Migraine, depression, and brain volume

The AGES-Reykjavik Study

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ABSTRACT

Objective: To examine the joint association of migraine headache and major depressive disorder on brain volume in older persons without dementia.

Methods: Participants (n = 4,296, 58% women) from the population-based Age, Gene/Environment Susceptibility-Reykjavik Study were assessed for migraine headache in 1967–1991 (age 51 years [range 33–65]) according to modified International Classification of Headache Disorders–II criteria. In 2002–2006 (age 76 years [range 66–96]), lifetime history of major depressive disorder (depression) was diagnosed according to DSM-IV criteria, and full-brain MRI was acquired, which was computer postprocessed into total brain volume (TBV) (gray matter [GM], white matter [WM], white matter hyperintensities) and CSF volume for each study subject. We compared brain tissue volumes by headache categories with or without depression using linear regression, adjusting for intracranial volume and other factors.

Results: Compared with the reference group (no headache, no depression) TBV and WM and GM volumes were smaller in those with both migraine and depression (TBV –19.2 mL, 95% confidence interval [CI] –35.3, –3.1, $p = 0.02$; WM –12.8 mL, CI –21.3, –4.3, $p = 0.003$; GM –13.0 mL, CI –26.0, 0.1, $p = 0.05$) but not for those with migraine alone (TBV 0.4 mL, WM 0.2 mL, GM 0.6 mL) or depression alone (TBV –3.9 mL, WM –0.9 mL, GM –2.9 mL).

Conclusions: Reporting both migraine and major depressive disorder was associated with smaller brain tissue volumes than having one or neither of these conditions. Migraineurs with depression may represent a distinct clinical phenotype with different long-term sequelae. Nonetheless, the number of subjects in the current study is relatively small and these findings need to be confirmed in future studies. *Neurology*® 2013;80:2138–2144

GLOSSARY

AGES-Reykjavik = Age, Gene/Environment Susceptibility-Reykjavik Study; **CI** = confidence interval; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **GDS** = Geriatric Depression Scale; **ICHD-I and II** = International Classification of Headache Disorders, version I and II; **ICV** = intracranial volume; **MA** = migraine with aura; **MINI** = Mini-International Neuropsychiatric Interview; **MO** = migraine without aura; **NMH** = nonmigraine headache; **TBV** = total brain volume; **WMH** = white matter hyperintensities.

Migraine and depression are comorbid conditions, with migraineurs having an approximately 2-fold risk of depression compared to others.¹ Longitudinal studies further suggest that the relationship between migraine and depression is bidirectional, i.e., migraine increases risk of incident depression and depression increases risk of incident migraine.^{2,3} Several small clinical studies have reported reduced volume in some brain structures in migraineurs compared with others.⁴ Recent epidemiologic studies suggest some migraineurs have evidence of clinical and subclinical brain lesions including stroke, small infarct-like lesions in the cerebellum, and white matter hyperintensities (WMH).^{4–11} Likewise, many small clinical studies have suggested that patients with depression have reduced volume in limbic and cortical structures compared with others.^{12,13} In the population-based Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik

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Study), subjects with current major depressive disorder had reduced total brain volume (TBV) compared with others.¹⁴

While migraine and depression have both separately been reported to be associated with reduced brain volume,^{4,12,13} to our knowledge the joint effect of migraine and depression on brain volume has not been studied. We aim to study, in a large population-based cohort, the joint association of migraine headache and depression on brain volume.

METHODS The AGES-Reykjavik Study has been described in detail.¹⁵ Briefly, the Reykjavik Study is a population-based cohort study established in 1967 by the Icelandic Heart Association to prospectively study cardiovascular disease in Iceland. The cohort included a random sample of men and women born between 1907 and 1935 and living in Reykjavik at baseline. In 2002, the Reykjavik Study continued as the AGES-Reykjavik Study to examine risk factors, genetic susceptibility, and gene–environment interactions in relation to disease and disability in old age.¹⁵ Of the 11,549 (58% women) surviving members of the Reykjavik cohort (64% of the original examined cohort), 8,030 (68.6% of men and 70.1% of women) were randomly selected and invited to participate in the AGES-Reykjavik Study; 71.8% participated (74.0% of men and 70.2% of women), giving a final sample of 5,764 (58% women).¹⁵

Standard protocol approvals, registrations, and patient consents. The AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee (VSN 00-063), the Icelandic Data Protection Authority, and the Institutional Review Board of the US National Institute on Aging, NIH. Informed consent was signed by all participants.

Diagnosis of headache and migraine. MRI acquisition and classification of headache have been described previously.^{8,16} Briefly, as part of the original Reykjavik Study, a questionnaire was administered that inquired about headache symptoms. Subjects reporting headache once or more per month in the previous year were asked whether headaches were associated with nausea, unilateral location, photophobia, and visual or sensory symptoms.¹⁶

Participants were classified into 4 mutually exclusive categories of headache: no headache once or more per month, nonmigraine headache (NMH), migraine without aura (MO), and migraine with aura (MA). The MO category included individuals with headache and at least 2 of the 3 non-aura symptoms (nausea, unilateral location, photophobia). The MA category included those who reported visual aura or sensory aura, or both. Individuals with headache but no aura symptoms or only one non-aura symptom were defined as having NMH. Aura symptoms took precedence over other symptoms. The classification scheme represents an approximation of the 2004 International Classification of Headache Disorders (ICHD-II) diagnostic criteria for migraine with or without aura.¹⁷

Diagnosis of major depressive disorder (depression). The protocol for screening and diagnosing subjects with major depressive disorder (depression) in the AGES-Reykjavik Study has been described previously.¹⁴ Depression in the preceding 2 weeks and in the past was assessed according to *DSM-IV* criteria¹⁸ using the Mini-International Neuropsychiatric Interview (MINI).¹⁹ The MINI was administered to subjects who screened positive for

possible depression by satisfying any of the following criteria: scored ≥ 6 on the Geriatric Depression Scale (GDS)²⁰; scored 4 or 5 on the GDS and reported occurrences of anxiety; reported ever having a physician diagnosis of depression; reported ever using antidepressant medications; currently using antidepressant medications as assessed from medication vials brought to the clinic. In addition, to reduce unreliable answers to the screening and depression questions due to cognitive impairment, participants with a Mini-Mental State Examination²¹ score of ≤ 21 were not eligible to receive the MINI and were excluded from the study population. Subjects in these analyses were classified as “ever” or “never” having depression based on the MINI. Current depression was defined as depression in the last 2 weeks.

Brain MRI measures. All participants without contraindications were offered an MRI examination of the brain performed on a study-dedicated 1.5-T Signa Twinspeed system (General Electric Medical Systems, Waukesha, WI). The image protocol, described previously,²² included an axial T1-weighted 3-dimensional, a proton density/T2-weighted fast-spin echo (T2), and a fluid-attenuated inversion recovery sequence. The intracranial volume and the brain parenchyma compartments were segmented automatically as previously described.²² The pipeline algorithm segments the whole brain (cerebrum and cerebellum) into gray matter, normal white matter, WMH, and CSF. TBV was defined as the sum of gray matter volume, white matter volume, and WMH volume. Intracranial volume (ICV) was defined as the sum of total brain tissue volume and CSF volume.

Data analyses. Analytical sample. Of the 5,764 AGES-Reykjavik participants, 4,614 participants had complete data for the current analysis. The majority of the persons not included (953/1,150) did not have an MRI due to contraindications ($n = 290$), refusal ($n = 227$), scheduling conflicts ($n = 54$), or having a home rather than clinic visit ($n = 382$). In addition, 197 subjects were not included because they did not receive all of the imaging sequences necessary for this analysis ($n = 85$) or due to acquisition artifacts ($n = 59$) or postprocessing failures ($n = 53$).²² An additional 260 (5.6%) subjects had a diagnosis of dementia²³ and were excluded, as well as 58 individuals who were older than 65 years at the time of the midlife examination, leaving 4,296 subjects for analysis. Of those included, 158 had missing data on lifetime depression or cognition status (subjects presumed likely to have dementia); these subjects were classified as “unknown” depression status in the analysis, although we do not show results for this group for brevity.

We used linear regression (to compare mean ICV, TBV, white matter, and gray matter, which were normally distributed) or quantile regression (to compare median WMH, which was not normally distributed) between headache and depression groups. The outcome variable in all models was the indicated volume in milliliters and the independent variables were the headache/depression categories and potentially confounding variables as described below.

Headache without regard to depression status. We first examined the effects of having either migraine or NMH on brain volume compared with subjects without headache by splitting the cohort into 3 mutually exclusive groups: 1) (reference category) subjects without headache, 2) NMH, and 3) migraine.

Joint association of headache and depression. In order to study the individual and joint association of headache and depression on brain volume, we defined 6 mutually exclusive categories: 1) (reference category) subjects without headache and without depression (past or current depression), 2) NMH only, 3) migraine headache only, 4) depression only, 5) NMH and depression, and 6) migraine headache and depression. We tested for the interaction

between depression and headache type by comparing the effects of having both headache and depression vs (headache alone + depression alone). We also formally tested for headache type by sex interactions. We a priori examined the results separately for men and women, but due to sample size limitations for men, we present the results for the total sample and note differences by sex when relevant.

We calculated minimally adjusted (model 1) and fully adjusted (model 2) models. Model 1 was adjusted for sex, age at the midlife examination, years of follow-up, birth year, and ICV. Model 2 was in addition adjusted for midlife variables: height, education level (4 levels), systolic and diastolic blood pressure, and antihypertensive medication use. Blood pressure measurements were the mean of 2 measurements by a standard mercury sphygmomanometer. Analyses were conducted with STATA version 10 (StataCorp LP, College Station, TX); for main effect comparisons, a $p < 0.05$ was considered significant; for interaction effects, we used $p < 0.1$.

Sensitivity analyses. Since subjects reporting a recent first onset of depression might have subclinical dementia, thus confounding the association under study, we performed a sensitivity analysis in which we excluded 14 such subjects.

RESULTS The analytical sample consisted of 1,794 men and 2,502 women who were on average 50.7 years of age (range 33–65 years) at the midlife Reykjavik Study interview and 76.0 years of age (range 66–96 years) at the late-life AGES-Reykjavik Study interview (summary characteristics, table 1). Overall, the reference group (no headache and no depression) consisted of 75% of the men and 56% of the women (table 1). Subjects in the reference group were somewhat older compared with those in the other groups (table 1: 0.6–2.7 years older for men, 1.4–4.4 years older for women).

There was a difference in ICV between headache categories and the reference group (table 1). Therefore, we compared ICV adjusting for age, sex, birth year, and years of follow-up. Adjusted ICV was smaller for the subjects with NMH (−9.6 mL, 95% confidence interval [CI] −18.9, −0.3, $p = 0.04$), with migraine (−15.9 mL, CI −27.3 to −4.6, $p = 0.006$), and with NMH + depression (−41.0 mL, CI −75.7, −6.2, $p = 0.02$) compared with the reference group. No difference was found in adjusted ICV for the subjects with migraine + depression (−18.0 mL, CI −54.6, 18.7, $p = 0.34$) or for subjects with depression (alone) (0.1 mL, CI −21.7, 21.9, $p = 0.99$) compared with the reference group.

Migraine and brain volume regardless of depression status. Compared with subjects without headache ($n = 2,954$), in a model adjusted for sex, age, birth year, and follow-up, subjects with migraine ($n = 538$) had reduced TBV (−10.5 mL, CI −11.8, −2.6, $p = 0.009$), but when also adjusted for ICV the difference was attenuated (TBV −1.8 mL, CI −6.5, 3.0, $p = 0.47$). Subjects with NMH ($n = 804$) did not have reduced TBV (−4.2 mL, CI −10.8, 2.4,

$p = 0.21$ without ICV adjustment, and TBV 1.7 mL, CI −2.2, 5.6, $p = 0.40$ with ICV adjustment).

Headache, migraine, depression, and brain volume. Compared with the reference group, there were no differences in ICV-adjusted TBV, white matter, gray matter, and WMH volume in subjects with NMH, migraine, depression, or NMH + depression (table 2) (see tables e-1 and e-2 on the *Neurology*® Web site at www.neurology.org for results by sex). However, subjects with migraine + depression had less TBV (−19.2 mL, $p = 0.02$), white matter (−12.8 mL, $p = 0.003$), and gray matter (−13.0 mL, $p = 0.05$) (table 2, model 2) compared with the reference group. Results were similar when we excluded subjects with recent first onset of depression ($n = 14$) (data not shown).

We tested for interaction between headache/migraine and depression in the minimally adjusted (model 1) and the fully adjusted model (model 2). No interaction was found between NMH and depression. For TBV, there was no interaction between migraine and depression in the total sample (TBV −19.2 mL for migraine + depression vs −3.5 mL for migraine alone + depression alone, $p = 0.12$) (table 2, model 2), although the data did suggest interaction among women (model 2 in tables e-1 and e-2). Interaction was found in the total sample between migraine and depression for white matter and again the interaction was found among women and not among men in sex-stratified models (model 2 in tables e-1 and e-2). No interaction was found between migraine and depression for gray matter or WMH in the total sample or in the sex-stratified models (table 2 and table e-3). The results by migraine subtype did not suggest any difference between MO and MA (tables e-3 and e-4).

DISCUSSION In this population-based cohort where headache status was determined in midlife and a lifetime history of major depressive disorder (depression) and brain MRI were acquired in late life, the results are as follows: we found that migraineurs with depression had reduced TBV, white matter volume, and gray matter volume compared with controls; this did not vary by whether migraine aura was present or not. Further, we found women with migraine and depression had an increased volume of WMH compared with controls. Studies on migraine and brain volume have been inconsistent, with a number of small clinical studies reporting findings about global and regional differences in brain structure between migraineurs and controls, but other studies not showing any differences.^{4,24} Possibly, the extant studies were too small and underpowered to detect differences in global brain tissue volume. In addition, there was no adjustment for ICV, which our study suggests may differ between migraineurs and

Table 1 Characteristics by headache and depression status: AGES-Reykjavik Study^a

	No headache, no depression (n = 2,753)	NMH only (n = 732)	Migraine only (n = 468)	Depression only (n = 107)	NMH + depression (n = 41)	Migraine + depression (n = 37)
Men, n (%)	1,352 (75.4)	245 (13.7)	88 (4.9)	39 (2.2)	11 (0.6)	9 (0.5)
Birth year, mean (SD)	1926.9 (5.2)	1927.5 (5.3)	1928.8 (4.9)	1928.6 (4.7)	1930.1 (4.4)	1928.0 (4.6)
Midlife measures						
Age, y, mean (SD)	49.8 (5.7)	49.1 (6.0)	47.5 (5.6)	48.7 (5.2)	48.6 (6.6)	47.9 (4.2)
SBP, mm Hg, mean (SD)	135.0 (15.7)	134.5 (16.8)	133.1 (11.7)	131.7 (14.7)	131.9 (10.9)	123.6 (13.5)
DBP, mm Hg, mean (SD)	86.3 (9.4)	87.2 (9.7)	87.4 (8.2)	84.7 (9.0)	89.3 (10.1)	81.5 (10.1)
Height, cm, mean (SD)	178.3 (5.9)	177.4 (6.3)	178.3 (6.0)	178.3 (5.9)	177.2 (7.3)	179.7 (5.4)
Antihypertensive use, %	3.8	4.1	4.6	2.6	18.2	0
Elementary education only, %	15.2	13.2	20.5	10.3	9.1	0
Late-life measures						
Age, y, mean (SD)	76.4 (5.2)	75.8 (5.2)	74.5 (4.5)	74.7 (4.5)	73.7 (4.6)	74.9 (4.3)
ICV, mL, mean (SD)	1,619 (124)	1,607 (117)	1,592 (118)	1,594 (107)	1,614 (168)	1,657 (130)
TBV, % of ICV, mean (SD)	70.7 (5.8)	71.2 (5.8)	71.2 (5.7)	70.8 (5.7)	71.1 (7.1)	70.3 (3.9)
WM, % of ICV, mean (SD)	25.5 (2.9)	25.7 (2.6)	25.6 (2.6)	25.4 (2.6)	26.3 (3.3)	25.5 (2.2)
GM, % of ICV, mean (SD)	43.8 (3.7)	44.1 (3.8)	44.4 (4.0)	44.1 (3.9)	44.0 (4.2)	43.4 (2.8)
WMH, % of ICV, median (IQR)	0.9 (0.5–1.7)	0.9 (0.5–1.7)	0.8 (0.5–1.6)	0.9 (0.5–2.1)	0.6 (0.5–1.2)	1.1 (0.7–1.4)
Women, n (%)	1,401 (56.0)	487 (19.5)	380 (15.2)	68 (2.7)	30 (1.2)	28 (1.1)
Birth year, mean (SD)	1926.8 (5.3)	1928.2 (5.2)	1928.6 (5.1)	1929.0 (5.1)	1929.1 (4.5)	1930.8 (3.9)
Midlife measures						
Age, y, mean (SD)	52.3 (6.0)	50.5 (6.3)	49.9 (6.1)	51.5 (6.3)	50.3 (6.8)	48.2 (5.7)
SBP, mm Hg, mean (SD)	129.1 (16.6)	130.4 (17.0)	128.3 (15.3)	123.9 (16.2)	128.4 (18.2)	128.0 (18.6)
DBP, mm Hg, mean (SD)	80.4 (8.8)	81.3 (8.7)	81.2 (8.8)	78.4 (8.9)	80.5 (8.0)	80.6 (8.7)
Height, cm, mean (SD)	164.3 (5.3)	164.4 (5.6)	164.7 (5.2)	165.5 (5.3)	163.8 (5.3)	166.3 (4.7)
Antihypertensive use, %	6.6	9.5	7.9	7.4	13.3	7.1
Elementary education only, %	28.0	27.3	26.9	23.5	30.0	21.4
Late-life measures						
Age, y, mean (SD)	76.5 (5.2)	75.1 (5.1)	74.7 (5.0)	74.5 (5.2)	73.8 (4.3)	72.1 (3.9)
ICV, mL, mean (SD)	1,401 (105)	1,418 (108)	1,414 (104)	1,441 (89)	1,375 (95)	1,397 (87)
TBV, % of ICV, mean (SD)	74.2 (6.0)	73.5 (6.2)	73.7 (5.7)	73.6 (6.0)	74.0 (5.5)	73.2 (4.8)
WM, % of ICV, mean (SD)	26.2 (2.8)	25.9 (2.9)	26.0 (2.7)	26.2 (2.7)	25.7 (2.8)	25.3 (1.6)
GM, % of ICV, mean (SD)	46.7 (3.8)	46.4 (4.0)	46.4 (3.6)	46.2 (3.7)	46.9 (3.4)	46.3 (3.2)
WMH, % of ICV, median (IQR)	0.9 (0.5–1.7)	0.8 (0.4–1.6)	0.8 (0.4–1.5)	0.7 (0.4–1.6)	1.1 (0.5–1.6)	1.1 (0.5–1.7)

Abbreviations: AGES-Reykjavik = Age, Gene/Environment Susceptibility-Reykjavik Study; DBP = diastolic blood pressure; GM = gray matter; ICV = intracranial volume (WM + GM + WMH + CSF); IQR = interquartile range (25%–75%); NMH = nonmigraine headache; SBP = systolic blood pressure; TBV = total brain volume (WM + GM + WMH); WM = white matter; WMH = white matter hyperintensities.

^aDepression = lifetime major depressive disorder. A total of 158 subjects (50 men [2.8%] and 108 women [4.3%]) were missing values for depression or cognitive status.

nonmigraineurs. In our study, when compared with the 2,954 subjects without headache, the 538 subjects with migraine had reduced TBV in late life but when adjusted for ICV the difference was attenuated. Many studies have shown brain volume reduction among people with depression.^{12,13} Lifetime major depressive disorder and brain volume have been analyzed in the AGES-Reykjavik Study excluding subjects with dementia. The results

showed that among elderly men and women, current depression, irrespective of prior history, was associated with more brain atrophy, while major depressive disorder in remission was not associated with more brain atrophy/brain volume reduction.¹⁴

Several studies have suggested that the migraine depression comorbidity may be stronger for MA compared with MO.^{25,26} Given the number of studies

Table 2 Adjusted brain volumes^a by headache/depression^b status for men and women combined (n = 4,296): AGES-Reykjavik Study

	No. (%)	Model 1	p Value	Model 2	p Value
TBV					
No headache, no depression	2,753 (64.1)	0 (ref)		0 (ref)	
NMH only	732 (17.0)	1.6 (−2.5, 5.7)	0.43	2.5 (−1.6, 6.6)	0.24
Migraine only	468 (10.9)	−0.7 (−5.6, 4.3)	0.80	0.4 (−4.6, 5.4)	0.87
Depression only	107 (2.5)	−3.5 (−13.1, 6.1)	0.48	−3.9 (−13.5, 5.6)	0.42
NMH and depression	41 (1.0)	−6.3 (−21.7, 9.0)	0.42	−4.3 (−19.6, 11.0)	0.58
Migraine and depression	37 (0.9)	−18.5 (−34.7, −2.4)	0.03	−19.2 (−35.3, −3.1)	0.02
WM					
No headache, no depression	2,753 (64.1)	0 (ref)		0 (ref)	
NMH only	732 (17.0)	−0.3 (−2.4, 1.9)	0.80	0.1 (−2.1, 2.3)	0.92
Migraine only	468 (10.9)	−0.4 (−3.1, 2.2)	0.75	0.2 (−2.4, 2.9)	0.87
Depression only	107 (2.5)	−0.7 (−5.8, 4.4)	0.80	−0.9 (−6.0, 4.2)	0.72
NMH and depression	41 (1.0)	−3.1 (−11.3, 5.0)	0.45	−2.3 (−10.4, 5.8)	0.58
Migraine and depression	37 (0.9)	−12.7 (−21.3, −4.2) ^c	0.004	−12.8 (−21.3, −4.3) ^c	0.003
GM					
No headache, no depression	2,753 (64.1)	0 (ref)		0 (ref)	
NMH only	732 (17.0)	1.7 (−1.6, 5.1)	0.31	2.6 (−0.7, 5.9)	0.13
Migraine only	468 (10.9)	−0.1 (−4.1, 4.0)	0.98	0.6 (−3.4, 4.7)	0.76
Depression only	107 (2.5)	−2.5 (−10.3, 5.4)	0.54	−2.9 (−10.6, 4.9)	0.47
NMH and depression	41 (1.0)	−4.8 (−17.2, 7.0)	0.45	−2.8 (−15.2, 9.6)	0.65
Migraine and depression	37 (0.9)	−12.3 (−25.4, 0.8)	0.07	−13.0 (−26.0, 0.1)	0.05
WMH					
No headache, no depression	2,753 (64.1)	0 (ref)		0 (ref)	
NMH only	732 (17.0)	0.7 (−0.4, 1.9)	0.20	0.2 (−1.0, 1.4)	0.73
Migraine only	468 (10.9)	0.8 (−0.6, 2.2)	0.24	0.4 (−1.1, 1.9)	0.64
Depression only	107 (2.5)	1.1 (−1.5, 3.7)	0.41	1.0 (−1.8, 3.9)	0.48
NMH and depression	41 (1.0)	1.5 (−2.7, 5.7)	0.48	1.3 (−3.2, 5.9)	0.57
Migraine and depression	37 (0.9)	2.9 (−1.5, 7.2)	0.20	3.0 (−0.3, 3.6)	0.22

Abbreviations: AGES-Reykjavik = Age, Gene/Environment Susceptibility-Reykjavik Study; CI = confidence interval; DBP = diastolic blood pressure; GM = gray matter; NMH = nonmigraine headache; SBP = systolic blood pressure; TBV = total brain volume (WM + GM + CSF + WMH); WM = white matter; WMH = white matter hyperintensities.

^a The headache and depression categories are mutually exclusive. For TBV, WM, and GM, the numbers represent average differences in brain volume (mL) (95% CI) and *p* values compared with the reference group (subjects without headache and without depression). For WMH, the values represent median differences (95% CI). Interaction between headache and depression was calculated by comparing headache + depression vs (headache alone + depression alone) and noted when *p* < 0.1. The headache + depression term was not different between men and women for TBV, WM, GM, or WMH (*p* > 0.1). Model 1 is adjusted for sex, midlife age, years of follow-up, birth year, and intracranial volume. Model 2 is additionally adjusted for midlife height, education, SBP, DBP, and antihypertensive medication.

^b Depression: lifetime major depressive disorder. Subjects with dementia were excluded.

^c *p* < 0.1 for interaction between headache and depression.

reporting WMH, subclinical brain infarcts, and stroke mainly in subjects with MA rather than MO^{5–9,11} and the association of depression with vascular factors,²⁷ we expected greater brain volume differences among subjects with MA + depression vs MO + depression. In addition to sample size limitations, not finding a difference may reflect increased mortality in persons with depression²⁸ and MA⁶ during the time between midlife and late-life examination, which was on average about 26 years. Therefore it cannot be ruled out that subjects

with the greatest brain volume reduction may have been at greater risk of death and died before late-life examination was performed, thus attenuating the observed results. Similarly, results may have been attenuated for subjects with depression and migraine overall.

There are several studies that have shown migraine and depression to be comorbid conditions.^{1,10,11} Some of the mechanisms leading to a joint or additive effect of migraine and depression on brain volume include pain,^{2,26,29} neurogenic inflammation,³⁰ genetic factors,^{31,32}

and differences in socioeconomic factors.³³ Since depression is associated with increased risk of dementia,³⁴ we excluded subjects with dementia in all of our analyses, although it is possible that subjects with subclinical dementia were included. We did a sensitivity analysis in which we excluded subjects with recent onset of depression without prior history of depression (possibly reflecting subclinical dementia) but that did not change the results. It has also been suggested that childhood environment and trauma may be a shared determinant in both migraine and depression.³ Finally, comorbid depression may reflect disease severity in subjects with migraine³⁵ and thus be a surrogate marker for migraineurs with the most painful or frequent attacks who would presumably be most likely to exhibit the brain volume reductions measured herein.

We found that adjusted ICV was smaller among subjects with NMH, migraine, and NMH + depression compared to controls. This is an incidental finding that to our knowledge has not been previously reported in a population-based study. We can speculate on why ICV might be smaller in headache sufferers: it may be a spurious finding, a marker for lower socioeconomic status, or related to a genetic variant³¹ or some other developmental influence that affected both brain growth and susceptibility to headache, among other potential factors.

The strengths of the current study include the large, well-characterized random sample from a general population, which adds to the generalizability of our results. A structured interview, based on the *DSM-IV*, was used to diagnose lifetime history of depression. Migraine and headache assessment was performed in midlife (age 33–65 years), when many still experienced migraines, and migraine classification is less likely to be affected by recall bias compared with late-life ascertainment. Our exclusion of subjects with dementia in late life reduces, but does not eliminate, the risk of recall bias when estimating depression.

The classification of migraine in our study was established in 1967, preceding the 1988 ICHD-I³⁶ by more than 2 decades. Even so, the questions used are similar to those currently used in the ICHD-I and ICHD-II and they cover the most common symptoms of migraine. Although the classification of migraine resembles that of the ICHD-II, the screening question “Do you have headache once or more per month?” excludes migraine sufferers with infrequent attacks. The prevalence of aura (as a proportion of the total migraine population) is higher than has been reported in other population studies and might include people with headache who experience nonspecific visual symptoms such as blurring. This type of misclassification would presumably have attenuated the findings reported herein. We note that our prevalence of migraine overall (with and without aura combined), however, is highly consistent with previous studies.³⁷ Further, we do not have detailed

information on attack frequency, intensity, or for how many years participants have had migraine symptoms.

Our results suggest that migraine with major depressive disorder was associated with reduced TBV, white matter, and gray matter. Migraineurs with depression may represent a distinct clinical phenotype and should be examined separately when considering long-term sequelae of migraine. Future studies need to determine what chronic pain mechanisms may lead to brain volume reduction among people with both migraine and major depressive disorder.

Reduced brain volume may indicate a decline in cognition,³⁸ although we note that there is no evidence from prospective studies that suggests reduced cognition or increased cognitive decline in migraineurs.^{9,39,40}

Therefore, more studies are needed to consider the clinical relevance of these findings. In addition, the number of subjects with both migraine and depression is relatively small in the current study, which calls for caution when interpreting these findings.

AUTHOR CONTRIBUTIONS

Study concept and design: L.S.G., A.I.S., L.J.L. Acquisition of data: S.S., G.E., M.I.G., T.B.H., O.K., T.A., V.G., L.J.L. Analysis and interpretation of data: L.S.G., A.I.S., L.J.L. Critical revision of the manuscript for important intellectual content: L.S.G., A.I.S., S.S., M.I.G., J.-S.V., G.E., M.I.G., T.B.H., O.K., T.A., M.A.v.B., V.G., L.J.L. Study supervision: A.I.S., S.S., G.E., V.G., L.J.L.

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