scientific reports

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Associations of pain phenotypes and pain relief medications with stroke and its subtypes: a prospective cohort study

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This prospective study aimed to explore whether the associations between pain phenotypes, pain relief medications, and stroke risk differ by sex. We used data from 473,729 participants in the UK Biobank. Pain phenotypes were categorized as no pain, short-term pain, chronic localized pain (CLP), and chronic widespread pain (CWP). Stroke events, including ischaemic stroke and haemorrhagic stroke, were identified through hospital and death records. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) for stroke, with interaction terms included to assess sex differences. We also evaluated the association between pain relief medications and stroke risk among the chronic pain subcohort. CWP was associated with higher stroke risks in both men (HR 1.36, 95% CI 1.11–1.65) and women (HR 1.31, 95% CI 1.08–1.60); however, women with CLP exhibited a significantly higher risk of stroke (HR 1.16, 95% CI 1.08–1.25) and ischaemic stroke (HR 1.18, 95% CI 1.09–1.28), while no significant associations between CLP and stroke and subtypes were observed in men (*p* for sex interactions < 0.001). Regarding pain relief, aspirin use was associated with an increased risk of stroke (HR 1.19, 95% CI 1.08–1.30), and opioid use was linked to a greater increase in the risk of subarachnoid haemorrhage (HR 1.92, 95% CI 1.25–2.95). Chronic pain phenotypes, particularly in women and individuals with multiple CLP sites and CWP, were significantly associated with increased risks of stroke. Use of aspirin and opioids was also associated with higher stroke risks.

Keywords Body pain, Stroke, Pain relief, Sex difference

Stroke remains a leading cause of mortality and long-term disability worldwide, imposing a substantial burden on individuals, families, and healthcare systems[1]. The economic impact of stroke is profound, encompassing direct medical costs, rehabilitation expenses, and loss of productivity[1,2]. In 2019, value of lost welfare attributable to stroke was $2059.67 billion, approximately 1.66% of the global gross domestic product[2]. Despite advancements in prevention and treatment, the global incidence of stroke continues to rise, largely due to the aging population and the increasing prevalence of risk factors[3]. These risk factors are traditionally categorized as either modifiable (e.g., hypertension, smoking, and diet) or non-modifiable (e.g., age and genetic predisposition)[4,5]. Given these significant public health implications, there is a pressing need to identify and address additional modifiable or partially modifiable risk factors that may contribute to stroke prevention.

One emerging area of interest is the potential role of pain in stroke risk. Pain, both acute and chronic, is a multifaceted sensory and emotional experience with various underlying etiologies, ranging from musculoskeletal conditions like arthritis to neurological disorders such as neuropathy and fibromyalgia[6,7]. While pain itself is not typically classified as a modifiable risk factor in the same way as hypertension or smoking, its management and the conditions causing pain can be influenced by medical interventions and lifestyle modifications[8–10]. Importantly, growing evidence has demonstrated that chronic pain may be associated with cardiovascular diseases, including stroke[11,12]. Proposed mechanisms include activation of the hypothalamic–pituitary–adrenal (HPA) axis, increased sympathetic nervous system activity, promotion of hypertension, and acceleration of atherosclerosis, all of which are risk factors for stroke[13–15]. In addition to pain itself, the pharmacological

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management of chronic pain may further influence stroke risk[15]. Pain relief medications, including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, can affect blood pressure, coagulation, renal function, and systemic inflammation, all of which may contribute to cerebrovascular events[16–18]. Despite their widespread use, the long-term vascular consequences of these medications, particularly in populations with chronic pain, remain incompletely understood.

In addition to the general link between pain and stroke, sex differences in both stroke epidemiology and pain experiences have been well-documented. Women are more likely to report chronic pain conditions and use pain relief medications more frequently than men[19,20]. Women also have a higher lifetime risk of stroke compared to men and suffer worse post-stroke functional outcomes[1,21,22]. Despite this, most prior studies have not examined pain-stroke associations through a sex-specific approach, often pooling data from both men and women, thus potentially masking important sex-specific effects[21].

To fill the research gaps, we leveraged the large prospective cohort with comprehensive longitudinal data of the UK Biobank (UKB). The primary objective of this study was to investigate the associations between various pain phenotypes—categorized by duration, widespreadness, number of pain sites, and specific pain locations—and the risk of stroke and its subtypes. The secondary objective was to assess the associations between commonly used pain relief medications (aspirin, NSAIDs, opioids) and the risk of stroke among participants with chronic pain. An exploratory objective was to examine potential sex differences in these associations using stratified analyses.

Methods

Study population

This prospective cohort study utilized data from the UKB, a large, prospective, population-based cohort with over half a million participants aged 40–69 years. UKB's recruitment strategies, data collection protocols, and ethical considerations have been comprehensively detailed in prior publications[23]. At baseline (March 2006–August 2010), participants attended one of the 22 centers across the UK. Comprehensive demographic, socioeconomic, lifestyle, and health-related information was collected via self-completed touchscreen questionnaires and verbal interviews. Physical measurements were then made, and biological samples (including blood, urine, and saliva) were taken for long-term storage[24]. This study was approved by the Northwest Multicenter Research Ethics Committee, and all participants provided written informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

Pain phenotypes and pain relief medication

Participants underwent a comprehensive pain assessment via a touchscreen questionnaire at baseline. They were asked whether they had experienced pain at the sites of the head, face, neck/shoulder, back, stomach/abdomen, hip, knee in the last month that interfered with their usual activities[25]. Respondents had the option to report multiple pain sites or select "all over the body", "none of the above" or "prefer not to answer". If recent pain was reported, the duration was further ascertained, specifically to determine whether the pain extended beyond three months. Based on the answers to these questions about duration and widespreadness, participants were divided into the following four exclusive groups: no pain (control group), short-term pain (pain in the last month, but not > 3 months), chronic localized pain (CLP, pain from one to seven body sites for > 3 months), and chronic widespread pain (CWP, "pain all over the body" for > 3 months)[26]. According to the number of pain sites, CLP was further classified into four subgroups: 1 CLP, 2 CLP, 3 CLP, and 4 + CLP. For men and women, four distinct CLP patterns were respectively generated with latent class analysis (LCA) based on pain sites (appendix Figure S1). For men, namely P0—axial pain pattern (hip pain being predominant with significant back, keen, neck and shoulder pain), P1—back pain pattern (back pain being predominant with some knee and neck or shoulder pain), P2—cervical pain pattern (predominance of neck and shoulder pain, with some headache), and P3- lower extremity pain pattern (knee pain being predominant). For women namely P0-cervical pain pattern (neck and shoulder pain being predominant), P1—headache pattern (headache being predominant), P2—axial pain pattern (predominance of back pain, with some association with neck/shoulder, knee and hip pain), and P3- lower extremity pain pattern (knee pain being predominant).

Participants with chronic pain were asked their regular use of pain relief medications, particularly whether they regularly consumed Aspirin, Ibuprofen (e.g., Nurofen), Paracetamol, Ranitidine (e.g., Zantac), Omeprazole (e.g., Zanprol), or Laxatives (e.g., Dulcolax, Senokot). Then in a nurse-led interview, information on regular treatments were collected[27]. The focus was on habitual treatments, excluding short-term medications (such as a course of antibiotics) or untaken prescribed medications. The interviewers recorded these medications selected from a predefined list, without noting dosage or formulation details[28]. Pain medications were categorized into five mutually exclusive categories based on pharmacological class and frequency of use: aspirin, ibuprofen, paracetamol, NSAIDs (excluding aspirin and ibuprofen), and opioids. Participants were then organized into seven mutually exclusive groups based on their reported pain relief medication usage profiles: no pain medication, aspirin only, ibuprofen only, paracetamol only, NSAIDs only (excluding aspirin and ibuprofen), opioids only, and 2 + pain medications. Detailed definitions and grouping criteria are provided in appendix Table S1.

Incident stroke and subtypes (outcome)

We leveraged a robust set of adjudication algorithms, recommended by the UK Biobank Outcome Adjudication Group, to ascertain incident cases of fatal and non-fatal stroke (Ninth Revision, 430–431, 434, 436; Tenth Revision, I60–I61, I63–I64), including its subtypes- ischemic (Ninth Revision, 434, 436; Tenth Revision, I63–I64), and hemorrhagic (Ninth Revision, 430–431; Tenth Revision, I60–I61) stroke. These algorithms synthesized data from national death registries and hospital admission records, employing International Classification of

Diseases (ICD) Ninth and Tenth Revision codes. The algorithms have been described in detail elsewhere and were used to adjudicate stroke events accrued up to 30 November 2022 for England and Wales and Scotland[29]. The median follow-up was 13.8 years for overall stroke (interquartile range [IQR], 13.0–14.5 years), ischemic stroke (IQR, 13.0–14.5 years), and for hemorrhagic stroke (IQR, 13.0–14.5 years).

Definitions of covariates

Age was determined from the date of birth and calculated with reference to the baseline assessment date. Area-based socioeconomic status (SES) was quantified using the Townsend deprivation index (TDI) derived from residential postcodes, with higher values representing lower SES. Ethnicity was self-reported and categorized into White or non-White. Household income was measured by annual average total household income before tax, and classified as less than 18,000 £, 18,000–30,999 £, 31,000–51,999 £, 52,000–100,000 £, and greater than 100,000 £. Educational attainment was self-reported and coded as an ordinal variable, with categories ranging from no formal qualifications to higher education degrees and professional qualifications. Employment status was dichotomized into being employed, retired and others. Individual-level SES was synthesized through LCA method, encompassing household income, highest educational attainment, and employment status, as low, medium, and high (appendix Figure S2). Smoking status was categorized into never, previous, or current smokers. Alcohol consumption details were coded as never, previous, or current drinkers. Discretionary sedentary behaviors were quantified by summing durations of driving, computer use, and television watching during leisure time. Physical activity was measured based on the frequency (days per week) of vigorous or moderate physical activity for 10 min or more. Sleep duration was self-reported and categorized into normal (7–9 h), long (> 9 h), or short (< 7 h). Diagnoses of hypertension, diabetes, hyperlipidemia, depression or anxiety, chronic inflammatory diseases were ascertained based on self-reported medical codes at baseline through a nurse-led interview and the first occurrence fields of 3-character ICD-10 codes from UK Biobank Category 1712. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the left arm. Blood biochemistry parameters, including c-reactive protein (CRP), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TGs), Glucose and Glycated haemoglobin (HbA1c), were assayed within 24 h of sample collection. Body-mass index (BMI) was calculated as weight divided by the square of height (kg/m^2). Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or prior physician diagnosis[30]. Diabetes was defined as HbA1c level of 6.5% or greater or prior physician diagnosis[31]. Hyperlipidemia was defined as total cholesterol (TC) level of above 5.72 mmol/L or prior physician diagnosis. Use of lipid-lowering medication was self-reported. Chronic inflammatory diseases were defined as self-report, primary care records or hospitalization records confirming a clinical diagnosis of osteoarthritis, arthritis (NOS), rheumatoid arthritis, spine arthritis/spondylitis, fibromyalgia, osteomyelitis, and myositis/myopathy.

Statistical analysis

The present study was based on a total of 473,729 participants who self-reported their pain status, had no self-reported or diagnosed stroke at baseline or within one year follow-up, and had full information on all adjusted covariates (Fig. 1). Continuous data are presented as mean with standard deviation (SD) or in case of non-normal distribution as median with IQR. Categorical data are presented as frequency and percentage. Since pain phenotypes and stroke risk differ between sexes, baseline characteristics were presented for men and women separately. Differences in baseline characteristics between men and women were compared using unpaired t-tests for continuous variables and χ^2 tests for categorical variables. LCA was chosen to define individual-level SES and chronic pain patterns because it provides a model-based method for uncovering unobserved (latent) subgroups within a heterogeneous population based on individuals' response patterns to categorical indicators. In the case of chronic pain patterns, the use of LCA allows for the identification of pain phenotypes that are not defined a priori and may capture important variation in pain experience relevant to stroke risk. We fitted multiple LCA models with different number of latent class (3, 4, and 5) for both the individual-level SES and chronic pain patterns, and the Bayesian Information Criterion (BIC) was used to select the optimal number of classes, provided that the learned latent patterns have a meaningful interpretation. To fit the LCA model, we adopted a three-step approach which was implemented in the StepMix Python package (Version 2.2.1): first run the expectation–maximization (EM) estimation on the measurement model, assign class probabilities, then fit the structural model via maximum likelihood with 5000 EM iterations. We also applied different bias correction methods and tested different estimation strategies implemented in StepMix to ensure the robustness and reproducibility of the learned latent patterns.

We verified the proportional hazards assumption through tests based on Schoenfeld residuals, as detailed in appendix Figure S3, and identified no significant violations. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of pain phenotypes (no pain as the reference) and pain relief medication with stroke were estimated using Cox proportional hazards models with years of follow-up as the timescale. The follow-up period was calculated from baseline assessment date until the date of the first stroke diagnosis, death, or the censoring date (16 Dec 2022), whichever occurred first.

In the primary analyses, interaction by sex for the association between pain phenotypes and stroke events was formally tested using an interaction term, as significant sex interaction was detected, we assessed the sex-specific associations of pain phenotypes with incident stroke. An incremental adjustment strategy was employed across multiple models. Model 1 adjusted for age and ethnicity. Model 2 adjusted for all covariates in model 1, TDI, individual level SES, BMI, and lifestyle factors (smoking status, alcohol drinking, sleep duration, physical activity, and discretionary sedentary behaviors). Model 3 also accounted for additional health factors (hypertension, diabetes, hyperlipidemia, chronic inflammatory disease, lipid lowering medication and pain relief medications) and psychological problems (depression or anxiety). Variance inflation factor (VIF) was used to determine the occurrence of multicollinearity. A variable whose VIF value is greater than 10 may merit further

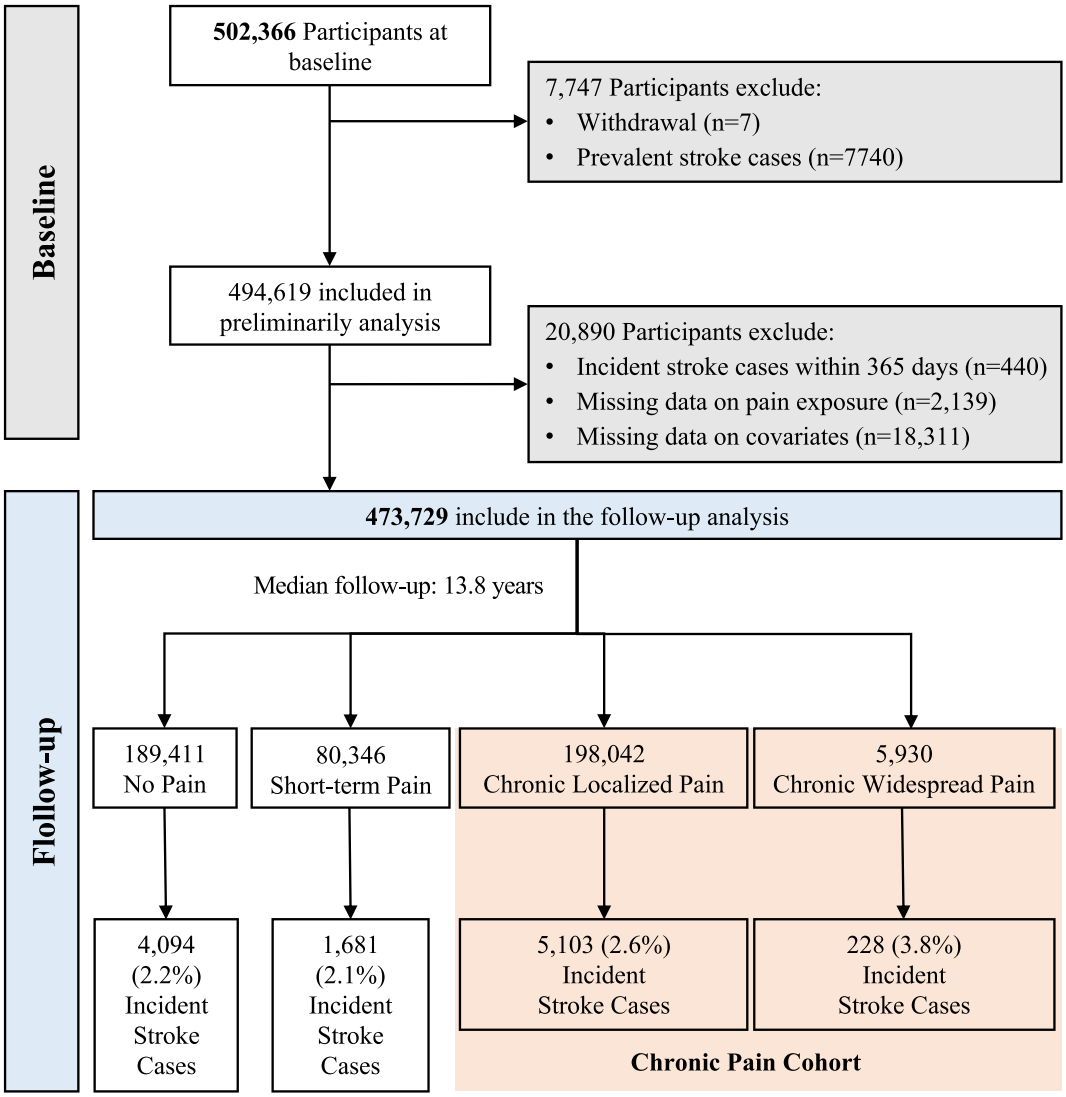

Fig. 1. Flowchart of the study sample selection from the UK Biobank study.

investigation (all variables in this study have small VIF, see appendix Table S2). The cumulative crude hazard rate of incident stroke and its subtypes by pain phenotype was estimated using the Nelson-Aalen estimator. The rate advancement period (RAP) was also estimated, defined as the number of additional chronologic years that would be required to yield the equivalent risk rate for stroke incidence among the pain phenotypes[32]. For its estimation, the logarithm HR for incidence of the pain phenotype was divided by the corresponding incidence associated with each yearly increase in age—e.g., $\log(HR_{pain})$ divided by $\log(HR_{age})$. Additionally, the population attributable fraction (PAF) was calculated to estimate the hypothetical reduction in event rates had all individuals been pain-free, based on the fully adjusted HR derived from Cox models and the prevalence of pain phenotypes in the sample.

In the secondary analyses, we restricted the analyses in a subset of cohort of participants with chronic pain, and examined the association between pain relief medication use and incident stroke. The interaction by sex for the association between pain relief medication and stroke in the chronic pain subcohort was tested, as no sex as an interaction between the association between pain relief medication and stroke, we didn't conduct sex-specific strategy. The "no pain medication" group served as the reference category. The fully adjusted HR (aHR) of incident stroke associated with pain relief medication among participants with chronic pain were estimated with the same adjustment set as in Model 3 of the primary analyses.

Several sensitivity analyses were conducted to enhance the robustness of our findings. First, we restricted our analyses among participants without baseline CVDs (including coronary heart disease, valvular heart disease, heart failure, transient ischaemic attack, myocardial infarction, angina, and stroke) to minimize residual confounding. Second, we excluded stroke events that occurred within two years of recruitment to minimize risk of reverse causality. Third, we censored data up to Dec 31, 2019, to account for the impact of the COVID-19 pandemic.

A two-tailed P value less than 0.05 was considered statistically significant. All analyses were performed with the R version 4.3.1 and Python version 3.9.11 (2001–2022 Python Software Foundation).

Results

Baseline characteristics

We included a full cohort of 473,729 stroke-free participants, 215,743 (45.5%) men and 257,986 (54.5%) women. The mean age was 56.6 ± 8.2 years for men and 56.2 ± 8.0 years for women. As shown in Table 1, men and women had similar rates of 1 CLP (23.0% vs. 23.0%), while women had higher rates of 2 CLP (11.9% vs. 9.9%), 3 CLP (5.7% vs. 4.1%), 4 + CLP (3.4% vs. 2.1%), and CWP (1.5% vs. 1.0%) ($P < 0.001$). Individual SES varied, with more men in high SES (31.9% vs. 26.2%) and more women in low SES (26.7% vs. 21.0%) ($P < 0.001$). Smoking status showed higher proportion of current smoking in men (12.2% vs. 8.7%) ($P < 0.001$). Alcohol consumption was higher among men (94.1% vs. 91.1%) ($P < 0.001$). Men reported less 7–9 h of sleep (73.4% vs. 74.2%) ($P < 0.001$), had higher rates of diabetes (7.7% vs. 3.9%) and hypertension (61.8% vs. 48.2%), but lower rates of hyperlipidemia (53.7% vs. 57.7%), depression (13.0% vs. 17.8%), and chronic inflammatory conditions (17.3% vs. 23.1%) (all $P < 0.001$). In terms of pain medication, men were less likely to use paracetamol (7.7% vs. 13.2%) and ibuprofen (5.4% vs. 7.6%) but more likely to use aspirin (12.9% vs. 5.5%) (all $P < 0.001$). Significant differences were also observed in age, BMI, and various cardiovascular and metabolic parameters (all $P < 0.001$). The baseline characteristics of participants by pain phenotype for men and women are presents in (appendix Tables S3–S4).

Sex-specific associations of pain phenotypes with incident stroke and subtypes

Among men, over a median follow-up of 13.7 years (IQR, 12.9–14.5), 6330 (2.93%) developed a fatal or nonfatal stroke event (5318 with IS, 1006 with ICH, and 372 with SAH). Among women, over a median follow-up of 13.8 years (IQR, 13.1–14.5), 4776 (1.85%) developed a fatal or nonfatal stroke event (3598 with IS, 886 with ICH, and 660 with SAH) (Table 1, appendix Table S5). The sex-specific cumulative incidence of stroke and its subtypes stratified by pain phenotype is shown in appendix Figure S4.

The sex-specific associations between the pain phenotype and incident stroke are shown in Fig. 2, Table 2 and appendix Tables S6–S7. In fully adjusted models, men and women with CLP had different risks for stroke outcomes. For women with CLP, the aHR was 1.16 (95% CI 1.08–1.25) for overall stroke and 1.18 (95% CI 1.09–1.28) for IS, with a PAF of 6.14% (95% CI 3.41%–8.68%) for overall stroke and 6.74% (95% CI 3.62%–9.63%) for IS. Women with CLP were likely to experience overall stroke 1.77 years (95% CI 0.94–2.59) earlier and IS 1.75 years (95% CI 0.89–2.60) earlier than those without pain. For CWP, the aHR for overall stroke was 1.31 (95% CI 1.08–1.60) in women and for IS, it was 1.34 (95% CI 1.07–1.67), with a PAF of 0.35% (95% CI 0.11–0.55%) for overall stroke and 0.37% (95% CI 0.10–0.59%) for IS, and they were likely to experience overall stroke 3.19 years (95% CI 0.87–5.50) earlier and IS 3.08 years (95% CI 0.75–5.41) earlier. In men, the aHR for overall stroke with CWP was 1.36 (95% CI 1.11–1.65) and for IS, it was 1.43 (95% CI 1.16–1.76), with a PAF of 0.26% (95% CI 0.10–0.39%) for overall stroke and 0.29% (95% CI 0.14–0.42%) for IS. Men with CWP were likely to experience overall stroke 4.11 years (95% CI 1.44–6.78) earlier and IS 4.59 years (95% CI 1.89–7.29) earlier than those without pain.

Within the number of CLP sites, the risk increased with the number of CLP sites among women. The aHRs for overall stroke ranged from 1.11 (95% CI 1.02–1.20) for women with one CLP site to 1.43 (95% CI 1.24–1.65) for those with 4 + CLP. Similarly, the PAF for overall stroke ranged from 2.23% (95% CI 0.51–3.82%) to 1.03% (95% CI 0.67–1.35%), and the years earlier that stroke was likely to occur ranged from 1.19 years (95% CI 0.26–2.13) to 4.20 years (95% CI 2.53–5.87). Similarly, for IS, the aHRs also increased with the number of CLP sites. Women with one CLP site had an aHR of 1.11 (95% CI 1.01–1.21), while those with 4 + CLP sites had an aHR of 1.48 (95% CI 1.26–1.73). The PAF for IS ranged from 2.23% (95% CI 0.21–4.06%) to 1.11% (95% CI 0.71–1.45%), and the RAP ranged from 1.06 years (95% CI 0.10–2.03) to 4.08 years (95% CI 2.39–5.77). Additionally, women with 4 + CLP sites had a significantly increased risk of SAH with an aHR of 1.59 (95% CI 1.12–2.28). The PAF for SAH in this group was 1.28% (95% CI 0.36–1.92%), and the RAP was 14.16 years (95% CI 2.07–26.26). In contrast, none of the results for men with different sites of CLP were statistically significant.

Regarding chronic pain patterns, the axial pain pattern (predominantly back pain with some neck/shoulder, knee, and hip pain) among women was associated with an increased risk of stroke (aHR 1.23, 95% CI 1.14–1.33) and IS (aHR 1.27, 95% CI 1.16–1.39). The PAF for stroke in women with the axial pain pattern was 1.78% (95% CI 1.16–2.36%), and the RAP was 2.45 years (95% CI 1.52–3.38). For IS, the PAF was 2.04% (95% CI 1.34–2.68%), and the RAP was 2.54 years (95% CI − 1.58 to 3.50). In contrast, men did not show a statistically significant association between any pain pattern and stroke risk.

Associations of pain relief medication with incident stroke and subtypes analysis

Among 203,972 participants with chronic pain, with a mean age of 56.7 (8.0), among whom 117,435 (57.6%) were women. The basic characteristics are listed in appendix Table S8. Over 13.7 (12.9–14.5) years of follow up, 5331, 4304, 872 and 485 developed overall stroke, IS, ICH, and SAH. Among the chronic pain cohort, the use of different pain medications was associated with varying risks of incident stroke and its subtypes (Fig. 3 and appendix Table S9). Aspirin was significantly associated with an increased risk of overall stroke (HR 1.19, 95% CI 1.08–1.30) and IS (HR 1.20, 95% CI 1.08–1.33). Opioid use was significantly associated with an increased risk of overall stroke (HR 1.24, 95% CI 1.06–1.45) and SAH (HR 1.92, 95% CI 1.25–2.95). The use of 2 + pain medications was significantly associated with an increased risk of overall stroke (HR 1.18, 95% CI 1.10–1.27) and IS (HR 1.20, 95% CI 1.10–1.30).

Baseline characteristics[a]	Overall N = 473,729	Female N = 257,986	Male N = 215,743	*P* value
Stroke, n (%)	11,106 (2.3)	4776 (1.9)	6330 (2.9)	< 0.001
IS, n (%)	8916 (1.9)	3598 (1.4)	5318 (2.5)	< 0.001
ICH, n (%)	1892 (0.4)	886 (0.3)	1006 (0.5)	< 0.001
SAH, n (%)	1032 (0.2)	660 (0.3)	372 (0.2)	< 0.001
Pain group, n (%)				
No pain	189,411 (40.0)	99,806 (38.7)	89,605 (41.5)	< 0.001
Short-term pain	80,346 (17.0)	40,745 (15.8)	39,601 (18.4)	
Chronic one	109,073 (23.0)	59,413 (23.0)	49,660 (23.0)	
Chronic two	52,197 (11.0)	30,749 (11.9)	21,448 (9.9)	
Chronic three	23,483 (5.0)	14,621 (5.7)	8862 (4.1)	
Chronic four+	13,289 (2.8)	8846 (3.4)	4443 (2.1)	
Chronic widespread pain	5930 (1.3)	3806 (1.5)	2124 (1.0)	
Ethnic, n (%)				
White	450,226 (95.0)	245,133 (95.0)	205,093 (95.1)	0.476
Non-white	23,503 (5.0)	12,853 (5.0)	10,650 (4.9)	
TDI, n (%)				
Q1	97,771 (20.6)	52,865 (20.5)	44,906 (20.8)	< 0.001
Q2	96,540 (20.4)	52,561 (20.4)	43,979 (20.4)	
Q3	94,439 (19.9)	52,030 (20.2)	42,409 (19.7)	
Q4	94,668 (20.0)	52,325 (20.3)	42,343 (19.6)	
Q5	90,311 (19.1)	48,205 (18.7)	42,106 (19.5)	
SES class, n (%)				
High	136,357 (28.8)	67,639 (26.2)	68,718 (31.9)	< 0.001
Medium	223,141 (47.1)	121,388 (47.1)	101,753 (47.2)	
Low	114,231 (24.1)	68,959 (26.7)	45,272 (21.0)	
Smoking status, n (%)				
Never	260,696 (55.0)	154,027 (59.7)	106,669 (49.4)	< 0.001
Previous	164,304 (34.7)	81,475 (31.6)	82,829 (38.4)	
Current	48,729 (10.3)	22,484 (8.7)	26,245 (12.2)	
Alcohol drinker, n (%)				
Never	19,556 (4.1)	14,041 (5.4)	5515 (2.6)	< 0.001
Previous	16,168 (3.4)	8991 (3.5)	7177 (3.3)	
Current	438,005 (92.5)	234,954 (91.1)	203,051 (94.1)	
Sleep duration, n (%)				
< 7 h	115,878 (24.5)	61,930 (24.0)	53,948 (25.0)	< 0.001
7–9 h	349,756 (73.8)	191,506 (74.2)	158,250 (73.4)	
> 9 h	8095 (1.7)	4550 (1.8)	3545 (1.6)	
Diabetes, n (%)	26,572 (5.6)	10,021 (3.9)	16,551 (7.7)	< 0.001
Hypertension, n (%)	257,701 (54.4)	124,403 (48.2)	133,298 (61.8)	< 0.001
Hyperlipidemia, n (%)	264,903 (55.9)	148,964 (57.7)	115,939 (53.7)	< 0.001
Depression, n (%)	73,836 (15.6)	45,845 (17.8)	27,991 (13.0)	< 0.001
Chronic inflammatory, n (%)	96,715 (20.4)	59,492 (23.1)	37,223 (17.3)	< 0.001
Lipid-lowering, n (%)	79,727 (16.8)	31,123 (12.1)	48,604 (22.5)	< 0.001
Pain medication, n (%)				
No pain medication	272,887 (57.6)	143,589 (55.7)	129,298 (59.9)	< 0.001
Aspirin	41,984 (8.9)	14,087 (5.5)	27,897 (12.9)	
Ibuprofen	31,383 (6.6)	19,704 (7.6)	11,679 (5.4)	
Paracetamol	50,793 (10.7)	34,141 (13.2)	16,652 (7.7)	
NSAIDs	6282 (1.3)	3408 (1.3)	2874 (1.3)	
Opioids	5649 (1.2)	3600 (1.4)	2049 (0.9)	
2 + Pain medications	64,751 (13.7)	39,457 (15.3)	25,294 (11.7)	
Age, mean (SD)	56.4 (8.1)	56.2 (8.0)	56.6 (8.2)	< 0.001
BMI, mean (SD)	27.4 (4.7)	27.0 (5.1)	27.8 (4.2)	< 0.001
SBP, mean (SD)	137.7 (18.6)	135.1 (19.2)	140.9 (17.4)	< 0.001
DBP, mean (SD)	82.2 (10.1)	80.7 (10.0)	84.1 (10.0)	< 0.001
Continued				

Baseline characteristics[a]	Overall N = 473,729	Female N = 257,986	Male N = 215,743	*P* value
Sedentary (hours), mean (SD)	4.5 (2.5)	4.1 (2.3)	5.0 (2.7)	< 0.001
Physical activity, mean (SD)	5.3 (3.7)	5.1 (3.6)	5.5 (3.8)	< 0.001
HDL-C, mean (SD)	1.5 (0.4)	1.6 (0.4)	1.3 (0.3)	< 0.001
LDL direct, mean (SD)	3.6 (0.9)	3.6 (0.9)	3.5 (0.9)	< 0.001
TG, mean (SD)	1.7 (1.0)	1.5 (0.9)	2.0 (1.2)	< 0.001
HbA1c, mean (SD)	36.0 (6.5)	35.7 (5.8)	36.4 (7.3)	< 0.001
CRP, mean (SD)	2.5 (4.3)	2.6 (4.3)	2.4 (4.3)	< 0.001
Cys C, mean (SD)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	< 0.001

Table 1. Baseline characteristics of participants in the primary cohort, by sex. *IS* ischemic stroke, *ICH* intracerebral hemorrhage, *SAH* subarachnoid hemorrhage, *TDI* townsend deprivation index, *SES* socioeconomic status, *NSAIDs* nonsteroidal antiinflammatory drugs, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein, *TG* triglycerides, *HbA1c* glycated hemoglobin, *CRP* c-reactive protein, *Cys C* cystatin c, *SD* standard deviation. [a]Values are presented as number (N) with percent (%) or means with standard deviations (SDs).

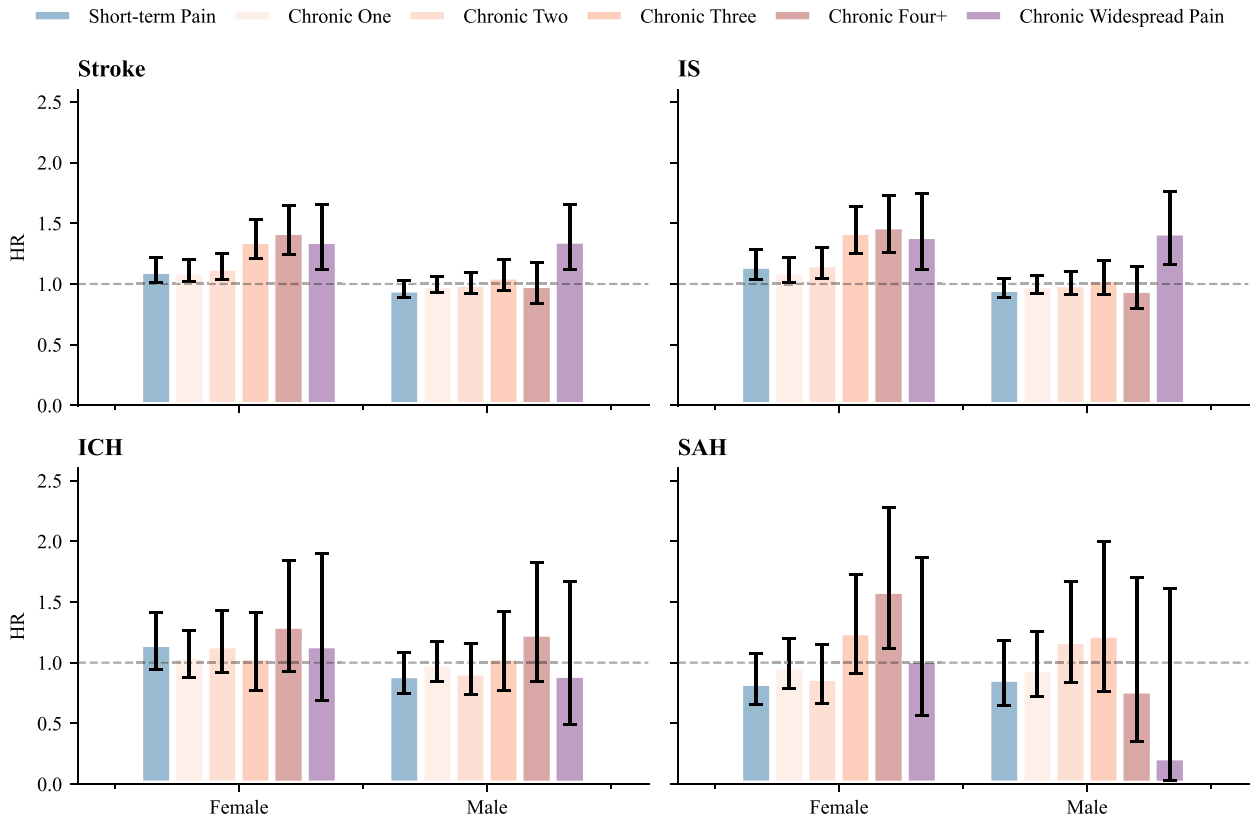

Fig. 2. Associations between pain group and the risk of incident stroke and its subtypes Notes: IS, ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

Discussion

In this large, prospective cohort study, we explored the sex-specific associations of various pain phenotypes and pain relief medications with stroke and its subtypes. Our findings indicate that chronic pain, especially CWP, was associated with a higher risk of overall stroke and IS in women; the use of aspirin and opioids was associated with increased risks of IS and SAH respectively. In addition, polypharmacy in pain management was associated with a higher risk of IS. These findings underscore the need for sex-specific approaches in the clinical assessment and management of individuals with chronic pain.

Pain phenotype	Men, HR (95% CI)[a]				Women, HR (95% CI)[a]			
	Stroke	IS	ICH	SAH	Stroke	IS	ICH	SAH
Duration and widespreadness								
Short-term Pain	0.96 (0.89–1.03)	0.96 (0.89–1.04)	0.90 (0.75–1.08)	0.87 (0.64–1.18)	1.11 (1.01–1.21)	1.15 (1.03–1.27)	1.15 (0.94–1.41)	0.83 (0.65–1.07)
CLP	1.00 (0.95–1.07)	1.00 (0.94–1.06)	0.99 (0.86–1.15)	1.03 (0.81–1.30)	1.16 (1.08–1.25)	1.18 (1.09–1.28)	1.09 (0.93–1.28)	1.01 (0.84–1.21)
CWP	1.36 (1.11–1.65)	1.43 (1.16–1.76)	0.89 (0.48–1.64)	0.22 (0.03–1.59)	1.31 (1.08–1.60)	1.34 (1.07–1.67)	1.13 (0.68–1.87)	0.96 (0.53–1.76)
CLP number								
One	1.00 (0.93–1.06)	0.99 (0.92–1.07)	0.89 (0.85–1.17)	0.95 (0.73–1.25)	1.11 (1.02–1.20)	1.11 (1.01–1.21)	1.06 (0.88–1.27)	0.97 (0.79–1.20)
Two	1.01 (0.92–1.10)	1.00 (0.91–1.10)	0.89 (0.74–1.16)	1.18 (0.84–1.67)	1.14 (1.03–1.26)	1.17 (1.04–1.30)	1.15 (0.92–1.43)	0.88 (0.67–1.15)
Three	1.07 (0.95–1.20)	1.04 (0.92–1.19)	0.89 (0.77–1.42)	1.24 (0.76–2.00)	1.36 (1.21–1.53)	1.43 (1.25–1.64)	1.05 (0.77–1.42)	1.25 (0.91–1.73)
Four +	0.99 (0.84–1.17)	0.95 (0.80–1.14)	0.89 (0.85–1.83)	0.77 (0.35–1.70)	1.43 (1.24–1.65)	1.48 (1.26–1.73)	1.31 (0.93–1.84)	1.59 (1.12–2.28)
CLP pattern								
P0	1.08 (0.98–1.19)	1.04 (0.94–1.16)	0.89 (0.90–1.44)	1.05 (0.70–1.60)	1.04 (0.90–1.19)	1.00 (0.85–1.18)	1.09 (0.80–1.49)	0.99 (0.69–1.43)
P1	0.99 (0.91–1.07)	0.99 (0.91–1.09)	0.90 (0.68–1.05)	1.05 (0.75–1.47)	1.14 (0.99–1.31)	1.10 (0.93–1.30)	1.19 (0.88–1.62)	1.13 (0.82–1.56)
P2	1.01 (0.93–1.10)	1.00 (0.92–1.10)	0.90 (0.89–1.32)	1.09 (0.79–1.51)	1.23 (1.14–1.33)	1.27 (1.16–1.39)	1.13 (0.94–1.36)	1.02 (0.83–1.26)
P3	0.95 (0.86–1.05)	0.96 (0.87–1.07)	0.90 (0.73–1.20)	0.87 (0.57–1.34)	1.08 (0.97–1.20)	1.10 (0.97–1.24)	0.94 (0.73–1.22)	0.93 (0.68–1.26)

Table 2. Sex-specific associations between pain phenotypes and incident stroke and subtypes. *HR* hazard ratio, *CI* confidence interval, *IS* ischemic stroke, *ICH* intracerebral hemorrhage, *SAH* subarachnoid hemorrhage, *CLP* chronic localized pain, *CWP* chronic widespread pain. [a]HRs (95% CIs) were adjusted for age, ethnicity, townsend deprivation index, individual level socioeconomic status, body mass index, lifestyle factors (smoking status, alcohol drinking, sleep duration, physical activity, and discretionary sedentary behaviors), health factors (hypertension, diabetes, hyperlipidemia, chronic inflammatory disease, lipid lowering medication and pain relief medications) and psychological problems (depression or anxiety).

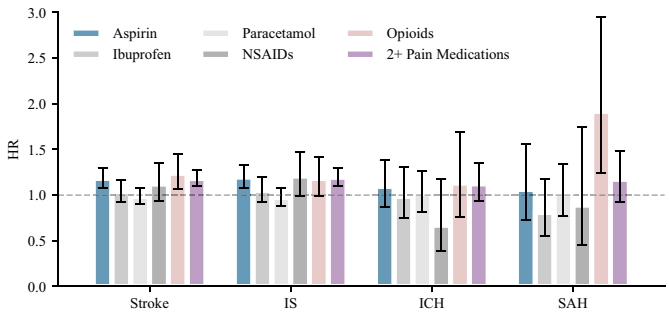

Fig. 3. Associations between pain medications and the risk of incident stroke and its subtypes within the chronic pain subcohort Notes: HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; IS, ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

We found that CLP was significantly associated with increased stroke risk in women, but not in men. The risk increased with the number of pain sites and was most pronounced in women with an axial pain pattern, which included predominant back pain along with the neck, shoulder, hip, and knee. This pattern has been associated with elevated levels of systemic inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), as well as autonomic nervous system dysfunction, all of which are implicated in the pathogenesis of atherosclerosis and thromboembolic events[15,33–37]. Furthermore, chronic pain is frequently accompanied by psychological stress, which may activate the HPA axis and result in elevated cortisol levels, endothelial dysfunction, and heightened platelet aggregation, further exacerbating stroke risk[38–40]. The observed sex differences may be because women generally exhibit higher pain sensitivity and report more severe pain than men, which could lead to greater physiological stress and inflammation. Hormonal factors, particularly oestrogen, also play a key role in modulating pain perception, immune function, and vascular integrity, and its decline during menopause may heighten vulnerability to vascular inflammation and endothelial injury[41–43]. CWP, in contrast to CLP, was significantly associated with stroke risk in both sexes. This may be due to the more systemic nature of CWP, which is often associated with central sensitisation, widespread inflammation, and a higher burden of comorbidity, all of which may contribute to vascular risk irrespective of sex[44,45].

Among participants with chronic pain, our findings indicated that aspirin use was associated with a higher risk of IS, potentially due to its impact on gastrointestinal bleeding and subsequent anemia, which may compromise cerebral perfusion[46]. While aspirin is typically protective against thrombotic events due to its antiplatelet effects, it may paradoxically increase stroke risk in some contexts, potentially due to gastrointestinal

bleeding, anaemia, or plaque destabilisation leading to embolic events[47]. The use of multiple pain medications was associated with higher IS, which may reflect the cumulative adverse effects of polypharmacy on blood pressure regulation, renal function, and endothelial health[45,48,49]. Opioid use was associated with an increased risk of SAH. This may be mediated by opioid-induced haemodynamic instability, including fluctuations in blood pressure, increased myocardial contractility, and vasodilation of small vessels, which may predispose individuals to vascular rupture[28,50]. Additionally, opioids have been shown to trigger cerebral vasospasm via cholinergic pathways and to contribute to hormonal imbalances through opioid-induced endocrinopathy, which could affect vascular integrity over time[51,52]. These observations underscore the importance of cautious prescription and monitoring of pain relief medications in individuals with chronic pain, emphasizing the need for personalized pain management strategies that consider each patient's unique risk factors for cerebrovascular events.

A major strength of our study is the use of UK Biobank, a large, well-characterised cohort with extensive baseline data, long-term follow-up, and comprehensive stroke ascertainment. The prospective design, detailed pain phenotyping, and the inclusion of various pain relief medications provided a comprehensive understanding of the associations between chronic pain, medication use, and stroke risk with considerable statistical power. Importantly, sex-stratified analyses revealed patterns that would have been obscured in sex-aggregated models, reinforcing the value of a sex-specific approach in epidemiological research on chronic pain and stroke.

Several limitations must be acknowledged. First, the UK Biobank cohort is not fully representative of the general population: participants tend to be healthier, less socioeconomically deprived, and have lower rates of cardiovascular disease. While this may affect the generalisability of absolute risk estimates, it is unlikely to bias the observed associations. Second, pain status, medication use and lifestyle behaviors were assessed at baseline via self-report and thus may have been subject to social desirability or recall bias. Third, we were unable to capture changes in pain or medication use over time, which may have resulted in exposure misclassification. However, because exposure was assessed prior to the onset of stroke outcomes, such misclassification is likely to be non-differential and would therefore be expected to bias the observed associations toward the null. Finally, the pain patterns identified through LCA were data-driven constructs based on observed co-occurrence patterns of chronic pain across body sites, and may not correspond directly to clinically recognized pain syndromes. Therefore, these patterns should be interpreted with caution, and further research is needed to assess their external validity and reproducibility in independent populations.

Our findings have important implications for clinical practice, public health, and future research. The observed sex-specific associations between chronic pain and stroke, particularly the elevated risks among women with CWP and axial pain, underscore the need for sex-informed assessment and management strategies. Comprehensive pain assessments, including the number and distribution of pain sites, may help identify individuals at elevated cerebrovascular risk. Additionally, the associations between commonly used analgesics and specific stroke subtypes, such as increased risk of IS with aspirin use, elevated risk of SAH with opioids, and higher IS risk with polypharmacy, highlight the importance of cautious prescribing, especially in individuals with existing cardiovascular risk factors. These findings support the need for regular medication reviews and careful clinical decision-making in chronic pain management. From a public health perspective, targeted educational efforts are warranted to raise awareness of the cerebrovascular risks associated with chronic pain and its treatment, particularly among women. Although some estimates of RAP and PAF were modest in absolute terms, they remain meaningful in light of the high prevalence of chronic pain and the substantial burden of stroke. A RAP of one to two years reflects a measurable shift in stroke onset among individuals with chronic pain, and even relatively low PAF values may correspond to a significant number of preventable cases at the population level. As chronic pain is not traditionally included in stroke risk prediction models, its identification as a potentially independent risk factor may help enhance current etiological frameworks and improve risk stratification. Given that pain is routinely assessed in clinical and epidemiological settings, its integration into stroke prevention strategies may support more comprehensive and individualized approaches. Further research is needed to clarify the biological, hormonal, and psychosocial mechanisms underlying these associations and to evaluate the impact of different pain management strategies, including non-pharmacological interventions, on reducing stroke risk.

Conclusions

In conclusion, our comprehensive prospective cohort study reveals that chronic pain, particularly CWP, is significantly associated with an increased risk of overall stroke and IS in women. Additionally, the use of aspirin and opioids is linked to heightened risks of IS and SAH respectively, while polypharmacy in pain management correlates with a higher IS risk. These findings highlight the need for sex-specific clinical approaches and careful evaluation of pain relief medications to mitigate stroke risks. Public health initiatives should promote awareness and cardiovascular monitoring for individuals with chronic pain. Future research should investigate underlying mechanisms and explore non-pharmacological interventions to reduce stroke risk.

Data availability

Data from the UK Biobank is available to researchers by application via the UK Biobank online Access Management System (https://www.ukbiobank.ac.uk/). This study was conducted under the Application Number 65155.

Received: 24 February 2025; Accepted: 26 May 2025
Published online: 01 July 2025

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Author contributions

PS designed the study. YZ managed and analyzed the data. YZ and PS prepared the first draft. YZ, WS, YS, and DC reviewed and edited the manuscript, with comments from PS and KR. All authors were involved in revising the paper, had full access to the data, and gave final approval of the submitted versions.

Declarations

Ethics approval and consent to participants

Ethical approval for the UKB was granted by the Northwest Multicenter Research Ethics Committee (REC: 16/NW/0274), and all participants provided written informed consent.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-04238-3.

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