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# Association of ocular pseudoexfoliation syndrome with ischemic heart disease, arterial hypertension, and diabetes mellitus

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## Abstract

**Aim—**To determine the prevalence of pseudoexfoliation syndrome (PEX) in Lithuanian urban population and its association with ischemic heart disease (IHD), arterial hypertension (AH), and diabetes mellitus (DM).

**Methods—**In this population-based study 1,065 participants aged 45–72 years were randomly drawn from the population register of Kaunas, Lithuania. They were classified as having PEX if any pseudoexfoliation material was determined by a slit-lamp examination in at least one eye. The data was acquired from questionnaire, register of myocardial infarction, electrocardiogram, biochemical blood analyses and blood pressure measurement were used to determine IHD, AH, DM, and smoking habits. Poststratification weights based on Kaunas population sex and age distribution were applied.

**Results—**PEX was estimated in 9% of a population. The AH rate was higher in PEX subjects than in non-PEX subjects (p=0.017) and the rates of IHD, DM, and cholesterol levels did not differ statistically significantly. $\chi^2$ linear-by-linear association test found higher AH rate in unilateral PEX subjects and even higher AH rate in bilateral PEX subjects than in non-PEX subjects (p=0.014). PEX increased odds for AH by 1.8 times (p = 0.021). Median of systolic blood pressure was higher in the PEX group than in non-PEX group (p=0.04). But all associations could not be confirmed after adjusting for age. Smoking duration increased age-adjusted odds for PEX. PEX did not increase risk for IHD, AH or DM.

**Conclusions—**PEX prevalence is high in Lithuania. No clear PEX association with IHD, AH, and DM was proven after controlling for effect of age.

### Keywords

pseudoexfoliation; ischemic heart disease; arterial hypertension; diabetes mellitus

## Introduction

Pseudoexfoliation syndrome (PEX) is an age-related systemic disease of the extracellular matrix characterized by the multifocal production and progressive accumulation of a fibrillary extracellular material in intra- and extraocular tissues that is either the result of an

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excessive production or insufficient breakdown, or both (Ritch & Schlötzer-Schrehardt 2001).

PEX etiology and pathogenesis are still unknown, but it is thought to be a systemic biochemical process (Schlötzer-Schrehardt & Naumann 2006). Geographical clustering for PEX and variable prevalence in the same country suggests environmental and genetic risk factors. Single nucleotide polymorphisms in the coding region of the lysyl-oxidase-like 1 (LOXL1) gene, that is responsible for cross-linking of elastin, were found associated with PEX in several populations (Malukiewicz et al. 2011; Jonasson 2009; Schlötzer-Schrehardt 2011). Molecular biological and biochemical data support the pathogenetic concept of PEX as a type of stress-induced elastic microfibrillopathy (Ovodenko et al. 2007).

PEX in the eye is recognized by the presence of white fibrillogranular deposits on various anterior eye segment structures. Pseudoexfoliation fibers histologically were found in conjunctival stroma, extraocular muscles and orbital connective tissue, also in other visceral organs: heart, lungs, liver, kidney, gallbladder, as well as in walls of blood vessels, skin and cerebral meninges (Vesti & Kivelä 2000; Schlötzer-Schrehardt & Naumann 2006). Imunohistochemical analysis with HNK-1 antibodies suggests that either the exfoliation matrix or the molecular structure of exfoliation fibres may be distinct within the eye in comparison to extraocular sites (Vesti & Kivelä 2000). The structural findings in various organs suggest PEX being not only object of ophthalmology.

PEX appears to be associated with numerous clinical complications in the affected eye, cardiovascular system, brain, and ears (Schlötzer-Schrehardt & Naumann 2006; Mitchell et al. 1997; Yüksel et al. 2006; Turacli et al. 2007). So far, there is no convincing evidence that the fibers would cause degeneration of any of the extraocular tissues mentioned (Vesti & Kivelä 2000). But some studies experimentally showed systemic vascular endothelial dysfunction and impaired dilation (Naji et al. 2008; Atalar et al. 2006). Also elevated plasma homocysteine, a risk factor for cardiovascular disease, has been found more common in PEX syndrome than in healthy controls (Altintas et al. 2005). PEX associations with ischemic heart disease (IHD), arterial hypertension (AH), and diabetes mellitus (DM) has been investigated, but reports are conflicting and no clear association of PEX with any specific systemic disease has yet been proven. (Tarkkanen et al. 2008; Andrikopoulos et al. 2009). Morphological, experimental, and biochemical findings suggest PEX associations with various pathologies and controversial results stimulate new population based studies in countries with high PEX prevalence.

The aim of our study was to determine the prevalence of PEX in Lithuanian urban population and its association with IHD, AH, and DM.

## Material and Methods

Participants of the population-based study were 45–72 year-old residents of the second largest city in Lithuania (Kaunas) randomly drawn from the population register of the city (population of 352,000 residents). This study is a part of an ongoing prospective cohort study on Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE) (Peasey et al. 2006). In this study 7087 individuals participated (response rate 65%). The subjects for ophthalmological examination were randomly drawn from the main study. Informed consent was obtained from each participant. The study was approved by regional ethics committee and was carried out in accordance with the Declaration of Helsinki. Diagnosis of PEX was made by slit-lamp examination after diagnostic mydriasis with 1 drop of 1% cyclopentolate. The participants were classified as having PEX if any pseudoexfoliation material was

present in at least one eye. Participants with aphakia (3), luxated lens (1), and phtysis after eye globe injury (2) were excluded from the analysis.

Standard questionnaire included questions regarding the responder's smoking habits. A subject who smoked at least one cigarette per day was classified as current smoker. The examination also included measurement of height, weight, and blood pressure. Prior to blood pressure measurement participants were asked to sit still for 5 minutes. Blood pressure was measured three times with a two-minute interval between measurements, using an Omron M5-I (OMRON Matsusaka Co. Ltd., Japan) digital blood pressure monitor. AH was diagnosed if the systolic blood pressure was 140 and/or diastolic blood pressure 90 mmHg or higher, or drugs were used during the past 2 weeks (Mancia et al. 2007).

Biochemical analyses were done for responders fasting for at least 12 hours. The concentration of glucose in capillary blood was determined by an individual glucometer "Glucotrend" (Roche Diagnostics, Switzerland). Serum triglycerides and high-density lipoprotein (HDL) cholesterol concentrations were determined enzymatically: triglycerides - by the glycerol phosphate oxidase-p-aminophenazone (GPO-PAP) method, and HDL cholesterol - by the cholesterol oxidase phenol 4-aminoantipyrine peroxidase (CHOD-PAP) Monotest, Boehringer-Mannheim method (Germany), after precipitation of serum very low-density lipoprotein and low-density lipoprotein.

Identification of non-fatal cardiovascular events was based on existing registers of myocardial infarction (MI) and stroke established by the WHO MONICA Project (Tunstall-Pedoe et al. 1994).

IHD was determined according to the following: 1) documented history of MI and (or) ischemic changes on electrocardiogram (ECG) coded by the Minnesota codes (MC) 1-1 or 1–2 (Prineas et al. 1982); 2) angina pectoris (AP) was defined by G. Rose questionnaire (Rose 1962) (without MI and (or) MC 1-1 or 1–2); 3) ECG findings by MC 1–3, 4-1, 4-2, 4-3, 5-1, 5-2, 5-3, 6-1, 6-2, 7-1, 8-3 (without MI and (or) MC 1-1, 1–2 and without AP).

The presence of DM was determined if responders gave positive answer of to the question: "Has a doctor ever told you that you have diabetes?" or fasting glycaemia was 6.8 mmol/l or more.

Statistical analysis was performed using IBM SPSS Statistics version 19 software. Poststratification weights based on Kaunas city population sex and age distribution (Demographic Statistics Division) were applied. All analyses are weighted using "Weight cases" command in SPSS. Descriptive statistics were applied for various signs in PEX group and non-PEX group. Unilateral and bilateral PEX cases were separated into subgroups. Normality assumption of continuous variables was checked using Kolmogorov-Smirnov test. In case it failed, medians and interquartile ranges (IQR) were calculated and Mann-Whitney U-test was used to compare continuous data between groups. *Chi square* ($\chi^2$) test or Fisher exact 2-sided test was used to compare categorical variables. For ordinal data $\chi^2$ linear-by-linear association test was used for confirmation of the linear trend. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by univariate logistic regression. Risk factors were analysed further by multivariate logistic regression controlling for effect of age, since this variable has been shown to influence the frequency of PEX.

## Results

In this study, 1,065 participants were examined, among them 419 (39%) males and 646 (61%) females. The subjects' distribution by age, sex and occurrence of PEX are shown in Table 1.

There were 152 (14%) cases of PEX, 90 (8%) of them were unilateral and 62 (6%) cases – bilateral. No statistically significant difference in occurrence of PEX was found between males and females. PEX rate was increasing significantly with age ($p<0.001$). $\chi^2$ linear-by-linear association analysis showed a significant linear increase of unilateral and bilateral PEX with age ($p<0.001$). There were 32 (3%) subjects after cataract surgery, 2 (6%) of them with PEX.

When study sample was weighted by age and sex the estimated rate of PEX in urban population was 9%.

The evaluation of PEX rate in three age groups showed that the OR in 55 – 64 year-old group was 6.0 (weighted 95 % CI: 2.8 – 13.0) times higher ($p < 0.001$, Wald test) and in 65 – 72 year-old group − 13.5 (weighted 95 % CI: 6.3 – 28.8) times higher ($p < 0.005$, Wald test) in comparison with 45 – 54 year-old group.

PEX association with IHD, AH, and DM in weighted sample was investigated (Table 2).

The differences between rates of IHD and DM were not statistically significant in PEX and non-PEX groups. The rates of ischemic changes in ECG and angina pectoris between groups did not differ significant. MI was found only in 2 (2%) cases in PEX group and 15 (1.6%) cases in non-PEX group ($p=0.67$ Fisher 2-sided exact test). AH was found in more subjects with PEX in comparison with no PEX ($p=0.017$). Statistically significant difference in AH rates remained after splitting the PEX group into uni- and bilateral PEX subgroups ($p=0.046$). $\chi^2$ linear-by-linear association test found higher AH rate in unilateral PEX cases and even higher AH rate in bilateral cases than in non-PEX group ($p=0.014$).

OR for likelihood of IHD, AH, and DM were calculated. PEX did not influence OR for IHD or DM (1.6 (weighted 95% CI: 1.0 – 2.6), $p=0.07$ and 1.1 (weighted 95% CI: 0.5 – 2.4), $p=0.9$, accordingly). Subjects with PEX were 1.8 times (weighted 95% CI: 1.1 – 2.8) more likely to have AH ($p = 0.021$), but this relation disappeared after controlling for the effect of age ($p=0.82$).

Treatment of DM and glycaemia in subjects with and without PEX was analysed. Only on diet were 14% of subjects with PEX vs. 22% of non-PEX subjects, oral medication used 43% vs. 52% subjects and insulin therapy − 43% vs. 26% subjects ($p=0.64$, $\chi^2$ test) respectively.

Median of glycaemia in subjects with DM diagnosis was 7.6 (IQR 4.5) mmol/l in the PEX group, and 6.9 (IQR 2.0) mmol/l - in the non-PEX group ($p=0.55$, Mann Whitney U-test).

The median values of various IHD, AH, and DM risk factors are presented in Table 3.

Statistically significant longer smoking duration and higher mean systolic blood pressure were found in PEX group in comparison with non-PEX group.

Age-adjusted OR for PEX increased by 3.1% (weighted 95% CI: 1.001–1.061) with each year of smoking duration ($p=0.04$, Wald test). Number of smoked cigarettes per day did not influence PEX ($p=1.00$, Wald test). Current smoker's status had 10 (10%) subjects with PEX and 188 (20%) subjects with no PEX, ex-smoker's status – 18 (18%) vs. 170 (18%) and never smoker's – 71 (72%) vs. 605 (63%), $p=0.07$. Systolic blood pressure did not increase age-adjusted OR of PEX ($p=0.86$, Wald test).

In multiple logistic regression analysis independent risk factors for investigated diseases were determined. Age, sex, HDL cholesterol level, and AH were independent risk factors of

IHD. Age, sex, triglyceride level, and body mass index (BMI) were independent risk factors for AH and age, HDL cholesterol level, BMI, AH - for DM ($p<0.05$, Wald test). PEX was not confirmed as additional independent predictor for IHD, AH or DM in these multiple logistic regression analyses ($p>0.05$).

## Discussion

Due to the lack of randomized population based studies, differences in sample selection, definition of PEX, and data presentation comparison of PEX prevalence is complicated. We found PEX prevalence in Lithuania as high as in Nordic European countries: 8.1% in Finland (Forsman et al. 2007), 10.7% in Iceland (Arnarsson 2009), and 17.2% in Sweden (Ekstrom & Alm 2008).

The results in studies that are analysing the associations of PEX with other chronic non-ophthalmological diseases are sensitive to diagnostic capabilities of these diseases. Moreover, in some studies primary open-angle glaucoma (PAOG) and exfoliation glaucoma (EG) groups are compared. The chance of underdiagnosing EG is even higher than PEX, because it depends on diagnostics of both glaucoma and PEX. Most of these studies are hospital or registry based. The strengths of the present study compared to the previous ones are that it is a population-based study, participants were drawn randomly and all calculations were weighted by sex and age.

Studies, that analysed IHD and PEX association, provided conflicting results. Our data agree with some studies, which found no statistically significant associations between PEX and IHD. Registry data of POAG and EG patients in Finland and Norway did not prove any difference in IHD rates (Tarkkanen et al. 2008; Ritland et al. 2004). Two hospital based studies also support the view that PEX and IHD are not associated, although study in India had sample of only 160 subjects and study in Craotia included relatively young 50 years-aged subjects (Praveen et al. 2011; Brajković et al. 2007). All studies were varying in size and design, therefore more reliable data could provide population-based study in Spain that applied compensatory weights developed from the target population as was done in our study too. In the mentioned study PEX increased OR for cardiovascular disease by 2%, but not statistically significant (Viso et al. 2010). In a study of Icelandic families containing three or more members aged 70 or older with at least one member with PEX, did not find any PEX association with IHD (Allingham et al. 2001).

IHD is influenced by many well known major risk factors. Histological and clinical studies have found PEX relations with alteration of blood vessels, therefore significant PEX influence to IHD might be found in cases with severe coronary impairment. Two hospital-based studies in Turkey confirmed PEX associations with coronary artery disease (CAD). In the first study comparison of 50 patients with CAD proven by coronary angiography and 50 sex and age matched controls showed higher PEX rates in the study group. When all patients were regrouped according to the presence of PEX, patients with PEX did not differ from patients without PEX in terms of age and sex, but the prevalence of CAD was higher (Citirik et al. 2007). In the second study of 1480 patients sheduled for cataract surgery, subjects with PEX were 1.49 times statistically significant more likely to have coronary heart disease, but the methodology used to prove CAD was not detailed (Sekeroglu et al. 2008). In Greece a hospital-based study of 2140 cataract patients found PEX to be positively associated with the risk for CAD among subjects 50 years or older (Andrikopoulos et al. 2009). In addition, the Blue Mountains Eye Study found PEX statistically significantly associated with a history of angina or a combined history of angina, acute myocardial infarction, or stroke (Mitchell et al. 1997).

In case of association between PEX and IHD higher mortality in PEX subjects would be expected. In Sweden and Norway, where PEX prevalence is high, no association between PEX and all-cause mortality was found (Grødum et al. 2004; Ringvold et al. 1997). In Minnesota no association was found between PEX and specific cardiovascular mortality also (Shrum et al. 2000).

In many studies the rates of AH in PEX and non-PEX groups did not differ significantly (Praveen et al. 2011; Viso et al. 2010; Tarkkanen et al. 2008; Sekeroglu et al. 2008; Citirik et al. 2007; Brajković et al. 2007; Allingham et al. 2001). Referral-based study of EG and age matched control group (Jonas & Gründler 1998) found lower rate of AH in the first group (18.8% vs. 30.2%, $p=0.04$). Also other referral-based study (Shingleton et al. 2003) found lower rate of AH in cataract patients with PEX than in those without PEX (38% vs. 50%, $p<0.01$).

It is important to have high rates of both PEX and AH in the study sample, whereas low rates may not reveal or distort their relation. We found AH in more than a half of PEX and non-PEX group subjects, statistically significantly higher rate was in the first group. PEX association with AH or higher systolic blood pressure couldn't be confirmed after controlling for effect of age. Cross-sectional study of 1844 participants in Japan found 50 PEX cases, rates of AH in PEX group 50.2% vs. 42.0% in non-PEX group were significantly different. Age-adjusted and multivariate-adjusted logistic regression analyses found significant AH association with PEX (Miyazaki et al. 2005). The Blue Mountains Eye Study found 81 PEX cases in 3546 subjects and identified significant association of PEX and AH (Mitchell et al. 1997).

Some studies investigated suspected relations between PEX and DM. Two studies after comparison of EG group with POAG or normal control groups found lower trend of DM rate in the first group, but statistically borderline ($p=0.05$) difference was identified (Tarkkanen et al. 2008; Jonas & Gründler 1998). In six other studies DM rates did not vary between patients with and without PEX (Praveen et al. 2011; Sekeroglu et al. 2008; Brajković et al. 2007; Citirik et al. 2007; Miyazaki et al. 2005; Allingham et al. 2001). In our study a small number of DM patients did not show any significant difference in glycaemia, treatment methods and the rate of DM considering presence of PEX.

Nevertheless, there are also studies that have statistically significant results. In Greek patients undergoing filtration surgery DM was 3.5 times more frequent in POAG group than in EG group, although average age in the first group was significantly higher (Konstas et al. 1998). Another study in Greece had found that PEX occurred less frequently in diabetic patients with background or proliferative diabetic retinopathy than in diabetic patients without diabetic retinopathy, considering both groups had comparable ages (Psilas et al. 1991). DM was significantly less frequent in cataract patients with PEX than in those without PEX (Shingleton et al. 2003).

The smoking status was analysed in some studies, but none of them found significant associations with PEX as well as our study (Mitchell et al. 1997; McCarty & Taylor 2000; Viso et al. 2010; Arnarsson 2009; Arnarsson et al. 2012). But our analysis identified, that longer smoking duration increases the risk of PEX, and should be investigated in the future studies.

In summary, we found age and smoking duration as the risk factors of PEX. The rates of IHD, AH, and DM in subjects with PEX were higher, however statistically significant difference was found only for AH. Systolic blood pressure in PEX group was higher as well. After controlling for effect of age PEX did not increase the risk of IHD, AH, and DM.

## Limitations

The main limitation of this investigation is the cross-sectional type of study: the risk of PEX, IHD, AH, and DM was estimated at the same time. Our data show only the association with conditions that are presently risk factors, but they do not directly predict the risk of future events. The incidence of PEX was not evaluated.

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**Table 1**

Characteristics of subjects by sex, age and occurrence of pseudoexfoliation syndrome in study sample.

| | No PEX [n (%)] | PEX [n (%)] | p-value | No PEX [n (%)] | Unilateral PEX [n (%)] | Bilateral PEX [n (%)] | p-value |
|---|---|---|---|---|---|---|---|
| Sex | | | | | | | |
| Male | 352 (84) | 67 (16) | | 352 (84) | 35 (8.4) | 32 (7.6) | |
| Female | 561 (86.8) | 85 (13.2) | 0.2 | 561 (86.8) | 55 (8.5) | 30 (4.6) | 0.13 |
| Age group | | | | | | | |
| 45–54 years | 225 (97.8) | 5 (2.2) | | 225 (97.8) | 3 (1.3) | 2 (0.9) | |
| 55–64 years | 300 (89.6) | 35 (10.4) | | 300 (89.6) | 29 (8.6) | 6 (1.8) | |
| 65–72 years | 388 (77.6) | 112 (22.4) | 0.001 | 388 (77.6) | 58 (11.6) | 54 (10.8) | 0.001 |
| Total | 913 (85.7) | 152 (14.3) | | 913 (85.7) | 90 (8.5) | 62 (5.8) | |

PEX = pseudoexfoliation syndrome.

Statistical comparisons were performed using the $\chi^2$ test. $p < 0.05$ was considered to be statistically significant.

**Table 2**

Comparison of ischemic heart disease, arterial hypertension, and diabetes mellitus rates in pseudoexfoliation syndrome and non-pseudoexfoliation syndrome groups (weighted by sex and age).

| Pathology | No PEX [n (%)] | PEX [n (%)] | p-value | No PEX [n (%)] | Unilateral PEX [n (%)] | Bilateral PEX [n (%)] | p-value |
|---|---|---|---|---|---|---|---|
| Ischemic heart disease | 164 (17) | 24 (24) | 0.08 | 164 (17) | 17 (26.2) | 7 (20) | 0.16 |
| Ischemic changes in electrocardiogram | 114 (11.8) | 15 (15.0) | 0.35 | 114 (11.8) | 10 (15.6) | 5 (14.3) | 0.61 |
| Angina pectoris | 57 (5.9) | 10 (10.0) | 0.11 | 57 (5.9) | 8 (12.3) | 2 (5.7) | 0.12 |
| Arterial hypertension | 626 (64.9) | 76 (76.8) | 0.017 | 626 (64.9) | 49 (75.4) | 28 (80.0) | 0.046 |
| Diabetes mellitus | 59 (6.8) | 7 (7.4) | 0.82 | 59 (6.8) | 3 (4.9) | 3 (9.4) | 0.71 |

PEX = pseudoexfoliation syndrome.

Ischemic heart disease is defined as ischemic changes in electrocardiogram, angina pectoris or myocardial infarction in the past.

Statistical comparisons were performed using the $\chi^2$ test. $p < 0.05$ was considered to be statistically significant.

## Table 3

Median values of ischemic heart disease, arterial hypertension, and diabetes mellitus risk factors in pseudoexfoliation syndrome and non- pseudoexfoliation syndrome groups (weighted by sex and age).

| Risk factors | No PEX [Median (IQR)] | PEX [Median (IQR)] | p-value |
|---|---|---|---|
| Smoking duration (years) | 28 (19) | 40 (24) | 0.001 |
| Total cholesterol level (mmol/l) | 5.8 (1.5) | 5.9 (1.5) | 0.24 |
| HDL cholesterol level (mmol/l) | 1.5 (0.5) | 1.5 (0.5) | 0.32 |
| LDL cholesterol level (mmol/l) | 3.7 (1.4) | 3.8 (1.3) | 0.38 |
| Triglyceride level (mmol/l) | 1.2 (0.9) | 1.2 (0.9) | 0.24 |
| Body mass index ($kg/m^2$) | 28 (7) | 30 (8) | 0.07 |
| Systolic blood pressure (mmHg) | 140 (30) | 147 (29) | 0.04 |
| Diastolic blood pressure (mmHg) | 88 (15) | 90 (15) | 0.27 |

PEX = pseudoexfoliation syndrome, IQR = interquartile range, HDL = high density lipoprotein, LDL = low density lipoprotein.

Data distributions were assessed using Kolmogorov-Smirnov test. Statistical comparisons of non-normal distributed data were performed using the Mann Whitney U-test. $p < 0.05$ was considered to be statistically significant.