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Increased incidence of subarachnoid hemorrhage during cold temperatures and influenza epidemics

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Objective: This study investigated whether the increased incidence of aneurysmal subarachnoid hemorrhage (SAH) in winter is related to temperature or increased incidence of influenza. Such relationships may elucidate the pathogenesis of intracranial aneurysm rupture.

Methods: A nationwide sample of 18,714 patients with SAH was linked with weekly temperature and influenza-like illness consultation data. Poisson regression analyses were used to calculate incidence density ratios (IDRs) with corresponding 95% CIs for the association of SAH incidence with temperature and influenza epidemics; IDRs were adjusted for study year (aIDR). In addition, SAH incidence data from 30 European population-based studies were linked with daily temperature data from the European Climate Assessment.

Results: The aIDR for SAH during influenza epidemics was 1.061 (95% CI 1.022–1.101) in the univariable and 1.030 (95% CI 0.989–1.074) in the multivariable analysis. This association declined gradually during the weeks after epidemics.

Per 1°C temperature drop, the aIDR was 1.005 (95% CI 1.003–1.008) in the univariable and 1.004 (95% CI 1.002–1.007) in the multivariable analysis. In the European population-based studies, the IDR was 1.143 (95% CI 1.129–1.157) per 1°C temperature drop.

Conclusions The incidence of SAH is increased during cold temperatures and epidemic influenza. Future studies with individual patient data are needed to investigate causality between temperature or influenza and SAH.

The incidence of aneurysmal subarachnoid hemorrhage (SAH) varies during the year, with higher incidences in winter than in summer, and a peak in January.^{10,13,15} The underlying cause for this seasonal variation remains uncertain but may shed

some light on the pathogenesis of intracranial aneurysm rupture. Meteorological factors such as temperature, humidity, and atmospheric pressure have been suggested as underlying causes in studies from many different countries, but the data are inconsistent.¹⁰ Other studies hypothesized that infections such as influenza may contribute to the increased incidence of SAH during winter, but the reported associations were conflicting.^{14,24,30,52,58} These inconsistencies may be due to the small number of included patients, resulting in low precision. Moreover, most studies that investigated associations between meteorological factors or infections and SAH incidence were single-center or regional studies, which may have been subject to selection or referral bias. Therefore, we conducted a large nationwide study with additional analysis of SAH incidence data from European population-based studies to investigate the association between influenza epidemics or temperature and the incidence of SAH.

METHODS

Data Sources

Approval for this study was obtained from the Institutional Research Ethics Board of the University Medical Center Utrecht, the Netherlands. For the purpose of this study, we used 4 databases: 1) a nationwide cohort of patients with SAH registered by Statistics Netherlands (<http://www.cbs.nl>); 2) prospectively collected influenza consultation data registered by the sentinel general practices of the Netherlands Institute for Health Services Research (NIVEL) Primary Care Database (www.nivel.nl/peilstations); 3) European data on daily temperature collected by the European Climate Assessment (ECA), including daily temperature data measured at the weather station of the Royal Netherlands Meteorological Institute in the Bilt, Utrecht, the Netherlands;²⁸ and 4) data on SAH incidence in Europe with emphasis on geographical region, which were collected in a systematic review.⁹

Dutch SAH Cohort

This nationwide cohort was constructed by Statistics Netherlands with information from the national Hospital Discharge Register (HDR) and the Cause of Death Register (CDR), and includes all SAH admissions and deaths between October 1995 and October 2010, thereby covering a population of approximately 16 million inhabitants. These registries have been described and validated in previous studies, which showed that the diagnosis of nontraumatic SAH was accurate in more than 95% of the cases.^{37,38,55} In summary, for each hospital admission a new record was created in the HDR, including information regarding age, admission date, and principal diagnosis on admission. The principal diagnosis was determined at discharge and was coded with the WHO International Classification of Diseases, Ninth Revision (ICD-9). The CDR holds records of the underlying and contributing causes, place, and date of death for all Dutch citizens, and is coded with the 10th revision of the ICD (<http://www.who.int/classifications/icd/en/>). All hospital admissions for SAH (ICD-9 code 430) and all out-of-hospital mortality records with SAH as the underlying cause of death (ICD-10 code I60) between 1995 and 2010 were selected from the HDR and CDR.

Dutch Influenza-Like Illness Cohort

The NIVEL (www.nivel.nl/peilstations) uses a network of general practitioners throughout the Netherlands that covers 0.7%–1% of the Dutch population. It is

representative of the entire Dutch population with regard to age, sex, regional distribution, and degree of urbanization.

The NIVEL influenza-like illness cohort includes all patients who presented to the general practitioner in sentinel general practices with influenza-like illness, which is defined as an illness with an acute onset (prodromal stage ≤ 4 days), fever (defined as a rectal temperature $\geq 38^{\circ}\text{C}$), and ≥ 1 of the following symptoms: cough, nasal catarrh, sore throat, frontal headache, retrosternal pain, or myalgia.

The incidence of influenza-like illness per week was calculated by dividing the total number of influenza-like illness consultations per week by the total number of citizens in the corresponding sentinel general practices coverage area. According to our national influenza surveillance program, an influenza epidemic was defined as an incidence of influenza-like illness $> 51/100,000$ citizens during 2 consecutive weeks, and if nose and throat swabs from these weeks were found to contain influenza viruses (www.nivel.nl/peilstations). We used influenza-like illness consultation data between 1995 and 2010, which were stratified per week according to the International Organization for Standardization 8601 standard (<http://www.iso.org>).

Temperature Data

The ECA collects daily meteorological data from more than 10,000 meteorological stations situated in 62 countries throughout Europe and the Mediterranean.²⁸ The reliability of the ECA data set has been validated with the nearest meteorological land-grid boxes, with a correlation coefficient of 0.8 for 93% of the daily temperature series.²⁸

European SAH Incidence Data

We used data on SAH incidence with emphasis on geographical region from a systematic review, which included all population-based studies on SAH incidence published between 1960 and 2005.⁹ The methods of literature search, inclusion criteria for studies, and diagnostic criteria for SAH have been described in the original publication.⁹ For this study, we included data on SAH incidence from all included population-based studies performed in European countries.

Statistical Analysis

In the Dutch SAH cohort, the day of admission was used to stratify the total number of SAH events per week.

Influenza epidemics were dichotomized (present or absent) for further statistical analysis. Because the influenza season runs from October to May of the following year, influenza epidemics may cross the calendar year (www.nivel.nl/peilstations). For this reason, a study year was defined from the week of October 1 until the week of October 1 the following year.

First, we performed nationwide analyses with data from the Dutch SAH cohort, influenza-like illness data, and Dutch temperature data. The incidence of SAH during influenza epidemics was compared with the incidence in times without influenza epidemics, by calculating incidence density ratios (IDRs) with corresponding 95% CIs using univariable Poisson regression analyses. In addition, we performed time-window shift analysis up to 8 weeks after the start of the epidemic to investigate if there was a delay between onset of the influenza epidemic and the incidence of SAH (Fig. 1). Subsequently, we used mean weekly temperatures measured at the weather station of the Royal Netherlands Meteorological Institute in the Bilt, Utrecht, the Netherlands, to calculate the IDR with corresponding 95% CI for SAH per 1°C drop

in temperature, using univariable Poisson regression analysis.²⁸ Then, mean weekly temperature and the presence of influenza epidemics (present or absent) were entered into a multivariable Poisson regression analysis to calculate the IDRs with corresponding 95% CIs for SAH as outcome. All analyses were repeated with adjustment for study year.

[FIGURE 1].

Second, we analyzed the association between temperature and SAH incidence. We used 1) SAH incidence data from European population-based studies and 2) mean daily temperature data (from weather stations closest to the corresponding geographical region in which the SAH incidence study was performed) from the ECA database to calculate the IDR and corresponding 95% CI for SAH for each 1°C drop in temperature.^{9,28} The mean temperature during the study period of each population-based study was calculated by the average of all mean daily temperatures during the study period. Missing mean daily temperature values were imputed by using the average of the mean daily temperature values of adjacent days.

RESULTS

Influenza Epidemics and SAH in the Netherlands

A total of 18,714 SAH events were registered in the Netherlands between October 1995 and October 2010, with a mean of 1248 events per study year (SD ± 63). During the study period, there was a total of 34,404 influenzalike illness consultations at the sentinel practices, with a mean of 2294 consultations per study year (SD ± 851).

Extrapolated to the whole country, this would have been 3.4–4.9 million consultations. The mean incidence of influenza-like illness and the mean number of SAH events per week during the study period, including 95% CI and regression trend lines, are shown in Fig. 2. The mean incidence of influenza-like illness was 1809/100,000 per study year (SD ± 570). The median duration of epidemic influenza per study year was 9 weeks (range 3–16 weeks), with the beginning of the influenza epidemics varying from early October to the end of February. The IDRs for the association between SAH and epidemic influenza are shown in Table 1. The IDR of SAH during epidemic influenza was 1.047 (95% CI 1.009–1.087), and after adjustment for study year it was 1.061 (95% CI 1.022–1.101). In the analyses in which the incidence of SAH was analyzed 1–8 successive weeks after an influenza epidemic, there was a gradual decline of the IDR during the weeks following the start of an epidemic.

Mean Weekly Temperature and SAH in the Netherlands

The mean weekly temperature measured at the weather station of the Royal Netherlands Meteorological Institute in the Bilt, Utrecht, the Netherlands between October 1995 and October 2010 was 10.5°C (range -7.4°–24.5°C). The mean weekly temperature and the mean number of SAH events per week during the study period, including 95% CI and regression trend lines, are shown in Fig. 3. The IDR for the association between SAH and 1°C drop in mean weekly temperature was 1.004 (95% CI 1.002–1.007), and after adjustment for study year it was 1.005 (95% CI 1.003–1.008) (Table 1).

Influenza Epidemics, Mean Weekly Temperature, and SAH in the Netherlands

[FIGURE 2].

The IDRs of the multivariable Poisson regression analyses for the associations among SAH, mean weekly temperature in °C, and influenza epidemics are shown in Table 1. The IDR for the association between SAH and influenza epidemics was 1.021 (95% CI 0.980–1.064) after adjustment for mean weekly temperature, and 1.030 (95% CI 0.989–1.074) after adjustment for mean weekly temperature and study year. The IDR for SAH per 1°C drop in mean weekly temperature was 1.004 (95% CI 1.001–1.006) after adjustment for influenza epidemics, and 1.004 (95% CI 1.002–1.007) after adjustment for influenza epidemics and study year.

European Temperature and SAH Incidence Data

We included SAH incidence data from 30 European population-based studies, which were included in a previous systematic review.⁹ These 30 studies covered 33 study periods and included populations from 12 countries.^{1–5, 7,8,11,17,19,21,23,25,27,29,31,39–44,46,48,49,51,53,57,59,60} For 6 studies, data on mean daily temperature measured at weather stations closest to the geographical region in which the study was performed were imputed because of missing values (< 3% missing mean daily temperature values).^{2,3,27,42,48,53} For 1 study with a duration of 3 years, the mean daily temperature values of the first 2 years were used to calculate the mean temperature of the entire study period because of missing values.⁷ Study region, midyear of study period, number of patient-years, number of patients with SAH, SAH incidence, weather stations, and mean temperature during the study period for all included studies are shown in Table 2. The geographical regions per study are shown in Fig. 4. The IDR for the association between SAH and 1°C drop in mean temperature during the study period was 1.143 (95% CI 1.129–1.157).

[TABLE 1][FIGURE 3].

DISCUSSION

Our study shows a seasonal pattern in SAH incidence, with an increased SAH incidence during cold temperatures and epidemic influenza. For influenza, the association with SAH incidence gradually declines during the weeks after the start of an influenza epidemic. For temperature, cold temperatures were associated with increased SAH incidence, which was independent of the presence of influenza epidemics. The association between cold temperatures and SAH was confirmed in our analysis of 30 European population-based studies.

Previous studies from different geographical regions described associations between SAH and meteorological factors such as temperature or season, but results are conflicting.^{10,13,16,22,32,36} These conflicting results may be explained by referral bias or lack of power due to small sample size in single-center or small regional studies, a limited study period, or variety in study definitions (i.e., mean/ maximum/minimum temperature, temperature difference, season, or wind chill). The evidence on recent infection in relation to the incidence of SAH is limited.^{14,24,30,52,58} The results of a Canadian study from the Calgary region were comparable with our findings and showed a small but significant increase in the incidence of SAH during influenza

epidemics, with a delay between increased influenza and SAH rates of 0.9 week.¹⁴ [TABLE 2].

A case-control study found that an upper respiratory tract infection was an independent trigger factor for SAH, but this study included only 44 patients. In addition, this study's retrospective design, in which patients were asked if they had infections within 4 weeks prior to hospitalization, might have led to recall bias.³⁰ A case-crossover study on trigger factors for SAH found a relative risk of 2.4 (95% CI 0.3–16) for flu-like illness during the 24 hours prior to SAH.⁵⁸ Two other small case-control studies investigated antibody serum titers of influenza and other viral infections in patients with aneurysmal SAH.^{24,52} The first study showed elevated antibodies against influenza virus in patients with SAH, but the second study could not confirm these results.^{24,52} No study thus far has performed a multivariable analysis to examine the relationship of SAH incidence to influenza and temperature independently.

A growing body of evidence points to a key role of inflammation in the process of aneurysm rupture.^{6,54} Infection with the influenza virus causes an innate immune response that releases proinflammatory mediators, which lead to symptoms within 2 days.^{20,50} Moreover, tumor necrosis factor- α , one of the proinflammatory mediators released after influenza infection, is a key modulator in intracranial aneurysm formation and rupture.^{6,47} Another biological hypothesis for our findings is that cold temperatures cause physiological changes such as increased sympathetic nerve activity and catecholamine release. These changes lead to an increase in blood pressure,^{26,35} which in turn may trigger aneurysm rupture.⁵⁸ A strength of our nationwide study is that the catchment area during the study period did not change. Also, the sample size was large because we used nationwide data on the incidence of SAH and influenza-like illness. Moreover, climate differences within the Netherlands are minimal due to the relatively small surface area of approximately 41,500 km². Another strength of our study is the use of reliable and validated registries such as the NIVEL influenza-like illness registry, the Dutch HDR and CDR, and the ECA data set of daily temperature values.^{12,28,33,34,38,45,56} Another strength of our study is the analysis, in which we used 1) population-based SAH incidence data from 12 European countries and 2) data on mean daily temperature from the ECA data set, to confirm the association between cold temperature and SAH found in our nationwide analyses.

A limitation of the present study may be that we only used daily temperature data from European countries, which might affect the generalizability of our findings to non-European populations.

[FIGURE 4].

Another limitation of the present study may be that we were not able to use the day of aneurysm rupture in our nationwide data set, but rather used the day of admission or death as a surrogate. However, because of the acute onset of symptoms such as severe headache (often the worst headache the patient had ever experienced), loss of consciousness, neurological deficits, or vomiting, the majority of all patients with SAH present to a hospital within 24 hours after rupture.¹⁸ Another limitation is that we were not able to link data on SAH and influenza infection on an individual patient basis. Therefore, we could not adjust for well-established risk factors for SAH such as smoking status and hypertension.

Moreover, we could not assess whether a causal relationship exists between occurrence of SAH and the proinflammatory immune response initiated by influenza or the physiological changes in blood pressure caused by cold temperatures. Future studies using individual patient data could shed light on a possible causal relationship between temperature or influenza and SAH.

CONCLUSIONS

Influenza epidemics and cold temperatures are associated with an increased incidence of SAH. Although the increased incidence of SAH during influenza epidemics and cold temperatures is unlikely to be caused by a single factor, our findings support the hypothesis that inflammation and physiological changes in blood pressure are contributing factors in the pathogenesis of intracranial aneurysm rupture.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Backes, Rinkel, Algra, Vergouwen.

Acquisition of data: Backes, Algra, Vaartjes, Donker, Vergouwen. Analysis and interpretation of data: all authors.

Drafting the article: Backes, Rinkel, Vergouwen. Critically revising the article: Rinkel, Algra, Vaartjes, Donker, Vergouwen.

Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Backes. Statistical analysis: Backes, Algra, Vaartjes, Vergouwen.

Administrative/technical/material support: Vaartjes, Donker, Vergouwen. Study supervision: Rinkel, Vergouwen.

Supplemental Information

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FIGURES AND TABLES

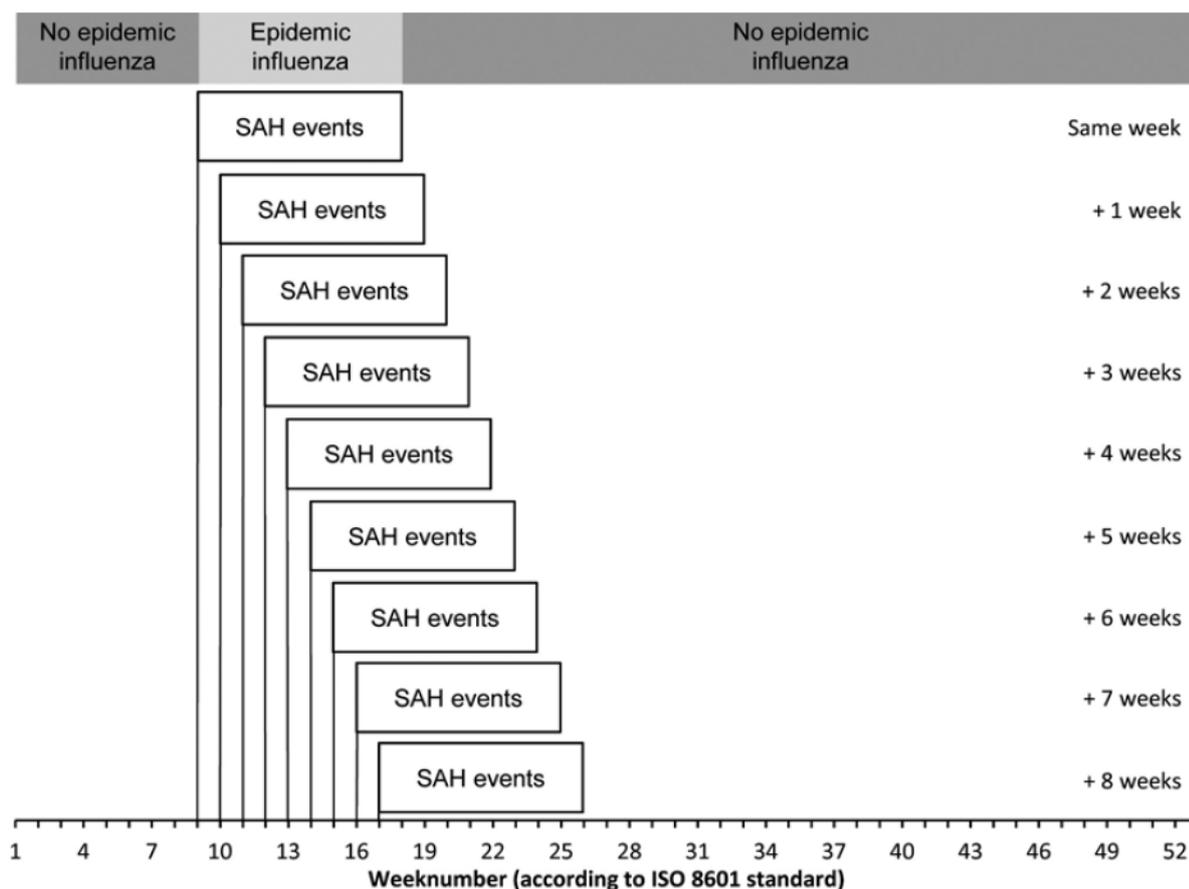


FIG. 1. Schematic illustration of the time frame shift analyses. The number of SAH events that occurred within 1–8 successive weeks after the start of the epidemic influenza was used in additional analysis to investigate whether there was a delayed association of epidemic influenza with the incidence of SAH. ISO = International Organization for Standardization.

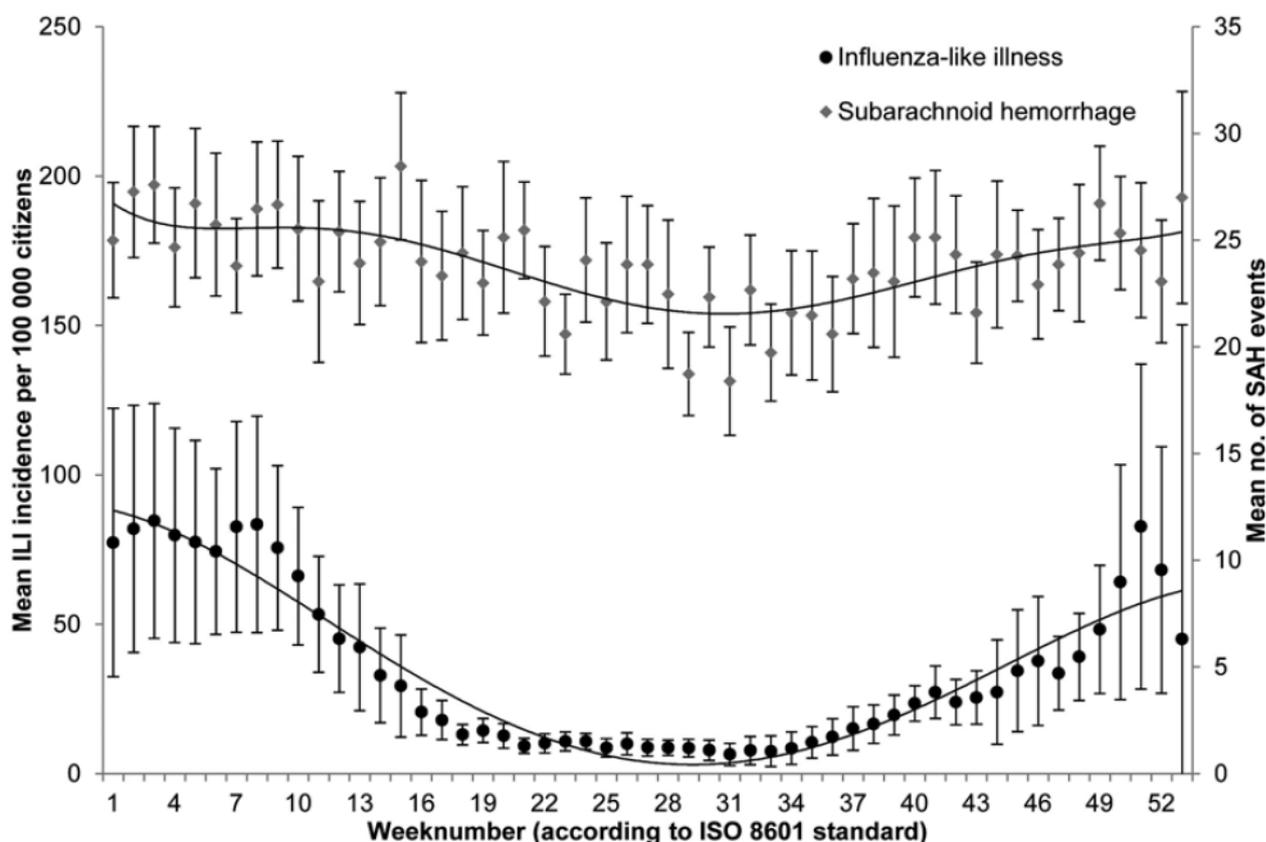


FIG. 2. Graph showing the incidence of influenza-like illness and number of SAH events per week, with corresponding 95% CIs and regression trend lines for the study period October 1995 through October 2010. ILI = influenza-like illness.

TABLE 1. Univariable (influenza epidemics or weekly temperature) and multivariable (influenza epidemics and weekly temperature) Poisson regression analyses with IDRs for SAH and corresponding 95% CIs

Variable	Univariable Model, Influenza or Temperature IDR (95% CI)	Adjusted Univariable Model, Influenza or Temperature aIDR (95% CI)	Multivariable Model, Influenza & Temperature IDR (95% CI)	Adjusted Multivariable Model, Influenza & Temperature aIDR (95% CI)
Influenza epidemics (wk)				
Same	1.047 (1.009–1.087)	1.061 (1.022–1.101)	1.021 (0.980–1.064)	1.030 (0.989–1.074)
+1	1.038 (1.001–1.078)	1.052 (1.013–1.091)	—	—
+2	1.020 (0.982–1.058)	1.032 (0.995–1.072)	—	—
+3	1.029 (0.992–1.068)	1.042 (1.004–1.082)	—	—
+4	1.021 (0.983–1.059)	1.033 (0.996–1.073)	—	—
+5	1.024 (0.986–1.063)	1.037 (0.999–1.076)	—	—
+6	1.030 (0.992–1.069)	1.043 (1.005–1.082)	—	—
+7	1.015 (0.978–1.053)	1.028 (0.990–1.067)	—	—
+8	1.014 (0.977–1.053)	1.027 (0.989–1.066)	—	—
Weekly temperature				
Per 1°C decrease	1.004 (1.002–1.007)	1.005 (1.003–1.008)	1.004 (1.001–1.006)	1.004 (1.002–1.007)

aIDR = IDR adjusted for study year; — = not applicable.

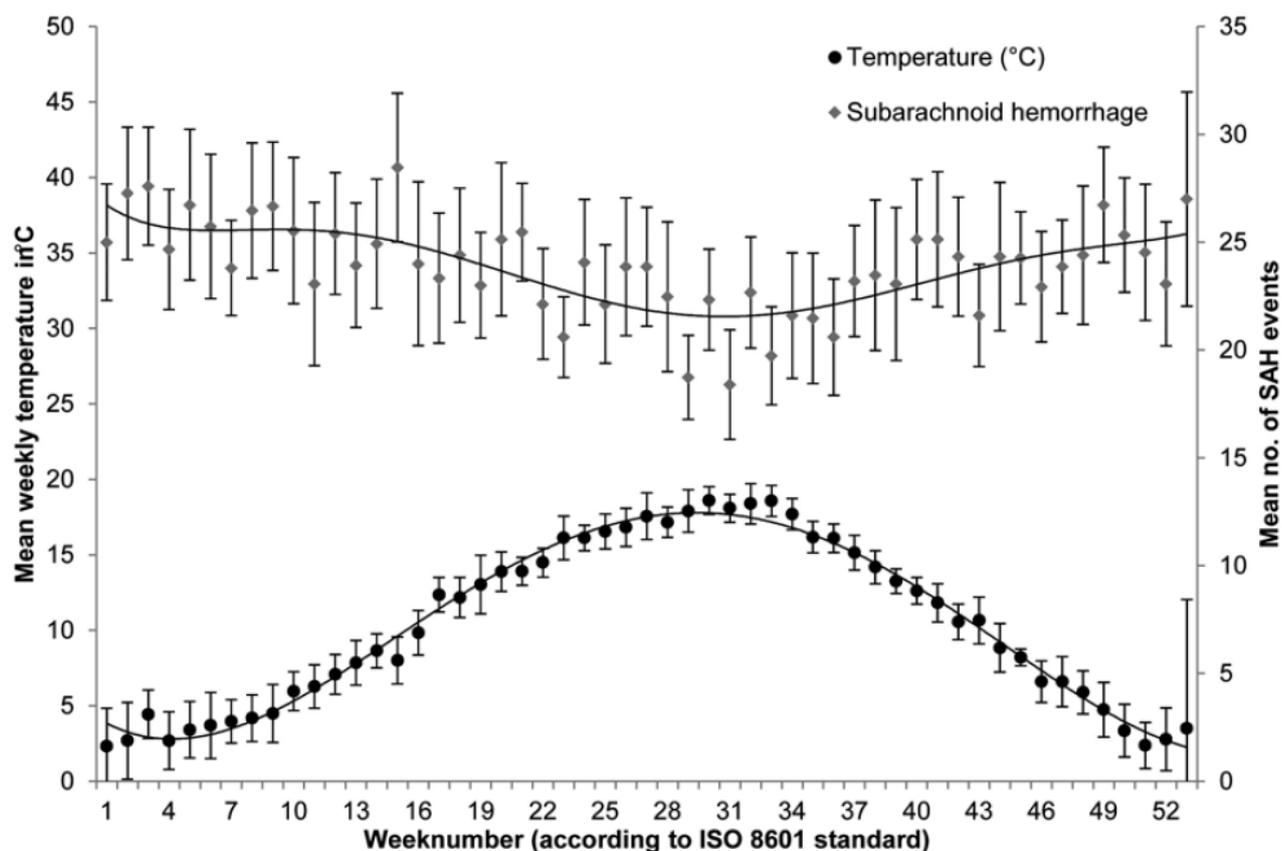


FIG. 3. Graph showing the mean weekly temperature and number of SAH events per week, with corresponding 95% CIs and regression trend lines for the study period October 1995 through October 2010.

TABLE 2. Mean temperature and incidence of SAH in European population-based studies according to region and sorted by mean temperature during the study period

Study Population	Region	Midyear of Study	No. of PY	No. of Pts w/ SAH	SAH Incidence/100,000 PY (95% CI)	Weather Station	Mean Temperature, °C
Kuopio ⁴⁶	Finland	1979	159,033	24	15.1 (9.1–21.1)	Kuopio Inkilänmaki	0.3
North Karelia ⁴⁴	Finland	1984	1,890,000	411	21.7 (19.6–23.8)	Liperi Joensuu Lentoasema & Turku Kupittaa	2.1
Sweden, north ^{48*}	Sweden	1993	8,212,800	984	12.0 (11.2–12.8)	Umea	3.2
Finland ⁴¹	Finland	1990	269,608	39	14.5 (10.3–19.8)	Kuopio Kampula	3.6
Söderhamn ⁵¹	Sweden	1985	92,208	10	10.8 (4.1–17.6)	Söderhamn	3.9
Espoo ⁴¹	Finland	1979	273,700	33	12.1 (8.3–16.9)	Helsinki Kampula	4.2
Söderhamn ⁵¹	Sweden	1977	96,690	13	13.4 (6.1–20.8)	Söderhamn	4.3
Espoo-Kauniainen ¹	Finland	1972	107,673	26	24.1 (14.9–33.4)	Espoo Nupuri	5.3
Espoo ⁴¹	Finland	1972	226,200	42	18.6 (13.4–25.1)	Helsinki Kampula	5.9
Tartu ⁵⁷	Estonia	2000	101,122	8	7.9 (3.4–15.6)	Tartu	6.4
Sweden, south ³⁹	Sweden	1996	1,140,000	106	9.3 (7.6–11.2)	Lund	7.3
Orebro ^{2*}	Sweden	1999	123,503	11	8.9 (4.4–15.9)	Orebro	7.3
Scotland ⁴⁹	UK	1999	212,704	23	10.8 (6.9–16.2)	Eskdalemuir	7.8
Lund-Orup ⁴⁰	Sweden	1984	600,573	28	4.7 (2.9–6.4)	Lund	8.0
Copenhagen ^{53*}	Denmark	1984	295,470	49	16.6 (12.3–21.9)	Copenhagen Landbohojskolen	8.9
Malmö ^{27*}	Sweden	1995	2,674,144	197	7.4 (6.4–8.5)	Malmö	8.9
Tilburg ²¹	Netherlands	1979	302,712	24	7.9 (4.8–11.1)	Gilze-Rijen	9.0
Dijon ¹⁷	France	1987	678,560	15	2.2 (1.1–3.3)	Langres	9.2
Frederiksberg ¹⁹	Denmark	1972	197,542	13	6.6 (3.0–10.2)	Copenhagen Landbohojskolen	9.3
Oxford ^{3*}	UK	1984	420,000	33	7.9 (5.2–10.5)	Oxford	9.3
Dijon ⁵⁹	France	1996	429,264	12	2.8 (1.4–4.9)	Langres	9.5
Asturias ⁴	Spain	1991	417,033	28	6.7 (4.5–9.7)	Oviedo	9.6
Erlangen ²⁹	Germany	1997	202,900	12	5.9 (3.1–10.3)	Nurnberg	9.7
Malmö ²³	Sweden	1989	232,000	14	6.0 (2.9–9.2)	Malmö	9.9
London ⁶⁰	UK	1996	938,132	74	7.9 (6.2–9.9)	London	10.1
Frederiksberg ²⁵	Denmark	1990	85,611	2	2.3 (0.9–5.6)	Copenhagen Landbohojskolen	10.5
Oxford ⁴³	UK	2003	181,084	16	8.8 (5.1–14.3)	London	10.5
Valle d'Aosta ⁸	Italy	1997	118,723	14	11.8 (6.4–19.8)	Geneve Cointrin	10.9
Portugal, north ^{7*}	Portugal	1999	246,224	23	9.3 (5.9–14.0)	Braganca	12.4
Belluno ³¹	Italy	1992	211,389	12	5.7 (2.9–9.9)	Verona Villafranca	13.3
Umbria ^{42*}	Italy	1988	147,654	15	10.2 (5.0–15.3)	Roma Ciampino	15.3
L'Aquila ⁵	Italy	1994	297,838	24	8.0 (5.2–12.0)	Roma Ciampino	16.5
Vibo Valentia ¹¹	Italy	1996	179,186	12	6.7 (3.5–11.7)	Brindisi	16.5

Pts = patients; PY = patient-years.

* Missing values for temperature were imputed.



FIG. 4. Map showing the geographical regions of included population-based studies. Numbers indicate the reference number.