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Seasonal variation in the incidence of primary intracerebral hemorrhage: a 16-year nationwide analysis

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Introduction: Data on nationwide trends and seasonal variations in the incidence of Intracerebral Hemorrhage (ICH) in the United States (US) are lacking.

Methods: We used the Nationwide Inpatient Sample (2004–2019) and Census Bureau data to calculate the quarterly (Q1:January–March; Q2:April–June; Q3:July–September; Q4:October–December) incidence rates (IR) of adult (≥ 18 years) ICH hospitalizations, aggregated across Q1–Q4 and Q2–Q3. We report adjusted incidence rate ratios (aIRR) and 95% confidence intervals (CI) for differences in the quarterly incidence of ICH, as compared to acute ischemic stroke (AIS), between Q1Q4 and Q2Q3 using a multivariable Poisson regression model. We additionally performed stratified analyses across the four US regions.

Results: Among 822,143 (49.0% female) ICH and 6,266,234 (51.9% female) AIS hospitalizations, the average quarterly crude IR of ICH was consistently higher in Q1Q4 compared to Q2Q3 (5.6 vs. 5.2 per 100,000) (aIRR, CI: 1.09, 1.08–1.11)—this pattern was similar across all four US regions. However, a similar variation pattern was not observed for AIS incidence. The incidence (aIRR, CI) of both ICH (1.01, 1.00–1.02) and AIS (1.03, 1.02–1.03) is rising.

Conclusion: Unlike AIS, ICH incidence is consistently higher in colder quarters, underscoring the need for evaluation and prevention of factors driving seasonal variations in ICH incidence.

KEYWORDS

intracerebral hemorrhage, acute ischemic stroke, incidence rate, trends, seasonal variations

Introduction

Primary Intracerebral Hemorrhage (ICH) is the second most common and most debilitating type of stroke accounting for 26% of all strokes globally (1) and 10% of all strokes in the United States (2). Seasonal variations in the incidence rate of ICH have been studied across the globe with largely inconsistent and conflicting findings (3–7). Specifically, some of these studies demonstrated the existence of significant seasonal variations in the incidence rate of ICH (3, 8, 9), with higher incidence rates reported in the colder months, and lower incidence rates reported in warmer months. In contrast, other studies indicated that seasonal variation does not exist for ICH (4, 6). Of note, nationwide data on seasonal fluctuations in the incidence of ICH across the United States have not been reported in the contemporary

decade. Therefore, in this study, we evaluate trends and seasonal variations in ICH incidence and the association of age, sex, and race, with ICH incidence, across the United States between 2004 and 2019. We also utilized a comparison population of patients with acute ischemic stroke (AIS) and evaluated seasonal variations in AIS incidence. We hypothesized that ICH incidence will demonstrate significant seasonal variation across colder and warmer calendar quarters.

Methods

Ethics statement

The present study uses de-identified and publicly available data from the Healthcare Cost and Utilization Project (HCUP) (10) for analyses, and thereby meets the criteria for exempt research under our institution's policy. We followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

Data availability

Qualified researchers can purchase the NIS data through the Health Care Utilization Project's central distributor (<https://www.distributor.hcup-us.ahrq.gov/>) upon completion of a data use agreement training.

Data source, study design, and case identification

In a repeated cross-sectional design, adults (≥ 18 years) discharged with a principal diagnosis of ICH or AIS were identified from the Nationwide Inpatient Sample (NIS) between 2004 and 2019. NIS is the United State's largest all-payer in-hospital database representing over 90% of inpatient visits in the United States (11). We applied trend weights to pre-2012 NIS data to account for a sampling redesign that NIS underwent in 2012, making pre-2012 and post-2012 estimates comparable. Validated (12) International Classification of Disease (ICD), Ninth Revision and Tenth Revision codes were used to identify patients with ICH (ICD-9: 431; ICD-10: I61.0–I61.6 and I61.8–I61.9) and AIS (ICD-9: 433.x1, 434.x1, and 436; ICD-10: I63). Age was categorized as 18–44, 45–64, 65–74, and ≥ 75 years. Race/ethnicity was coded as non-Hispanic White, non-Hispanic Black, Asian American and Pacific Islanders, Hispanic, and Others (including Native Americans and Others). We excluded ICH patients with concurrent diagnoses of head trauma, arteriovenous malformations, intracranial aneurysms, and brain malignancy to focus our ICH sample on patients with primary non-traumatic ICH. Because the unit of observation in the NIS database is hospitalization, rather than individual patient, we excluded patients transferred to an acute care hospital to avoid double counting the same patient. We also excluded patients with missing age, sex, or race information. Similar to previous analyses (13), we obtained time-specific denominators

for incidence rate calculation from the Census Bureau's public use microdata sample, based on the 1-year American community Survey (14).

Statistical analysis

We aggregated ICH hospitalizations for each year into four discharge quarters: January–March (Q1); April–June (Q2); July–September (Q3) and October–December (Q4). Utilizing NIS discharge and trend weights, we calculated nationally representative estimates of the quarter-specific incidence of ICH and AIS hospitalizations across age, sex, and race/ethnicity sub-cohorts. Crude and adjusted per quarter incidence rates of ICH and AIS were calculated across colder (Q1Q4) and warmer quarters (Q2Q3). We used panel data Poisson regression model with random effects and robust standard errors to report the crude and adjusted incidence rate ratio (aIRR) and 95% confidence interval (CI) for the differences in the average quarterly incidence rate of ICH and AIS hospitalizations between Q1Q4 and Q2Q3. We additionally performed stratified analyses of seasonal differences in ICH incidence across the four US regions: Northeast, Midwest, South, and West. Also, to further assess the potential role of age in the observed seasonal variation in ICH incidence, we performed a stratified analysis among those aged < 65 years and those aged ≥ 65 years. All analyses were conducted in STATA version 16. The alpha level of significance was set at 0.05.

Sensitivity analyses

To evaluate the potential effect of the change in stroke incidence trend observed from 2007 to 2008, we performed sensitivity analyses, which excluded years prior to 2008.

Results

Across 16 years of NIS data, we identified 985,959 ICH and 7,067,178 AIS hospitalizations. Among these, 822,143 ICH and 6,266,234 AIS hospitalizations were included in the final analytic sample. A majority of the ICH patients were males (51%) and non-Hispanic White (65%), and approximately 64% of the ICH patients are aged ≥ 65 years (Table 1). In contrast, a majority of the AIS patients are females (52%). However, similar to the ICH population, most of the AIS patients are non-Hispanic White (70%) and aged ≥ 65 years (68%) (Table 1). Further details of the age, sex, and race distributions of AIS and ICH patients are provided in Table 1. The average quarterly crude incidence rate of ICH in Q1Q4 (5.6 per 100,000) was higher than the average rate of 5.2 per 100,000 observed in Q2Q3 (aIRR, CI: 1.09, 1.08–1.11), indicating a 9% higher ICH incidence in Q1Q4 compared to Q2Q3. The adjusted incidence rate of ICH was consistently higher in Q1Q4 (vs. Q2Q3) across all 16 years of data analyzed (Figure 1). Furthermore, we observed a similar pattern of higher ICH incidence in Q1Q4 (vs. Q2Q3) among all US regions [(Region: aIRR, CI)

TABLE 1 Factors associated with incidence rates of AIS and ICH hospitalizations.

Variables	ICH (<i>n</i> = 822,143)		AIS (<i>n</i> = 6,266,234)	
	<i>N</i> (%)	aIRR (95% CI)	<i>N</i> (%)	aIRR (95% CI)
Q1Q4 (vs. Q2Q3)	429,452 (52.24)	1.09 (1.08–1.11)***	3,135,267 (50.03)	1.00 (0.99–1.02)
Female	402,485 (48.96)	0.68 (0.65–0.71)***	3,253,451 (51.92)	0.79 (0.76–0.83)***
Race				
Non-Hispanic White	530,364 (64.51)	Reference	4,384,103 (69.96)	Reference
Non-Hispanic Black	142,274 (17.31)	2.30 (2.11–2.52)***	1,044,095 (16.66)	2.13 (1.97–2.30)***
Hispanic	78,330 (9.53)	1.22 (1.15–1.29)***	482,617 (7.70)	0.92 (0.88–0.96)***
Asian American and Pacific Islanders	39,648 (4.82)	1.38 (1.30–1.48)***	171,974 (2.74)	0.69 (0.65–0.73)***
Others	31,527 (3.83)	2.98 (2.77–3.21)***	183,445 (2.93)	2.08 (1.95–2.22)***
Age				
18–44 years	50,836 (6.18)	Reference	260,833 (4.16)	Reference
45–64 years	249,015 (30.29)	8.09 (7.52–8.71)***	1,743,895 (27.83)	10.60 (10.01–11.23)***
65–74 years	172,379 (20.97)	18.56 (17.38–19.82)***	1,418,900 (22.64)	30.46 (28.86–32.15)***
≥75 years	349,913 (42.56)	45.70 (42.14–49.56)***	2,842,606 (45.36)	76.01 (70.93–81.47)***
Year [♣]	–	1.01 (1.00–1.01)**	–	1.03 (1.02–1.03)***

Indicates *p*-value < 0.01; *indicates *p*-value < 0.001.

♣The aIRR (95% confidence interval) for the year variable among ICH patients, rounded to three decimal figures is 1.005 (1.002–1.008).

All models were adjusted for age, sex, race/ethnicity and year of analysis.

Northeast: 1.08, 1.06–1.10; Midwest: 1.09, 1.06–1.11; South: 1.10, 1.08–1.12; West: 1.09, 1.07–1.12] and among those aged < 65 years and those aged ≥ 65 years [(Age-group: aIRR, CI) < 65 years: 1.07, 1.06–1.09; ≥65 years: 1.11, 1.09–1.12]. For AIS, however, the average quarterly incidence in Q1Q4 (41.2 per 100,000) was similar to the incidence rate in Q2Q3 (41.2 per 100,000) (aIRR, CI: 1.00, 0.99–1.02). The incidence of both ICH (aIRR, CI: 1.01, 1.00–1.02) and AIS (aIRR, CI: 1.03, 1.02–1.03) significantly increased over time. Furthermore, the incidence rate of ICH was higher among non-Hispanic Blacks (aIRR, CI: 2.26, 1.90–2.68); Hispanic (aIRR, CI: 1.23, 1.10–1.38); Asian American and Pacific Islanders (1.42, 1.27–1.58) and the “Other” race/ethnicity category (aIRR, CI: 2.72, 2.39–3.10), compared to non-Hispanic Whites (Table 1). While non-Hispanic Blacks (aIRR, CI: 2.13, 1.82–2.48) and the “Other” race/ethnicity category (2.00, 1.80–2.22) had higher AIS incidence rate, compared to non-Hispanic Whites, the Asian American and Pacific Islanders had a lower AIS incidence rate than non-Hispanic Whites (aIRR, CI: 0.70, 0.64–0.77). We observed a progressive increase in the risk of both AIS and ICH with advancing age (Table 1).

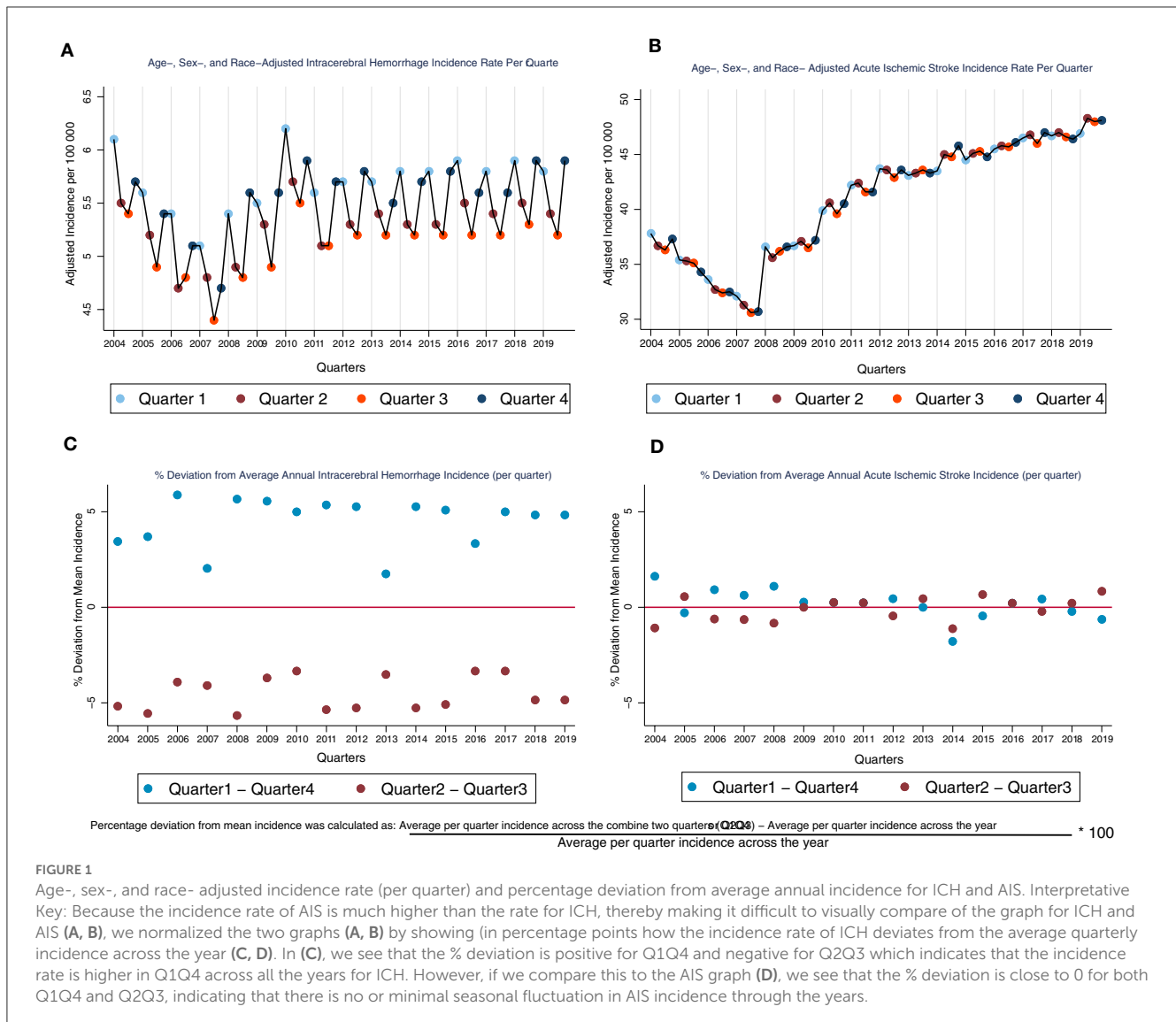
Sensitivity analysis

After restricting our years of analysis to 2008–2019, we found, similar to the main analyses, that ICH incidence is significantly higher in Q1Q4, compared to Q2Q3 (aIRR, CI: 1.09, 1.08–1.11), and AIS incidence in Q1Q4 was not significantly different from the incidence in Q2Q3 (aIRR, CI: 1.00, 0.98–1.02).

Discussion

Across 16 years of nationwide data, our analyses demonstrate that the average per quarter incidence of ICH is consistently higher in the colder calendar months (Q1Q4), compared to the warmer months (Q2Q3). This difference was consistently significant across each of the 16 years analyzed and across all four United States census regions. However, we did not observe a similar pattern of seasonal variations in incidence among AIS patients.

To our knowledge, this is the first study to report nationwide seasonal variations in ICH incidence in the contemporary decade. The specific causes of seasonal fluctuations in ICH incidence are not fully understood; however, there are several potentially contributing mechanisms. For example, a recent meta-analysis demonstrated that blood pressure is higher during colder seasons of the year among both normotensive and hypertensive patients (15). Exposure to colder weather may therefore contribute to variation in ICH incidence via such hemodynamic changes (16). Other potential explanations for the observed variations in ICH incidence may include holiday stress—which may contribute to changes in health behaviors, such as diet, physical activity, and medication adherence—as well as seasonal changes in biochemical markers, including blood viscosity, serum fibrinogen, and cholesterol levels (17, 18). Furthermore, although AIS and ICH largely share common predisposing factors, ICH, compared to AIS, is more sensitive to acute changes in blood pressure, which is widely believed to be the most important risk factor for ICH (19–21). On the other hand, the risk of AIS has been demonstrated to be largely driven by atherosclerotic processes (21–23). It is likely that acute changes in health behavior influence vascular dynamics altering blood pressure. In contrast, the effect of health



behaviors on the advancement of atherosclerosis to critical levels may be more insidious. Therefore, the fact that blood pressure significantly increases during colder seasons of the year may explain why significant seasonal variations were only observed for ICH incidence, and not for AIS incidence (15, 24–27). Overall, the mechanistic basis of higher ICH incidence across particular seasons needs to be further investigated and will directly contribute to developing risk-specific preventive strategies.

Furthermore, we found a similar pattern of seasonal variation in ICH incidence across all four regions of the United States, further corroborating the findings of a recent meta-analysis, which showed that regardless of a region's climate characteristics, ICH incidence is higher in colder seasons, compared to warmer seasons, of the year (3). Moreover, the existence of seasonal variation in ICH incidence across all four regions of the United States potentially reflects the consequence of the globally reported rise in blood pressure during colder seasons (15, 24–27). We would also like to state that a more granular categorization of geographic regions based on climate characteristics in lieu of the census regions provided by NIS may

be necessary to study the effect of seasonal temperature variations on ICH incidence.

Our data also indicates that the incidence of both ICH and AIS are rising over time, reinforcing the need to further strengthen stroke prevention programs in the US. Also, similar to previous reports (2, 28), we found that the incidence rates of both ICH and AIS are higher among males and non-Hispanic Blacks (vs. non-Hispanic Whites). While a higher prevalence of poorly controlled stroke risk factors among these sociodemographic subpopulations may explain the observed differences in incidence rate (12), further evaluation of the epidemiological underpinnings of these differences is warranted.

Potential study limitations include the utilization of ICD codes for ICH and AIS identification rather than neuroimaging, which may lead to misclassification bias. However, ICD codes are highly accurate in identifying acute stroke cases (27). Our analysis may have missed non-hospitalized stroke cases, but given that 95% of acute stroke cases are followed by immediate hospitalization (29), our methodology complies with the Health

Care Utilization Project's recommendation for IR estimation using NIS (28, 29). Finally, the potential inclusion of recurrent AIS and ICH hospitalizations may lead to overestimation of AIS and ICH incidence rates. However, the 1-year risk of AIS and ICH have been reported to be <10 and 5%, respectively (30, 31).

Conclusions

Unlike AIS, ICH hospitalizations consistently demonstrate significant seasonal variations, with higher rates observed in colder quarters, compared to warmer quarters. Our findings call for an evaluation of the factors contributing to seasonal variations in ICH incidence and underscore the need for season-specific preventive measures to reduce the incidence of intracerebral hemorrhage.

Data availability statement

The data analyzed in this study was obtained from the Agency for Healthcare Research and Quality (AHRQ) Health Care Utilization Project (HCUP) Central Distributor (<https://www.distributor.hcupus.ahrq.gov/>), the following licenses/restrictions apply: Qualified researchers can purchase the Nationwide Inpatient Sample (NIS) data upon completion of a Data Use Agreement (DUA) training. Requests to access these datasets should be directed to AHRQ HCUP Central Distributor, hcup@ahrq.gov.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation

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and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

EB and AB: drafting/revision of the manuscript, study concept and design, and analysis and interpretation of data. JT, TPo, AP, and TPr: critical revision of the manuscript, study concept and design, and interpretation of data. GB: critical revision of the manuscript for content and major role in the acquisition of data. FV: drafting/revision of the manuscript for content, study concept and design, and analysis and interpretation of data. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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