

Supplementary Table 1. Clinical characteristic according to homeostasis model assessment of insulin resistance (HOMA-IR) levels

Variables	HOMA-IR levels (%)		
	<1.6	1.6-2.4	≥2.5
Number of participants	2,344	556	197
Age, y	71.1 (5.1)	71.0 (4.9)	71.7 (5.5)
Women, %	60.2	58.1	60.9
<i>ApoE</i> $\epsilon 4$, present, %	17.4	19.8	16.2
Hypertension, %	66.3	79.5	83.2*
BMI, kg/m ²	22.3 (2.7)	24.9 (3.3)	26.3 (3.3)*
Serum LDL-chol, mg/dL	122.9 (30.7)	121.9 (30.3)	116.4 (32.7)
Serum HDL-chol, mg/dL	67.3 (16.8)	58.1 (15.1)	54.0 (13.5)*
Education \leq 9 y, %	20.0	23.2	22.8
Current smoking habits, %	7.8	7.2	8.6
Current alcohol intakes, %	47.2	44.8	35.5*
Regular exercise, %	46.3	41.0	32.0*
Estimated intracranial volume, $\times 10^3$ mm ³	1385.1 (147.7)	1373.1 (148.9)	1365.8 (140.8)*

Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; HDL-chol, high-density lipoprotein cholesterol; HOMA- β , homeostasis model assessment of beta cell function; LDL-chol, low-density lipoprotein cholesterol

Values were shown as mean values (standard deviations or frequencies).

* p for trend < 0.05.

Supplementary Table 2. Clinical characteristic by presence or absence of each risk factors

	Overall	Age, years		Gender		<i>ApoE</i> $\epsilon 4$, present		Hypertension		BMI	
		<75	≥ 75	Man	Woman	No	Yes	No	Yes	<25.0	≥ 25.0
Number of participants	7,400	5,137	2,263	3,030	4,370	5,807	1,202	2,015	5,268	5,265	2,019
Age, y	72.1 (5.6)	69.0 (2.7)	79.2 (3.9)	71.9 (5.5)	72.3 (5.7)	72.3 (5.7)	71.3 (5.0)	70.9 (5.0)	72.6 (5.8)	72.2 (5.6)	71.9 (5.5)
Women, %	59.1	58.5	60.3	-	-	59.2	58.9	66.0	56.5	61.3	53.6
<i>ApoE</i> $\epsilon 4$, present, %	17.1	18.6	13.9	17.2	17.1	-	-	17.1	17.2	17.2	17.0
Hypertension, %	72.3	69.0	79.8	77.0	69.1	71.9	72.2	-	-	67.9	83.4
BMI, kg/m ²	23.3 (3.3)	23.4 (3.3)	23.3 (3.2)	23.8 (2.9)	23.0 (3.4)	23.3 (3.3)	23.3 (3.3)	22.3 (2.9)	23.8 (3.3)	21.8 (2.0)	27.4 (2.3)
Serum LDL-chol, mg/dL	118.1 (30.3)	120.3 (30.4)	113.1 (29.5)	111.5 (29.6)	122.7 (30.0)	117.5 (30.3)	121.6 (30.9)	123.2 (30.1)	116.1 (30.2)	119.1 (30.5)	115.5 (29.7)
Serum HDL-chol, mg/dL	62.9 (16.9)	63.9 (17.3)	60.8 (15.9)	57.9 (16.1)	66.4 (16.6)	63.0 (17.0)	62.8 (16.7)	65.2 (17.5)	62.1 (16.6)	65.4 (17.4)	56.6 (14.0)
Education ≤ 9 y, %	25.7	19.5	39.9	23.0	27.6	25.7	22.6	19.3	27.9	24.0	29.5
Current smoking habits, %	8.4	10.2	4.4	17.3	2.3	8.5	8.0	8.3	8.4	8.7	7.7
Current alcohol intakes, %	44.3	48.3	35.1	71.8	25.2	44.3	45.4	39.7	46.0	44.2	44.6
Regular exercise, %	43.7	43.1	45.0	44.6	43	43.6	46.1	45.0	43.4	47.0	35.9
Estimated intracranial volume, $\times 10^3$ mm ³	1419.2 (154.0)	1418.4 (155.7)	1421.0 (149.9)	1533.2 (132.4)	1340.2 (112.9)	1418.3 (154.0)	1421.4 (155.4)	1415.4 (150.8)	1419.8 (154.9)	1409.0 (152.6)	1444.0 (155.0)

(Continued) Supplementary Table 2. Clinical characteristic by presence or absence of each risk factors

	Serum LDL-chol		Serum HDL-chol		Education		Current smoking habits		Current alcohol intakes		Regular exercise		Estimated intracranial volume	
	<140	≥140	<40	≥40	≤9 y	>9 y	No	Yes	No	Yes	No	Yes	<1405.9 × 10 ³	≤1405.9 × 10 ³
Number of participants	5,552	1,638	400	6,790	1,899	5,484	6,718	617	4,089	3,247	4,065	3,152	3,700	3,700
Age, y	72.4 (5.7)	71.1 (5.0)	73.1 (6.1)	72.1 (5.6)	74.7 (6.0)	71.2 (5.2)	72.3 (5.7)	70.0 (4.4)	72.8 (5.9)	71.2 (5.1)	72.0 (5.8)	72.3 (5.4)	72.1 (5.6)	72.1 (5.6)
Women, %	56.0	70.2	32.3	60.8	63.3	57.5	63.0	15.9	79.3	33.6	59.7	58.1	85.8	32.3
<i>ApoE</i> ε4, present, %	16.3	19.9	16.5	17.2	15.4	17.7	17.2	16.3	16.9	17.5	16.5	18.0	16.7	17.6
Hypertension, %	73.6	66.9	78.6	71.7	79.1	70.0	72.3	72.5	70.1	75.2	72.7	71.4	71.5	73.2
BMI, kg/m ²	23.4 (3.3)	23.0 (3.0)	25.0 (3.1)	23.2 (3.2)	23.7 (3.3)	23.2 (3.3)	23.4 (3.0)	23.1 (3.1)	23.3 (3.4)	23.4 (3.0)	23.6 (3.4)	23.0 (3.0)	23.0 (3.3)	23.7 (3.2)
Serum LDL-chol, mg/dL	158.9 (20.9)	159.7 (18.0)	107.0 (32.7)	118.8 (30.1)	114.2 (29.8)	119.4 (30.4)	118.8 (30.3)	110.9 (30.0)	120.4 (30.0)	115.2 (30.6)	117.1 (30.8)	119.4 (29.6)	121.4 (30.2)	114.8 (30.1)
Serum HDL-chol, mg/dL	62.4 (17.0)	64.7 (16.7)	34.9 (3.7)	64.6 (16.0)	61.0 (16.1)	63.6 (17.2)	63.4 (16.8)	57.9 (17.3)	62.4 (16.5)	63.6 (17.5)	61.6 (16.4)	64.6 (17.5)	65.8 (16.8)	60.0 (16.5)
Education ≤9 y, %	26.3	21.6	31.3	24.9	-	-	26.0	21.6	28.7	21.9	28.3	21.5	28.6	22.8
Current smoking habits, %	9.2	5.6	15.9	8.0	7.1	8.9	-	-	4.5	13.4	10.1	6.3	4.2	12.7
Current alcohol intakes, %	46.1	38.6	38.3	44.7	37.7	46.6	41.9	70.5	-	-	42.2	47.1	32.1	56.5
Regular exercise, %	43.6	45.2	36.8	44.4	37.0	45.9	44.8	32.9	41.6	46.5	-	-	43.9	43.4
Estimated intracranial volume, × 10 ³ mm ³	1426.4 (154.6)	1390.3 (148.6)	1472.2 (156.3)	1415.0 (153.2)	1400.0 (152.9)	1425.9 (153.9)	1410.8 (151.5)	1506.0 (154.0)	1379.9 (140.1)	1467.5 (156.7)	1419.5 (154.3)	1417.8 (153.6)	-	-

Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol

Values were shown as mean values (standard deviations) or frequencies.

Classification of estimated intracranial volume used median values.

Supplementary Table 3. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subregions according to hemoglobinA_{1c} levels among non-diabetic participants

	Hemoglobin A _{1c} levels, %			p for trend	q-value of FDR correction
	<5.7 (n=3,187)	5.7-6.4 (n=2,546)	≥6.5 (n=0)		
Whole hippocampus, HV, mm ³	6187.947 (6140.402-6235.493)	6198.326 (6149.158-6247.495)	-	0.458	-
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	97.034 (95.637-98.431)	96.796 (95.325-98.214)	-	0.520	0.624
Fimbria, HV, mm ³	102.607 (99.631-105.583)	100.548 (97.470-103.625)	-	0.019*	0.114
Hippocampal fissure, HV, mm ³	346.067 (341.602-350.533)	348.317 (343.699-352.935)	-	0.087	0.261
Molecular_layer, HV, mm ³	802.592 (794.998-810.186)	804.343 (796.490-812.196)	-	0.443	0.590
GC ML DG, HV, mm ³	541.076 (536.202-545.949)	541.503 (536.463-546.543)	-	0.765	0.765
CA1, HV, mm ³	1213.239 (1201.965-1224.514)	1215.816 (1204.157-1227.476)	-	0.437	0.655
CA3, HV, mm ³	397.849 (393.234-402.465)	400.155 (395.382-404.927)	-	0.089	0.213
CA4, HV, mm ³	478.363 (474.107-482.620)	479.565 (475.163-483.966)	-	0.337	0.577
Subiculum, HV, mm ³	838.946 (831.122-846.771)	837.896 (829.804-845.988)	-	0.648	0.706
Presubiculum, HV, mm ³	560.948 (554.680-567.215)	558.687 (552.206-565.169)	-	0.220	0.440
Parasubiculum, HV, mm ³	109.728 (107.445-112.011)	108.462 (106.101-110.822)	-	0.059	0.236
Hippocampal tail, HV, mm ³	1045.565 (1033.637-1057.493)	1054.582 (1042.247-1066.917)	-	0.010*	0.120

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA-β, homeostasis model assessment of percent beta cell function; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus

or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 4. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subregions according to serum glycated albumin levels among non-diabetic participants

	Serum glycated albumin levels, %				p for trend	q-value of FDR correction
	<13.9 (n=1,626)	13.9-14.8 (n=1,706)	14.9-16.0 (n=1,578)	≥16.1 (n=768)		
Whole hippocampus, HV, mm ³	6181.675 (6129.961-6233.389)	6185.163 (6133.511-6236.816)	6199.915 (6147.757-6252.073)	6167.791 (6109.583-6225.999)	0.527	-
<i>Hippocampal subregions</i>						
HATA, HV, mm ³	97.498 (95.938-99.058)	97.795 (96.203-99.315)	97.954 (96.383-99.524)	97.534 (95.783-99.286)	0.854	0.854
Fimbria, HV, mm ³	103.050 (99.818-106.281)	102.798 (99.570-106.026)	101.883 (98.624-105.142)	97.859 (94.221-101.496)	0.003*	0.036 [†]
Hippocampal fissure, HV, mm ³	344.258 (339.429-349.087)	343.663 (338.840-348.486)	346.717 (341.847-351.588)	347.948 (342.512-353.383)	0.120	0.480
Molecular_layer, HV, mm ³	804.181 (795.920-812.443)	803.830 (795.579-812.082)	801.184 (792.851-809.516)	800.836 (791.537-810.165)	0.664	0.796
GC ML DG, HV, mm ³	540.910 (535.610-546.210)	540.711 (535.418-546.005)	542.532 (537.187-547.877)	537.094 (531.129-543.060)	0.145	0.435
CA1, HV, mm ³	1213.256 (1200.983-1225.528)	1211.417 (1199.159-1223.675)	1215.496 (1203.118-1227.874)	1209.176 (1195.362-1222.989)	0.642	0.856
CA3, HV, mm ³	397.123 (392.103-402.143)	398.255 (393.241-403.270)	400.307 (395.244-405.370)	397.380 (391.729-403.031)	0.311	0.622
CA4, HV, mm ³	477.785 (473.155-482.414)	477.945 (473.321-482.569)	480.209 (475.540-484.878)	476.441 (471.234-481.652)	0.236	0.566
Subiculum, HV, mm ³	838.860 (830.346-847.374)	837.846 (829.342-846.349)	839.414 (830.827-848.001)	833.474 (823.891-843.057)	0.445	0.762
Presubiculum, HV, mm ³	560.102 (553.288-566.917)	558.638 (551.832-565.444)	560.379 (553.507-567.252)	557.416 (549.746-565.086)	0.721	0.786
Parasubiculum, HV, mm ³	109.527 (107.047-112.007)	108.915 (106.438-111.393)	109.283 (106.782-111.785)	107.893 (105.102-110.685)	0.514	0.771
Hippocampal tail, HV, mm ³	1039.885 (1026.916-1052.855)	1047.827 (1034.873-1060.781)	1052.215 (1039.135-1065.296)	1053.881 (1039.283-1068.479)	0.038*	0.228

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 5. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subregions according to homeostasis model assessment of beta cell function (HOMA-β) levels among non-diabetic participants

	HOMA-β levels, %		p for trend	q-value of FDR correction
	≤30 (n=139)	>30 (n=2,579)		
Whole hippocampus, HV, mm ³	6106.078 (5988.242-6223.913)	6206.146 (6123.606-6288.685)	0.031*	-
<i>Hippocampal subregions</i>				
HATA, HV, mm ³	94.122 (91.160-97.882)	95.122 (92.768-97.477)	0.650	0.709
Fimbria, HV, mm ³	99.601 (92.103-107.098)	108.196 (102.944-113.448)	0.004*	0.048†
Hippocampal fissure, HV, mm ³	336.790 (325.836-347.744)	334.559 (326.886-342.232)	0.605	0.726
Molecular_layer, HV, mm ³	864.716 (845.627-883.805)	880.295 (866.924-893.666)	0.038*	0.152
GC ML DG, HV, mm ³	526.973 (515.260-538.686)	534.692 (526.487-542.896)	0.017*	0.102
CA1, HV, mm ³	1180.405 (1152.537-1208.273)	1195.335 (1175.814-1214.855)	0.174	0.261
CA3, HV, mm ³	393.128 (381.787-404.468)	396.257 (388.313-404.200)	0.484	0.645
CA4, HV, mm ³	465.390 (455.202-475.578)	471.058 (463.922-478.194)	0.158	0.316
Subiculum, HV, mm ³	807.831 (788.866-826.797)	823.361 (810.076-836.646)	0.038*	0.152
Presubiculum, HV, mm ³	537.608 (522.698-552.517)	545.632 (535.188-556.075)	0.172	0.294
Parasubiculum, HV, mm ³	109.124 (103.634-114.614)	109.923 (106.078-113.769)	0.712	0.712
Hippocampal tail, HV, mm ³	1026.781 (996.690-1056.873)	1046.275 (1025.197-1067.353)	0.100	0.240

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA-β, homeostasis model assessment of beta cell function; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E ε4, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 6. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subregions according to homeostasis model assessment of insulin resistance (HOMA-IR) levels

	HOMA-IR levels, %			p for trend	q-value of FDR correction
	<1.6 (n=2,344)	1.6-2.4 (n=556)	≥2.5 (n=197)		
Whole hippocampus, HV, mm ³	6204.847 (6128.106-6281.588)	6175.624 (6087.439-6263.809)	6159.157 (6051.619-6266.695)	0.378	-
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	95.357 (93.166-97.547)	94.692 (92.175-97.209)	94.981 (91.911-98.050)	0.673	1.009
Fimbria, HV, mm ³	107.462 (102.530-112.395)	107.443 (101.775-113.111)	105.801 (98.889-112.713)	0.821	0.985
Hippocampal fissure, HV, mm ³	338.230 (331.071-345.390)	336.653 (328.426-344.880)	334.242 (324.209-344.275)	0.549	1.098
Molecular_layer, HV, mm ³	880.071 (867.609-892.532)	874.931 (860.610-889.251)	873.615 (856.152-891.078)	0.386	2.316
GC ML DG, HV, mm ³	534.773 (527.124-542.421)	533.070 (524.281-541.860)	530.922 (520.204-541.640)	0.595	1.020
CA1, HV, mm ³	1197.294 (1179.159-1215.429)	1190.461 (1169.622-1211.301)	1195.738 (1170.325-1221.151)	0.545	1.308
CA3, HV, mm ³	395.261 (387.885-402.636)	394.583 (386.108-403.058)	391.951 (381.616-402.286)	0.714	0.952
CA4, HV, mm ³	0.0339 (0.0334-0.0344)	0.0341 (0.0335-0.0347)	0.0341 (0.0334-0.0348)	0.527	1.581
Subiculum, HV, mm ³	825.931 (813.633-838.228)	819.421 (805.289-833.553)	810.004 (792.771-827.237)	0.037*	0.444
Presubiculum, HV, mm ³	546.029 (536.393-555.666)	544.127 (533.053-555.201)	539.109 (525.605-552.614)	0.410	1.640
Parasubiculum, HV, mm ³	109.213 (105.632-112.794)	108.617 (104.502-112.732)	108.321 (103.303-113.340)	0.837	0.913
Hippocampal tail, HV, mm ³	1042.290 (1022.628-1061.953)	1038.961 (1016.366-1061.556)	1041.664 (1014.110-1069.218)	0.884	0.884

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA-IR, homeostasis model assessment of insulin resistance; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 7. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subregions according to homeostasis model assessment of insulin resistance (HOMA-IR) levels among non-diabetic participants

	HOMA-IR levels, %			p for trend	q-value of FDR correction
	<1.6 (n=2,140)	1.6-2.4 (n=451)	≥2.5 (n=127)		
Whole hippocampus, HV, mm ³	6206.000 (6123.148-6288.852)	6165.340 (6069.715-6260.964)	6162.896 (6037.719-6288.019)	0.312	-
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	95.235 (92.873-97.597)	94.623 (91.897-97.348)	93.608 (90.041-97.176)	0.465	0.697
Fimbria, HV, mm ³	107.815 (102.538-113.091)	107.172 (101.082-113.262)	104.414 (96.444-112.385)	0.574	0.688
Hippocampal fissure, HV, mm ³	334.875 (327.176-342.574)	333.747 (324.861-342.632)	334.629 (323.000-346.258)	0.914	0.914
Molecular_layer, HV, mm ³	880.415 (866.995-893.835)	873.282 (857.793-888.770)	872.832 (852.562-893.103)	0.255	1.020
GC ML DG, HV, mm ³	534.749 (526.516-542.983)	531.766 (522.263-541.269)	529.660 (517.223-542.097)	0.418	0.716
CA1, HV, mm ³	1195.587 (1176.002-1215.172)	1185.924 (1163.319-1208.528)	1192.612 (1163.029-1222.196)	0.364	0.728
CA3, HV, mm ³	396.301 (388.330-404.271)	394.632 (385.433-403.831)	394.969 (382.929-407.008)	0.824	0.898
CA4, HV, mm ³	471.255 (464.095-478.415)	468.151 (459.887-476.414)	466.690 (455.875-477.505)	0.333	0.999
Subiculum, HV, mm ³	823.884 (810.556-837.212)	816.670 (801.288-832.053)	808.480 (788.348-828.611)	0.083	0.996
Presubiculum, HV, mm ³	545.818 (535.340-556.296)	543.212 (531.119-555.305)	536.754 (520.927-552.582)	0.339	0.813
Parasubiculum, HV, mm ³	110.248 (106.932-114.103)	108.785 (104.434-113.235)	106.200 (100.376-112.025)	0.175	1.050
Hippocampal tail, HV, mm ³	1044.694 (1023.540-1065.848)	1014.124 (1016.709-1065.539)	1056.647 (1024.694-1088.601)	0.523	0.697

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA-IR, homeostasis model assessment of insulin resistance; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus

or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 8. Multiple linear-regression analysis about hemoglobinA_{1c} levels

	B	SE B	t	p for trend	q-value of FDR correction
Whole hippocampus	- 41.486	10.030	- 4.136	<0.01*	-
<i>Hippocampal subregions</i>					
HATA	- 0.918	0.293	- 3.131	0.002*	0.004†
Fimbria	- 4.834	0.629	- 7.689	<0.001*	<0.001†
Hippocampal fissure	1.059	0.948	1.117	0.264	0.264
Molecular_layer	- 3.956	1.604	- 2.467	0.014*	0.024†
GC ML DG	- 3.851	1.034	- 3.726	<0.001*	<0.001†
CA1	- 6.572	2.376	- 2.766	0.006*	0.012†
CA3	- 1.573	0.979	- 1.607	0.108	0.144
CA4	- 2.192	0.903	- 2.427	0.015*	0.022†
Subiculum	- 8.117	1.646	- 4.933	<0.001*	<0.001†
Presubiculum	- 5.411	1.312	- 4.124	<0.001*	<0.001†
Parasubiculum	- 0.578	0.481	- 1.201	0.230	0.250
Hippocampal tail	- 3.484	2.517	- 1.384	0.166	0.199

Abbreviations: B, partial regression coefficient; CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA- β , homeostasis model assessment of beta cell function; HV, hippocampal volume; SE, standard error.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV.

* p value < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 9. Multiple linear-regression analysis about glycated albumin levels

	B	SE B	t	p for trend	q-value of FDR correction
Whole hippocampus	- 11.831	2.638	- 4.485	<0.001*	-
<i>Hippocampal subregions</i>					
HATA	- 0.324	0.077	- 4.214	<0.001*	<0.001†
Fimbria	- 1.405	0.165	- 8.512	<0.001*	<0.001†
Hippocampal fissure	0.388	0.248	1.563	0.118	0.141
Molecular_layer	- 1.428	0.422	- 3.386	<0.001*	0.001†
GC ML DG	- 1.378	0.272	- 5.074	<0.001*	<0.001†
CA1	- 1.905	0.625	- 3.046	0.002*	0.003†
CA3	-0.713	0.257	- 2.771	0.006*	0.008†
CA4	- 0.820	0.237	- 3.453	<0.001*	0.001†
Subiculum	- 2.156	0.433	- 4.979	<0.001*	<0.001†
Presubiculum	- 1.305	0.345	- 3.781	<0.001*	<0.001†
Parasubiculum	- 0.135	0.126	- 1.070	0.284	0.309
Hippocampal tail	- 0.260	0.662	- 0.393	0.694	0.694

Abbreviations: B, partial regression coefficient; CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA- β , homeostasis model assessment of beta cell function; HV, hippocampal volume; SE, standard error.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV.

* p value < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 10. Multiple linear-regression analysis about logarithmic transform of homeostasis model assessment of β cell function (HOMA- β) levels

	B	SE B	t	p for trend	q-value of FDR correction
Whole hippocampus	104.942	42.957	2.443	0.015*	-
<i>Hippocampal subregions</i>					
HATA	0.904	1.227	0.736	0.462	0.554
Fimbria	8.499	2.759	3.081	0.002*	0.024 [†]
Hippocampal fissure	0.544	4.011	0.136	0.892	0.892
Molecular_layer	10.210	6.980	1.463	0.144	0.216
GC ML DG	8.811	4.282	2.058	0.040*	0.120
CA1	21.308	10.153	2.099	0.036*	0.144
CA3	3.879	4.131	0.939	0.348	0.464
CA4	5.824	3.725	1.564	0.118	0.202
Subiculum	11.952	6.893	1.734	0.083	0.199
Presubiculum	9.093	5.397	1.685	0.092	0.184
Parasubiculum	1.283	2.006	0.640	0.522	0.569
Hippocampal tail	23.178	11.006	2.106	0.035*	0.210

Abbreviations: B, partial regression coefficient; CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA- β , homeostasis model assessment of beta cell function; HV, hippocampal volume; SE, standard error.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV.

* p value < 0.05. [†] q-value of FDR correction < 0.05.

Supplementary Table 11. Multiple linear-regression analysis about logarithmic transform of homeostasis model assessment of insulin resistance (HOMA-IR) levels

	B	SE B	t	p for trend	q-value of FDR correction
Whole hippocampus	-13.698	47.748	-0.278	0.774	-
<i>Hippocampal subregions</i>					
HATA	-1.400	1.362	-1.027	0.304	3.648
Fimbria	0.161	3.068	0.052	0.958	0.958
Hippocampal fissure	1.149	4.454	0.258	0.796	1.364
Molecular_layer	-4.218	7.753	-0.544	0.586	2.344
GC ML DG	-1.592	4.758	-0.334	0.738	1.771
CA1	-1.821	11.282	-0.161	0.872	1.046
CA3	1.140	4.588	0.249	0.804	1.206
CA4	-1.828	4.138	-0.442	0.659	1.977
Subiculum	-7.083	7.657	-0.925	0.335	2.010
Presubiculum	-0.909	5.996	-0.152	0.879	0.958
Parasubiculum	0.408	2.228	0.183	0.855	1.140
Hippocampal tail	3.443	12.231	-0.282	0.778	1.556

Abbreviations: B, partial regression coefficient; CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA- β , homeostasis model assessment of beta cell function; HV, hippocampal volume; SE, standard error.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV.

* p value < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 12. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields by age according to hemoglobinA_{1c} levels

	<75 years old, hemoglobin A _{1c} levels, %			<75 years old p for trend	<75 years old q-value of FDR correction
	<5.7 (n=2,376)	5.7-6.4 (n=2,074)	≥6.5 (n=542)		
Whole hippocampus, HV, mm ³	6240.568 (6145.144-6335.992)	6258.864 (6163.400-6354.327)	6166.923 (6064.911-6268.935)	0.002*	-
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	98.396 (95.624-101.168)	98.182 (95.408-100.956)	96.584 (93.621-99.548)	0.056	0.084
Fimbria, HV, mm ³	107.567 (101.565-113.570)	104.620 (98.615-110.625)	98.651 (92.234-105.068)	<0.001*	<0.001 [†]
Hippocampal fissure, HV, mm ³	348.677 (339.847-357.508)	351.965 (343.131-360.799)	352.303 (342.862-361.743)	0.067	0.089
Molecular_layer, HV, mm ³	813.880 (798.798-828.962)	816.156 (801.068-831.244)	805.492 (789.368-821.615)	0.034*	0.081
GC ML DG, HV, mm ³	544.462 (534.753-554.171)	545.911 (536.198-555.624)	539.293 (528.914-549.672)	0.043*	0.086
CA1, HV, mm ³	1222.191 (1199.391-1244.992)	1228.272 (1205.462-1251.081)	1213.866 (1189.492-1238.241)	0.045*	0.077
CA3, HV, mm ³	399.636 (390.390-408.881)	402.922 (393.673-412.171)	399.523 (389.639-409.406)	0.087	0.104
CA4, HV, mm ³	481.002 (472.569-489.435)	483.145 (474.709-491.581)	479.066 (470.051-488.082)	0.125	0.125
Subiculum, HV, mm ³	847.014 (831.444-862.584)	845.920 (830.343-861.496)	829.503 (812.858-846.148)	<0.001*	<0.001 [†]
Presubiculum, HV, mm ³	563.940 (551.620-576.261)	560.303 (547.977-572.629)	551.044 (537.873-564.215)	<0.001*	0.002 [†]
Parasubiculum, HV, mm ³	109.007 (104.679-113.335)	107.511 (103.181-111.841)	107.299 (102.671-111.926)	0.093	0.101
Hippocampal tail, HV, mm ³	1053.472 (1028.916-1078.028)	1065.921 (1014.356-1090.487)	1046.603 (1020.351-1072.854)	0.001*	0.003 [†]

(Continued) Supplementary Table 12. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields by age according to hemoglobinA_{1c} levels

	≥75 years old, hemoglobin A _{1c} levels, %			≥75 years old p for trend	≥75 years old q-value of FDR correction	P for interaction
	<5.7 (n=1,030)	5.7-6.4 (n=915)	≥6.5 (n=253)			
Whole hippocampus, HV, mm ³	5802.290 (5733.706-5870.874)	5791.643 (5721.502-5861.784)	5757.065 (5665.989-5848.141)	0.491	-	0.539
<i>Hippocampal subregions</i>						
HATA, HV, mm ³	90.408 (88.390-92.427)	90.162 (88.098-92.226)	89.222 (86.542-91.903)	0.570	1.140	0.842
Fimbria, HV, mm ³	82.554 (78.270-86.838)	80.605 (76.224-84.986)	74.327 (68.638-80.016)	0.002*	0.024 [†]	0.658
Hippocampal fissure, HV, mm ³	347.047 (340.472-353.621)	347.849 (341.125-354.573)	351.745 (343.014-360.476)	0.433	1.299	0.569
Molecular_layer, HV, mm ³	748.092 (737.520-758.665)	750.079 (739.266-760.891)	747.125 (733.086-761.165)	0.819	0.982	0.500
GC ML DG, HV, mm ³	504.765 (497.487-512.042)	502.638 (495.195-510.080)	498.017 (488.353-507.681)	0.236	0.944	0.829
CA1, HV, mm ³	1141.216 (1125.193-1157.239)	1136.782 (1120.395-1153.168)	1135.077 (1113.800-1156.354)	0.667	1.000	0.642
CA3, HV, mm ³	379.218 (372.477-385.959)	379.487 (372.592-386.381)	371.718 (362.766-380.670)	0.096	0.576	0.400
CA4, HV, mm ³	451.326 (444.900-457.751)	450.092 (443.521-456.663)	446.939 (438.407-455.472)	0.463	1.111	0.976
Subiculum, HV, mm ³	782.103 (770.648-793.559)	779.127 (767.412-790.842)	777.171 (761.959-792.383)	0.653	1.119	0.333
Presubiculum, HV, mm ³	528.317 (519.067-537.566)	527.970 (518.511-537.430)	524.630 (512.346-526.913)	0.764	1.018	0.670
Parasubiculum, HV, mm ³	108.513 (104.860-112.166)	108.534 (104.799-112.270)	109.586 (104.736-114.437)	0.857	0.934	0.805
Hippocampal tail, HV, mm ³	985.778 (969.778-1001.778)	986.168 (969.804-1002.531)	983.252 (962.004-1004.499)	0.946	0.946	0.061

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or

hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 13. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields by age according to glycated albumin levels

	<75 years old, glycated albumin levels				<75 years old p for trend	<75 years old q-value of FDR correction
	<13.9 (n=1,377)	13.9-14.8 (n=1,341)	14.9-16.0 (n=1,207)	≥16.1 (n=1,024)		
Whole hippocampus, HV, mm ³	6243.645 (6146.370-6340.920)	62573942 (6460.939-6354.946)	6266.331 (6168.183-6364.480)	6193.739 (6096.646-6290.833)	0.008*	-
<i>Hippocampal subregions</i>						
HATA, HV, mm ³	98.387 (95.562-101.212)	98.688 (95.871-101.505)	98.557 (95.707-101.408)	96.827 (94.007-99.646)	0.018*	0.043 [†]
Fimbria, HV, mm ³	108.473 (102.378-114.569)	108.054 (101.976-114.133)	106.916 (100.766-113.067)	98.264 (92.180-104.348)	<0.001*	<0.001 [†]
Hippocampal fissure, HV, mm ³	348.474 (339.477-357.470)	348.100 (339.128-357.071)	351.504 (342.426-360.581)	353.949 (344.969-362.929)	0.015*	0.045 [†]
Molecular_layer, HV, mm ³	815.967 (800.596-831.338)	817.577 (802.249-832.905)	813.297 (797.788-828.806)	807.904 (792.562-823.247)	0.039*	0.066
GC ML DG, HV, mm ³	545.385 (535.496-555.273)	546.148 (536.287-556.009)	547.850 (537.873-557.827)	539.606 (529.736-549.477)	0.003*	0.018 [†]
CA1, HV, mm ³	1225.049 (1201.809-1248.289)	1225.122 (1201.947-1248.297)	1230.369 (1206.921-1253.818)	1216.466 (1193.270-1239.663)	0.084	0.112
CA3, HV, mm ³	339.229 (389.804-408.654)	401.187 (391.788-410.586)	403.403 (393.893-412.912)	400.771 (391.363-410.178)	0.254	0.277
CA4, HV, mm ³	481.302 (472.709-489.895)	482.449 (473.880-491.019)	484.611 (475.940-493.281)	479.327 (470.750-487.904)	0.062	0.093
Subiculum, HV, mm ³	846.736 (830.857-862.616)	847.276 (831.440-863.111)	847.246 (831.224-863.268)	836.095 (820.245-851.945)	0.005*	0.020 [†]
Presubiculum, HV, mm ³	563.676 (551.111-576.241)	562.282 (549.752-574.812)	561.87 (549.209-574.565)	555.067 (542.525-567.608)	0.018*	0.043 [†]
Parasubiculum, HV, mm ³	108.255 (103.842-112.669)	108.750 (104.349-113.151)	108.248 (103.795-112.701)	107.378 (102.973-111.783)	0.602	0.602
Hippocampal tail, HV, mm ³	1051.187 (1026.137-1076.236)	1060.408 (1035.428-1085.388)	1063.946 (1038.671-1089.221)	1056.035 (1031.031-1081.038)	0.112	0.134

(Continued) Supplementary Table 13. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields by age according to glycated albumin levels

	≥75 years old, glycated albumin levels				≥75 years old p for trend	≥75 years old q-value of FDR correction	p for interaction
	<13.9 (n=359)	13.9-14.8 (n=513)	14.9-16.0 (n=608)	≥16.1 (n=682)			
Whole hippocampus, HV, mm ³	5813.822 (5733.609-5894.035)	5781.341 (5704.625-5858.056)	5818.887 (5744.858-5892.916)	5764.871 (5691.341-5838.402)	0.249		0.184
<i>Hippocampal subregions</i>							
HATA, HV, mm ³	90.858 (88.496-93.219)	89.866 (87.608-92.124)	90.709 (88.530-92.888)	89.483 (87.319-91.647)	0.410	0.615	0.322
Fimbria, HV, mm ³	82.733 (77.713-87.754)	81.643 (76.842-86.445)	82.199 (77.565-86.832)	78.165 (73.563-82.768)	0.086	1.032	0.041 ^z
Hippocampal fissure, HV, mm ³	347.607 (339.914-355.300)	345.270 (337.912-352.627)	347.501 (340.401-354.600)	350.095 (343.043-357.148)	0.460	0.552	0.045 ^z
Molecular_layer, HV, mm ³	749.918 (737.546-762.290)	747.980 (736.147-759.812)	750.657 (739.239-762.075)	746.897 (735.555-758.238)	0.851	0.851	0.085
GC ML DG, HV, mm ³	506.791 (498.280-515.301)	503.127 (494.988-511.267)	505.211 (497.356-513.066)	498.989 (491.187-506.790)	0.122	0.732	0.214
CA1, HV, mm ³	1146.091 (1127.346-1164.836)	1135.210 (1117.282-1153.137)	1140.112 (1122.812-1157.412)	1134.958 (1117.775-1152.141)	0.509	0.555	0.050
CA3, HV, mm ³	381.428 (373.541-389.315)	379.260 (371.716-387.661)	380.381 (373.102-387.661)	374.511 (367.280-381.741)	0.124	0.496	0.058
CA4, HV, mm ³	452.906 (445.390-460.422)	449.776 (442.587-456.964)	451.598 (445.049-458.922)	447.598 (440.709-454.488)	0.302	0.517	0.183
Subiculum, HV, mm ³	786.071 (772.678-799.464)	777.535 (767.727-790.344)	783.737 (771.377-796.098)	775.310 (763.033-787.587)	0.173	0.519	0.177
Presubiculum, HV, mm ³	528.528 (517.768-539.395)	524.956 (514.614-535.298)	532.711 (522.731-542.690)	524.890 (514.977-534.803)	0.179	0.429	0.425
Parasubiculum, HV, mm ³	110.275 (106.004-114.546)	106.704 (102.619-110.788)	109.457 (105.516-113.399)	108.016 (104.101-111.931)	0.219	0.438	0.195
Hippocampal tail, HV, mm ³	978.170 (959.457-996.884)	985.284 (967.386-1003.182)	991.727 (974.456-1008.998)	986.054 (968.900-1003.209)	0.434	0.578	0.214

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein

cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05. χ p for interaction < 0.05.

Supplementary Table 14. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields by age according to homeostasis model assessment of β cell function (HOMA- β) levels

	<75 years old, HOMA- β levels		<75 years old p for trend	<75 years old q-value of FDR correction
	≤ 30 (n=195)	> 30 (n=2,161)		
Whole hippocampus, HV, mm ³	6130.823 (5935.229-6326.427)	6230.690 (6047.986-6413.396)	0.013*	
<i>Hippocampal subregions</i>				
HATA, HV, mm ³	96.153 (90.546-101.760)	98.179 (92.942-103.416)	0.079	0.118
Fimbria, HV, mm ³	112.490 (99.865-125.116)	120.054 (108.260-131.848)	0.004*	0.048 [†]
Hippocampal fissure, HV, mm ³	339.352 (321.037-357.666)	337.039 (319.931-354.146)	0.539	0.588
Molecular_layer, HV, mm ³	877.844 (845.999-909.688)	0890.006 (860.260-919.751)	0.063	0.126
GC ML DG, HV, mm ³	527.744 (508.453-547.035)	536.790 (518.771-554.809)	0.023*	0.138
CA1, HV, mm ³	1182.261 (1135.867-1228.654)	1200.850 (1157.514-1244.185)	0.051	0.153
CA3, HV, mm ³	395.494 (376.665-414.324)	400.458 (382.870-418.047)	0.119	0.158
CA4, HV, mm ³	465.237 (448.511-481.963)	471.900 (456.276-487.523)	0.053	0.127
Subiculum, HV, mm ³	806.631 (775.366-837.897)	818.418 (789.213-847.622)	0.067	0.114
Presubiculum, HV, mm ³	541.727 (517.334-566.120)	548.005 (525.220-570.790)	0.210	0.252
Parasubiculum, HV, mm ³	117.645 (108.859-126.431)	117.165 (108.958-125.372)	0.790	0.790
Hippocampal tail, HV, mm ³	1007.601 (956.356-1058.846)	1028.865 (980.998-1076.732)	0.044*	0.176

(Continued) Supplementary Table 14. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields by age according to homeostasis model assessment of β cell function (HOMA- β) levels

	≥ 75 years old, HOMA- β levels		≥ 75 years old p for trend	≥ 75 years old q-value of FDR correction	p for interaction
	≤ 30 (n=62)	> 30 (n=679)			
Whole hippocampus, HV, mm ³	5716.771 (5548.371-5885.171)	5774.374 (5658.364-5890.384)	0.427	-	0.593
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	85.416 (80.679-90.153)	86.386 (83.123-89.649)	0.634	0.951	0.726
Fimbria, HV, mm ³	79.642 (68.973-90.312)	85.146 (77.795-92.496)	0.231	2.772	0.716
Hippocampal fissure, HV, mm ³	350.778 (335.493-366.063)	343.256 (332.726-353.785)	0.253	1.012	0.152
Molecular_layer, HV, mm ³	807.348 (782.644-832.910)	811.348 (794.034-828.662)	0.742	0.890	0.502
GC ML DG, HV, mm ³	486.938 (469.617-504.258)	494.443 (482.511-506.375)	0.315	0.945	0.264
CA1, HV, mm ³	1125.731 (1085.930-1165.532)	1128.746 (1101.328-1156.165)	0.860	0.860	0.161
CA3, HV, mm ³	366.431 (350.468-382.393)	370.711 (359.715-381.708)	0.534	1.068	0.647
CA4, HV, mm ³	435.432 (420.265-450.598)	440.508 (430.060-450.956)	0.437	1.048	0.917
Subiculum, HV, mm ³	758.385 (730.929-785.842)	772.316 (753.401-791.231)	0.239	1.434	0.924
Presubiculum, HV, mm ³	506.002 (484.318-527.685)	511.025 (496.088-525.963)	0.591	1.013	0.876
Parasubiculum, HV, mm ³	102.367 (93.653-111.081)	103.199 (97.197-109.202)	0.824	0.898	0.872
Hippocampal tail, HV, mm ³	962.651 (923.014-1002.288)	970.546 (943.240-997.852)	0.644	0.858	0.715

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA- β , homeostasis model assessment of percent beta cell function; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or

hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05. χ p for interaction < 0.05.

Supplementary Table 15. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields by age according to homeostasis model assessment of insulin resistance (HOMA-IR) levels

	<75 years old, HOMA-IR levels, %			<75 years old p for trend	<75 years old q-value of FDR correction
	<1.6 (n=1,790)	1.6-2.4 (n=422)	≥2.5 (n=144)		
Whole hippocampus, HV, mm ³	6223.522 (6040.517-6406.526)	6204.943 (6015.162-6394.725)	6192.928 (5988.506-6397.350)	0.735	-
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	98.025 (92.782-103.267)	97.489 (92.052-102.926)	98.137 (92.281-103.993)	0.804	1.378
Fimbria, HV, mm ³	119.311 (107.492-131.130)	119.450 (107.193-131.707)	117.131 (1003.929-130.333)	0.769	2.307
Hippocampal fissure, HV, mm ³	337.837 (320.729-354.946)	335.235 (317.493-352.977)	332.140 (313.029-351.251)	0.379	2.274
Molecular_layer, HV, mm ³	889.088 (859.310-918.866)	887.240 (856.359-918.121)	885.171 (851.907-918.434)	0.857	1.285
GC ML DG, HV, mm ³	535.901 (517.854-553.948)	535.603 (516.888-554.319)	534.797 (514.638-554.956)	0.973	0.973
CA1, HV, mm ³	1199.594 (1156.209-1242.980)	1195.520 (1150.528-1240.512)	1193.862 (1145.325-1242.325)	0.796	1.592
CA3, HV, mm ³	400.022 (382.421-417.624)	399.328 (381.075-417.582)	399.801 (380.139-419.462)	0.972	1.060
CA4, HV, mm ³	471.388 (455.746-487.030)	470.288 (454.067-486.509)	469.752 (452.280-487.225)	0.875	1.166
Subiculum, HV, mm ³	818.571 (789.362-847.781)	811.883 (781.592-842.174)	803.881 (771.253-836.509)	0.110	1.320
Presubiculum, HV, mm ³	547.676 (524.876-570.475)	546.158 (522.514-569.802)	543.780 (518.312-569.248)	0.791	1.898
Parasubiculum, HV, mm ³	117.168 (108.959-125.377)	116.970 (108.457-125.483)	119.054 (109.885-128.224)	0.653	2.612
Hippocampal tail, HV, mm ³	1026.776 (978.847-1074.706)	1025.014 (975.310-1074.718)	1027.562 (974.023-1081.100)	0.969	1.162

(Continued) Supplementary Table 15. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields by age according to homeostasis model assessment of insulin resistance (HOMA-IR) levels

	≥75 years old, HOMA-IR levels, %			≥75 years old p for trend	≥75 years old q-value of FDR correction	p for interaction
	<1.6 (n=554)	1.6-2.4 (n=134)	≥2.5 (n=53)			
Whole hippocampus, HV, mm ³	5784.288 (5667.280-5901.295)	5716.705 (5571.435-5861.976)	5704.414 (5522.320-5886.508)	0.359	-	0.829
<i>Hippocampal subregions</i>						
HATA, HV, mm ³	86.535 (83.242-89.828)	85.451 (81.362-89.539)	85.294 (80.168-90.419)	0.772	0.926	0.771
Fimbria, HV, mm ³	84.589 (77.161-92.018)	83.585 (74.363-92.808)	84.277 (72.717-95.837)	0.959	1.046	0.999
Hippocampal fissure, HV, mm ³	344.215 (333.575-354.856)	345.135 (331.924-358.345)	343.291 (326.732-359.851)	0.969	0.969	0.488
Molecular_layer, HV, mm ³	814.121 (796.691-831.552)	797.959 (776.318-819.600)	804.473 (777.347-831.600)	0.130	1.560	0.786
GC ML DG, HV, mm ³	495.387 (483.351-507.423)	489.225 (474.282-504.168)	484.732 (466.001-503.462)	0.316	0.948	0.510
CA1, HV, mm ³	1129.848 (1102.207-1157.488)	1113.451 (1079.134-1147.768)	1137.910 (1094.894-1180.925)	0.341	0.682	0.843
CA3, HV, mm ³	371.274 (360.182-382.365)	370.515 (356.744-384.286)	361.090 (343.828-378.351)	0.417	0.714	0.248
CA4, HV, mm ³	441.470 (430.934-452.006)	437.152 (424.071-450.233)	431.249 (414.852-447.645)	0.322	0.772	0.370
Subiculum, HV, mm ³	773.393 (754.309-792.477)	766.572 (742.878-790.265)	753.859 (724.160-783.559)	0.310	1.240	0.649
Presubiculum, HV, mm ³	512.150 (497.083-527.217)	508.883 (490.177-527.590)	498.907 (475.459-522.355)	0.446	0.669	0.641
Parasubiculum, HV, mm ³	104.056 (98.008-110.104)	102.296 (94.788-109.307)	96.895 (87.482-106.307)	0.231	1.386	0.368
Hippocampal tail, HV, mm ³	971.463 (943.902-999.025)	961.617 (927.398-995.835)	965.730 (922.838-1008.623)	0.739	0.985	0.997

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA-IR, homeostasis model assessment of insulin resistance; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05. χ p for interaction < 0.05.

Supplementary Table 16. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields with or without *ApoE* $\epsilon 4$ according to hemoglobinA_{1c} levels

	<i>ApoE</i> $\epsilon 4$ +, hemoglobin A _{1c} levels, %			<i>ApoE</i> $\epsilon 4$ + p for trend	<i>ApoE</i> $\epsilon 4$ + q-value of FDR correction
	<5.7 (n=609)	5.7-6.4 (n=487)	≥6.5 (n=117)		
Whole hippocampus, HV, mm ³	6180.011 (6062.438-6297.584)	6156.560 (6035.441-6277.680)	6083.188 (5934.651-6231.726)	0.190	-
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	96.454 (93.029-99.879)	94.192 (90.664-97.720)	94.216 (89.889-98.543)	0.040*	0.160
Fimbria, HV, mm ³	104.964 (97.601-112.328)	97.559 (89.972-105.145)	91.537 (82.234-100.840)	<0.001*	<0.001 [†]
Hippocampal fissure, HV, mm ³	351.315 (340.150-362.479)	352.467 (340.966-363.968)	356.194 (342.089-370.299)	0.626	0.834
Molecular_layer, HV, mm ³	807.906 (788.719-827.093)	802.932 (783.167-822.698)	799.004 (774.764-823.245)	0.470	0.928
GC ML DG, HV, mm ³	539.723 (527.506-551.940)	539.427 (526.842-552.013)	535.801 (520.367-551.236)	0.774	0.974
CA1, HV, mm ³	1207.625 (1180.152-1235.098)	1203.784 (1175.483-1232.086)	1195.421 (1160.712-1230.129)	0.602	0.9433
CA3, HV, mm ³	397.188 (385.820-408.557)	397.633 (385.922-409.345)	395.125 (380.789-409.514)	0.893	0.974
CA4, HV, mm ³	478.154 (467.589-488.719)	478.865 (467.981-489.748)	477.400 (464.053-490.747)	0.943	0.943
Subiculum, HV, mm ³	843.728 (824.751-862.705)	838.138 (818.589-857.688)	824.125 (800.151-848.100)	0.069	.0.207
Presubiculum, HV, mm ³	561.069 (545.740-576.398)	555.767 (539.975-571.559)	547.306 (527.939-566.672)	0.109	0.261
Parasubiculum, HV, mm ³	106.442 (100.969-111.915)	102.556 (96.918-108.915)	104.006 (97.092-110.920)	0.034*	0.204
Hippocampal tail, HV, mm ³	1036.758 (1006.003-1067.512)	1045.706 (1014.024-1077.388)	1019.220 (980.366-1058.074)	0.152	0.304

(Continued) Supplementary Table 16. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields with or without *ApoE* $\epsilon 4$ according to hemoglobinA_{1c} levels

	<i>ApoE</i> $\epsilon 4$ -, hemoglobin A _{1c} levels, %			<i>ApoE</i> $\epsilon 4$ – p for trend	<i>ApoE</i> $\epsilon 4$ – q-value of FDR correction	p for interaction
	<5.7 (n=2,748)	5.7-6.4 (n=2,456)	≥6.5 (n=667)			
Whole hippocampus, HV, mm ³	6193.611 (6148.240-6238.982)	6205.362 (6159.166-6251.557)	6134.264 (6076.682-6191.846)	0.009*	-	0.678
<i>Hippocampal subregions</i>						
HATA, HV, mm ³	97.249 (95.921-98.577)	97.359 (96.007-98.711)	95.815 (94.129-97.500)	0.068	0.090	0.096
Fimbria, HV, mm ³	102.074 (99.229-104.919)	100.284 (97.387-103.181)	94.273 (0.0064-0.0070)	<0.001*	<0.001 [†]	0.035%
Hippocampal fissure, HV, mm ³	344.543 (340.262-348.824)	347.487 (343.128-351.846)	349.247 (343.813-354.680)	0.036*	0.061	0.846
Molecular_layer, HV, mm ³	802.846 (795.628-810.064)	805.800 (798.451-813.149)	796.612 (787.452-805.773)	0.040*	0.060	0.467
GC ML DG, HV, mm ³	514.246 (536.579-545.912)	514.353 (536.602-546.104)	535.337 (529.415-541.259)	0.032*	0.064	0.927
CA1, HV, mm ³	1213.519 (1202.746-1224.293)	1216.626 (1205.657-1227.596)	1206.674 (1193.001-1220.347)	0.186	0.202	0.853
CA3, HV, mm ³	397.188 (392.757-401.619)	400.067 (395.556-404.579)	394.918 (389.295-400.542)	0.031*	0.074	0.785
CA4, HV, mm ³	478.559 (474.473-482.644)	479.519 (475.359-483.679)	475.668 (470.483-480.853)	0.182	0.218	0.912
Subiculum, HV, mm ³	838.814 (831.343-846.286)	837.372 (829.765-844.980)	826.479 (816.996-835.961)	0.005*	0.030 [†]	0.762
Presubiculum, HV, mm ³	560.447 (554.512-566.382)	557.626 (551.583-563.669)	551.294 (543.761-558.827)	0.011*	0.044 [†]	0.732
Parasubiculum, HV, mm ³	109.973 (107.610-111.976)	109.195 (106.973-111.418)	109.449 (106.678-112.220)	0.707	0.707	0.087
Hippocampal tail, HV, mm ³	1051.875 (1040.601-1063.149)	1060.160 (1048.681-1071.639)	1047.744 (1033.436-1062.052)	0.025*	0.075	0.675

Abbreviations: *ApoE* $\epsilon 4$, apolipoprotein E $\epsilon 4$; CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or

hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05. χ p for interaction < 0.05.

Supplementary Table 17. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields with or without *ApoE* $\epsilon 4$ according to glycated albumin levels

	<i>ApoE</i> $\epsilon 4$ +, glycated albumin levels				<i>ApoE</i> $\epsilon 4$ + p for trend	<i>ApoE</i> $\epsilon 4$ + q-value of FDR correction
	<13.9 (n=276)	13.9-14.8 (n=322)	14.9-16.0 (n=311)	≥ 16.1 (n=278)		
Whole hippocampus, HV, mm ³	6196.034 (6070.276-6321.792)	6163.145 (6037.431-6288.858)	6218.527 (6092.914-6344.140)	6074.272 (5946.541-6202.002)	0.007*	-
<i>Hippocampal subregions</i>						
HATA, HV, mm ³	96.483 (92.836-100.131)	95.450 (91.804-99.096)	96.763 (93.120-100.406)	93.176 (89.472-96.881)	0.023*	0.055
Fimbria, HV, mm ³	105.141 (97.218-113.064)	103.495 (95.539-111.379)	101.811 (93.897-109.724)	94.217 (86.170-102.264)	<0.001*	0.009 [†]
Hippocampal fissure, HV, mm ³	351.050 (339.169-362.931)	353.086 (341.210-364.963)	352.079 (340.212-363.947)	353.643 (341.576-365.711)	0.933	0.933
Molecular_layer, HV, mm ³	813.681 (793.120-834.242)	804.368 (783.814-824.922)	806.093 (785.556-826.631)	795.796 (774.913-816.680)	0.126	0.168
GC ML DG, HV, mm ³	541.692 (528.651-554.733)	538.049 (525.013-551.085)	545.900 (532.874-558.925)	530.215 (516.969-543.460)	0.005*	0.030 [†]
CA1, HV, mm ³	1214.934 (1185.478-1244.390)	1203.516 (1174.070-1232.962)	1213.289 (1183.866-1242.711)	1187.598 (1157.680-1217.516)	0.036*	0.072
CA3, HV, mm ³	396.978 (384.801-409.154)	396.192 (384.020-408.364)	402.639 (390.477-414.801)	392.657 (380.289-405.024)	0.113	0.169
CA4, HV, mm ³	478.622 (467.321-489.922)	477.187 (465.891-488.483)	484.574 (473.287-495.861)	472.218 (460.741-483.695)	0.016*	0.048 [†]
Subiculum, HV, mm ³	842.824 (822.489-863.158)	845.877 (825.550-866.205)	846.105 (825.794-866.415)	825.521 (804.868-866.415)	0.011*	0.044 [†]
Presubiculum, HV, mm ³	559.898 (543.448-576.348)	560.815 (544.372-577.259)	560.283 (543.852-576.714)	552.124 (535.416-568.832)	0.399	0.435
Parasubiculum, HV, mm ³	106.546 (100.686-112.406)	104.966 (99.108-110.824)	105.040 (99.187-110.894)	102.694 (96.742-108.646)	0.350	0.420
Hippocampal tail, HV, mm ³	1039.236 (1006.262-1072.210)	1033.265 (1000.302-1066.227)	1056.030 (1023.094-1088.966)	1028.056 (994.565-1061.548)	0.066	0.113

(Continued) Supplementary Table 17. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields with or without *ApoE* $\epsilon 4$ according to glycated albumin levels

	<i>ApoE</i> $\epsilon 4$ -, glycated albumin levels				<i>ApoE</i> $\epsilon 4$ – p for trend	<i>ApoE</i> $\epsilon 4$ – q-value of FDR correction	p for interaction
	<13.9 (n=1,429)	13.9-14.8 (n=1,483)	14.9-16.0 (n=1,456)	≥ 16.1 (n=1,379)			
Whole hippocampus, HV, mm ³	6189.441 (6139.733-6239.149)	6195.885 (6146.037-6245.733)	6202.989 (6152.960-6253.017)	6154.271 (6104.529-6204.014)	0.073		0.312
<i>Hippocampal subregions</i>							
HATA, HV, mm ³	97.297 (95.845-98.748)	97.418 (95.962-98.873)	97.360 (95.899-98.821)	96.222 (94.770-97.657)	0.135	0.270	0.399
Fimbria, HV, mm ³	103.101 (99.994-106.209)	102.484 (99.367-105.600)	101.919 (98.791-105.047)	95.163 (92.053-98.273)	<0.001*	<0.001 [†]	0.947
Hippocampal fissure, HV, mm ³	342.730 (338.065-347.395)	341.938 (337.259-346.616)	345.530 (340.835-350.225)	348.007 (343.338-352.675)	0.005*	0.030 [†]	0.795
Molecular_layer, HV, mm ³	804.395 (796.487-812.302)	805.574 (797.644-813.504)	801.972 (794.014-809.931)	799.179 (791.266-807.092)	0.202	0.303	0.530
GC ML DG, HV, mm ³	541.119 (536.010-546.228)	541.614 (536.491-546.737)	542.081 (536.939-547.222)	536.055 (530.943-541.167)	0.012*	0.048 [†]	0.231
CA1, HV, mm ³	1213.138 (1201.329-1224.948)	1212.102 (1200.259-1223.945)	1216.287 (1204.402-1228.173)	1208.391 (1196.573-1220.208)	0.414	0.496	0.376
CA3, HV, mm ³	396.833 (391.981-401.685)	398.355 (393.489-403.220)	399.159 (394.276-404.042)	396.336 (391.481-401.191)	0.430	0.469	0.445
CA4, HV, mm ³	478.075 (473.601-482.548)	478.760 (474.274-483.246)	479.684 (475.182-484.187)	476.049 (471.573-480.526)	0.219	0.292	0.221
Subiculum, HV, mm ³	839.210 (831.020-847.401)	836.793 (828.579-845.006)	838.597 (830.354-846.840)	830.365 (822.169-838.561)	0.032*	0.076	0.474
Presubiculum, HV, mm ³	560.163 (553.665-566.661)	557.418 (550.902-563.934)	559.669 (553.130-556.209)	552.995 (546.493-559.497)	0.027*	0.081	0.886
Parasubiculum, HV, mm ³	109.575 (107.190-111.961)	109.156 (106.764-111.548)	109.495 (107.094-111.896)	108.893 (106.506-111.280)	0.887	0.887	0.903
Hippocampal tail, HV, mm ³	1046.535 (1034.187-1058.883)	1056.212 (1043.829-1068.595)	1056.765 (1044.338-1069.192)	1054.622 (1042.266-1066.979)	0.145	0.248	0.154

Abbreviations: *ApoE* $\epsilon 4$, apolipoprotein E $\epsilon 4$; CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. [†] q-value of FDR correction < 0.05. χ p for interaction < 0.05.

Supplementary Table 18. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields with or without *ApoE* $\epsilon 4$ according to homeostasis model assessment of β cell function (HOMA- β) levels

	<i>ApoE</i> $\epsilon 4$ +, HOMA- β levels		<i>ApoE</i> $\epsilon 4$ + p for trend	<i>ApoE</i> $\epsilon 4$ + q-value of FDR correction
	≤ 30 (n=51)	> 30 (n=499)		
Whole hippocampus, HV, mm ³	6162.191 (5945.217-6379.166)	6178.053 (6004.535-6351.571)	0.846	
<i>Hippocampal subregions</i>				
HATA, HV, mm ³	93.990 (88.178-99.802)	93.036 (88.388-97.684)	0.662	0.794
Fimbria, HV, mm ³	100.307 (86.834-113.779)	108.645 (97.871-119.419)	0.100	0.600
Hippocampal fissure, HV, mm ³	341.256 (321.497-361.015)	339.461 (323.659-355.262)	0.809	0.882
Molecular_layer, HV, mm ³	867.292 (831.381-903.203)	876.749 (848.030-905.467)	0.484	0.968
GC ML DG, HV, mm ³	526.438 (505.232-547.644)	535.272 (518.313-552.231)	0.268	0.804
CA1, HV, mm ³	1168.780 (1119.131-1218.429)	1193.924 (1154.219-1233.629)	0.178	0.712
CA3, HV, mm ³	387.889 (367.678-408.101)	391.316 (375.153-407.479)	0.652	0.869
CA4, HV, mm ³	467.474 (448.998-485.950)	472.377 (457.601-487.152)	0.480	1.152
Subiculum, HV, mm ³	819.045 (784.101-853.990)	825.068 (797.122-853.013)	0.647	0.970
Presubiculum, HV, mm ³	547.546 (521.154-573.938)	541.532 (520.426-562.639)	0.544	0.932
Parasubiculum, HV, mm ³	106.316 (96.588-116.044)	105.998 (98.218-113.777)	0.931	0.931
Hippocampal tail, HV, mm ³	1077.114 (1019.782-1134.447)	1034.138 (988.289-1079.988)	0.047*	0.564

(Continued) Supplementary Table 18. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields with or without *ApoE* $\epsilon 4$ according to homeostasis model assessment of β cell function (HOMA- β) levels

	<i>ApoE</i> $\epsilon 4$ -, HOMA- β levels		<i>ApoE</i> $\epsilon 4$ – p for trend	<i>ApoE</i> $\epsilon 4$ – q-value of FDR correction	p for interaction
	≤ 30 (n=199)	> 30 (n=2,275)			
Whole hippocampus, HV, mm ³	6123.140 (6014.841-6231.439)	6222.850 (6139.005-6306.694)	0.011*	-	0.479
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	93.492 (90.358-96.625)	95.876 (93.450-98.303)	0.035*	0.105	0.228
Fimbria, HV, mm ³	101.711 (94.712-108.710)	108.734 (103.315-114.152)	0.005*	0.030 [†]	0.899
Hippocampal fissure, HV, mm ³	340.858 (330.683-351.033)	336.371 (328.494-344.248)	0.222	0.296	0.578
Molecular_layer, HV, mm ³	871.864 (854.344-889.384)	881.303 (867.740-894.867)	0.135	0.202	0.718
GC ML DG, HV, mm ³	527.422 (516.581-538.263)	535.821 (527.428-544.214)	0.032*	0.128	0.915
CA1, HV, mm ³	1190.310 (1164.533-1216.088)	1200.974 (1181.017-1220.931)	0.252	0.274	0.368
CA3, HV, mm ³	392.252 (381.765-402.739)	396.753 (388.634-404.872)	0.234	0.280	0.948
CA4, HV, mm ³	465.245 (455.811-474.678)	471.639 (464.336-478.943)	0.060	0.120	0.906
Subiculum, HV, mm ³	815.262 (797.899-832.625)	827.182 (813.739-840.624)	0.057	0.136	0.913
Presubiculum, HV, mm ³	538.613 (524.919-552.307)	546.200 (535.598-556.802)	0.125	0.214	0.251
Parasubiculum, HV, mm ³	109.870 (104.768-114.972)	109.575 (105.625-113.524)	0.873	0.873	0.798
Hippocampal tail, HV, mm ³	1017.100 (989.576-1044.625)	1048.793 (1027.484-1070.102)	0.001*	0.012 [†]	0.003 [‡]

Abbreviations: *ApoE* $\epsilon 4$, apolipoprotein E $\epsilon 4$; CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA- β , homeostasis model assessment of percent beta cell function; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05. χ p for interaction < 0.05.

Supplementary Table 19. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields with or without *ApoE* $\epsilon 4$ according to homeostasis model assessment of insulin resistance (HOMA-IR) levels

	<i>ApoE</i> $\epsilon 4$ +, HOMA-IR levels, %			<i>ApoE</i> $\epsilon 4$ + p for trend	<i>ApoE</i> $\epsilon 4$ + q-value of FDR correction
	<1.6 (n=408)	1.6-2.4 (n=110)	≥ 2.5 (n=32)		
Whole hippocampus, HV, mm ³	6185.408 (6013.206-6357.610)	6158.564 (5958.676-6358.453)	6002.188 (5738.507-6265.868)	0.236	-
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	93.346 (88.727-97.965)	93.176 (87.814-983538)	89.766 (82.693-96.838)	0.453	0.543
Fimbria, HV, mm ³	107.061 (96.328-117.793)	109.826 (97.368-122.284)	101.487 (85.053-117.921)	0.446	0.669
Hippocampal fissure, HV, mm ³	340.279 (342.562-355.997)	338.180 (319.935-356.425)	333.618 (309.550-357.686)	0.778	0.778
Molecular_layer, HV, mm ³	875.772 (847.233-904.311)	877.253 (844.125-910.380)	852.432 (808.733-896.131)	0.377	0.754
GC ML DG, HV, mm ³	535.075 (518.228-551.921)	530.133 (510.578-549.688)	517.037 (491.241-542.832)	0.215	0.860
CA1, HV, mm ³	1190.279 (1150.759-1229.798)	1193.229 (1147.356-1239.103)	1161.818 (1101.305-1222.332)	0.451	0.601
CA3, HV, mm ³	392.318 (376.277-408.358)	383.992 (365.373-402.612)	379.063 (354.501-403.625)	0.217	0.651
CA4, HV, mm ³	472.979 (458.332-487.626)	457.195 (450.193-484.197)	454.309 (431.881-476.737)	0.106	1.272
Subiculum, HV, mm ³	825.311 (797.608-853.015)	824.957 (792.800-857.115)	790.766 (748.346-833.186)	0.123	0.738
Presubiculum, HV, mm ³	541.837 (520.860-562.814)	549.165 (524.815-573.514)	534.165 (502.044-566.285)	0.429	0.735
Parasubiculum, HV, mm ³	105.813 (98.076-113.550)	107.806 (98.826-116.787)	105.007 (93.160-116.854)	0.723	0.788
Hippocampal tail, HV, mm ³	1045.619 (999.931-1091.306)	1021.832 (968.799-1074.865)	1016.338 (946.380-1086.296)	0.278	0.667

(Continued) Supplementary Table 19. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields with or without *ApoE* $\epsilon 4$ according to homeostasis model assessment of insulin resistance (HOMA-IR) levels

	<i>ApoE</i> $\epsilon 4$ -, HOMA-IR levels, %			<i>ApoE</i> $\epsilon 4$ - p for trend	<i>ApoE</i> $\epsilon 4$ - q-value of FDR correction	p for interaction
	<1.6 (n=554)	1.6-2.4 (n=134)	≥ 2.5 (n=53)			
Whole hippocampus, HV, mm ³	6217.663 (6133.415-6301.910)	6188.357 (6090.931-6285.783)	6197.078 (6080.013-6314.142)	0.591	-	0.576
<i>Hippocampal subregions</i>						
HATA, HV, mm ³	95.679 (93.242-98.116)	94.950 (92.132-97.768)	96.174 (92.788-99.560)	0.581	1.394	0.403
Fimbria, HV, mm ³	108.157 (102.710-113.604)	107.642 (101.344-113.941)	107.272 (99.704-114.841)	0.936	1.248	0.631
Hippocampal fissure, HV, mm ³	337.278 (329.370-345.185)	335.793 (326.648-344.937)	333.442 (322.455-344.429)	0.635	1.270	0.898
Molecular_layer, HV, mm ³	881.396 (867.781-895.010)	874.630 (858.887-890.374)	877.498 (858.581-896.415)	0.353	1.412	0.453
GC ML DG, HV, mm ³	535.106 (526.674-543.538)	534.501 (524.750-544.252)	534.356 (522.640-546.073)	0.972	0.972	0.768
CA1, HV, mm ³	1200.650 (1180.623-1220.678)	1191.717 (1168.557-1214.878)	1203.565 (1175.736-1231.394)	0.371	1.113	0.307
CA3, HV, mm ³	396.225 (388.074-404.375)	397.745 (388.320-407.171)	395.115 (383.790-406.441)	0.804	1.206	0.711
CA4, HV, mm ³	471.155 (463.819-478.490)	470.473 (461.990-478.956)	470.119 (459.926-480.312)	0.945	1.030	0.625
Subiculum, HV, mm ³	827.852 (814.363-841.340)	819.676 (804.078-835.275)	815.283 (796.541-834.026)	0.089	1.068	0.342
Presubiculum, HV, mm ³	546.454 (535.813-557.095)	542.212 (529.907-554.518)	539.335 (524.550-554.121)	0.319	1.914	0.473
Parasubiculum, HV, mm ³	109.784 (105.821-113.748)	108.660 (104.076-113.244)	109.030 (103.522-114.538)	0.707	1.212	0.775
Hippocampal tail, HV, mm ³	1045.206 (1023.774-1066.637)	1046.149 (1021.364-1070.933)	1049.329 (1019.549-1079.110)	0.939	1.126	0.478

Abbreviations: *ApoE* $\epsilon 4$, apolipoprotein E $\epsilon 4$; CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA-IR, homeostasis model assessment of insulin resistance; HV, hippocampal volume.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05. χ p for interaction < 0.05.

Supplementary Table 20. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields according to hemoglobinA_{1c} levels in people with dementia, MCI and normal cognitive function

	Hemoglobin A _{1c} levels, %			p for trend	q-value of FDR correction
	<5.7 (n=4,404)	5.7-6.4 (n=3,740)	≥6.5 (n=1,050)		
Whole hippocampus, HV, mm ³	6056.946 (6023.050-6090.843)	6050.420 (6015.311-6085.530)	5986.232 (5940.151-6032.314)	0.002*	-
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	95.147 (94.198-96.095)	94.624 (93.642-95.606)	93.532 (92.243-94.821)	0.014*	0.033 [†]
Fimbria, HV, mm ³	96.875 (94.880-98.870)	94.547 (92.481-96.613)	88.972 (86.260-91.682)	<0.001*	<0.001 [†]
Hippocampal fissure, HV, mm ³	342.056 (338.967-345.144)	344.135 (340.936-347.334)	345.251 (341.052-349.450)	0.097	0.116
Molecular_layer, HV, mm ³	790.270 (784.955-795.586)	790.792 (785.286-796.297)	784.948 (777.721-792.174)	0.167	0.182
GC ML DG, HV, mm ³	528.586 (525.114-532.058)	527.210 (523.614-530.806)	521.550 (516.829-526.270)	0.003*	0.009 [†]
CA1, HV, mm ³	1187.535 (1179.730-1195.340)	1187.889 (1179.805-1195.974)	1179.498 (1168.888-1190.109)	0.171	0.171
CA3, HV, mm ³	388.390 (385.198-391.582)	389.292 (385.986-392.598)	385.001 (380.662-389.341)	0.076	0.114
CA4, HV, mm ³	467.782 (464.732-470.832)	467.273 (464.114-470.432)	463.607 (459.460-467.753)	0.066	0.113
Subiculum, HV, mm ³	817.256 (811.657-822.855)	813.954 (808.155-819.754)	802.947 (795.335-810.559)	<0.001*	<0.001 [†]
Presubiculum, HV, mm ³	547.443 (543.094-551.793)	543.805 (539.299-548.310)	535.647 (529.734-541.560)	<0.001*	<0.001 [†]
Parasubiculum, HV, mm ³	108.323 (106.756-109.891)	107.091 (105.468-108.715)	107.057 (104.926-109.188)	0.091	0.121
Hippocampal tail, HV, mm ³	1029.339 (1021.220-1037.458)	1033.943 (1025.533-1042.352)	1023.473 (1012.453-1034.510)	0.065	0.130

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HV, hippocampal volume; MCI, mild cognitive impairment.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-

density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 21. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields according to serum glycated albumin levels in people with dementia, MCI and normal cognitive function

	Serum glycoalbumin levels, %				p for trend	q-value of FDR correction
	<13.9 (n=2,083)	13.9-14.8 (n=2,258)	14.9-16.0 (n=2,284)	≥16.1 (n=2,374)		
Whole hippocampus, HV, mm ³	6056.398 (6017.755-6095.040)	6061.151 (6022.986-6099.316)	6073.036 (6034.689-6111.384)	5992.818 (5955.083-6030.553)	<0.001*	-
<i>Hippocampal subregions</i>						
HATA, HV, mm ³	95.288 (94.209-96.367)	95.065 (93.999-96.131)	95.289 (94.218-96.360)	93.655 (92.601-94.709)	0.001*	0.002 [†]
Fimbria, HV, mm ³	98.092 (95.823-100.360)	97.092 (94.955-99.436)	96.470 (94.219-98.721)	89.499 (87.284-91.714)	<0.001*	<0.001 [†]
Hippocampal fissure, HV, mm ³	340.416 (336.908-343.924)	341.191 (337.727-344.655)	344.420 (340.939-347.901)	344.202 (340.776-347.627)	0.021*	0.025 [†]
Molecular_layer, HV, mm ³	792.533 (786.470-798.595)	792.822 (786.835-798.810)	789.945 (783.929-795.961)	784.116 (778.196-790.036)	0.004*	0.006 [†]
GC ML DG, HV, mm ³	528.976 (525.021-532.932)	529.173 (525.266-533.080)	530.174 (526.249-534.100)	520.911 (517.048-524.774)	<0.001*	<0.001 [†]
CA1, HV, mm ³	1189.278 (1180.371-1198.185)	1187.159 (1178.363-1195.956)	1191.820 (1182.982-1200.659)	1178.117 (1169.420-1186.815)	0.003*	0.005 [†]
CA3, HV, mm ³	388.004 (384.366-391.642)	389.688 (386.095-393.282)	390.643 (387.033-394.254)	385.231 (381.678-388.784)	0.004*	0.006 [†]
CA4, HV, mm ³	467.397 (463.921-470.873)	468.325 (464.892-471.758)	469.658 (466.208-473.107)	462.782 (459.388-466.176)	0.001	0.002 [†]
Subiculum, HV, mm ³	817.188 (810.798-823.578)	816.517 (810.206-822.827)	817.579 (811.238-823.920)	804.942 (798.702-811.182)	<0.001*	<0.001 [†]
Presubiculum, HV, mm ³	547.403 (542.442-552.364)	545.780 (540.880-550.680)	547.008 (542.085-551.931)	538.076 (533.232-542.921)	<0.001*	<0.001 [†]
Parasubiculum, HV, mm ³	108.104 (106.319-109.889)	107.789 (106.025-109.552)	108.031 (106.259-109.803)	106.800 (105.057-108.544)	0.330	0.233
Hippocampal tail, HV, mm ³	1024.134 (1014.878-1033.390)	1031.638 (1022.496-1040.779)	1036.418 (1027.233-1045.604)	1028.688 (1019.649-1037.726)	0.027*	0.029 [†]

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HV, hippocampal volume; MCI, mild cognitive impairment.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density

lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05.

Supplementary Table 22. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields according to homeostasis model assessment of β cell function (HOMA- β) levels in people with dementia, MCI and normal cognitive function

	HOMA- β levels		p value	q-value of FDR correction
	≤ 30 (n=313)	> 30 (n=3,321)		
Whole hippocampus, HV, mm ³	6014.941 (6167.114-6167.114)	6043.407 (5958.247-6128.566)	0.070	-
<i>Hippocampal subregions</i>				
HATA, HV, mm ³	93.987 (91.643-96.331)	95.693 (93.982-97.405)	0.068	0.204
Fimbria, HV, mm ³	97.155 (91.977-102.333)	104.000 (100.220-107.781)	<0.001*	0.011 [†]
Hippocampal fissure, HV, mm ³	339.327 (331.630-347.025)	333.173 (327.554-338.793)	0.045*	0.270
Molecular_layer, HV, mm ³	856.053 (842.557-869.548)	865.300 (855.447-875.153)	0.086	0.206
GC ML DG, HV, mm ³	519.308 (510.872-527.744)	525.676 (519.517-531.835)	0.059	0.236
CA1, HV, mm ³	1169.985 (1150.366-1189.604)	1178.213 (1163.890-1192.536)	0.294	0.441
CA3, HV, mm ³	384.113 (376.163-392.062)	387.191 (381.388-392.995)	0.332	0.398
CA4, HV, mm ³	458.919 (451.546-466.292)	462.836 (457.453-468.218)	0.183	0.313
Subiculum, HV, mm ³	807.711 (797.697-817.724)	802.319 (788.603-816.035)	0.325	0.433
Presubiculum, HV, mm ³	537.695 (527.208-548.183)	540.986 (533.329-548.643)	0.432	0.471
Parasubiculum, HV, mm ³	110.894 (108.119-113.668)	110.678 (106.878-114.478)	0.887	0.887
Hippocampal tail, HV, mm ³	1013.194 (992.205-1034.184)	1026.441 (1011.117-1041.764)	0.114	0.228

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA- β , homeostasis model assessment of beta cell function; HV, hippocampal volume; MCI, mild cognitive impairment.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. [†] q-value of FDR correction < 0.05.

Supplementary Table 23. Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subfields according to homeostasis model assessment of insulin resistance (HOMA-IR) levels in people with dementia, MCI and normal cognitive function

	HOMA-IR levels, %			p for trend	q-value of FDR correction
	<1.6 (n=2,767)	1.6-2.4 (n=637)	≥2.5 (n=230)		
Whole hippocampus, HV, mm ³	6204.847 (6128.106-6281.588)	6175.624 (6087.439-6281.588)	6159.157 (6051.619-6266.695)	0.378	-
<i>Hippocampal subregions</i>					
HATA, HV, mm ³	95.357 (93.166-97.547)	94.692 (92.175-97.209)	94.981 (91.911-98.050)	0.673	1.00
Fimbria, HV, mm ³	107.462 (102.530-112.395)	107.443 (101.775-113.111)	105.801 (98.889-112.713)	0.821	0.985
Hippocampal fissure, HV, mm ³	338.230 (331.071-345.390)	336.653 (328.426-344.880)	334.242 (324.209-344.275)	0.549	1.098
Molecular_layer, HV, mm ³	880.071 (867.609-892.532)	874.931 (860.610-889.251)	873.615 (856.152-891.078)	0.386	2.316
GC ML DG, HV, mm ³	534.773 (527.124-542.421)	533.070 (524.281-541.860)	530.922 (520.204-541.640)	0.595	1.020
CA1, HV, mm ³	1197.294 (1179.159-1215.429)	1190.461 (1169.622-1211.301)	1195.738 (1170.325-1221.151)	0.545	1.308
CA3, HV, mm ³	395.261 (387.885-402.636)	394.583 (386.108-403.058)	391.951 (381.616-402.286)	0.714	0.952
CA4, HV, mm ³	471.167 (464.517-477.818)	469.318 (461.675-476.960)	467.052 (457.732-476.371)	0.453	1.359
Subiculum, HV, mm ³	825.931 (813.633-838.228)	819.421 (805.289-833.553)	810.004 (792.771-827.237)	0.037*	0.444
Presubiculum, HV, mm ³	546.029 (536.393-555.666)	544.127 (533.053-555.201)	539.109 (525.605-552.614)	0.410	1.640
Parasubiculum, HV, mm ³	109.213 (105.632-112.794)	108.617 (104.502-112.732)	108.321 (103.303-113.340)	0.837	0.913
Hippocampal tail, HV, mm ³	1042.290 (1022.628-1061.953)	1038.961 (1016.366-1061.556)	1041.664 (1014.110-1069.218)	0.884	0.884

Abbreviations: CA, Cornu Ammonis; eTIV, estimated intracranial volume; FDR, false discovery rate; GC ML DG, granule cell and molecular cell layer of the dentate gyrus; HATA, hippocampus amygdala transition area; HOMA-IR, homeostasis model assessment of insulin resistance; HV, hippocampal volume; MCI, mild cognitive impairment.

Values are shown as multivariable-adjusted mean values (95% confidence intervals), where values are calculated as follows: (left + right) volumes of hippocampus

or hippocampal subregions.

Adjusted for age, sex, educational level, research site, apolipoprotein E $\epsilon 4$, body mass index, hypertension, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, current smoking habits, current alcohol intakes, regular exercise, eTIV. * p for trend < 0.05. † q-value of FDR correction < 0.05.