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Glucose metabolism and smaller hippocampal volume in elderly people with normal cognitive function

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We investigated associations of glycemic measures, and insulin resistance and secretion measures with hippocampal and subfield volumes. In this cross-sectional study, 7400 community-dwelling participants underwent brain MRI and health checkups between 2016 and 2018. Hemoglobin A_{1c} (HbA_{1c}), glycated albumin (GA), homeostasis model assessment for insulin resistance (HOMA-IR), and HOMA of percent β-cell function (HOMA-β) were evaluated. The associations of each measure with a smaller volume of the hippocampus and twelve hippocampal subfields were investigated. As a result, higher HbA_{1c} or GA and lower HOMA-β levels were significantly associated with smaller volumes in multiple hippocampal subfields. Furthermore, even when we analyzed non-diabetic individuals, substantial associations remained between higher GA or lower HOMA-β levels and smaller volumes of the whole hippocampus or the fimbria. Our findings indicate that postprandial glucose fluctuations, postprandial hyperglycemia, and low insulin secretion have a specific effect on the development of smaller hippocampal volume, suggesting that primary prevention of diabetes and/or sufficient glucose control are important for the prevention of dementia.

Alzheimer's disease (AD) and cognitive impairments are costly medical problems worldwide, and diabetes mellitus (DM) is a major risk factor for AD and cognitive impairments[1–8]. It has been reported that patients with type 2 DM and animal models with DM have impaired cognitive functions such as memory, particularly episodic and spatial memory, learning, cognitive flexibility, executive function, processing speed, and attention[5,6,9].

Several studies have shown considerable associations between type 2 DM and smaller volume of the hippocampus and its subfields[1–4,10–12], and found that abnormalities of some glycemic measures, insulin resistance, and secretion measures were associated with smaller volume of the hippocampus and its subfields[2,10–12]. Hyperglycemia, impaired insulin secretion, and insulin resistance have been considered to impair the hippocampus to cause oxidative stress[13,14], inflammation, and vascular damage[11], decreased neurogenesis[2,12] and excessive production of amyloid-β (Aβ)[11], and phosphorylation of tau[11]. However, there were inconsistent findings on which subfields had been smaller in patients with DM or abnormalities of glycemic or insulin resistance/secretion measures. There have been no reports of simultaneous studies of glycemic measures, insulin resistance, and secretion in the same participant group, and few papers have excluded patients with dementia and mild cognitive impairment. Large-scale studies examining the associations between glucose metabolism markers and the hippocampus in people without dementia are essential to understanding these relationships.

The Japan Prospective Studies Collaboration for Aging and Dementia (JPSC-AD) is an ongoing community-based observational study for dementia in eight research sites in Japan, in which ~10,000 older participants have undergone a brain MRI examination and the following glycemic measures at the baseline survey[15]. Hemoglobin A_{1c} (HbA_{1c}) is a commonly used glycemic measure in clinical fields, and glycated albumin (GA) is an alternative glycemic measure of postprandial glucose fluctuations[16]. Because the glycation speed of albumin is faster than that of hemoglobin[17], therefore, the GA levels rise faster than the HbA_{1c} levels in response to the rapid increase in blood glucose levels[16]. Furthermore, the homeostasis model assessment for insulin resistance (HOMA-IR) is utilized as a marker of insulin resistance[18], and the homeostasis model assessment of percent beta

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cell function (HOMA-β) is considered to be the marker of insulin secretion. This study aimed to clarify which hippocampal subfields are vulnerable to glucose dysmetabolism. We investigated the associations between glycemic measures (HbA_{1c} and GA) and insulin resistance (HOMA-IR) and secretion (HOMA-β) measures with hippocampal and subfield volumes in an older Japanese population with normal cognition. By targeting only cognitively normal individuals, we were able to exclude some individuals with moderate or greater AD pathology, and further clarify the association between glycemic measures or insulin resistance/ secretion and hippocampus.

Results

Characteristics of participants

The baseline survey was conducted from 2016 to 2018. A total of 11,957 community residents in 8 research sites consented to participate in the study, of which 11,410 individuals were aged 65 years or older. Full community surveys were conducted at 6 rural sites; at each of these sites, all residents aged 65 years or older were recruited based on the basic resident registers at the initial year of the baseline survey and were encouraged to participate in the surveys. As a consequence, 8030 individuals aged 65 years or older (participation rate, 67% of the total residents of this age group across the 6 sites) consented to participate in these surveys: Yahaba Town (n = 962), Nakajima Town (n = 2128), Ama Town (n = 722), Nakayama Town (n = 927), Hisayama Town (n = 1714), and Arao City (n = 1577). The remaining 3380 individuals were selected by a simple random sampling (Arakawa Ward, n = 1099) and a voluntary response sampling (Hirosaki City, n = 2281) at the 2 sites with larger populations. The recruited residents visited the research facilities (e.g., the health centers, clinics, or hospitals) for the baseline survey, MRI scans, and blood samplings. We enrolled 7400 participants with normal cognitive function (3030 men and 4370 women) in this study. Among them, 210 and 289 individuals without available measurements of HbA_{1c} and GA, respectively, were excluded. Therefore, we analyzed 7,190 and 7,111 individuals for HbA_{1c} and GA, respectively (Fig. 1).

Additionally, 3492 individuals in the sites where blood is not measured on fasting state, 747 individuals without available measurement of fasting glucose, 64 individuals with a fasting glucose level ≥7.8 mmol/L in the analysis of the HOMA-IR and the analysis of the HOMA-β were excluded. The remaining 3097 individuals were enrolled for HOMA-IR and HOMA-β levels, respectively (Fig. 1). The median values of HbA_{1c}, GA, HOMA-IR, and HOMA-β in the study population were 5.7% [interquartile range (IQR): 5.5–6.0%], 14.8% (IQR: 13.9–16.0%), 1.08% (IQR:0.78–1.58%), and 67.0% (IQR: 47.7–93.6%), respectively. The clinical characteristics are summarized according to the levels of HbA_{1c}, GA, HOMA-β, and HOMA-IR (Table 1 and supplementary Table 1). Table 1 shows the clinical characteristics of the participants according to HbA_{1c}, GA and HOMA-β levels. The frequencies of hypertension, smoking habits, the mean values of age and BMI all increased significantly with higher HbA_{1c} levels. Conversely, the frequencies of female sex, *APOE ε4*, the mean values of serum LDL cholesterol, and serum HDL cholesterol all decreased significantly with higher HbA_{1c} levels. Similar findings were obtained for GA, except for the presence of *APOE ε4*, BMI, educational levels, and smoking habits. For HOMA-β, similar findings were obtained except for age, the presence of *APOE ε4*, hypertension, BMI, and drinking habits (Table 1). Similar findings were obtained for GA, except for the presence of *APOE* ε4, BMI, educational levels, and smoking habits. For HOMA-β, except for age, the presence of *APOE* ε4, hypertension, BMI, drinking habits, and estimated total intracranial volume (eTIV) (Table 1). Similar findings were obtained for serum HOMA-IR, except for age, sex, presence of *APOE* ε4, smoking habits, regular exercise, and eTIV (Supplementary Table 1). We also show the clinical characteristics of 7400 participants according to the status of each risk factor as supplementary Table 2.

Associations of hippocampal and subfield volumes with diabetic status

We analyzed the hippocampal volume (HV) and volume of 12 hippocampal subfields [hippocampus amygdala transition area (HATA), fimbria, hippocampal fissure, molecular layer, granule cell and molecular cell layer of the dentate gyrus (GC ML DG), Cornu Ammonis (CA) 1, CA3, CA4, subiculum, presubiculum, parasubiculum, and hippocampal tail] (Fig. 2A). When we checked the normality, the distributions of outcome variables such as HV and the volume of 12 hippocampus subfields were found to be normal. Figure 3A–C show the whole hippocampus with a significantly

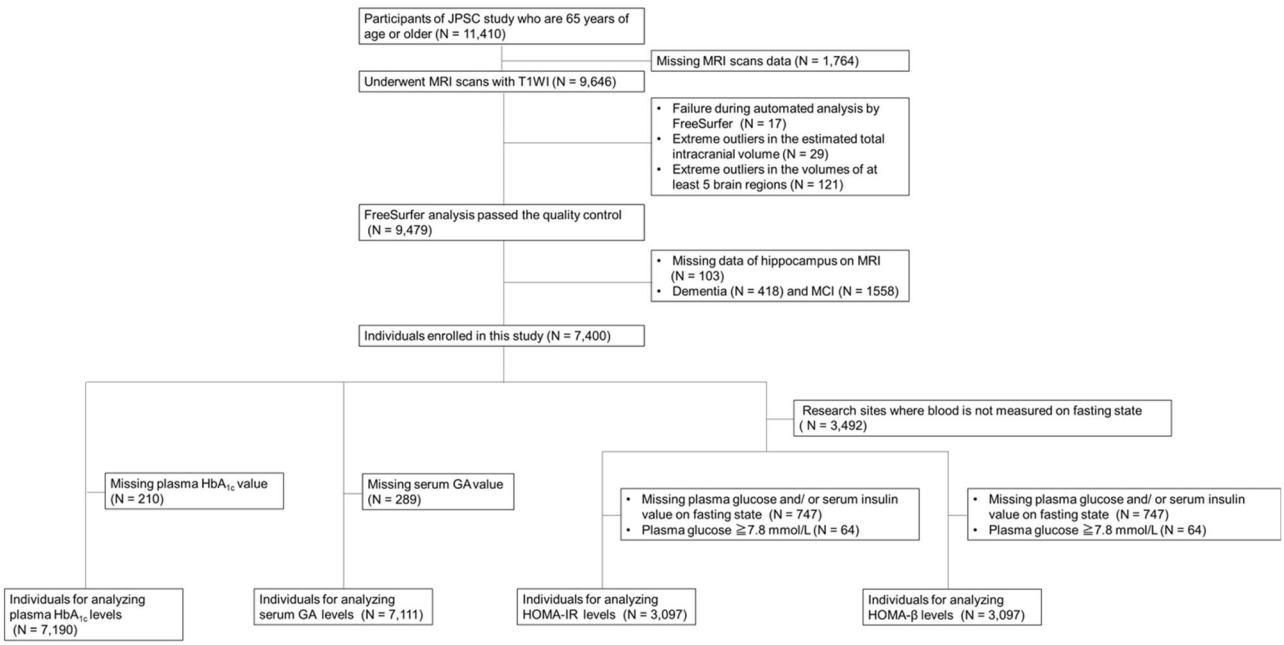

Fig. 1 | A flow chart of enrolled individuals for each analysis of the associations between the hippocampus volumes and each diabetes status, HbA_{1c} levels, GA levels, HOMA-IR, and HOMA-β. GA glycated albumin, HbA_{1c} hemoglobin A_{1c}, HOMA-β homeostasis model assessment of percent β-cell function, HOMA-IR homeostasis model assessment for insulin resistance, JPSC-AD the Japan Prospective Studies Collaboration for Aging and Dementia, MRI magnetic resonance imaging, T1WI T1-weighted imaging.

Table 1 | Clinical characteristics according to hemoglobinA_{1c}, serum glycated albumin, and homeostasis model assessment of β cell function (HOMA-β) levels

Variables	Hemoglobin A_{1c} levels (%)			Serum glycated albumin levels (%)				HOMA-β levels	
	<5.7	5.7–6.4	≥6.5	<13.9	13.9–14.8	14.9–16.0	≥16.1	≤30	>30
Number of participants	3406	2989	795	1736	1854	1815	1706	257	2840
Age, *y*	72.0 (5.7)	72.2 (5.6)	72.4 (5.4)*	70.6 (4.8)	71.5 (5.1)	72.7 (5.7)	73.7 (6.2)*	71.3 (4.9)	71.1 (5.1)
Women, %	60.1	61.1	48.0*	54.7	62.7	64.2	54.5*	31.9*	62.3
ApoE ε4, present, %	18.1	16.5	15.0*	16.1	17.8	17.6	16.7	19.8	17.6
Hypertension, %	48.6	56.6	64.8*	52.1	49.5	51.7	61.6*	70.3	69.6
BMI, kg/m^2	23.3 (3.3)	23.7 (3.3)	24.6 (3.5)*	24.1 (3.2)	23.3 (3.1)	22.8 (3.2)	23.1 (3.4)*	21.6 (2.6)*	23.1 (3.1)
Serum LDL-chol, mg/dL	118.7 (30.3)	118.7 (30.3)	113.3 (30.6)*	121.1 (31.6)	120.3 (29.5)	117.9 (29.4)	113.1 (29.8)*	113.8 (31.5)*	123.1 (30.6)
Serum HDL-chol, mg/dL	65.4 (16.9)	61.9 (16.5)	56.2 (15.3)*	60.6 (15.8)	64.0 (16.9)	65.0 (17.2)	62.3 (17.6)*	70.0 (18.3)*	64.4 (16.7)
Education ≤ 9 y, %	25.1	25.1	25.1	22.1	23.9	23.9	27.7*	23.3	20.4
Current smoking habits, %	8.5	7.8	9.8*	11.8	7.4	6.9	7.3*	15.2*	7.0
Current alcohol intakes, %	47.5	41.1	43.2	52.9	43.9	40.7	40	62.3*	44.5
Regular exercise, %	43.9	44.2	43.5	42.9	44.9	42.7	45.6	48.6	44.0
Estimated intracranial volume, $\times 10^3\ mm^3$	1421.3 (155.8)	1409.6 (150.7)	1433.1 (156.1)	1423.8 (155.2)	1410.4 (153.8)	1408.0 (150.5)	1430.3 (155.0)	1449.6* (140.8)	1375.6 (146.7)

APOE apolipoprotein E, *BMI* body mass index, *eTIV* estimated intracranial volume, *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.

Table 2 | Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subregions according to hemoglobinA_{1c} levels

	Hemoglobin A_{1c} levels, %			*p* for trend	*q* value of FDR correction
	<5.7 (*n* = 3406)	5.7–6.4 (*n* = 2989)	≥6.5 (*n* = 795)		
Whole hippocampus, HV, mm^3	6187.727 (6144.512–6230.942)	6193.960 (6149.737–6238.183)	6122.181 (6067.664–6176.698)	0.003*	–
Hippocampal subregions					
HATA, HV, mm^3	97.152 (95.889–98.416)	96.858 (95.565–98.152)	95.597 (94.003–97.191)	0.046*	0.069
Fimbria, HV, mm^3	102.353 (99.642–105.064)	99.652 (96.878–102.427)	93.592 (90.172–97.012)	<0.001*	<0.001†
Hippocampal fissure, HV, mm^3	346.103 (342.022–350.184)	348.721 (344.545–352.898)	350.870 (345.721–356.019)	0.025*	0.060
Molecular_layer, HV, mm^3	803.394 (796.486–810.303)	805.025 (797.955–812.094)	796.674 (787.959–805.389)	0.049*	0.065
GC ML DG, HV, mm^3	540.797 (536.343–545.251)	540.954 (536.396–545.511)	535.250 (529.632–540.869)	0.026*	0.052
CA1, HV, mm^3	1211.672 (1201.436–1221.908)	1213.804 (1203.328–1224.279)	1203.977 (1191.063–1216.890)	0.150	0.180
CA3, HV, mm^3	397.392 (393.178–401.607)	399.835 (395.523–404.148)	395.177 (389.860–400.494)	0.038*	0.065
CA4, HV, mm^3	478.310 (474.420–482.201)	479.303 (475.322–483.284)	475.788 (470.880–480.696)	0.180	0.196
Subiculum, HV, mm^3	838.303 (831.211–845.395)	836.156 (828.898–843.413)	824.620 (815.673–833.567)	<0.001*	0.002†
Presubiculum, HV, mm^3	560.557 (554.904–566.210)	557.340 (551.555–563.125)	550.431 (543.300–557.562)	0.001*	0.004†
Parasubiculum, HV, mm^3	109.487 (107.416–111.557)	108.293 (106.174–110.412)	108.706 (106.094–111.318)	0.180	0.196
Hippocampal tail, HV, mm^3	1048.310 (1037.476–1059.144)	1056.740 (1045.653–1067.827)	1042.368 (1028.701–1056.036)	0.006*	0.018†

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 *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.

lower volume in the higher levels of HbA_{1c} or GA, or the lower levels of HOMA-β in the Models 1 and 2 analysis (Fig. 3A–C). Figure 2B–D show the hippocampal subfields with significantly lower volumes in the higher levels of HbA_{1c} or GA, or the lower levels of HOMA-β in the Model 2 analysis (Fig. 2B–D). Regarding the levels of HbA_{1c}, substantial differences were observed in the whole hippocampus and following subfields: fimbria, hippocampal fissure, subiculum, presubiculum, and hippocampal tail after adjusting for age, sex, research site, educational levels, and eTIV (Model 1), and fimbria, subiculum, presubiculum, and hippocampal tail after adjusting for age, sex, research site, educational levels, eTIV, presence of *APOE* ε4, hypertension, BMI levels, serum LDL and HDL cholesterol levels, regular exercise and smoking and drinking habits (Model 2) (Table 2, Fig. 2B). Higher HbA_{1c} levels showed smaller hippocampal subfield volume (HSV) in the fimbria subiculum, presubiculum, and hippocampal tail (Table 2, Fig. 2B). No

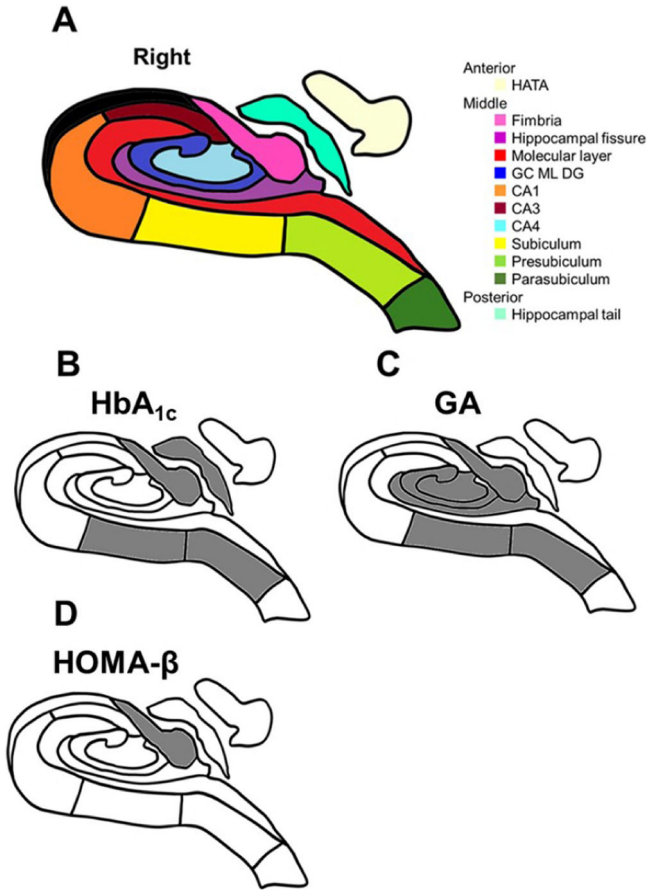

Fig. 2 | Hippocampal subfields and the relationships between hippocampal subfields and glycemic measures or insulin secretion. A A schematic representation of the right hippocampus in a coronal section. Hippocampal subfields are represented in different colors. HATA Hippocampus-amygdala-transition-area, GC, DG, ML, Granule cell and molecular cell layer of the dentate gyrus, CA Cornu Ammonis. Notice that the subfield HATA is transposed from an anterior coronal section, while the tail is transposed from a posterior coronal section. **B**–**D** A schematic representation displaying the substantial associations between hippocampal subregions and glycemic measures or insulin secretion measures in the analysis of the multivariable-adjusted values (Model 2): HbA_{1c} (**B**), GA (**C**), and HOMA-β value (**D**). Gray color represents a substantially smaller volume in the subfields.

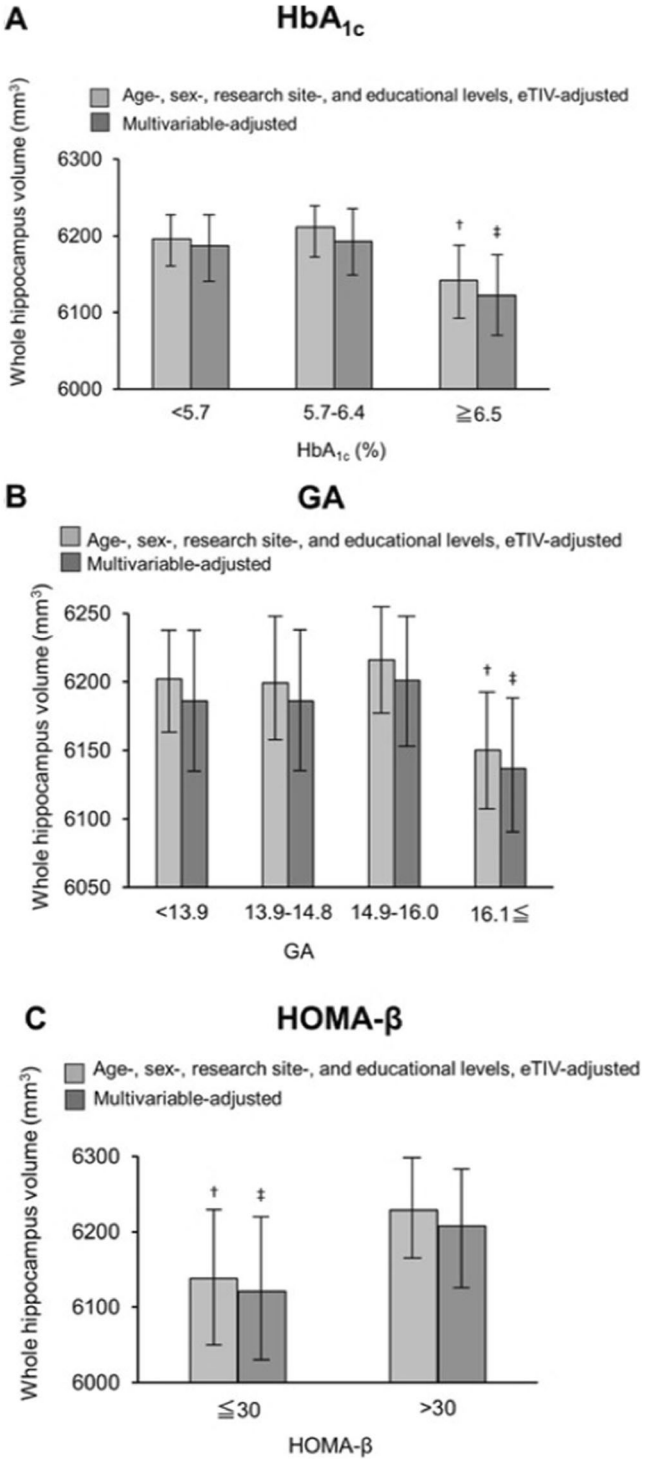

Fig. 3 | The mean values of the volumes of the whole hippocampus according to HbA1c, GA, and HOMA-β value. A–**C** The mean values of the volumes of the whole hippocampus according to HbA_{1c} (**A**), GA (**B**), and HOMA-β value (**C**), with analysis of the age-, sex-, research site-, and educational levels-, estimated intracranial volume (eTIV)- adjusted values (Model 1) and multivariable-adjusted values (Model 2). †<0.05. ‡<0.001.

subfields showed significant differences in the non-DM participants (Supplementary Table 3).

Significant associations were observed between the GA levels and HV and HSV. Substantial differences were found in the whole hippocampus and the following subfields: HATA, fimbria, hippocampal fissure, GC ML DG, CA4, subiculum, and presubiculum in Model 1, and fimbria, hippocampal fissure, GC ML DG, CA4, subiculum, and presubiculum in Model 2 (Table 3, Figs. 2C and 3B). The group with higher GA levels showed smaller HSV in the fimbria, GC ML DG, CA4, subiculum, and presubiculum, and larger HSV in the hippocampal fissure. A significant difference was found only in the fimbria in the analysis of the non-DM participants (Supplementary Table 4).

There were substantial associations between HOMA-β levels and the HV and HSV. Significant differences were found in the whole hippocampus and the fimbria in both Model 1 and Model 2 (Table 4, Figs. 2D and 3C). The HV and HSV in these areas were smaller in the group with a lower HOMA-β. In the analysis of participants without DM, substantial differences were found in the whole hippocampus and the fimbria (Supplementary Table 5).

We did not find any significant associations between the HOMA-IR level and either the HV or HSV (Supplementary Table 6). Analyses of non-DM participants showed similar results (Supplementary Table 7).

The results of multiple linear-regressions analysis for sensitivity analysis, showed that HbA_{1c} and GA were similar to the original analysis, and log-transformed HOMA-β was significantly related to fimbria, GC ML DG, and CA1, and FDR correction also showed an association with fimbria (supplementary Tables 8–11).

Table 3 | Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subregions according to serum glycated albumin levels

	Serum glycated albumin levels, %				*p* for trend	*q* value of FDR correction
	<13.9 (*n* = 1736)	13.9–14.8 (*n* = 1854)	14.9–16.0 (*n* = 1815)	≥16.1 (*n* = 1706)		
Whole hippocampus, HV, mm^3	6186.512 (6139.262–6233.762)	6186.906 (6139.777–6234.035)	6201.668 (6154.382–6248.945)	6137.553 (6090.263–6184.843)	0.003*	–
Hippocampal subregions						
HATA, HV, mm^3	97.551 (96.134–98.967)	97.781 (96.396–99.193)	98.047 (96.631–99.463)	96.525 (95.109–97.942)	0.031*	0.053
Fimbria, HV, mm^3	103.165 (100.207–106.122)	102.379 (99.429–105.330)	101.703 (98.743–104.663)	94.823 (91.863–97.783)	<0.001*	<0.001†
Hippocampal fissure, HV, mm^3	344.556 (340.118–348.994)	344.140 (339.714–348.567)	347.012 (342.570–351.453)	349.329 (344.888–353.771)	0.009*	0.027†
Molecular_layer, HV, mm^3	805.593 (798.038–813.147)	805.133 (797.598–812.668)	802.392 (794.832–809.952)	798.359 (790.799–805.920)	0.059	0.078
GC ML DG, HV, mm^3	541.073 (536.208–545.938)	540.880 (536.027–545.733)	542.606 (537.737–547.475)	534.958 (530.088–539.827)	<0.001*	0.001†
CA1, HV, mm^3	1212.591 (1201.390–1223.792)	1209.935 (1198.763–1221.108)	1214.922 (1203.712–1226.131)	1204.180 (1192.969–1215.390)	0.075	0.112
CA3, HV, mm^3	396.994 (392.388–401.600)	398.176 (393.581–402.770)	399.892 (395.282–404.502)	395.893 (391.283–400.503)	0.125	0.136
CA4, HV, mm^3	478.029 (473.777–482.281)	478.330 (474.089–482.571)	480.370 (476.115–484.625)	475.274 (471.019–479.530)	0.019*	0.038†
Subiculum, HV, mm^3	838.538 (830.778–846.299)	836.945 (829.205–844.686)	838.422 (830.656–846.188)	828.178 (820.411–835.945)	0.001*	0.004†
Presubiculum, HV, mm^3	560.138 (553.959–564.161)	557.998 (551.835–564.161)	559.778 (553.595–565.961)	552.829 (546.645–559.013)	0.009*	0.027†
Parasubiculum, HV, mm^3	109.262 (107.003–111.521)	108.682 (106.429–110.935)	108.994 (106.734–111.255)	108.092 (105.831–110.353)	0.585	0.585
Hippocampal tail, HV, mm^3	1043.944 (1032.095–1055.793)	1051.311 (1039.492–1063.129)	1055.309 (1043.450–1067.167)	1049.210 (1037.350–1061.069)	0.092	0.110

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 *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.

Regarding the stratified analysis by age, only the group under 75 years of age showed significant differences and the *p* value for the interaction effect was less than 0.05 in fimbria and hippocampal fissure for GA (Supplementary Tables 12–15). About the results of stratified analysis by presence/absence of *ApoE ε4*, the group without *ApoE ε4* showed significant differences and the *p* value for the interaction effect was <0.05 in fimbria for HbA_{1c} and hippocampal tail for HOMA-β (Supplementary Tables 16–19).

When we analyzed including people with dementia or MCI, we observed substantially the same results except for the number of subfields of hippocampus showing significant association increased from 4 to 5 for HbA_{1c} and 6 to 11 for GA and disappeared the differences of HV for HOMA-β (Supplementary Tables 20–23).

Discussion

This cross-sectional study showed substantial associations between a higher blood hyperglycemic state or lower insulin secretion and extensive smaller hippocampal volume in some subregions. Particularly, it was found that higher levels of HbA_{1c} caused a smaller volume of the hippocampal tail, fimbria, subiculum, and presubiculum, that higher levels of GA caused a smaller volume of fimbria, dentate gyrus (GC ML DG), CA4, subiculum, presubiculum, and that lower levels of the HOMA-β caused the smaller volume of fimbria. In particular, the higher levels of GA, the more subfields had smaller volumes.

The significant interaction effects between GA and age were observed in fimbria, and hippocampal fissure. We considered that this result reflected more AD pathology, vascular disease, florid changes, and other pathologies added in older participants, and the relationships between diabetes markers and hippocampal subregion volume changes with age. The mechanism of the interaction effect between HbA_{1c} or HOMA-β and the presence/absence of *ApoE ε4* in the fimbria and hippocampal tail of the group without *ApoE ε4* is not known.

For HOMA-β, when we added people with cognitively impaired, the significant differences of HV were disappeared. We speculate that it was because people with cognitively impaired had different reasons that associated for hippocampal atrophy other than decreased insulin secretions.

The hippocampal subfields are primarily composed of the ammon horn (CA1-4), dentate gyrus that includes the molecular layer and granule cells of the molecular layer, subiculum, presubiculum, and parasubiculum. Additionally, the hippocampus includes the fimbria and HATA. The hippocampus sends major outputs from the CA1 and subiculum to the cortical regions. The CA1 and subiculum are considered the most important regions for the formation of memories such as episodic memory, spatial memory, and autonoetic consciousness[19–23]. Another output from the hippocampus is sent through the fimbria, which is composed of myelinated axons and comprises the Papez circuit and polysynaptic pathway. Fimbria is important for memory and learning[24,25]. The hippocampus receives major inputs through the dentate gyrus. The dentate gyrus is thought to contribute to the formation of novelty detection, pattern separation, pattern completion, spatial working memory, information encoding, and memory consolidation and retention[26–28]. The fact that higher HbA_{1c} or GA or lower HOMA-β impairs these areas might be related to the various cognitive dysfunctions, including episodic memory, spatial memory, and learning in patients with DM. However, the present study did not assess detailed cognitive functions such as episodic memory, spatial memory, and learning, therefore the mediation of the association between the hippocampal subfields where showed lower volume in the present results and cognitive function, could not be established.

Regarding the hyperglycemia index, this study demonstrated more widespread smaller hippocampal volume, particularly with elevated GA, than with HbA_{1c}. HbA_{1c} reflects the mean glucose level over the preceding 3 months[29], and GA has been reported to reflect the state of glucose level over the preceding 2-3 weeks[30]. A disadvantage of HbA_{1c} is that HbA_{1c} levels fluctuates with anemia[31], and more than 10% of community-dwelling adults

Table 4 | Multivariable-adjusted mean values of the volumes of the hippocampus and hippocampal subregions according to homeostasis model assessment of β cell function (HOMA-β) levels

	HOMA-β levels		*p* value	*q* value of FDR correction
	≤30 (*n* = 257)	>30 (*n* = 2840)		
Whole hippocampus, HV, mm^3	6121.331 (6024.162–6218.500)	6208.870 (6132.305–6285.434)	0.013*	–
Hippocampal subregions				
HATA, HV, mm^3	93.744 (90.970–96.518)	95.459 (93.273–97.645)	0.087	0.130
Fimbria, HV, mm^3	101.041 (94.801–107.281)	108.221 (103.304–113.138)	0.001*	0.012†
Hippocampal fissure, HV, mm^3	341.212 (0332.141–350.284)	337.296 (330.148–344.444)	0.232	0.253
Molecular_layer, HV, mm^3	870.085 (854.298–885.872)	880.248 (867.808–892.687)	0.075	0.150
GC ML DG, HV, mm^3	526.831 (517.148–536.515)	535.342 (527.712–542.972)	0.015*	0.09
CA1, HV, mm^3	1183.722 (1160.750–1206.694)	1198.105 (1180.004–1216.205)	0.083	0.142
CA3, HV, mm^3	390.998 (381.655–400.342)	395.505 (388.142–402.867)	0.182	0.242
CA4, HV, mm^3	465.290 (456.866–473.713)	471.411 (464.773–478.048)	0.044*	0.132
Subiculum, HV, mm^3	813.709 (798.120–829.297)	825.507 (813.224–837.790)	0.036*	0.144
Presubiculum, HV, mm^3	540.658 (528.446–552.870)	545.982 (536.360–555.605)	0.227	0.272
Parasubiculum, HV, mm^3	109.341 (104.803–113.879)	109.044 (105.469–112.620)	0.856	0.856
Hippocampal tail, HV, mm^3	1025.912 (1001.013–1050.811)	1044.046 (1024.427–1063.665)	0.044*	0.132

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.

aged 65 years and older have been reported to have WHO-defined anemia[32]. Therefore, it is possible that HbA_{1c} may have been less effective in indicating blood glucose levels compared to GA. Furthermore, GA has been reported to reflect short-term average glucose and fluctuations in glucose[33]. Past studies have reported that smaller hippocampal volume might be preceded by not only chronic hyperglycemia but also glycemic variability[11], and this result is consistent with that of a previous study. Possible mechanisms underlying the association between hyperglycemia or glycemic variability and smaller hippocampal volume is known to cause oxidative stress, inflammation, and vascular damage. Hyperglycemia is believed to promote the production of advanced glycation end products (AGEs), and the blood receptor of AGEs (i.e., RAGE levels) is altered in patients with prediabetes associated with higher oxidative stress levels[13,14]. In animal studies, prediabetes rat models with cognitive decline showed neuroinflammation and neuronal apoptosis in the hippocampus[34]. Glucose toxicity causes microvascular ischemic damage, and chronic hypoxia causes microglia activation, phosphorylation of tau, and cell death, all of which could lead to smaller volume of the hippocampus[11].

This study showed that the low insulin secretory capacity results in smaller volume of the whole hippocampus and numerous hippocampal subregions. Furthermore, this study showed that even in people without DM, reduced levels of HOMA-β were associated with smaller volume of the whole hippocampus and fimbria, which are important for memory. The possible mechanisms of smaller hippocampal volume induced by decreased insulin levels are decreased neurogenesis and excessive production of amyloid-β (Aβ), and phosphorylation of tau[2,12]. Insulin and its receptors are widely expressed in the brain and play important roles in neuronal proliferation and differentiation[2]. The subgranular zone, which is located in the dentate gyrus in the hippocampus, is one of the two major neural stem cell regions of adults, and insulin and insulin-like growth factors are crucial in neurogenesis and neural stem cell self-renewal through different ligand-receptor interactions[2]. Furthermore, insulin has previously been reported to promote dendritic spines formation in rat hippocampal neurons[35]. Therefore, decreased insulin might weaken neurogenesis and decrease volumes of hippocampus or hippocampal subfields. Another possible mechanism is Aβ overproduction and hyperphosphorylation of the tau protein[11]. Insulin has been reported to be involved in the regulation of Aβ fibrillization, and to protect neurons against Aβ-induced cell-death[36], and Aβ overproduction has been reported in the brain of mice that were administered streptozotocin[37,38]. Furthermore, the deficiency in insulin signaling promotes the tau phosphorylation mediated by glycogen synthase kinase 3β, which is one of the tau phosphorylases[39].

In this study, no substantial association was observed between HOMA-IR values and hippocampal volume. Insulin resistance was hypothesized to reduce the insulin concentration in the cerebrospinal fluid[40], and result in Aβ overproduction and excessive amount of hyperphosphorylated tau protein[41]. Some studies reported that HOMA-IR levels were significantly associated with smaller volume of hippocampus and its subfields in non-elderly patients with type 2 DM and postmenopausal women undergoing hormone therapy[2,42]. Further large-scaled studies are required to clarify the association between HOMA-IR levels and atrophies of hippocampus and its subregions in community-dwelling elderly.

This study had several limitations. First, we did not obtain data on the duration of DM. Second, this study did not exclude patients with preclinical AD because amyloid PET and/or cerebrospinal fluid tests were not performed. Thus, smaller hippocampal volume may also be associated with AD pathogenesis. Third, because the findings of this study were derived from cross-sectional data, the temporal trends of glycemic measures, insulin secretion and atrophy of the hippocampus and its subfields were unknown. Fourth, some study areas used 1.5 T MRIs, and others used 3 T MRIs. Although we standardized MRI images, and we tried to adjust for errors in advance by including the survey sites as an adjustment variable, the MRI conditions might not be exactly the same. Finally, the data in this study are for the Japanese only; therefore, generalizability to other ethnicities, and races has not been examined. The strengths of this study are that it was a large study that could adjust for many factors. In conclusion, this study revealed that higher plasma HbA_{1c} levels, higher serum GA levels, and lower HOMA-β levels were related to smaller hippocampal volume including multiple subfields. Particularly higher serum GA levels or low levels of HOMA-β can be associated with smaller hippocampal volume even in patients with non-DM. Our findings indicate that sufficient glucose control or primary prevention of diabetes is important for the prevention of dementia, and that postprandial hyperglycemia, postprandial glucose fluctuations, and low insulin secretion have a more specific effect on the

development of smaller hippocampal volume. Further basic research and prospective longitudinal studies are required to verify these findings.

Methods

Study population

Among the 11,410 participants in the JPSC-AD study aged 65 years or older, 9646 underwent MRI scans with 3-dimensional T1-weighted images. After excluding 167 participants who did not pass the quality control of the FreeSurfer analysis, 103 participants who did not have hippocampal measurement data, and 1976 participants who were diagnosed with dementia or mild cognitive impairment, 7400 participants with normal cognitive function (3030 men and 4370 women) were enrolled in this study (Fig. 1).

Standard protocol approvals, registrations, and patient consents

The study was approved by the Kyushu University Institutional Review Board for clinical research (approval number 686-10) and by each of the local ethics committee of the eight research institutes: Kanazawa University (approval number 2185), Hirosaki University (approval number 2019-064-3), Iwate Medical University (approval number HG2020-017), Keio University School of Medicine (approval number 20160214), Matsue Medical Center (approval number H28-14), and Ehime University (approval number 1610004 and 2210016), Kumamoto University (approval number 333), and Tohoku University (approval number 2021-1-245). The all participants gave their informed consent.

MRI analysis

Structural MRI studies were performed using 1.5 T MRI (four Philips, one Hitachi, and one General-Electric [GE]) and 3 T MRI (one GE and one Siemens) machines. The two sites, Arakawa Ward and Hirosaki City used 3 T MRI, and the other sites used 1.5 T MRI. 3D volumetric acquisition of T1-weighted turbo field echo images was conducted according to the brain MRI protocol for the Alzheimer's Disease Neuroimaging Initiative (ADNI) study[43]. In addition, the brain MRI data were standardized by using the MRI Phantom, Human Phantom, and ADNI Phantom to correct geometric distortions among the different pieces of equipment. All T1-structural images were analyzed using FreeSurfer version 7.0 (FreeSurfer version 7.0; http://surfer.nmr.mgh.harvard.edu)[44] in Tohoku University and preprocessed according to the standard method. The volumes of the area of interest were created using FreeSurfer 7.0[45], in particular, the HV and volume of 12 HSV (Fig. 2A) and eTIV were calculated automatically. The hippocampal and subfield volumes were calculated as the sum of the right and left volumes, respectively.

Measurements of HbA_{1c}, GA, HOMA-IR, and HOMA-β and diagnosis of DM

Plasma HbA_{1c} levels were measured using the National Glycohemoglobin Standardization Program (NGSP), and serum GA levels were determined using the enzymatic method. Additionally, serum insulin levels were measured using a chemiluminescence immunoassay. Detailed measurement methods of blood chemistry have been previously reported[15]. For analyses of the association between the HbA_{1c} category and hippocampal volumes, we categorized HbA_{1c} using standard clinical cutoff points: normal, ≤5.7%; prediabetes, 5.7–6.5%; and diabetes, ≤6.5%. For the analyses, the GA value was divided into quartiles. We calculated the HOMA-IR using the following formula: HOMA-IR = fasting serum insulin (μU/mL)/fasting plasma glucose (mmol/L)/22.5[46]. Subsequently, we calculated the HOMA-β using the following equation: HOMA-β = fasting serum insulin (μU/mL) × 20/[fasting plasma glucose (mmol/L)–3.5][46]. For analyses, the HOMA-IR was categorized using standard clinical cutoff points: ≤1.6%, 1.6–2.5%, ≥2.5%, and HOMA-β was also categorized using standard clinical cutoff points: ≤30%, and >30%. For the HOMA-IR and HOMA-β analysis, we excluded individuals who administered insulin injections to remove the effects of exogenous insulin[46]. DM was determined by the 2010 American Diabetes Association (ADA) criteria[47].

Other risk factor and confounding factors measurements

We identified gender, *ApoE ε4* status, alcohol consumption, low education, and exercise habits as confounding factors associated with reduced hippocampal volume. Furthermore, hypertension, obesity, hyper-LDL-cholesterolemia, hypo-HDL-cholesterolemia, and smoking, identified as risk factors for vascular disease that could serve as modifiers. Each participant completed a self-administered questionnaire containing questions on sociodemographic data (age, sex, and educational level), medical history (hypertension), regular exercise, and smoking and drinking habits. Regular exercise was defined as physical activity specifically undertaken for exercise or sports performed for at least 30 min twice per week over the most recent year or longer. Completed questionnaires were reviewed by trained researchers to identify unanswered or inconsistent items. The body mass index (BMI) (kg/m^2) was used as an indicator of obesity. Serum HDL and LDL cholesterol were enzymatically measured[15]. To determine Apolipoprotein E (*APOE*) polymorphisms, two single nucleotide polymorphisms (rs429358 and rs7412) were genotyped using a multiplex PCR-based targeted sequencing method, as previously reported[48].

Statistical analyses

Clinical characteristics were evaluated using the t-test or Jonckheere-Tsrpsta test and chi-squared test or Mantel-Haenszel test for continuous and categorical variables, respectively. Analysis of covariance was used to estimate and compare multivariable-adjusted values and their 95% confidence intervals for HV and each HSV. Model 1 was adjusted for age, sex, research site, educational levels and eTIV. Model 2 was further adjusted for the presence of *APOE* ε4 allele, hypertension, BMI levels, serum LDL and HDL cholesterol levels, regular exercise, and smoking and drinking habits. We performed additional analyses on participants without DM. The problem of multiple comparisons was addressed by controlling Benjamini–Hochberg false discovery rate (FDR)[49]. The FDR-adjusted p-values (i.e., *q* values) below 0.05 were considered statistically significant. SPSS software package (version 29; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. For sensitivity analysis, multiple linear-regressions analysis was performed using the HV and each HSV and the real values of HbA_{1c}, GA. Since HOMA-IR and HOMA-β were not normally distributed, a log transformation was performed to confirm that they were normally distributed, and the log-transformed HOMA-IR and HOMA-β values were used. The covariates were which of the above model 2 covariates.

Furthermore, to confirm the interaction between the diabetes markers and other risk factors for hippocampal atrophy, a stratified analysis of age and the presence of *ApoE ε4* as a representative was also performed and confirmed the interaction effect. The stratified analysis about age was analyzed separately for those under 75 and over 75 years of age.

We also performed a sensitivity analysis that included individuals with dementia and MCI.

Data availability

The datasets used in the present study are not publicly available, because they contain confidential clinical data on the study participants. However, the data are available upon reasonable request and with the permission of the Principal Investigator of this study, Toshiharu Ninomiya.

Code availability

No custom code or mathematical algorithm was developed for this study. Details regarding the specific codes used can be found in the references cited. As indicated in the references, any access restrictions or licensing information associated with the codes used can be obtained from the respective sources.

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Author contributions

Research idea and study design: A.S., M.N.-S., T.N., K.O.; data acquisition: A.S., M.N.-S., S.S., Y.U., Y.T., B.T., J.H., T.O., T.H., Y.T., S.N,. T.M., M.M., K.N,. J.I, M.T.; data analysis/interpretation and supervision or mentorship: M.N.-S., H.N., T.N., K.O.; statistical analysis: A.S., M.N.-S. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Competing interests

A.S., M.N.-S., S.S., Y.U., Y.T., B.T., J.H., T.O., T.H., Y.T., S.N., T.M., M.M., K.N., J.-i.I., M.T., H.N., and K.O. declares no competing financial or non-financial interests. T.N. declares no competing non-financial interests but the following competing financial interests: Grants from Suntory Holdings Limited.

Additional information

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