UDC 613.1
DOI: 10.21668/health.risk/2023.1.12.eng

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Research article

META-ANALYSIS OF THE INFLUENCE OF GENDER AND AGE ON THE SEASONAL DYNAMICS OF CEREBRAL STROKES

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The purpose of this work is to investigate dependence of the seasonal dynamics of HS (hemorrhagic strokes) and IS (ischemic strokes) risk on sex and age using meta-analysis.

In total, 22 publications were selected for this meta-analysis, studying the seasonal dynamics of HS, of which 8 publications presented statistics separately for men and women, and three papers presented statistics for different age groups. Also, 28 publications studying the seasonal dynamics of IS were selected for meta-analysis, of which 11 publications presented statistics separately for men and women, and three papers presented statistics for different age groups.

The meta-analysis of the seasonal dynamics of HS showed that HS risk is less likely in a warmer season compared with a colder one. In men, HS risk was the highest in winter and spring, and in women in winter. Dependence between HS risk and a decrease in air temperature was the same in men and women. According to the results of the meta-analysis (without regard to sex and age), the minimum probability of IS occurs in autumn. In women, IS risk was significantly higher in winter compared to other seasons. In men, the seasonal dynamics of IS was not expressed. In older people, the overall risk of stroke increased, especially IS. In people over 65 years of age, there was a significant dependence of an increase in HS risk on a decrease in air temperature. In people younger than 65 years, HS risk was not associated with cold. A decrease in temperature equally increased IS risk in both age groups.

These results suggest that sex and age may influence the seasonal stroke risk.

Keywords: *hemorrhagic stroke, ischemic stroke, season, gender, age, risk, seasonal dynamics, meta-analysis.*

In 2019, approximately 101 million people had a stroke, and 6.55 million people died from it [1]. Stroke is one of the main causes of disability in the population.

Age-adjusted DALY (Disability Adjusted Life Years) and stroke mortality are significantly higher in men than in women, but the prevalence is higher in women [1]. Almost a third of all strokes occur over the age of 80 [2], but men, on average, have a stroke at a younger age than women [3]. In women of reproductive age, on the one hand, a high level of estrogen serves as protection against cardiovascular events (CVE), on the other hand, pregnancy and contraceptive use increase the risk of stroke. In addition, CVE risk is increased by lifestyle factors (overeating, alcohol abuse, smoking), which are more typical for men than for women [4].

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The change of seasons is accompanied by both changes in external meteorological conditions (air temperature and humidity, magnitude and variability of atmospheric pressure, partial density of oxygen in the air), and changes in the functioning of the body and lifestyle. In winter, as opposed to summer, people have higher levels of BP (blood pressure), body mass index, thyroid hormone activity, hematocrit, hemoglobin, lipid profile and glucose levels [5–9], which may contribute to an increased CVE risk in winter. Our earlier meta-analyses showed that there are no significant differences in the seasonal dynamics of body functioning between men and women [5–10].

Our studies did not reveal convincing evidence that age could influence the seasonal dynamics of the body functioning in healthy people [5–10]. However, it is known that old age is associated with inhibition of vegetative control mechanisms, and as a result the coherence of the body's response to various stimuli, including meteorological ones, changes [11, 12]. Cooling causes a greater rise in systolic BP and in the activity of the sympathetic nervous system in older people compared with young people, and moderate hyperthermia causes a weakened tachycardia reaction and a tendency to reduce the hypotensive response of diastolic BP [13]. During hypoxia, older volunteers compared with young ones demonstrated a similar or increased rise in BP, but a smaller increase in heart rate [14, 15]. Age-related disorders of cerebral circulation, when brain perfusion changes during heat, cold, or hypoxia, can provoke fainting and strokes. The presence of cardiovascular pathology further exacerbates the imbalance. For example, patients with heart failure have a weakening of the cardiovascular response under hyperthermia compared with healthy people of the same age [12]. In patients with arterial hypertension, there is an increase in the hypertensive response under exposure to cold [16]. Hypertensive patients, compared with healthy people, show a large difference between BP values in winter and summer [17].

The purpose of this work is to investigate dependence of the seasonal dynamics of HS (hemorrhagic strokes) and IS (ischemic strokes) on sex and age using a meta-analysis of publications.

Materials and methods. The meta-analysis was performed in accordance with the PRISMA guidelines[1]. In this meta-analysis, publications selected for the meta-analysis [18] of dependence between HS and IS and climate of a given region were used. The strategy for searching and selecting publications is described in detail in [18]. It was similar for this meta-analysis but the exact geographic location of the study was not important. The search was carried out in PubMed and Scopus databases using the keywords: stroke, ischemic stroke, hemorrhagic stroke, cerebral infarction, cerebral ischemia, and season.

Publications devoted to the study of the seasonal dynamics of events / hospitalizations of HS, IS, but not deaths from them, were selected. The HS and IS data had to be presented separately in absolute terms (or in a form that allows calculating the absolute value for a year and for each season). When selecting publications, the methods of diagnostics were taken into account; due to the imperfection of diagnostics, studies conducted before 1980 were excluded.

In the course of the meta-analysis, the seasonal risk of HS and IS was calculated considering sex and age and without such consideration. If the publication presented statistics on subtypes within HS and IS, then it was combined, as in the meta-analysis [18].

Statistics. Meta-analysis was performed using the statistical program Review Manager 5.3 (Cochrane Library). The Mantel Haenszel (odds ratio – chance coefficient test that allows determining the strength of the connection between events) test was used for analysis. The heterogeneity of the studies included in the meta-analysis was determined by the criterion I^2. The choice of a fixed or randomized effects model was carried out in accordance with the recommendations[2]. Z-test was used to evalu-

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ate the statistical significance of the weighted mean effect size. Confidence interval was 95 %. Differences were considered statistically significant at $p < 0.05$. Funnel plots were used to identify bias in the selection of publications.

Results. 746 publications were found on the topic of the meta-analysis, of which 42 were reviews [18]. For this meta-analysis, 22 publications studying the seasonal dynamics of HS were selected, of which 8 publications presented statistics separately for men and women, and three papers presented statistics for different age groups (Table 1). Also, 28 publications studying the seasonal dynamics of IS were selected for meta-analysis, of which 11 publications presented statistics separately for men and women, and three papers presented statistics for different age groups (Table 1). In 16 publications, the seasonal dynamics of HS and IS were simultaneously studied.

Table 1

Publications selected for meta-analysis

Publications	Total number of strokes		Average age (years)	Sex, male (%)		Diagnostics
	HS	IS		HS	IS	
Biller J., 1988 [19]	690	1357	-	43	55.7	HCSR
Cho S., 2018 [20]	-	63,564	≥ 40	-	53	WHOC
Choi Y.I., 2015 [21]	-	968	67.6	-	60.9	MRI
Ding J, 2018 [22]	-	84	39.9	-	52.2	CT, MRI
Evzel'man M.A., 2019 [23]	-	1144	73.5		30	CT, MRI
Feigin V.L., 1998 [24]	64	214	49.5*	36**	38**	CT
Fodor D.M., 2018 [25]	114	969	70.5*	55.3**	52.5**	WHOC
Giroud M., 1989 [26]	45	226	≥ 10	-	-	CT
Hakan T., 2003 [27]	761	-	8–82	45**	-	CT
Huang Q., 2019 [28]	2555	-	55.1	37.5	-	CT
Jakovljević D., 1996 [29]	2493	12,737	≥ 25*	52**	49**	WHOC
Karagiannis A., 2010 [30]	-	1452	72.5	-	50**	-
Khan F.A., 2005 [31]	896	5086	75. 1	48**	49**	CT
Klimaszewska K., 2007 [32]	-	1173	72.4	-	-	-
Knezovic M., 2018 [33]	251	1712	18–104	50	50	-
Kumar P., 2015 [34]	436	663	54	69**	70.6**	-
Liu Y., 2018 [35]	-	961	69.1	-	66.9	CT, MRI
Manfredini R., 2010 [36]	-	43,642	76.8	-	45.5**	WHOC
Mao Y., 2015 [37]	632	2202	71	57.6	55.4	CT
Ogata T., 2004 [38]	-	12,660	71	-	62.7**	-
Ostbye T., 1997 [39]	20,545	-	≥ 15	39**	-	-
Palm F., 2013 [40]	202	1547	71.7	-	-	CT, MRI
Park H., 2008 [41]	1472	1357	59	-	-	-
Passero S., 2000 [42]	1018	-	63.6	62	-	CT
Ricci S., 1992 [43]	52	286	-	-	-	CT
Salam A., 2019 [44]	698	2956	54.4	-	-	WHOC
Simovic S., 2017 [45]	-	415	72.1*	-	50.4	CT, MRI
Soomro M.A., 2011 [46]	46	85	15–88	58.7**	57.6**	CT
Spengos K., 2003 [47]	197	823	22–95	-	-	CT, MRI
Telman G., 2017 [48]	974	-	18–101	59.8	-	CT, MRI
Toyoda K., 2018 [49]	-	2965	74.1	-	60.5**	CT, MRI
van Donkelaar C.E., 2018 [50]	1535	-	56	38	-	CT
Vodonos A., 2017 [51]	-	1174	73.8	-	56.6**	-
Zhong H., 2018 [52]	421	1115	54	-	-	CT, MRI

Note: HI is hemorrhagic stroke, IS is ischemic stroke, HCSR is Harvard Cooperative Stroke Registry; WHOC is World Health Organization Criteria; MRI is Magnetic Resonance Imaging; CT is Computed Tomography; * means statistics are presented separately for groups of different ages, ** means statistics are presented separately for men and women, (-) means no information available.

In total, 36,097 cases of HS were analyzed without considering sex or age, as well as 10,489 cases in men and 14,866 in women; 606 cases in young and middle-aged people; 708 in old people (over 65 years old). Although the results of studies that present HS statistics separately for men and women indicate that HS occurred more often in women, the overall statistics of all selected studies gives evidence that HS occurred with the same frequency in men and women. A meta-analysis of the seasonal dynamics of HS showed that the HS risk is less likely in a warmer season compared to a colder one (Table 2, Fig. 1). On average, the minimum probability of HS was in summer, and the maximum was in winter (Table 2). In men, HS risk was the highest in winter and spring; in women, in winter (Table 2, Fig. 1). Dependence of HS risk on a decrease in air temperature was the same in men and women (Fig. 1). According to the results of three studies, old age increased HS risk on average by 14 % in all seasons (Table 3). In people over 65 years of age, there was a significant dependence of the increase in HS risk on a decrease in air temperature. In the younger group, there was no such dependence; on the contrary, HS risk was higher in spring and autumn than in winter (Table 2, Fig. 2).

In total, 165,196 cases of IS were analyzed without considering sex or age, as well as 40,838 cases in men and 40,809 in women, 3585 cases in young and middle-aged people and 7133 in old people (over 65 years old). Although the publication [45] presents the seasonal dynamics of IS events for sex and age groups, we did not use it due to the obvious error of the authors in the calculations. The conducted meta-analysis showed that, on average, the minimum probability of IS occurs in autumn (Table 3). IS occurred with approximately the same frequency in men and women. A significant increase in the risk of IS in winter compared with other seasons was observed in women, but not in men (Fig. 1). In addition, there was a tendency (P = 0.08) for women to have increased IS risk in summer compared with autumn and spring (Fig. 1). According to the results of three studies, IS risk increased with age by approximately 2 times in all seasons. In the group of people older than 65 years, the severity of the seasonal dynamics of IS risk in winter compared to other seasons was slightly higher than in people younger than 65 years (Table 3, Fig. 2). However, dependence of IS risk on a decrease in air temperature did not significantly increase in people with aging (Fig. 2).

Table 2

Dependence of hemorrhagic stroke risk on a season

Compared seasons		Number of studies	Total	Odds ratio	I^2, %	Overall effect test	
Season 1 / total	Season 2 / total					Z	P
Hemorrhagic stroke (all)							
winter / 9611	summer / 8223	22	36,097	1.40 [1.25, 1.56]	81	5.98	0.00001
winter / 9611	spring / 9245	22	36,097	1.10 [1.02, 1.18]	62	2.34	0.02
winter / 9611	autumn / 9018	22	36,097	1.14 [1.04, 1.26]	74	2.82	0.005
autumn / 9018	summer / 8223	22	36,097	1.20 [1.12, 1.27]	38	5.55	0.00001
spring / 9245	summer / 8223	22	36,097	1.26 [1.16, 1.36]	59	5.78	0.00001
spring / 9245	autumn / 9018	22	36,097	1.04 [0.97, 1.12]	49	1.20	0.23
Hemorrhagic stroke (men)							
winter / 2674	summer / 2478	8	10,489	1.29 [0.99, 1.67]	82	1.86	0.06
winter / 2674	spring / 2752	8	10,489	1.04 [0.86, 1.25]	66	0.39	0.70
winter / 2674	autumn / 2585	8	10,489	1.21 [0.97, 1.52]	75	1.67	0.10
autumn / 2585	summer / 2478	8	10,489	1.06 [0.99, 1.13]	0	1.73	0.08
spring / 2752	summer / 2478	8	10,489	1.15 [1.08, 1.22]	0	4.36	0.0001
spring / 2752	autumn / 2585	8	10,489	1.09 [1.02, 1.16]	0	2.64	0.008

End of the Table 2

Compared seasons		Number of studies	Total	Odds ratio	I², %	Overall effect test	
Season 1 / total	Season 2 / total					Z	P
Hemorrhagic stroke (women)							
winter / 3967	summer / 3470	8	14,866	1.25 [1.04, 1.49]	60	2.42	0.02
winter / 3967	spring / 3723	8	14,866	1.08 [0.98, 1.18]	13	1.59	0.11
winter / 3967	autumn / 3706	8	14,866	1.17 [0.96, 1.42]	68	1.54	0.12
autumn / 3706	summer / 3470	8	14,866	1.10 [0.99, 1.22]	18	1.82	0.07
spring / 3723	summer / 3470	8	14,866	1.15 [0.99, 1.35]	48	1.82	0.07
spring / 3723	autumn / 3706	8	14,866	1.04 [0.94, 1.15]	20	0.71	0.48
Hemorrhagic stroke (people under 65 y.o.)							
winter / 134	summer / 134	3	606	1.00 [0.75, 1.32]	2	0.01	0.99
winter / 134	spring / 170	3	606	0.73 [0.55, 0.98]	4	2.13	0.03
winter / 134	autumn / 168	3	606	0.74 [0.57, 0.96]	0	2.25	0.02
autumn / 168	summer / 134	3	606	1.19 [0.73, 1.96]	43	0.71	0.48
spring / 170	summer / 134	3	606	1.19 [0.75, 1.89]	37	0.73	0.47
spring / 170	autumn / 168	3	606	1.02 [0.79, 1.31]	0	0.13	0.89
Hemorrhagic stroke (people over 65 y.o.)							
winter / 202	summer / 138	3	708	1.65 [1.29, 2.11]	0	3.96	0.0001
winter / 202	spring / 179	3	708	1.18 [0.93, 1.49]	0	1.37	0.17
winter / 202	autumn / 189	3	708	1.23 [0.79, 1.94]	28	0.91	0.36
autumn / 189	summer / 138	3	708	1.50 [1.17, 1.93]	0	3.20	0.001
spring / 179	summer / 138	3	708	1.40 [1.09, 1.80]	0	2.60	0.009
spring / 179	autumn / 189	3	708	0.93 [0.73, 1.18]	0	0.61	0.54

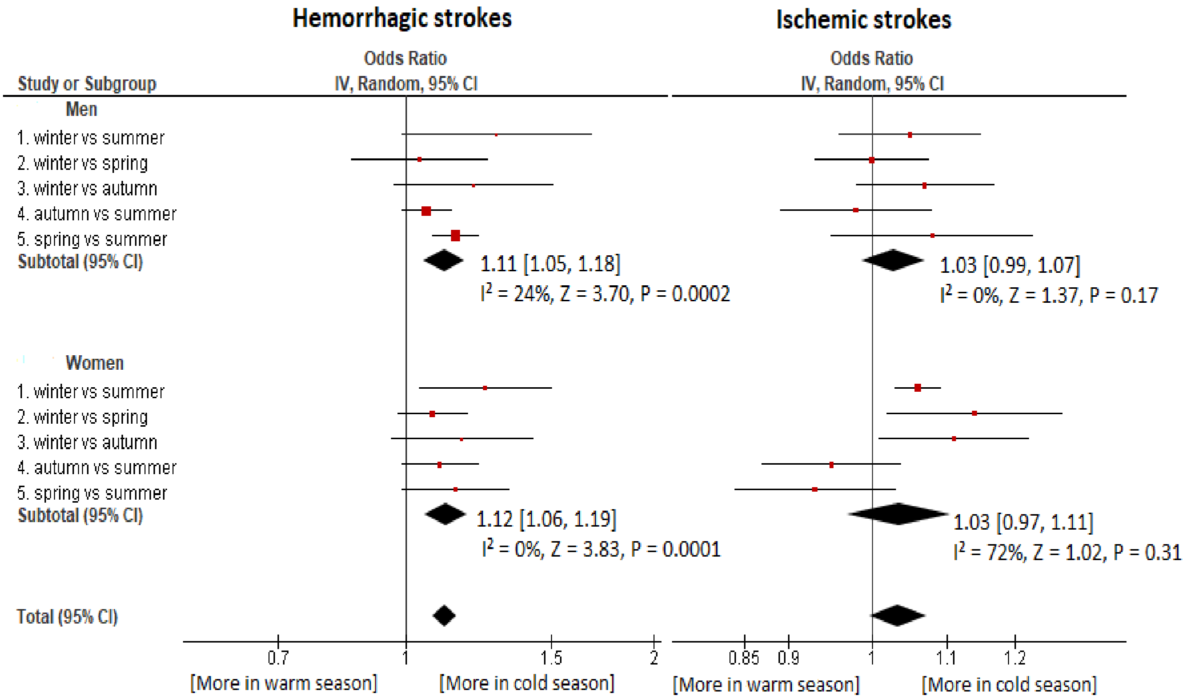

Figure 1. Dependence of strokes risk on a decrease in air temperature for men and women

Table 3

Dependence of ischemic stroke risk on a season

Compared seasons		Number of studies	Total	Odds ratio	I^2, %	Overall effect test	
Season 1 / total	Season 2 / total					Z	P
Ischemic stroke (all)							
winter / 40080	summer / 42247	28	165,196	0.97 [0.90, 1.04]	93	0.81	0.42
winter / 40080	spring / 42467	28	165,196	1.01 [0.94, 1.10]	94	0.35	0.73
winter / 40080	autumn / 40402	28	165,196	1.05 [1.00, 1.11]	82	2.01	0.04
autumn / 40402	summer / 42247	28	165,196	0.91 [0.85, 0.98]	91	2.65	0.008
spring / 42467	summer / 42247	28	165,196	0.96 [0.89, 1.03]	92	1.11	0.27
spring / 42467	autumn / 40402	28	165,196	1.06 [0.97, 1.15]	94	1.32	0.19
Ischemic stroke (men)							
winter / 10284	summer / 10096	11	40,838	1.05 [0.96, 1.15]	78	1.07	0.29
winter / 10284	spring / 10049	11	40,838	1.00 [0.93, 1.08]	66	0.08	0.94
winter / 10284	autumn / 10409	11	40,838	1.07 [0.98, 1.18]	77	1.53	0.13
autumn / 10409	summer / 10096	11	40,838	0.98 [0.89, 1.08]	81	0.43	0.67
spring / 10049	summer / 10096	11	40,838	1.08 [0.95, 1.23]	90	1.15	0.25
spring / 10049	autumn / 10409	11	40,838	1.11 [0.98, 1.25]	88	1.64	0.10
Ischemic stroke (women)							
winter / 10501	summer / 10047	11	40,809	1.06 [1.03, 1.09]	0	3.66	0.0003
winter / 10501	spring / 9961	11	40,809	1.14 [1.02, 1.26]	80	2.40	0.02
winter / 10501	autumn / 10300	11	40,809	1.11 [1.01, 1.21]	73	2.16	0.03
autumn / 10300	summer / 10047	11	40,809	0.95 [0.87, 1.05]	76	0.96	0.34
spring / 9961	summer / 10047	11	40,809	0.93 [0.84, 1.04]	82	1.26	0.21
spring / 9961	autumn / 10300	11	40,809	0.98 [0.89, 1.08]	78	0.41	0.68
Ischemic stroke (people under 65 y.o.)							
winter / 937	summer / 830	3	3585	1.04 [0.69, 1.58]	77	0.21	0.84
winter / 937	spring / 945	3	3585	0.94 [0.76, 1.17]	36	0.55	0.58
winter / 937	autumn / 873	3	3585	1.10 [0.99, 1.22]	0	1.74	0.08
autumn / 873	summer / 830	3	3585	1.01 [0.73, 1.40]	64	0.07	0.95
spring / 945	summer / 830	3	3585	1.20 [0.74, 1.95]	84	0.73	0.46
spring / 945	autumn / 873	3	3585	1.11 [1.00, 1.24]	1	1.89	0.06
Ischemic stroke (people over 65 y.o.)							
winter / 1828	summer / 1721	3	7133	1.30 [0.95, 1.77]	78	1.66	0.10
winter / 1828	spring / 1788	3	7133	1.21 [0.91, 1.61]	75	1.29	0.20
winter / 1828	autumn / 1796	3	7133	1.57 [0.89, 2.76]	93	1.56	0.12
autumn / 1796	summer / 1721	3	7133	0.92 [0.69, 1.23]	71	0.55	0.58
spring / 1788	summer / 1721	3	7133	1.05 [0.97, 1.14]	0	1.30	0.19
spring / 1788	autumn / 1796	3	7133	1.16 [0.85, 1.58]	75	0.95	0.34

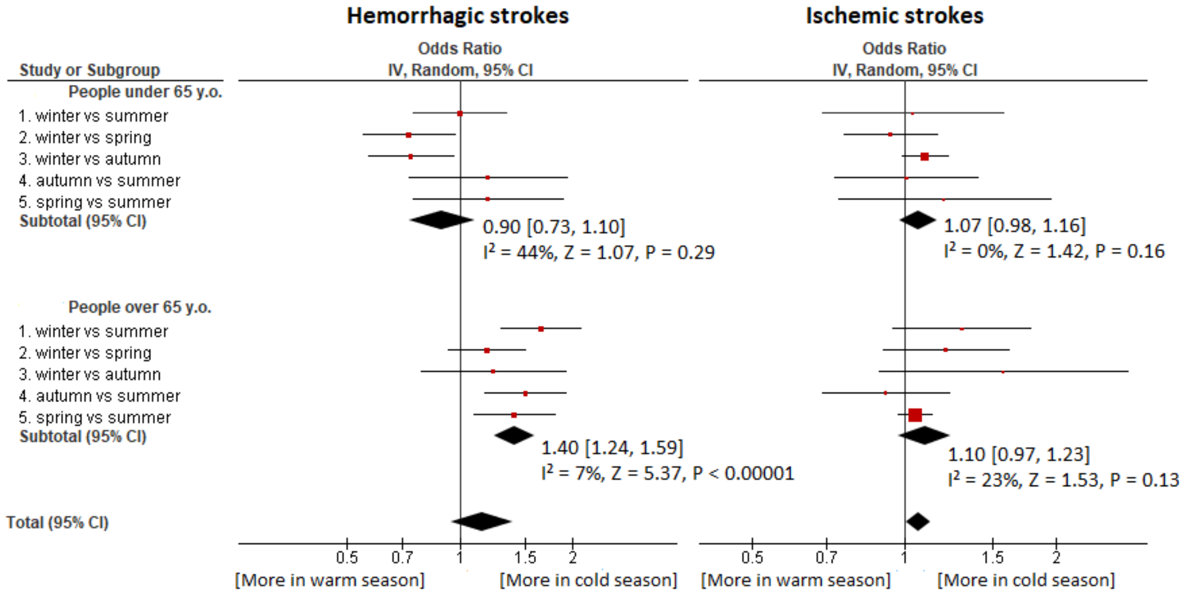

Figure 2. Dependence of strokes risk on a decrease in air temperature for people of different age groups

Age dependence of seasonal stroke risk needs further research due to the small number of studies included in the meta-analysis. Although formally a meta-analysis can be carried out if there are two studies, but, with an increase in the number of studies, the statistical power of the meta-analysis increases, which is especially important when the results tend to be significantly heterogenic [53].

Discussion. High BP is a well-known major factor that can provoke stroke. The seasonal dynamics of HS risk completely coincides with the seasonal dynamics of BP. HS risk and BP level are higher in the cold season compared with the warmer one [5]. In addition to high BP, IS are associated with narrowing and blockage of the arteries, usually as a result of thrombosis or atherosclerosis. Therefore, factors that enhance thrombosis and ischemia will also provoke IS. It has been established that hemoconcentration and lipid profile indicators are maximum in winter [8, 9]. On the other hand, according to the results of our previous meta-analysis, the seasonal dynamics of IS depends on climate of a region [18]. In regions where there was a significant decrease in atmospheric pressure and partial oxygen density in the air and an increase in relative humidity in summer, IS risk at this season increased significantly compared with winter, despite low values of BP, hematocrit and cholesterol in summer. In a climate without significant annual fluctuations in atmospheric pressure and with wet winter, the seasonal dynamics of IS was not pronounced or slightly shifted to winter [18]. According to the results of all publications included in the meta-analysis, the minimum risk of IS was on average in autumn.

Our meta-analysis showed that stroke occurs with approximately the same frequency in men and women, but sex brings nuances to the seasonal dynamics of stroke risk. HS risk was the highest in winter and spring for men, and in winter for women. In addition, the seasonal dynamics of IS (with a maximum risk in winter and a minimum in summer) was expressed in women, but not in men. Seasonal dynamics of levels of sex hormones, which have a protective effect on CVE [54], can also affect the seasonal CVE risk. Testosterone levels in men have been found to be at their lowest in spring [10], which may explain the increased HS risk in men during this season. It is known that there is an inverse relationship between testosterone levels and BP [55]. In women of reproductive age, estrogen levels decrease with a short day and increase with a long day [56, 57]. Melatonin is known to produce an anti-estrogenic effect by inhibiting the aromatase enzyme, which is involved in the synthesis of estrogens from androgenic precursors [58]. In addition, women show a greater dependence between a risk of stroke and abdominal obesity, elevated BP and glucose levels [59–61]. Also, women have been shown to cool faster than men [62]. These reasons may be responsible for the greater winter risk of strokes in women. At the same time, there are observations that women tolerate heat worse than men, in particular, due to a lower level of sweating [63]. Also, women have more pronounced physiological responses to hypoxia [64]. According to our meta-analysis, a trend towards an increased IS risk in summer compared with spring and autumn was observed in women, but not in men.

The meta-analysis has shown that the overall risk of stroke increases in older people, especially the incidence of IS. In addition, HS risk in the group of people older than 65 years increased with decreasing air temperature. In people younger than 65 years, HS risk was not associated with cold. The increase in IS risk in winter compared with other seasons was also slightly greater in the group of older people; however, a decrease in temperature equally increased IS risk in both age groups. Old age is known to be associated with increased BP reactivity to fluctuations in air temperature [13]. Studies have shown that fluctuations in air temperature are more likely to cause strokes in elderly than in young people [65, 66]. On the other hand, according to A.H. Nave et al. (2015) [67], an increase in the level of lipoproteins, as a risk factor for IS, is most relevant for young people.

Prevention of the seasonal risk of stroke should be aimed at minimizing, on the one hand, uncomfortable external conditions (heating, air conditioning, clothing, etc.), and, on the other hand, seasonal changes in the functioning of the body. For the latter, both adherence to a proper lifestyle (moderate nutrition, sufficient fluid intake, physical activity) and drug correction of blood pressure, lipid profile, glucose, and blood viscosity are important. The prevention of seasonal risk of IS is especially in need of research, since IS constitutes the bulk of all strokes. In addition, the seasonal IS risk is often not associated with seasonal increase in BP, lipid profile, and hematocrit, but is associated with hypoxic conditions in summer, which are typical, for example, for East Asia [5, 8, 9, 18]. In this case, an excessive medical decrease in BP in summer may not improve the condition of patients, but, on the contrary, worsen it. It is known that IS can provoke both rise and fall in BP [68]. Many researchers note that the regimen and dosage of antihypertensive drugs need seasonal adjustment [69, 70]. According to the results of our meta-analysis, fluctuations in air temperature are the most dangerous in relation to the risk of stroke for women and people over 65.

Conclusions:

1. HS risk is less likely in a warmer season compared with a colder one. In men, HS risk was the highest in winter and spring; in women, in winter. Dependence of HS risk on a decrease in air temperature is the same in men and women.
2. On average, the minimum probability of IS occurs in autumn. In winter, IS risk in women was significantly higher compared to other seasons. In men, the seasonal dynamics of IS was not expressed.
3. In older people, the overall risk of stroke increased, especially IS. In people over 65 years of age, there was a significant dependence of an increase in HS risk on a decrease in air temperature. In people younger than 65 years, HS risk was not associated with cold. A decrease in temperature equally increased IS risk in both age groups.

Funding. The work was granted financial support from the State Assignment 056-00119-22-00.

Competing interests. The authors declare no competing interests.

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Received: 01.12.2022
Approved: 18.03.2023
Accepted for publication: 25.03.2023