Supplemental data

Figure e-1. Selection of study participants

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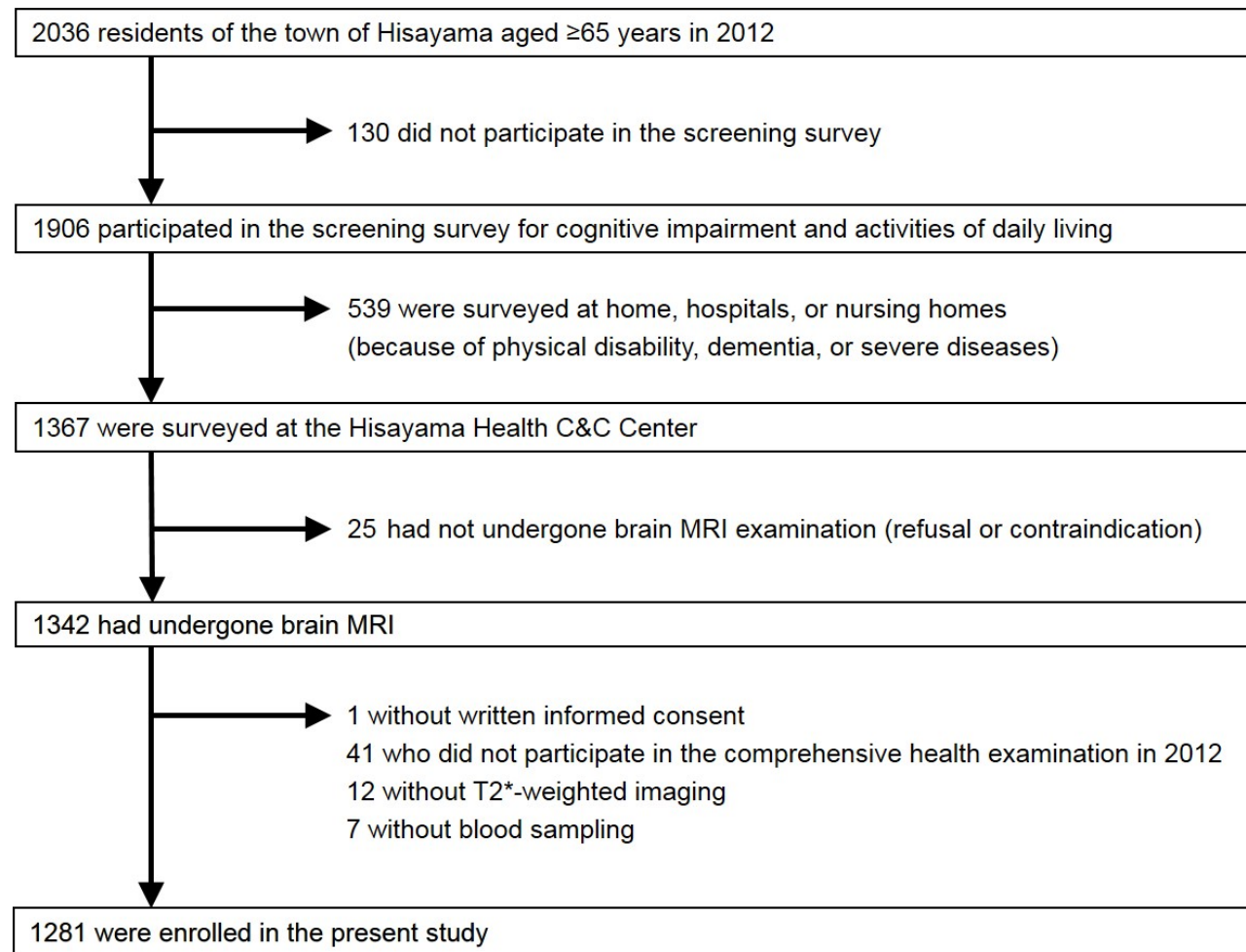
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┌─────────────────────────────────────────────────────────────────────────┐
│ 2036 residents of the town of Hisayama aged ≥65 years in 2012             │
└─────────────────────────────────────────────────────────────────────────┘
          │
          ├──────────►  130 did not participate in the screening survey
          ▼
┌─────────────────────────────────────────────────────────────────────────┐
│ 1906 participated in the screening survey for cognitive impairment and    │
│ activities of daily living                                                │
└─────────────────────────────────────────────────────────────────────────┘
          │
          ├──────────►  539 were surveyed at home, hospitals, or nursing homes
          │             (because of physical disability, dementia, or severe diseases)
          ▼
┌─────────────────────────────────────────────────────────────────────────┐
│ 1367 were surveyed at the Hisayama Health C&C Center                       │
└─────────────────────────────────────────────────────────────────────────┘
          │
          ├──────────►  25 had not undergone brain MRI examination (refusal or contraindication)
          ▼
┌─────────────────────────────────────────────────────────────────────────┐
│ 1342 had undergone brain MRI                                              │
└─────────────────────────────────────────────────────────────────────────┘
          │
          ├──────────►  1 without written informed consent
          │             41 who did not participate in the comprehensive health examination in 2012
          │             12 without T2*-weighted imaging
          │             7 without blood sampling
          ▼
┌─────────────────────────────────────────────────────────────────────────┐
│ 1281 were enrolled in the present study                                   │
└─────────────────────────────────────────────────────────────────────────┘
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Figure e-1. Selection of study participants

A total of 1906 individuals participated in a screening survey for cognitive impairment and activities of daily living in 2012. The present study included 1342 participants with T2*-weighted imaging of MRI and data for cardiovascular risk factors.

Table e-1. Association of risk factors with the presence of strictly lobar cerebral microbleeds

Variables	Age-sex-adjusted			Multivariable-adjusted		
	OR	95%CI	*P*	OR	95%CI	*P*
Age (per 10 year increase)	1.48	(1.02-2.15)	0.04	1.41	(0.91-2.20)	0.13
Men	1.96	(1.15-3.34)	0.01	2.13	(1.11-4.11)	0.02
Hypertension	2.09	(1.03-4.24)	0.04	2.12	(1.00-4.50)	0.04
Diabetes mellitus	0.49	(0.23-1.06)	0.08	0.42	(0.18-0.97)	0.04
Serum total cholesterol (per 1 mmol/l increase)	1.33	(0.97-1.82)	0.08	1.30	(0.93-1.83)	0.12
BMI (per 1 kg/m^2 increase)	0.99	(0.91-1.07)	0.77	0.99	(0.91-1.09)	0.90
Current smoking	0.84	(0.29-2.47)	0.75	0.91	(0.30-2.74)	0.87
Current drinking	1.20	(0.66-2.19)	0.55	1.03	(0.55-1.93)	0.92
Regular exercise	0.78	(0.38-1.64)	0.52	0.80	(0.38-1.71)	0.57
Antithrombotic treatment	1.32	(0.70-2.49)	0.39	1.21	(0.60-2.45)	0.59
APOE-ε2 carrier	1.05	(0.44-2.53)	0.91	1.44	(0.58-3.59)	0.44
APOE-ε4 carrier	2.95	(1.69-5.14)	<0.001	2.97	(1.66-5.34)	<0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; APOE, apolipoprotein E.

Strictly lobar cerebral microbleeds (CMBs) were defined as lobar CMBs without deep/infratentorial CMBs.

Table e-2. Prevalence of CMBs by APOE-ε4 status

	APOE-ε4 genotype		
	Carrier	Non-carrier	
	(n=209)	(n=897)	*P*
Any CMBs, %	24.9	18.5	0.04
Deep/infratentorial CMBs, %	15.6	15.1	0.95
Lobar CMBs, %	16.0	9.9	0.02

CMBs, cerebral microbleeds; APOE, apolipoprotein E.

Table e-3. Association of blood pressure levels and antihypertensive treatment status with the presence of cerebral microbleeds

Variables	Any CMBs			Deep/infratentorial CMBs			Lobar CMBs		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Blood pressure levels									
<140/90 mmHg	1.00	(reference)		1.00	(reference)		1.00	(reference)	
140-159/90-99 mmHg	1.10	(0.78-1.55)	0.59	1.15	(0.77-1.70)	0.50	1.17	(0.74-1.83)	0.50
≥160/100 mmHg	1.45	(0.85-2.47)	0.17	1.84	(1.04-3.26)	0.03	0.83	(0.35-1.94)	0.60
Antihypertensive treatment									
No	1.00	(reference)		1.00	(reference)		1.00	(reference)	
Yes	2.09	(1.44-3.01)	<0.001	2.01	(1.31-3.07)	0.001	2.14	(1.30-3.54)	0.03

CMBs, microbleeds; OR, odds ratio; CI, confidence interval.

OR (95% CI) was estimated using the multivariable logistic regression model including blood pressure levels (3 categories), antihypertensive treatment status, and other cardiovascular risk factors (age, sex, hypertension, diabetes, serum total cholesterol, body mass index, current smoking, current drinking, regular exercise, use of antithrombotic agents, and APOE polymorphisms (ε2 and ε4)).

Table e-4. Association of CMBs with other neurological disorders

Variables	History of symptomatic ischemic stroke			History of symptomatic intracerebral hemorrhage			Dementia		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Any CMBs	2.85	(1.58-5.15)	<0.001	29.16	(5.36-113.80)	<0.001	2.51	(1.65-3.83)	<0.001
Deep/infratentorial CMBs	2.74	(1.40-5.37)	0.003	43.82	(9.45-203.10)	<0.001	2.87	(1.81-4.54)	<0.001
Lobar CMBs	2.76	(1.32-5.79)	0.01	34.56	(6.89-173.28)	<0.001	3.77	(2.24-6.33)	<0.001

Variables	Lacunar infarction on MRI			White matter hyperintrensity (Fazecas grade 2 or 3) on MRI		
	OR	95% CI	*P*	OR	95% CI	*P*
Any CMBs	3.24	(2.37-4.42)	<0.001	2.35	(1.73-3.17)	<0.001
Deep/infratentorial CMBs	4.37	(1.38-2.13)	<0.001	2.74	(1.93-3.90)	<0.001
Lobar CMBs	3.01	(2.00-4.54)	<0.001	3.11	(2.05-4.72)	<0.001

CMBs, cerebral microbleeds; OR, odds ratio; CI, confidence interval.

OR (95% CI) was adjusted for age and sex.

Table e-5. Prevalence of CMBs among the elderly subjects in the previous population-based studies and the present study

Study	Country	Study period	Age (year)	Prevalence of CMBs (%)
Rotterdam Study[9]	Netherlands	2005-2006	≥60	23.5
AGES-Reykjavik Study[10]	Iceland	2002-2004	67-92	11.1
Washington Heights/Inwood Columbia Aging Project[11]	United States	2005-2007	≥65	27.6
Swedish BioFinder Study[12]	Sweden	2009-2013	>60	12.1
EDIS Study[13]	Singapore	2010-2015	≥60	34.4
RISK Study[13]	Hong Kong	2011-2015	≥65	21.1
Hisayama Study (the present study)	Japan	2012	65-97	18.7

CMBs, cerebral microbleeds; AGES, Age, Gene/Environment Susceptibility; EDIS, Epidemiology of Dementia In Singapore; RISK, Risk Index for Subclinical brain lesions in Hong Kong.

Table e-6. Baseline characteristics of the subjects included in and excluded from the present study

Variables	Included (n=1281)	Excluded * (n=323)	P
Age, years	74 ± 7	81 ± 9	<0.001
Men, %	43.4	33.8	0.002
Systolic blood pressure, mmHg	70.7	76	0.08
Diastolic blood pressure, mmHg	134 ± 19	140 ± 24	<0.001
Hypertension, %	76 ± 11	76 ± 13	0.54
Antihypertensive agent, %	55.6	55.6	1.00
Diabetes mellitus, %	23.3	22.2	0.99
Serum total cholesterol, mmol/l	5.12 (0.93)	4.86 (0.98)	<0.001
BMI, kg/m^2	23.1 (3.3)	21.8 (3.9)	<0.001
Current smoking, %	8.6	5.0	0.04
Current drinking, %	40.3	21.1	<0.001
Regular exercise, %	19.1	5.3	<0.001
Antithrombotic use, %	19.4	31.6	<0.001
Antiplatelet use, %	15.5	23.8	<0.001
Anticoagulant use, %	5.3	10.8	<0.001
APOE-ε2 carrier, %	9.6	9.5	1.00
APOE-ε4 carrier, %	18.9	26.3	0.01
History of symptomatic stroke, %	5.3	16.4	<0.001
Ischemic stroke, %	3.9	10.2	<0.001
Intracerebral hemorrhage, %	1.1	4.0	<0.001
Subarachnoid hemorrhage, %	0.3	2.2	0.001
Dementia, %	10.6	45.3	<0.001

BMI, body mass index; APOE, apolipoprotein E.

Values are shown as means (standard deviation) or frequencies.

*Baseline characteristics data were available for 323 of the 625 residents excluded from the study.