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Уровень эстрогенов и риск сердечно-сосудистых событий у женщин пожилого и старческого возраста

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АННОТАЦИЯ

Обоснование. Эстрогены играют важную роль в физиологии репродуктивной, сердечно-сосудистой, скелетной и центральной нервной систем. Однако данные литературы по влиянию уровня эстрогенов на риск сердечно-сосудистых событий в пожилом и старческом возрасте противоречивы.

Цель — оценить влияние уровня эстрогенов на частоту инфаркта миокарда и острого нарушения мозгового кровообращения у женщин пожилого и старческого возраста.

Материалы и методы. Поперечное когортное исследование «Хрусталь» случайной выборки женщин в возрасте 65 лет и старше (n = 280). Основные методы: опрос и анализ медицинской документации для получения данных о сопутствующих хронических заболеваниях, лабораторные тесты (исследованы эстрадиол, тиреотропный гормон, гликированный гемоглобин, общий белок, альбумин, липидограмма, С-реактивный белок, клинический анализ крови, креатинин).

Результаты. Острое нарушение мозгового кровообращения в анамнезе зафиксировано у 18,9 % (n = 54) обследованных, инфаркт миокарда — у 11,9 % (n = 34). Острое нарушение мозгового кровообращения у лиц с уровнем эстрадиола выше 4-го квинтеля (более 55 пмоль/л) после поправки на возраст и уровень холестерина липопротеинов высокой плотности регистрировали в 2,5 раза чаще (отношение шансов 2,480; 95 % доверительный интервал 1,180–5,211), инфаркт миокарда — в 2 раза чаще (отношение шансов 2,003; 95 % доверительный интервал 1,088–3,687).

Заключение. Уровень эстрадиола более 55 пмоль/л является независимым фактором риска развития острого нарушения мозгового кровообращения и инфаркта миокарда у женщин в возрасте 65 лет и старше.

Ключевые слова: эстрогены; смертность; пожилые; инфаркт миокарда; инсульт.

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Estrogen levels and the risk of cardiovascular events in older women

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ABSTRACT

BACKGROUND: Estrogens play a crucial role in the functioning of the reproductive, cardiovascular, skeletal, and central nervous systems. However, existing literature on the correlation between estrogen levels and the risk of cardiovascular events in elderly populations is limited and contradictory.

AIM: To assess the effect of estrogen levels on the incidence of myocardial infarction and stroke in older women.

MATERIALS AND METHODS: The Crystal study was a population-based cross-sectional cohort study which included community-dwelling individuals aged 65 and older (n = 280). Key study parameters included survey responses and medical record analysis for non-communicable chronic diseases, alongside laboratory assessments for estradiol, thyroid-stimulating hormone, glycated hemoglobin, total protein, albumin, lipid panel, C-reactive protein, complete blood count, and creatinine levels.

RESULTS: A history of stroke was recorded in 18.9% (n = 54) of participants, while myocardial infarction was reported in 11.9% (n = 34). In participants with estradiol levels in the 4th quintile (>55 pmol/l), stroke incidence was 2.5 times higher (odds ratio 2.480; 95% confidence interval 1.180–5.211) and myocardial infarction incidence was 2 times higher (odds ratio 2.003; 95% confidence interval 1.088–3.687) after adjustments for age and high-density lipoprotein levels.

CONCLUSIONS: An estradiol level greater than 55 pmol/l is an independent risk factor for the development of stroke and myocardial infarction in women aged 65 years and older.

Keywords: estrogens; mortality; older adults; myocardial infarction; stroke.

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BACKGROUND

Estrogens play a significant role in the physiology of the reproductive, cardiovascular, skeletal, and central nervous systems. The onset of menopause is characterized by a decline in the ovarian function followed by the development of endogenous estrogen deficiency. Since endogenous estrogens have a beneficial effect on lipoprotein levels, hemostasis, and vasomotor function, researchers hypothesize that decreased estrogen levels are associated with an increased risk of developing cardiovascular disease. However, despite the undeniable benefits of estrogens in maintaining women's health, the evidence regarding its impact on the incidence of myocardial infarction (MI) and stroke remains inconclusive.

Statistical data indicates that approximately 55,000 additional stroke-related deaths occur annually in women compared to men [1]. Globally, the lifetime risk of stroke (starting at the age of 25) is 25.1% in women and 24.7% in men [2]. Additionally, there are gender-based differences in the forms of stroke, with a higher prevalence and incidence of intracranial aneurysms and subarachnoid hemorrhages in women and a higher incidence of hemorrhagic strokes in men.

Recent data from Canada indicate that the risk of developing stroke is higher in women under the age of 30, higher in men in middle age, and equal in men and women over the age of 80 [3]. Concerning the oldest age category (over 85 years), studies indicate that women are more susceptible to stroke than men [1]. The gender differences in the incidence of stroke across age groups can be attributed to the higher life expectancy observed in women, as well as the fluctuating levels of estrogen throughout the menstrual cycle and the subsequent decline in estrogen levels at the onset of menopause. Nevertheless, the latter has been challenged by recent studies in both animals and humans, particularly the Women's Health Initiative, which have indicated a negative impact of estrogen hormone replacement therapy on the risk of stroke in women [4, 5]. Furthermore, although the incidence of stroke is higher in men, women who experience a stroke have a higher mortality rate, poorer recovery, and a higher risk of disability [6]. The latest studies have demonstrated that women with higher postmenopausal estrogen levels are at an increased risk of developing a stroke itself, as well as its severity [7, 8].

Coronary heart disease, and MI in particular, is another common cause of death among women worldwide[1]. In elderly women, its incidence is lower than in men, with a tendency to manifest 5–10 years after the onset of menopause [9].

The lower incidence of coronary heart disease in women than in men, particularly during the reproductive years, is frequently attributed to the cardioprotective function of female sex hormones. Experimental studies show that the major circulating female hormone estrogen has multiple cardioprotective properties, including the reduction of fibrosis and oxidative stress, the stimulation of angiogenesis and vasodilation, and the enhancement of mitochondrial function [9]. However, the use of hormone replacement therapy in postmenopausal women has been observed to exert a negligible impact on the reduction of the risk of MI, particularly in women who initiated treatment within the first 10 years following the onset of menopause [9].

Moreover, clinical trials of the efficacy of hormone replacement therapy in postmenopausal women have failed to show its positive effect on the risk of cardiovascular disease and have rather suggested an increased risk of stroke and venous thromboembolic events. Those who started therapy less than 10 years after menopause had low risk scores for coronary heart disease and all-cause mortality, but remained at an increased risk of venous thromboembolic events [10].

The study aimed to assess the effect of estradiol levels on the risk of developing stroke and MI in elderly and old-age women.

MATERIALS AND METHODS

This paper presents the findings of a cross-sectional study based on the second screening of the prospective cohort study, Crystal [11], with a random sample of women aged 65 years and older (n = 280).

Main methods:

- Interview and analysis of medical records to obtain data on non-communicable chronic diseases;
- Laboratory tests (estradiol, thyroid-stimulating hormone, glycated hemoglobin, total protein, albumin, lipid profile, C-reactive protein, complete blood count, and creatinine).

SPSS 20.0 software (SPSS Inc., USA) was used for the statistical analysis. The mean and standard deviation ($M \pm SD$) were determined for continuous data with normal distribution, whereas the median and interquartile range [Me (IQR)] were determined for data with non-normal distribution. The Mann–Whitney U test and the χ^2 test were used to assess between-group differences. Multivariate analysis using logistic regression was conducted to assess the association between estradiol levels and the stroke and MI risk of developing. The critical significance limit was set at p = 0.05.

RESULTS

The study involved 286 women aged 67 to 94 years. The mean age was 78.3 ± 6.1 years. A history of stroke was documented in 18.9% (n = 54) of the subjects, while a history of MI was present in 11.9% (n = 34). The group

[1] GBD Compare Data Visualization. 2019. Available from: http://vizhub.healthdata.org/gbd-compare. Date of access: 14.07.2024.

with a history of stroke or MI exhibited higher estradiol levels ($p < 0.05$) (Tables 1, 2). Additionally, triglyceride levels were higher ($p < 0.05$) in women with a history of stroke (Table 1). The data revealed a significant correlation between lower values of high-density lipoprotein (HDL) cholesterol and a history of MI ($p < 0.05$) (Table 2). However, no other statistically significant differences were observed in the analyzed clinical and demographic characteristics between women with a history of stroke and/or MI and those without a history of such diseases ($p > 0.05$) (Tables 1, 2).

After adjustment for age, subjects with estradiol levels above the 4th quintile (>55 pmol/L) were 2 times more

Table 1. Clinical and demographic indicators of study participants with and without a history of stroke

Таблица 1. Клинико-демографические показатели обследованных с наличием и отсутствием острого нарушения мозгового кровообращения в анамнезе

Parameters	No stroke (*n* = 232)	History of stroke (*n* = 54)	*p*-value
Demographic characteristics			
Age, mean, and standard deviation, years	77.4 ± 5.7	78.5 ± 6.1	$p > 0.05$
Smoking:			
• Never smoked, *n* (%)	179 (96.8)	35 (97.2)	$p > 0.05$
• Smokers, *n* (%)	1 (0.5)	–	
• Quit smoking, *n* (%)	5 (2.7)	1 (2.8)	
Frequency of detection of chronic non-communicable diseases			
Atrial fibrillation, *n* (%)	101 (43.5)	21 (38.9)	$p > 0.05$
Myocardial infarction, *n* (%)	22 (9.5)	12 (22.2)	$p < 0.05$
Coronary heart disease, *n* (%)	50 (92.6)	210 (90.5)	$p > 0.05$
Blood pressure:			
• Optimal, *n* (%)	16 (6.9)	1 (1.9)	
• High normal, *n* (%)	26 (11.2)	6 (11.1)	
Hypertension:			$p > 0.05$
• Grade I, *n* (%)	96 (41.4)	20 (37.0)	
• Grade II, *n* (%)	59 (25.4)	17 (31.5)	
• Grade III, *n* (%)	35 (15.1)	10 (18.5)	
Atherosclerosis obliterans of the lower extremities, *n* (%)	97 (41.8)	21 (38.9)	$p > 0.05$
Diabetes mellitus, *n* (%)	57 (24.6)	9 (16.7)	$p > 0.05$
Chronic obstructive pulmonary disease, *n* (%)	38 (16.4)	5 (9.3)	$p > 0.05$
Bronchial asthma, *n* (%)	18 (7.8)	1 (1.9)	$p > 0.05$
Cancer, *n* (%)	12 (5.2)	4 (7.4)	$p > 0.05$
Body mass index:			
• <18,5 kg/m^2, *n* (%)	2 (0.9)	–	
• 18,5–24,9 kg/m^2, *n* (%)	38 (16.4)	11 (20.4)	
• 25–29,9 kg/m^2, *n* (%)	88 (37.9)	22 (40.7)	$p > 0.05$
• 30–34,9 kg/m^2, *n* (%)	71 (30.6)	11 (20.4)	
• 35–39,9 kg/m^2, *n* (%)	26 (11.2)	7 (13.0)	
• ≥40 kg/m^2, *n* (%)	7 (3.0)	3 (5.6)	
Laboratory parameters			
Anemia, *n* (%)	57 (24.8)	11 (20.4)	$p > 0.05$
C-reactive protein level >5 g/L, *n* (%)	47 (20.3)	11 (20.4)	$p > 0.05$
Total cholesterol, *Me* (*IQR*), mmol/L	5.7 (5.0–6.6)	6.1 (5.2–6.9)	$p > 0.05$
LDL cholesterol, *Me* (*IQR*), mmol/L	3.7 (3.0–4.4)	3.9 (3.4–4.5)	$p > 0.05$
HDL cholesterol, *Me* (*IQR*), mmol/L	1.4 (1.2–1.6)	1.4 (1.0–1.6)	$p > 0.05$
Triglycerides, *Me* (*IQR*), mmol/L	1.2 (0.9–1.7)	1.5 (1.0–2.0)	$p < 0.05$
Glycated hemoglobin, *Me* (*IQR*), %	5.7 (5.4–6.1)	5.7 (5.5–6.0)	$p > 0.05$
Thyroid-stimulating hormone, *Me* (*IQR*), μIU/mL	2.0 (1.2–3.2)	1.7 (1.0–3.2)	$p > 0.05$
GFR (CKD-EPI) <60 mL/min/1.73 m^2, *n* (%)	42 (18.1)	11 (20.4)	$p > 0.05$
Estradiol, *Me* (*IQR*), pmol/L	48.0 (37.0–65.0)	37.0 (57.0–86.5)	$p < 0.05$

Note: *Me* (*IQR*), median and interquartile range; GFR (CKD-EPI), glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration Formula.

Table 2. Clinical and demographic indicators of study participants with and without a history of myocardial infarction

Таблица 2. Клинико-демографические показатели обследованных с наличием и отсутствием инфаркта миокарда в анамнезе

Parameters	No MI (*n* = 252)	History of MI (*n* = 34)	*p*-value
Demographic characteristics			
Age, mean, and standard deviation, years	77.5 ± 5.8	78.2 ± 5.5	$p > 0.05$
Smoking:			
• Never smoked, *n* (%)	188 (96.4)	26 (100)	$p > 0.05$
• Smokers, *n* (%)	1 (0.5)	–	
• Quit smoking, *n* (%)	6 (3.1)	–	
Frequency of detection of chronic non-communicable diseases			
Atrial fibrillation, *n* (%)	100 (39.7)	22 (64.7)	$p < 0.05$
Stroke, *n* (%)	42 (16.7)	12 (35.3)	$p < 0.05$
Coronary heart disease, *n* (%)	226 (89.7)	34 (100.0)	$p < 0.05$
Blood pressure:			
• Optimal, *n* (%)	16 (6.3)	1 (2.9)	
• High normal, *n* (%)	28 (11.1)	4 (11.8)	
Hypertension:			$p > 0.05$
• Grade I, *n* (%)	99 (39.3)	17 (50.0)	
• Grade II, *n* (%)	69 (27.4)	7 (20.6)	
• Grade III, *n* (%)	40 (15.9)	5 (14.7)	
Atherosclerosis obliterans of the lower extremities, *n* (%)	102 (40.5)	16 (47.1)	$p > 0.05$
Diabetes mellitus, *n* (%)	39 (15.5)	8 (23.5)	$p > 0.05$
Chronic obstructive pulmonary disease, *n* (%)	40 (15.9)	3 (8.8)	$p > 0.05$
Bronchial asthma, *n* (%)	15 (6.0)	4 (11.8)	$p > 0.05$
Cancer, *n* (%)	14 (5.6)	2 (5.9)	$p > 0.05$
Body mass index:			
• <18,5 kg/m^2, *n* (%)	1 (0.4)	1 (2.9)	
• 18,5–24,9 kg/m^2, *n* (%)	40 (15.9)	9 (26.5)	
• 25–29,9 kg/m^2, *n* (%)	100 (39.7)	10 (29.4)	$p > 0.05$
• 30–34,9 kg/m^2, *n* (%)	72 (28.6)	10 (29.4)	
• 35–39,9 kg/m^2, *n* (%)	30 (11.9)	3 (8.8)	
• ≥40 kg/m^2, *n* (%)	9 (3.6)	1 (2.9)	
Laboratory parameters			
Anemia, *n* (%)	64 (25.6)	4 (11.8)	$p > 0.05$
C-reactive protein level >5 g/L, *n* (%)	54 (21.5)	4 (11.8)	$p > 0.05$
Total cholesterol, *Me* (*IQR*), mmol/L	5.7 (5.0–6.6)	6.0 (5.1–6.9)	$p > 0.05$
LDL cholesterol, *Me* (*IQR*), mmol/L	3.7 (3.1–4.4)	4.0 (3.0–4.4)	$p > 0.05$
HDL cholesterol, *Me* (*IQR*), mmol/L	1.4 (1.2–1.6)	1.3 (1.1–1.7)	$p > 0.05$
Triglycerides, *Me* (*IQR*), mmol/L	1.3 (0.9–1.7)	1.4 (0.9–1.9)	$p > 0.05$
Glycated hemoglobin, *Me* (*IQR*), %	5.7 (5.6–6.0)	5.8 (5.3–6.2)	$p > 0.05$
Thyroid-stimulating hormone, *Me* (*IQR*), μIU/mL	1.9 (1.2–3.2)	1.9 (1.0–3.9)	$p > 0.05$
GFR (CKD-EPI) <60 mL/min/1.73 m^2, *n* (%)	47 (18.7)	6 (17.6)	$p > 0.05$
Estradiol, *Me* (*IQR*), pmol/L	47.0 (37.0–66.0)	58.6 (41.1–84.7)	$p < 0.05$

Note: *Me* (*IQR*), median and interquartile range; GFR (CKD-EPI), glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration Formula.

likely to have stroke (odds ratio [OR]: 2.148; 95% confidence interval [CI]: 1.180–3.911) than those with estradiol levels below the 4th quintile, and 2.5 times more likely to have MI (OR: 2.516; 95% CI: 1.203–5.264).

Subjects with high estradiol levels were older and more likely to have lower HDL levels ($p < 0.05$) (Table 3). These differences between the two groups could have influenced the stroke and MI higher risk in the group with high estradiol levels. However, the stroke and MI risk remained elevated in the group of respondents with estradiol levels above 55 pmol/L after adjusting for HDL levels and age, with ORs and 95% CIs of 2.480 (1.180–5.211) versus 2.003 (1.088–3.687).

Table 3. Clinical and demographic indicators of study participants with estradiol levels greater and less than 55 pmol/l

Таблица 3. Клинико-демографические показатели участников исследования с уровнем эстрадиола больше и меньше 55 пмоль/л

Parameters	Estradiol ≤55 pmol/L (*n* = 175)	Estradiol >55 pmol/L (*n* = 114)	*p*-value
Demographic characteristics			
Age, mean, and standard deviation, years	76.9 ± 5.7	78.5 ± 5.8	$p < 0.05$
Smoking:			
• Never smoked, *n* (%)	142 (95.9)	73 (97.3)	$p > 0.05$
• Smokers, *n* (%)	1 (0.7)	–	
• Quit smoking, *n* (%)	5 (3.4)	2 (2.7)	
Frequency of detection of chronic non-communicable diseases			
Atrial fibrillation, *n* (%)	68 (38.9)	54 (49.1)	$p > 0.05$
Myocardial infarction, *n* (%)	14 (8.0)	20 (18.2)	$p < 0.05$
Stroke, *n* (%)	25 (14.3)	29 (26.4)	$p > 0.05$
Coronary heart disease, *n* (%)	161 (92.0)	98 (89.1)	$p > 0.05$
Blood pressure:			
• Optimal, *n* (%)	12 (6.9)	5 (4.5)	
• High normal, *n* (%)	14 (8.0)	18 (16.4)	
Hypertension:			$p > 0.05$
• Grade I, *n* (%)	70 (40.0)	45 (40.9)	
• Grade II, *n* (%)	57 (32.6)	19 (17.3)	
• Grade III, *n* (%)	22 (12.6)	23 (20.9)	
Atherosclerosis obliterans of the lower extremities, *n* (%)	74 (42.3)	45 (40.5)	$p > 0.05$
Diabetes mellitus, *n* (%)	34 (19.4)	31 (28.2)	$p > 0.05$
Chronic obstructive pulmonary disease, *n* (%)	29 (16.6)	14 (12.7)	$p > 0.05$
Bronchial asthma, *n* (%)	11 (6.3)	8 (7.3)	$p > 0.05$
Cancer, *n* (%)	14 (8.0)	2 (1.8)	$p > 0.05$
Body mass index:			
• <18,5 kg/m^2, *n* (%)	–	2 (1.8)	
• 18,5–24,9 kg/m^2, *n* (%)	26 (14.9)	23 (20.5)	
• 25–29,9 kg/m^2, *n* (%)	73 (41.7)	37 (33.0)	$p > 0.05$
• 30–34,9 kg/m^2, *n* (%)	55 (31.4)	28 (25.0)	
• 35–39,9 kg/m^2, *n* (%)	17 (9.7)	16 (14.3)	
• ≥40 kg/m^2, *n* (%)	4 (2.3)	6 (5.4)	
Laboratory parameters			
Anemia, *n* (%)	22 (19.3)	46 (26.6)	$p > 0.05$
C-reactive protein level >5 g/L, *n* (%)	28 (16.0)	30 (26.3)	$p > 0.05$
Total cholesterol, *Me* (*IQR*), mmol/L	5.8 (5.1–6.6)	5.7 (5.0–6.6)	$p > 0.05$
LDL cholesterol, *Me* (*IQR*), mmol/L	3.7 (3.1–4.4)	3.8 (3.0–4.3)	$p > 0.05$
HDL cholesterol, *Me* (*IQR*), mmol/L	1.4 (1.2–1.6)	1.3 (1.1–1.6)	$p < 0.05$
Triglycerides, *Me* (*IQR*), mmol/L	1.3 (1.0–1.7)	1.3 (0.9–1.8)	$p > 0.05$
Glycated hemoglobin, *Me* (*IQR*), %	5.7 (5.6–6.0)	5.8 (5.8–6.1)	$p > 0.05$
Thyroid-stimulating hormone, *Me* (*IQR*), μIU/mL	1.9 (1.2–3.4)	1.9 (1.1–3.0)	$p > 0.05$
GFR (CKD-EPI) <60 mL/min/1.73 m^2, *n* (%)	28 (16.0)	25 (21.9)	$p > 0.05$

Note: *Me* (*IQR*), median and interquartile range; GFR (CKD-EPI), glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration Formula.

Given that both MI and atrial fibrillation are risk factors for the development of stroke, an additional correction was made for a history MI and atrial fibrillation when assessing the impact of high estradiol levels on the stroke risk. Nevertheless, the risk of stroke development with high estradiol levels remained statistically significant even after correction for age, HDL level, and a history of MI and atrial fibrillation, with OR of 1.888 and 95% CI of 1.008–3.538.

DISCUSSION

High estrogen levels (>55 pmol/L) are an independent risk factor for the development of stroke and MI in the elderly and old-age subjects.

The results of the present study have been confirmed in other studies. In a prospective study of 9,704 women aged 65 years and older, the risk of stroke was also 2.3 times higher in women with estradiol levels above the 4th quartile who did not receive hormone replacement therapy during 8 years of follow-up than in those with estradiol levels in the lowest quartile [7]. Moreover, this association was most pronounced among older postmenopausal women with more prominent central obesity [7]. Similarly, an increased risk of stroke in women with high estradiol levels was also identified in the Rotterdam 10-year prospective observational study of individuals aged 45 years and older [12].

However, a study conducted in Rancho Bernardo (USA) involving 651 postmenopausal women found no association between estradiol levels and the risk of death from cardiovascular disease [13]. Similarly, a case–control study of 400 postmenopausal women in the Women's Health Study found no association between estradiol levels and cardiovascular risk, regardless of hormone replacement therapy [14]. Conversely, the Copenhagen Prospective Study of 4,716 women showed that extremely low concentrations of endogenous estradiol, rather than high levels, were associated with a greater risk of coronary heart disease and mortality [15]. In addition, there is evidence that women with earlier menopause have a higher risk of developing coronary heart disease [16]. However, there is an opposing view that it is cardiovascular disease that affects the timing of menopause and the decline in estradiol levels, not the other way around [17]. This is explained by the fact that the ovaries are highly vascularized organs, and their ischemic damage secondary to cardiovascular disease increases the risk of ovarian dysfunction and early menopause [17]. Furthermore, cardiovascular disease and early menopause share common risk factors, which may also explain the association between early menopause and higher cardiovascular risk [18]. This is indirectly supported by the evidence that obese women have lower blood levels of estradiol before menopause and conversely, higher estradiol levels after menopause than women with a normal body mass index [19].

The conflicting data from studies of the effect of estrogen levels on the risk of stroke and MI in postmenopausal women may be due to several factors.

17β-estradiol (E2) is the predominant and most biologically active estrogen. It is synthesized primarily by the ovaries. However, it is generally accepted that other organs and tissues, such as adipose tissue, various brain regions (neurons, astrocytes, and microglia), immune system cells, skin, skeletal muscle, vascular smooth muscle cells, and even bone, are also involved in estradiol synthesis [20]. Moreover, during postmenopause, the para-, auto-, and intracrine effects of estradiol in the tissues or cells begin to play a greater role than its systemic effects. Consequently, local estrogen concentrations may be high despite low circulating estradiol levels. In addition, despite the decrease in ovarian synthesis of estradiol, it is theoretically expected that its synthesis by other organs and tissues will be maintained during postmenopause and even increased in blood levels under certain conditions. Research indicates that central obesity is one of the factors that increases the level of endogenous estradiol in postmenopausal women [19]. Additionally, adipose tissue in postmenopausal women can account for approximately 100% of circulating estrogens in the blood [21]. Thus, the increased risk of cardiovascular complications in postmenopausal women with high estradiol levels may be largely due to its combination with central obesity and metabolic syndrome, whereas estradiol as such may not cause an increased risk of stroke and MI. This was indirectly confirmed in the study by J.S. Lee et al, where the risk of stroke in women with high estradiol levels became statistically insignificant after adjustment for body mass index and waist circumference [7]. Nevertheless, the risk of stroke was significantly higher with high estradiol levels, even after adjustment for HDL, low-density lipoprotein (LDL) cholesterol, total cholesterol, C-reactive protein, and diabetes mellitus [7]. In the present study, body mass index did not affect estradiol levels and the risk of developing stroke or MI, which may be partly due to the cross-sectional nature of the study and the weight loss of the subjects after these diseases.

The results of experimental studies demonstrate a direct effect of estradiol on the vascular system and the composition of atherosclerotic plaques, including processes such as lipid metabolism, inflammation, oxidative stress, fibrinolysis, and thrombosis [22–24]. The administration of estrogens has been demonstrated to reduce the levels of tumor necrosis factor alpha and interleukin-1 within plaques. These factors are pivotal in the development of atherosclerosis and key to instability of atherosclerotic plaques. Additionally, estrogen administration has been shown to decrease the levels of activated nuclear factor kappa B and matrix metalloproteinase-9 activity and to increase collagen content, which provides further atherosclerotic plaque stability [22]. Conversely, women with elevated endogenous estradiol levels are at an increased risk of intraplaque hemorrhage and, consequently, an elevated risk of cardiovascular events [23]. Additionally, estradiol has been observed to stimulate calcification in pre-existing atherosclerotic plaques by promoting the differentiation of vascular smooth muscle cells into osteoblast-like cells [23]. Furthermore, estradiol seems to enhance the overall blood supply to the atherosclerotic plaque,

thereby accelerating the progression of atherosclerosis and the onset of cardiovascular events [24].

Inflammation plays a significant role in the pathogenesis of many vascular diseases, including atherosclerosis and the response to acute vascular injury. It is postulated that estradiol exerts anti-inflammatory effects in addition to its cardio- and neuroprotective properties. However, under specific circumstances, the influence of estradiol may vary. The type of receptors activated, the target organ, and the duration of exposure to the damaging factor can all influence the outcome. In some cases, estradiol may have a proinflammatory effect, which can further exacerbate tissue damage. Nevertheless, the precise mechanism by which estradiol exerts its proinflammatory effect remains unclear [21, 22].

As previously stated, elevated estradiol levels in postmenopausal women are associated with a more severe clinical course of stroke and an increased risk of disability and mortality [8]. These associations may be explained by several mechanisms. Estradiol exerts its effects by activating the synthesis of nitric oxide (NO) in response to vascular injury. In the vascular system, NO is synthesized by two main isoforms of NO synthase (NOS): endothelial (eNOS, NOS III) and inducible (iNOS, NOSII). Endothelial NOS is present in all endothelial cells, whereas inducible NOS is found only in damaged arteries. Upon activation, iNOS can produce 1,000 times more NO for a longer time than eNOS. At these concentrations, NO, due to interaction with reactive oxygen species, becomes toxic and causes tissue damage [22]. Furthermore, high levels of NO resulting from iNOS expression are also involved in the formation of neointima in damaged vessels [22].

Conversely, estradiol may also exert a protective effect on ischemic brain tissue by modulating the levels of pro- and anti-inflammatory cytokines [25]. Estradiol plays a pivotal role in neuronal differentiation, synaptogenesis, and the structural organization of neurons in the cerebral cortex, hippocampus, and subventricular zone [26, 27].

Estrogen is known to inhibit hepatic lipase. Consequently, the decline in endogenous estrogen that occurs during postmenopause contributes to a reduction in HDL cholesterol and an increase in LDL cholesterol, thereby elevating cardiovascular risk [28]. However, the present study did not identify any statistically significant differences in total cholesterol, LDL and HDL cholesterol levels between women with low and high estradiol levels.

Additionally, elevated estradiol levels in postmenopausal women were associated with an elevated risk of thrombosis. This may represent a central mechanism underlying the heightened risk of coronary heart disease and cerebrovascular accident during this period [29]. In experimental animal models, estrogen has been demonstrated to facilitate transferrin expression and, moreover, to induce hypercoagulability. In women receiving estrogen, an increase in the number of platelets and thrombin production was observed, as well as a decrease in erythrocyte count, which resulted in the development of ischemic stroke and iron deficiency anemia [30].

A limitation of the current study is its cross-sectional nature. However, the study's randomly selected sample and comprehensive range of examinations allowed for the consideration of potential confounding factors that may contribute to the elevated risk of stroke and MI in women with high estradiol levels.

CONCLUSIONS

1. An estradiol level exceeding 55 pmol/L is an independent risk factor for the development of stroke and MI in women aged 65 years and older.
2. Further research is required to identify the underlying pathogenesis mechanisms responsible for the increased cardiovascular risk in postmenopausal women with elevated blood estradiol levels.

ADDITIONAL INFORMATION

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Personal contribution of each author: *A.V. Turusheva* — concept and design of the study, survey, data analysis, text writing, editing; *K.A. Panchishina* — review of the literature, text writing.

Ethics approval. The present study protocol was approved by the local Ethics Committee of the North-Western State Medical University named after I.I. Mechnikov (No. 1 of 22.01.2014).

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