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ORIGINAL PAPER

Link of ocular pseudoexfoliation syndrome and vascular system changes: results from 10-year follow-up study

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Abstract

Purpose To examine the 10-year incidence of the pseudoexfoliation syndrome (PEX) in adults in a population-based follow-up study, to determine its link with vascular diseases, and to identify possible risk factors of the PEX.

Methods The baseline examination was performed in 2006 on a random sample of 1033 participants from Kaunas city (Lithuania) population. In 2016, a follow-up study of 686 participants who returned for the examination was conducted. The respondents filled out a questionnaire, an ophthalmological examination was performed, and the presence of vascular diseases was determined by the anamnesis and electrocardiogram evaluation data. Binary univariate and multivariate logistic regression analyses were conducted with the PEX and vascular diseases as predictors, controlling for age. Odds ratios (OR) and 95% confidence intervals of OR were calculated for the risk of new PEX cases.

Results During 10 years, the prevalence of the PEX in the study population increased from 10.3 to 34.2%. The rates of ischemic heart disease (IHD) and IHD combined with stroke were significantly higher in the PEX subjects than in the non-PEX subjects. The risk of the PEX among persons with IHD was, on the average, by 1.5-fold higher, and among those with IHD and stroke, on the average, by 1.6-fold higher as compared to persons without the aforementioned pathologies (accordingly, $p = 0.014$ and $p = 0.010$).

Conclusion The prevalence of the PEX increased significantly with age. The risk of the PEX was significantly higher among persons with IHD and even higher among persons with IHD and stroke. In the future, a greater understanding of the cardiovascular, metabolic, and environmental components associated with the PEX may lead to more specific lifestyle-related preventive strategies to decrease the disease burden.

Keywords Pseudoexfoliation syndrome · Prevalence · Cardiovascular diseases · Ischemic heart disease · Stroke · Arterial hypertension

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Introduction

The pseudoexfoliation syndrome (PEX) is an age-related disorder in which grayish-white flakes accumulate in different tissues in the anterior segment of the eye. PEX fibrils appear to be multifocally produced by various intraocular cell types including the pre-equatorial lens epithelium, non-pigmented ciliary epithelium, trabecular endothelium, corneal endothelium, vascular endothelial cells, and virtually all cell types of the iris. Abnormal elastin fibrils identified by electron microscopy in the heart, lung, liver, kidney, gallbladder, and meninges [1] gave rise to the theory that the PEX might be a part of a generalized disorder [2]. The PEX affects about 0.2–30.0% of people older than 60 years worldwide [3, 4]. Clinically, ocular involvement is described as unilateral in 48.0% to 76.0% of patients. Progression to bilateral involvement was reported in up to 50.0% of patients within 5 to 10 years after the diagnosis [5]. Clinically, unilateral exfoliation is asymmetric rather than truly monocular. The findings in fellow eyes suggest that blood vessels of the iris become abnormal early in the process, even before exfoliation deposits can be histopathologically seen in the posterior chamber. The evidence supports the theory that the vasculopathy may represent an early preclinical stage of this syndrome and that it is an integral part of the disease [6].

The widespread distribution of exfoliation fibers led to a search of potential systemic comorbidity in patients with the PEX [7].

It was postulated that PEX might contribute to increased morbidity—mainly from systemic vascular diseases [2] such as ischemic heart disease (IHD), arterial hypertension (AH), or cerebrovascular disease or from an ocular pathology such as a cataract, glaucoma, or age-related macular degeneration. Selective studies showed that the PEX increased the odds of IHD by 1.6-fold, the odds of cerebrovascular disease by 1.6-fold, and the odds of for aortic aneurysm by 2.5-fold [4]. Unfortunately, all the above studies were performed as non-repeated investigations. We could not find any follow-up studies in the available data bases, which would examine the associations of ophthalmological abnormalities with IHD or stroke.

In 2006, in the Hospital of the Lithuanian University of Health Sciences Kauno Klinikos, a population-based epidemiological study on Health, Alcohol, and Psychosocial Factors In Eastern Europe (HAPIEE) was conducted [8], which examined the associations between ophthalmological disturbances and cardiovascular diseases. In 2016, this study was conducted with same group of patients. The aim of the present population-based follow-up study was to determine the 10-year incidence of the PEX in Lithuanian urban population and its link with vascular diseases (IHD, stroke, and AH), and to identify possible risk factors of the PEX.

Materials and methods

Research sample

The respondents of the population-based epidemiological study were residents of Kaunas—the second largest city in Lithuania. The study was carried out as a part of an ongoing prospective cohort study HAPIEE. In the HAPIEE study, during 2006–2008, 10,937 individuals (45 to 72 years of age) were randomly drawn from the population register of the city (the population of 352,000 residents). In total, 7087 respondents participated in the study (the response rate was 65.0%). At baseline, 1033 subjects were randomly drawn from the main study for ophthalmological and cardiological examination [8, 9].

This study is a part of an ongoing prospective cohort study HAPIEE, which is participating in the E3 consortium [10]. The study was approved by the Regional Bioethics committee and was carried out in accordance with the Declaration of Helsinki (No. P5/09-2005). During the study, an informed consent was obtained from each participant.

In 2016–2017, after 10 years, the follow-up study investigated 686 (the response rate was 66.4% of the number of the primary participants, 78.9% of the alive participants) 55- to 83-year-old subjects, while 347 individuals did not return to the follow-up study because of death (n = 164) (Table 1), migration, or refusal (n = 183).

During the study period, we investigated 631 respondents (239 (37.9%) males and 392 (62.1%) females), and their data were compared to the data of the baseline study. The data of 55 respondents were not included (and thus were excluded from further analysis as missing) in the data analysis due to pseudophakia in both eyes because it is very difficult

Table 1 Participants' death causes until follow-up study

Death causes	Non-PEX, *n* (%)	PEX, *n* (%)	Total
Ischemic heart disease	26 (20.6)	8 (24.2)	34
Stroke	15 (11.9)	3 (9.1)	18
Acute myocardial infarction	9 (7.1)	–	9
Other	76 (60.3)	22 (66.7)	98
Total	126 (100.0)	33 (100.0)	159**

PEX, pseudoexfoliation syndrome

*$p > 0.05$, to compare non-PEX with PEX group

**5 participants data missing

to evaluate the PEX material when there is no anterior lens capsule after the cataract extraction operation.

Research instruments

All participants underwent an ophthalmological examination according to a standard examination protocol and methodology. The examination was carried out by two ophthalmologists who did not know any of the subjects' medical histories.

Clinical diagnosis of the PEX was made by a slit-lamp examination after diagnostic mydriasis with 1 drop of 1% cyclopentolate. The diagnosis of the PEX was confirmed by the presence of the typical grayish-white exfoliation material on the anterior capsule surface of the lens (complete or partial peripheral band and/or a central shield); other changes associated with the PEX such as grayish-white deposits elsewhere in the anterior chamber or precapsular frosting or haze supported the diagnosis of the PEX. If, however, the peripheral band or the central shield could not be identified, individuals with the latter characteristics were classified as those with suspected/possible PEX. The participants were classified as having the PEX if any typical pseudoexfoliation material was present in at least one eye. For statistical analysis, we used data for the respondents with the definite PEX diagnosis as the PEX group. Persons with suspected PEX were grouped together with those without any signs of the PEX.

All the respondents filled out a standard questionnaire regarding lifestyle, subjective health, diseases such as IHD by epidemiological criteria, AH, stroke, dyslipidemia (DL), physical activity, and previous surgery and medication use. The presence of AH, stroke, or DL was also determined based on the anamnesis data.

The presence of IHD or stroke was determined whether the respondents gave positive answers to the questions: "Has a doctor ever told you that you have/had acute myocardial infarction (AMI) or a stroke?"

All the respondents' data about cardiovascular diseases were verified using data of Kaunas City IHD and Stroke registers.

DL was determined based on the anamnesis and was compared to blood tests (serum triglycerides, high-density lipoprotein, and cholesterol concentrations) made during the baseline study.

Based on the weekly hours of physical activity doing household work (PhAH), the subjects were distributed into subgroups: inactive (< 19 h/week) and active (≥ 19 h/week).

Cardiological evaluation

The examination included the measurements of height, weight, and blood pressure. Prior to the blood pressure measurement, the participants were asked to sit still for 5 min. Blood pressure was measured three times with a 2-min interval between the measurements, using an Omron M5-I (OMRON Matsusaka Co. Ltd., Japan) digital blood pressure monitor. AH was diagnosed whether the systolic blood pressure was 140 mmHg and/or diastolic blood pressure 90 mmHg or higher, or antihypertensive medications had been used during the past 2 weeks [11].

A resting electrocardiogram was recorded in the 12 standard leads, with the calibration of 10 mm per 1 mV and the paper speed of 25 mm per second. ECG records were read by 2 independent experienced

coders (trained cardiologists). IHD at baseline and in the follow-up study was determined by: (1) a documented history of AMI and/or ischemic changes on electrocardiogram (ECG) coded by Minnesota codes (MC) 1–1 or 1–2 [12]; (2) angina pectoris as defined by G. Rose's questionnaire (without MI and/or MC 1–1 or 1–2) [13]; (3) ECG findings coded by MC 1–3, 4–1, 4–2, 4–3, 5–1, 5–2, 5–3, 6–1, 6–2, 7–1, or 8–3 (without MI and/or MC 1–1, 1–2 and without AP). Both cardiovascular research epidemiologists were the same as in the baseline study. When evaluating the ECG, they did not know the subjects' medical histories.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 20 software.

Descriptive statistics were applied for various signs in the PEX group and the non-PEX group. Unilateral and bilateral PEX cases were separated into subgroups.

The level of statistical significance was set at $p < 0.05$.

Data normality of continuous variables was checked using the Kolmogorov–Smirnov test. In case of non-normality, medians and interquartile ranges (IQR) were calculated, and the Mann–Whitney *U* test was used to compare continuous data between the groups.

The *Chi square* (χ^2) test or *Fisher's exact 2-sided test* were used to compare categorical variables. For ordinal data, the χ^2 linear-by-linear association test was used for the confirmation of the linear trend.

McNemar's χ^2 *test* was used to assess the difference between paired proportions.

Binary univariate and multivariate logistic regression analyses (Enter and Forward methods) were conducted with the PEX and vascular diseases (IHD, IHD and stroke, stroke, ischemic changes in ECG, AP, AH, MI, DM, and DL) and other risk factors (weekly hours of physical activity doing household work, weekly hours of physical activity doing sports, the body mass index (BMI), alcohol consumption, education, marital status, and smoking habits) as predictors controlling for age and sex, and verified by the Cox and Snell R Square Odds ratios (OR) and 95% confidence intervals (CI) of OR calculated for the possibility of new PEX cases.

Results

We investigated 631 subjects (239 (37.9%) males and 392 (62.1%) females). During the baseline investigation (2006–2008), the prevalence of the PEX for this contingent was 10.3% (data not shown separately). During the 10 years of follow-up (2016–2017), the prevalence of the PEX increased to 34.2% (216 subjects, of which 85 (39.4%) were males and 131 (60.6%) females (data not shown separately)). The frequency of the PEX among males and females was same 35.6% and 33.4% ($p > 0.05$), respectively. The mean age was significantly higher in the PEX group (73.01 ± 7.97 years) than in the non-PEX group (68.70 ± 8.16 years) ($p < 0.05$). The results of the study showed that the prevalence of the PEX significantly increased with age (Table 2).

At follow-up, the frequency of IHD in the PEX group was found to be 37.5% compared to 28.0% in the group without the PEX ($p = 0.014$) (Table 3).

The follow-up evaluation found 130 (20.6%) new cases of IHD as compared to baseline. The prevalence of IHD increased from 18.4% at baseline to 31.2% at the follow-up survey after 10 years ($p < 0.001$). A strong tendency of higher rates of new IHD cases was detected in the PEX group (23.6%) when compared to the group of subjects without the PEX (19.0%) ($p = 0.067$). At follow-up, the frequency of IHD combined with stroke in the PEX group was significantly higher compared to that in the group of subjects without PEX: 42.1% and 31.8% ($p = 0.010$), respectively. The evaluation of the frequency of stroke alone did not reveal any significant differences when those two groups were compared (Table 3).

The rates of ischemic ECG changes and AP were higher in the PEX group (21.4% and 11.6%, respectively) than in the group of subjects without the PEX (15.4% and 9.4%, respectively), but did not reach the level of statistical significance (Table 3).

The differences between the rates of stroke, AH, AMI, and DL were not significant in the PEX group as compared to those in the subjects without the PEX (Table 3). No statistically significant differences were found when comparing the proportions of all the analyzed cardiovascular and metabolical pathologies in the two PEX subgroups (Table 3).

The risk of the PEX among the subjects with IHD was, on the average, by 1.5-fold higher as compared to those without IHD (OR = 1.547, 95% CI 1.091–2.193,

Table 2 The prevalence of PEX at follow-up survey by gender and age groups

	Non-PEX, *n* (%)	PEX, *n* (%)	Total, *n* (%)	*p* value
Gender				
Male	154 (64.4)	85 (35.6)	239 (100.0)	0.581
Female	261 (66.6)	131 (33.4)	392 (100.0)	
Age				
55–65	158 (38.1)	48 (22.2)	206 (100.0)	
66–75	148 (35.7)	70 (32.4)	218 (100.0)	0.001
76–83	109 (26.2)	98 (45.4)*	207 (100.0)	
Mean (± SD)	68.70 (8.16)	73.01 (7.97)		0.001
Median	68.0	74.0		0.001

PEX, pseudoexfoliation syndrome

*$p < 0.05$, to compare non-PEX with PEX group

$p = 0.014$) (Table 4). The odds of the PEX among patients with IHD and stroke were, on the average, by 1.6-fold higher as compared to those without the combination of IHD and stroke (OR = 1.561, 95% CI 1.111–2.193, $p = 0.010$) (Table 4).

Adjusting by multivariate risk factors, AH significantly reduced the probability of having the PEX (OR = 0.567, 95% CI 0.364–0.884, $p = 0.012$) (Table 4).

According to the data of the multiple logistic regression analysis, DL did not increase the risk of the development of the PEX (OR = 1.129, 95% CI 0.631–1.225, $p = 0.447$).

The odds of the PEX among patients with physical activity of less than 19 h per week were, on the average, by 1.4-fold higher as compared to those with physical activity of 19 or more hours per week (OR = 1.415, 95% CI 1.006–1.991, $p = 0.046$) (Table 4).

Discussion

The PEX typically affects several structures of the anterior segment of the eye. There are many studies on the incidence and prevalence of the PEX in different parts of world, but there is no homogeneous distribution of results for the studies [2]. Various pathogenetic mechanisms have been postulated to explain the higher risk for vascular disease in patients with the PEX, including the deposition of the PEX material in blood vessels, increasing vascular resistance, and vascular dysregulation. Insults to the vascular endothelium and smooth muscle function by the PEX deposits have also been postulated as a mechanism for atherosclerosis and thrombus formation, which could lead to cardiac events [14–16]. The prevalence of the PEX has been found to be 0.2–30.0% regardless of geographical features. Another important finding is that the prevalence of the condition increases at the age of 50. The variation in study results may be explained by differences in geographical, ethnic, and race features, as well as by age and sex distributions of the examined participants and a variety of methods and criteria that have been used to diagnose the PEX [4, 17–23].

The highest prevalence rates of the PEX have been described in the Nordic countries [19, 24]. It was interesting to explore Lithuania's population to evaluate whether the prevalence of the PEX was as high as in other Northern countries. Lithuania is situated on the eastern shore of the Baltic Sea in Northern Europe. The country is in a cool moderate climate zone. Lithuania is assigned to the 5–6th climate zone by climate harshness. The highest elevation is 297.84 meters above the sea level. The prevalence of the PEX in the 80-year-old population in Lithuania (34.2%) was found to be as high as in Iceland (40.6%) [19].

The results of studies that analyzed the associations between IHD and the PEX are conflicting. We found that the frequency of medically treated patients with IHD in the PEX group was significantly higher comparing to the group of subjects without the PEX. The tendency of higher rates of cases of new IHD and ischemic ECG changes was found in the PEX group when compared with the group of subjects without the PEX. The same was confirmed by other investigators [16].

Our data are in agreement with Turkish and other studies that found differences in the rates of IHD among patients with and without the PEX [23, 25–27]. At the same time, other investigators did not find any

Table 3 Cardiovascular and metabolical pathology distribution at baseline and follow-up studies in the PEX and non-PEX groups, in unilateral and bilateral PEX subgroups, and new cases of pathology at follow-up study in the PEX and non-PEX groups

Pathology	Baseline study (n = 1033)			Follow-up study (n = 631)					New cases of pathology at follow-up study (n = 631)		
	Non-PEX, n (%)	PEX, n (%)	p value	Non-PEX, n (%)	PEX, n (%)	p value	Unilateral* PEX, n (%)	Bilateral* PEX, n (%)	p value	Non-PEX, n (%)	PEX, n (%)	p value
Ischemic heart disease	180 (20.2)	38 (26.6)	0.084	116 (28.0)	81 (37.5)	**0.014**	44 (22.3)	57 (28.9)	**0.01**	66 (18.6)	64 (23.1)	0.063
Ischemic heart disease + stroke	187 (21.0)	39 (27.3)	0.093	132 (31.8)	91 (42.1)	**0.01**	49 (22.0)	66 (29.6)	**0.004**	75 (21.2)	76 (27.4)	**0.029**
Stroke	13 (1.5)	3 (2.1)	0.567	29 (7.0)	16 (7.4)	0.846	9 (20.0)	13 (28.9)	0.72	19 (5.4)	22 (7.9)	0.137
Ischemic changes in ECG	128 (14.4)	26 (18.2)	0.236	64 (15.4)	46 (21.4)	0.061	27 (24.5)	34 (30.9)	**0.01**	32 (9.0)	45 (16.3)	**0.032**
Angina pectoris	59 (6.6)	12 (8.4)	0.439	39 (9.4)	25 (11.6)	0.38	12 (18.8)	18 (28.1)	0.83	29 (8.2)	26 (9.4)	0.829
Arterial hypertension	630 (71.2)	113 (79.6)	**0.038**	327 (78.8)	167 (77.3)	0.669	86 (17.3)	134 (27.1)	0.37	55 (15.7)	28 (10.2)	0.101
Acute myocardial infarction	58 (6.5)	20 (14.0)	**0.002**	38 (9.2)	21 (9.7)	0.817	12 (20.3)	8.0 (14)	0.61	22 (6.2)	15 (5.4)	0.876
Diabetes mellitus	68 (8.4)	12 (8.9)	0.839	46 (11.1)	28 (13.0)	0.486	19 (25.7)	22 (29.7)	**0.037**	20 (5.6)	26 (9.4)	0.189
Dyslipidemia	211 (23.8)	33 (23.2)	0.8	188 (45.3)	91 (42.1)	0.447	46 (44.7)	65 (37.4)	0.089	99 (28.4)	66 (24.0)	0.193

PEX, pseudoexfoliation syndrome

*Comparing unilateral and bilateral PEX subgroups with the non-PEX group in follow-up study

$p < 0.05$, results are statistically significant

Table 4 Odds ratio of rates for development of PEX by sociodemographical, cardiovascular, and metabolical events (multiple logistic regression)

	B	OR	95% CI	*p* value
Model 1				
Age	**0.065**	**1.067**	**1.045–1.090**	**0.001**
Gender (female ref.)	0.095	1.100	0.784–1.542	0.582
AH (no ref.)	− 0.086	0.917	0.617–1.363	0.669
IHD (no ref.)	**0.436**	**1.547**	**1.091–2.193**	**0.014**
Stroke (no ref.)	0.063	1.065	0.565–2.007	0.846
IHD + stroke (no ref.)	**0.445**	**1.561**	**1.111–2.193**	**0.010**
Dyslipidemia (no ref.)	− 0.129	0.879	0.631–1.225	0.447
Model 2				
Age	**0.066**	**1.068**	**1.046–1.091**	**0.001**
AH (55–65 years ref.)				
AH (66–75 years)	0.014	1.014	0.670–1.534	0.947
AH (76–83 years)	**0.755**	**2.127**	**1.436–3.150**	**0.0001**
Physical activity (hours/week) (≥ 19 h ref.)	**0.347**	**1.415**	**1.006–1.991**	**0.046**
Model 3				
Age	**0.071**	**1.073**	**1.049–1.098**	**0.0001**
AH (no ref.)	**− 0.567**	**0.567**	**0.364–0.884**	**0.012**
IHD + stroke (no ref.)	**0.381**	**1.463**	**1.013–2.115**	**0.043**

PEX, pseudoexfoliation syndrome; *AH,* arterial hypertension; *IHD,* ischemic heart disease

B, regression coefficient; *OR,* odds ratio; *95% CI,* 95% confidence interval

$p < 0.05$, results are statistically significant

Model 1—adjusted by age (Enter method)

Model 2—adjusted by age (Enter method)

Model 3—adjusted by age, gender, body mass index, education, marital status, alcohol consumption, smoking habits, physical activity, arterial hypertension, ischemic heart disease, stroke, dyslipidemia (Forward stepwise method)

significant differences in IHD rates in the PEX group [7].

We found significant associations of the PEX with the combination of IHD and stroke. However, we failed to confirm any significant differences in the rates of stroke between the PEX and the non-PEX groups—similarly to other studies on cerebrovascular disease [23]. The opposite results were found in Turkey, where higher rates of cerebrovascular disease in the PEX group were observed [28]. Many studies did not find any significant differences between the rates of AH and the PEX [7, 15, 29–31]. In the follow-up study, we could not confirm the baseline data of the significant association of the rates of AH and higher systolic blood pressure with the PEX because of the small size of the sample and a higher number of risk factors in older age [9].

Other researchers also found a higher systolic blood pressure in the PEX patients [16, 25, 27]. A study conducted by Mitchell et al. [32] showed a significant association between the PEX and AH.

A study by M. Citirik demonstrated a higher prevalence of coronary artery disease ($p = 0.001$) and more prominent fundoscopic findings of vascular diseases ($p = 0.0001$) in PEX patients [25], while controversial results were found in other studies [31].

We investigated the coherence between MI, AP, DL, and the PEX, but found no significant associations. The same conclusion was made by other investigators [23, 27].

Particular vascular diseases that have an apparent association with the PEX include those that affect the arterial wall. According to Akdemir et al., the PEX was more common in patients with coronary artery ectasia [33].

A study conducted in Australia detected a possible link between the PEX and vascular events, including AMI and stroke [32].

Wang et al. [4] found that the PEX increased the odds of vascular disease by 72%, and thus, the detection of the PEX during a routine ophthalmologic examination could be an important indicator of the risk for a systemic vascular disease. In contrast, Vardhan et al. [16] have found no association between the PEX and other cardiovascular risk factors.

During the 10 years of follow-up, the incidence of the PEX among the investigated persons aged 55-83 years increased by over 3 times (from 10.3 to 34.2%). At follow-up, the rate of IHD in subjects of the PEX group was higher compared to that in the group of subjects without the PEX. The mean probability of the PEX in cases of IHD and stroke was by 1.6-fold higher as compared to that in patients without the combination of IHD and stroke. The logistic regression analysis showed that both PEX and AH were significantly associated with cerebrovascular disease, and this association was stronger in the AH than in the PEX group [28].

When using multivariate logistic regression models, the subjects were found to have significantly higher odds of developing PEX with increasing age and the presence of an established ischemic heart disease and stroke. On the other hand, in the multivariate regression model, the odds of developing the PEX with established AH were significantly lower than those with no AH after adjusting the data by the sociodemographic and lifestyle factors analyzed above. It is interesting to note that AH significantly reduced the risk of the PEX in the logistic regression model. On the other hand, the evaluation of the development of the PEX in AH persons by age group showed that AH in the oldest age group (76–83 years) increased the risk of the development of the PEX by more than 2 times, with no significant changes in the youngest (66–75 years) age group. It can be argued that the control of AH in the PEX group was better in younger age groups, and this resulted in a lower incidence of the PEX. Certain age-related changes in the development of the PEX at the oldest age cannot be ruled out.

Other researchers also found similar trends in the interactions between AH and the PEX [7, 31]. This may be due to the fact that persons with AH have effectively controlled their blood pressure, thereby reducing the risk of developing the PEX. On the other hand, AH, like DL, is also one of the components of the metabolic syndrome, and its successful control can also reduce the risk of developing metabolic syndrome in cases of the PEX.

Some authors noted that in the multiple logistic regression analysis, having systemic AH as the outcome variable and including the study groups, age, and sex as the prognostic variables showed that the odds of having systemic AH in the PEX group over the controls was 1.12 (95% CI, 0.87–1.46) [16].

The positive effects of physical activity on the development of the PEX cannot be ruled out. Among our investigated patients, the risk of having the PEX was significantly lower in those who were physically active. It has been shown that higher physical activity predisposes lower levels of homocysteine in the blood, while lower homocysteine levels are significantly associated with a lower chance of most cardiovascular events and a lower risk for the PEX syndrome [34]. Other researchers like Vesani et al. [35] have suggested that the common findings between the PEX and homocystinuria in terms of vascular disorders can be explained by the direct relation between the PEX and homocysteine level.

Strengths and limitations

The main advantage of this study is that it is a population-based follow-up study where we compared the status of the same respondents at baseline and at follow-up. The standardized examinations were performed, and the definitions were made by the same experienced examiners using the same technique over many years.

The main limitation includes the response rate of 66.4%, which makes it difficult to reach denominate significance ($p < 0.001$). Cataract surgery (performed in 8.02% of the investigated subjects; both pseudophakic eyes after 10 years of follow-up) and the small amount of the respondents who returned may also misrepresent some data.

In the future, a greater understanding of the cardiovascular, metabolic, and environmental components associated with the PEX may lead to more specific lifestyle-related preventive strategies to decrease the disease burden.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Regional Bioethics committee and was carried out in accordance with the Declaration of Helsinki.

Informed consent Informed consent and the consent form for case reports were obtained from all individual participants.

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