	-0.23 (-0.32, -0.15)	0.03 (-0.14, 0.20)		
Model 2	-0.06 (-0.15, 0.02)	-0.23 (-0.31, -0.14)	0.03 (-0.14, 0.21)	0.03 (-0.05, 0.12)	
Model 3	-0.04 (-0.15, 0.08)	-0.23 (-0.32, -0.15)	0.03 (-0.14, 0.20)	0.03 (-0.05, 0.12)	-0.06 (-0.23, 0.11)
Hippocampus					
Model 1	0.11 (0.01, 0.20)	-0.18 (-0.27, -0.09)	0.09 (-0.08, 0.26)		
Model 2	0.12 (0.02, 0.21)	-0.20 (-0.29, -0.10)	0.09 (-0.08, 0.26)	-0.07 (-0.15, 0.01)	
Model 3	0.16 (0.04, 0.28)	-0.20 (-0.29, -0.11)	0.08 (-0.09, 0.25)	-0.07 (-0.14, 0.01)	-0.11 (-0.28, 0.06)
Insular cortex					
Model 1	0.12 (0.04, 0.21)	-0.21 (-0.29, -0.13)	0.07 (-0.09, 0.24)		
Model 2	0.12 (0.04, 0.21)	-0.21 (-0.30, -0.13)	0.07 (-0.09, 0.24)	0.01 (-0.07, 0.08)	
Model 3	0.12 (0.01, 0.24)	-0.21 (-0.30, -0.13)	0.07 (-0.09, 0.24)	0.01 (-0.07, 0.08)	0.00 (-0.17, 0.16)
Lateral orbitofrontal cortex					
Model 1	0.02 (-0.06, 0.11)	-0.22 (-0.30, -0.14)	0.06 (-0.11, 0.23)		
Model 2	0.03 (-0.06, 0.11)	-0.22 (-0.30, -0.14)	0.07 (-0.10, 0.24)	0.05 (-0.03, 0.13)	
Model 3	0.04 (-0.07, 0.15)	-0.22 (-0.30, -0.14)	0.07 (-0.10, 0.24)	0.05 (-0.03, 0.13)	-0.03 (-0.20, 0.13)
Medial orbitofrontal cortex					
Model 1	0.09 (0.01, 0.17)	-0.22 (-0.30, -0.14)	0.07 (-0.10, 0.24)		
Model 2	0.10 (0.01, 0.18)	-0.22 (-0.30, -0.13)	0.07 (-0.10, 0.23)	-0.04 (-0.12, 0.04)	
Model 3	0.10 (0.00, 0.20)	-0.22 (-0.30, -0.13)	0.07 (-0.10, 0.23)	-0.04 (-0.12, 0.04)	-0.01 (-0.18, 0.17)

Abbreviation: SIT-12, 12-item “Sniffin’ Sticks” odor identification test.
[a] Volumetric measures (including OBV) from the right and left side were averaged, head-size adjusted, and normalized.
[b] Separate multivariable linear regressions were performed for each regional brain volumes with adjustment for age, sex, and nasal patency:
Model 1: OBV ~ central olfactory volume + age + sex + nasal patency
Model 2: OBV ~ central olfactory volume + age + sex + nasal patency + central olfactory volume × age
Model 3: OBV ~ central olfactory volume + age + sex + nasal patency + central olfactory volume × age + central olfactory volume × sex

eTable 5. Relation Between Olfactory Bulb Volume and Volumes of Central Olfactory Structures

	Difference (95% CI) in central olfactory structure [a,b]				
	OBV	**age**	**sex**	**OBV × age**	**OBV × sex**
Entorhinal cortex					
Model 1	0.00 (-0.08, 0.09)	-0.02 (-0.11, 0.07)	-0.02 (-0.19, 0.16)		
Model 2	0.00 (-0.09, 0.09)	-0.02 (-0.11, 0.06)	-0.02 (-0.19, 0.16)	-0.02 (-0.11, 0.07)	
Model 3	0.00 (-0.11, 0.12)	-0.02 (-0.11, 0.06)	-0.02 (-0.19, 0.16)	-0.02 (-0.11, 0.07)	-0.01 (-0.18, 0.17)
Amygdala					
Model 1	0.07 (-0.01, 0.15)	-0.38 (-0.46, -0.30)	0.09 (-0.07, 0.24)		
Model 2	0.07 (-0.01, 0.15)	-0.38 (-0.46, -0.30)	0.09 (-0.07, 0.24)	0.02 (-0.06, 0.10)	
Model 3	0.11 (0.00, 0.21)	-0.38 (-0.46, -0.30)	0.09 (-0.07, 0.24)	0.02 (-0.06, 0.10)	-0.08 (-0.24, 0.08)
Parahippocampal cortex					
Model 1	-0.06 (-0.14, 0.03)	-0.18 (-0.26, -0.09)	-0.42 (-0.58, -0.26)		
Model 2	-0.05 (-0.14, 0.03)	-0.17 (-0.26, -0.09)	-0.42 (-0.59, -0.26)	0.04 (-0.05, 0.12)	
Model 3	-0.04 (-0.15, 0.07)	-0.17 (-0.26, -0.09)	-0.42 (-0.59, -0.26)	0.04 (-0.05, 0.12)	-0.03 (-0.20, 0.13)
Hippocampus					
Model 1	0.09 (0.01, 0.17)	-0.38 (-0.46, -0.30)	-0.32 (-0.47, -0.16)		
Model 2	0.09 (0.01, 0.17)	-0.38 (-0.46, -0.30)	-0.32 (-0.47, -0.16)	-0.03 (-0.11, 0.06)	
Model 3	0.12 (0.02, 0.22)	-0.38 (-0.46, -0.31)	-0.31 (-0.47, -0.16)	-0.03 (-0.11, 0.06)	-0.09 (-0.24, 0.07)
Insular cortex					
Model 1	0.13 (0.04, 0.21)	-0.07 (-0.16, 0.01)	-0.13 (-0.30, 0.04)		
Model 2	0.13 (0.04, 0.22)	-0.07 (-0.16, 0.01)	-0.13 (-0.30, 0.04)	0.00 (-0.09, 0.09)	
Model 3	0.09 (-0.02, 0.21)	-0.07 (-0.16, 0.01)	-0.13 (-0.30, 0.04)	0.00 (-0.09, 0.08)	0.08 (-0.09, 0.25)
Lateral orbitofrontal cortex					
Model 1	0.02 (-0.06, 0.11)	-0.17 (-0.26, -0.09)	-0.22 (-0.38, -0.05)		
Model 2	0.03 (-0.06, 0.12)	-0.17 (-0.25, -0.08)	-0.22 (-0.38, -0.05)	0.04 (-0.05, 0.13)	
Model 3	0.03 (-0.08, 0.15)	-0.17 (-0.25, -0.08)	-0.22 (-0.39, -0.05)	0.04 (-0.05, 0.13)	-0.01 (-0.18, 0.16)
Medial orbitofrontal cortex					
Model 1	0.10 (0.01, 0.18)	-0.01 (-0.09, 0.08)	-0.15 (-0.32, 0.02)		
Model 2	0.09 (0.00, 0.18)	-0.01 (-0.10, 0.07)	-0.15 (-0.32, 0.02)	-0.04 (-0.13, 0.04)	
Model 3	0.10 (-0.02, 0.21)	-0.01 (-0.10, 0.07)	-0.15 (-0.32, 0.02)	-0.04 (-0.13, 0.05)	-0.02 (-0.19, 0.15)

Abbreviation: OBV, olfactory bulb volume

[a] Volumetric measures (including OBV) from the right and left side were averaged, head-size adjusted, and normalized.

[b] Separate multivariable linear regressions were performed for each regional brain volumes with adjustment for age, sex, and nasal patency:

Model 1: central olfactory volume ~ OBV + age + sex + nasal patency

Model 2: central olfactory volume ~ OBV + age + sex + nasal patency + OBV × age

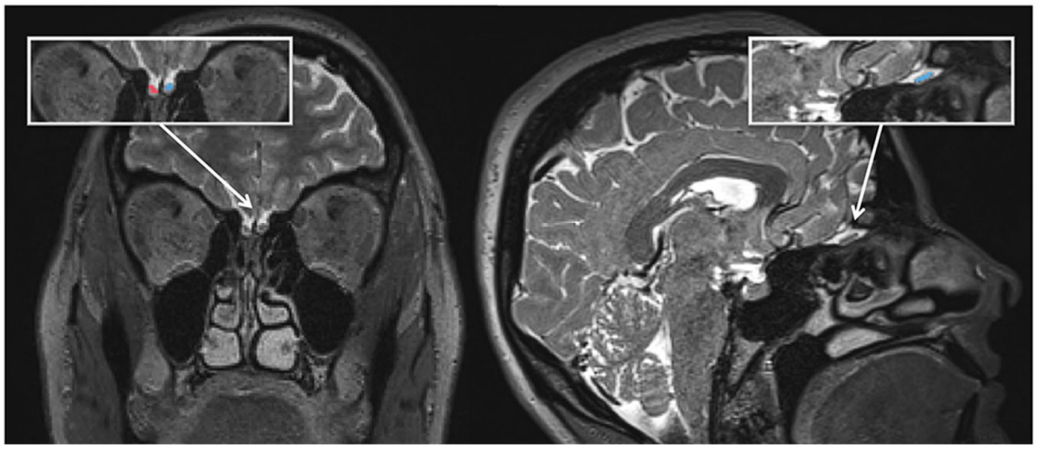
Model 3: central olfactory volume ~ OBV + age + sex + nasal patency + OBV × age + OBV × sex

eTable 6. Mediation Effect of Central Olfactory Structure Volumes of the Association Between Olfactory Bulb Volume and Olfactory Function[a]

Volume[b] of	Models [c, d]	Indirect effect	Direct effect	Total effect	Moderated mediation index[e]
Amygdala	Model A	0.003 (-0.005, 0.024)	0.508 (0.342, 0.711)	0.512 (0.344, 0.714)	
	Model B				0.010 (0.000, 0.031)
	1-SD below	-0.009 (-0.034, 0.001)	0.394 (0.175, 0.628)	0.385 (0.166, 0.623)	
	mean age	0.001 (-0.007, 0.018)	0.539 (0.363, 0.743)	0.540 (0.362, 0.747)	
	1-SD above	0.012 (-0.002, 0.045)	0.683 (0.404, 0.982)	0.695 (0.405, 0.992)	
Hippocampus	Model A	-0.001 (-0.019, 0.012)	0.513 (0.348, 0.715)	0.512 (0.344, 0.714)	
	Model B				0.022 (0.007, 0.051)
	1-SD below	-0.026 (-0.063, -0.007)	0.429 (0.203, 0.660)	0.403 (0.187, 0.643)	
	mean age	-0.004 (-0.024, 0.007)	0.556 (0.378, 0.765)	0.552 (0.377, 0.762)	
	1-SD above	0.017 (-0.001, 0.055)	0.683 (0.405, 0.973)	0.701 (0.415, 0.996)	
Insular cortex	Model A	-0.014 (-0.041, 0.003)	0.526 (0.355, 0.725)	0.512 (0.344, 0.714)	
	Model B				-0.003 (-0.025, 0.014)
	1-SD below	-0.011 (-0.039, 0.005)	0.389 (0.164, 0.626)	0.378 (0.156, 0.612)	
	mean age	-0.014 (-0.039, 0.002)	0.558 (0.377, 0.764)	0.544 (0.360, 0.747)	
	1-SD above	-0.017 (-0.061, 0.009)	0.727 (0.417, 1.038)	0.710 (0.397, 1.008)	
Medial orbitofrontal cortex	Model A	-0.002 (-0.026, 0.014)	0.513 (0.339, 0.703)	0.512 (0.344, 0.714)	
	Model B				-0.007 (-0.041, 0.006)
	1-SD below	0.006 (-0.009, 0.038)	0.372 (0.156, 0.601)	0.378 (0.163, 0.620)	
	mean age	0.000 (-0.019, 0.017)	0.542 (0.363, 0.736)	0.541 (0.362, 0.748)	
	1-SD above	-0.007 (-0.056, 0.014)	0.711 (0.402, 1.006)	0.704 (0.401, 1.004)	

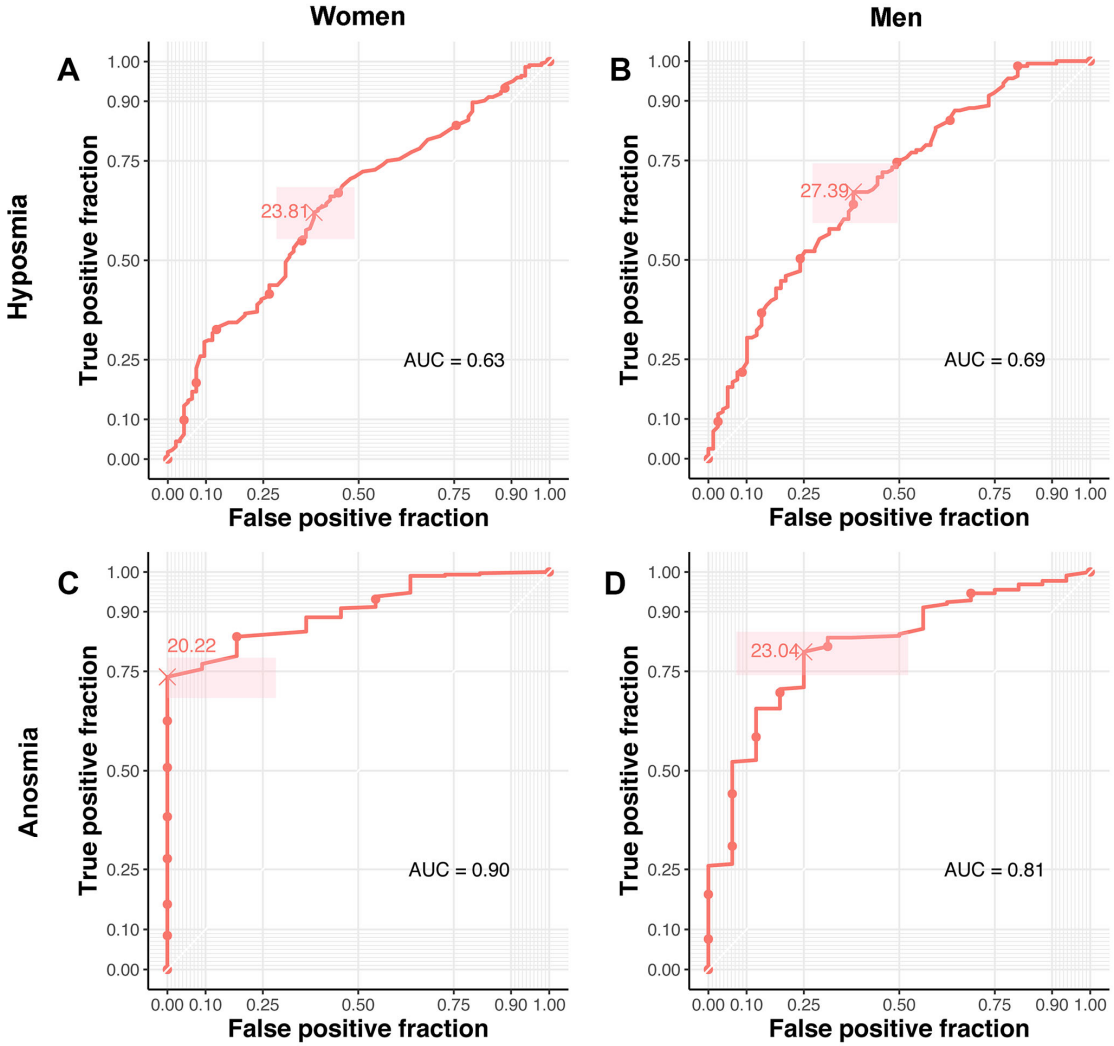
[a] The data are expressed as estimate (95% CI).
[b] Separate mediation analyses (OBV as the independent variable, the volume of each central olfactory structure as the mediator and SIT-12 as the outcome variable) were performed for each central olfactory structures. Volumetric measures (including OBV) from the right and left side were averaged, head-size adjusted and normalized.
[c] Model A: without age as a moderator; Model B: with age as a moderator.
[d] The estimate (95% CI) of moderated mediation analysis was reported for mean age and 1-SD below or above the mean age.
[e] The moderated mediation index and interaction effects were presented only for Model B.

eFigure 1. Coronal and Sagittal Depictions of the Annotated Olfactory Bulb Volumes (OBVs) on T2-Weighted Images



Abbreviation: OBV, olfactory bulb volume.
The left and right OBV are labeled in blue and red, respectively.

eFigure 2. The Optimal Cut-off Points for Detecting Hyposmia and Anosmia Based on Mean OBV



Abbreviations: OBV, olfactory bulb volume; AUC, area under the curve.
Using Youden's index, the optimal cut-off points for detecting hyposmia (defined as a SIT-12 score of 9 or lower) based on mean OBV were ≤ 23.81 mm^3 for females and ≤ 27.39 mm^3 for males. These values corresponded to areas under the curve (AUC) of the receiver operating characteristic (ROC) curve of 0.63 (95% CI: 0.57 to 0.70) for females, and 0.69 (95% CI: 0.62 to 0.76) for males, respectively (**eFigure 2A** and **B**). Similarly, the optimal cut-off points for detecting anosmia (defined as a SIT-12 score of 6 or lower) based on mean OBV were ≤ 20.22 mm^3 for females and ≤ 23.04 mm^3 for males. These values corresponded to AUCs of the ROC curve of 0.90 (95% CI: 0.85 to 0.96) for females, and 0.81 (95% CI: 0.73 to 0.90) for males, respectively (**eFigure 2C** and **D**).
The optimal cut-off point is indicated by a cross and the pink rectangle around this point represents the corresponding 95% CIs for the true and false positive fractions.