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Genetic and lifestyle risk factors for MRI-defined brain infarcts in a population-based setting

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Abstract

Objective

To explore genetic and lifestyle risk factors of MRI-defined brain infarcts (BI) in large population-based cohorts.

Methods

We performed meta-analyses of genome-wide association studies (GWAS) and examined associations of vascular risk factors and their genetic risk scores (GRS) with MRI-defined BI and a subset of BI, namely, small subcortical BI (SSBI), in 18 population-based cohorts (n = 20,949) from 5 ethnicities (3,726 with BI, 2,021 with SSBI). Top loci were followed up in 7 population-based cohorts (n = 6,862; 1,483 with BI, 630 with SBBI), and we tested associations with related phenotypes including ischemic stroke and pathologically defined BI.

Results

The mean prevalence was 17.7% for BI and 10.5% for SSBI, steeply rising after age 65. Two loci showed genome-wide significant association with BI: FBN2, $p = 1.77 \times 10^{-8}$; and LINC00539/ZDHHC20, $p = 5.82 \times 10^{-9}$. Both have been associated with blood pressure (BP)–related phenotypes, but did not replicate in the smaller follow-up sample or show associations with related phenotypes. Age- and sex-adjusted associations with BI and SSBI were observed for BP traits (p value for BI, $p_{[BI]} = 9.38 \times 10^{-25}$; $p_{[SSBI]} = 5.23 \times 10^{-14}$ for hypertension), smoking ($p_{[BI]} = 4.4 \times 10^{-10}$; $p_{[SSBI]} = 1.2 \times 10^{-4}$), diabetes ($p_{[BI]} = 1.7 \times 10^{-8}$; $p_{[SSBI]} = 2.8 \times 10^{-3}$), previous cardiovascular disease ($p_{[BI]} = 1.0 \times 10^{-18}$; $p_{[SSBI]} = 2.3 \times 10^{-7}$), stroke ($p_{[BI]} = 3.9 \times 10^{-69}$; $p_{[SSBI]} = 3.2 \times 10^{-24}$), and MRI-defined white matter hyperintensity burden ($p_{[BI]} = 1.43 \times 10^{-157}$; $p_{[SSBI]} = 3.16 \times 10^{-106}$), but not with body mass index or cholesterol. GRS of BP traits were associated with BI and SSBI ($p \leq 0.0022$), without indication of directional pleiotropy.

Conclusion

In this multiethnic GWAS meta-analysis, including over 20,000 population-based participants, we identified genetic risk loci for BI requiring validation once additional large datasets become available. High BP, including genetically determined, was the most significant modifiable, causal risk factor for BI.

Introduction

Brain infarcts (BI) detected on MRI are commonly seen in older persons, being described in 8%–28% of participants in population-based cohort studies.[1] Most MRI-defined BI are covert, not being associated with overt, clinical stroke symptoms.[2,3] Nonetheless, they cannot be considered silent or benign, as they are often associated with subtle neurologic symptoms and with increased risk of future stroke, cognitive decline, and in some studies dementia.[4,5] Most MRI-defined BI are small subcortical BI (SSBI), believed to be primarily caused by small vessel disease (SVD).[6]

Mechanisms and predictors of BI and SSBI remain incompletely understood. No genetic risk variants for BI and SSBI have been consistently identified to date,[7–16] and findings with vascular risk factors have been inconsistent.[1] Partly reflecting this uncertainty, recommendations to direct clinicians on how to best manage covert MRI-defined BI are lacking.

To enhance understanding of risk factors for BI and SSBI, we first conducted a large meta-analysis of genome-wide association studies (GWAS) from 18 population-based studies, comprising 20,949 participants from 5 ethnic groups, using the 1000 Genomes reference panel (1000G), more than doubling the size of a prior GWAS.[16] Second, we examined the association of vascular risk factors with BI and SSBI in this large sample, using both vascular risk factor measurements and their genetic risk scores (GRS).

Methods

Study design and samples

The meta-analyses included 18 prospective population-based cohorts participating in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (table e-1 and additional Methods e-1, doi.org/10.5061/dryad.hk07677). Although the cohorts contributing participants are longitudinal, this study is cross-sectional, based on the analysis of BI and SSBI at one timepoint in the subset of cohort participants with brain MRI. These cohorts comprised 5 ethnic groups and ancestries: European (n = 17,956), African (n = 1,834), Hispanic (n = 737), Malay (n = 215), and

Glossary

1000G = 1000 Genomes reference panel; **BI** = brain infarcts; **BMI** = body mass index; **BP** = blood pressure; **DBP** = diastolic blood pressure; **FLAIR** = fluid-attenuated inversion recovery; **GRS** = genetic risk scores; **GWAS** = genome-wide association studies; **HDL** = high-density lipoprotein; **IS** = ischemic stroke; **IS-SVD** = small vessel disease subtype of ischemic stroke; **IVW** = inverse-variance weighting; **L_{10}BF** = Log_{10} of Bayesian factor; **LD** = linkage disequilibrium; **LDL** = low-density lipoprotein; **MAP** = mean arterial pressure; **PP** = pulse pressure; **SNP** = single nucleotide polymorphism; **SBP** = systolic blood pressure; **SSBI** = small subcortical brain infarcts; **SVD** = small vessel disease; **WMH** = white matter hyperintensities.

Chinese (n = 207). Some cohorts contributed to data for more than one ethnic group, resulting in a total of 23 datasets (tables e-1 to e-3, doi.org/10.5061/dryad.hk07677). Out of a total of 20,949 participants, 3,726 had MRI-defined BI. We did not exclude participants with a history of overt, clinically defined stroke prior to the MRI, except in 4 cohorts where patients with history of stroke were excluded by design. Three datasets did not contribute to the SSBI analysis either due to small numbers or absence of BI subtyping. Out of a total of 19,073 participants in the remaining 20 datasets, 3,533 had BI, of whom 2,021 (57.2%) had SSBI.

Variable definitions

Detailed MRI scanning protocols, as well as BI and SSBI definitions, for each study are described in table e-4 (doi.org/10.5061/dryad.hk07677). All protocols comprised at least T1, T2, and proton density or fluid-attenuated inversion recovery (FLAIR) sequences. On MRI, BI were defined as an area of abnormal signal intensity lacking mass effect with a size ≥3–4 mm; in the white matter, they were required to be hypointense on T1-weighted images, approaching the hypointensity of CSF, to distinguish them from diffuse white matter lesions; and they were distinguished from dilated perivascular spaces based on their irregular shape, presence of a hyperintense rim in FLAIR, and absence of a typical vascular shape following the orientation of perforating vessels.[17] SSBI corresponded to BI with a size <15–20 mm, located in the basal ganglia, the white matter, or the brainstem. Participants with large BI or BI located in the cerebral cortex or cerebellum were excluded from analyses of SSBI. We also measured burden of white matter hyperintensities (WMH), a quantitative MRI marker of SVD, corresponding to signal abnormalities of variable size in the white matter, appearing as hyperintensity on T2-weighted or FLAIR images, but without cavitation. Details of WMH measurements have been described previously.[18]

Vascular risk factors

Vascular risk factor levels measured closest to brain MRI acquisition were used. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg or use of one or more blood pressure (BP)–lowering medications. We defined pulse pressure (PP) as the difference between SBP and DBP and mean arterial pressure (MAP) as DBP + 1/3 × PP. Diabetes was defined as a previous diagnosis of diabetes, a fasting plasma glucose >7.0 mmol/L, or antidiabetic drug use. Fasting serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using enzymatic methods. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. Body mass index (BMI) was defined as the ratio of weight (kg) to the square of height (m). Active smoking was defined according to study-specific criteria. History of overt, clinically defined stroke and other cardiovascular events was based on ongoing surveillance prior to brain MRI acquisition in most studies since participant recruitment had started prior to the initial brain MRI. In studies that had brain MRI scanning at the initial visit, the history and examination at this visit were used to identify prior overt, clinically defined stroke. History of cardiovascular events included history of angina, myocardial infarction, cardiac bypass surgery, angioplasty, or peripheral vascular disease.

Genotypes

All participating discovery cohorts had genome-wide genotypes imputed on the 1000G (phase 1, version 3).[19] Genome-wide genotyping platforms, quality control measures, and imputation parameters used in each study are presented in tables e-5–e-7 (doi.org/10.5061/dryad.hk07677).

Genome-wide association analyses with BI and small subcortical BI

For genome-wide association analyses with BI and SSBI, each study performed logistic regression under an additive genetic model after adjusting for age, sex, principal components of population stratification, and additional study-specific covariates, such as study site or family structure, as needed (additional Methods e-2, doi.org/10.5061/dryad.hk07677, for centralized quality control description). Our primary multiethnic GWAS meta-analysis was performed using MANTRA, based on a Bayesian framework.[20] In secondary analyses, we also ran the multiethnic GWAS meta-analysis with 2 alternative methods (additional Methods e-2, doi.org/10.5061/dryad.hk07677): (1) using fixed effects inverse variance weighting with METAL[21,22] and (2) using the random effects meta-analysis model implemented in METASOFT.[23] During meta-analysis, genomic control correction was applied to the individual studies and ethnic-specific results to remove any residual inflation of association statistics. We did not observe any systematic inflation of association statistics (figure e-1, doi.org/10.5061/dryad.hk07677). Statistical measures from MANTRA, the primary meta-analysis method, were used to define genome-wide significance (Log_{10} of Bayesian factor [L_{10}BF] > 6)[24] and to choose single nucleotide

polymorphisms (SNPs) for follow-up ($L_{10}BF > 4.5$) in either the BI or SSBI meta-analysis. Details of functional annotation of top loci are provided in additional Methods e-3 (doi.org/10.5061/dryad.hk07677).

Follow-up and extension

For follow-up and extension studies, genotypes imputed to the 1000G reference panel were available in most instances for in silico look-up of the selected risk variants. Three follow-up studies performed de novo genotyping of the top 6 loci (additional Methods e-1, doi.org/10.5061/dryad.hk07677). The lead variant (with lowest p value) was genotyped at each suggestive or genome-wide significant locus, and if not feasible, another variant in strong linkage disequilibrium (LD, $r^2 > 0.8$) was genotyped. A p value <0.0083, correcting for 6 loci, was considered significant evidence for replication.

The follow-up sample, in which we sought to confirm associations observed in the discovery analysis, included 6,862 participants, of whom 1,483 had BI and 630 had SSBI, from 6 community-based studies of European origin and one of Japanese origin (table e-1, doi.org/10.5061/dryad.hk07677).

As an extension, to test whether genetic variants associated with MRI-defined BI or SSBI in the discovery analysis are also associated with correlated phenotypes, we first explored their association with ischemic stroke (IS) overall and the small vessel disease subtype (IS-SVD) when available in 4 collaborative studies (table e-1, doi.org/10.5061/dryad.hk07677). Second, we explored whether genetic variants associated with MRI-defined BI and SSBI were associated with neuropathologically defined BI based on 2,940 brain autopsies in participants without dementia from the Alzheimer's Disease Genetics Consortium (ADGC). Participants with large infarcts or lacunes (n = 857, 29%) were compared to participants without any infarcts or having only microscopic infarcts (n = 2,083).[25]

We calculated power of the follow-up and extension studies using Quanto V1.2.3 (biostats.usc.edu/software; table e-8 and figure e-2, doi.org/10.5061/dryad.hk07677).

Association of vascular risk factors with BI and SSBI

Individual studies performed logistic regression to test for association of vascular risk factor measurements with presence or absence of at least one BI or SSBI. Analyses were performed with and without adjustments for age and sex. Analyses with BP or lipid traits as the main independent variable were additionally adjusted for treatment with disease-specific medications, and association analyses with fasting plasma glucose were limited to participants without type 2 diabetes. Except for WMH burden, the regression coefficients and standard errors for risk factors in the individual studies belonging to one ethnic group were combined using fixed-effects inverse variance-weighted meta-analysis and subsequently the betas and standard errors obtained in each ethnic group were combined using fixed-effects inverse variance-weighted meta-analysis, in the absence of heterogeneity ($p < 1 \times 10^{-6}$), to derive the multiethnic meta-analysis estimates. For WMH burden, the statistics were combined using the Z score–based sample size weighted meta-analysis as WMH burden was measured on different scales in participating studies.[18]

We then explored whether genetic variants previously shown in published GWAS to be associated with specific vascular risk factors were, in aggregate, also associated with BI and SSBI. This approach was selected to assess to what extent genetically determined vascular risk factor levels are associated with BI and SSBI and to provide evidence for a causal relation between a given vascular risk factor and risk of BI or SSBI, provided that Mendelian randomization assumptions are fulfilled.[26] We combined known genetic risk variants for each individual vascular risk factor into a weighted GRS, using effect estimates from the largest published GWAS of that risk factor as weights. We then tested for association of these GRS with BI and SSBI using the inverse-variance weighting (IVW) method. Construction of the GRS, selection of variants for the GRS analysis, as well as effect estimates used as weights are detailed in additional Methods e-4 and tables e-9–e-12 (doi.org/10.5061/dryad.hk07677). For significant GRS associations with BI or SSBI, we further conducted sensitivity analyses using the MR-Egger method implemented as an R package (TwoSampleMR),[27] which unlike the IVW method estimates the intercept term as part of the analysis. An intercept term significantly differing from zero suggests the presence of directional (unbalanced) pleiotropy, meaning that the pleiotropic effects of genetic variants are not balanced about the null.[27] We used a conservative significance threshold of $p < 0.05$ for the intercept.

After Bonferroni correction for 12 independent vascular phenotypes tested for association with BI and SSBI, $p < 0.0042$ was considered significant for associations with vascular risk factor measurements or GRS. The number of independent vascular phenotypes, taking into account correlation between the phenotypes considered, was estimated based on individual level data from the 3C-Dijon study using the online tool matSpDlite (neurogenetics.qimrberghofer.edu.au/matSpDlite/).

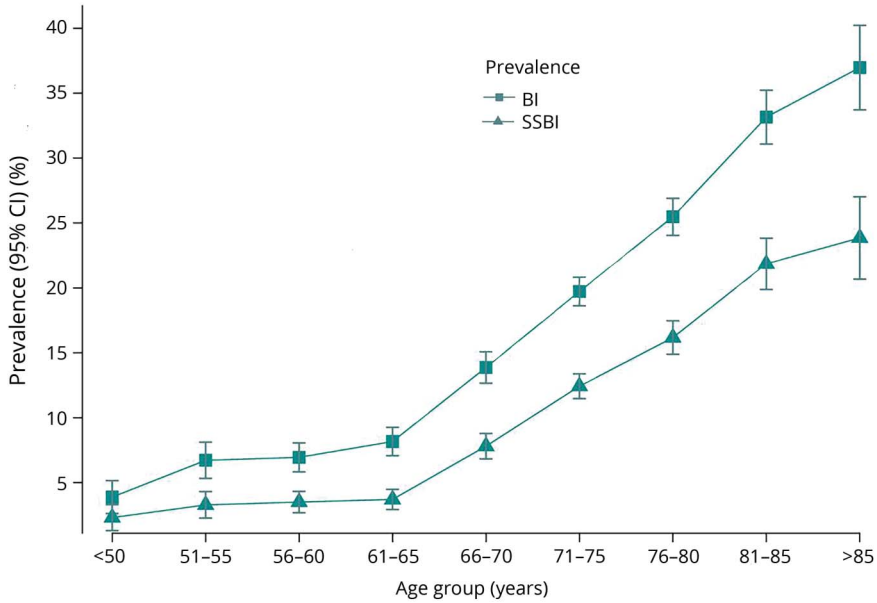
Standard protocol approvals, registrations, and patient consents

Institutional review boards approved all of these studies, and all participants provided informed consent.

Data availability

Summary statistics of the top SNPs are available from Dryad for both BI and SSBI. Other data that support the findings of this study are available from the corresponding authors upon reasonable request.

Figure 1 Prevalence of MRI-defined brain infarcts (BI) and small subcortical brain infarcts (SSBI) by different age groups



BI	Cases	36	85	140	199	432	991	888	644	311
	Total	892	1,181	1,878	2,239	2,647	3,961	2,597	1,298	530
SSBI	Cases	21	40	68	85	221	559	499	362	166
	Total	892	1,181	1,878	2,239	2,647	3,961	2,597	1,298	530

CI = confidence interval.

Results

In this large population-based dataset comprising 18 cohort studies, the frequency of MRI-defined BI ranged from 4% to 38% in participating cohorts (table e-1, doi.org/10.5061/dryad.hk07677). A description of demographic characteristics in all participants with BI (n = 3,726), with SSBI (n = 2,021), and without BI (n = 17,223) is provided in tables e-2 and e-3 (doi.org/10.5061/dryad.hk07677) for individual studies. Participants with BI and SSBI were on average 6 years older and more often men compared to those without BI. In age-stratified analyses, the prevalence of BI and SSBI increased with age, most prominently beyond age 65, after which a 25.8% (range 13.9%–37.0%) increment in BI prevalence was observed compared to participants younger than 65 years (figure 1). Overall, the prevalence of BI ranged from less than 5% before age 50 to over 30% beyond age 80, with similar findings when we analyzed men and women separately (figures e-3 and e-4, doi.org/10.5061/dryad.hk07677). Only 11% of those with BI and 9% of those with SSBI had a history of stroke (12.5% and 9.8% when removing cohorts that excluded participants with history of stroke by design); hence, the vast majority of MRI-defined BI were covert.

Genome-wide association plots for GWAS of BI and SSBI are displayed in figures e-5 and e-6 (doi.org/10.5061/dryad.hk07677). Two loci were associated with risk of BI at genome-wide significant level ($L_{10}BF > 6$): rs39938 in *FBN2* (chr5q23) and rs12583648 in *LINC00539* and near *ZDHHC20* (chr13q12). In addition, 2 SNPs were associated with BI at a suggestive level of significance ($L_{10}BF > 4.5$): rs12373108 near *CALB2/ZNF23* (chr16q22) and rs74587705 in *SV2B* (chr15q26) (table 1). No genome-wide significant association was observed for SSBI, but 2 loci reached the threshold for suggestive association ($L_{10}BF > 4.5$): rs9371194 in *PLEKHG1* (chr6q25) and rs75889566 in *FRMD1* (chr6q27, table 1). These 6 loci were taken forward for the follow-up stage (table 2). For all SNPs reaching $Log_{10}BF > 4.5$ in the discovery stage, association statistics are shown in table e-13 and figure e-7 (doi.org/10.5061/dryad.hk07677).

In the substantially smaller population-based follow-up studies, we could not replicate the 2 genome-wide significant or the 4 suggestive loci associated with BI or SSBI (table 2). Of the 6 loci that we followed up, we had limited power for 2 of the loci for BI (52%) and 4 of the loci for SSBI (50%–58%) (table e-8, doi.org/10.5061/dryad.hk07677). Power estimates in the follow-up study are even lower when accounting for the winner's curse phenomenon, which leads to inflated effect estimates in the discovery cohort.[28] One suggestive locus for SSBI (*PLEKHG1*) showed nominal association with BI and SSBI in the follow-up studies ($p_{BI} = 0.03$ and $p_{SSBI} = 0.02$), but in the opposite direction (table 2).

Likewise, none of the genome-wide significant or suggestive loci for BI and SSBI showed association with IS (overall or IS-SVD) or pathologically defined BI in the extension studies after correcting for multiple testing (table 2 and table e-14, doi.org/10.5061/dryad.hk07677). Whereas the sample size

Table 1 Loci reaching Log_{10} of Bayesian factor ($L_{10}BF$) >4.5 in the discovery stage of the genome-wide association studies with brain infarcts (BI) or small subcortical brain infarcts (SSBI)

Genes	Lead SNP (chr:position)	Chr region	Function (distance from gene)	Minor allele frequency	Phenotype	Multiethnic fixed-effects meta-analysis			Multiethnic random-effects meta-analysis	Bayesian-based approach of MANTRA		Cases/ controls, n
						OR (95% CI)	p_{FE}	*p*-het	p_{RE}	$L_{10}BF$	*p*-het	
FBN2	rs39938 (5:127663579)	5q23	Intronic	T (0.21)	BI	1.21 (1.13–1.30)	1.77×10^{-8}[a]	0.42	4.83×10^{-8}	6.52[a]	0.31	3,603/16,464
					SSBI	1.23 (1.13–1.34)	3.93×10^{-6}	0.58	1.43×10^{-5}	4.28	0.25	1975/13,260
PLEKHG1	rs9371194 (6:151034730)	6q25	Intronic	T (0.46)	BI	1.12 (1.06–1.18)	5.94×10^{-5}	0.47	4.28×10^{-4}	3.10	0.16	3,726/17,223
					SSBI	1.19 (1.11–1.28)	1.90×10^{-6}	0.50	3.63×10^{-5}	4.54	0.18	2,112/15,432
FRMD1	rs75889566 (6:168476856)	6q27	Intronic	T (0.08)	BI	0.82 (0.73–0.92)	7.71×10^{-4}	0.47	2.03×10^{-3}	1.99	0.27	3,181/12,731
					SSBI	0.65 (0.55–0.78)	1.82×10^{-6}	1.00	4.40×10^{-5}	4.63	0.17	1,584/8,538
LINC00539/ZDHHC20	rs12583648 (13:21900055)	13q12	Intronic	C (0.33)	BI	1.21 (1.13–1.29)	5.82×10^{-9}[a]	0.29	2.33×10^{-7}	7.00[a]	0.22	3,685/17,085
					SSBI	1.20 (1.10–1.30)	2.95×10^{-5}	0.26	7.66×10^{-5}	3.07	0.30	1985/14,705
SV2B	rs74587705 (15:91764992)	15q26	Intronic	T (0.03)	BI	1.85 (1.46–2.34)	3.36×10^{-7}	0.62	5.69×10^{-6}	5.25	0.29	2,291/6,072
					SSBI[b]	—	—	—	—	—	—	—
CALB2/ZNF23	rs12373108 (16:71432507)	16q22	Intergenic (8.1 kb)	T (0.17)	BI	1.21 (1.12–1.31)	5.02×10^{-7}	0.66	1.53×10^{-5}	4.90	0.21	3,418/15,607
					SSBI	1.23 (1.12–1.36)	1.40×10^{-5}	0.47	1.37×10^{-4}	3.61	0.18	1,851/12,794

Abbreviations: chr = chromosome (chromosomal positions are based on GRCh37); CI = confidence interval; FE = fixed effect; OR = odds ratio; *p*-het = *p* for heterogeneity; RE = random effect; SNP = single nucleotide polymorphism.
[a] Loci reaching genome-wide significance, $L_{10}BF$ >6.
[b] Due to the low minor allele frequency of this variant and the small number of cases with SSBI, this variant was excluded for association analyses with SSBI after applying the filter on "2 × minor allele frequency × imputation quality × number of cases ≤10."

Table 2 Follow-up and clinical extension of loci reaching Log_{10} of Bayesian factor ($L_{10}BF$) >4.5 in the discovery stage of the genome-wide association studies

		Follow-up (BI, n = 1,452 and SSBI, n = 600)		Meta-analysis discovery + follow-up		Clinical extension ischemic stroke (IS, n = 21,608 and IS-SVD, n = 4,325)[a]		Pathologically defined infarcts (n = 857)[b]	
Gene (lead SNP)	**Phenotype**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
***FBN2* (rs39938)**	BI	0.98 (0.91–1.05)	0.61	1.10 (1.05–1.15)	1.65×10^{-4}	1.01 (0.985–1.04)	0.61	1.09 (0.94–1.27)	0.27
	SSBI	1.01 (0.93–1.09)	0.88	1.10 (1.04–1.16)	1.58×10^{-3}	1.00 (0.94–1.07)	0.9		
***PLEKHG1* (rs9371194)**	BI	0.94 (0.89–0.99)	0.03	1.03 (0.99–1.07)	0.2	1.02 (0.99–1.05)	0.08	0.98 (0.87–1.11)	0.72
	SSBI	0.93 (0.88–0.99)	0.02	1.03 (0.99–1.08)	0.17	1.01 (0.96–1.06)	0.75		
***FRMD1* (rs75889566)**	BI	1.06 (0.96–1.18)	0.23	0.95 (0.88–1.03)	0.19	0.99 (0.94–1.04)	0.67	1.04 (0.82–1.31)	0.77
	SSBI	1.03 (0.92–1.15)	0.61	0.90 (0.82–0.99)	0.03	0.97 (0.87–1.07)	0.52		
***LINC00539/ZDHHC20* (rs12583648)**	BI	0.98 (0.91–1.06)	0.63	1.11 (1.05–1.16)	4.08×10^{-5}	1.01 (0.98–1.04)	0.53	0.95 (0.84–1.08)	0.46
	SSBI	0.97 (0.89–1.06)	0.55	1.08 (1.02–1.15)	8.95×10^{-3}	1.01 (0.95–1.06)	0.86		
***SV2B* (rs74587705)**	BI	1.07 (0.92–1.24)	0.41	1.25 (1.10–1.42)	5.82×10^{-4}	1.01 (0.92–1.09)	0.9	1.19 (0.80–1.79)	0.39
	SSBI	1.01 (0.86–1.18)	0.92	NA		1.07 (0.91–1.27)	0.41		
***CALB2/ZNF23* (rs12373108)**	BI	1.01 (0.94–1.10)	0.73	1.12 (1.06–1.18)	8.99×10^{-5}	1.00 (0.97–1.04)	0.87	0.94 (0.80–1.10)	0.44
	SSBI	1.05 (0.95–1.14)	0.34	1.13 (1.06–1.21)	2.20×10^{-4}	1.04 (0.97–1.11)	0.28		

Abbreviations: BI = brain infarcts; CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism; SSBI = small subcortical brain infarcts.
Values are OR (95% CI) with respect to the minor allele followed by *p* value of association.
[a] For ischemic stroke, meta-analysis results of METASTROKE-IS, CHARGE-IS, and SiGN-IS are presented. For ischemic stroke due to small vessel disease, meta-analysis results of METASTROKE-IS-SVD, Young Lacunar Stroke DNA Resource-SVD, and SiGN-IS-SVD are presented.
[b] Data presented for the following SNPs are for their proxies: rs75889566 = rs902393 ($r^2 = 0.96$), rs12583648 = rs12584792 ($r^2 = 0.96$), rs74587705 = rs7170681 ($r^2 = 0.67$).

for overall IS and IS-SVD was relatively large, it was limited for pathologically defined BI, and power was insufficient for 4 of the loci (25%–70%) (table e-8, doi.org/10.5061/dryad.hk07677).

Associations of vascular risk factors with risk of BI or SSBI adjusted for age and sex are presented in table 3 (for unadjusted results, see table e-15, doi.org/10.5061/dryad.hk07677). Both BI and SSBI were significantly associated with all BP indices, the lowest p value being observed for SBP and MAP. Smoking and diabetes were also associated with both BI and SSBI. Triglycerides were significantly associated with BI only. We did not observe significant associations with levels of HDL cholesterol, LDL cholesterol, BMI, or fasting plasma glucose in nondiabetic participants. Both BI and SSBI were associated with history of cardiovascular disease and history of stroke. The most significant association by far was observed with WMH burden on brain MRI, both for BI and SSBI. As hypertension is an important risk factor for WMH as well, we additionally adjusted the regression model for hypertension to rule out a confounding effect by this variable; however, the association became even more significant ($p = 5.71 \times 10^{-172}$ for BI and $p = 4.47 \times 10^{-114}$ for SSBI) (table e-16, doi.org/10.5061/dryad.hk07677). No significant heterogeneity was seen for these associations across participating studies.

When exploring the relation of weighted genetic risk scores for vascular risk factors with BI and SSBI, we found that GRS for SBP and MAP were significantly associated with increased risk of BI and SSBI after correction for multiple testing (table 4). In sensitivity analyses using MR-Egger regression, evidence for directional pleiotropy was lacking for these associations between SBP or MAP GRS and BI or SSBI (p intercept >0.36). GRS for DBP, BMI, coronary artery disease, WMH burden, and IS were nominally associated with BI ($p < 0.05$, table 4), but these associations did not survive correction for multiple testing.

Discussion

This multiethnic meta-analysis comprising over 20,000 community participants provides noteworthy insight into risk factors for MRI-defined brain infarcts. The described BI distributions across different age groups and by sex may also serve as a reference for comparison with BI and SSBI frequency in other settings. Of note, about 90% of BI were covert, not being associated with a history of stroke. In this multiethnic GWAS of BI and SSBI, we identified 2 genome-wide significant risk loci for BI, *FBN2* on chr5q23 and *LINC00539/ZDHHC20* on chr13q12, although these could not be replicated in a smaller follow-up sample. We further describe the association of MRI-defined BI with vascular risk factors, combining the vast majority of population-based cohort studies with BI and SSBI measurements available. We find high BP, both phenotypically expressed high BP and genetically determined risk for high BP, to be the most significant modifiable risk factor for BI. No association with cholesterol levels or BMI was found.

To identify novel genetic risk loci for MRI-defined BI and SSBI, we have more than doubled the sample size compared to the previously published GWAS of MRI-defined BI,[16] used imputed genotypes based on the 1000G reference panel to increase the marker coverage, and included samples from 5 ethnicities for a broader representation of individuals from different origins. Moreover, we studied both BI and SSBI, while only BI were analyzed in the previously published GWAS meta-analysis.[16] Our inability to replicate the genome-wide significant and suggestive findings could reflect false-positive results but may also be explained by insufficient power in the follow-up stage (table e-8, doi.org/10.5061/dryad.hk07677). Further studies on larger samples with MRI-defined BI are required to confirm or refute these findings. Moreover, while we could not provide evidence for an association of genome-wide significant and suggestive risk loci for BI and SSBI with IS, IS-SVD, or pathologically defined BI, this inability could reflect differences in the biology underlying these phenotypes, as well as limited power in the extension studies.

The 2 loci that crossed the genome-wide significance threshold, while requiring confirmation in larger independent samples, do harbor plausible biological candidates. *Fibrillin2* (*FBN2*) encodes a protein that is part of the connective tissue microfibrils and elastic fiber assembly of the cell.[29] Rare and common variants in *FBN2* have been associated with age-related macular degeneration.[30] Recent studies have also implicated common variants in *FBN2* to be associated with SBP,[31] although the variants differ (rs6595838-SBP and rs39938-BI, $r^2 = 0.017$). The *LINC00539/ZDHHC20* locus was a suggestive hit in a GWAS of adverse metabolic response to hydrochlorothiazide, a drug commonly used to treat hypertension.[32] The lead SNP in the region could also influence the expression of the long noncoding RNA *LINC00539* (table e-17, doi.org/10.5061/dryad.hk07677).

Our findings provide definitive evidence for a major and predominant association of increasing BP levels with increased risk of BI and SSBI.[1,33] Beside significant associations with hypertension, a continuous association was observed for increasing levels of all BP measurements (SBP, DBP, PP, MAP), consistent with elevated BP being the major modifiable risk factor for BI, as is the case for overt, clinically defined IS.[34–36] The importance and causal nature of the relation between high BP and risk of BI and SSBI is further supported by the significant association of BP genetic risk scores, for SBP and MAP, with increased risk of BI, especially SSBI, with no indication of directional pleiotropy using the MR-Egger approach.[27]

Previous publications on the association of BI and SSBI with vascular risk factors other than elevated BP were inconsistent.[1,33,37] Our study provides evidence for a significant association of current smoking and diabetes with risk of

Table 3 Association of vascular risk factors with MRI-defined brain infarcts and small subcortical brain infarcts

	Brain infarcts				Small subcortical brain infarcts			
Vascular risk factors[a]	OR (95% CI)	*p* Value	*p*-het	Cases/total, n	OR (95% CI)	*p* Value	*p*-het	Cases/total, n
Modifiable vascular risk factors								
Hypertension status	1.62 (1.48–1.78)	9.38×10^{-25}[b]	0.3	3,533/20,555	1.58 (1.40–1.78)	5.23×10^{-14}[b]	0.63	2,015/17,521
Systolic blood pressure, mm Hg	1.01 (1.00–1.01)	7.50×10^{-9}[b]	0.26	3,687/19,840	1.01 (1.00–1.01)	3.55×10^{-9}[b]	0.59	2,017/16,816
Diastolic blood pressure, mm Hg	1.01 (1.00–1.01)	2.32×10^{-5}[b]	0.74	3,686/19,838	1.01 (1.01–1.02)	1.38×10^{-6}[b]	0.81	2,017/16,815
Mean arterial pressure, mm Hg	1.01 (1.01–1.01)	1.35×10^{-8}[b]	0.45	3,686/19,838	1.01 (1.01–1.02)	1.18×10^{-9}[b]	0.77	2,017/16,815
Pulse pressure, mm Hg	1.00 (1.00–1.01)	1.07×10^{-5}[b]	0.25	3,686/19,838	1.01 (1.00–1.01)	2.63×10^{-5}[b]	0.42	2,017/16,815
Triglycerides, mmol/L	1.15 (1.05–1.26)	0.0015[b]	0.31	3,229/16,220	1.15 (1.02–1.28)	0.0163	0.64	1,751/13,374
HDL cholesterol, mmol/L	0.90 (0.84–0.98)	0.0108	0.53	2,590/19,655	0.92 (0.80–1.05)	0.2116	0.14	1,584/16,704
LDL cholesterol, mmol/L	0.96 (0.92–1.01)	0.1441	0.88	3,038/15,449	0.95 (0.89–1.01)	0.1298	0.98	1,644/12,702
BMI, kg/m^2	1.00 (0.91–1.01)	0.9515	0.24	2,773/20,509	1.00 (0.99–1.01)	0.5433	0.73	1,511/17,476
Diabetes status	1.40 (1.24–1.57)	1.66×10^{-8}[b]	0.45	3,259/17,135	1.26 (1.08–1.47)	0.0028[b]	0.46	1,753/11,836
Fasting plasma glucose, mmol/L	1.00 (1.00–1.00)	0.4366	0.82	3,668/11,599	1.01 (0.99–1.02)	0.2139	0.71	2,007/9,430
Current smoking status	1.47 (1.30–1.66)	4.38×10^{-10}[b]	0.29	2,911/15,438	1.37 (1.17–1.62)	1.18×10^{-4}[b]	0.65	1,588/12,032
Vascular comorbidities								
History of CVD	1.62 (1.46–1.81)	1.03×10^{-18}[b]	0.03	3,202/14,712	1.46 (1.27–1.69)	2.27×10^{-7}[b]	0.12	1,747/12,268
History of stroke	5.72 (4.71–6.95)	3.86×10^{-69}[b]	0.61	2,212/1,1374	4.47 (3.35–5.96)	3.15×10^{-24}[b]	0.75	5,89/4,657
WMH burden	26.74[c]	1.43×10^{-157}[b]		3,620/13,499	21.89[b]	3.16×10^{-106}[b]		1,990/9,917

Abbreviations: BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; HDL = high-density lipid; LDL = low-density lipid; OR = odds ratio; *p*-het = *p* for heterogeneity; WMH = white matter hyperintensity.
[a] All association analyses presented were adjusted for sex and age and meta-analyses estimates presented are from fixed effects inverse variance weighted meta-analyses, except for WMH burden. Association analyses for blood pressure factors were additionally adjusted for usage of blood pressure–lowering drugs. Association analyses for lipid factors were additionally adjusted for usage of lipid-lowering drugs. Association analysis for glucose was performed only on participants without type 2 diabetes.
[b] Associations significant after correcting for the number of independent phenotypes (n = 12, $p < 0.0042$).
[c] Meta-analyses for WMH burden were performed using sample size weighted meta-analysis, which yielded *Z* scores as effect estimates and not ORs with CIs; this is because WMH burden was measured on different scales in participating studies (quantitative measures in mL in all but 2 studies and semiquantitative measures on a 10-grade scale in the Atherosclerosis Risk in Communities study and the Cardiovascular Health Study [Additional Methods 1, doi.org/10.5061/dryad.hk07677]).

Table 4 Association of genetic risk scores (GRS) for vascular risk factors with brain infarcts and small subcortical brain infarcts

Phenotype	Brain infarcts			Small subcortical brain infarcts		
	SNPs, n[a]	OR (95% CI)	*p* Value	SNPs, n[a]	OR (95% CI)	*p* Value
Modifiable vascular risk factors						
Systolic blood pressure, *GRS-1*[b]	94	1.03 (1.01–1.04)	0.00053[c]	93	1.03 (1.01–1.05)	0.0014[c]
Systolic blood pressure, *GRS-2*[d]	72	1.03 (1.01–1.05)	0.00036[c]	71	1.03 (1.01–1.06)	0.0014[c]
Diastolic blood pressure, *GRS-1*[b]	109	1.03 (1.01–1.06)	0.011	109	1.05 (1.01–1.08)	0.0070
Diastolic blood pressure, *GRS-2*[d]	71	1.04 (1.01–1.07	0.0142	70	1.05 (1.02–1.09)	0.0057
Pulse pressure, *GRS-1*[b]	56	1.02 (0.99–1.05)	0.1234	55	1.01 (0.98–1.05)	0.4724
Pulse pressure, *GRS-2*[d]	23	1.03 (1.00–1.06)	0.0695	23	1.02 (0.98–1.07)	0.2969
Mean arterial pressure	30	1.06 (1.02–1.09)	0.0022[c]	30	1.09 (1.04–1.14)	0.00032[c]
Triglycerides	38	1.07 (0.89–1.29)	0.4578	37	1.21 (0.95–1.54)	0.1252
HDL cholesterol	71	0.95 (0.82–1.10)	0.4761	71	0.86 (0.71–1.05)	0.1373
LDL cholesterol	52	1.11 (0.96–1.29)	0.1633	52	1.09 (0.90–1.33)	0.3598
Body mass index	76	0.76 (0.59–0.99)	0.0412	76	0.81 (0.58–1.14)	0.2354
Type 2 diabetes	51	1.06 (0.97–1.16)	0.1710	51	1.11 (0.99–1.25)	0.0653
Fasting plasma glucose	36	1.44 (0.96–2.15)	0.0777	36	1.41 (0.83–2.39)	0.2038
Smoking (cigarettes per day)	3	1.00 (0.95–1.05)	0.9921	3	1.07 (1.00–1.14)	0.0624
Smoking (ever vs never smokers)	1	0.96 (0.89–1.03)	0.2769	1	0.95 (0.86–1.05)	0.3007
Smoking (former vs current smokers)	1	1.01 (0.91–1.13)	0.8028	1	1.03 (0.89–1.19)	0.6767
Vascular comorbidities						
Ischemic stroke	12	1.49 (1.12–1.97)	0.0057	12	1.36 (0.94–1.97)	0.1011
Coronary artery disease	57	1.12 (1.00–1.25)	0.0441	57	1.08 (0.93–1.24)	0.3169
WMH burden	8	1.41 (1.01–1.96)	0.0416	8	1.49 (0.97–2.30)	0.0702

Abbreviations: CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OR = odds ratio; SNP = single nucleotide polymorphism; WMH = white matter hyperintensity.
[a] Number of independent SNPs ($r^2 < 0.01$).
[b] Comprises only risk variants for systolic blood pressure, diastolic blood pressure, and pulse pressure that were previously reported as genome-wide significant and validated in the UK biobank according to prespecified criteria.
[c] Associations significant after correcting for the number of independent phenotypes (n = 12, $p < 0.0042$).
[d] Comprises, in addition to previously reported variants, all novel variants identified as genome-wide significant for the first time in the UK biobank (Additional methods 4, doi.org/10.5061/dryad.hk07677).

BI and SSBI, while no association with BMI and cholesterol could be demonstrated, despite the very large sample size. These findings are consistent with epidemiologic data on IS.[35] Interestingly, in contrast with cholesterol levels, a significant association of increasing triglyceride levels with BI risk was observed, although for SSBI the association did not withstand correction for multiple testing. Inconsistent results have been reported regarding association of triglycerides with overt, clinically defined IS,[38,39] but the present results are in line with evidence of an association in older community-dwelling persons between high triglyceride levels and WMH burden, another MRI marker of SVD.[40]

As previously described, we show a significant association of WMH burden with BI and SSBI, reaching $p < 10^{-100}$ in this study. Surprisingly, shared genetic variation among the top loci for WMH burden and BI was limited. While this observation could be due to lack of power, it could also suggest that WMH and BI share more environmental than genetic risk factors. A more comprehensive search for shared genetic variation between WMH burden and BI or SSBI at the genome-wide level using the LD score regression method[41] could not be performed in the present study due to low variance in the BI GWAS, also hampering the calculation of BI heritability using the same method. Of note, based on estimates from previously published family-based studies, heritability for SSBI was described to be low at 29%, in contrast with a moderate to high heritability for WMH burden at 49%–80%.[42–44] Hypertension is a major risk factor for WMH as well, and a BP GRS was also significantly associated with WMH burden in a prior study.[18]

However, the association of WMH burden with BI and SSBI was still significant after adjusting for hypertension status (table 3), or for SBP levels and BP-lowering treatment (table e-16, doi.org/10.5061/dryad.hk07677), suggesting that BP is not the only mediator of this association.

An important strength of the present study is that we have gathered nearly all large population-based studies with MRI-based identification of BI, genome-wide genotypes, and detailed vascular risk factor and comorbidity assessment, totaling over 20,000 participants covering 5 ethnic groups. Despite the unprecedented sample size, we were underpowered for the discovery of novel, robust genetic risk loci and even more so for the follow-up of genome-wide significant findings. Our ability to discover robust genetic risk variants may also have been hampered by the heterogeneity in BI and SSBI etiology, even though SVD is likely the predominant mechanism,[45] and by some heterogeneity in the way BI and SSBI have been measured in participating studies. Finally, although the majority of participants had covert BI, 10% had a history of overt, clinically defined stroke, but including both covert and overt BI also enables a better representation of the spectrum of participants with MRI-defined BI in the general population. Whereas history of stroke was more common in participants with BI than those without, we do not believe that this inclusion has driven the associations we observed, given both the small number of participants with a stroke history and the significance level of the observed associations. Moreover, in this population-based setting, determining whether an MRI-defined BI could be attributed to the history of clinically defined stroke was not always possible.

In clinical practice, MRI-defined BI are commonly seen on brain MRI scans performed for various reasons in older persons. They have been shown to be powerful predictors of incident stroke and incident dementia.[1,4,46] Hence BI represent an important marker for detection of high-risk individuals and initiation of preventive interventions. However, no randomized trials and no recommendations are currently available for the management of covert MRI-defined BI. The observational evidence is overwhelming for a strong causal relation between high BP and risk of BI and SSBI. A randomized trial will be needed to decide if persons with MRI-defined BI will benefit from more intensive BP-lowering strategies than is recommended currently for primary prevention.

This multiethnic, population-based study on 20,949 participants sheds important new light on susceptibility factors of MRI-defined brain infarcts, a marker of covert vascular brain injury commonly observed in older persons.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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