Twelve-Year Incidence and Baseline Risk Factors for Pseudoexfoliation: The Thessaloniki Eye Study (An American Ophthalmological Society Thesis)

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• PURPOSE: To determine the 12-year incidence of pseudoexfoliation (PEX), baseline risk factors for incident PEX and risk factors for incident pseudoexfoliative glaucoma (PEXG) among those with PEX in an elderly white population.

• METHODS: Longitudinal, population-based study in Thessaloniki, the major urban center in Northern Greece. The baseline cohort included 2554 participants ≥60 years old. The surviving cohort was re-examined 12 years later using the same methodology. PEX was defined as typical fibrillar material at the pupil margin and/or on the lens capsule. Glaucoma was defined as both structural and functional damage, irrespective of intraocular pressure (IOP).

• RESULTS: Of 1468 eligible subjects in the surviving cohort, 1092 (74%) participated in the follow-up study. The mean age ± standard deviation (SD) at baseline was 68.9 ± 4.6 years. The mean follow-up time was 11.6 ± 1.6 years. The 12-year incidence of PEX was 19.6% (95% confidence interval (CI), 17.1-22.2), with women more likely to be affected than men (Fisher's exact test, $P = .0197$). Higher axial length was associated with lower odds of incident PEX (odds ratio [OR], 0.72 per mm; 95% CI, 0.57-0.92). PEX at baseline was not associated with an increased likelihood of major vascular disease ($P = .9038$). Higher baseline IOP (OR, 1.26 per mm Hg; 95% CI, 1.07-1.48) and history of heart attack at baseline (OR, 13.49; 95% CI, 2.85-63.87) were associated with a greater likelihood of developing PEXG among those with PEX. A history of alcohol consumption at baseline was protective of individuals developing PEXG if they had PEX at baseline.

• CONCLUSION: This is one of the very few longitudinal population-based studies that has specifically assessed the incidence of PEX. The association with axial length was previously found only in a cross-sectional study. The associations with heart attack and alcohol consumption are new findings. In individuals with baseline PEX, higher IOP at baseline, history of heart attack at baseline, and no alcohol consumption were associated with a greater likelihood of developing glaucomatous damage approximately 12 years later. NOTE: Publication of this article is sponsored by the American Ophthalmological Society. (Am J Ophthalmol 2019;206:192–214. © 2019 Elsevier Inc. All rights reserved.)

BY INVESTIGATING THE PREVALENCE AND INCIdence of a disease in a population, as well as the factors that influence it, epidemiology provides the foundation for disease prevention and control.[1] Prevalence describes the proportion being diseased at a certain point of time, whereas incidence describes the proportion becoming diseased during a certain period of time. Prevalence can be estimated through cross-sectional studies, whereas incidence requires the longitudinal follow-up of a sizable population cohort over time. As opposed to other types of studies in medical research, subjects enrolled in population-based studies are selected from the general population. Therefore, "*in many respects, population-based studies are the most valid, and often the only way to determine the prevalence and incidence of a disease; the population-attributable risk (and hence impact) of new risk factors for conditions with complex, multifactorial etiologies*."[2] Although both cross-sectional and longitudinal population-based studies have immensely increased our knowledge of ocular diseases, longitudinal studies are particularly valued because they have the optimum design[3,4]: to measure the absolute risk of developing a disease in a given period, thus providing information with clinical and public health applications; to identify risk factors for a disease, thus providing the foundation for disease prevention; to establish causation, thus providing insight into disease pathophysiology, which is crucial for developing effective treatments; to evaluate the natural history of a disease, which can lead to better understanding of the disease itself.

To date, a number of population-based studies conducted in different parts of the world have provided prevalence data on

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pseudoexfoliation (PEX) syndrome. First described in 1917 by John G. Lindberg,[5] PEX is an age-related disorder of the extracellular matrix, characterized by the production and progressive accumulation of abnormal fibrillar material in various intraocular and extraocular tissues. Since then, there has been a wealth of knowledge on the molecular biology of PEX, its genetic background and pathophysiology, its epidemiology, and its association with ocular and systemic alterations[6–15]; PEX is an established risk factor for the prevalence,[16,17] incidence,[18] and progression of glaucoma,[19] which is the leading cause of global irreversible blindness.[20] Pseudoexfoliative glaucoma (PEXG) is considered to be the most common type of secondary glaucoma.[6] Typically associated with high intraocular pressure (IOP) and large IOP fluctuations, PEXG is more aggressive in its course and more resistant to medical treatment than primary open-angle glaucoma (POAG).[21] However, in all populations, most people with PEX do not have glaucoma[9] and the precise interaction between PEX and glaucoma is still unclear.[13] Other ocular associations with PEX include alterations of the iris vasculature[22] and the blood-aqueous barrier,[23] higher incidence of nuclear cataract and cataract surgery,[24] and damage to the zonular apparatus, which, combined with poor pupillary dilation, increases the risk of complications from cataract surgery.[25] The identification of PEX material in the visceral organs, skin, and vessel walls[15] has prompted scientists to investigate the association of PEX with cardiovascular diseases and mortality.[8] To date, study results have been inconsistent and therefore this association has not been established.[26–37]

Based on our current state of knowledge, PEX occurs worldwide, but the reported prevalence estimates vary considerably. Possible reasons for these discrepancies include differences among populations in terms of genetic predisposition and environmental exposures, differences in study methodology, and inconsistencies in the criteria used to define PEX. This topic is extensively discussed in a recently published review on the epidemiology of PEX.[13] According to population-based data, the prevalence of PEX is as high as 40% in elderly Scandinavian populations.[38–40] The Thessaloniki Eye Study found that the prevalence of PEX in Greece is 11.9% in those ≥60 years old,[41] considerably higher than in other parts of the world, such as the United States,[42,43] Australia,[16,44] and Asia.[45–50] Conversely, there are limited data on the incidence of PEX and on factors associated with the development of PEX.[13] This is mainly because few population-based studies in the field of glaucoma have re-examined their initial population to collect longitudinal data[3,4,40,51–60] and even fewer studies have specifically assessed PEX. The Reykjavik Eye Study (5-year and 12-year follow-up),[51,52] the study by Aström and coworkers[53] in Skellefteå, northern Sweden (21-year follow-up) and the Chennai Eye Disease Incidence Study (6-year follow-up)[60] are the only prospective longitudinal population-based studies to have provided incidence data for PEX. In addition, a large, retrospective, community-based study in the United States has provided data on the occurrence of PEX over a period of 15 years.[61]

In view of the scarcity of data on the incidence of PEX and the aforementioned gaps in the literature, the present study aimed to investigate the following: (1) the 12-year incidence of PEX and its characteristics, (2) baseline factors associated with the development of PEX, (3) whether baseline PEX increases the risk of major cardiovascular diseases, and (4) baseline factors associated with the development of PEXG among those with PEX, in a well-defined elderly white population.

METHODS

THE THESSALONIKI EYE STUDY IS A POPULATION-BASED study of chronic eye diseases in Thessaloniki,[41] which is the major urban center in Northern Greece and the second largest city in Greece after Athens. The main objectives of the study were to determine the prevalence, incidence, progression, and risk factors for major eye diseases in this European population. After an initial baseline prevalence phase (2000-2005), the surviving cohort members were re-examined approximately 12 years later in the Thessaloniki Eye Study follow-up visit (2013-2015). According to historical data from the Hellenic Statistical Authority, at the time of the prevalence phase, the population of Thessaloniki was homogenous, with 97.7% of people identified as being of Greek ethnicity and representative of the overall Greek population. The Institutional Review Board (Ethics Committee) of the Aristotle University Medical School approved prospectively both the prevalence and the follow-up visit of the Thessaloniki Eye Study. Also, the Institutional Review Board of the University of California, Los Angeles approved the plans for data analyses. In both phases, all study procedures adhered to the principles outlined in the Declaration of Helsinki for research involving human subjects and all participants gave written informed consent before their participation.

• **THESSALONIKI EYE STUDY: PREVALENCE STUDY (2000-2005):** Details about the randomization and recruitment processes have been previously published.[41] Briefly, the initial recruitment frame of the Thessaloniki Eye Study consisted of 5000 people ≥60 years of age, randomly selected from 321 000 persons included in the municipality registers of the city of Thessaloniki. All subjects were contacted by phone or mail to ascertain their willingness to participate in the study. Those who agreed to participate were invited to the study center at the Aristotle University of Thessaloniki for an extensive ophthalmic screening examination. To increase participation rate and to minimize potential nonparticipation bias, a home-visit eye examination was arranged for persons unable to visit the study examination center because of illness or major disability. Details on observation procedures and definitions used in

the Thessaloniki Eye Study have been previously published.[41] Among the 3617 eligible subjects, 2554 participated in the Thessaloniki Eye Study prevalence phase (participation rate 71%); of these, 2261 (89%) had the clinic examination and 293 (11%) had the home-visit examination.[41]

• **THESSALONIKI EYE STUDY: INCIDENCE STUDY (2013-2015):** Approximately 10 years after the prevalence phase, the Thessaloniki Eye Study directory of phone numbers and addresses of all study participants was used to contact each of the 2554 study participants from the original cohort. This directory also includes contact information of close family members. Phone calls were made between 09:00 and 14:00 and 17:30 and 20:00 during weekdays. In the elderly Greek population, resting/afternoon sleep typically takes place between 14:00 and 17:30. In case of no response, repeated phone calls were made on different days, making sure that the study subject had been contacted both in the morning and in the afternoon. In case of no response after multiple attempts, updated contact information on the participants was requested by family members, who were contacted using the previously described process. In the event of no response from family members, information was requested from neighbors identified through the same addresses and from phone registries.

Those from the original cohort who had not died or had not moved to a distant geographic location were considered to be eligible and were re-invited to the Thessaloniki Eye Study center for an extensive ophthalmic examination. Similar to the prevalence phase, a home-visit eye examination was arranged for those unable to attend because of illness or major disability. Those who refused to participate were asked about the reason for their refusal.

Data were collected using the same methodology that was followed during the prevalence phase and details are provided later in this article.[41] Ophthalmic technicians and nurses who were specifically trained for the purposes of the study were responsible for questionnaire interview and data collection, using standard operating procedures to ensure standardization and homogeneity of data. Three glaucoma-trained ophthalmologists were responsible for ophthalmic examination at the slit-lamp, including Goldmann tonometry. At least 2 among them examined each patient, and all diagnoses were made by consensus agreement.

In-clinic examination. All participants were interviewed for demographic data (age, sex), ophthalmic and systemic diseases (hypertension; diabetes; cardiovascular disease; history of heart attack, coronary artery bypass, or vascular surgery; and migraine), systemic medications (use of antihypertensive and diabetes treatment) and lifestyle (smoking, alcohol consumption, diet, and hours of sleep per day). All participants underwent a standardized eye examination with visual acuity measurement, visual field testing, slit-lamp anterior segment examination, applanation tonometry, gonioscopy, and dilated fundus slit-lamp biomicroscopy. Central corneal thickness (CCT), axial length, corneal hysteresis, and body weight and height were also measured.

Visual acuity was measured with Early Treatment of Diabetic Retinopathy Study (ETDRS) charts and participants' spectacles were measured with focimetry. When visual acuity was less than 20/30 with habitual correction, a full refraction was performed and best-corrected visual acuity was measured. IOP was measured using a calibrated Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland). The mean IOP of 3 readings in each eye was defined as the pressure for that eye. In the presence of nonoccludable iridocorneal angles, 5% phenylephrine and 0.5% tropicamide were instilled for pupil dilation. When the angle was potentially occludable, participants were referred for laser peripheral iridotomy in both eyes. Dilated lens and fundus examinations were conducted after the iridotomies were performed. Optic disc assessment involved the clinical estimation of vertical cup-to-disc ratio, the identification of neuroretinal rim thinning and/or rim notching, peripapillary atrophy, and optic disc hemorrhage. CCT was measured with an ultrasound pachymeter (Quantel Medical, Paris, France). The mean value of 5 readings in each eye was defined as the CCT for that eye. Axial length was measured with standard biometry. The in-clinic examination also included fundus photography, imaging with optical coherence tomography, Heidelberg retina tomography, and blood sample collection. However, these data were not used in the analyses of this specific report.

Protocol for visual field testing

Humphrey automated perimetry (Carl Zeiss Meditec, Dublin, California, USA) was used for visual field examination. Eyes with visual acuity of counting fingers or worse did not undergo visual field testing. The examination protocol used in the prevalence phase of the Thessaloniki Eye Study[41] was also followed in the follow-up visit. In brief, all study participants underwent suprathreshold screening visual field testing. In case of unreliable or abnormal results, full-threshold perimetry was performed with the 24-2 Swedish Interactive Threshold Algorithm (SITA).[62] In case of unreliable or borderline results, a second 24-2 SITA standard test was performed. The following reliability criteria were used: fixation losses, and false-negative and false positive errors <33%. The screening test was considered abnormal when at least 1 point (not including points near blind spot) was missed. A reliable threshold field was considered to be borderline when the glaucoma hemifield test was borderline with P value of pattern SD >.05.

Protocol for measurement of corneal hysteresis and quality control

Corneal hysteresis was measured with the Ocular Response Analyzer (ORA; Reichert, Inc, Depew, New York, USA). The acquisition protocol required up to 4

high-quality measurements per eye, with a maximum of 8 measurements obtained in each eye. The following quality criteria were applied[63]: (1) the waveform score (WS) had to be ≥6, and (2) the "in" and "out" signal peaks in the applanation diagram had to be symmetrical.

To ensure that only high-quality measurements would be included in the analysis, an algorithm implemented in Python programming language was developed and used to process exported data from the ORA software. These data included both WS and applanation signal values. The algorithm calculates the corneal hysteresis per eye as the mean of the 3 (of 4) measurements with the highest quality. When fewer than 3 measurements fulfilled the quality criteria, 1 or 2 high-quality measurements were used. As a first step, the algorithm rejects all measurements with WS <6. As a second step, the algorithm uses dynamic-type warping to calculate the similarity of each applanation signal diagram to the one with the highest WS and spots the extreme outliers. For the purposes of the analyses, corneal hysteresis was defined by subject, and the eye that had the highest number and highest quality of reliable measurements was selected. When these were equal between the 2 eyes, the eye was selected randomly.

Home-visit examination. All study participants underwent the same questionnaire as in the clinic visits, visual acuity measurement with ETDRS charts, IOP measurement with Perkins applanation tonometer, ophthalmic examination before and after pupil dilation with a portable slit-lamp, direct and indirect ophthalmoscopy, and blood sample collection.

Definitions. The definitions that were previously used in the prevalence phase of the Thessaloniki Eye Study were also used in the follow-up visit.[41] Consensus agreement between at least 2 of the 3 glaucoma-trained ophthalmologists was required to confirm the presence and location of PEX, and to assign the diagnosis of glaucoma. In case of disagreement, an open discussion for the final classification was carried out. The principal investigator (F.T.) examined all the glaucoma cases and was responsible for the final adjudication of the diagnosis.

Definition of PEX[26]

PEX was defined as the presence of typical fibrillar material in either eye at the pupil margin and/or on the lens capsule. The location of PEX was recorded (iris only/lens only/both on the iris and the lens). Before pupil dilation, a detailed high-magnification slit-lamp assessment of the pupil margin was performed. After pupil dilation, the anterior lens surface from each eye was scanned from left to right using a narrow slit-lamp beam and then was examined using a broad slit-lamp beam, looking specifically for early signs of PEX, including pregranular radial lines, as well as established granular deposits. As mentioned previously, dilation was conducted in all study participants, even in those with occludable iridocorneal angles, after bilateral laser iridotomy. The location of PEX either on the iris, the lens, or both was recorded. The detection and exact location of PEX required consensus agreement between at least 2 of the 3 glaucoma-trained ophthalmologists.

Definition of glaucoma[41]

Glaucoma was defined as the presence of both structural and functional damage according to specific criteria, irrespective of IOP. To avoid omitting subjects with mildly atypical findings or those with some missing data, a glaucoma diagnosis also was made when the clinical judgment was strongly in favor of the presence of glaucoma, even though the strict criteria, requiring both visual field defect and optic disc abnormality, were not fulfilled. This was applied in cases with (1) missing data (home visits, unable or unreliable visual field test secondary to low vision), (2) only visual field damage presenting typical characteristics of glaucomatous visual field defect, (3) only optic disc damage (thinning or notching of the optic disc rim combined with matching asymmetry of more than 0.2 cup-to-disc ratio), or (4) high IOP or a history of high IOP combined with optic disc findings (thinning or notching of the optic disc rim or asymmetry between the 2 eyes of more than 0.2 cup-to-disc ratio). Subjects were classified as having PEXG if they had glaucoma and PEX in either eye.

• **STATISTICAL METHODS:** Statistical analyses were performed using statistical software SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina, USA).

The number of participants included in each analysis depended on several factors, such as the objective of the analysis itself (eg, who the population at risk was), whether it was necessary to exclude some study participants (eg, those with bilateral pseudophakia or aphakia), the study variables to be considered in the analyses (eg, axial length and corneal hysteresis were available only in clinic visits), or whether both eyes had to be bilaterally phakic. All relevant data are provided in the methods, results, and tables.

Incidence of PEX. All study participants with PEX in at least one eye at baseline were excluded from all analyses described in this section. The incidence of PEX and corresponding 95% confidence intervals (CIs) were calculated:

- for the overall population, consisting of clinic-visit and home-visit participants
- for clinic visits, who had uniformly collected data
- for clinic visits after excluding those with bilateral pseudophakia/aphakia at baseline and/or incidence, to minimize potential misclassification bias with regard to the presence of PEX in the absence of the crystalline lens

In the overall population, the following proportions were also calculated among those who were bilaterally phakic:

- proportion of incident PEX by eye (right only, left only, both eyes)
- proportion of unilateral and bilateral PEX

To minimize potential misclassification bias, the same proportions also were calculated among clinic-visit participants, who had uniformly collected data.

To calculate the proportion of incident PEX by location of pseudoexfoliative material (iris only, lens only, both iris and lens), the location of PEX was determined by subject; for example, if one eye had PEX on the iris only and the fellow eye had PEX on the lens only, the study participant was classified as having PEX on both iris and lens. For this reason, we calculated these proportions in clinic-visit participants who were bilaterally phakic.

Risk factors for incident PEX. Only clinic visits were included in the risk factors analysis. Study participants with PEX at baseline and those with bilateral pseudophakia/aphakia at baseline or at follow-up were excluded from the analysis. Potential risk factors for PEX were selected based on the literature and a previous Thessaloniki Eye Study report investigating risk factors for open-angle glaucoma.[17] In view of the high prevalence of PEX in Greece, compared with other parts of the world,[41] we also included parameters that are considered to be typical of the Greek population of this age range (afternoon sleep and consumption of ouzo). Subjects with incident PEX in at least one eye were compared with controls (defined as those without incident PEX in either eye), with regard to the following baseline characteristics:

- demographic: age and sex
- ocular: higher IOP and higher vertical cup-to-disc ratio between 2 eyes, proportion of subjects with IOP ≥22 mm Hg in either eye, vertical cup-to-disc ratio ≥0.7 in either eye, vertical cup-to-disc ratio >0.2 asymmetry between 2 eyes, myopia, and lower CCT, lower corneal hysteresis, and higher axial length between 2 eyes
- systemic: body mass index (BMI) and self-reported history of systemic hypertension, diabetes, cardiovascular disease, migraine, heart attack, coronary artery bypass, or vascular surgery, and any systemic disease (defined as any of the previous conditions)
- lifestyle: afternoon sleep, smoking status, smoking pack-years, consumption of ouzo, alcohol consumption.

All of the previous data had been collected during the prevalence phase of the study, except CCT, corneal hysteresis, and axial length, which were measured at follow-up. These parameters were included in the analysis on the premise that they remain stable during adulthood.[64–67]

The spherical equivalent of refractive error was calculated as the spherical value plus half of the cylindrical value. Myopia was analyzed among subjects with at least 1 phakic eye and was defined as mild (less than −1 diopter), moderate (between −1 and −3 diopters) and high (more than −3 diopters). BMI was calculated as weight divided by the square of height, and study participants were classified as normal (<25), overweight (≥25 and <30), or obese (≥30). The following categories were used to describe afternoon sleep: none, 1 to 2 days per week, 3 to 4 days per week, more than 4 days per week. Three categories were used to describe smoking status: nonsmoker (has never smoked at least once a day for 1 year), current smoker (has smoked at least once a day for 1 year and has smoked within past year) and ex-smoker (has smoked at least once a day for 1 year but has not smoked within past year). Smoking pack-years were calculated as number of cigarettes smoked per day divided by 20, and multiplied by the number of years of smoking. For this parameter, the comparison was done only among current and ex-smokers. The consumption of ouzo was described as less than once per week vs equal or more than once per week. On the basis that 1 average glass of an alcoholic beverage corresponds to approximately 10 g of alcohol, the overall consumption of alcohol was described as the sum of grams per day for beer, wine, liquor, and ouzo, using the following formula: none = 0 g/d; <1 glass a month = 0.33 g/d; ≥1 glass a month, but <1 glass a week = 0.83 g/d; 1 to 3 glasses a week = 2.9 g/d; 4 to 7 glasses a week = 7.9 g/d; 8 to 14 glasses a week = 15.7 g/d; >14 glasses a week = 20 g/d.

The Kruskal-Wallis test was used for continuous variables and the Fisher's exact test for categorical variables. All variables with $P < .25$ in the univariable analysis were included in a multivariable model. P values were considered statistically significant when <.05.

Analysis on baseline PEX as a potential risk factor for major vascular disease (MVD). The analysis included all study participants (clinic visits and home visits), except those with MVD at baseline and those with bilateral pseudophakia/aphakia at baseline. MVD at baseline and MVD at follow-up were defined as self-reported history of at least 1 of the following at baseline or at follow-up, respectively: cardiovascular disease, heart attack, and coronary artery bypass or vascular surgery. The following factors were included in a logistic regression model: PEX at baseline, age, sex, self-reported hypertension, and self-reported diabetes.

Risk factors for PEXG among those with PEX. The population at risk for this analysis consisted of those with PEX at baseline or incident PEX, excluding those with PEXG in either eye at baseline. Therefore, it was not necessary to exclude those with bilateral pseudophakia or aphakia. However, as noted previously, we ran the analysis only in

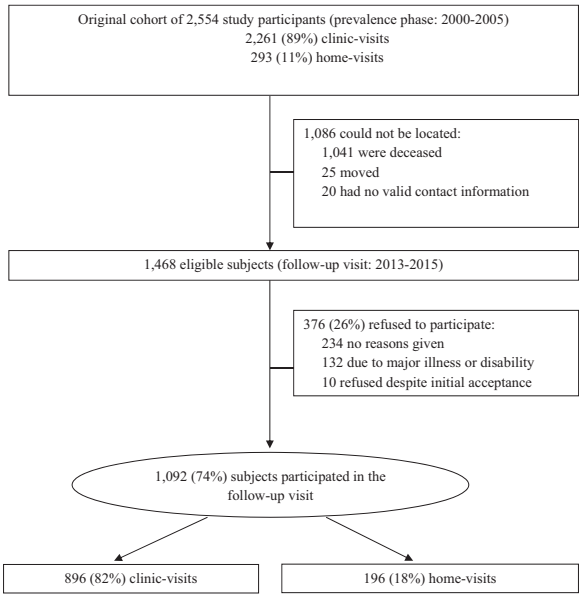

FIGURE 1. Follow-up visit of the Thessaloniki Eye Study: participation flow chart.

clinic-visit participants, who had uniformly collected data. Subjects with incident PEXG were compared with subjects without incident PEXG with regard to all of the parameters mentioned previously and a similar analysis was followed. Incident PEX and IOP-lowering treatment (medication, laser, or surgery) also were included in the analysis as potential risk factors for PEXG among those with PEX.

In a separate model, we also examined whether the location of PEX (iris only, lens only, iris and lens) is a risk factor for PEXG among those with PEX. To minimize possible misclassification bias with regard to the location of PEX, the analysis included all clinic-visit participants with PEX at baseline or incidence, excluding those with bilateral pseudophakia/aphakia. One eye was included per subject, provided that it had incident PEXG and was phakic. For this specific analysis, the location of PEX had to be determined by eye and was defined as the location of PEX at follow-up in the eye that had developed PEXG (conversely, in the previous analysis, because incident PEX was determined by subject, the proportion of incident PEX by location of PEX was also defined by subject). When both eyes had incident PEXG and were phakic, the right eye was included in the analysis. Fisher's exact test was used for comparisons between the groups.

RESULTS

• **STUDY POPULATION:** Figure 1 presents the study flow chart of the Thessaloniki Eye Study follow-up visit. Of the 2554 study participants of the original cohort, 1041 (41%) were deceased and 45 (2%) had moved to a distant geographic location or had no valid contact information. Hence, there were 1468 (57%) eligible subjects for the follow-up visit, and all of them were invited to participate. Of these, 376 (26%) refused participation, with major illness or disability being one of the main reasons for refusal (132/376; 35%). The remaining 1092 (74%) subjects participated in the follow-up visit of the Thessaloniki Eye Study. Among these, 896 (82%) had the clinic-visit and 196 (18%) had the home-visit examination. Figures 2 and 3 describe the study population in each analysis with regard to the presence of PEX and lens status (for the overall population and clinic visits, respectively).

The mean age ± SD of the 1092 study participants was 68.9 ± 4.6 years, with 566 (51.8%) men and 526 (48.2%) women. The mean follow-up time was 11.6 ± 1.6 years. Table 1 presents the baseline characteristics of those who participated, those who refused, and those who had died or could not be located. Statistically significant differences between the groups were found with regard to age (Kruskal-Wallis test, $P < .0001$), sex (Fisher's exact test, $P < .0001$), PEX (Fisher's exact test, $P = .0003$) and myopia (Fisher's exact test, $P < .0001$). When participants were compared only with those who refused, those who participated were younger (68.91 ± 4.64 vs 70.17 ± 4.88, Kruskal-Wallis test, $P < .0001$) and were more likely to be men (51.8 vs 42, Fisher's exact test, $P = .0012$) compared with those who refused participation. There were no other statistically significant differences between the groups.

• **INCIDENCE OF PEX:** Results are presented in Table 2. Of the 1092 overall study participants, 96 (9%) had PEX at baseline and were excluded from the analysis. Thus, the overall population at risk for developing PEX consisted of 996 (91%) subjects. Of these, 195 subjects had incident PEX, which corresponds to a 19.6% (95% CI, 17.1-22.2) overall 12-year incidence of PEX in the Thessaloniki Eye Study. Among the 787 subjects who had clinic visits only, 179 had incident PEX, corresponding to an incidence of 22.7% (95% CI, 19.0-25.8). When we further excluded those with bilateral pseudophakia/aphakia, 114 of 595 subjects at risk had incident PEX, corresponding to an incidence of 19.2% (95% CI, 16.1-22.6).

Incidence of PEX by age. Results are presented in Table 3. In the overall population, the incidence of PEX was 18.9% (95% CI, 16%–22%) in those 60 to 69 years old, 23.9% (95% CI, 18.5%–30%) in those 70 to 74 years old, and 14.7% (95% CI, 8.5%–23.1%) in those ≥75 years old (Fisher's exact test, $P = .114$). However, only 102 of 996 (10.2%) subjects in the population were ≥75 years old. In subjects who had in-clinic visits, the incidence of PEX was higher in all age groups compared with the overall population, although the comparison between the groups did not reach statistical significance (Fisher's exact test, $P = .067$). Only 51 of 787 (6.5%) subjects who had in-clinic visits were ≥75 years old.

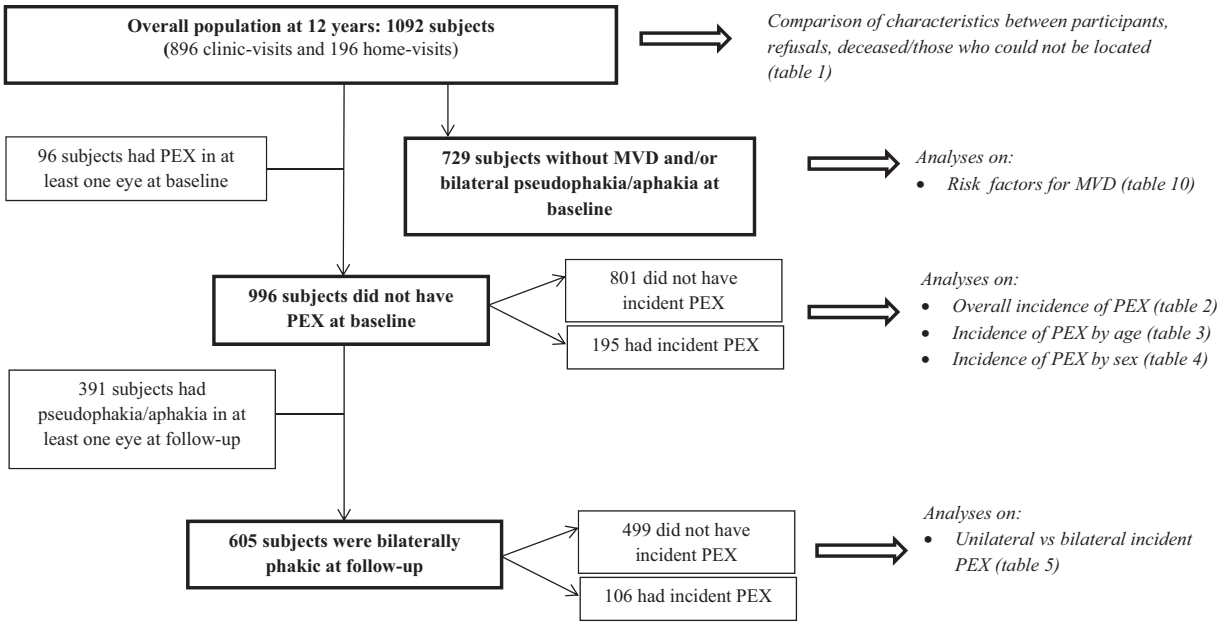

FIGURE 2. Flowchart of analyses in the follow-up visit of the Thessaloniki Eye Study: overall population. MVD = major vascular disease; PEX = pseudoexfoliation.

Incidence of PEX by sex. Results are presented in Table 4. In the overall population, the incidence of PEX was 18.6% (95% CI, 15.3%–22.2%) in men vs 20.7% (95% CI, 17.1%–24.6%) in women, and this difference was not statistically significant (Fisher's exact test, $P = .425$). In subjects who had in-clinic visits, the difference between the incidence of PEX in men (19.7%; 95% CI, 16.2%–23.7%) vs women (27%; 95% CI, 22.3%–32.2%) was statistically significant (Fisher's exact test, $P = .0197$).

In accordance with the preceding results, in the overall population, female sex (vs male sex) was not statistically significantly associated with the incidence of PEX (OR, 1.14; 95% CI, 0.84-1.56; $P = .41$). Conversely, in subjects who had in-clinic visits, female sex (vs male sex) was statistically significantly associated with the incidence of PEX (OR, 1.50; 95% CI, 1.08-2.10; $P = .017$). After adjustment for age, this association remained statistically significant (age-adjusted OR, 1.51; 95% CI, 1.08-2.12; $P = .016$).

Unilateral vs bilateral incident PEX. Results are presented in Table 5. In the overall population, of 605 participants who were bilaterally phakic and did not have PEX at baseline, 65 (10.7%; 95% CI, 8.4%–13.5%) had developed unilateral PEX: 37 of 65 (57%) in the right eye and 28 of 65 (43%) in the left eye. The proportion of bilateral PEX was 41/605 (6.8%; 95% CI, 4.9–9.1). The corresponding proportions for unilateral vs bilateral PEX in clinic visits only were 59 of 498 (11.9%) vs 36 of 498 (7.2%), respectively. The proportions of right vs left eyes in those with unilateral PEX were 36 of 59 (61%) and 23 of 59 (39%), respectively.

Location of incident PEX (lens/iris/both). Results are presented in Table 6. Of 498 clinic-visit participants who were bilaterally phakic, 14 (2.8%; 95% CI, 1.6%–4.7%) had developed PEX only on the lens, 36 (7.2%; 95% CI, 5.1%–9.9%) only on the iris, and 45 (9%; 95% CI, 6.7%–11.9%) both on the lens and the iris.

• BASELINE RISK FACTORS FOR THE DEVELOPMENT OF PEX: Of the 1092 overall study participants, 209 had the home-visit examination at baseline and/or at follow-up and 192 had bilateral pseudophakia/aphakia and were excluded from this analysis. Thus, 595 subjects were included in the risk factor analysis.

Comparisons of characteristics between those with and without incident PEX are presented in Table 7. Axial length (defined as "higher axial length between 2 eyes") was statistically significantly lower in those with incident PEX, compared with those who had not developed PEX (23.1 ± 0.8 vs 23.5 ± 1.0; Kruskal-Wallis test, $P = .0030$). None of the other variables were statistically significantly different between the groups.

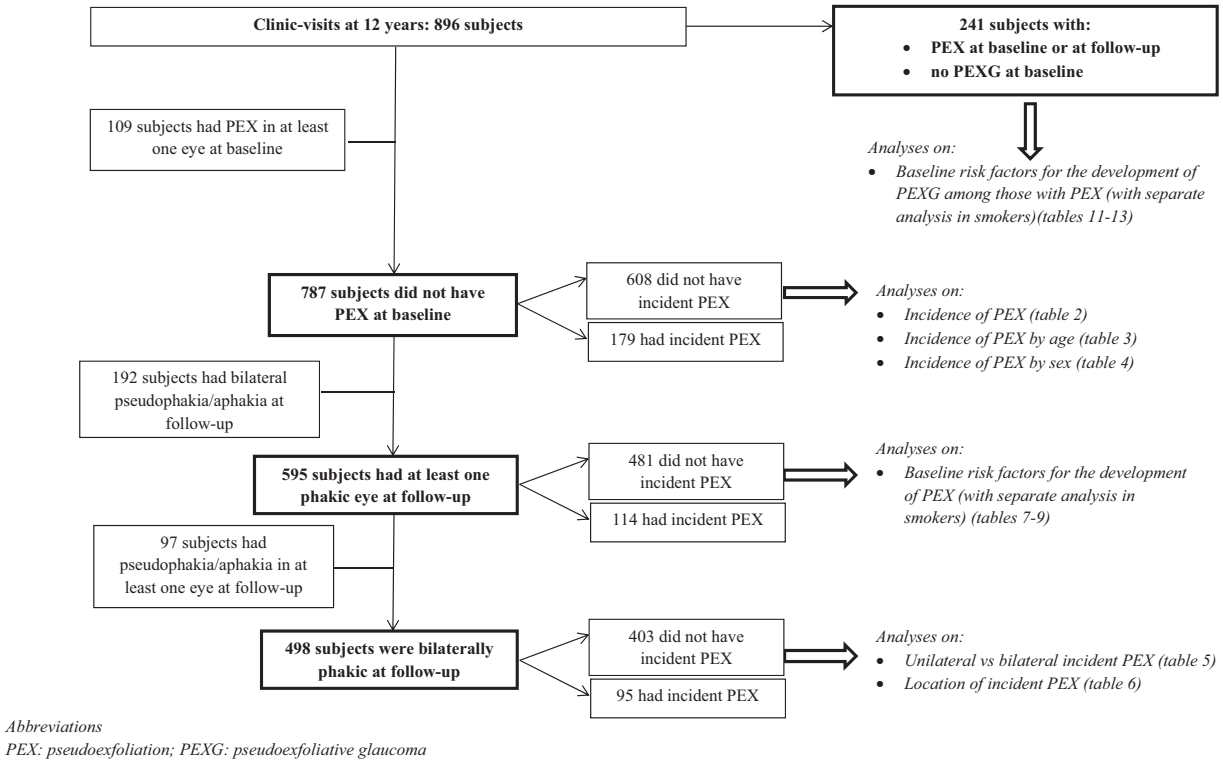

FIGURE 3. Flowchart of analyses in the follow-up visit of the Thessaloniki Eye Study: clinic visits only. MVD = major vascular disease; PEX = pseudoexfoliation; PEXG = pseudoexfoliative glaucoma.

Table 8 presents the results of the multivariable logistic regression model on risk factors for PEX. Higher axial length was significantly associated with decreased risk of incident PEX (OR, 0.72 per mm; 95% CI, 0.57-0.92; P = .0091). There was a borderline statistically significant association between older age and higher odds for incident PEX, (OR, 1.05 per year; 95% CI, 1.0-1.1, P = .0578). Age, sex, cup-to-disc (C/D) ratio >0.7, diabetes, and the consumption of ouzo were not statistically significantly associated with the development of PEX.

To investigate the overall exposure to tobacco smoke as a potential risk factor for PEX, we ran the logistic regression model only in current and ex-smokers for whom the variable "smoking pack-years" was available (Table 9). The model did not reveal any statistically significant associations with incident PEX.

• IS BASELINE PEX A RISK FACTOR FOR THE DEVELOPMENT OF MVD?: Of the 1092 overall study participants, 327 had MVD and 33 had bilateral pseudophakia/aphakia at baseline, and were excluded from the analysis. Three additional subjects were excluded due to missing data with regard to their MVD status at baseline or at follow-up. Of the remaining 729 subjects who were included in the analysis, 67 (9.2%) had PEX at baseline and 229 (31.4%) subjects in total developed MVD during the follow-up. Of the 67 subjects with PEX at baseline, 22 (32.8%) had incident MVD and 45 (67.2%) did not. The difference between the groups was not statistically significant (Fisher's exact test, P = .7838).

To consider the potential effect of age, sex, hypertension, and diabetes in the association of baseline PEX with incident MVD, all these variables were included in a logistic regression model (Table 10). The association between PEX at baseline and incident MVD was not statistically significant (OR, 1.03; 95% CI, 0.6-1.8, P = .9038). Those with hypertension at baseline had 46% higher risk of MVD compared with those who did not have hypertension (OR, 1.46; 95% CI, 1.05-2.01; P = .0227). None of the other variables were statistically significantly associated with the development of MVD.

• BASELINE RISK FACTORS FOR THE DEVELOPMENT OF PEXG AMONG THOSE WITH PEX: The analysis included the 241 study participants who fulfilled all of the following criteria: (1) in-clinic examination both at baseline and at follow-up examination, (2) PEX at baseline or incident PEX, and (3) no PEXG at baseline. Out of these, 22 (9.1%) were diagnosed with PEXG during the follow-up examination in the Thessaloniki Eye Study.

Comparisons of characteristics between those with and without incident PEXG are presented in Table 11. Those with incident PEXG had significantly higher

TABLE 1. Comparison of Baseline Characteristics Between Participants, Refusals and Deceased/Those Who Could Not Be Located in the Follow-up Visit of the Thessaloniki Eye Study

	Participants (n = 1092)	Refusals (n = 376)	Deceased or Not Located (n = 1086)	*P* Value[a]	*P* Value[b]
Age (yr ± SD)	68.91 ± 4.64	70.17 ± 4.88	74.60 ± 6.78	**<.0001**[d]	**<.0001**[d]
Gender (% male)	51.8	42	57.8	**<.0001**[e]	**.0012**[e]
Pseudoexfoliation (%)[c]	8.2	10.4	13.9	**.0003**[e]	.1979[e]
IOP (mm Hg ± SD)	15.80 ± 3.53	15.88 ± 3.83	16.18 ± 4.37	.5099[d]	.7206[d]
Vertical cup-to-disc ratio	0.3 ± 0.2	0.32 ± 0.22	0.31 ± 0.21	.5296[d]	.2814[d]
Myopia ≤ −3 diopters (%)[c]	3.7	5.1	6.8	**<.0001**[e]	.5445[e]
Family history of glaucoma (%)	7.9	7.3	8.6	.7424[e]	.8163[e]

IOP = intraocular pressure.
Bold values indicate statistical significance.
[a]Refers to the comparison among all 3 groups.
[b]Refers to the comparison between participants and refusals.
[c]Only in those with at least 1 phakic eye.
[d]Kruskal-Wallis test.
[e]Fisher Exact Test.

TABLE 2. Twelve-Year Incidence of PEX in the Thessaloniki Eye Study

Population at Risk (n)[a]	Subjects with Incident PEX (n)	Incidence (%)	95% CI
Clinic visits and home visits			
996	195	19.6	17.1–22.2
Clinic visits			
787	179	22.7	19.0–25.8
Clinic visits excluding those with bilateral pseudophakia/ aphakia			
595	114	19.2	16.1–22.6

CI = confidence interval; PEX = pseudoexfoliation.
[a]Defined as those without PEX at baseline.

TABLE 3. Twelve-Year Incidence of PEX in the Thessaloniki Eye Study by Age

Age at Baseline (yr)	Population at Risk[a] (n)	Subjects with Incident PEX (n)	Incidence (%)	95% CI
In the overall population (clinic visits and home visits)				
60 to 69	668	126	18.9	16–22
70 to 74	226	54	23.9	18.5–30
≥75	102	15	14.7	8.5–23.1
Total	996	195		
Fisher's exact test, *P* = .114				
In-clinic visits				
60 to 69	571	118	20.7	17.4–24.2
70 to 74	165	48	29.1	22.3–36.7
≥75	51	13	25.5	14.3–39.6
Total	787	179		
Fisher's exact test, *P* = .067				

CI = confidence interval; PEX = pseudoexfoliation.
[a]Defined as those without PEX at baseline.

IOP (defined as "higher IOP between 2 eyes") (17.9 ± 2.9 vs 15.5 ± 3.3; Kruskal-Wallis test, $P = .0004$) and a significantly higher proportion of a history of heart attack at baseline (5 [22.7%] vs 8 [3.7%]; Fisher's exact test, $P = .0032$), compared with those who had not developed PEXG. There were no other statistically significant differences between the groups.

Table 12 presents the results of the multivariable logistic regression model on risk factors for PEXG among those with PEX. Increased IOP (OR, 1.26 per mm Hg; 95% CI, 1.07-1.48; $P = .0051$) and history of heart attack (OR, 13.49; 95% CI, 2.85-63.87, $P = .001$) were statistically significantly associated with higher odds for PEXG among those with PEX. Alcohol consumption (any amount of grams per day compared with zero) was associated with decreased risk of PEXG among those with PEX. In addition, those with incident PEX (PEX in either eye at follow-up, but not at baseline) had lower odds for PEXG compared with those who had PEX at baseline, but the association did not reach statistical significance (OR, 0.37; 95% CI, 0.12-1.11, $P = .0750$). Sex, IOP-lowering treatment, vertical C/D ratio, axial length, BMI, and hypertension were not significantly associated with higher odds for PEXG among those with PEX.

TABLE 4. Twelve-Year Incidence of PEX in the Thessaloniki Eye Study by Sex

Sex	Population at Risk[a] (n)	Subjects with Incident PEX (n)	Incidence (%)	95% CI
In the overall population (clinic visits and home visits)				
Men	522	97	18.6	15.3–22.2
Women	474	98	20.7	17.1–24.6
Total	996	195		
Fisher's exact test, $P = .425$				
In-clinic visits				
Men	461	91	19.7	16.2–23.7
Women	326	88	27	22.3–32.2
Total	787			
Fisher's exact test, $P = .0197$				

CI = confidence interval; PEX = pseudoexfoliation.
[a]Defined as those without PEX at baseline.

TABLE 5. Twelve-Year Incidence of PEX in the Thessaloniki Eye Study by Eye and Laterality

	Subjects with Incident PEX (n)	Percentage (%)	95% CI
In the overall population (clinic visits and home visits), only bilaterally phakic subjects: n = 605[a]			
Unilateral	65	10.7	8.4–13.5
Right eye only	37	6.1	4.3–8.3
Left eye only	28	4.6	3.1–6.6
Bilateral	41	6.8	4.9–9.1
Total	106		
In-clinic visits, only bilaterally phakic subjects: n = 498[a]			
Unilateral	59	11.9	9.1–15
Right eye only	36	7.2	5.1–9.9
Left eye only	23	4.6	3–6.9
Bilateral	36	7.2	5.1–9.9
Total	95		

CI = confidence interval; PEX = pseudoexfoliation.
[a]This was the population at risk in each category, defined as those without PEX at baseline.

When we reran the logistic regression model only in current and ex-smokers, for whom the variable "smoking pack-years" was available (Table 13), smoking was not significantly associated with the development of PEXG among those with PEX. The associations with increased IOP (OR, 1.34 per mm Hg; 95% CI, 1.02-1.76; $P = .0382$) and history of heart attack (OR, 23.83; 95% CI, 3.26-174.14; $P = .0018$) remained statistically significant. None of the other variables were statistically significant in the model.

• **IS THE LOCATION OF PEX A RISK FACTOR FOR THE DEVELOPMENT OF PEXG AMONG THOSE WITH PEX?:** Among the 241 subjects who had clinic visits and who had PEX at baseline or incident PEX and no PEXG at baseline, 95 were excluded because of bilateral pseudophakia or aphakia at the follow-up examination. Among the remaining 146 subjects, 19 were also excluded because they had PEX in the pseudophakic/aphakic eye, but not in the phakic eye. Thus, the analysis included the 127 study participants who had PEX in at least one phakic eye. Among these, 46 had PEX only on the iris, 19 had PEX only on the lens, and 62 had PEX both on the iris and the lens. The corresponding proportions of PEXG cases among these groups were 2 of 46 (4.4%), 0 of 19 (0%), and 7 of 62 (11.3%), respectively. There was no statistically significant difference between the groups (Fisher's exact test, $P = .2491$). Given that there were no PEXG cases among those with PEX on the lens only, it was not possible to adjust the results for potential confounders in a logistic regression model.

TABLE 6. Twelve-Year Incidence of PEX in the Thessaloniki Eye Study by Location of Pseudoexfoliative Material

	Subjects with Incident PEX (n)	Percentage (%)	95% CI
In-clinic visits, only bilaterally phakic subjects: n = 498[a]			
Lens only	14	2.8	1.6–4.7
Iris only	36	7.2	5.1–9.9
Both lens and iris	45	9	6.7–11.9
Total	95		

CI = confidence interval; PEX = pseudoexfoliation.
[a]This was the population at risk, defined as those without PEX at baseline.

DISCUSSION

• **MAIN FINDINGS:** This longitudinal population-based study reports on the incidence of PEX over a 12-year period in an elderly white population. The main findings of our study are the following: (1) the 12-year incidence of PEX in the Thessaloniki Eye Study was 19.6%; (2) there was some evidence for higher incidence of PEX with older age and women were more commonly affected than men; (3) of those who were bilaterally phakic and had developed PEX at 12 years, approximately 60% had unilateral PEX and 40% had bilateral PEX; (4) almost half of these bilaterally phakic subjects had developed PEX both on the lens and the iris, whereas 38% had developed PEX only on the iris and 15% only on the lens; (5) higher axial length was associated with lower risk for developing PEX; (6) PEX at baseline was not associated with higher odds for MVD, systemic hypertension at baseline increased the risk of MVD by 46% at 12 years; (7) increased IOP and history of heart attack were significantly associated with higher odds for PEXG

TABLE 7. Comparison of Baseline Characteristics Between Those Who Developed PEX vs Those Who Did Not in the Follow-up Visit of the Thessaloniki Eye Study

Characteristics	Population at Risk[a]		P
	Subjects Without Incident PEX (n = 481)	Subjects with Incident PEX (n = 114)	
Age (yr) (mean ± SD)	67.5 ± 3.8	68.3 ± 4.6	.0735[m]
Age (yr range), n (%)			.179[n]
60-69	375 (78)	80 (70.2)	
70-74	84 (17.5)	26 (22.8)	
≥75	22 (4.6)	8 (7)	
Male sex, n (%)	293 (60.9)	59 (51.8)	.0897[n]
Higher IOP between 2 eyes (mm Hg) (mean ± SD)[b]	15.6 ± 3.5	15.7 ± 3.4	.6257[m]
IOP ≥22 mm Hg in either eye, n (%)[b]	20 (4.2)	5 (4.4)	1.00[n]
Higher vertical C/D ratio between 2 eyes (mean ± SD)[c]	0.3 ± 0.2	0.3 ± 0.2	.8849[m]
Vertical C/D ratio ≥0.7 in either eye, n (%)[c]	34 (7.1)	12 (10.5)	.2411[n]
Vertical C/D ratio asymmetry >0.2 between 2 eyes, n (%)[d]	11 (2.3)	2 (1.8)	1.00[n]
Myopia,[e] n (%)			.3372[n]
Mild (less than −1 diopter)	453 (94.4)	104 (91.2)	
Moderate (between −1 and −3 diopters)	17 (3.5)	7 (6.1)	
High (more than −3 diopters)	10 (2.1)	3 (2.6)	
Lower CCT between 2 eyes (μm) (mean ± SD)[f]	545.5 ± 34.7	542.3 ± 34.1	.3747[m]
Lower corneal hysteresis between 2 eyes (mm Hg) (mean ± SD)[g]	10.1 ± 1.5	10.0 ± 1.4	.3367[m]
Higher axial length between 2 eyes (mm) (mean ± SD)[h]	23.5 ± 1.0	23.1 ± 0.8	**.0030**[m]
BMI (mean ± SD)[i]	28.0 ± 4.3	28.2 ± 3.8	.9104[m]
BMI, n (%)[i]			.9602[n]
Normal (<25)	90 (18.0)	22 (19.3)	
Overweight (≥25 and <30)	247 (51.6)	60 (52.6)	
Obese (≥30)	142 (29.7)	32 (28.1)	
Systemic hypertension, n (%)[j]	207 (43.1)	48 (42.1)	.9162[n]
Diabetes, n (%)	39 (8.1)	16 (14)	.0699[n]
Cardiovascular disease, n (%)[j]	116 (24.2)	26 (22.8)	.8080[n]
Migraine, n (%)	24 (5)	7 (6.1)	.6392[n]
Heart attack, n (%)[j]	39 (8.1)	6 (5.3)	.4298[n]
Coronary artery bypass or vascular surgery, n (%)	42 (8.7)	10 (8.8)	1.00[n]
Any systemic disease, n (%)[k]	277 (57.6)	69 (60.5)	.5986[n]
Afternoon sleep (d/wk), n (%)			.3687[n]
None	136 (28.3)	33 (29)	
1-2	36 (7.5)	7 (6.1)	
3-4	41 (8.5)	8 (7)	
More than 4	268 (55.7)	66 (58)	
Smoking status, n (%)			.3687[n]
Nonsmoker	214 (44.5)	57 (50)	
Current smoker	108 (22.5)	19 (16.7)	
Ex-smoker	159 (33)	38 (33.3)	
Smoking pack-years (pack-years) (mean ± SD)[l]	34.7 ± 36.9	32.0 ± 36.7	.2032[m]
Consumption of ouzo ≥once/wk, n (%)	186 (38.7)	33 (29)	.0660[n]
Consumption of ouzo (g/d) (median [minimum-maximum])	0.8 (0–20)	0.3 (0–15.7)	.3833[m]

Continued on next page

TABLE 7. Comparison of Baseline Characteristics Between Those Who Developed PEX vs Those Who Did Not in the Follow-up Visit of the Thessaloniki Eye Study (*Continued*)

Characteristics	Population at Risk[a]		*P*
	Subjects Without Incident PEX (n = 481)	Subjects with Incident PEX (n = 114)	
Overall consumption of alcohol (g/d in quartiles), n (%)			.6961[n]
Q1: 0	97 (20.2)	24 (21.1)	
Q2: 1-3	145 (30.2)	40 (35.1)	
Q3: 4-8	134 (27.9)	27 (23.7)	
Q4: ≥9	105 (21.8)	23 (20.2)	

Only clinic visits were included in the analysis. Subjects with bilateral pseudophakia/aphakia were excluded.

BMI = body mass index; CCT = central corneal thickness; C/D = cup-to-disc; IOP = intraocular pressure; PEX = pseudoexfoliation; Q = quartile.

Bold values indicate statistical significance.

[a]Defined as those without PEX at baseline.

[b]Number of subjects excluded due to missing values: 3,

[c]1,

[d]6,

[e]1,

[f]10,

[g]12,

[h]11,

[i]2,

[j]1.

[k]Defined as at least 1 of the following: systemic hypertension, diabetes, cardiovascular disease, migraine, heart attack, coronary artery bypass, or vascular surgery.

[l]Calculated only in current smokers and ex-smokers (n = 324; 267 did not have incident PEX and 57 had incident PEX).

[m]Kruskal-Wallis Test.

[n]Fisher's Exact Test.

among those with PEX, an inverse association was noted between alcohol consumption (any amount of grams per day compared with zero) and the development of PEXG; and (8) no association was found between the overall exposure to tobacco smoke and the risk of developing PEX or PEXG among those with PEX.

• **INCIDENCE OF PEX:** To minimize the risk of misclassification bias in our results with regard to the presence of PEX, we calculated the 12-year incidence of PEX first in the overall population, and then in participants with clinic visits only, on whom we had uniformly collected data. When we further excluded those with bilateral pseudophakia or aphakia, the results were similar, with the 12-year incidence of PEX ranging from 19.2% to 22.7%. The similarity of these surpasses the robustness of the findings of the Thessaloniki Eye Study.

A summary of published data on the incidence of PEX is presented in Table 14. The annual incidence of PEX in the Thessaloniki Eye Study was 1.6% per year, remarkably similar to the 1.8% per year reported in the study by Aström and coworkers in Sweden[53] and twice as high as the 0.7% per year found in the Reykjavik Eye Study.[52] Given that the prevalence of PEX is higher in Scandinavia[38–40] compared with Greece,[41] one would expect a similar "geographic distribution" in the incidence of PEX. However, study participants in the Thessaloniki Eye Study were older than those in the aforementioned studies. The incidence of PEX increases with older age[52,53,60]; therefore, the age-adjusted incidence rates of PEX in the Scandinavian studies would probably be higher than those reported. In addition, the incidence of PEX in the Reykjavik Eye Study is likely to be underestimated because those >80 years old at baseline and those with pseudophakia in either eye were excluded from the 12-year analysis. Given the aforementioned association between PEX and older age, and the fact that PEX is a predictive factor for cataract development and pseudophakia,[60] many of these excluded individuals would be expected to have developed PEX. The criteria used to define PEX also need to be considered in the incidence rates reported by the Reykjavik Eye Study. We discuss this issue in more detail in one of the following sections, with regard to our data on the location of PEX. Conversely, the annual incidence of PEX in the Chennai Eye Disease Incidence Study[60] and the study by Jeng and coworkers in Olmsted County, Minnesota,[68] was much lower

TABLE 8. Logistic Regression Model on Risk Factors for Pseudoexfoliation in the Follow-up Visit of the Thessaloniki Eye Study (n = 583)

Variable	Odds Ratio	95% CI		*P*
Age (per yr)	1.05	1.00	1.10	.0578
Sex (female vs male)	1.20	0.75	1.92	.4444
Higher axial length between 2 eyes (per mm)	0.72	0.57	0.92	**.0091**
Vertical cup-to-disc ratio ≥0.7 in either eye (yes vs no)	1.70	0.83	3.49	.1482
Diabetes (yes vs no)	1.67	0.87	3.22	.1221
Consumption of ouzo ≥once/wk (yes vs no)	0.73	0.45	1.19	.2080

Only clinic visits were included in the analysis, after excluding those with pseudoexfoliation at baseline and those with bilateral pseudophakia/aphakia (12 additional subjects were excluded due to missing values).
CI = confidence interval.
Bold value indicates statistical significance.

TABLE 9. Logistic Regression Model on Risk Factors for Pseudoexfoliation in Current Smokers and Ex-smokers in the Follow-up Visit of the Thessaloniki Eye Study (n = 319)

Variable	Odds Ratio	95% CI		*P*
Age (per yr)	1.07	0.99	1.15	.0716
Sex (female vs male)	1.72	0.82	3.61	.1508
Higher axial length between two eyes (per mm)	0.75	0.53	1.07	.1093
Vertical cup-to-disc ratio ≥0.7 in either eye (yes vs no)	1.84	0.70	4.82	.2155
Diabetes (yes vs no)	1.67	0.69	4.02	.2570
Consumption of ouzo ≥once/wk (yes vs no)	0.70	0.38	1.30	.2614
Smoking pack-years (per pack-year)	1.00	0.99	1.01	.8056

Only clinic visits were included in the analysis, after excluding those with pseudoexfoliation at baseline and those with bilateral pseudophakia/aphakia (5 additional subjects were excluded because of missing values).
CI = confidence interval.

compared with our study. This is partly due to the younger age of study participants in the former studies, especially in the study from the United States, which included all ages from newborn to elderly, but is also likely to reflect differences between populations in terms of genetic predisposition and exposure to environmental factors.

• **INCIDENCE OF PEX AND ASSOCIATION WITH OLDER AGE:** It has been previously found that the incidence of PEX increases with older age.[52,53,60] In our data, the incidence of PEX was higher in those 70 to 74 years old compared with those 60 to 69 years old at baseline, both in the overall population and in clinic visits only. However, when the incidence of PEX was compared across all age groups, including those ≥75 years old at baseline, there was no statistically significant difference. This is most likely due to the small number of study participants in the older age group due to serious illness or death, because those who were ≥75 years old at baseline would be expected to be ≥87 years old at 12 years of follow-up. Indeed, based on the comparison of baseline characteristics among participants, refusals, and deceased (or those who could not be located), the latter group was statistically significantly older than the former groups. Table 3 shows that the incidence of PEX was lower in those ≥75 years old compared with the other age groups in the overall population and compared with the 70- to 74-year-old group who had in-clinic visits. A possible explanation is that study participants in the older age group were more likely to have the home-visit examination and/or were more likely to be pseudophakic; thus, PEX would be less likely to be detected. One may also hypothesize that there are limitations in the detection of PEX with portable equipment used in home visits, compared with the slit-lamp biomicroscopy used in clinic visits. However, the similarity in the incidence rates between the overall population and the clinic visits after excluding those with bilateral pseudophakia/aphakia does not support this

TABLE 10. Logistic Regression Model on Risk Factors for Major Vascular Disease in the Follow-up visit of the Thessaloniki Eye Study (n = 729)

Variable	Odds Ratio	95% CI		*P*
Pseudoexfoliation at baseline (yes vs no)	1.03	0.60	1.78	.9038
Age (per yr)	1.00	0.97	1.04	.8786
Gender (female vs male)	0.89	0.65	1.22	.4763
Hypertension at baseline (yes vs no)	1.46	1.05	2.01	**.0227**
Diabetes at baseline (yes vs no)	1.53	0.93	2.52	.0936

Both clinic visits and home visits were included in the analysis, after excluding those with major vascular disease and/or bilateral pseudophakia/aphakia at baseline. Three additional subjects were excluded because of missing values.

CI = confidence interval.

Bold values indicate statistical significance.

hypothesis. Selective mortality among those with PEX is another possible explanation for the lower incidence of PEX in the older, compared with the younger age groups. Interestingly, our data showed a higher proportion of PEX at baseline in those who died or could not be located, compared with refusals and those who agreed to participate in the follow-up visit of the study.

• **INCIDENCE OF PEX AND ASSOCIATION WITH FEMALE SEX:** In subjects who had clinic visits, the incidence of PEX was statistically significantly higher in women than in men. Also, female sex was significantly associated with higher odds for incident PEX, and age had no effect on this association. This finding is in accordance with prevalence data from the Thessaloniki Eye Study, although the difference in the prevalence of PEX between women and men did not reach statistical significance.[26] Other cross-sectional studies that have investigated the association of PEX with sex have had conflicting results, reporting higher frequency of PEX in either women or in men, or no difference between the sexes.[13,15] With regard to longitudinal data, higher incidence of PEX in women than in men was also found in the Reykjavik Eye Study[51,52] and the study from Olmsted County, Minnesota,[61] but was not confirmed in the study by Aström and coworkers[53] or in the Chennai Eye Disease Incidence Study.[60]

• **UNILATERAL VS BILATERAL INCIDENT PEX:** Based on the definition of PEX as a disorder of the extracellular matrix, one would expect to detect PEX in both eyes of affected individuals. However, the Framingham study has previously shown that in more than 75% of those affected with PEX, the latter could be detected only unilaterally.[43] Similarly, in the prevalence phase of the Thessaloniki Eye Study, 54% of those with PEX had only one eye affected.[26] In the present study we found that 60% of those who were bilaterally phakic and had developed PEX at 12 years had clinically detectable PEX only in one eye. The corresponding percentages in the 5-year follow-up visit of the Reykjavik Eye Study[51] and the study from Olmsted County, Minnesota,[61] were 57% and 73%, respectively, which are in accordance with our data. Previous studies have documented ultrastructural and immunohistochemical alterations typical of PEX in the seemingly unaffected eyes of those with unilateral PEX.[69–72] For this reason, it has been suggested that clinically unilateral PEX is asymmetric, rather than truly monocular.[15] It also has been proposed that the definition of PEX in epidemiologic studies should include "histologic" PEX, diagnosed with conjunctival biopsies.[13] However, performing conjunctival biopsies in the context of a population-based study is unlikely to be feasible. In addition, the clinical importance of "histologic" PEX is unknown.

• **LOCATION OF INCIDENT PEX:** To better understand the natural course of PEX and its association with glaucoma, ideally one should be able to quantify the amount of PEX material in an eye. To date, no such method exists. Instead, the location of PEX can be recorded and may serve as a surrogate for the overall amount of ocular PEX. According to our data, 62% of those who were bilaterally phakic and had developed PEX at 12 years had clinically detectable PEX on the lens capsule (15% on the lens only and 47% both on the lens and the iris), whereas in 38% of incident cases, PEX could be detected only on the iris. These results are in accordance with cross-sectional data from the Thessaloniki Eye Study on the location of PEX (27% on the lens only, 53% both on the lens and the iris, 20% on the iris only).[26] The risk of misclassification bias in the Thessaloniki Eye Study is low because all study participants had been examined under pupil dilation, even those with occludable angles, following YAG laser peripheral iridotomy. Our data reinforce the notion that, although PEX material on the lens capsule may be easier to recognize, it should not be the only criterion for the diagnosis of PEX.[73] In the Reykjavik Eye Study, the definitive criterion for PEX was the "complete or partial peripheral band and/ or a central shield of exfoliative material on the anterior lens capsule"; those with PEX on the iris only were classified as PEX suspects/possible PEX and were not considered in the overall

TABLE 11. Comparison of Characteristics Between Those Without and With PEXG Among Those With PEX, in the Follow-up Visit of the Thessaloniki Eye Study

Characteristics	Population at Risk[a]		P
	Subject Without Incident PEXG (n = 219)	Subjects with Incident PEXG (n = 22)	
Age (yr) (mean ± SD)	69.0 ± 4.4	69.5 ± 4.5	.4625[k]
Age (yr range), n (%)			.6458[l]
60-69	138 (63)	12 (54.6)	
70-74	62 (28.3)	8 (36.7)	
≥75	19 (8.7)	2 (9.1)	
Male sex, n (%)	110 (50.2)	15 (68.2)	.1219[l]
Incident PEX, n (%)	60 (27.4)	45.5	.0871[l]
Higher IOP between 2 eyes (mm Hg) (mean ± SD)[b]	15.5 ± 3.3	17.9 ± 2.9	**.0004**[k]
IOP ≥22 mmHg in either eye, n (%)[b]	9 (4.1)	1 (4.6)	1.00[l]
IOP-lowering treatment (medication, laser, or surgery)	8 (3.6)	1 (4.5)	.5839[l]
Higher vertical C/D ratio between 2 eyes (mean ± SD)	0.3 ± 0.2	0.4 ± 0.2	.0580[k]
Vertical C/D ratio ≥0.7 in either eye, n (%)	11 (5)	2 (9.1)	.3366[l]
Vertical C/D ratio asymmetry >0.2 between 2 eyes, n (%)[c]	3 (1.4)	0 (0)	1.00[l]
Myopia, n (%)[d]			.7072[l]
Mild (less than −1 diopter)	179 (89.5)	19 (90.5)	
Moderate (between −1 and −3 diopters)	12 (6)	2 (9.5)	
High (more than −3 diopters)	9 (4.5)	0 (0)	
Lower CCT between 2 eyes (μm) (mean ± SD)[e]	544.4 ± 36.0	549.1 ± 39.1	.3986[k]
Lower corneal hysteresis between 2 eyes (mm Hg) (mean ± SD)[f]	9.8 ± 1.5	9.7 ± 1.7	.6872[k]
Higher axial length between 2 eyes (mm) (mean ± SD)[g]	23.3 ± 1.1	23.5 ± 0.9	.1415[k]
BMI (mean ± SD)[h]	28.5 ± 4.2	26.9 ± 3.4	.1688[k]
BMI, n (%)[h]			.7369[l]
Normal (<25)	46 (21.1)	5 (22.7)	
Overweight (≥25 and <30)	103 (47.3)	12 (54.6)	
Obese (≥30)	69 (31.7)	5 (22.7)	
Systemic hypertension, n (%)	110 (50.2)	7 (31.8)	.1195[l]
Diabetes, n (%)	26 (11.9)	4 (18.2)	.4931[l]
Cardiovascular disease, n (%)	56 (25.6)	5 (22.7)	1.00[l]
Migraine, n (%)	11 (5)	1 (4.6)	1.00[l]
Heart attack, n (%)	8 (3.7)	5 (22.7)	**.0032**[l]
Coronary artery bypass or vascular surgery, n (%)	15 (6.9)	3 (13.6)	.2181[l]
Any systemic disease, n (%)[i]	147 (67.1)	13 (59.1)	.4816[l]
Afternoon sleep (d/wk), n (%)			.8816[l]
None	72 (32.9)	8 (36.4)	
1-2	14 (6.4)	2 (9.1)	
3-4	16 (7.3)	1 (4.6)	
More than 4	117 (53.4)	11 (50)	
Smoking status, n (%)			.9550[l]
Nonsmoker	110 (50.2)	12 (54.6)	
Current smoker	40 (18.3)	4 (18.2)	
Ex-smoker	69 (31.5)	6 (27.3)	
Smoking pack-years (pack-years) (mean ± SD)[j]	33.9 ± 36.9	51.2 ± 40.4	.0740[k]
Consumption of ouzo ≥once/wk, n (%)	74 (33.8)	7 (31.8)	1.00[l]

Continued on next page

TABLE 11. Comparison of Characteristics Between Those Without and With PEXG Among Those With PEX, in the Follow-up Visit of the Thessaloniki Eye Study (*Continued*)

Characteristics	Population at Risk[a]		*P*
	Subject Without Incident PEXG (n = 219)	Subjects with Incident PEXG (n = 22)	
Consumption of ouzo (g/d) (median [minimum-maximum])	0.33 (0–15.7)	0.17 (0–7.9)	.5014[k]
Overall consumption of alcohol (g/d in quartiles), n (%)			.1531[l]
Q1: 0	46 (21)	9 (40.9)	
Q2: 1-3	67 (30.6)	3 (13.6)	
Q3: 4-8	53 (24.2)	5 (22.7)	
Q4: ≥9	53 (24.2)	5 (22.7)	

The analysis included those who fulfilled all of the following criteria: (1) in-clinic examination both at baseline and at follow-up, (2) PEX at baseline and/or incident PEX, and (3) no PEXG at baseline.

BMI = body mass index; CCT = central corneal thickness; C/D = cup-to-disc; IOP = intraocular pressure; PEX = pseudoexfoliation; PEXG = pseudoexfoliative glaucoma; Q = quartile.

Bold values indicate statistical significance.

[a]Defined as those without PEXG at baseline.

[b]Number of subjects excluded because of missing values: 1,

[c]1,

[d]20,

[e]1,

[f]8,

[g]4,

[h]1.

[i]Defined as at least 1 of the following: systemic hypertension, diabetes, cardiovascular disease, migraine, heart attack, coronary artery bypass, or vascular surgery.

[j]Calculated only in current smokers and ex-smokers (n = 119).

[k]Kruskal-Wallis Test.

[l]Fisher's Exact Test.

incidence of PEX.[52] Therefore, incidence rates in the Reykjavik Eye Study are likely to be underestimated, as has been previously discussed in the literature.[73] In the Chennai Eye Disease Incidence Study, PEX was defined as the presence of PEX material in at least 1 eye, at 1 or more of the following locations: pupillary margin, anterior lens capsule, anterior chamber angle, corneal endothelium, anterior vitreous face, and zonules.[60] The investigators reported that of 87 subjects with incident PEX 63 (72%) had PEX only on 1 location and 24 (28%) had PEX on 2 or more locations, with the anterior lens surface being the most common location. However, other details are not provided; thus, these results are not comparable with ours. In the study from Olmsted County, Minnesota,[61] of 290 subjects with newly diagnosed PEX over a 6-year study period, only 6 cases (2%) did not have PEX on the anterior lens. However, this was a retrospective community-based study, so there were no standardized criteria for the diagnosis of PEX.

• **BASELINE RISK FACTORS FOR THE DEVELOPMENT OF PEX:** We investigated several ocular, systemic, and lifestyle variables as potential risk factors for the development of PEX. The association of older age with the incidence of PEX was of borderline statistical significance. As was previously discussed, this may be due to the narrow age range of the Thessaloniki Eye Study population. Higher axial length was protective for the development of PEX, and this was the only statistically significant association in the multivariable model. Interestingly, the Beijing Eye Study 2011, which is a population-based, cross-sectional study, found that shorter axial length (OR, 0.82; 95% CI, 0.68-0.98; $P = 0.03$) and shallower anterior chamber (OR, 0.59; 95% CI, 0.36-0.95; $P = 0.03$) were significantly associated with the prevalence of PEX,[74] which is in accordance with our findings. Data interpretation relied on previously reported associations of PEX with angle closure.[45,75,76] The authors hypothesized that PEX predisposes to angle closure, because of anterior lens subluxation caused by zonular weakness.[74] This is a plausible explanation for the association of prevalent PEX with shallow anterior chamber, but does not seem to explain the association with shorter axial length. Conversely, our findings suggest that shorter axial length may a contributing factor for the development of PEX. This is more likely to explain the association with shallow anterior chamber found in

TABLE 12. Logistic Regression Model on Risk Factors for PEXG Among Those With PEX in the Follow-up Visit of the Thessaloniki Eye Study (n = 235)

Variable	Odds Ratio	95% CI		*P*
Sex (female vs male)	0.47	0.13	1.74	.2593
Incident PEX (yes vs no)[a]	0.37	0.12	1.11	.0750
Higher IOP between 2 eyes (per mm Hg)	1.26	1.07	1.48	**.0051**
Higher VCD between 2 eyes (per 0.1)	4.03	0.22	75.11	.3502
Higher axial length between 2 eyes (per mm)	1.14	0.67	1.94	.6215
BMI (per unit)	0.91	0.77	1.08	.2773
Hypertension (yes vs no)	0.46	0.14	1.46	.1879
Heart attack (yes vs no)	13.49	2.85	63.87	**.0010**
Overall consumption of alcohol (g/d) Q2: 1-3 vs Q1: 0	0.19	0.04	0.88	**.0335**
Overall consumption of alcohol (g/d) Q3: 4-9 vs Q1: 0	0.14	0.03	0.66	**.0129**
Overall consumption of alcohol (g/d) Q4: ≥10 vs Q1: 0	0.14	0.03	0.77	**.0237**

The analysis included those who fulfilled all of the following criteria: (1) in-clinic examination both at baseline and at follow-up, (2) PEX at baseline and or at follow-up, and (3) no PEXG at baseline (6 subjects were excluded because of missing values).

BMI = body mass index; IOP = intraocular pressure; PEX = pseudoexfoliation; PEXG = pseudoexfoliative glaucoma; Q = quartile; VCD = vertical cup-to-disc ratio.

Bold values indicate statistical significance.

[a]Meaning the presence of PEX in either eye at follow-up, but not at baseline.

TABLE 13. Logistic Regression Model on Risk Factors for PEXG Among Those With PEX in Current Smokers and Ex-smokers, in the Follow-up Visit of the Thessaloniki Eye Study (n = 117)

Variable	Odds Ratio	95% CI		*P*
Sex (female vs male)	0.34	0.02	5.86	.4593
Incident PEX[a] (yes vs no)	0.19	0.03	1.21	.0783
Higher IOP between 2 eyes (per mm Hg)	1.34	1.02	1.76	**.0382**
Higher VCD between 2 eyes (per 0.1)	0.42	0.00	35.75	.6997
Higher axial length between 2 eyes (per mm)	1.09	0.47	2.53	.8371
BMI (per unit)	0.99	0.73	1.33	.9264
Hypertension (yes vs no)	2.22	0.29	16.70	.4398
Heart attack (yes vs no)	23.83	3.26	174.14	**.0018**
Overall consumption of alcohol (g/d) Q2: 1-3 vs Q1: 0	0.16	0.01	2.93	.2195
Overall consumption of alcohol (g/d) Q3: 4-9 vs Q1: 0	0.17	0.01	2.10	.1654
Overall consumption of alcohol (g/d) Q4: ≥10 vs Q1: 0	0.16	0.01	2.25	.1731
Smoking pack-years (per pack-year)	1.00	0.98	1.03	.6763

The analysis included those who fulfilled all of the following criteria: (1) in-clinic examination both at baseline and at follow-up, (2) PEX at baseline and or at follow-up, and (3) no PEXG at baseline (2 subjects were excluded because of missing values).

BMI = body mass index; IOP = intraocular pressure; PEX = pseudoexfoliation; PEXG = pseudoexfoliative glaucoma; Q = quartile; VCD = vertical cup-to-disc ratio.

Bold values indicate statistical significance.

[a]Meaning the presence of PEX in either eye at follow-up, but not at baseline.

cross-sectional data. Longitudinal studies are invaluable in data interpretation, because there is no temporal ambiguity in the associations found. However, there are very limited longitudinal data on factors associated with the development of PEX. To the best of our knowledge, the Reykjavik Eye Study[52,77] and the Chennai Eye Disease Incidence

TABLE 14. Incidence of PEX in Longitudinal Studies

Study	Country	Age at Baseline (yr)	Participants at Baseline (n)	Follow-up (yr)	Participants at Follow-up (n)	Overall Incidence of PEX (%)	95% CI	Annual Incidence of PEX (% per yr)
Thessaloniki Eye Study (present study)	Greece	>60	2554	12	1092	19.6	17.1–22.2	1.6
Reykjavik Eye Study[52]	Iceland	>50	1045	12	573	8	5.6–10.4	0.7
Aström and coworkers[53]	Sweden	>45[a]	339	21	102[b]	Not provided	Not provided	1.8
Chennai Eye Disease Incidence Study[60]	India	>40	7774	6	4421	2.03	1.6–2.5	0.3
Jeng and coworkers[68]	United States	All ages from newborn to elderly	73 602[c]	16	No stated	0.0259 (25.9 per 100,000)	Not provided	0.0016 (1.6 per 100,000)

All of the listed studies are population-based, prospective, longitudinal studies, except for the study by Jeng and coworkers, which is a retrospective community-based study.
CI = confidence interval; PEX = pseudoexfoliation.
[a]The minimum age at the incidence phase was 66 years.
[b]Forty-two individuals were examined and 60 individuals had their data obtained from medical records.
[c]During the study period a total of 73 602 Olmsted County residents had ocular diagnoses recorded in their medical records, which were used for data collection (corresponding to more than 50% of the population).

Study[60] are the only studies to have conducted such analyses. The Reykjavik Eye Study initially explored potential risk factors for the prevalence of PEX: older age, female sex, increased iris pigmentation, moderate use of alcohol, and asthma were associated with higher prevalence of PEX; the consumption of vegetables and fruit was associated with lower prevalence of PEX.[77] When the same variables were included in a risk factor analysis on the 5-year incidence of PEX, significant associations were found only with age and the consumption of fruit.[77] However, in the risk factor analysis for the 12-year incidence of PEX, there were no statistically significant associations.[52] This was attributed to the far fewer cases of PEX compared with baseline, due to losses to follow-up.[77] In the Chennai Eye Disease Incidence Study, older age, rural residence, illiteracy, pseudophakia, and nuclear cataract were significantly associated with the 6-year incidence of PEX.[60] Among the investigated factors that showed no statistical significance in the previously mentioned studies, the ones that were also examined in the Thessaloniki Eye Study were sex, smoking, alcohol consumption, BMI, CCT, and systemic diseases (systemic hypertension, diabetes, cardiovascular disease). The association with axial length was not assessed in the Reykjavik Eye Study or the Chennai Eye Disease Incidence Study.

• **BASELINE PEX WAS NOT ASSOCIATED WITH THE DEVELOPMENT OF MVD:** Longitudinal data from the Thessaloniki Eye Study do not support baseline PEX as a risk factor for major cardiovascular disease even when these results were adjusted for potential confounders. This is in accordance with previously published data from the prevalence phase of the Thessaloniki Eye Study, which showed no association between PEX[26] or the LOXL1 gene[78] and systemic diseases, including self-reported history of hypertension, diabetes, cardiovascular disease, migraine, heart attack, and coronary artery bypass or vascular surgery. Despite the strong evidence that PEX is a generalized fibrotic matrix process with ocular and extraocular tissue involvement,[7] the clinical implications of extraocular PEX remain unclear. Several pathophysiological alterations associated with vascular dysfunction have been described in those with PEX.[79] Therefore, the hypothesis on the association of PEX with cardiovascular and cerebrovascular morbidity is compelling. However, studies that investigated these associations have had conflicting results.[8] In a systematic review and meta-analysis conducted in 2014, PEX was associated with increased risk of vascular disease.[80] It is unfortunate that the Thessaloniki Eye Study data[26] had not been included in the meta-analysis, because it is one of the very few population-based studies to have examined this association.[31] In a more recent meta-analysis that had included the Thessaloniki Eye Study data, PEX was also significantly associated with cardiovascular and cerebrovascular disease.[81] However, as was acknowledged by the authors, most of the studies in this meta-analysis were observational, whereas most cases (6046 of

9583; 63%) came from a single cross-sectional study on beneficiaries of the US Veterans Health Administration.[82] This was a retrospective study, in a predominantly male population, which has been found to have poorer health than civilians.[83] In addition, the diagnosis of PEX could not be confirmed, and the diagnosis of cardiovascular disease was not standardized. In view of these controversies, high-quality data are needed to elucidate the association of PEX with cardiovascular diseases. Aström and coworkers[53] reported that the presence of PEX did not influence the risk of death after 21 years of follow-up. To the best of our knowledge, other than the present study, no other longitudinal population-based study has examined the association of PEX specifically with cardiovascular diseases.

• **BASELINE RISK FACTORS FOR THE DEVELOPMENT OF PEXG AMONG THOSE WITH PEX:** Although PEX is an established risk factor for glaucoma,[16–19] the precise interaction between the 2 conditions is not well understood.[21] Based on cross-sectional data, most people with PEX do not have glaucoma.[9] The present study further showed that among those with PEX, only 9% had converted to PEXG over the 12-year period. This is in accordance with the study by Jeng and coworkers[68] in Olmsted County, Minnesota, which found a 15% probability of developing glaucomatous damage among those with PEX after 10 years of follow-up. However, these data refer to untreated individuals, whereas in our population those who were taking IOP-lowering treatment were not excluded from the analysis. This may explain the higher conversion rate to PEXG in the study by Jeng and coworkers,[68] compared with our study. Non–population-based studies have reported variable conversion rates from PEX to PEXG[84–89]; however, comparisons with our data would not be appropriate because of differences in study methodology, especially with regard to the inclusion/exclusion criteria used in these studies. Our risk factor analysis confirmed the role of IOP as a strong risk factor for PEXG, with 26% increased risk for glaucoma among those with PEX, per mm Hg. This is remarkably similar to the 25% increased risk for glaucoma among those with PEX, per mm Hg, previously found in our cross-sectional data.[17] We also found the history of heart attack to be strongly associated with the development of PEXG among those with PEX, whereas this association was not found in the prevalence phase of the Thessaloniki Eye Study report.[17] In the previous analysis, vascular systemic diseases and their treatment were associated with POAG among those without PEX, but not with PEXG among those with PEX. Jeng and coworkers[68] also conducted a risk factor analysis for PEXG among those with PEX; IOP at initial diagnosis and bilateral involvement were the only variables associated with the development of glaucoma, whereas vascular parameters had not been considered in the analysis. We are not aware of any previously reported associations between the history of heart attack and the risk of PEXG among those with PEX; however, this association is biologically plausible and may be independent of PEX. Reperfusion injury from marked hemodynamic fluctuations is known to be associated with an intense inflammatory response[90,91] and has been previously suggested as a potential pathogenetic mechanism of glaucoma.[92]

Association with alcohol consumption. The inverse association between alcohol consumption and the risk of PEXG among those with PEX is also a new finding. The role of alcohol consumption has been investigated in other neurodegenerative diseases.[93] Although heavy alcohol consumption has both immediate and long-term effects on the brain anatomy and neuropsychology,[94,95] there is an emerging body of literature that suggests that moderate alcohol consumption, particularly red wine, may serve as a protective factor for cognitive decline in Alzheimer disease.[96,97] Biologic mechanisms that have been suggested for this protective effect include the antioxidant properties of wine flavonoids,[98] the effects against amyloid-β protein,[99] and the prevention of ischemia or stroke by alcohol.[100] In addition, a recent meta-analysis suggests an inverse association between alcohol consumption and the risk of Parkinson disease.[101] Based on these studies, there is evidence to suggest that moderate alcohol consumption may have a protective effect against neurodegeneration. In our analysis, all categories used to describe alcohol consumption were associated with lower odds for PEXG among those with PEX; however, it is unclear whether PEX has a specific role in the preceding mechanisms.

Location of PEX as a potential risk factor for PEXG among those with PEX. The analysis on the location of PEX (iris only, lens only, iris and lens) as a potential risk factor for PEXG among those with PEX did not reveal any statistically significant associations. This may be because of the relatively small number of study participants included in this analysis. However, the strict criteria used for this analysis were necessary to ensure the accuracy of data. Interestingly, in our data, there were no PEXG cases among those with PEX on the lens capsule only. This seems to be in accordance with a previous Thessaloniki Eye Study report that found differences in IOP, depending on the location of PEX material in the eye.[26] Specifically, compared with non-PEX eyes, the presence of PEX on the iris (with or without PEX on the lens) was associated with higher IOP, whereas the presence of PEX on the lens only was not. As was discussed in our previous report,[26] there is evidence to support a direct causative relationship between the build-up of PEX material in the trabecular meshwork and the development or progression of glaucoma.[102]

• **STRENGTHS AND LIMITATIONS:** Strengths of the study include the population-based study design, the robust methodology, including well-defined criteria for the

definition of PEX, and the high prevalence of PEX in the Thessaloniki Eye Study population. The fact that study participants were elderly at baseline may have favored the analysis with regard to the number of cases with incident PEX, but was probably also one of the contributing factors in the large number of losses to follow-up, which is a limitation in our study. Although the participation rate among eligible subjects was 74% (1092 of 1468), the 1092 participants in the follow-up visit of the Thessaloniki Eye Study represent fewer than half of the original population at baseline. Also, as was discussed previously, many of the nonparticipants may have had PEX because they were older, and the possibility of selective mortality among those with PEX cannot be excluded. For all these reasons, although the incidence of PEX in the Thessaloniki Eye Study was 19.6%, which is a higher percentage than the 11.9% prevalence of PEX at baseline, the absolute number of affected individuals was naturally lower in the incidence, compared with the prevalence phase of the study and may explain the lack of statistical significance in the examined associations. Similarly, the risk factor analysis on the development of PEXG among those with PEX is limited by the relatively small number of glaucoma cases. This is an inherent limitation of longitudinal studies with extended follow-up, as has been previously highlighted.[52]

SUMMARY

IN SUMMARY, THE THESSALONIKI EYE STUDY IS ONE OF the very few longitudinal population-based studies on the incidence of PEX. The 12-year incidence of PEX was 19.6% (1.6% per year), and women were more commonly affected than men. Most of those with incident PEX had "monocular" involvement, whereas in more than one-third of cases PEX material could be detected only on the iris. Although the concept of "histologic" PEX may be biologically accurate, its clinical importance remains unknown and its implementation in epidemiologic studies would be unfeasible. Our risk factor analysis revealed an association of shorter axial length with the incidence of PEX; this is a new finding and needs to be further explored. In the present study, most study participants with PEX at baseline did not develop PEXG over the 12-year period. We confirmed the role of IOP as an important risk factor for the development of glaucoma among those with PEX. The history of heart attack was also associated with higher odds for glaucoma among those with PEX and is a new finding. The inverse association of alcohol consumption with the risk of glaucoma among those with PEX is an interesting finding and is biologically plausible. None of the other lifestyle factors, including the overall exposure to tobacco smoke, was associated with higher risk of PEX or higher risk of glaucoma among those with PEX. Losses to follow-up, especially among the elderly, may explain the lack of statistical significance with regard to other variables in the risk factor analyses, such as age. However, this is an inherent limitation of the longitudinal population-based study design, especially when follow-up is extended. Longitudinal data from the present study do not support the role of PEX as a risk factor for cardiovascular diseases. To the best of our knowledge, this association has not been previously investigated in a longitudinal population-based study. Such data are highly valued in order to elucidate the clinical implications of extraocular PEX.

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