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ORIGINAL RESEARCH

CEREBROVASCULAR DISEASE AND STROKE

Multisite Pain and Myocardial Infarction and Stroke

A Prospective Cohort and Mendelian Randomization Analysis

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ABSTRACT

BACKGROUND Whether individuals with multisite pain had a higher risk of cardiovascular diseases is unclear.

OBJECTIVES The purpose of this study was to investigate the longitudinal association of pain in multiple sites with incident myocardial infarction (MI) and stroke, and to disentangle the genetic causality of these associations.

METHODS A total of 281,760 participants (mean age: 56.3 years) who had no MI and stroke at baseline from UK Biobank study were included. Data on pain in the hip, knee, back and neck/shoulder, or 'all over the body' were collected. Chronic pain was defined if pain had lasted for ≥3 months. MI and stroke events were determined from hospital admission records and death registries. Cox regression and 2-sample Mendelian randomization were used for the analyses.

RESULTS During a median follow-up of 11.9 years, 4,854 had a first MI and 2,827 had a first stroke. In multivariable analyses, greater number of painful sites was dose-responsively associated with higher risks of incident MI and stroke, with a higher risk among participants with pain 'all over the body' (MI: HR: 1.65, 95% CI: 1.32-2.07; stroke: HR: 1.44, 95% CI: 1.13-1.85). Similar trends and associations were observed in those with chronic pain. Two-sample Mendelian randomization results supported a causal effect of multisite pain on MI risk, but not vice versa. No causal association was found between multisite pain and stroke risk.

CONCLUSIONS Pain in multiple sites causally increases the risk of MI, highlighting that pain should be considered when assessing individuals' MI risk, and pain treatment and management may prevent MI risk. (JACC Adv 2023;2:100295)

Musculoskeletal pain is a prevalent health concern afflicting approximately 30% of the adult population worldwide,[1] and has a major impact on individuals' health and health-related quality of life. Pain in the lower back and the neck has been consistently ranked as the leading causes of years lived with disability in the Global Burden of Disease Study.[2] Musculoskeletal pain seldom occurs in one single-site, with as high as 75% of older adults experiencing pain in multiple sites.[3] Pain in multiple sites has been linked to worse physical and mental health,[3,4] increased risk of falls,[5]

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ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular diseases

GWAS = genome-wide association studies

hs-CRP = high sensitivity C-reactive protein

IVW = inverse variance weighted

MI = myocardial infarction

MR = Mendelian randomization

NSAID = non-steroidal anti-inflammatory drug

SNP = single-nucleotide polymorphism

and fractures[6] compared with single-site pain in previous studies, indicating that multisite pain may be a distinct pain phenotype.

Musculoskeletal pain is often comorbid with cardiovascular diseases (CVD). A recent meta-analysis including 20 cross-sectional studies concluded that patients with musculoskeletal pain are 1.91-times more likely to have a CVD as compared with those without musculoskeletal pain.[7] Several potential mechanisms of the pain-CVD link have been proposed, such as inflammation,[8,9] sympathetic activation,[10-12] and endothelial function.[10-12] Few longitudinal studies that investigated the links of musculoskeletal pain to CVD mortality reported conflicting results, with some reporting an increased risk of mortality from CVD,[13,14] while others failed to detect a significant association.[15,16] Other than differences in studied population characteristics, follow-up period and pain definition, the observed inconsistencies may be also ascribed to inadequately control for confounding factors. Some important factors, such as psychological problems (eg, depression), use of commonly prescribed pain medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]) and poor sleep, which are strongly associated with both pain and CVD, were not considered; therefore, whether the excess risks of CVD are independent of these factors is unknown. In addition, exploration of the longitudinal relationships of musculoskeletal pain with specific types of CVD and their subtypes is scarce. No study has examined their associations with pain in multiple sites. Data of this kind are important as they will help unveil the underlying mechanisms linking these two, thereby facilitating the assessment of patients' risk and allowing an optimal use of diagnostic and therapeutic efforts in high-risk patients.

Mendelian randomization (MR) which utilizes genetic variants as instrumental variables for the exposure of interest can provide unconfounded estimates, overcoming the limitations of residual confounding, reverse causation, and various bias (ie, measurement error) in traditional observational studies.[17] The rationale for the MR design is that genetic variants are randomly assorted to individuals and fixed at conception, and there is a high certainty of genotyping. However, to our knowledge, no study has employed this approach to investigate the casual associations of pain with myocardial infarction (MI) and stroke risk. This study, therefore, was to examine whether incident risk of MI, stroke, and their subtypes was increased with increasing number of painful sites, independent of a variety of confounders, and to disentangle the genetic causality of these associations using 2-sample MR approach.

METHODS

DATA SOURCE AND STUDY POPULATION. Participants were from the UK Biobank study-a large, population-based prospective cohort, with over 0.5 million participants (aged 40-69 years) recruited in 2006 to 2010 in the United Kingdom. Detailed description of this study including scientific rationale, study design, survey methods, and data collection has been previously published.[18] The UK Biobank study was approved by the North West Multi-centre Research Ethics Committee and all participants provided written informed consent.

PAIN ASSESSMENT. Participants were asked to report whether they experienced pain (yes/no) at the sites of the hip, knee, back, and neck/shoulder in the last month that interfered with their usual activities via a touchscreen pain questionnaire at baseline. More than one site could be selected. The number of painful sites was then summed to create a total number of painful sites ranging from 0 to 4. Alternatively, participants could choose pain 'all over the body'. However, the option of choosing individual painful sites was not offered if they reported pain 'all over the body'.

Participants who reported pain at least in one site or pain 'all over the body' were further asked whether the reported pain had lasted for ≥3 months (yes/no). Similarly, the number of painful sites which lasted for ≥3 months was summed to create a total number of chronically painful sites. According to this information, participants were categorized into 6 groups: no chronic pain, 1-, 2-, 3-, and 4-site of chronic pain, and chronic pain 'all over the body'.

INCIDENT MI AND STROKE. The primary outcomes of this study were MI and stroke events which were identified according to a set of algorithms developed by the UK Biobank outcome adjudication group. Data sources on which the algorithms relied were linked to hospital admissions data, national death register data, and self-reported data. Detailed information on the definitions has been previously described.[19,20] Participants with MI or stroke prior to baseline assessment were excluded from the analyses. The incident MI and stroke events during the follow-up were identified through hospital admission records and national death registries.

We also considered the subtypes of MI and stroke, including ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation

myocardial infarction (NSTEMI) for MI, and ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage (SAH) for stroke.

COVARIATES. A range of variables were considered in multivariable analyses including: 1) sociodemographic factors: age, sex, body mass index (BMI), ethnicity (White and non-White), highest education qualification, and household income; 2) lifestyle factors: smoking status, frequency of alcohol consumption, and recommended moderate/vigorous physical activity (yes/no); 3) cardiometabolic health factors: systolic blood pressure, diastolic blood pressure, total cholesterol (mmol/L), high density lipoprotein (mmol/L), fasting blood glucose (mmol/L), glycated hemoglobin (HbA1c) (mmol/mol), and use of NSAIDs (yes/no) (Supplemental Text 1); and 4) other factors: psychological problems and sleep duration (Supplemental Text 2).

SUMMARY-LEVEL DATA AS INSTRUMENTAL VARIABLES. We obtained summary-level data from European genome-wide association studies (GWAS) of multisite chronic pain (n = 387,649 UK Biobank participants),[21] MI (n = 22,233 cases and 64,762 controls),[22] and stroke (n = 67,162 cases and 454,450 controls).[23] Detailed data processing steps were previously published. Briefly, the multisite pain GWAS defined the outcome phenotype as total sum of body sites (0-7 sites) where chronic pain was recorded for at least 3 months.[21] In the study, Johnston et al[21] performed the multisite pain GWAS using BOLT-LMM (statistics for testing association between phenotype and genotypes using a linear mixed model) method with adjustment for age, sex, and genotyping arrays. Schunkert et al[22] adjusted for age, sex, and genotyping uncertainty in the MI GWAS, while Malik et al[23] included age and sex as covariates in the additive model for stroke GWAS.

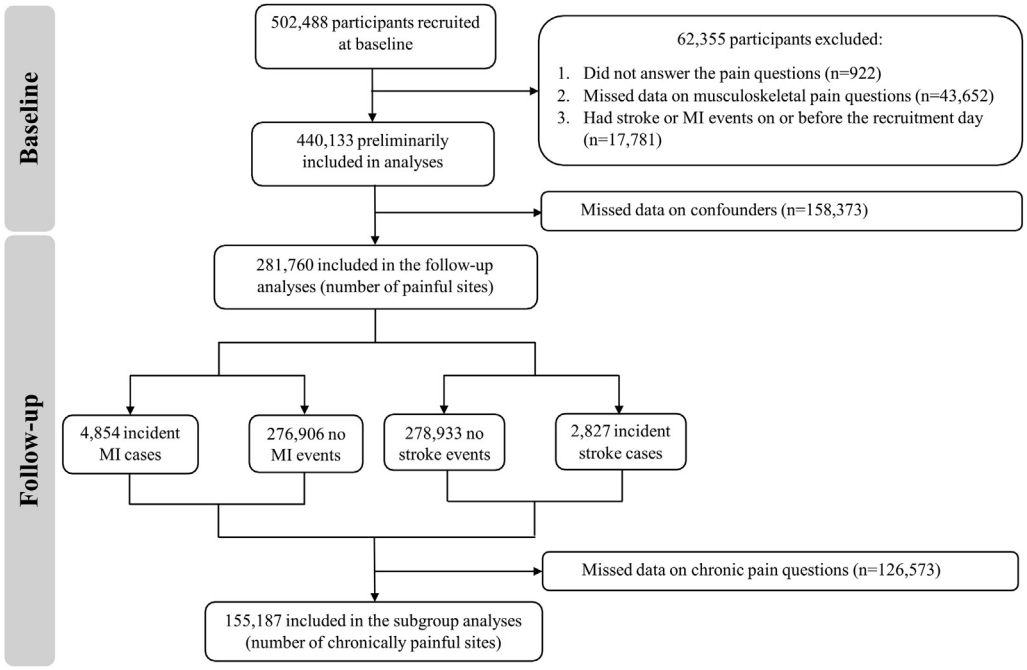
For single-nucleotide polymorphisms (SNPs) with >0.05 minor allele frequency and a *P* value of $<5 \times 10^{-8}$ in the exposure GWAS, we performed clumping (*PLINK 1.90*) to obtain independent GWAS-significant instrument SNPs. Based on the identified instrument SNPs, we then extracted their effects on the outcome, followed by effect harmonization to ensure effects of instrument variables on exposure and outcome corresponding to the same allele. Similarly, in our multivariable MR analysis, we applied the same instrumental variable selection criteria for incorporating published BMI GWAS data (n = 339,224 European adults) generated by Locke et al,[24] which used a 2-stage design meta-analyzing 80 GWAS (n = 234,069) in the first stage, and 34 additional studies (n = 88,137) genotyped with Metabochip in the second stage.[25]

STATISTICAL ANALYSES. Mean ± SD for continuous variables and percentage (number) for categorical variables were used to describe participants' characteristics by number of painful sites and number of chronically painful sites, respectively. ANOVA (analysis of variance) and ordinal chi-square test (Kruskal-Wallis test) were used to test if there was a trend of mean of each continuous and categorical variable across pain groups, respectively.

A proportional hazards model, which estimates HR and 95% CI, was used to assess the association of number of painful sites and number of chronically painful sites with the risk of MI and stroke where free of musculoskeletal pain and free of chronic pain served as the reference group, respectively. The follow-up period was calculated from the date of attending the baseline assessment to the first MI or stroke event, death, or censoring date (February 6, 2021). The proportional hazards assumption was verified for all analyses using Schoenfeld's residuals except for MI and STEMI, the analyses for MI and STEMI were; therefore, restricted to those with a follow-up of 4 years and over to meet the assumption. To examine whether the relationships between painful sites and MI or stroke were independent of confounders, the following models were performed: 1) univariable; 2) model 1: adjusted for sociodemographic and lifestyle factors; 3) model 2: model 1 + cardiometabolic health factors; 4) model 3: model 2 + psychological problems and sleep duration. Variance inflation factor was used to determine the occurrence of multicollinearity. A variable whose variance inflation factor value is >10 may merit further investigation. Significant interaction between number of painful sites and pain duration (≥3 or <3 months) was detected for MI, suggesting the effect of number of painful sites on incident MI was different in participants with and without chronic pain. Subgroup analyses according to pain duration were, therefore, performed. The Fine-Gray proportional subhazard model was used for competing risk analysis with death as a competing cause. To explore the mechanistic explanations of our findings, further analyses were performed: 1) by additionally adjusting for baseline high sensitivity C-reactive protein (hs-CRP) in models 2 and 3; and 2) by excluding self-reported rheumatoid arthritis (RA) patients at baseline.

Complementing our observational findings, we used 2-sample MR to assess genetic causality of multisite pain with MI and stroke. Two-sample MR

FIGURE 1 Flow Chart of the Study



MI = myocardial infarction.

analyses were planned for 4 trait-pairs (pain-MI, pain-stroke, MI-pain, and stroke-pain) using the "*TwoSampleMR*" R-package (version 0.4.26). Since there was only one valid genetic instrument for stroke, we could not assess the genetic causal effect of stroke on multisite pain. Inverse variance weighted (IVW) method[26] was implemented in the main MR analysis,[27] followed by sensitivity analyses with additional MR methods including generalized summary-data-based MR,[28] MR Egger (MR-Egger),[29] MR-PRESSO (Pleiotropy RESidual Sum and Outlier),[30] penalized weighted median,[31] simple median,[31] weighted median,[31] and weighted mode.[32] Each of these methods estimated the genetic causal effect based on different assumptions and weighting, and thus are useful as a complementing set of bioinformatic tools. For instance, the IVW method incorporates the SE of variant-outcome association estimate as the IVW estimator,[26] while the weighted median method uses the weighted median estimator to provide consistent causal effect estimate in presence of invalid instrument SNPs.[31] Further, generalized summary-data-based MR and MR-PRESSO methods could identify and correct for pleiotropic outliers, and testing for the intercept term in MR-Egger model can assess directional pleiotropic effects of the instrument SNPs.[29] For trait-pair(s) with significant MR associations, we further performed multivariable MR analysis using the "MVMR" R-package (version 0.3) to include BMI as an additional exposure in the model.[33]

Two-sample MR analyses were performed using R, version 3.6.1 and other statistical analyses were performed with STATA software, version 16 (Stata Corp). A 2-tailed P value <0.05 was considered statistically significant for the longitudinal analyses. The Bonferroni correction was used to account for multiple testing for the MR analyses with a P value of 0.025 (0.05/2 outcomes) considered significant.

RESULTS

The study sample consisted of 281,760 participants who had no MI and stroke at baseline. During a median follow-up of 11.9 years (IQR: 11.2-12.6) for MI and 11.9 years (IQR: 11.2-12.7 years) for stroke (**Figure 1**), 4,854 incident MI and 2,827 incident stroke events were ascertained (incidence rate of 1.48 and 0.86, respectively, per 1,000 person-years). Participants who had pain at least in one site and reported that the experienced pain lasted for ≥3 months were included in the subsample analyses of number of chronically

TABLE 1 Characteristics of Participants at Baseline, by Number of Painful Sites

		Number of Painful Sites						
	Total (N = 281,760)	**0 (n = 125,808)**	**1 (n = 87,753)**	**2 (n = 42,367)**	**3 (n = 16,324)**	**4 (n = 5,246)**	**Pain All Over the Body (n = 4,262)**	***P* Value**
Stroke events	1.0 (2,827)	0.9 (1,154)	1.0 (855)	1.1 (466)	1.2 (202)	1.5 (81)	1.6 (69)	<0.001
Ischemic stroke	0.8 (2,177)	0.7 (882)	0.7 (649)	0.9 (364)	1.0 (162)	1.2 (63)	1.3 (57)	<0.001
Intracerebral hemorrhage	0.2 (472)	0.2 (205)	0.2 (144)	0.2 (71)	0.2 (31)	0.2 (12)	0.2 (9)	0.363
Subarachnoid hemorrhage	0.1 (331)	0.1 (128)	0.1 (104)	0.1 (59)	0.1 (20)	0.3 (13)	0.2 (7)	0.007
Myocardial infarction (MI) events	1.7 (4,854)	1.4 (1,796)	1.7 (1,484)	2.1 (891)	2.3 (375)	3.3 (172)	3.2 (136)	<0.001
ST-segment elevation MI	0.5 (1,365)	0.4 (540)	0.5 (426)	0.6 (248)	0.5 (83)	0.7 (38)	0.7 (30)	<0.001
Non-ST-segment elevation MI	0.9 (2,502)	0.8 (970)	0.9 (764)	1.0 (437)	1.2 (189)	1.5 (81)	1.4 (61)	<0.001
Age (y)	56.3 ± 8.1	56.4 ± 8.1	56.1 ± 8.2	56.5 ± 8.1	56.9 ± 7.9	57.6 ± 7.6	56.4 ± 7.8	<0.001
Male	48.2 (135,690)	49.2 (61,846)	49.0 (43,025)	46.9 (19,880)	44.4 (7,255)	38.5 (2,018)	39.1 (1,666)	<0.001
Body mass index (kg/m^2)	27.3 ± 4.7	26.6 ± 4.2	27.4 ± 4.6	28.1 ± 4.9	28.9 ± 5.3	29.9 ± 5.8	29.3 ± 5.7	<0.001
Highest education qualification								<0.001
College or university degree/NVQ, HND, HNC, or equivalent/other professional qualifications	63.1 (177,716)	66.2 (83,224)	63.0 (55,258)	59.6 (25,248)	55.9 (9,128)	52.5 (2,753)	49.4 (2,105)	
A levels, AS levels, or equivalent	5.8 (16,338)	6.1 (7,667)	5.7 (5,041)	5.6 (2,353)	5.1 (832)	4.4 (230)	5.0 (215)	
O levels, GCSEs, CSE, or equivalent	16.7 (46,944)	16.2 (20,376)	16.7 (14,662)	17.2 (7,277)	18.1 (2,960)	17.1 (898)	18.1 (771)	
None of the Above	14.5 (40,762)	11.6 (14,541)	14.6 (12,792)	17.7 (7,489)	20.9 (3,404)	26 (1,365)	27.5 (1,171)	
Household income (£) before tax								<0.001
<18,000	18.3 (51,615)	15.1 (18,980)	17.8 (15,588)	21.7 (9,195)	27.3 (4,451)	34.8 (1,827)	36.9 (1,574)	
18,000-30,999	22.3 (62,765)	22.0 (27,625)	22.3 (19,599)	22.7 (9,602)	23.4 (3,824)	22.9 (1,201)	21.5 (914)	
31,000-51,999	23.9 (67,438)	25.0 (31,445)	24.4 (21,434)	22.5 (9,551)	20.6 (3,362)	17.5 (919)	17.1 (727)	
52,000-100,000	19.4 (54,788)	21.6 (27,229)	19.6 (17,190)	17.2 (7,281)	13.6 (2,220)	8.9 (465)	9.5 (403)	
>100,000	5.4 (15,153)	6.4 (8,094)	5.4 (4,705)	4.1 (1,732)	2.8 (459)	2.0 (104)	1.4 (59)	
Do not know/prefer not to answer	10.7 (30,001)	9.9 (12,435)	10.5 (9,237)	11.8 (5,006)	12.3 (2,008)	13.9 (730)	13.7 (585)	
White ethnicity	95.5 (269,111)	96.4 (121,325)	95.4 (83,673)	94.7 (40,102)	93.9 (15,324)	93.6 (4,912)	88.6 (3,775)	<0.001
Smoking status								<0.001
Never	54.9 (154,546)	58.0 (72,936)	54.5 (47,860)	50.8 (21,536)	47.4 (7,741)	44.6 (2,338)	50.1 (2,135)	
Former	35.0 (98,614)	33.5 (42,130)	35.0 (30,674)	37.5 (15,888)	39.2 (6,402)	39.6 (2,075)	33.9 (1,445)	
Current	10.2 (28,600)	8.5 (10,742)	10.5 (9,219)	11.7 (4,943)	13.4 (2,181)	15.9 (833)	16 (682)	
Alcohol consumption								<0.001
Daily or almost daily	21.9 (61,669)	23.2 (29,212)	21.8 (19,109)	20.8 (8,795)	19.4 (3,164)	15.9 (832)	13.1 (557)	
3-4 times/wk	24.4 (68,791)	26.2 (32,908)	24.6 (21,556)	22.6 (9,566)	19.8 (3,237)	17.0 (894)	14.8 (630)	
1-2 times/wk	25.8 (72,608)	26.0 (32,668)	26.1 (22,920)	25.8 (10,922)	24.4 (3,990)	22.7 (1,189)	21.6 (919)	
1-3 times/mo	10.7 (30,231)	10.1 (12,741)	10.8 (9,496)	11.3 (4,774)	12.2 (1,996)	12.6 (661)	13.2 (563)	
Special occasions only	10.3 (28,882)	8.8 (11,027)	10.1 (8,888)	11.7 (4,943)	14.0 (2,292)	17.7 (928)	18.9 (804)	
Never	7.0 (19,579)	5.8 (7,252)	6.6 (5,784)	8.0 (3,367)	10.1 (1,645)	14.1 (742)	18.5 (789)	
Meeting moderate/vigorous PA recommendation	54.8 (154,512)	55.9 (70,377)	54.9 (48,185)	53.9 (22,847)	52.9 (8,640)	48.5 (2,544)	45.0 (1,919)	<0.001
Systolic blood pressure (mm Hg)	137.9 ± 18.5	138.2 ± 18.8	137.6 ± 18.4	137.6 ± 18.2	137.9 ± 18.1	138.1 ± 17.9	137.4 ± 18.7	<0.001
Diastolic blood pressure (mm Hg)	82.4 ± 10.1	82.2 ± 10.1	82.4 ± 10.1	82.5 ± 10.0	82.6 ± 10.0	82.7 ± 9.7	82.6 ± 10.5	<0.001
Total cholesterol (mmol/L)	5.7 ± 1.1	5.7 ± 1.1	5.7 ± 1.1	5.7 ± 1.1	5.7 ± 1.2	5.7 ± 1.2	5.6 ± 1.2	<0.001
High density lipoprotein (mmol/L)	1.5 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	<0.001
Fasting blood glucose (mmol/L)	5.1 ± 1.2	5.1 ± 1.1	5.1 ± 1.2	5.1 ± 1.2	5.2 ± 1.3	5.3 ± 1.4	5.3 ± 1.7	<0.001
HbA1c (mmol/mol)	35.9 ± 6.4	35.6 ± 6.0	35.8 ± 6.4	36.2 ± 6.6	36.7 ± 7.1	37.4 ± 7.7	37.8 ± 8.8	<0.001
NSAIDs medication use	25.3 (71,183)	16.9 (21,257)	27.8 (24,418)	34.6 (14,677)	41.1 (6,711)	45.3 (2,374)	41.0 (1,746)	<0.001
Psychological problems	33.5 (94,513)	27.3 (34,318)	34.3 (30,052)	40.5 (17,148)	47.9 (7,825)	54.4 (2,856)	54.3 (2,314)	<0.001
Sleep duration								<0.001
Meet the recommendation (≥7 h and ≤8 h)	68.8 (193,958)	73.3 (92,173)	68.8 (60,367)	64.0 (27,103)	58.7 (9,575)	51.4 (2,696)	48.0 (2,044)	
Less than recommendation (<7 h)	23.9 (67,285)	20.1 (25,307)	24.1 (21,130)	28.2 (11,952)	32.5 (5,312)	38.2 (2,004)	37.1 (1,580)	
More than recommendation (>8 h)	7.3 (20,517)	6.6 (8,328)	7.1 (6,256)	7.8 (3,312)	8.8 (1,437)	10.4 (546)	15.0 (638)	

Values are % (n) or mean ± SD.

HbA1c = glycated hemoglobin; HNC = Higher National Certificate; HND = Higher National Diplomas; NSAIDs = nonsteroidal anti-inflammatory drugs; NVQ = National Vocational Qualification; PA = physical activity.

TABLE 2 Associations Between Number of Painful Sites and Incidence of Myocardial Infarction Over Follow-Up

	n	No. of Cases	No. of Painful Sites	Univariate Model	Model 1[a]	Model 2[b]	Model 3[c]
MI events[d]	123,975	1,131 (0.9)	0	Ref	Ref	Ref	Ref
	86,339	942 (1.1)	1	**1.20 (1.10-1.31)**	**1.13 (1.03-1.23)**	**1.10 (1.00-1.02)**	1.08 (0.99-1.18)
	41,564	572 (1.4)	2	**1.51 (1.37-1.67)**	**1.35 (1.21-1.49)**	**1.29 (1.16-1.43)**	**1.26 (1.13-1.39)**
	16,023	263 (1.6)	3	**1.81 (1.58-2.07)**	**1.49 (1.30-1.70)**	**1.40 (1.22-1.61)**	**1.34 (1.17-1.54)**
	5,123	117 (2.3)	4	**2.53 (2.09-3.06)**	**1.92 (1.58-2.33)**	**1.80 (1.48-2.18)**	**1.70 (1.39-2.06)**
	4,125	87 (2.1)	Pain all over the body	**2.34 (1.88-2.91)**	**1.88 (1.51-2.35)**	**1.76 (1.41-2.19)**	**1.65 (1.32-2.07)**
			P value for trend	**<0.001**	**<0.001**	**<0.001**	**<0.001**
ST-segment elevation MI[d]	124,339	321 (0.3)	0	Ref	Ref	Ref	Ref
	86,644	243 (0.3)	1	1.09 (0.92-1.28)	1.04 (0.88-1.23)	1.04 (0.88-1.23)	1.04 (0.88-1.23)
	41,753	149 (0.4)	2	**1.38 (1.14-1.68)**	**1.29 (1.06-1.57)**	**1.29 (1.06-1.58)**	**1.29 (1.05-1.57)**
	16,101	55 (0.3)	3	1.33 (1.00-1.77)	1.18 (0.88-1.58)	1.19 (0.89-1.59)	1.18 (0.88-1.58)
	5,155	23 (0.5)	4	**1.74 (1.14-2.65)**	1.50 (0.98-2.31)	**1.56 (1.01-2.39)**	**1.54 (1.00-2.38)**
	4,155	13 (0.3)	Pain all over the body	1.22 (0.70-2.13)	1.05 (0.60-1.84)	1.04 (0.59-1.83)	1.04 (0.59-1.82)
			P value for trend	**<0.001**	**0.021**	**0.020**	**0.024**
Non-ST-segment elevation MI	125,808	970 (0.8)	0	Ref	Ref	Ref	Ref
	87,753	764 (0.9)	1	**1.13 (1.03-1.24)**	1.06 (0.96-1.16)	1.04 (0.94-1.14)	1.02 (0.93-1.13)
	42,367	437 (1.0)	2	**1.34 (1.20-1.50)**	**1.18 (1.05-1.32)**	**1.15 (1.02-1.29)**	**1.12 (1.00-1.26)**
	16,324	189 (1.2)	3	**1.51 (1.29-1.76)**	**1.22 (1.04-1.43)**	**1.18 (1.00-1.38)**	1.13 (0.96-1.32)
	5,246	81 (1.5)	4	**2.02 (1.61-2.54)**	**1.50 (1.19-1.89)**	**1.45 (1.15-1.83)**	**1.37 (1.08-1.72)**
	4,262	61 (1.4)	Pain all over the body	**1.89 (1.46-2.44)**	**1.50 (1.16-1.95)**	**1.43 (1.10-1.87)**	**1.34 (1.03-1.75)**
			P value for trend	**<0.001**	**<0.001**	**<0.001**	**0.001**

Values are N or HR (95% CI) unless otherwise indicated. HRs (95% CIs) in **bold** represent statistically significant results. [a]Model 1: adjusted for baseline age, sex, body mass index, ethnicity, highest education level, house income, smoking status, alcohol frequency, and meeting recommended moderate/vigorous physical activity. [b]Model 2: Model 1 + systolic blood pressure, diastolic blood pressure, total cholesterol, high density lipoprotein, fasting blood glucose, glycated hemoglobin, and use of nonsteroidal anti-inflammatory drugs. [c]Model 3: Model 2 + psychological problems and sleep duration. [d]Analyses were restricted to those with a follow-up of 4 years and over.

MI = myocardial infarction; Ref = reference group.

painful sites (n = 155,187) (**Figure 1**). Baseline characteristics across number of painful sites are presented in **Table 1**. Compared to those without pain, participants reporting greater number of painful sites were more likely to be older, female, heavier, non-White ethnicity, current smoker, and physically inactive, and had a lower frequency of alcohol consumption, lower education level and household income, worse cardiometabolic health profiles, higher reported use of NSAIDs, had worse psychological problems, and shorter/longer sleep duration (<7 hours or >8 hours). Similar differences in participants' characteristics were found in those with greater number of chronically painful sites (Supplemental Table 1).

Results for number of painful sites and incident MI and stroke are presented in **Tables 2 and 3** and **Central Illustration**. No evidence of multicollinearity was identified (data not shown). There was a dose-response pattern for the associations of number of painful sites with incident MI and stroke. On average, every painful site increase was associated with a 12% and 6% higher risk of incident MI and stroke in the fully adjusted model, respectively. In univariable analysis, compared to those without pain, participants reporting pain in 1-, 2-, 3-, 4-site, and 'all over the body' had a 20%, 51%, 81%, 153%, and 134% higher risk of incident MI, respectively (**Table 2**). Adjustment for covariates attenuated the associations, but the significant associations remained (**Table 2**, **Central Illustration**). Similarly, participants who reported pain in 2-, 3-, 4-site, and 'all over the body' had a 20%, 36%, 70%, and 79% higher risk of incident stroke (**Table 3**). After adjustment for covariates, participants with pain in 4 sites and 'all over the body' had a higher risk of incident stroke than those without pain, although the effect sizes were slightly attenuated (**Table 3**, **Central Illustration**).

Subgroup analyses by MI subtypes were performed and showed a similar trend toward a higher risk of incident STEMI and NSTEMI with increasing number of painful sites before and after adjustment for confounding variables (**Table 2**). Relative to those without pain, greater number of painful sites was associated with increased risks of both STEMI and NSTEMI in univariable analyses. Adjustment for covariates largely did not change the significant associations with NSTEMI, whereas pain in 2- and 4-site remained statistically significant with STEMI. Similarly, a dose-responsive relationship between number of painful sites and ischemic stroke and SAH

TABLE 3 Associations Between Number of Painful Sites and Incidence of Stroke Over Follow-Up

	n	No. of Cases (%)	No. of Painful Sites	Univariate Model	Model 1[a]	Model 2[b]	Model 3[c]
Stroke events	125,808	1,154 (0.9)	0	Ref	Ref	Ref	Ref
	87,753	855 (1.0)	1	1.06 (0.97-1.16)	1.02 (0.94-1.12)	1.02 (0.94-1.12)	1.02 (0.93-1.12)
	42,367	466 (1.1)	2	**1.20 (1.08-1.34)**	1.09 (0.98-1.22)	1.10 (0.98-1.22)	1.09 (0.97-1.21)
	16,324	202 (1.2)	3	**1.36 (1.17-1.57)**	1.14 (0.98-1.32)	1.14 (0.98-1.33)	1.12 (0.96-1.31)
	5,246	81 (1.5)	4	**1.70 (1.35-2.13)**	**1.31 (1.04-1.64)**	**1.31 (1.04-1.64)**	**1.28 (1.02-1.61)**
	4,262	69 (1.6)	Pain all over the body	**1.79 (1.41-2.29)**	**1.49 (1.17-1.91)**	**1.48 (1.16-1.89)**	**1.44 (1.13-1.85)**
			P value for trend	**<0.001**	**<0.001**	**<0.001**	**0.001**
Ischemic stroke	125,808	882 (0.7)	0	Ref	Ref	Ref	Ref
	87,753	649 (0.7)	1	1.06 (0.95-1.17)	1.00 (0.90-1.11)	1.00 (0.90-1.11)	0.99 (0.90-1.10)
	42,367	364 (0.9)	2	**1.23 (1.09-1.39)**	1.09 (0.96-1.23)	1.09 (0.96-1.23)	1.08 (0.95-1.22)
	16,324	162 (1.0)	3	**1.42 (1.20-1.68)**	1.15 (0.97-1.36)	1.14 (0.96-1.36)	1.12 (0.95-1.34)
	5,246	63 (1.2)	4	**1.73 (1.34-2.23)**	1.27 (0.98-1.64)	1.26 (0.97-1.63)	1.23 (0.94-1.59)
	4,262	57 (1.3)	Pain all over the body	**1.94 (1.48-2.53)**	**1.56 (1.19-2.05)**	**1.54 (1.17-2.02)**	**1.49 (1.13-1.96)**
			P value for trend	**<0.001**	**0.001**	**0.001**	**0.003**
Intracerebral hemorrhage	125,808	206 (0.2)	0	Ref	Ref	Ref	Ref
	87,753	144 (0.2)	1	1.01 (0.81-1.25)	1.01 (0.82-1.25)	1.03 (0.83-1.27)	1.03 (0.83-1.27)
	42,367	71 (0.2)	2	1.03 (0.79-1.35)	1.10 (0.76-1.31)	1.02 (0.78-1.35)	1.03 (0.78-1.36)
	16,324	31 (0.2)	3	1.17 (0.80-1.71)	1.09 (0.74-1.59)	1.12 (0.76-1.64)	1.13 (0.77-1.66)
	5,246	12 (0.2)	4	1.41 (0.79-2.53)	1.26 (0.70-2.27)	1.29 (0.71-2.33)	1.30 (0.72-2.36)
	4,262	9 (0.2)	Pain all over the body	1.32 (0.67-2.56)	1.22 (0.62-2.40)	1.24 (0.63-2.44)	1.25 (0.63-2.45)
			P value for trend	0.195	0.454	0.350	0.330
Subarachnoid hemorrhage	125,808	128 (0.1)	0	Ref	Ref	Ref	Ref
	87,753	104 (0.1)	1	1.17 (0.90-1.51)	1.16 (0.89-1.50)	1.15 (0.89-1.49)	1.14 (0.88-1.48)
	42,367	59 (0.1)	2	**1.37 (1.01-1.87)**	1.32 (0.97-1.81)	1.31 (0.96-1.80)	1.29 (0.94-1.77)
	16,324	20 (0.1)	3	1.21 (0.75-1.94)	1.12 (0.70-1.81)	1.11 (0.69-1.80)	1.08 (0.67-1.75)
	5,246	13 (0.3)	4	**2.45 (1.39-4.34)**	**2.12 (1.18-3.79)**	**2.11 (1.17-3.78)**	**2.04 (1.14-3.68)**
	4,262	7 (0.2)	Pain all over the body	1.64 (0.76-3.50)	1.48 (0.68-3.18)	1.46 (0.68-3.17)	1.41 (0.65-3.07)
			P value for trend	**0.003**	**0.021**	**0.026**	**0.043**

Values are N or HR (95% CI) unless otherwise indicated. HRs (95% CIs) in **bold** represent statistically significant results. [a]Model 1: adjusted for baseline age, sex, body mass index, ethnicity, highest education level, house income, smoking status, alcohol frequency, and meeting recommended moderate-vigorous physical activity. [b]Model 2: Model 1 + systolic blood pressure, diastolic blood pressure, total cholesterol, high density lipoprotein, fasting blood glucose, glycated hemoglobin, and use of nonsteroidal anti-inflammatory drugs. [c]Model 3: Model 2 + psychological problems and sleep duration.

Ref = reference group.

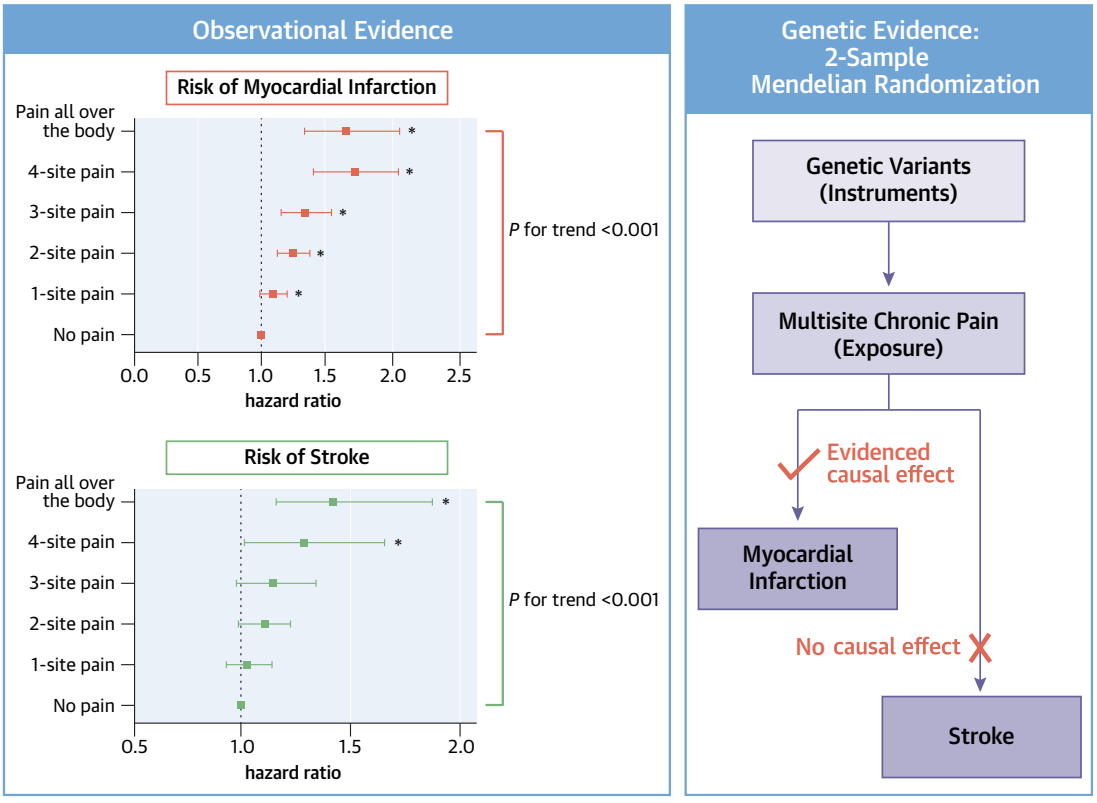
was found, but not for intracerebral hemorrhage. Compared to participants without pain, those reporting pain in 4-site or 'all over the body' consistently had an increased risk of SAH and ischemic stroke before and after adjustment for covariates (**Table 3**).

Secondary analyses by pain duration (≥3 months) revealed similar results and trends of the associations of number of chronically painful sites with incident MI and stroke (**Table 4**). Similarly, there was no evidence of multicollinearity in our models (data not shown). Also, competing risk analyses showed similar estimates and CI (Supplemental Tables 2 and 3).

The levels of hs-CRP were higher in those with greater number of musculoskeletal painful sites (Supplemental Table 4) than those without pain. Our results were largely unchanged after additionally adjusting for baseline CRP in models 2 and 3 (Supplemental Tables 5 to 7) or after excluding RA patients at baseline (Supplemental Tables 8 to 10).

Genetic effects of instrument SNPs used in 2-sample MR analysis are summarized in Supplemental Table 11 for 3 trait-pairs (pain-MI, pain-stroke, and MI-pain). As shown in **Table 5** and **Figure 2**, evidence from the main IVW ($P = 9.96 \times 10^{-4}$) method supported a genetic causal effect of multisite chronic pain on MI. Additionally, test for the Egger intercept term showed no evident presence of directional pleiotropic effects (intercept estimate = −0.006; $P = 0.81$). The consistent effect sizes and direction for pain-MI trait pair across 8 different MR methods reinforced a true causal relationship of genetically predicted higher multisite chronic pain increasing MI risk (**Figure 2**, **Table 5**, **Central Illustration**), although the MR-Egger ($P = 0.48$) and weighted mode methods ($P = 0.11$) were not

CENTRAL ILLUSTRATION **Multisite Musculoskeletal Pain With Incident MI and Stroke**



Tian J, et al. JACC Adv. 2023;2(3):100295.

Observational analyses found that increasing number of painful sites was proportionately associated with higher risks of incident MI and stroke. The excess risks were independent of known risk factors including age, sociodemographic, obesity, lifestyle, nonsteroidal anti-inflammatory drugs use, cardiometabolic, psychological, and sleep duration factors **(left)**. Further, 2-sample Mendelian randomization analyses provided evidence for a genetic causal effect of multisite pain on MI susceptibility **(right)**.

statistically significant. Upon adding BMI in the multivariable MR model for the pain-MI trait pair, the estimated causal effect of multisite pain on MI risk remained similar (Supplemental Table 12). There was no evidence supporting a genetic causal effect of MI on multisite chronic pain, and that of multisite chronic pain on stroke (**Table 5**, **Central Illustration**).

DISCUSSION

The present study found that people having greater number of painful sites had higher risks of incident MI and stroke in a large population-based cohort. The excess risks were independent of a range of known factors including age, sociodemographic, obesity, lifestyle, NSAIDs use, cardiometabolic, psychological, and sleep duration factors. Our complementary 2-sample MR analyses support a genetic causal effect of multisite chronic pain on MI, but not on stroke. These findings suggest that pain in multiple sites is an independent risk factor for MI, and highlight the importance of an increase in awareness of the detrimental effect of experiencing musculoskeletal pain on CVD. To our knowledge, this study is the first to examine the relationship between painful sites and specific types of CVD while considering a range of potential explanatory factors.

Few prior studies have evaluated the relationship between certain pain conditions and specific types of CVD. A recent study by Chung et al[34] found that chronic pain conditions were associated with a 20% increased risk of MI as compared to individuals without chronic pain over a median follow-up of 12 years. In a study with a median follow-up of 9 years, Tsai et al[35] reported a 2-fold higher risk of coronary heart disease in patients with fibromyalgia

TABLE 4 Associations Between Number of Chronically Painful Sites and Incident MI and Stroke Over Follow-Up

	n	No. of Cases	No. of Chronically Painful Sites	Univariate Model	Model 1[a]	Model 2[b]	Model 3[c]
MI events[d]	39,808	413 (1.0)	0	Ref	Ref	Ref	Ref
	67,566	799 (1.2)	1	**1.14 (1.01-1.28)**	1.07 (0.95-1.20)	1.07 (0.95-1.20)	1.06 (0.94-1.19)
	28,069	410 (1.5)	2	**1.41 (1.23-1.62)**	**1.25 (1.09-1.43)**	**1.23 (1.07-1.42)**	**1.21 (1.05-1.39)**
	10,316	193 (1.9)	3	**1.82 (1.53-2.15)**	**1.45 (1.22-1.73)**	**1.41 (1.19-1.68)**	**1.36 (1.14-1.62)**
	3,424	83 (2.4)	4	**2.36 (1.86-2.99)**	**1.70 (1.33-2.16)**	**1.64 (1.29-2.08)**	**1.56 (1.23-1.99)**
	3,237	78 (2.4)	Pain all over the body	**2.35 (1.85-3.00)**	**1.83 (1.43-2.34)**	**1.78 (1.39-2.27)**	**1.69 (1.32-2.16)**
			P value for trend	**<0.001**	**<0.001**	**<0.001**	**<0.001**
ST-segment elevation MI[d]	39,930	107 (0.3)	0	Ref	Ref	Ref	Ref
	67,826	198 (0.3)	1	1.09 (0.86-1.38)	1.09 (0.86-1.38)	1.10 (0.87-1.40)	1.10 (0.87-1.40)
	28,213	106 (0.4)	2	**1.41 (1.07-1.84)**	**1.38 (1.05-1.81)**	**1.41 (1.08-1.85)**	**1.41 (1.07-1.85)**
	10,375	43 (0.4)	3	**1.55 (1.09-2.21)**	**1.45 (1.01-2.08)**	**1.49 (1.04-2.13)**	**1.49 (1.04-2.14)**
	3,446	15 (0.4)	4	1.63 (0.95-2.80)	1.46 (0.84-2.52)	1.54 (0.89-2.67)	1.54 (0.89-2.68)
	3,261	11 (0.3)	Pain all over the body	1.27 (0.68-2.36)	1.15 (0.62-2.16)	1.16 (0.62-2.18)	1.17 (0.63-2.20)
			P value for trend	**0.002**	**0.017**	**0.011**	**0.011**
Non-ST-segment elevation MI	40,437	327 (0.8)	0	Ref	Ref	Ref	Ref
	68,709	642 (0.9)	1	**1.16 (1.01-1.32)**	1.08 (0.94-1.23)	1.08 (0.95-1.24)	1.08 (0.94-1.23)
	28,645	319 (1.1)	2	**1.38 (1.19-1.61)**	**1.21 (1.04-1.41)**	**1.22 (1.04-1.42)**	**1.19 (1.02-1.39)**
	10,536	134 (1.3)	3	**1.58 (1.29-1.93)**	**1.25 (1.02-1.53)**	**1.24 (1.01-1.52)**	1.20 (0.97-1.47)
	3,505	55 (1.6)	4	**1.96 (1.47-2.60)**	**1.39 (1.04-1.86)**	**1.39 (1.04-1.85)**	1.32 (0.98-1.76)
	3,355	52 (1.5)	Pain all over the body	**1.87 (1.39-2.52)**	**1.47 (1.09-1.98)**	**1.45 (1.07-1.96)**	**1.37 (1.01-1.85)**
			P value for trend	**<0.001**	**<0.001**	**<0.001**	**0.003**
Stroke events	40,437	372 (0.9)	0	Ref	Ref	Ref	Ref
	68,709	689 (1.0)	1	1.09 (0.96-1.24)	1.00 (0.88-1.13)	1.01 (0.89-1.14)	1.00 (0.89-1.14)
	28,645	348 (1.2)	2	**1.33 (1.15-1.53)**	1.14 (0.98-1.32)	**1.16 (1.00-1.34)**	1.15 (0.99-1.34)
	10,536	140 (1.3)	3	**1.45 (1.20-1.77)**	1.15 (0.94-1.40)	1.15 (0.95-1.41)	1.14 (0.94-1.39)
	3,505	55 (1.6)	4	**1.72 (1.29-2.28)**	1.25 (0.94-1.66)	1.27 (0.95-1.69)	1.25 (0.94-1.67)
	3,355	63 (1.9)	Pain all over the body	**2.08 (1.59-2.72)**	**1.66 (1.27-2.18)**	**1.66 (1.26-2.17)**	**1.62 (1.23-2.13)**
			P value for trend	**<0.001**	**<0.001**	**<0.001**	**0.001**
Ischemic stroke	40,437	293 (0.7)	0	Ref	Ref	Ref	Ref
	68,709	526 (0.8)	1	1.06 (0.92-1.22)	0.96 (0.83-1.10)	0.97 (0.84-1.12)	0.97 (0.84-1.11)
	28,645	266 (0.9)	2	**1.29 (1.09-1.52)**	1.09 (0.92-1.28)	1.10 (0.93-1.31)	1.09 (0.92-1.29)
	10,536	108 (1.0)	3	**1.42 (1.14-1.78)**	1.09 (0.87-1.36)	1.09 (0.87-1.36)	1.07 (0.86-1.34)
	3,505	45 (1.3)	4	**1.78 (1.30-2.44)**	1.24 (0.90-1.70)	1.25 (0.91-1.72)	1.22 (0.89-1.68)
	3,355	52 (1.6)	Pain all over the body	**2.18 (1.62-2.93)**	**1.68 (1.25-2.27)**	**1.67 (1.24-2.26)**	**1.62 (1.20-2.19)**
			P value for trend	**<0.001**	**0.001**	**0.001**	**0.003**
Intracerebral hemorrhage	40,437	60 (0.2)	0	Ref	Ref	Ref	Ref
	68,709	112 (0.2)	1	1.10 (0.80-1.50)	1.02 (0.75-1.40)	1.03 (0.75-1.42)	1.04 (0.76-1.42)
	28,645	57 (0.2)	2	1.35 (0.94-1.93)	1.21 (0.84-1.75)	1.25 (0.87-1.80)	1.25 (0.87-1.81)
	10,536	21 (0.2)	3	1.35 (0.82-2.22)	1.17 (0.71-1.94)	1.21 (0.73-2.00)	1.21 (0.73-2.01)
	3,505	6 (0.2)	4	1.16 (0.50-2.69)	0.99 (0.42-2.30)	1.02 (0.44-2.39)	1.03 (0.44-2.41)
	3,355	9 (0.3)	Pain all over the body	1.84 (0.91-3.71)	1.67 (0.82-3.40)	1.69 (0.83-3.44)	1.69 (0.83-3.46)
			P value for trend	**0.039**	0.169	0.131	0.128
Subarachnoid hemorrhage	40,437	42 (0.1)	0	Ref	Ref	Ref	Ref
	68,709	81 (0.1)	1	1.14 (0.78-1.65)	1.06 (0.73-1.54)	1.07 (0.74-1.56)	1.07 (0.73-1.55)
	28,645	49 (0.2)	2	**1.65 (1.09-2.49)**	1.49 (0.98-2.26)	1.51 (1.00-2.30)	1.49 (0.98-2.27)
	10,536	18 (0.2)	3	1.65 (0.95-2.87)	1.45 (0.83-2.53)	1.47 (0.84-2.58)	1.43 (0.82-2.52)
	3,505	8 (0.2)	4	**2.21 (1.04-4.70)**	1.82 (0.84-3.92)	1.86 (0.86-4.01)	1.80 (0.83-3.90)
	3,355	5 (0.2)	Pain all over the body	1.45 (0.58-3.68)	1.26 (0.49-3.22)	1.28 (0.50-3.27)	1.24 (0.48-3.17)
			P value for trend	**0.005**	**0.040**	**0.035**	**0.049**

Values are N or HR (95% CI) unless otherwise indicated. HRs (95% CIs) in **bold** represent statistically significant results. [a]Model 1: adjusted for baseline age, sex, body mass index, ethnicity, highest education level, house income, smoking status, alcohol frequency, and meeting recommended moderate-vigorous physical activity. [b]Model 2: Model 1 + systolic blood pressure, diastolic blood pressure, total cholesterol, high density lipoprotein, fasting blood glucose, glycated hemoglobin, and use of nonsteroidal anti-inflammatory drugs. [c]Model 3: Model 2 + psychological problems and sleep duration. [d]Analyses were restricted to those with a follow-up of 4 years and over.

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; Ref = reference group.

TABLE 5 Genetic Causality of Multisite Pain With Myocardial Infarction and Stroke

Exposure	Outcome	MR Method	nSNP	β	SE	*P* Value
Pain	MI	IVW	**30**	**0.70**	**0.21**	**9.96×10^{-4}**
		GSMR	30	0.70	0.18	1.10×10^{-4}
		MR Egger	**30**	**1.06**	**1.47**	**0.48**
		MR-PRESSO	**30**	**0.70**	**0.21**	**2.62×10^{-3}**
		Penalized weighted median	**30**	**0.75**	**0.27**	**4.75×10^{-3}**
		Simple median	**30**	**0.79**	**0.28**	**4.12×10^{-3}**
		Weighted median	**30**	**0.74**	**0.25**	**3.57×10^{-3}**
		Weighted mode	30	0.94	0.58	0.11
MI	Pain	IVW	15	−0.012	0.009	0.18
		GSMR	13	−0.004	0.006	0.50
		MR Egger	15	0.014	0.024	0.57
		MR-PRESSO	13	−0.004	0.006	0.56
		Penalized weighted median	15	−0.001	0.008	0.95
		Simple median	15	−0.013	0.010	0.17
		Weighted median	15	−0.002	0.008	0.79
		Weighted mode	15	0.000	0.008	0.98
Pain	Stroke	IVW	37	−0.11	0.20	0.58
		GSMR	37	−0.11	0.20	0.58
		MR Egger	37	0.95	1.42	0.51
		MR-PRESSO	37	−0.11	0.19	0.56
		Penalized weighted median	37	−0.19	0.28	0.49
		Simple median	37	−0.19	0.29	0.51
		Weighted median	37	−0.19	0.28	0.49
		Weighted mode	37	−0.40	0.60	0.52

Values in **bold** are statistically significant results.

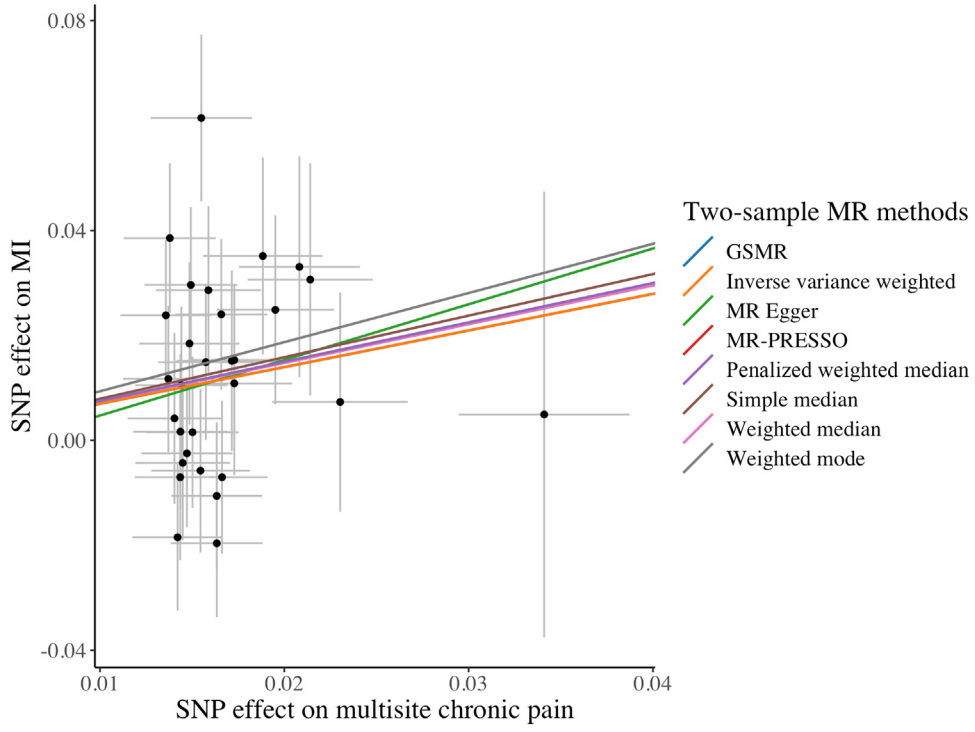
β = Effect estimate; GSMR = Generalized summary-data-based Mendelian randomization; IVW = inverse variance weighted; MI = myocardial infarction; MR = Mendelian randomization; nSNP = number of genetic instrument SNPs; PRESSO = Pleiotropy RESidual Sum and Outlier; SE = Standard Error.

than those without fibromyalgia. Similarly, one study by Su et al[36] showed that patients with fibromyalgia had a 47% increased risk of coronary heart disease relative to age- and sex-matched nonfibromyalgia controls over a mean follow-up of 9 years. Partially consistent with these studies, the current study found that people with greater number of painful sites had a higher risk of MI compared to those without musculoskeletal pain. Although the findings from our study are not directly comparable with these studies due to the differences in pain definition, follow-up period, confounding factors adjusted, and outcome measures, our study combined with prior studies appears to support a pathophysiologic link of musculoskeletal pain to vascular disease. Furthermore, using genetic variants associated with multisite chronic pain, our 2-sample MR results support the causal effect of multisite chronic pain on MI risk.

The current study found a greater risk of stroke in association with number of painful sites, which seems to align with the only one longitudinal study which reported a 30% increased risk of stroke in patients with chronic pain conditions than those without over 12 years of follow-up.[34] Our findings are contrary to a recent meta-analysis on the cross-sectional associations between musculoskeletal pain and stroke,[7] which reported no evidence of co-occurrence of 2 conditions. This discrepancy may be explained by the study design (cross-sectional vs longitudinal study), suggesting musculoskeletal pain as a risk factor involved in the development of stroke. However, our 2-sample MR results showed no evidence of genetic causal link between multisite chronic pain and stroke. Inconsistency between observational and MR findings may be ascribed to the assumption of MR analysis that there is a linear relationship between genetically increased number of chronic pain sites and the risk of stroke, which is estimated from a number of common variants. It is, therefore, less likely to detect the causality induced by rare loss of function mutations.

Our study found that the increased risk of stroke was largely contributed by the ischemic subtype and a relatively consistent association of painful sites with 2 subtypes of MI. This may indicate that a potential biological connection of musculoskeletal pain with MI and stroke is due to occluded vessels through inflammation, which has a negative impact on vasculature by impaired endothelial function—an early atherosclerotic process.[8,9] However, consistent

FIGURE 2 **Genetic Causal Effects of Multisite Chronic Pain on Myocardial Infarction**



There were 30 instrument Single-Nucleotide Polymorphisms (SNPs), with their genetic effects on multisite chronic pain shown on x-axis, and their effects on MI shown on y-axis. Each **black dot** represents an instrument SNP with error bars for their effects shown in **light grey**. Slopes of the 8 lines are the estimated effect of multisite chronic pain on MI using GSMR method **(blue)**, inverse variance weighted method **(orange)**, MR Egger method **(green)**, MR-PRESSO method **(red)**, penalized weighted median method **(purple)**, simple median method **(brown)**, weighted median method **(pink)** and weighted mode method **(grey)**. GSMR = generalized summary-data-based Mendelian randomization; MI = myocardial infarction; MR = Mendelian randomization; PRESSO = Pleiotropy RESidual Sum and Outlier; SNP = single-nucleotide polymorphism.

results were found even after further adjustment for hs-CRP or excluding participants with RA at baseline. It is likely that the mechanism linking multisite pain to ischemic stroke and MI may not be largely driven by inflammation. Sympathetic activation may be another important pathophysiological mechanism underlying the observed relationship between multisite pain and MI and stroke. There is evidence that enhanced sympathetic activity related to chronic pain may lead to elevated blood pressure, which has an adverse influence on endothelial function.[10-12] Furthermore, chronic pain itself, as an ongoing stress factor, can lead to elevated levels of catecholamine, thereby causing catecholamine-induced endothelial damage.[37]

There are several implications raised from this study. First, pain occurring in multiple sites (≥2) is highly prevalent (24%) in this community-based cohort and the association between musculoskeletal pain with MI and stroke risk appeared to be stronger in those with greater number of painful sites. These findings are of clinical relevance with regards to the MI and stroke prevention in individuals with pain. Careful consideration needs to be given to patients with greater number of painful sites when assessing patients' MI and stroke risk. Second, in light of a causal association of number of painful sites with incident MI, pain management and treatment may aid MI prevention with the potential to reduce morbidity and mortality of MI. Third, the relationships between number of painful sites and MI and stroke were independent of NSAID use, hence, the risk-benefit of use of NSAIDs needs to be appraised in patients at high risk of MI and stroke.

STUDY LIMITATIONS. A large-scale population-based national sample, accounting for a range of potential

confounding factors (eg, NSAIDs use and psychological factors), and exploring specific types of diseases and their subtypes are the strengths of this study. Most importantly, we employed the 2-sample MR approach to disentangle the genetic causal associations of multisite pain with the risk of MI and stroke. However, several limitations should be acknowledged. First, pain severity was not available in this study; consequently, precluding investigations as to whether more severe pain is associated with an increased risk of incident MI/stroke. However, there is evidence suggesting that widespread pain or pain in multiple sites is reflective of increased pain sensitization in the central nervous system,[4,38] which has been linked to more severe pain.[39] For instance, in a longitudinal, population-based cohort study with 1,099 participants aged 50 to 80 years, we found that greater number of painful sites was significantly associated with more severe pain at each time-point (Supplemental Table 13). Therefore, it is possible that people with more severe pain likely have an increased risk of incident MI/stroke. Second, we could not assess the genetic effect of stroke on multisite pain due to insufficient number of valid genetic instruments.

CONCLUSIONS

Pain in multiple sites causally increases the risk of MI but not stroke, highlighting the importance of an increase in awareness of the detrimental effect of chronic pain on CVD. Future studies will be needed to address whether pain is included in the CVD risk prediction scores, and whether management of pain can reduce MI risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Pain in multiple sites causally increases the risk of MI but not stroke, highlighting the importance of an increase in awareness of the detrimental effect of multisite pain on CVD.

TRANSLATIONAL OUTLOOK: Future studies will need to address whether pain is included as a risk marker, and whether management of pain can reduce MI risk.

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KEY WORDS causality, Mendelian randomization, musculoskeletal pain, myocardial infarction, risk, stroke

APPENDIX For supplemental tables and texts, please see the online version of this paper.