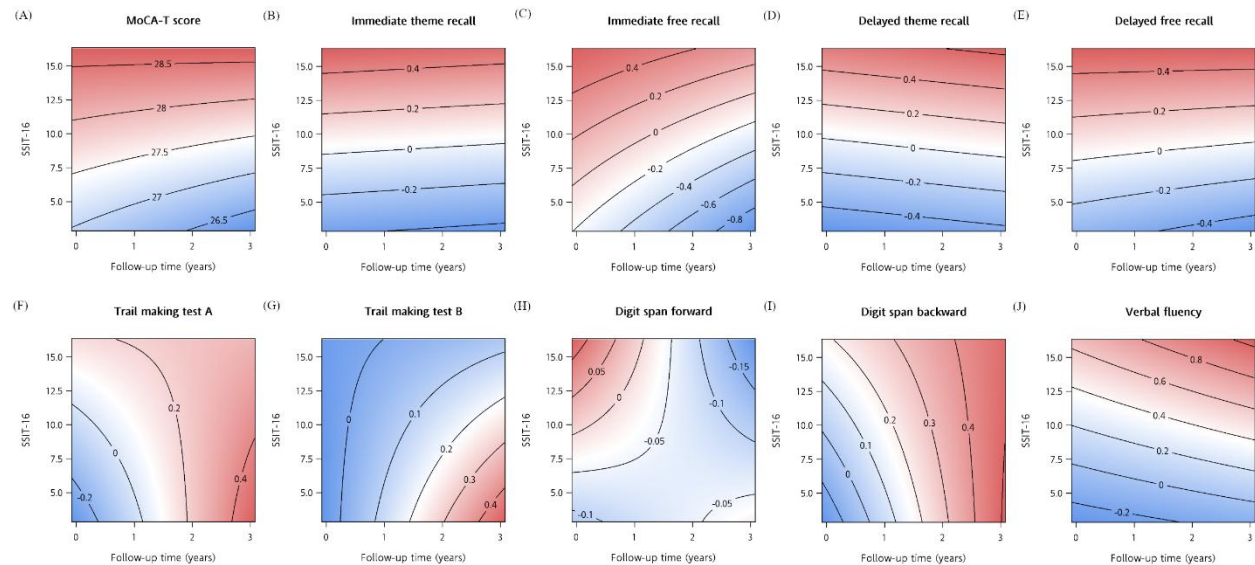


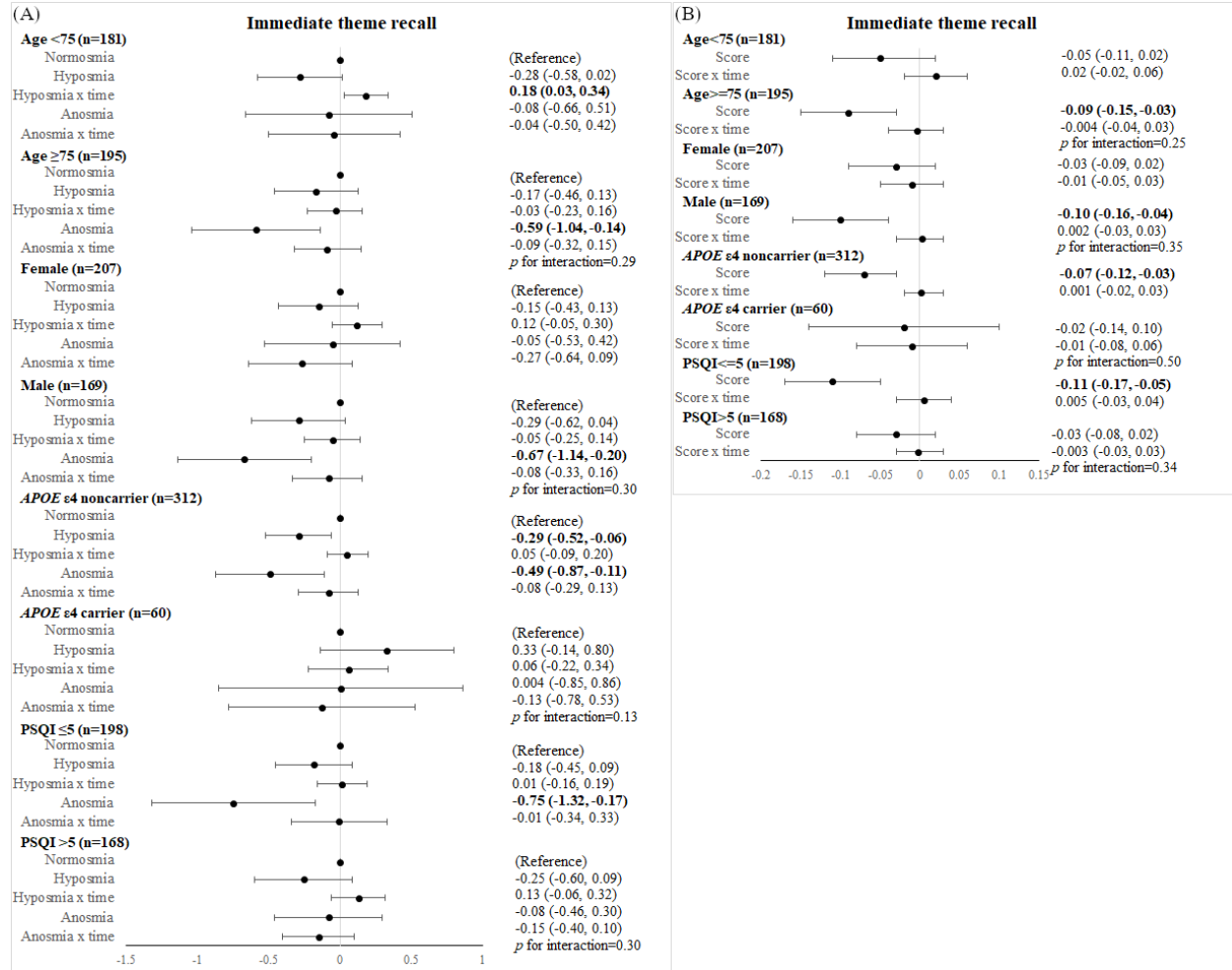
# Supplementary Material

## Association Between Olfactory Dysfunction and Cognitive Impairment in Dementia-Free Older Adults: A Prospective Cohort Study in Taiwan

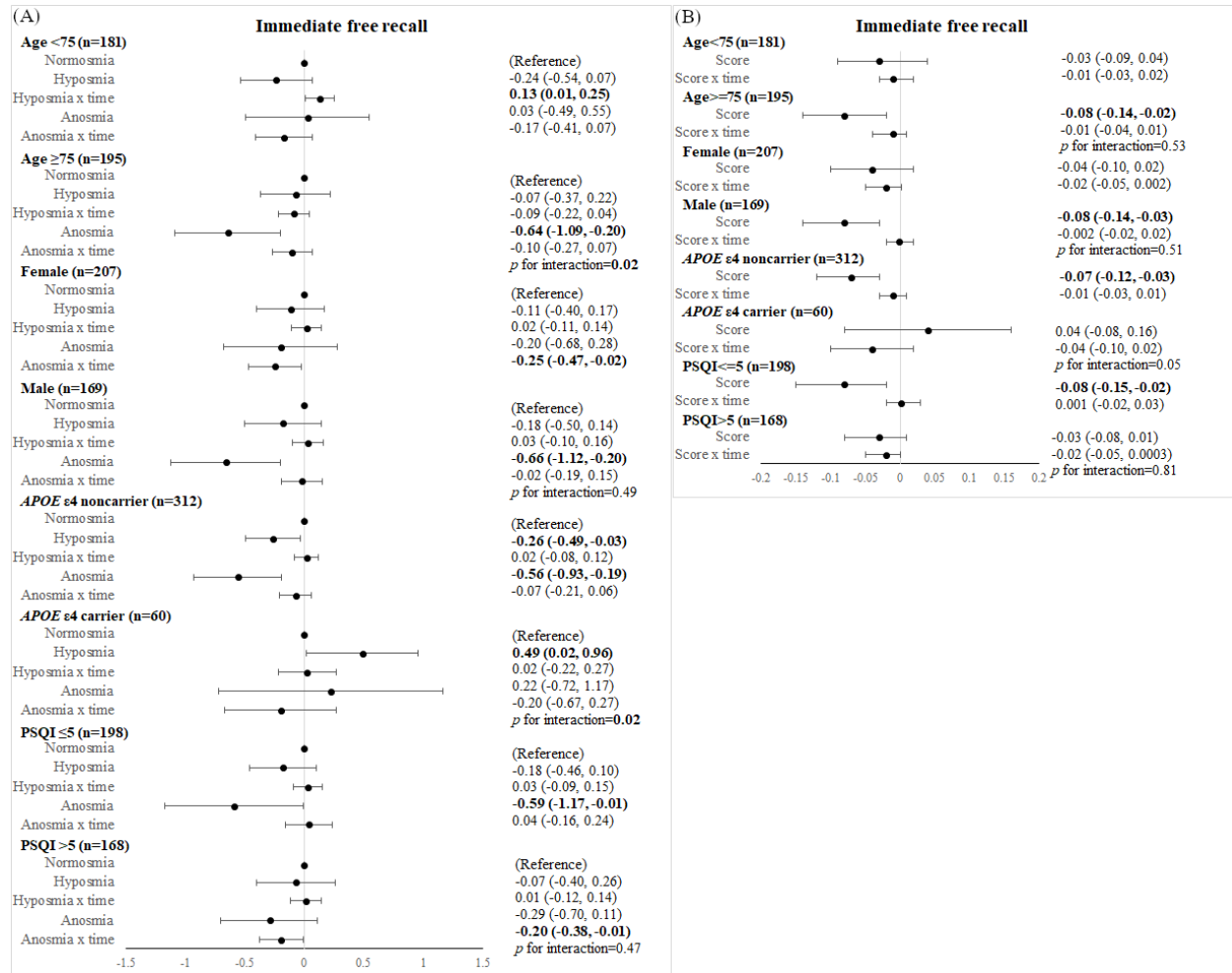
Supplementary Figure 1. The contour plots (Panels A to J) illustrating the 3-dimensional relationship with the follow-up time and 16-item Sniffin' Sticks Identification Test (SSIT-16) score plotted on the x- and y-axis, respectively, and the predicted cognitive scores represented by contours. Plots generated using multivariable adjusted models with the covariates listed in Table 2 Footnotes a-j.



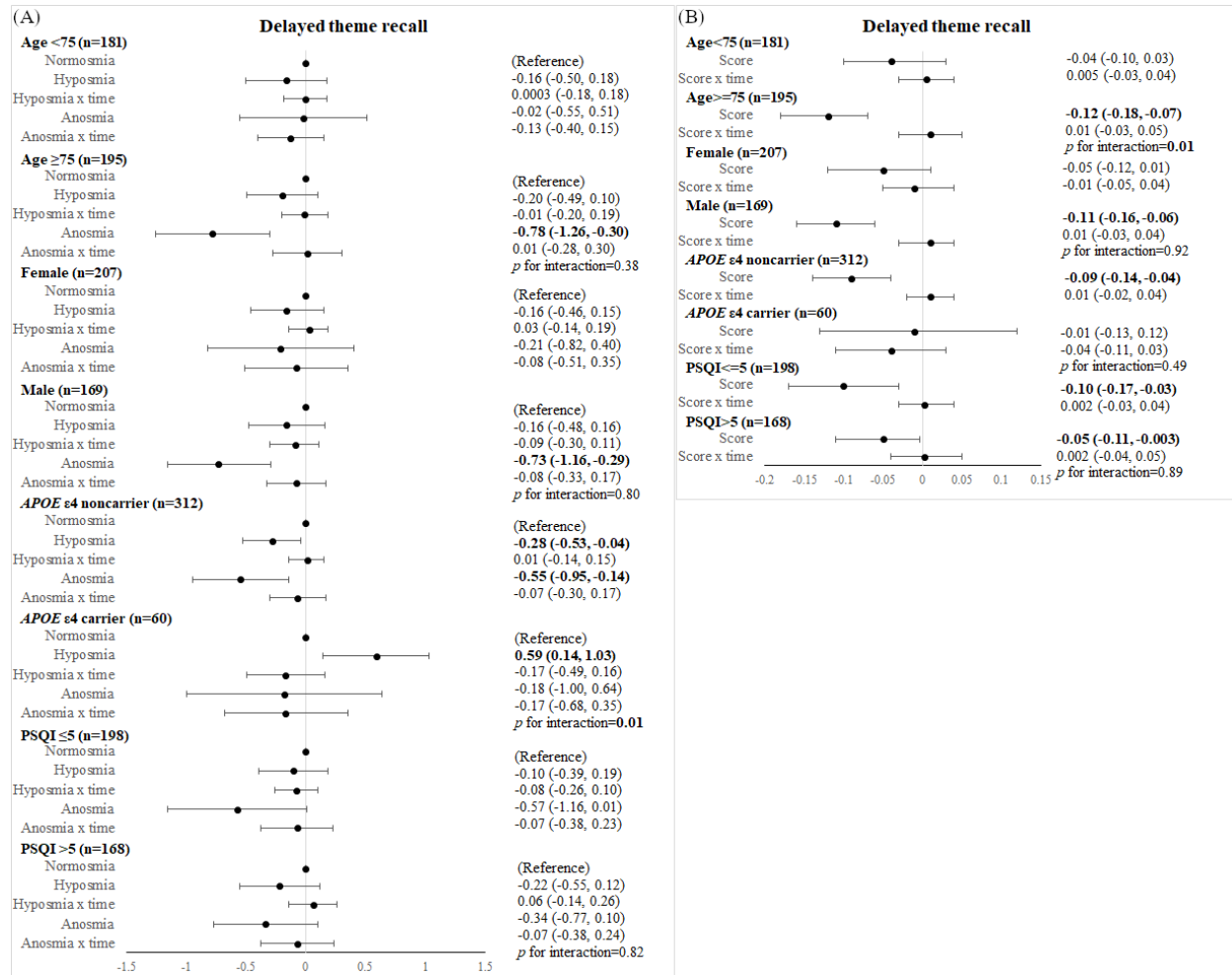
Supplementary Figure 2. The association of olfactory levels (A) and scores (B) with immediate theme recall according to subgroups of age, sex, *APOE*  $\epsilon 4$  status, PSQI score.



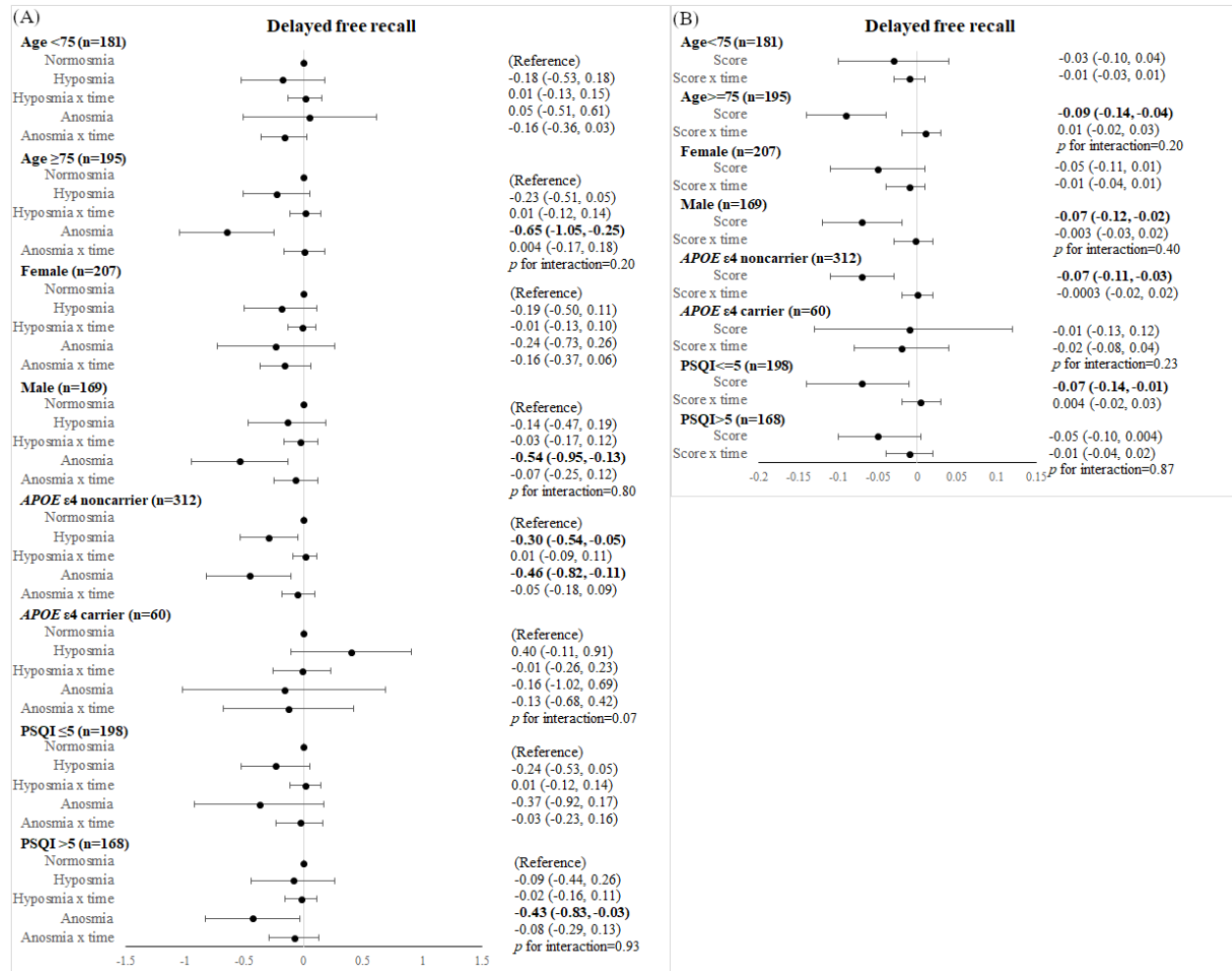
Supplementary Figure 3. The association of olfactory levels (A) and scores (B) with immediate free recall according to subgroups of age, sex, *APOE*  $\epsilon 4$  status, and PSQI score.



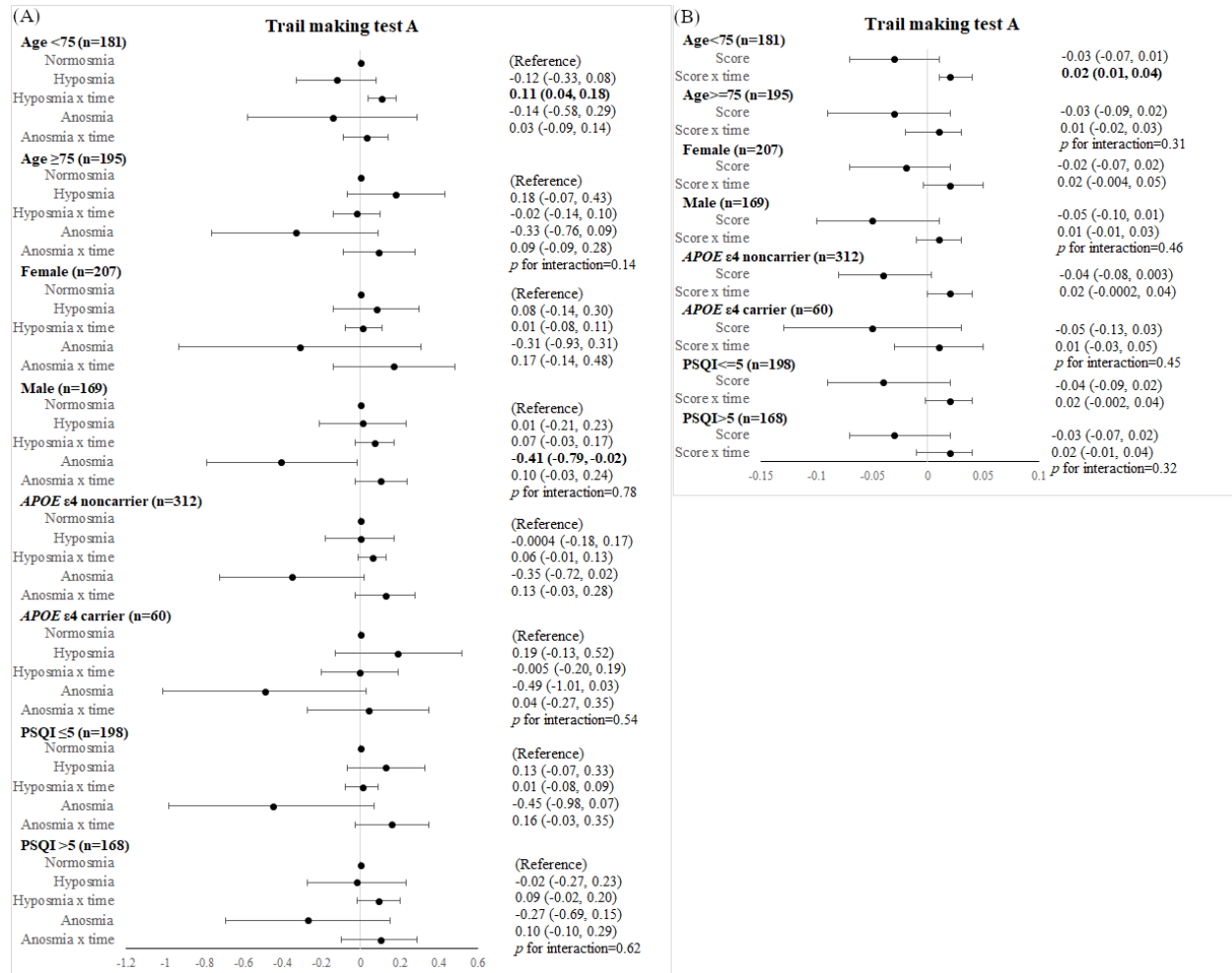
Supplementary Figure 4. The association of olfactory levels (A) and scores (B) with delayed theme recall according to subgroups of age, sex, *APOE*  $\epsilon 4$  status, and PSQI score.



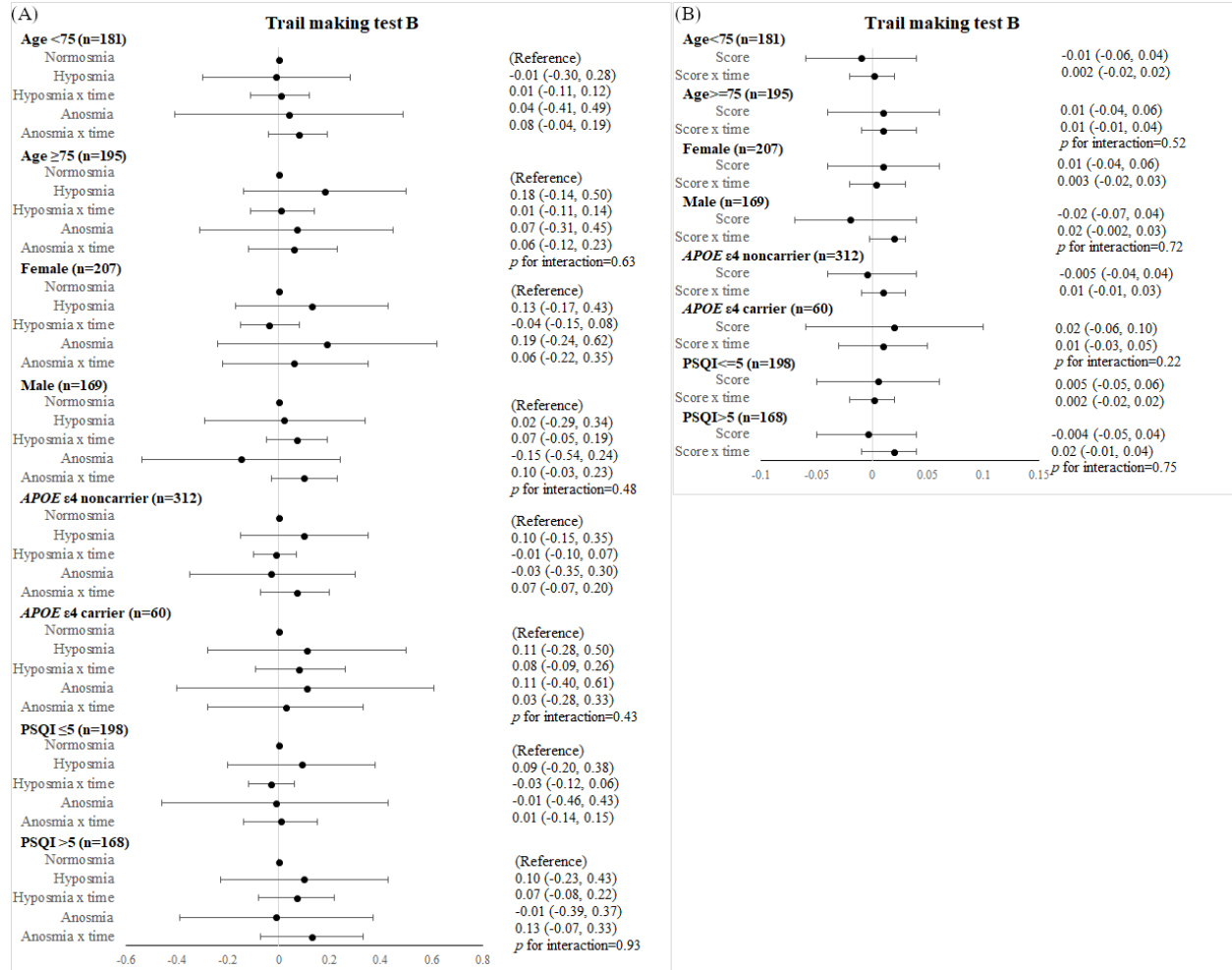
Supplementary Figure 5. The association of olfactory levels (A) and scores (B) with delayed free recall according to subgroups of age, sex, *APOE*  $\epsilon 4$  status, and PSQI score.



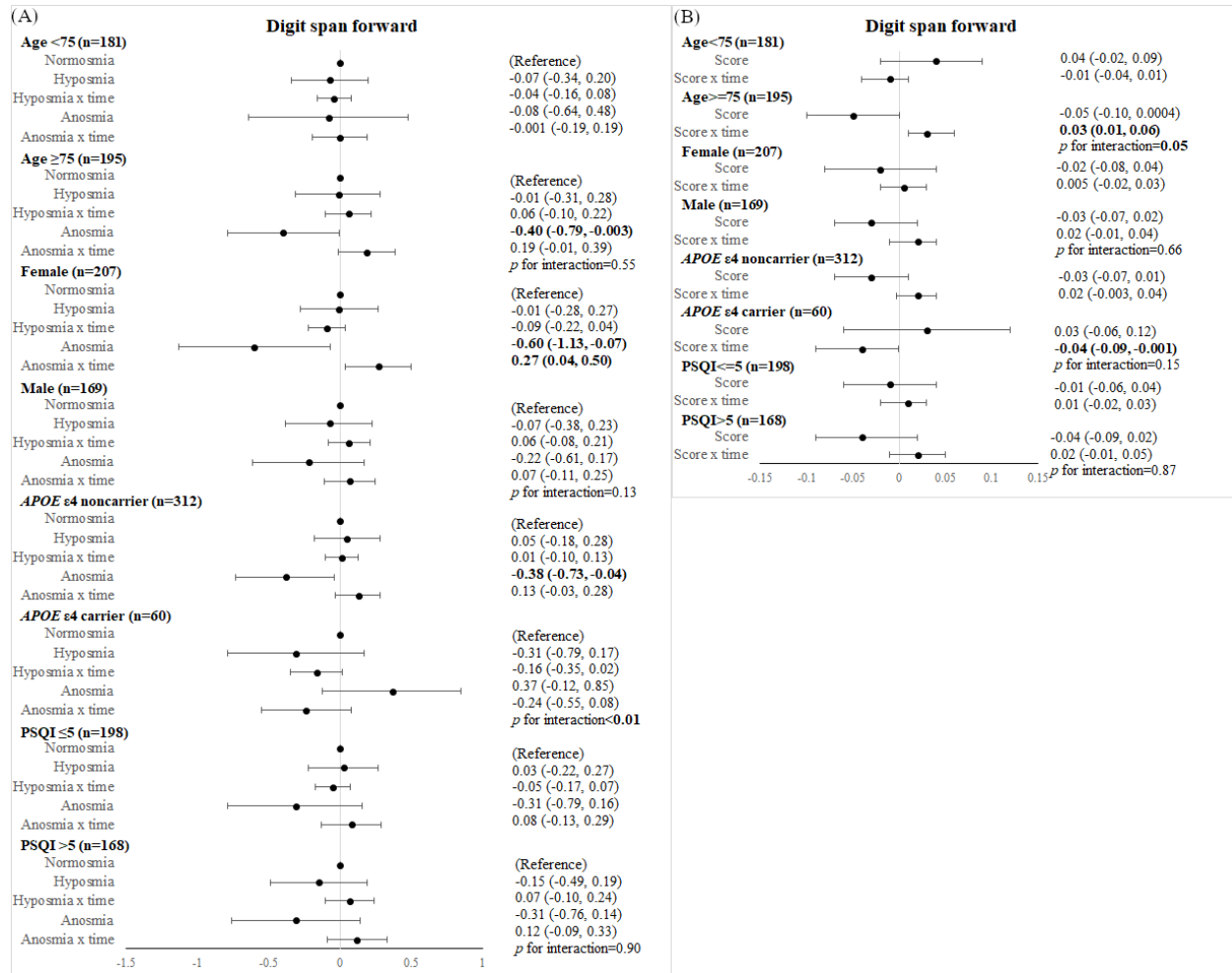
Supplementary Figure 6. The association of olfactory levels (A) and scores (B) with Trail Making Test A according to subgroups of age, sex, *APOE*  $\epsilon 4$  status, and PSQI score.



Supplementary Figure 7. The association of olfactory levels (A) and scores (B) with Trail Making Test B according to subgroups of age, sex, *APOE*  $\epsilon 4$  status, and PSQI score.

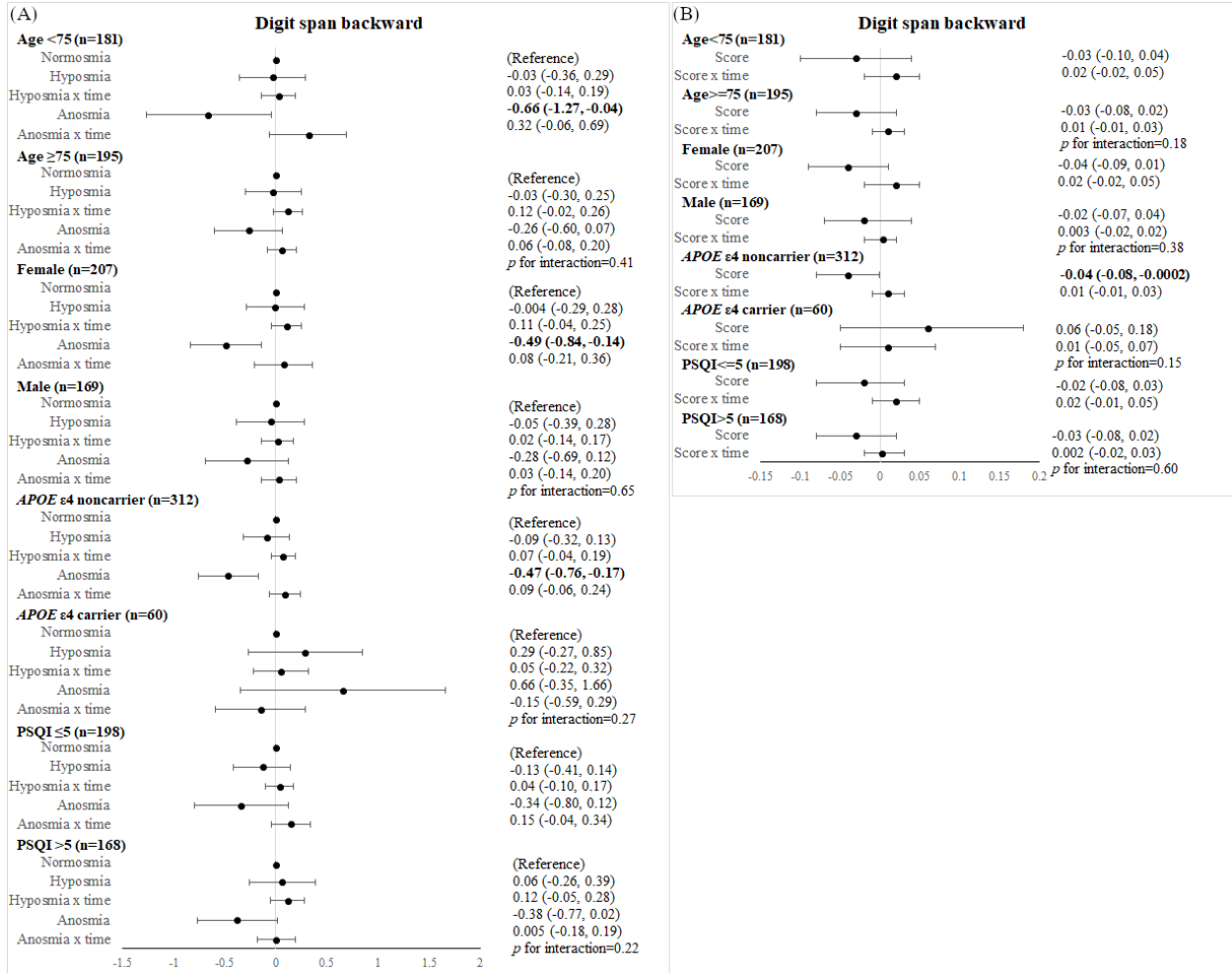


Supplementary Figure 8. The association of olfactory levels (A) and scores (B) with digit span forward according to subgroups of age, sex, *APOE*  $\epsilon 4$  status, and PSQI score.

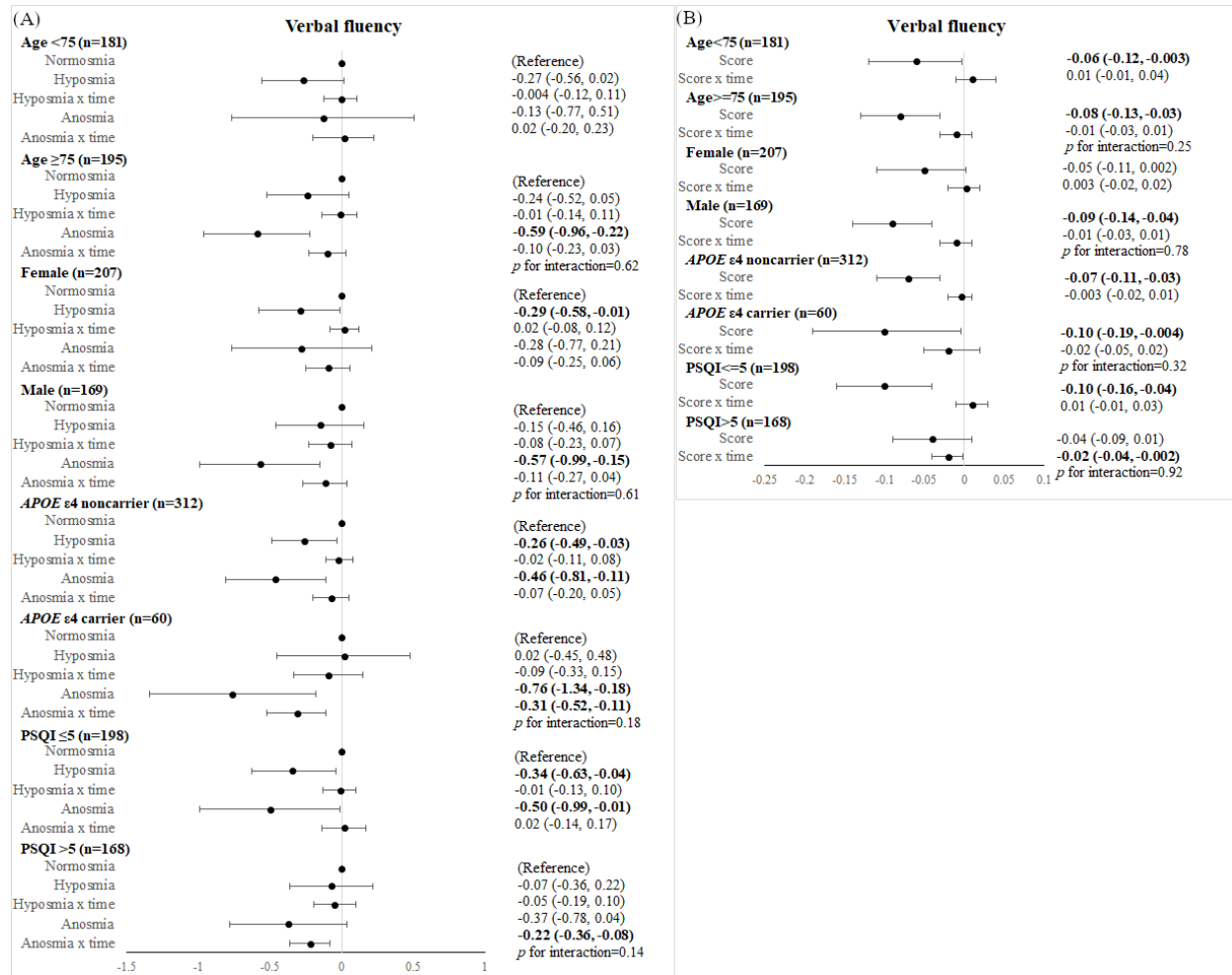




Supplementary Figure 9. The association of olfactory levels (A) and scores (B) with digit span backward according to subgroups of age, sex, *APOE*  $\epsilon 4$  status, and PSQI score.



Supplementary Figure 10. The association of olfactory levels (A) and scores (B) with verbal fluency according to subgroups of age, sex, *APOE*  $\epsilon 4$  status, and PSQI score.



In Supplementary Figures 2-10, the confidence intervals have not been adjusted for multiple comparisons; hence, definitive effects for the subgroups cannot be inferred.

Supplementary Table 1

The comparisons of cognitive variables and other covariates between baseline (2015-2017) and follow-up (2017-2019)

Cognitive test	Baseline (n=376)	Follow-up (n=327)	Difference <sup>a</sup>	p
	Mean (SD)			
MoCA-T	27.5 (1.9)	27.4 (2.6)	-0.1	0.327
LM-Immediate theme recall	16.3 (3.7)	17.1 (4.0)	0.8	<b>0.001</b>
LM-Immediate free recall	37.7 (10.8)	39.2 (11.2)	1.5	<b>0.017</b>
LM-Delayed theme recall	10.3 (3.0)	10.7 (3.3)	0.4	0.085
LM-Delayed free recall	22.6 (8.7)	23.8 (9.6)	1.2	<b>0.024</b>
Trail Making Test A <sup>b</sup>	50.6 (25.5)	47.4 (17.1)	-3.2	0.191
Trail Making Test B <sup>b</sup>	151.5 (73.5)	151.2 (76.9)	-0.3	<b>0.024</b>
Digit span forward	12.8 (2.3)	12.5 (2.4)	-0.3	<b>&lt;0.001</b>
Digit span backward	7.0 (2.5)	7.4 (2.5)	0.4	0.106
Verbal fluency	35.7 (8.2)	37.2 (8.9)	1.5	<b>&lt;0.001</b>
Age (y)	75.6 (4.8)	77.2 (4.5)	1.6	<b>&lt;0.001</b>
BMI (kg/m <sup>2</sup> )	23.6 (3.1)	23.8 (3.2)	0.2	<b>&lt;0.001</b>
ADL score	99.3 (3.0)	98.7 (3.6)	-0.6	<b>0.001</b>
IADL score	7.8 (0.7)	7.9 (0.7)	0.1	0.729 <sup>c</sup>
	Number (%)			
Cigarette smoking	56 (14.9)	58 (15.4)	0.5	0.500 <sup>d</sup>
Alcohol consumption	91 (24.2)	104 (27.7)	3.5	<b>&lt;0.001<sup>d</sup></b>
Depressive symptom	26 (6.9)	26 (8.0)	1.1	0.248
Hypertension	253 (67.3)	221 (67.6)	0.3	0.210 <sup>d</sup>
Diabetes	71 (18.9)	65 (19.9)	1.0	0.109 <sup>d</sup>
Dyslipidemia	232 (61.7)	212 (56.4)	-5.3	<b>0.016</b>
Respiratory disease	60 (16.0)	82 (25.2)	9.2	<b>&lt;0.001</b>

<sup>a</sup>Difference in means for continuous variables and in percentages for categorical variables between the baseline and follow-up. The paired *t*-test was used to compare continuous variables and McNemar's test to compare categorical variables.

<sup>b</sup>Trail Making Test A and B scores are multiplied by -1.

<sup>c</sup>The Wilcoxon signed-rank test was used to compare nonnormally distributed difference in means.

<sup>d</sup>The exact McNemar's test was used to compare correlated categorical variables with discordant pairs <20.

SD, standard deviation; MoCA-T, Taiwanese version of Montreal Cognitive Assessment; LM, logical memory; BMI: body mass index; ADL, activity of daily living; IADL, instrumental activity of daily living.

Supplementary Table 2

Association of olfactory function with global and domain-specific cognition over two years (n=369)

Cognitive function	Global cognitive function	Logical memory				Trail Making Test		Digit span	Verbal fluency	
	MoCA-T $\hat{\beta}$ (95% CI) <sup>a</sup>	Immediate theme recall $\hat{\beta}$ (95% CI) <sup>b</sup>	Immediate free recall $\hat{\beta}$ (95% CI) <sup>c</sup>	Delayed theme recall $\hat{\beta}$ (95% CI) <sup>d</sup>	Delayed free recall $\hat{\beta}$ (95% CI) <sup>e</sup>	A $\hat{\beta}$ (95% CI) <sup>f</sup>	B $\hat{\beta}$ (95% CI) <sup>g</sup>	Forward $\hat{\beta}$ (95% CI) <sup>h</sup>	Backward $\hat{\beta}$ (95% CI) <sup>i</sup>	$\hat{\beta}$ (95% CI) <sup>j</sup>
Odor identification										
SSIT score	<b>-0.14</b> (-0.22, -0.06)	<b>-0.07</b> (-0.11, -0.03)	<b>-0.06</b> (-0.10, -0.02)	<b>-0.08</b> (-0.13, -0.04)	<b>-0.06</b> (-0.10, -0.02)	-0.03 (-0.07, 0.004)	0.002 (-0.03, 0.04)	-0.01 (-0.05, 0.02)	-0.03 (-0.06, 0.01)	<b>-0.07</b> (-0.11, -0.03)
SSIT score×time	-0.001 (-0.06, 0.06)	0.004 (-0.02, 0.03)	-0.01 (-0.03, 0.01)	0.01 (-0.02, 0.03)	-0.0004 (-0.02, 0.02)	<b>0.02</b> ( <b>0.01, 0.04</b> )	0.01 (-0.004, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	-0.003 (-0.02, 0.01)
Normosmia <sup>a</sup>	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Hyposmia <sup>a</sup>	<b>-0.43</b> (-0.84, -0.03)	-0.19 (-0.40, 0.02)	-0.13 (-0.34, 0.09)	-0.14 (-0.37, 0.08)	-0.17 (-0.40, 0.05)	0.03 (-0.13, 0.18)	0.09 (-0.12, 0.31)	-0.02 (-0.22, 0.19)	-0.03 (-0.24, 0.19)	<b>-0.22</b> (-0.43, -0.01)
Hyposmia×time	0.19 (-0.06, 0.44)	0.06 (-0.07, 0.19)	0.02 (-0.07, 0.11)	-0.01 (-0.14, 0.12)	0.002 (-0.09, 0.10)	0.05 (-0.02, 0.12)	0.02 (-0.07, 0.10)	-0.01 (-0.11, 0.09)	0.07 (-0.04, 0.18)	-0.02 (-0.11, 0.07)
Anosmia <sup>a</sup>	<b>-1.08</b> (-1.74, -0.42)	<b>-0.42</b> (-0.77, -0.06)	<b>-0.45</b> (-0.80, -0.10)	<b>-0.48</b> (-0.86, -0.10)	<b>-0.42</b> (-0.75, -0.08)	-0.34 (-0.69, 0.01)	0.02 (-0.27, 0.32)	-0.26 (-0.59, 0.07)	<b>-0.34</b> (-0.63, -0.04)	<b>-0.45</b> (-0.77, -0.12)
Anosmia×time	-0.37 (-1.00, 0.27)	-0.07 (-0.27, 0.13)	-0.08 (-0.22, 0.06)	-0.05 (-0.27, 0.16)	-0.05 (-0.19, 0.09)	<b>0.14</b> ( <b>0.01, 0.28</b> )	0.08 (-0.04, 0.20)	0.08 (-0.07, 0.23)	0.06 (-0.08, 0.21)	-0.10 (-0.21, 0.01)

For continuous (SSIT scores) or categorical (normosmia, hyposmia, anosmia) olfactory function variables, GLMMs were used to estimate  $\hat{\beta}$  coefficients for cognitive variables (MoCA-T scores or z scores of cognitive domains).

<sup>a</sup>Model covariates: olfaction, time, olfaction by time, age, sex, education level, *APOE* ε4 status, depression, sleep quality, respiratory disease, smoking, hypertension, IADL, practice effect.

<sup>b</sup>Model covariates: olfaction, time, olfaction by time, age, sex, education level, *APOE* ε4 status, depression, sleep quality, respiratory disease, smoking, IADL, practice effect.

<sup>c</sup>Model covariates: olfaction, time, olfaction by time, age, sex, sex by time, education level, *APOE* ε4 status, depression, sleep quality, respiratory disease, smoking, practice effect.

<sup>d</sup>Model covariates: olfaction, time, olfaction by time, age, sex, sex by time, education level, *APOE* ε4 status, depression, sleep quality, respiratory disease, smoking, IADL, practice effect.

<sup>e</sup>Model covariates: olfaction, time, olfaction by time, age, sex, education level, *APOE* ε4 status, depression, sleep quality, respiratory disease, smoking, practice effect.

<sup>f</sup>Model covariates: olfaction, time, olfaction by time, age, sex, education level, education level by time, *APOE* ε4 status, depression, sleep quality, respiratory disease, smoking, hypertension, IADL, practice effect.

<sup>g</sup>Model covariates: olfaction, time, olfaction by time, age, sex, sex by time, education level, education level by time, *APOE* ε4 status, *APOE* ε4 status by time, depression, sleep quality, sleep quality by time, respiratory disease, smoking, hypertension, IADL, practice effect.

<sup>h</sup>Model covariates: olfaction, time, olfaction by time, age, sex, sex by time, education level, *APOE* ε4 status, *APOE* ε4 status by time, depression, sleep quality, respiratory disease, smoking, hypertension, IADL, practice effect.

<sup>i</sup>Model covariates: olfaction, time, olfaction by time, age, sex, sex by time, education level, *APOE* ε4 status, *APOE* ε4 status by time, depression, sleep quality, respiratory disease, smoking, hypertension, IADL, practice effect.

<sup>j</sup>Model covariates: olfaction, time, olfaction by time, age, sex, education level, *APOE* ε4 status, depression, sleep quality, respiratory disease, smoking, IADL, practice effect.

Numbers in bold indicated statistically significant findings ( $p < 0.05$ ).

MoCA-T, Taiwanese version of Montreal Cognitive Assessment; SSIT, Sniffin' Stick Identification Test; CI, confidence interval; GLMM, generalized linear mixed model; *APOE*, apolipoprotein E; IADL, instrumental activity of daily living