

# Peptic Ulcer Does Not Increase the Risk of Stroke: a Longitudinal Follow-up Study Using a National Sample Cohort

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## Research

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# Abstract

**Background:** Studies have reported that several gastrointestinal diseases increase the risk of stroke. We aimed to evaluate the risk of stroke in patients with peptic ulcer disease (PUD) using a national sample cohort from South Korea.

**Methods:** We extracted data entered into the Korean National Health Insurance Service for patients with PUD (n = 129,531) and for 1:1 matched control participants (n = 129,531) and analyzed the risk of stroke using Cox proportional hazard model. Subgroup analyses were performed based on age and sex.

**Results:** The rates of hemorrhagic and ischemic stroke were lower in the PUD group than in the control group. In a subgroup analysis according to age, the adjusted hazard ratios (HRs) of PUD for hemorrhagic and ischemic stroke were 0.76 (95% CI = 0.63-0.90) and 0.85 (95% CI = 0.73-0.98) in the < 50-year-old group and 0.72 (95% CI = 0.65-0.80) and 0.84 (95% CI = 0.80-0.89) in the  $\geq$  50-year-old group, respectively (each  $p < 0.05$ ). In a subgroup analysis according to sex, the adjusted HRs of PUD were 0.71 (95% CI = 0.63-0.81) and 0.81 (95% CI = 0.5-0.87) in men and 0.75 (95% CI = 0.66-0.86) and 0.88 (95% CI = 0.82-0.95) in women, respectively (each  $p < 0.05$ ).

**Conclusions:** Our study concluded that PUD does not increase the risk of ischemic or hemorrhagic stroke regardless of age and sex.

## Background

Stroke is a neurological condition in which the blood vessels that supply blood to the central nervous system are obstructed (ischemic stroke) or ruptured (hemorrhagic stroke), resulting in brain cell death [1]. Stroke is one of the main causes of permanent disability and death in men and women and has a serious negative impact on their lives. The conventional risk factors for stroke are age, sex, smoking, obesity, physical inactivity, hypertension, dyslipidemia, and diabetes mellitus (DM) [2]. Emotional stress, including depression, anger, hostility, and anxiety, may adversely affect the risk of stroke [3].

Peptic ulcer disease (PUD) is a painful sore caused by loss of the mucosal lining in the stomach and duodenum. The lifetime risk for developing PUD is approximately 5 to 10% worldwide [4]. Known risk factors for PUD are older age, *Helicobacter pylori* (HP) bacterial infection, smoking, use of nonsteroidal anti-inflammatory drugs (NSAIDs), stress and dietary factors [5].

HP infection is well known as a main risk factor for PUD, accounting for up to 48% of cases [6]. Studies have shown a positive association between the cytotoxin-associated gene A-positive strain of HP and vascular diseases such as coronary artery disease and stroke. HP infection-related chronic inflammation contributes to the pathogenesis of atherosclerosis [7]. Based on the above conclusions, there have been questions about the potential for PUD to increase the risk of stroke. Several previous studies have reported increased stroke risk in patients with PUD [8, 9]. Xu et al. reported a 1.85-fold greater risk of stroke recurrence in patients with a history of PUD in a study performed in China [9]. In another study,

ischemic stroke patients with PUD had an increased risk of a less favorable neurological outcome (odds ratios [OR] = 2.89, 95% confidence interval [CI], 1.79–2.48) [10]. However, there is a lack of other studies to generalize the association between PUD and stroke risk, so it is necessary to reevaluate the correlation between PUD and stroke risk through large population-based studies.

We aimed to evaluate the risk of stroke in patients with PUD in South Korea using national population-based data obtained from the National Health Insurance Service (NHIS).

## Materials And Methods

### Study Population and Data Collection

This national cohort study was conducted using the Korean Health Insurance Review and Assessment Service National Sample Cohort (HIRA-NSC). For a detailed explanation of these data, refer to those in previous studies [11]. This study was approved by the ethics committee of Hallym University (2017-I102). Written informed consent was waived by the Institutional Review Board.

### Participant Selection

Of 1,125,691 cases with 114,369,638 medical billing codes, PUD was defined using the International Classification of Disease-10 (ICD-10) codes including K25 (gastric ulcer), K26 (duodenal ulcer), and K27 (peptic ulcer, site unspecified). In all cases, endoscopy was performed and at least two outpatient visits were made to treat ulcers (N = 133,349). Of the patients, 67.5% were prescribed proton pump inhibitors (PPIs), and the rest were prescribed other drugs, including H<sub>2</sub> blockers.

Hospitalization histories for hemorrhagic stroke (I60: subarachnoid hemorrhage, I61: intracerebral hemorrhage, and I62: other nontraumatic intracranial hemorrhage) and ischemic stroke (I63: cerebral infarction) were confirmed using ICD-10 codes. We selected participants who were hospitalized and treated for stroke at least once. These methods have been used in other studies evaluating stroke incidence in Korea [12, 13].

We matched participants who were diagnosed with PUD at a 1:1 ratio with patients (control group) not diagnosed with PUD in the cohort group from 2002 through 2013 (Fig. 1). The control participants were selected from the general population (N = 992,342). Potential matches for age group, sex, income group, region of residence, and past medical histories (hypertension, DM, and dyslipidemia) were processed. To avoid selection bias when selecting matching participants, the control group participants were sorted in random order, and then selected from top to bottom. The matched control participants were assumed to be involved simultaneously with each matched patient who was diagnosed with PUD (index date). Therefore, potential participants who died before the index date were excluded. Participants with a history of hemorrhagic or ischemic stroke before the index date were excluded from both the PUD and control groups. In the PUD group, 754 participants were excluded. Participants belonging to the PUD group, for whom enough matched participants could not be identified, were excluded (N = 5). In addition, we

excluded participants under 20 years of age (N = 3,059). Finally, 1:1 matching included 129,531 PUD participants and 129,531 control participants. However, because strict matching increases the dropout rate of PUD patients, we did not match 1:1 for ischemic heart disease and depression history. The participants were followed up for up to 12 years.

## Variables

The classification of groups by age was divided into 5-year intervals: 20–24, 25–29, 30–34, etc. through 85 + years old for a total of 14 age groups. The income groups were initially classified into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were reclassified into 5 classes (class 1 [lowest income]-5 [highest income]) according to income level. Region of residence was divided into 16 areas according to administrative district. The residential areas were reclassified into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

Participants' past medical histories were assessed using ICD-10 codes. For the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were examined if the participants were treated more than two times. Ischemic heart disease (I24 and I25) was identified if the participants were treated more than once. Depression was defined by the psychiatrist through the ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder).

## Statistical Analyses

We used a chi-square test to compare the general characteristics between the PUD and control groups.

The Cox proportional hazard model was used to analyze the hazard ratio (HR) of PUD for hemorrhagic stroke and ischemic stroke. In these analyses, a crude (simple) and adjusted (age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, and depression) model were used. The 95% confidence interval (CI) was calculated.

For the subgroup analyses, participants were divided by age (< 50 years old vs. ≥ 50 years old) and sex (men vs. women).

Two-tailed analyses were performed, and *p*-values less than 0.05 were considered statistically significant. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY, USA).

## Results

The general characteristics (age, income, region of residence, hypertension, DM, and dyslipidemia) of the participants were not significantly different between the two groups due to matching (*p* = 1.000). However, the incidence of ischemic heart disease and depression history was higher in the PUD group than in the control group (each *p* < 0.05). The rate of hemorrhagic stroke was lower in the PUD group (0.6% [787/129,531]) than in the control group (0.8% [1,067/129,531]; *p* < 0.001). Ischemic stroke was

also lower in the PUD group (2.1% [2,732/129,531]) than in the control group (2.4% [3,140/129,531];  $p < 0.001$ , Table 1).

Table 1  
General characteristics of the participants

Characteristics	Total participants		
	Peptic ulcer (N, %)	Control (N, %)	<i>p-value</i>
Age (years old)			1.000
20–24	5,899 (4.6)	5,899 (4.6)	
25–29	8,543 (6.6)	8,543 (6.6)	
30–34	11,486 (8.9)	11,486 (8.9)	
35–39	13,878 (10.7)	13,878 (10.7)	
40–44	16,403 (12.7)	16,403 (12.7)	
45–49	16,761 (12.9)	16,761 (12.9)	
50–54	14,830 (11.4)	14,830 (11.4)	
55–59	12,437 (9.6)	12,437 (9.6)	
60–64	11,530 (8.9)	11,530 (8.9)	
65–69	8,869 (6.8)	8,869 (6.8)	
70–74	5,250 (4.1)	5,250 (4.1)	
75–79	2,495 (1.9)	2,495 (1.9)	
80–84	882 (0.7)	882 (0.7)	
85+	268 (0.2)	268 (0.2)	
Sex			1.000
Male	62,560 (48.3)	62,560 (48.3)	
Female	66,971 (51.7)	66,971 (51.7)	
Income			1.000
1 (lowest)	18,618 (14.4)	18,618 (14.4)	
2	19,788 (15.3)	19,788 (15.3)	
3	24,318 (18.8)	24,318 (18.8)	
4	30,454 (23.5)	30,454 (23.5)	
5 (highest)	36,353 (28.1)	36,353 (28.1)	
Region of residence			1.000
*Chi-square test or Fisher's exact test. Significance at <i>p-value</i> < 0.05			

Characteristics	Total participants	
Urban	58,762 (45.4)	58,762 (45.4)
Rural	70,769 (54.6)	70,769 (54.6)
Hypertension		1.000
Yes	45,355 (35.0)	45,355 (35.0)
No	84,176 (65.0)	84,176 (65.0)
Diabetes mellitus		1.000
Yes	24,633 (19.0)	24,633 (19.0)
No	104,898 (81.0)	104,898 (81.0)
Dyslipidemia		1.000
Yes	39,359 (30.4)	39,359 (30.4)
No	90,172 (69.6)	90,172 (69.6)
Ischemic heart disease		< 0.001*
Yes	8,962 (6.9)	6,941 (5.4)
No	120,569 (93.1)	122,590 (94.6)
Depression		< 0.001*
Yes	16,384 (12.6)	9,908 (7.6)
No	113,147 (87.4)	119,623 (92.4)
Hemorrhagic stroke		< 0.001*
Yes	787 (0.6)	1,067 (0.8)
No	128,744 (99.4)	128,464 (99.2)
Ischemic stroke		< 0.001*
Yes	2,732 (2.1)	3,140 (2.4)
No	126,799 (97.9)	126,391 (97.6)
*Chi-square test or Fisher's exact test. Significance at <i>p-value</i> < 0.05		

The crude and adjusted HRs of hemorrhagic stroke were 0.74 (95% CI = 0.67–0.81) and 0.73 (95% CI = 0.67–0.80), respectively, in the PUD group. The crude and adjusted HRs of ischemic stroke were 0.87 (95% CI = 0.83–0.91) and 0.84 (95% CI = 0.80–0.89), respectively, in the PUD group (each  $p < 0.001$ , Table 2).

Table 2

Crude and adjusted hazard ratios (95% confidence interval) of peptic ulcers for hemorrhagic stroke and ischemic stroke

Group	Hemorrhagic stroke				Ischemic stroke			
	Crude	<i>p</i> -value	Adjusted†	<i>p</i> -value	Crude	<i>p</i> -value	Adjusted†	<i>p</i> -value
Peptic ulcer		< 0.001*		< 0.001*		< 0.001*		< 0.001*
Yes	0.74 (0.67–0.81)		0.73 (0.67–0.80)		0.87 (0.83–0.91)		0.84 (0.80–0.89)	
No	1.00		1.00		1.00		1.00	
* Cox proportional hazard regression model, significance at <i>p</i> -value < 0.05								
† Adjusted model for age, sex, income, region of residence, hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, and depression histories								

According to the subgroup analysis by age, the adjusted HRs of PUD for hemorrhagic and ischemic stroke were 0.76 (95% CI = 0.63–0.90) and 0.85 (95% CI = 0.73–0.98) in the < 50-year-old group and 0.72 (95% CI = 0.65–0.80) and 0.84 (95% CI = 0.80–0.89) in the ≥ 50-year-old group, respectively (each *p* < 0.05, Table 3).



Table 3

Crude and adjusted hazard ratios (95% confidence interval) of peptic ulcers for hemorrhagic stroke and ischemic stroke according to age

Group	Hemorrhagic stroke				Ischemic stroke			
	Crude	<i>p</i> -value	Adjusted†	<i>p</i> -value	Crude	<i>p</i> -value	Adjusted†	<i>p</i> -value
< 50 years old (N = 145,940)								
Peptic ulcer		0.005*		0.002*		0.073		0.025*
Yes	0.78 (0.65–0.93)		0.76 (0.63–0.90)		0.88 (0.76–1.01)		0.85 (0.73–0.98)	
No	1.00		1.00		1.00		1.00	
≥ 50 years old (N = 113,122)								
Peptic ulcer		< 0.001*		< 0.001*		< 0.001*		< 0.001*
Yes	0.72 (0.65–0.80)		0.72 (0.65–0.80)		0.87 (0.82–0.92)		0.84 (0.80–0.89)	
No	1.00		1.00		1.00		1.00	
* Cox proportional hazard regression model, significance at <i>p</i> -value < 0.05								
† Adjusted model for age, sex, income, region of residence, hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, and depression histories								

According to the subgroup analysis by sex, the adjusted HRs of PUD for hemorrhagic and ischemic stroke were 0.71 (95% CI = 0.63–0.81), and 0.81 (95% CI = 0.5–0.87), respectively, in men and 0.75 (95% CI = 0.66–0.86) and 0.88 (95% CI = 0.82–0.95) in women, respectively (each *p* < 0.05, Table 4).

Table 4

Crude and adjusted hazard ratios (95% confidence interval) of peptic ulcers for hemorrhagic stroke and ischemic stroke according to sex

Group	Hemorrhagic stroke				Ischemic stroke			
	Crude	<i>p</i> -value	Adjusted†	<i>p</i> -value	Crude	<i>p</i> -value	Adjusted†	<i>p</i> -value
Men (N = 125,120)								
Peptic ulcer		< 0.001*		< 0.001*		< 0.001*		< 0.001*
Yes	0.73 (0.64–0.83)		0.71 (0.63–0.81)		0.83 (0.78–0.89)		0.81 (0.75–0.87)	
No	1.00		1.00		1.00		1.00	
Women (N = 133,942)								
Peptic ulcer		< 0.001*		< 0.001*		0.015*		0.011*
Yes	0.75 (0.65–0.85)		0.75 (0.66–0.86)		0.91 (0.85–0.98)		0.88 (0.82–0.95)	
No	1.00		1.00		1.00		1.00	
* Cox proportional hazard regression model, significance at <i>p</i> -value < 0.05								
† Adjusted model for age, sex, income, region of residence, hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, and depression histories								

## Discussion

In our nationwide cohort study, PUD did not increase the risk of either ischemic or hemorrhagic stroke at any age or in either sex. This finding was inconsistent with the findings of previous cohort study [8].

Known risk factors for stroke are age, obesity, DM, high blood pressure, dyslipidemia, smoking, atrial fibrillation, and metabolic syndrome (MetS), and MetS was also shown to be associated with upper gastrointestinal diseases [14]. Several cohort studies have been performed on the association between stroke and gastrointestinal diseases, including gastroesophageal reflux disease and ulcerative colitis [15, 16].

Recently, several studies have been performed to investigate the association between PUD and the risk of stroke. A cohort study conducted in Sweden reported that gastric ulcers were significantly associated with the incidence of stroke risk factors (relative risk = 2.21, 95% CI = 1.03–4.71) [17]. In a study conducted in Taiwan, the authors concluded that PUD is a risk factor for ischemic stroke independent of conventional risk factors of stroke (HR 1.31, 95% CI = 1.20–1.41) [8]. In another cohort study, ischemic stroke patients

with PUD had an increased risk of stroke recurrence (HR 1.85, 95% CI = 1.11–3.09) [9]. Xu et al. reported that ischemic stroke patients with PUD have a higher risk of less favorable neurological outcomes (OR = 2.89, 95% CI, 1.79–2.48) [10].

HP infection has been considered the main cause of PUD due to gastrointestinal inflammation and immune reactions. Previous studies have been performed on the association between HP infection-related chronic infection and atherogenesis. HP-related chronic inflammation, endothelial dysfunction, and hyperhomocysteinemia can result in an increased risk of cardiovascular disease (CVD) [18, 19]. HP staining with seropositive cytotoxin-associated gene A (CagA) resulted in systemic inflammation, and higher infectivity of Cag-positive HP strains was associated with an increased risk of atherosclerotic stroke [20]. In a longitudinal study that enrolled new-onset stroke patients with seropositive HP infection, CagA-positive patients had a higher risk of stroke than CagA-negative patients, with an HR of 3.5 [21].

Psychological stress has been known to increase the risk of PUD through gastric mucosal damage by increasing the secretion of pepsin and gastric acid, and neurological dysfunction, which influences the hypothalamic-pituitary-adrenal axis and subsequently increases cortisol levels [22, 23]. Stress is also related to increased catecholamine release and sympathetic activation, which may affect blood pressure reactivity, the cerebral endothelium, or coagulation [24]. The amygdala is more active in individuals with posttraumatic stress disorder, anxiety and depression and increased activity of the amygdala increases bone marrow activity and inflammation in the arteries, which may result in an increased stroke risk [25].

In this study, PUD was not associated with an increased risk of stroke in either males or females, irrespective of age and this result was in contrast to previous studies. Yu et al. reported that the odds ratio for HP infection and stroke was 0.96 (95% CI, 0.78–1.14) in prospective observational studies and concluded that HP infection did not increase the risk of stroke [26]. The role of chronic inflammation caused by HP infection in atherosclerosis has been studied for the past decade, but the clinical significance is not strong enough to affect stroke incidence by HP infection. In addition, psychological stress can be a common risk factor for both PUD and stroke, so an increased risk of stroke may be due to sharing common risk factors rather than to PUD itself.

Rates of obesity and MetS have increased as a result of insufficient physical activity and excessive intake. Several studies have shown that obesity and MetS are associated with an increased risk of upper gastrointestinal disease including PUD [14, 27]. The gastric mucosa of patients with diabetes has increased vulnerability due to decreasing gastric acid secretion and motility, and PUD occurs with a high prevalence in patients with type 2 DM [28]. The plausible risk factors for PUD, including MetS, obesity, and DM, tend to have an increased risk of stroke compared with PUD itself.

This study has revealed some limitations. First, the diagnosis of stroke and PUD was made according to the ICD codes from the administrative billing data, and the number of visits for stroke or PUD was counted, which may not reflect the actual number of stroke or PUD events experienced by the patients. The use of ICD codes in the large claim code can lead to the possibility of misdiagnosis. Second, patient information, including alcohol intake, smoking, dietary factors, and body mass index all of which may

contribute to stroke and PUD, was unavailable in the administrative dataset. Thus, the association between PUD and stroke may be partially explained by the absence of these confounding factors. In the Korean National Health and Nutrition Examination Survey, the smoking rate in Korea was 30.8% in adult men and 6.3% in adult women [29]. Despite this difference between men and women in the rate of smoking, we found no association between PUD and stroke among either men or women. Moreover, the control group selected by the randomization process is likely to have a similar smoking rate to women with PUD because of the low rate of smoking. We think that the confounding effect of smoking is unlikely to affect our conclusion of an association between PUD and stroke. Third, potential confounders that our study did not control were HP infection and stress. Although PUD is currently considered an infectious disease associated with HP, only 5–10% of HP infections are known to cause PUD, and it was estimated that 2.2% of PUD cases were related to psychosocial stress, although it is difficult to measure the incidence and intensity of stress in individuals [30]. Since the control group was generated using a random selection process, the likelihood of a significant difference in HP infection rate and stresses between the PUD and control groups was low.

This study had several strengths. First, we used a population-based dataset of one million subjects with a 12-year follow-up period to assess stroke risk in patients with PUD. Second, our study was the first to evaluate the association between PUD and stroke using nationwide population-based data from South Korea. Third, the control group was matched with the PUD group for risk factors of stroke, such as hypertension, diabetes, dyslipidemia, and ischemic heart disease, as well as basic characteristics, including age, sex, income, and region of residence. This detailed matching may provide valid evidence of the effect of PUD on stroke.

## Conclusion

Our study concluded that PUD does not increase the risk of either ischemic or hemorrhagic stroke regardless of age and sex after adjusting for CVD risk factors, including hypertension, DM, and dyslipidemia.

## Abbreviations

PUD: peptic ulcer disease, HR: hazard ratio, DM: diabetes mellitus, HP: Helicobacter pylori, NSAID: nonsteroidal anti-inflammatory drug, OR: odds ratio, CI: confidence interval, NHIS: National Health Insurance Service, HIRA-NSC: Health Insurance Review and Assessment Service National Sample Cohort, ICD: International Classification of Disease, PPI: proton pump inhibitor, CVD: cardiovascular disease, cagA: cytotoxin-associated gene A

## Declarations

**Ethics approval:**

This study was approved by the ethics committee of Hallym University (2017-1102). Written informed consent was waived by the Institutional Review Board.

**Consent for publication:**

Not Applicable

**Conflict of interest:**

The authors declare that they have no conflict of interest.

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**Authors' contributions:**

Hyo Geun Choi: Conceptualization, Designed the study, acquired, analysed, and interpreted the data, Funding acquisition, Investigation, and Project administration

Jae Seung Soh: Conceptualization, Designed the study, and Methodology

Jae Sung Lim: Conceptualization, Designed the study, and Methodology

Song Yong Sim: Analysed and interpreted the data, and Supervision

Suk Woo Lee: Supervision, Writing – drafting & revising, and Responsibility to submit for publication

All authors have contributed to and have approved the final manuscript.

**Availability of data and materials:**

The data that support the findings of this study are available from Korean National Health Insurance Service but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however from the authors upon reasonable request and with permission of Korean National Health Insurance Service.

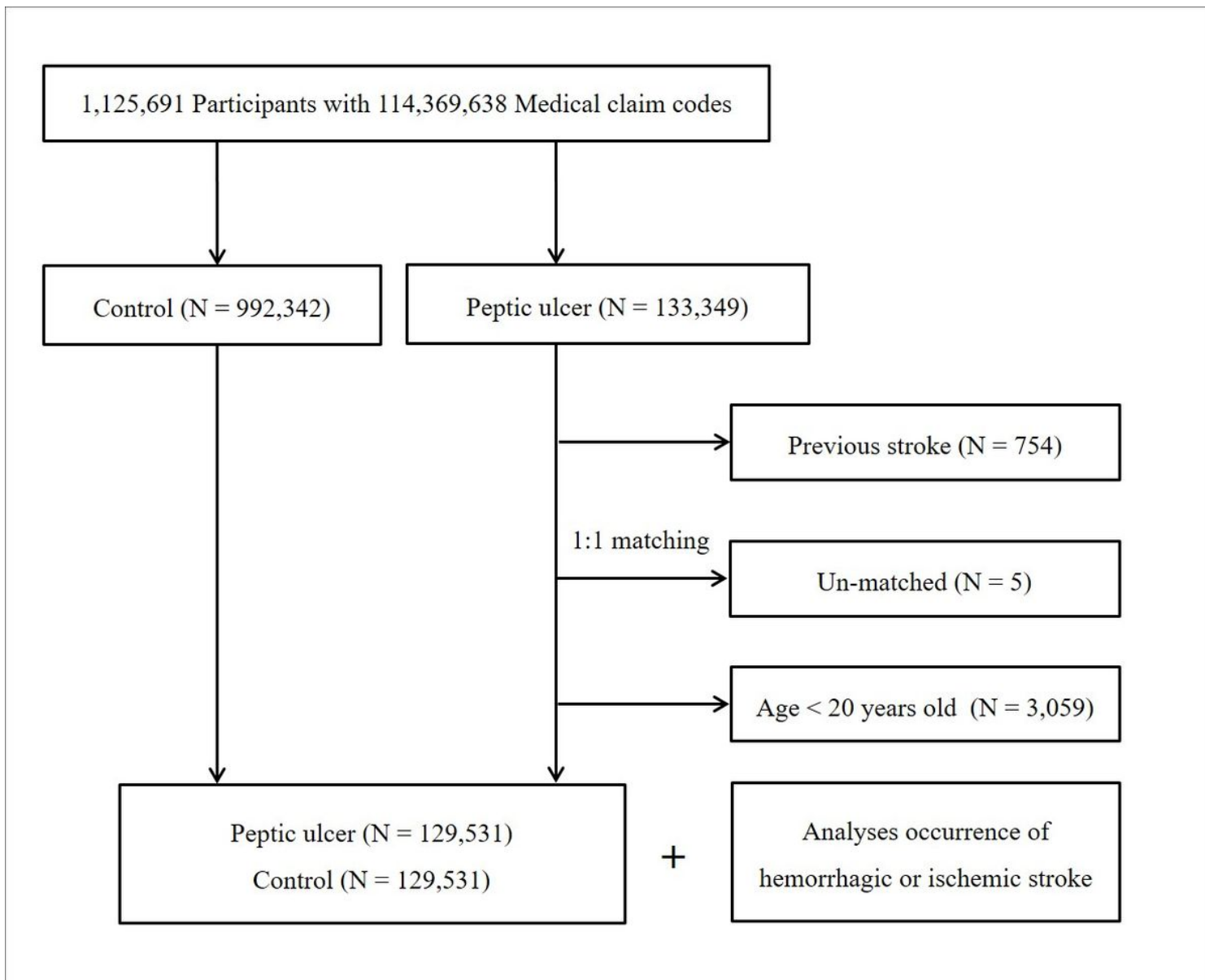
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## Figures



**Figure 1**

A schematic illustration of the participant selection process