Association between chronic low back pain and regional brain atrophy in a Japanese older population: the Hisayama Study

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Abstract

Chronic low back pain (CLBP) is the leading cause of years lived with disability. Recently, it has been reported that CLBP is associated with alterations in the central nervous system. The present study aimed to investigate the association between CLBP and regional brain atrophy in a Japanese older population. A total of 1106 community-dwelling participants aged ≥ 65 years underwent brain magnetic resonance imaging scans and a health examination in 2017 to 2018. We used the FreeSurfer software for the analysis of brain magnetic resonance imaging. Chronic pain was defined as subjective pain for ≥3 months. Participants were divided into 3 groups according to the presence or absence of chronic pain and the body part that mainly suffered from pain: a "no chronic pain (NCP)" group (n = 541), "CLBP" group (n = 189), and "chronic pain in body parts other than the lower back (OCP)" group (n = 376). The brain volumes of the ventrolateral and dorsolateral prefrontal cortex, the posterior cingulate gyrus, and the amygdala were significantly lower in the CLBP group than in the NCP group after adjustment for sociodemographic, physical, and lifestyle factors, and depressive symptoms. In addition, the left superior frontal gyrus was identified as a significant cluster by the Query, Design, Estimate, Contrast interface. There were no significant differences in the brain volumes of pain-related regions between the NCP and the OCP group. The present study suggests that CLBP is associated with lower brain volumes of pain-related regions in a general older population of Japanese.

1. Introduction

Chronic low back pain (CLBP) is the leading cause of years lived with disability, and a global burden both in the developed and developing countries [13]. Although CLBP is very common, approximately 90% of individuals with CLBP cannot identify a clear specific cause or origin of the pain [22]. The concept of nociplastic pain was recently proposed, in which augmented pain and sensory processing and altered pain modulation in the central nervous system are thought to play prominent roles [7,11,23]. CLBP is considered one of the most common nociplastic pain syndromes [11], and thus, alterations in the central nervous system may play an important role in the course of CLBP.

There is growing evidence that CLBP is significantly associated with alterations in brain structure and function. Several hospital-based studies have shown that individuals with CLBP have lower brain volumes in pain-related brain regions than those without [1,5,20,34,43]. However, the generalizability of these findings may be limited because most of these studies were case-control studies with a small sample size of less than 100 participants and only compared patients with severe CLBP and healthy controls. Conversely, a limited number of population-based studies with relatively large sample sizes have examined the association between CLBP and brain volume in general populations, including people with CLBP of different degrees of severity from mild to severe, and the findings have been inconsistent [8,12].

The present study sought to investigate the association between CLBP and regional brain atrophy by using brain magnetic resonance imaging (MRI) data from more than 1000 older people living in a community in Japan.

2. Methods

2.1. Study design and participants

The Hisayama Study is an ongoing population-based cohort study of cerebro-cardiovascular disease in the town of Hisayama, which is a metropolitan area of Fukuoka City in Japan. In addition to annual

health examination, for residents aged 65 years or older, comprehensive screening surveys of dementia and activities of daily living (ADL) have been conducted every 5 to 7 years since 1985. The detailed design of the study has been described elsewhere [25,26]. In 2017 and 2018, a total of 2202 residents aged ≥65 years (94.1% of the town's total population in this age group) participated in the screening surveys of dementia; of whom 1577 (71.6%) participants underwent brain MRI scans. Among these 1577 participants, we excluded the following from the present analysis: 7 individuals who did not provide consent to use the MRI data, 49 individuals whose brain MRI data were inappropriate for the FreeSurfer analysis in the visual check by the study team (7 with artifacts, 17 with skull stripping error, 9 with trace error, 8 with brain infarction, 1 with brain hemorrhage, 1 with chronic subdural hematoma, 1 with brain tumor, and 5 with any errors in the evaluation process of the regional brain volumes using the FreeSurfer software for the imaging analysis), 130 with history of dementia, and 285 without available data for chronic pain. The remaining 1106 individuals (491 men and 615 women) were included in the present study (Fig. 1). This study was approved by the Kyushu University Institutional Review Board for Clinical Research, and written informed consent was obtained from all the participants.

2.2 Assessment of chronic low back pain and pain-related measurement

Participants were asked the following questions using a questionnaire: "Do you have any pain on your body?", "Is the pain present for more than 3 months?", and "What part of your body mainly suffers from pain: your head, face, neck, shoulders, arms, chest, back, abdomen, low back, knees, feet, pelvic, buttocks, genital area, tongue, teeth, entire body or some other part?" They were also asked about average pain intensity over the previous week by using a visual analog scale (VAS) [15]. Chronic pain was defined as having any subjective pain for more than 3 months according to the International Association for the Study of Pain (IASP) definition [41]. Participants were classified into 3 groups based on the information on the questionnaire about the presence or absence of chronic pain and of the body part that mainly suffered from pain, as follows: a "no chronic pain (NCP)" group, a "CLBP" group, and a "chronic pain in body parts other than the lower back (OCP)" group.

2.3. Assessment of regional brain volume

MRI examinations included T1-weighted 3-dimensional magnetization-prepared rapid gradient echo images, conventional T1- and T2-weighted images, fluid-attenuated inversion recovery (FLAIR) images, T2*-weighted images, and magnetic resonance angiography of the brain. They were performed using a 1.5-Tesla MRI scanner (Intera Pulsar; Philips Medical Systems, Best, the Netherlands) with a multichannel head coil. T1-weighted 3-dimensional images acquired in the sagittal plane with the following parameters were used to determine regional brain atrophy: repetition time 8.5 milliseconds, echo time 4.0 milliseconds, inversion time 1000 milliseconds, flip angle 8°, a field of view 240 mm, acquisition matrix 192 × 192, slice thickness 1.2 mm, number of excitations 1. The segmentation and volume measurements of cortical and subcortical brain structures, and intracranial volume (ICV) were performed automatically using the FreeSurfer software (version 6.0.0; Harvard University, Boston, MA [http://surfer.nmr.mgh.harvard.edu]). The cortical parcellation was performed using a Desikan-Killiany atlas [9]. All Freesurfer automated segmentation results were visually checked for accuracy by the study team. Six study members, including an expert stroke neurologist and an expert psychiatrist, double-checked whether the cortex was correctly segmented by FreeSurfer according to the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) Cortical Quality Control Protocol 2.0 [10]. Among the cases identified as having inaccurate segmentation by at least 1 member, skull and dura matter misclassifications were corrected by command and reanalyzed. Reanalyzed images were double-checked again by the study members to determine whether they were appropriate for the present analysis.

As the brain regions of interest in the present analysis, we selected the following pain-related brain regions based on a previous study, in which the examined brain regions were determined by a systematic search of the literature [8]: (1) ventrolateral prefrontal cortex, (2) dorsolateral prefrontal cortex, (3) orbitofrontal cortex, (4) postcentral gyrus, (5) insular cortex, (6) thalamus, (7) anterior cingulate cortex, (8) posterior cingulate cortex, (9) amygdala, and (10) hippocampus. In addition to

the aforementioned 10 regions, we also examined the striatal brain regions (ie, the caudate nucleus, putamen, pallidum, and nucleus accumbens) and memory-related regions (ie, the entorhinal cortex and parahippocampal gyrus). The former have been reported to be associated with CLBP [2], whereas the latter are known to be associated with early cognitive dysfunction [28]. To adjust for head size, regional brain volume was calculated as a percentage of ICV as follows: ([left + right] regional brain volume / ICV) × 100 (%). Because there was no evidence of heterogeneity between the association of chronic pain status with the left and right regional brain volume (all *P* for heterogeneity > 0.40), we analyzed each regional brain volume as the sum of the left and right values.

2.4. Other covariates

Each participant answered a self-administered questionnaire and was checked by trained interviewers. The questionnaire included the information of medical history, medications for hypertension and diabetes, educational level, marital status, subjective economic status, current smoking, current drinking, regular exercise, ADL, and depressive symptoms. Low education level was defined as 9 years or less of formal education. Marital status was categorized into 2 groups: with or without a partner. Subjective economic status was assessed by the following question: "How do you feel about the economic status of your household?" Participants were asked to choose among 6 responses: high, rather high, neither high nor low, rather low, low, or unknown; participants who answered "low" or "rather low" were defined as having low subjective economic status [6]. Regular exercise was defined as engaging in physical exercise 3 or more times a week during leisure time. ADL disability was defined as a Barthel Index of ≤ 95 [36,40]. Depressive symptoms were assessed by the 15-item Geriatric Depression Scale (GDS), and a participant who had a GDS score of ≥ 6 was defined as having depressive symptoms [16]. Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated (in kilograms/square meter). Hypertension was defined as blood pressure levels of ≥ 140/90 mmHg (the mean of 3 measurements) and/or current use of antihypertensive medication [45]. Plasma glucose levels were measured by the hexokinase method. Diabetes was determined by plasma glucose level (fasting glucose level of ≥ 126 mg/dL, 2-h post-

load glucose level after 75-g oral glucose tolerance test of ≥ 200 mg/dL, or casual glucose level of ≥ 200 mg/dL, using the 2006 World Health Organization criteria [46]) and/or current use of medication for diabetes. Serum total cholesterol was measured enzymatically. Cerebrovascular lesions on MRI were defined as brain infarction or hemorrhage observed on MRI regardless of the presence or absence of neurological symptoms. Brain infarction included lesions of ≥ 3 mm in diameter visible on both the T1- and the T2-weighted image with a surrounding hyperintense rim on the FLAIR image. Brain hemorrhage was defined as any hemorrhagic lesions, including cerebral microbleeds, visible on the T2*-weighted image [17]. Each scan was read by 2 trained stroke neurologists who were blinded to the clinical information (interrater agreement ratio: 85.2% for the brain infarctions, 90.5% for the brain hemorrhages). In the case of different interpretations, a third stroke neurologist read the image and made a final decision.

2.5. Statistical analysis

The age- and sex-adjusted mean values of continuous variables and frequencies of categorical variables for risk factors were calculated and compared between groups using an analysis of covariance with the Dunnett method for multiple comparisons and a logistic regression analysis including age and sex in the relevant model, respectively, with the NCP group set as a reference. The multivariable-adjusted means and 95% confidence intervals of the regional brain volume/ICV were calculated by using an analysis of covariance. We evaluated 3 different models as follows: (1) model 1, adjusted for age and sex; (2) model 2, adjusted for age, sex, and sociodemographic, physical, and lifestyle factors (ie, educational status, marital status, subjective economic status, hypertension, diabetes, serum total cholesterol, BMI, current smoking, current drinking, regular exercise, cerebrovascular lesions on MRI, and ADL disability); and (3) model 3, adjusted for the covariates included in model 2 plus depressive symptoms as a psychological factor because depressive symptoms are often observed in individuals with CLBP and depression itself has been reported to be associated with lower regional brain volumes [44]. To assess the dose-response relationship between the severity of CLBP and the regional brain volume, we divided the CLBP group into low- and high-

intensity groups by a median VAS of 40 mm; individuals in the NCP and CLBP groups were included in this analysis (n = 730). As a sensitivity analysis, the relationship between the severity of CLBP and the regional brain volumes were assessed by using VAS as a continuous variable (VAS in the NCP group was set as 0 mm). For the subgroup analysis, we stratified participants by age (< 75 and ≥ 75 years). The heterogeneity in the magnitude of the association of CLBP status with the multivariable-adjusted mean values of pain-related brain regions across the age groups was tested by adding a multiplicative interaction term between the status of CLBP and age group to the relevant model. Additionally, a similar analysis was performed by using age as a continuous variable for a sensitivity analysis. The aforementioned analyses were performed using the SAS software package (version 9.4; SAS Institute Inc, Cary, NC). Two-sided values of $P < 0.05$ were considered statistically significant in all analyses.

We also used the Query, Design, Estimate, Contrast (QDEC) interface of FreeSurfer to perform a group analysis in which regions of interest were not set, to compare the difference in cortical volume between the CLBP group and the NCP group, after excluding the OCP group. QDEC supplies the statistical maps, which show the distribution of *P* values generated by means of a general linear model with covariates. The general linear model was computed on a vertex-by-vertex basis for the cortical volume of each hemisphere, using the following covariates: age, sex, educational status, marital status, subjective economic status, hypertension, diabetes, serum total cholesterol, BMI, current smoking, current drinking, regular exercise, cerebrovascular lesions on MRI, and ADL disability. Multiple comparisons were corrected using a Monte Carlo simulation method, which is a clusterwise correction using a threshold set at $P < 0.05$, with the initial cluster-forming criterion being set at $P < 0.005$ in accordance with previous studies [4,18].

3. Results

Individuals suffering mainly from CLBP accounted for 17.1% of the total study population. Among the individuals with chronic pain, the low back was the most common body part chosen as the main

site of pain, followed by the knees, shoulders, and feet (Table S1). The age- and sex-adjusted baseline characteristics of the study population according to the status of chronic pain are summarized in Table 1. Compared with the NCP group, the CLBP group had significantly higher proportions of the individuals with low education level, hypertension, and depressive symptoms, and a significantly lower proportion of the individuals with regular exercise. In the OCP group, the mean values of age and BMI, and the proportions of women and the individuals with low subjective economic status, ADL disability, and depressive symptoms were significantly higher, whereas the mean value of serum total cholesterol and the proportion of the individuals with regular exercise were significantly lower than in the NCP group.

Table 2 demonstrates multivariable-adjusted mean values of the pain-related brain regions according to the status of chronic pain. The CLBP group had significantly lower age- and sex-adjusted mean values of the ventrolateral prefrontal cortex, the dorsolateral prefrontal cortex, the posterior cingulate cortex, and the amygdala than the NCP group (model 1). These significant associations remained unchanged substantially after adjustment for age, sex, educational status, marital status, subjective economic status, hypertension, diabetes, serum total cholesterol, BMI, current smoking, current drinking, regular exercise, cerebrovascular lesions on MRI, and ADL disability (model 2), and after additional adjustment for depressive symptoms (model 3). There was no evidence of a significant difference between the CLBP group and the NCP group in the remaining brain regions of interest (ie, the orbitofrontal cortex, postcentral gyrus, insular cortex, anterior cingulate cortex, and hippocampus). Also, there was no evidence of a significant difference in brain volumes for any of the examined regions between the NCP group and the OCP group (all $P > 0.40$). Table S2 shows multivariable-adjusted mean values of the striatal brain regions and memory-related brain regions. For these regions, there was no evidence of a significant difference in brain volumes between the NCP and CLBP groups or between the NCP and OCP groups.

To assess the association between the severity of CLBP and the atrophy of the 4 above-mentioned

brain regions that were significantly associated with CLBP, the brain volumes of each region were compared across the NCP, low-intensity CLBP (VAS < 40 mm), and high-intensity CLBP (VAS ≥ 40 mm) groups among 730 individuals in the NCP and CLBP groups (Table 3). As the pain intensity increased, the age- and sex-adjusted mean values of the brain volumes in the above 4 brain regions tended to decrease significantly (all *P* for trend < 0.05, model 1). This association did not materially change after adjusting for covariates including depressive symptoms (model 2 and model 3). In the sensitivity analysis using VAS as a continuous variable in 726 individuals in the NCP group and CLBP group, higher VAS was significantly associated with lower brain volumes in the above 4 brain regions (Table S3).

As the sensitivity analysis, we performed a group analysis using FreeSurfer's QDEC interface, which does not set the regions of interest, comparing the difference in cortical volume between the CLBP and NCP groups after adjusting for confounders. After the clusterwise correction for multiple comparisons, one cluster in the left superior frontal gyrus was identified as the brain region with lower brain volumes in the CLBP group compared with the NCP group (cluster size 1463.66 mm^2, cluster-wise *P* = 0.002, Monte Carlo Null-Z simulation-corrected) (Figure 2).

Table S4 shows the results of the subgroup analysis according to age group (< 75 and ≥ 75 years) among individuals in the NCP and CLBP groups. In the individuals of age 65 to 74 years, the multivariable-adjusted mean values of the ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, insular cortex, posterior cingulate cortex, amygdala, and hippocampus were significantly lower in the CLBP group compared with the NCP group. Conversely, for the individuals aged 75 years or older, statistically significant associations with CLBP were observed only in the ventrolateral prefrontal cortex and the posterior cingulate cortex. The significant heterogeneity in the association of CLBP and regional brain atrophy between individuals of 65 to 74 years and individuals of 75 years or older was found only at the amygdala (*P* for heterogeneity = 0.007). We also estimated the interaction of presence/absence of CLBP and age taken as a continuous variable on

each regional brain volume, but the results of the significance of the interaction between the CLBP status and continuous age on each regional brain volume were not materially different from those in Table S4 (data not shown).

4. Discussion

In the present study, an association between CLBP and regional brain atrophy was found in a community-based older Japanese population in which pain intensity was not as severe as in clinically based investigations of this association [37]. CLBP was associated with lower brain volume of the prefrontal cortex (ventrolateral and dorsolateral), posterior cingulate cortex, and amygdala even after adjustment for sociodemographic factors, physical and lifestyle factors, and depressive symptoms. In addition, dose–response associations between the intensity of pain and the brain volumes of each region were observed. Notably, the left superior frontal gyrus was also a significant cluster in the group analysis in which no regions of interest were set. This gyrus is included on the medial side of the dorsolateral prefrontal cortex, and thus, the result that the dorsolateral prefrontal cortex was significant might be a robust finding when combined with the results of the region-of-interest analysis. CLBP is thought to have features of not only ongoing inflammation and damage on tissues or nerves but also alterations in the central nervous system [11]. Therefore, the current findings support the notion that CLBP is linked to the changes in the brain structure and function, even in non-clinical populations.

In the several hospital-based case-control studies investigating CLBP and brain volume in small sample sizes of less than 100 participants, individuals with CLBP were found to have lower brain volumes in brain regions such as the prefrontal cortex, insular cortex, postcentral gyrus, and amygdala than those without [1,5,20,34,43]. One population-based study enrolling 543 German individuals reported that those with CLBP had significantly lower regional brain volumes in the prefrontal cortex (right ventromedial, left ventrolateral, and left dorsomedial) and the insular cortex [12]. Another population-based study conducted in 3892 individuals in the Netherlands found that chronic joint pain

was associated with lower total brain volume and regional brain volumes in the temporal lobe, the frontal lobe, and the hippocampus in women, but there were no significant associations in men [8]. In the present analysis, we also found a significant association between CLBP and lower brain volume of the prefrontal cortex, whereas the associations of CLBP with the insular cortex, posterior cingulate cortex, and amygdala were inconsistent between the present study and the previous population-based studies. Meanwhile, CLBP was significantly associated with lower regional brain volumes in the ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, insular cortex, posterior cingulate cortex, amygdala, and hippocampus in individuals aged 65 to 74 years, suggesting that advancing age may influence the associations. Both the insular cortex and hippocampus were also reported as CLBP-related brain regions in a previous case-control study [43] and population-based studies, as described above [8,12]. The discrepancies in the identified brain region associated with CLBP across studies may be related to differences in the sample size, age, and race of the study populations, but it may be reasonable to suppose that CLBP is significantly associated with decreased brain volume in the frontal lobe, as shown in both the present study and many previous studies [8,12,20,24,31].

Several biological mechanisms could potentially explain the significant association between CLBP and the lower brain volumes of each region. First, persistent or repetitive nociceptive and inflammatory information by CLBP could cause the nociplastic pain and then lead to a decrease in the brain volume related to pain neural circuits. The central nucleus of the amygdala in a rat model of neuropathic pain showed significantly larger-amplitude postsynaptic currents compared with that of the sham-operated animals [19]. In addition, a functional MRI study comparing patients with fibromyalgia and healthy controls during an application of moderately painful pressure revealed greater activation at the regions of the somatosensory cortex, insular cortex, anterior and posterior cingulate cortex, and medial frontal gyrus in the fibromyalgia patients [14]. Therefore, nociceptive stimulation might cause the long-term potentiation of synaptic responses and the change of pain-related neural circuits, followed by decreased regional brain volume. As another possible explanation, the hypothalamic-pituitary-adrenal (HPA) axis

might be involved in the association between CLBP and the reduced brain volume of each region. Patients with CLBP have been reported to have higher cortisol levels than healthy controls [42]. Animal experiments have shown that hypercortisolemia induces dysfunction of the HPA axis and a subsequent decrease in dendric spines through the cytokines released by activated microglia [3,21,39]. Importantly, it has been reported that patients with chronic pain due to hip osteoarthritis had lower brain volumes in pain-related brain regions than a control group, and the lower brain volume was recovered in patients whose pain improved after total hip replacement surgery [29]. It is thus possible that the brain volume decrease is a reversible change and that CLBP causes the brain volume decrease. Conversely, there is also a possibility that the changes in the brain structure and function can worsen CLBP. It has been reported that those with a cognitive strategy for trying to cope with stress had high activity in the ventrolateral prefrontal cortex when anticipating pain, and the activity and subjective pain intensity showed a negative correlation [32]. The dorsolateral prefrontal cortex is known to be involved in pain discrimination and control [35] and in decision making in goal-directed activities [27]. The amygdala has roles in emotional, cognitive and behavioral processing of pain by connecting with the prefrontal cortex, the cingulate cortex and the insula [38]. It has also been suggested that the amygdala has the role of switching chronic pain on and off through corticotropin-releasing factor [30]. A decrease in these brain regions might lead to a decreased ability to recognize and control pain, and thereby exacerbate low back pain. Further research will be needed to elucidate the mechanism underlying the association between CLBP and regional brain atrophy.

As a strength of this study, the relatively large sample size compared to previous studies can be mentioned. However, several limitations should also be noted. First, since this study is an observational cross-sectional study, we cannot infer causality. Second, we could not exclude the possibility of residual confounders because of unmeasured data such as the use of pain medications (ie, opioids or antidepressants) that might also affect the regional brain volume [33,47]. Third, we did not have clinical assessments of the cause of chronic pain by pain physicians or additional information regarding pain, and thus, we could not perform an analysis accounting for the cause of pain (eg,

neuropathic pain, musculoskeletal pain, or the presence of structural disease) in the present study. Fourth, brain MRI images were acquired by a 1.5-Tesla scanner, which could have resulted in lower spatial resolution images than a 3-Tesla scanner. Fifth, we could not assess group differences in subcortical volumes in the analysis without regions of interest because the QDEC interface of FreeSurfer software does not support analysis for subcortical regions. Finally, there are limitations in generalizing the present findings to other ethnic populations with different genetic backgrounds, lifestyles and cultural differences in pain perception and management because this study was focused on one community in Japan.

In conclusion, the present study demonstrated that CLBP was associated with lower regional brain volumes of the prefrontal cortex, the posterior cingulate gyrus, and the amygdala in an older Japanese population. These findings suggest that CLBP is related to lower brain volumes of pain-related regions not only in clinical patients with severe pain but also in the general population. Further investigations are needed to clarify the mechanism underlying the association between CLBP and regional brain atrophy.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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Figure legends

Figure 1. Selection process of the examined population.

Abbreviation: MRI, magnetic resonance imaging.

Figure 2. Cortical volume differences between the chronic low back pain group and the no chronic pain group as assessed using the Query, Design, Estimate, Contrast interface (n=726)

726 participants in the no chronic pain group and chronic low back pain group were included in the analysis, after excluding 4 participants with missing data on some covariates. The colored brain regions on the surface map have lower volumes in the chronic low back pain group than the no chronic pain group, after cluster-wise correction using a threshold set at $P < 0.05$ for multiple comparisons (Monte Carlo 10,000 simulations), with the initial cluster-forming criterion set at $P < 0.005$. The model was adjusted for age, sex, educational status, marital status, subjective economic status, hypertension, diabetes, serum total cholesterol, body mass index, current smoking, current drinking, regular exercise, cerebrovascular lesions on magnetic resonance imaging, and activities of daily living disability. Abbreviation: MNI, Montreal Neurological Institute.

Table 1. Age- and sex-adjusted baseline characteristics of the study participants according to the status of chronic pain (n = 1,106)

Variables	Total participants	Status of chronic pain		
		No chronic pain	Chronic pain	
			Chronic pain in body parts other than the lower back	Chronic low back pain
	(n = 1,106)	(n = 541)	(n = 376)	(n = 189)
Age, mean (SE), years [a]	72.1 (0.2)	71.6 (0.2)	72.7 (0.3)*	72.4 (0.4)
Women, % [b]	55.6	52.7	60.2*	54.9
Formal education ≤ 9 years, %	21.6	18.2	24.3	26.2*
Marital status, without partner, %	20.6	20.4	21.2	19.8
Subjective economic status, low, %	7.0	3.9	11.0**	7.9
Hypertension, % [c]	63.7	59.5	66.4	70.1*
Diabetes, % [c]	26.1	26.0	28.0	22.4
Serum total cholesterol, mean (SE), mg/dL [c]	207.7 (1.0)	210.5 (1.5)	204.6 (1.8)*	205.7 (2.5)
BMI, mean (SE), kg/m^2 [c]	23.4 (0.1)	23.0 (0.1)	23.9 (0.2)**	23.6 (0.2)
Current smoking, % [c]	6.6	7.2	4.8	8.5
Current drinking, % [c]	46.1	46.4	43.6	50.5
Regular exercise, % [c]	23.7	28.9	19.0*	18.5*
Cerebrovascular lesions on MRI, % [d]	29.7	29.0	28.3	34.4
ADL disability, %	4.0	2.5	5.7*	5.2
Depressive symptoms, GDS score ≥ 6, % [e]	12.5	7.5	16.0**	19.9**
Pain VAS, mean (SE), mm	-	-	41.6 (0.8)	40.0 (1.1)

Abbreviations: ADL, activities of daily living; BMI, body mass index; GDS, Geriatric Depression Scale; MRI, magnetic resonance imaging; SE, standard error; VAS, visual analog scale.

[a] Age is sex-adjusted.

[b] Sex is age-adjusted.

[c] Two individuals with missing data on these variables were excluded.

[d] Three individuals with missing data on cerebrovascular lesions on MRI were excluded.

[e] Three individuals with missing data on GDS score were excluded.

*$P < 0.05$ vs. no chronic pain. **$P < 0.001$ vs. no chronic pain.

Table 2. Multivariable-adjusted mean values of the regional brain volumes according to the status of chronic pain (n = 1,106)

Status of chronic pain	No. participants	Multivariable-adjusted mean values (95% confidence intervals)					
		Model 1	*P* value	Model 2	*P* value	Model 3	*P* value
Ventrolateral prefrontal cortex, %ICV							
No chronic pain	541	1.228 (1.218–1.238)	(ref.)	1.228 (1.218–1.238)	(ref.)	1.227 (1.217–1.237)	(ref.)
Chronic pain in body parts other than the lower back	376	1.218 (1.206–1.231)	0.41	1.220 (1.208–1.232)	0.56	1.219 (1.207–1.232)	0.58
Chronic low back pain	189	1.200 (1.183–1.217)	0.01	1.199 (1.182–1.216)	0.009	1.200 (1.183–1.217)	0.02
Dorsolateral prefrontal cortex, %ICV							
No chronic pain	541	4.906 (4.876–4.936)	(ref.)	4.908 (4.877–4.939)	(ref.)	4.905 (4.875–4.936)	(ref.)
Chronic pain in body parts other than the lower back	376	4.899 (4.862–4.935)	0.94	4.901 (4.864–4.938)	0.95	4.902 (4.865–4.938)	0.99
Chronic low back pain	189	4.836 (4.785–4.887)	0.04	4.830 (4.779–4.882)	0.02	4.835 (4.783–4.887)	0.04
Orbitofrontal cortex, %ICV							
No chronic pain	541	1.650 (1.639–1.660)	(ref.)	1.650 (1.640–1.660)	(ref.)	1.649 (1.638–1.659)	(ref.)
Chronic pain in body parts other than the lower back	376	1.641 (1.629–1.653)	0.49	1.642 (1.630–1.654)	0.55	1.642 (1.630–1.654)	0.67
Chronic low back pain	189	1.633 (1.616–1.650)	0.19	1.633 (1.616–1.650)	0.17	1.635 (1.618–1.652)	0.33
Postcentral gyrus, %ICV							
No chronic pain	541	1.075 (1.067–1.084)	(ref.)	1.075 (1.066–1.083)	(ref.)	1.074 (1.065–1.082)	(ref.)
Chronic pain in body parts other than the lower back	376	1.077 (1.067–1.087)	0.96	1.078 (1.067–1.089)	0.86	1.078 (1.068–1.089)	0.76
Chronic low back pain	189	1.061 (1.046–1.075)	0.16	1.061 (1.046–1.075)	0.21	1.062 (1.048–1.077)	0.36
Insular cortex, %ICV							
No chronic pain	541	0.883 (0.877–0.890)	(ref.)	0.883 (0.877–0.890)	(ref.)	0.883 (0.877–0.890)	(ref.)
Chronic pain in body parts other than the lower back	376	0.885 (0.877–0.892)	0.93	0.885 (0.877–0.893)	0.95	0.885 (0.877–0.893)	0.92
Chronic low back pain	189	0.875 (0.865–0.886)	0.36	0.875 (0.864–0.886)	0.33	0.876 (0.865–0.887)	0.44
Thalamus, %ICV							
No chronic pain	541	0.832 (0.827–0.837)	(ref.)	0.832 (0.827–0.837)	(ref.)	0.832 (0.826–0.837)	(ref.)
Chronic pain in body parts other than the lower back	376	0.828 (0.822–0.834)	0.45	0.829 (0.822–0.835)	0.67	0.829 (0.822–0.835)	0.73
Chronic low back pain	189	0.831 (0.822–0.839)	0.95	0.831 (0.822–0.840)	0.99	0.832 (0.823–0.840)	1.00

Anterior cingulate cortex, %ICV							
No chronic pain	541	0.469 (0.464–0.475)	(ref.)	0.469 (0.463–0.474)	(ref.)	0.468 (0.463–0.474)	(ref.)
Chronic pain in body parts other than the lower back	376	0.472 (0.465–0.478)	0.82	0.473 (0.466–0.480)	0.57	0.473 (0.466–0.480)	0.53
Chronic low back pain	189	0.469 (0.460–0.478)	1.00	0.470 (0.460–0.479)	0.98	0.470 (0.461–0.479)	0.95
Posterior cingulate cortex, %ICV							
No chronic pain	541	0.378 (0.374–0.382)	(ref.)	0.378 (0.374–0.382)	(ref.)	0.377 (0.373–0.381)	(ref.)
Chronic pain in body parts other than the lower back	376	0.375 (0.370–0.379)	0.44	0.375 (0.370–0.380)	0.60	0.375 (0.371–0.380)	0.75
Chronic low back pain	189	0.369 (0.362–0.375)	0.03	0.369 (0.362–0.375)	0.03	0.369 (0.363–0.376)	0.08
Amygdala, %ICV							
No chronic pain	541	0.183 (0.181–0.185)	(ref.)	0.183 (0.181–0.185)	(ref.)	0.183 (0.181–0.185)	(ref.)
Chronic pain in body parts other than the lower back	376	0.184 (0.182–0.186)	0.73	0.183 (0.181–0.186)	0.97	0.184 (0.181–0.186)	0.89
Chronic low back pain	189	0.179 (0.176–0.182)	0.04	0.179 (0.176–0.182)	0.02	0.179 (0.176–0.182)	0.048
Hippocampus, %ICV							
No chronic pain	541	0.494 (0.490–0.498)	(ref.)	0.494 (0.490–0.498)	(ref.)	0.494 (0.490–0.498)	(ref.)
Chronic pain in body parts other than the lower back	376	0.494 (0.489–0.498)	0.99	0.494 (0.489–0.498)	0.95	0.494 (0.489–0.499)	1.00
Chronic low back pain	189	0.487 (0.480–0.494)	0.14	0.486 (0.479–0.493)	0.07	0.487 (0.480–0.493)	0.13

Abbreviation: ICV, intracranial volume.

Values are calculated as follows: ([left + right] regional brain volume / ICV) × 100 (%).

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, educational status, marital status, subjective economic status, hypertension, diabetes, serum total cholesterol, body mass index, current smoking, current drinking, regular exercise, cerebrovascular lesions on magnetic resonance imaging, and activities of daily living disability. Five participants with missing data on some covariates were excluded.

Model 3: Adjusted for covariates included in model 2 plus depressive symptoms. Eight participants with missing data on some covariates were excluded.

Table 3. Multivariable-adjusted mean values of the regional brain volumes according to the pain intensity of chronic low back pain (n = 730)

Status of chronic pain		No. participants	Multivariable-adjusted mean values (95% confidence intervals)					
			Model 1	*P* value	Model 2	*P* value	Model 3	*P* value
Ventrolateral prefrontal cortex, %ICV								
No chronic pain		541	1.228 (1.217–1.238)	(ref.)	1.229 (1.218–1.239)	(ref.)	1.228 (1.218–1.238)	(ref.)
Chronic low back pain	VAS < 40 mm	93	1.211 (1.186–1.236)	0.39	1.209 (1.184–1.234)	0.28	1.209 (1.184–1.234)	0.31
	VAS ≥ 40 mm	96	1.189 (1.165–1.214)	0.01	1.188 (1.163–1.213)	0.007	1.190 (1.165–1.216)	0.02
			P for trend = 0.004		*P* for trend = 0.002		*P* for trend = 0.005	
Dorsolateral prefrontal cortex, %ICV								
No chronic pain		541	4.906 (4.875–4.936)	(ref.)	4.910 (4.879–4.941)	(ref.)	4.908 (4.877–4.939)	(ref.)
Chronic low back pain	VAS < 40 mm	93	4.870 (4.796–4.944)	0.62	4.864 (4.789–4.939)	0.47	4.864 (4.789–4.939)	0.49
	VAS ≥ 40 mm	96	4.806 (4.732–4.879)	0.03	4.794 (4.719–4.870)	0.01	4.804 (4.728–4.881)	0.03
			P for trend = 0.01		*P* for trend = 0.005		*P* for trend = 0.01	
Posterior cingulate cortex, %ICV								
No chronic pain		541	0.378 (0.374–0.382)	(ref.)	0.378 (0.374–0.382)	(ref.)	0.378 (0.374–0.381)	(ref.)
Chronic low back pain	VAS < 40 mm	93	0.373 (0.364–0.382)	0.50	0.372 (0.363–0.381)	0.41	0.372 (0.363–0.381)	0.46
	VAS ≥ 40 mm	96	0.365 (0.356–0.374)	0.02	0.365 (0.355–0.374)	0.02	0.366 (0.357–0.376)	0.054
			P for trend = 0.007		*P* for trend = 0.006		*P* for trend = 0.02	
Amygdala, %ICV								
No chronic pain		541	0.183 (0.181–0.185)	(ref.)	0.183 (0.182–0.185)	(ref.)	0.183 (0.181–0.185)	(ref.)
Chronic low back pain	VAS < 40 mm	93	0.182 (0.178–0.186)	0.88	0.182 (0.178–0.186)	0.75	0.182 (0.178–0.186)	0.79
	VAS ≥ 40 mm	96	0.176 (0.172–0.181)	0.005	0.176 (0.172–0.180)	0.003	0.177 (0.173–0.181)	0.02
			P for trend = 0.005		*P* for trend = 0.002		*P* for trend = 0.01	

Abbreviations: ICV, intracranial volume; VAS, visual analog scale.

Values are calculated as follows: ([left + right] regional brain volume / ICV) × 100 (%).

730 participants in the groups of no chronic pain (n = 541) and chronic low back pain (n = 189) were included in the analysis.

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, educational status, marital status, subjective economic status, hypertension, diabetes, serum total cholesterol, body mass index, current smoking, current drinking, regular exercise, cerebrovascular lesions on magnetic resonance imaging, and activities of daily living disability. Four participants with missing data on some covariates were excluded.

Model 3: Adjusted for covariates included in model 2 plus depressive symptoms. Six participants with missing data on some covariates were excluded.

Table S1. Body part described as the main site of pain among the participants with chronic pain (n = 565)

Body part described as the main pain site	No. participants	Frequency (%)
Low back	189	33.5
Knees	139	24.6
Shoulders	81	14.3
Feet	38	6.7
Arms	25	4.4
Neck	20	3.5
Teeth	12	2.1
Head	10	1.8
Entire body	8	1.4
Back	8	1.4
Abdomen	6	1.1
Pelvic	6	1.1
Buttocks	6	1.1
Face	3	0.5
Chest	3	0.5
Genital area	0	0.0
Tongue	0	0.0
Other part	11	2.0
Total	565	100.0

Table S2. Multivariable-adjusted mean values of the other regional brain volumes according to the status of chronic pain (n = 1,106)

Status of chronic pain	No. participants	Multivariable-adjusted mean values (95% confidence intervals)					
		Model 1	*P* value	Model 2	*P* value	Model 3	*P* value
Caudate nucleus, %ICV							
No chronic pain	541	0.422 (0.417–0.427)	(ref.)	0.422 (0.417–0.427)	(ref.)	0.422 (0.417–0.427)	(ref.)
Chronic pain in body parts other than the lower back	376	0.423 (0.416–0.428)	1.00	0.423 (0.417–0.429)	0.96	0.423 (0.417–0.429)	0.99
Chronic low back pain	189	0.424 (0.416–0.432)	0.87	0.422 (0.414–0.430)	1.00	0.421 (0.413–0.430)	0.99
Putamen, %ICV							
No chronic pain	541	0.558 (0.552–0.564)	(ref.)	0.559 (0.553–0.565)	(ref.)	0.559 (0.553–0.565)	(ref.)
Chronic pain in body parts other than the lower back	376	0.555 (0.548–0.562)	0.79	0.555 (0.548–0.562)	0.65	0.555 (0.548–0.562)	0.63
Chronic low back pain	189	0.552 (0.542–0.562)	0.46	0.549 (0.539–0.559)	0.18	0.549 (0.539–0.559)	0.17
Pallidum, %ICV							
No chronic pain	541	0.241 (0.238–0.243)	(ref.)	0.241 (0.238–0.243)	(ref.)	0.241 (0.238–0.243)	(ref.)
Chronic pain in body parts other than the lower back	376	0.240 (0.237–0.242)	0.82	0.240 (0.237–0.242)	0.85	0.240 (0.237–0.242)	0.89
Chronic low back pain	189	0.241 (0.237–0.244)	1.00	0.241 (0.237–0.244)	1.00	0.241 (0.237–0.244)	0.99
Nucleus accumbens, %ICV							
No chronic pain	541	0.052 (0.051–0.053)	(ref.)	0.051 (0.050–0.051)	(ref.)	0.052 (0.051–0.053)	(ref.)
Chronic pain in body parts other than the lower back	376	0.050 (0.047–0.052)	0.18	0.050 (0.049–0.051)	0.60	0.052 (0.051–0.054)	0.90
Chronic low back pain	189	0.053 (0.051–0.055)	0.81	0.050 (0.048–0.051)	0.26	0.051 (0.050–0.053)	0.62
Entorhinal cortex, %ICV							
No chronic pain	541	0.273 (0.270–0.277)	(ref.)	0.273 (0.270–0.277)	(ref.)	0.273 (0.269–0.276)	(ref.)
Chronic pain in body parts other than the lower back	376	0.275 (0.271–0.279)	0.77	0.275 (0.271–0.279)	0.71	0.276 (0.271–0.280)	0.51
Chronic low back pain	189	0.274 (0.268–0.279)	0.99	0.273 (0.267–0.279)	1.00	0.274 (0.268–0.280)	0.92
Parahippocampal gyrus, %ICV							
No chronic pain	541	0.238 (0.235–0.240)	(ref.)	0.238 (0.235–0.241)	(ref.)	0.238 (0.235–0.240)	(ref.)
Chronic pain in body parts other than the lower back	376	0.240 (0.236–0.243)	0.62	0.240 (0.236–0.243)	0.62	0.240 (0.237–0.243)	0.53
Chronic low back pain	189	0.237 (0.233–0.242)	0.98	0.237 (0.233–0.242)	0.96	0.238 (0.233–0.242)	1.00

Abbreviation: ICV, intracranial volume.
Values are calculated as follows: ([left + right] regional brain volume / ICV) × 100 (%).
Model 1: Adjusted for age and sex.
Model 2: Adjusted for age, sex, educational status, marital status, subjective economic status, hypertension, diabetes, serum total cholesterol, body mass index, current smoking, current drinking, regular exercise, cerebrovascular lesions on magnetic resonance imaging, and activities of daily living disability. Five participants with missing data on some covariates were excluded.
Model 3: Adjusted for the covariates included in model 2 plus depressive symptoms. Eight participants with missing data on some covariates were excluded.

Table S3. Association between the pain visual analog scale and regional brain volume (n = 726)

Brain regions of interest	Pain visual analog scale		
	β	95% confidence intervals	*P* value
No chronic pain and chronic low back pain			
Ventrolateral prefrontal cortex	-0.0007	(-0.0011, -0.0002)	0.006
Dorsolateral prefrontal cortex	-0.0017	(-0.0031, -0.0004)	0.01
Posterior cingulate cortex	-0.0002	(-0.0004, -0.0001)	0.009
Amygdala	-0.0001	(-0.00018, -0.00003)	0.03

726 participants in the no chronic pain group and chronic low back pain group were included in the analysis, after excluding four participants with missing data on some covariates.

Adjusted for age, sex, educational status, marital status, subjective economic status, hypertension, diabetes, serum total cholesterol, body mass index, current smoking, current drinking, regular exercise, cerebrovascular lesions on magnetic resonance imaging, and activities of daily living.

Table S4. Multivariable-adjusted mean values of the regional brain volumes according to age group (n = 726)

Status of chronic pain	Age 65–74 years (n = 522)		Age ≥ 75 years (n = 204)		*P* for heterogeneity
	No. participants	Multivariable-adjusted mean values (95% confidence intervals)	No. participants	Multivariable-adjusted mean values (95% confidence intervals)	
Ventrolateral prefrontal cortex, %ICV					
No chronic pain	393	1.243 (1.230–1.256)	145	1.196 (1.178–1.214)	0.94
Chronic low back pain	129	1.209 (1.186–1.231)	59	1.161 (1.131–1.190)	
P value		0.01		0.048	
Dorsolateral prefrontal cortex, %ICV					
No chronic pain	393	4.964 (4.928–5.000)	145	4.782 (4.719–4.844)	0.36
Chronic low back pain	129	4.854 (4.790–4.918)	59	4.725 (4.626–4.826)	
P value		0.004		0.36	
Orbitofrontal cortex, %ICV					
No chronic pain	393	1.667 (1.654–1.679)	145	1.611 (1.593–1.630)	0.29
Chronic low back pain	129	1.639 (1.617–1.661)	59	1.606 (1.575–1.636)	
P value		0.03		0.75	
Postcentral gyrus, %ICV					
No chronic pain	393	1.080 (1.069–1.091)	145	1.059 (1.044–1.075)	0.63
Chronic low back pain	129	1.060 (1.041–1.079)	59	1.053 (1.028–1.078)	
P value		0.08		0.66	
Insular cortex, %ICV					
No chronic pain	393	0.892 (0.884–0.898)	145	0.868 (0.855–0.880)	0.20
Chronic low back pain	129	0.874 (0.860–0.887)	59	0.866 (0.846–0.885)	
P value		0.04		0.85	
Thalamus, %ICV					
No chronic pain	393	0.839 (0.833–0.845)	145	0.815 (0.804–0.826)	0.42
Chronic low back pain	129	0.833 (0.823–0.844)	59	0.816 (0.799–0.833)	
P value		0.35		0.93	
Anterior cingulate cortex, %ICV					
No chronic pain	393	0.472 (0.465–0.478)	145	0.463 (0.452–0.474)	0.34
Chronic low back pain	129	0.459 (0.458–0.480)	59	0.470 (0.452–0.487)	
P value		0.67		0.53	
Posterior cingulate cortex, %ICV					
No chronic pain	393	0.381 (0.376–0.385)	145	0.374 (0.366–0.381)	0.86
Chronic low back pain	129	0.371 (0.363–0.378)	59	0.357 (0.346–0.369)	
P value		0.03		0.02	
Amygdala, %ICV					

No chronic pain	393	0.188 (0.186–0.190)	145	0.172 (0.168–0.176)	0.007
Chronic low back pain	129	0.180 (0.176–0.183)	59	0.175 (0.169–0.181)	
P value		< 0.001		0.41	
Hippocampus, %ICV					
No chronic pain	393	0.503 (0.499–0.508)	145	0.472 (0.465–0.481)	0.12
Chronic low back pain	129	0.491 (0.483–0.499)	59	0.472 (0.459–0.484)	
P value		0.009		0.90	

Abbreviation: ICV, intracranial volume.

Values are calculated as follows: ([left + right] regional brain volume / ICV) × 100.

726 participants in the no chronic pain group and chronic low back pain group were included in the analysis, after excluding 4 participants with missing data on some covariates.

Values are adjusted for age, sex, educational status, marital status, subjective economic status, hypertension, diabetes, serum total cholesterol, body mass index, current smoking, current drinking, regular exercise, cerebrovascular lesions on magnetic resonance imaging and activities of daily living disability.

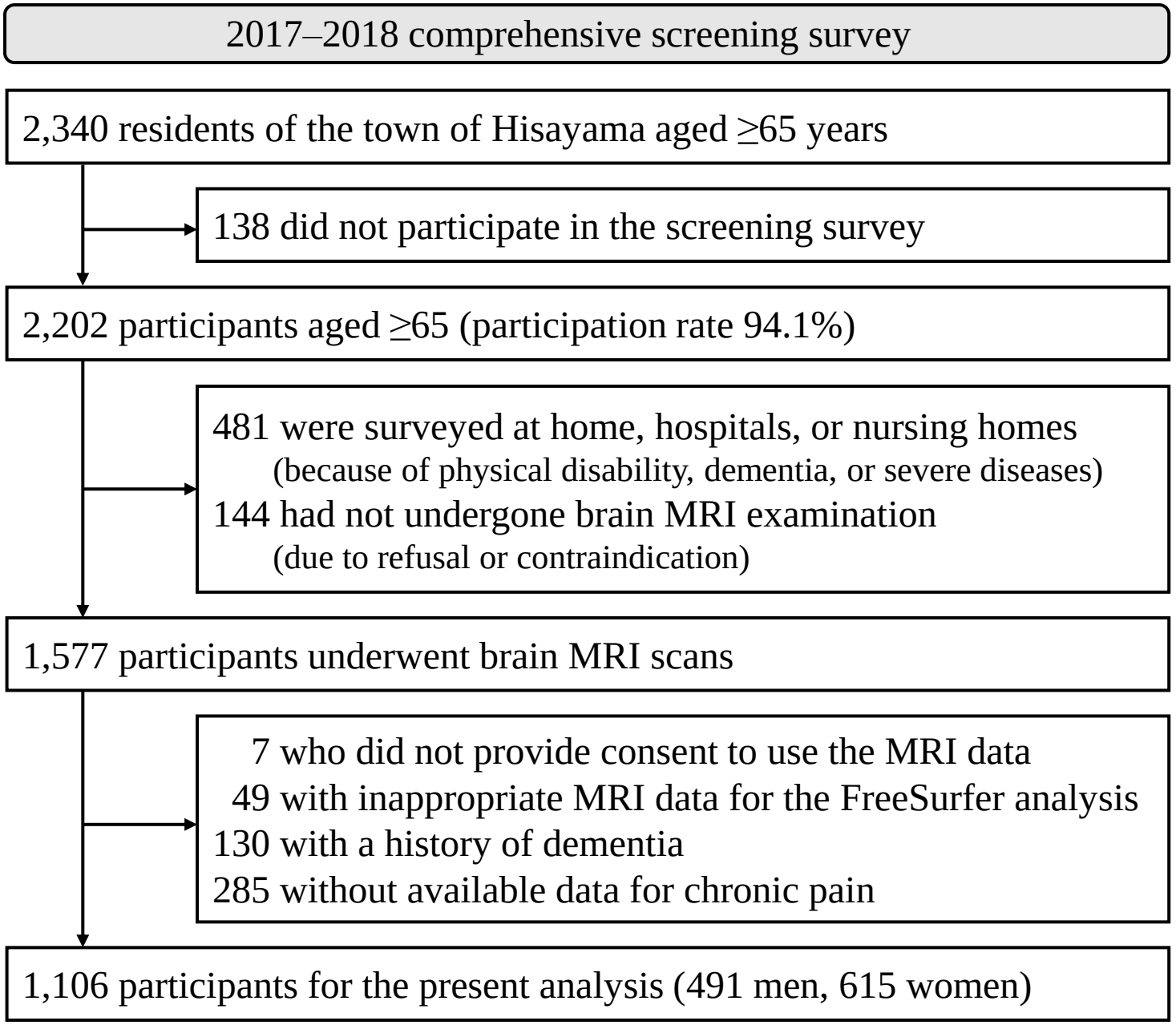
2017–2018 comprehensive screening survey
2,340 residents of the town of Hisayama aged ≥65 years
138 did not participate in the screening survey
2,202 participants aged ≥65 (participation rate 94.1%)
481 were surveyed at home, hospitals, or nursing homes
(because of physical disability, dementia, or severe diseases)
144 had not undergone brain MRI examination
(due to refusal or contraindication)
1,577 participants underwent brain MRI scans
7 who did not provide consent to use the MRI data
49 with inappropriate MRI data for the FreeSurfer analysis
130 with a history of dementia
285 without available data for chronic pain
1,106 participants for the present analysis (491 men, 615 women)

Figure 1.

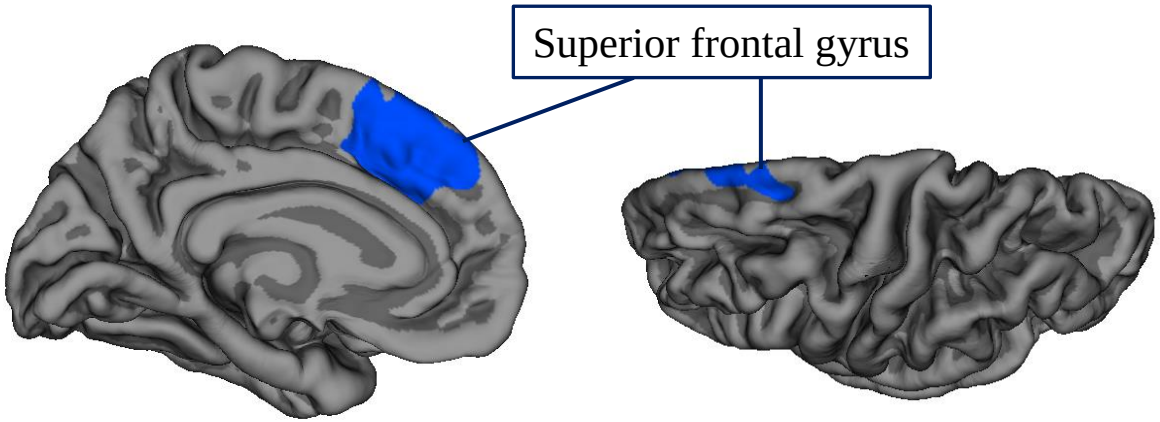
Left hemisphere
Superior frontal gyrus
Medial view
Superior view
Peak vertex MNI space
(x, y, z) = (-7.3, 39.5, 32.8)
Size 1463.66 mm2
Cluster-wise P = 0.002,
Monte-Carlo Null-Z corrected
1.00
0.005
0.0001
Peak level P value

Figure 2.