# Polski Merkuriusz Lekarski

## POLISH MEDICAL JOURNAL

ISSN 1426-9686



VOLUME LIII, ISSUE 6, NOVEMBER-DECEMBER 2025

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## POLISH MEDICAL JOURNAL

ISSN 1426-9686



VOLUME LIII, ISSUE 6, NOVEMBER-DECEMBER 2025

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REVIEW ARTICLE

# Modern view on the epidemiology, risk factors, prevention and screening of pseudoexfoliation syndrome in the context of glaucoma prophylaxis

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## ABSTRACT

**Aim:** The analysis of current data on the epidemiology of pseudoexfoliative syndrome (PES) and risk factors for its development, determination of the possibility of early detection of PES through screening to prevent the development of glaucoma.

**Materials and Methods:** The literature review was carried out using publications indexed in the scientometric databases PubMed and Scopus. A structured search was performed with the use of relevant keywords and their logical combinations, including: prevalence, morbidity, complications, pseudoexfoliation syndrome, glaucoma, pseudoexfoliative glaucoma, vision loss, blindness, risk factors, intraocular pressure, prevention, early diagnosis, differential diagnosis, screening, and others. The review is primarily based on recent studies; however, a significant proportion of earlier publications (dating back to 1997) was deliberately included to provide a historical perspective and to highlight the evolution of scientific knowledge in this field. Totally, 44 sources were analyzed. The analysis employed formal-logical and systemic-complex methods, ensuring a comprehensive and critical synthesis of the available evidence.

**Conclusions:** Early diagnosis of PES is necessary to prevent the development and progression of pseudoexfoliative glaucoma, which leads to blindness. Therefore, the development of a screening algorithm and its implementation for at-risk patients – people over 50 years old – is relevant. For patients diagnosed with PES, it is important to regularly visit an ophthalmologist to monitor the possible development of glaucoma.

**KEY WORDS:** pseudoexfoliation syndrome, glaucoma, epidemiology, prevention, screening

Pol Merkur Lek,2025;53(6):797-802 doi: 10.36740/Merkur202506113

## INTRODUCTION

Pseudoexfoliation syndrome (PES) is characterized by the accumulation of abnormal fibrillar-granular protein, known as pseudoexfoliative material (PEM), primarily in the anterior structures of the eye, but also in various other tissues and organs. PES is a widespread systemic age-related disease and the most common cause of secondary open-angle glaucoma, specifically pseudoexfoliative glaucoma (PEG), which leads to rapid vision loss, severe optic neuropathy, and marked increases in intraocular pressure (IOP) [1].

In contrast to PES, exfoliation syndrome (ES) was first described in 1922 by Austrian ophthalmologist A. Elschnig in workers chronically exposed to high temperatures, particularly infrared radiation, such as glassblowers, blacksmiths, and steelworkers. ES is characterized by delamination of the anterior lens capsule, whose epithelial cells are particularly sensitive to heat. ES is largely asymptomatic and does not require treatment. Currently, the so-called 'glassblower's lens' is rare due to improvements in occupational eye protection. PES was first described by Czech ophthalmologist D. Dvorak-Theobald in 1954. Because true exfoliation had already been described, the new condition was termed 'pseudoexfoliation' to reflect its later discovery. ES differs from PES by the absence of fluffy gray-white exfoliative material (EM) on the lens and pupil, and by more distinct lens capsule delamination. Unlike PES, ES does not increase the risk of glaucoma development [2].

Currently, numerous studies aim to elucidate the interactions of genetic, environmental, and lifestyle factors in the etiology and pathogenesis of PES, contributing to the development of novel preventive and therapeutic strategies. Public health approaches aimed at early detection of PES and PEG through screening may mitigate the socio-economic impact of the disease [3]. Patients diagnosed with PES should undergo regular ophthalmologic examinations to monitor for glaucoma development. For individuals without PES, preventive eye examinations are recommended starting at age 40, and subsequently every 1–2 years after age 65 [4].

## AIM

The analysis of current data on the epidemiology of PES and risk factors for its development, determination of the possibility of early detection of PES through screening to prevent the development of glaucoma.

## MATERIALS AND METHODS

The literature review was carried out using publications indexed in the scientometric databases PubMed and Scopus. A structured search was performed with the use of relevant keywords and their logical combinations, including: prevalence,

morbidity, complications, pseudoexfoliation syndrome, glaucoma, pseudoexfoliative glaucoma, vision loss, blindness, risk factors, intraocular pressure, prevention, early diagnosis, differential diagnosis, screening, and others. The review is primarily based on recent studies; however, a significant proportion of earlier publications (dating back to 1997) was deliberately included to provide a historical perspective and to highlight the evolution of scientific knowledge in this field. Totally, 44 sources were analyzed. The analysis employed formal-logical and systemic-complex methods, ensuring a comprehensive and critical synthesis of the available evidence.

ETHICAL APPROVAL

This review is based exclusively on the analysis of publicly available scientific evidence from peer-reviewed journals, clinical practice guidelines, and established databases. No patient-identifiable data were used, and no approval from an ethics committee was required, as the study did not involve new clinical interventions or the collection of primary patient data.

The authors confirm adherence to the ethical principles of the World Medical Association's Declaration of Helsinki and to the international standards for medical journal publications, including the recommendations of the International Committee of Medical Journal Editors (ICMJE). The manuscript contains no instances of plagiarism or data fabrication. All sources of information have been accurately cited and properly referenced.

FRAMEWORK

The research was conducted as part of the scientific project «Scientific Rationale for Improving Organizational Principles of the Healthcare System Under Modern Transformational Changes» (state registration number 0123U101432, registration date 03.03.2023).

## REVIEW AND DISCUSSION

PES can be found all over the world, its prevalence varies significantly from region to region, but the reason for such significant territorial differences is still unknown. The most common age group at the time of first presentation for PES was the seventh decade of life – 40,89% of patients [5]. The average age of patients with PES was 66,2 years, and the prevalence of PES increased with age (10,1% in the 41-50 age group and 28,8% in the over 81 age group) [6]. In general, worldwide, PES occurs in approximately 10-20% of the population over 50 years of age, with prevalence ranging from 1,5% to 40,9%, in Europe – from 3,6% to 34,2%, in Asia - from 1,5% to 22,1%, in African countries - from 1,5% to 40%. Other data show that the frequency of PES varies from 0,3% to 18% depending not only on the region but also on the examination method [7]. The global prevalence of PES is increasing, with approximately 70 million people living with this condition, and many patients with this condition may be undiagnosed. PES is more common in Finland, Scandinavia, Greece and Turkey, and the difference in rates can be explained by genetic, environmental or unknown factors [8]. In Scandinavian countries, the highest prevalence has been recorded, where approximately half of open-angle glaucoma cases are associated with PES [9]. It has been reported that in northern Sweden, PES affects every fourth person who reaches the age of 66 [10]. The prevalence of PES in Croatia was 3,6% [11]. In a study conducted in Jordan, the frequency of PES among patients over 50 years of age was 4,9% [12]. The prevalence rate among the population of Pakistan aged 45 and older was 6,45% [13]. In the defined population of the state of Minnesota (USA), the age- and sex-standardized incidence of PES was 25,9 per 100 000 population [14]. The prevalence of PES in the Indian state of Kashmir among individuals aged 49 to 89 years was 26,32% [15]. In Turkey, the prevalence of PES among patients over 40 years old was 5,0% [16]. Thus, it is obvious that the prevalence of PES depends on geographic location, ethnicity, as well as many other factors (environmental, demographic, and genetic).

No differences were found between PES-positive and PES-negative individuals in age- and sex-standardized median life expectancy and all-cause mortality rates [17].

It is worth noting that epidemiological studies conducted in different countries and at various times often lack consistency and are difficult to compare due to the involvement of populations of varying sizes and age-sex structures. On the other hand, this population-based approach to studying PES epidemiology is justified, as the prevalence of PES is different in each population. Thanks to population studies, it is possible to determine the individual needs of the population regarding the diagnosis and treatment of PES, and therefore, resources in this population can be used more effectively [18].

The epidemiological characteristics of PES include age and gender factors. All researchers agree that the prevalence of PES increases with age, although there are exceptions, such as reports of a 27-year-old man [19] and a 28-year-old woman [20] diagnosed with PES, albeit against the background of ocular diseases requiring surgical intervention. The prevalence of PES by gender varies in different regions; however, some researchers report a higher prevalence among men [5, 12, 15, 21]. For example, it has been stated that men were affected more frequently than women (55,2% and 44,8%, respectively).

In addition, PES is commonly observed among patients who have undergone cataract extraction surgery [6]. Overall prevalence is higher among individuals with lower socioeconomic status and retirees [5].

PES is associated with numerous genetic risk variants across different gene loci [22], and the syndrome exhibits a hereditary component [23]. Familial aggregation of PES and PEG indicates a genetic inheritance pattern, although the magnitude of risk varies among populations [24]. However, a purely genetic explanation is unlikely to account for certain characteristics of the disease, such as its progressive course, asymmetric ocular manifestations, age-related onset, and the development of PEG in only a subset of individuals with PES [25]. It appears that the development of PES is influenced by a combination of genetic predisposition and environmental factors; thus, further research into these external influences may improve understanding of PES pathogenesis and inform more effective, targeted therapeutic strategies [7].

Currently, the pathogenetic concept describes PES as an elastic microfibrillopathy, with key factors including transforming growth factor beta-1 (TGF-β1), oxidative stress, and impaired cellular defense mechanisms [26].

Environmental risk factors include residence in regions with high annual sunlight exposure, proximity to the equator, and higher altitudes. Prolonged outdoor exposure – due to work, leisure, or rural living – may increase risk via excessive ultraviolet (UV) radiation. Even in northern regions with low temperatures, UV exposure can occur due to sunlight reflected from snow or water surfaces [7, 15, 27].

Dietary influences may also play a role. Chronic alcohol consumption and high intake of coffee or tea can elevate homocysteine levels, which may also result from deficiencies in vitamins B6, B12, or folate [8, 28, 29].

Population-based studies indicate that PES and PEG may be associated with systemic conditions, particularly vascular diseases, inguinal hernia, and pelvic organ prolapse in women [30]. Additional reports suggest links between PES and hypertension, hearing loss, and the use of medications for cardiovascular and mental health disorders [16, 31]. Associations with heart failure and age-related macular degeneration further support a potential vascular contribution to the development of PES [31].

Patients with PES are frequently affected by cataracts, the most common type being nuclear sclerosis [15]. Cataracts were diagnosed in 65% of patients with PES [32], and cataract extraction surgery was performed in 25,9% of eyes with PES [5].

One of the serious consequences or complications of PES is recognized to be open-angle glaucoma. Patients with this syndrome have a tenfold higher risk of developing glaucoma compared to those without PES [8]. According to other data, glaucoma occurs 20 times more frequently in patients with PES than in the general population of the same age, which is why PES can be considered a true trigger for glaucoma development [33].

The guidelines of the European Glaucoma Society state that PEG develops in approximately 15-26% of eyes with PES over a five-year period [30]. However, data on the prevalence of PEG among patients with PES vary greatly. The age- and sex-standardized incidence of PEG was reported as 9,9 cases per 100,000 population in India [14]. In a Swedish study, the prevalence of PEG was 2,1% [10]. According to other data, PEG was present in one-quarter of patients, primarily in those with clinically bilateral PES [12].

Among patients with bilateral PES (65,2% of cases), glaucoma was registered in 34,7%, while among patients with unilateral PES, glaucoma was present in 45,0% [34]. Another study reported that PES was predominantly unilateral, with glaucoma detected in one-quarter of the affected eyes [5]. It has been established that the prevalence of glaucoma in patients with PES is 15,3% [35], while other researchers reported PEG in 26% of PES patients aged 59-90 years [36], and even 30,3% in some cases [32].

PEG accounts for 23,6% of all cases of open-angle glaucoma [11]. It is considered the most aggressive form of secondary glaucoma and is difficult to manage. A quarter of PEG patients are blind in one eye, and 7% are blind in both eyes [33]. The progression of PEG occurs approximately three times faster than that of primary open-angle glaucoma [30].

However, not every patient with PES will inevitably develop glaucoma, and it is impossible to accurately predict which individuals with PES will experience optic nerve damage and, ultimately, vision loss [23].

Knowledge of the characteristic ophthalmologic clinical signs of PES and PEG is essential for early detection. One of the most common manifestations of PES is elevated intraocular pressure (IOP), which is associated with the accumulation of pathological material within ocular structures, thereby disrupting the normal outflow of aqueous humor. In turn, increased IOP may lead to optic nerve damage and the development of glaucoma.

Normotensive fellow eyes of patients with unilateral hypertensive PEG carry a significant risk of glaucomatous damage, which is associated with the level and range of IOP fluctuations [37]. Eyes with PES are approximately six times more likely to exhibit elevated IOP compared to eyes without PES [10], and elevated IOP has been recorded in 9% of patients with PES [35].

At the time of PES diagnosis, elevated IOP and its diurnal fluctuations are usually observed [34], with the range of IOP fluctuations in PES being broader than in primary open-angle glaucoma [8]. Other studies have also confirmed an epidemiological link between PES and elevated IOP [13, 23, 31].

Patients with PES commonly exhibit diurnal IOP fluctuations: higher values in the morning and evening hours (28,8% of eyes) and normal IOP readings during the daytime (71,2% of eyes), which underscores the importance of IOP monitoring [36].

When measuring IOP, higher values (29-34 mmHg) were observed in patients with features of anterior chamber angle blockage (such as angle narrowing or closure, increased pigmentation, and the presence of confluent exfoliative conglomerates) [33].

An important manifestation of ocular pathology is undoubtedly reduced visual acuity. In patients with PES, visual acuity was significantly lower compared to patients without PES [15]. According to another study, mild visual impairment or its complete absence was observed in 70% and 20% of eyes with PES, respectively [5].

For early diagnosis, knowledge of the micro-symptoms of the disease is essential. In particular, an accurate diagnosis of PES can be made by detecting the presence and location of PEM [8]. PEM accumulates on the anterior lens capsule in a characteristic pattern known as the "moth-eaten pupil" due to pigment loss along the pupillary margin, which becomes more visible after pupil dilation [30]. The most common locations of PEM were the pupil (81,01% of eyes) and the iris (19,15%) [5].

Thus, patients with PES represent a high-risk group for vision impairment, primarily due to the development of glaucoma. Glaucoma is a major cause of vision loss in the elderly, making the early identification of such patients crucial for slowing glaucoma progression. Due to the subtle and uneven progression of PES, glaucoma is often diagnosed at an advanced stage [23].

The need for glaucoma screening in the elderly has been discussed for over 40 years, with proposed methods including intraocular pressure measurement, visual field testing, and optic disc evaluation. It was hypothesized that with the use of these early diagnostic techniques combined with effective treatment, significant progress in preventing blindness could be achieved [38].

Fifteen years later, a broader range of laboratory methods became available, including light and electron microscopy, as well as immunohistochemical and molecular-biological approaches. It was emphasized that clinical diagnosis relies on biomicroscopy, biocytology, and laser Tyndallometry [39]. Early forms of PES were found to be more frequently detected than expected in eyes with cataracts. Therefore, alongside biomicroscopy – which remains a valuable tool for early detection – there is a need to refine clinical criteria for the early diagnosis of PES [40].

Currently, to reduce glaucomatous damage in patients with PES, extended evaluation of the anterior segment is recommended to prevent missed early-stage diagnoses [1]. Monitoring the retinal nerve fiber layer (NFL) thickness and the average peripapillary retinal nerve fiber layer (RNFL) thickness in eyes with PES using optical coherence tomography (OCT) may aid in the early detection of eyes at risk of developing PEG [36]. Early identification of retinal damage provides clinically significant information for detecting initial glaucomatous changes in patients with PES [41].

OCT studies have revealed significant thinning of the retinal nerve fiber layer in patients with PES, with even more pronounced thinning in patients with PEG [33]. The diagnostic value of a portable pupillometer for differentiating eyes with PES from healthy controls by measuring pupil diameter was found to be low (sensitivity 14%, specificity 94%) [42]. Diagnostic errors in PES are also reported in pseudophakic patients, which may have significant consequences for future treatment. Therefore, precise attention to the anatomy of the pupillary margins and thorough gonioscopic evaluation of the iridocorneal angle are essential for accurate diagnosis [43].

Ophthalmologists should perform annual examinations of patients with PES and properly inform them, as the risk of glaucoma development may persist throughout life and increases with age [4, 34, 35]. Due to the increased incidence of cataract and postoperative complications associated with PES, careful preoperative clinical evaluation of patients is necessary to ensure the effectiveness of surgical intervention [15].

Public health strategies aimed at screening for PES and early detection of PEG may be important in alleviating the socio-economic burden of the syndrome, as it has been shown that eye care costs in patients with PEG are 27% higher than in patients with primary open-angle glaucoma due to additional costs for multiple ophthalmological visits, surgical interventions, and treatment of possible complications [3]. The experience of early diagnosis of PES in Sweden has been interesting. It is suggested that the possibility of diagnosing PES by primary care optometrists should be considered to reduce unnecessary referrals to secondary ophthalmology departments and to make wise use of limited health care resources. At the same time, the risk of missing glaucoma in its early stages can be reduced, even in patients with mildly elevated IOP [44].

## CONCLUSIONS

An increasing number of individual population studies on the prevalence of PES and its etiological relationship with PEG provide a clearer picture of the global epidemiological process. Recent research has improved understanding of the roles of genetic, environmental, and lifestyle factors in the development of PES, which may contribute to the design of more targeted treatment strategies. Evidence of systemic associations between PES and cardiovascular and cerebrovascular pathologies has grown, and knowledge of the pathophysiology of affected tissues has expanded through analysis of PES composition. Studying the effects of PES on ocular tissues allows for the refinement of diagnostic criteria, optimization of clinical management and treatment regimens, and reduction of surgical complications. However, prevention of PES remains an unresolved issue. Screening of at-risk populations – particularly individuals over 50 years old – remains the primary strategy to prevent the development of pseudoexfoliative glaucoma.

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**CONFLICT OF INTEREST**
The Authors declare no conflict of interest

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**RECEIVED:** 10.08.2025
**ACCEPTED:** 22.10.2025

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