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Journal Title: RETINA-THE JOURNAL OF RETINAL AND VITREOUS DISEASES

Volume: Volume 41, Number 7

Publisher: LIPPINCOTT WILLIAMS & WILKINS | 2021-07-01, Pages 1562-1569

Type of Work: Article | Post-print: After Peer Review

Publisher DOI: 10.1097/IAE.0000000000003078

Permanent URL: https://pid.emory.edu/ark:/25593/vt2zk

Final published version: http://dx.doi.org/10.1097/IAE.0000000000003078

Published in final edited form as:

Retina. 2021 July 01; 41(7): 1562–1569. doi:10.1097/IAE.0000000000003078.

Pentosan Polysulfate and Vision: Findings from an International Survey of Exposed Individuals

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Abstract

Purpose: To investigate patient-reported visual function in individuals taking pentosan polysulfate (PPS) for interstitial cystitis.

Methods: A 27-item online survey was distributed to an international listserv of individuals with interstitial cystitis in November of 2018. Demographic characteristics, PPS exposure history, subjective visual function, and prior macular diagnoses were queried. Impact of PPS use, grouped by tertile of cumulative exposure, on visual function and macular diagnoses was assessed with multivariate logistic regression.

Results: The survey was completed by 912 respondents. 861 (96.4%) were female, and the median age was 55 (IQR, 45-64 years). Among PPS users, the median exposure was 547.5 grams (IQR, 219-1314 g). Respondents in the highest PPS exposure tertile were more likely to report difficulty with reading small print (adjusted OR 2.29, 95%CI 1.15-4.57) and to have a diagnosis of macular degeneration and/or pigmentary maculopathy (adjusted OR 2.41, 95%CI 1.44-4.03) than unexposed respondents.

Conclusion: In this large sample of individuals with interstitial cystitis, those in the highest PPS exposure category were more likely to have difficulties reading small print and to report a prior diagnosis of macular disease. Further study of objective measures of visual function in PPS users is warranted.

Summary Statement:

Pentosan polysulfate (PPS), used for the treatment of interstitial cystitis, has been associated with a novel maculopathy. This international survey of individuals with interstitial cystitis showed that respondents with high PPS exposure are more likely to report a diagnosis of macular disease and difficulty reading small print than unexposed respondents.

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No conflicting relationship exists for any author.

Keywords

Drug-induced Maculopathy; Macular Degeneration; Elmiron; Pentosan Polysulfate; Pigmentary Maculopathy; Pattern Dystrophy; Interstitial Cystitis

Introduction:

Interstitial cystitis (IC) is a chronic pain syndrome of the bladder that is estimated to affect more than 1 million individuals, predominantly female, in the United States alone.[1-3] Pentosan polysulfate (PPS) is the only oral therapy approved by the U.S. Food and Drug Administration (FDA) to treat IC.[4] As a semisynthetic analogue of biologic glycosaminoglycans, it is thought to bind to bladder epithelium, alter cellular permeability, and act as a physical barrier to protect cells from potential irritants.[5]

Pentosan polysulfate has been a mainstay in the treatment of IC since its FDA approval in 1996, and was used for years prior in an off-label fashion.[6] Prescribers administer PPS in both its FDA-approved oral formulation as well as through an off-label intravesicular route.[1] Several randomized controlled trials have demonstrated improvements in abdominal pain, urinary urgency, and nocturia with PPS, although more recent studies have shown no significant benefit over placebo.[4,7-9] One study demonstrated that use above the standard 100mg three times daily dosing did not improve patient-reported outcomes and resulted in dose-dependent side effects, such as diarrhea, rectal bleeding, and hypertransaminasemia.[10] PPS is metabolized by the spleen, liver, and kidneys, though its pharmacokinetics have not been well-studied in patients with hepatic or renal disease.[11]

We recently described a novel maculopathy associated with long-term PPS use in 6 patients seen by a single retina specialist at a tertiary referral center.[12] These patients complained of prominent visual disability, particularly with reading and dark adaptation, but demonstrated relatively preserved visual acuity. On examination, patients exhibited pigmented macular spots amidst a background of yellowish subretinal deposits, with macular RPE atrophy in advanced disease. Fundus autofluorescence imaging demonstrated a symmetric, dense array of hypo- and hyperautofluorescent spots typically centered on and involving the fovea. [13]

Given the decades of widespread use of PPS, these findings represented a major patient safety issue.[13-15] However, our current understanding of PPS maculopathy is based on a relatively small number of cases observed in tertiary referral centers, and it is unclear if these findings are generalizable to a broader population of PPS users. Further, aside from reporting visual acuity data, these retrospective studies provide limited data regarding visual function in affected patients, with particularly limited insights into patient-reported visual outcomes. The purpose of this study is to deepen our understanding of the subjective functional impact of this problem in a larger population of exposed individuals, and to explore whether there is a dose-response relationship between PPS use and visual function. Here, we report the results of an international survey of individuals with IC taking PPS, with a focus on patient-reported visual function.

Methods:

This retrospective survey study was approved by Emory University's Institutional Review Board, and informed consent was obtained electronically for all participants. Information was gathered and secured in compliance with the Health Insurance Portability and Accountability Act.

A 27-item anonymous survey, titled "Interstitial Cystitis and Vision," was shared via an internet-based platform (SurveyGizmo®, Boulder, CO) with an international mailing list of individuals with IC maintained by the online support and educational community The Interstitial Cystitis Network (ICNetwork®, Healdsburg, CA). Founded in 1995, the ICNetwork Online is the older of two prominent IC online communities, and two peer reviewed studies have substantiated the quality of content maintained by the ICNetwork.[16,17] The purpose of the ICNetwork mailing list is to distribute IC-related news, and only ICNetwork members who opted to receive e-mails are included. There is no cost to participation in the ICNetwork or the mailing list. Participants may opt out of the mailing list at any time, and the database administrator reviews the list for inactive accounts once every year.

Individuals were invited to participate in the survey via a single e-mail distributed to the ICNetwork email list on November 23, 2018. The survey was conducted between November 23, 2018 and December 30, 2018. Survey questions explored past medical history, extent of PPS exposure, prior retinal diagnoses, and measures of vision-related quality of life (Table 1). Questions regarding vision-related quality of life were adapted from the National Eye Institute Visual Function Questionnaire-25 (VFQ) and selected based on prior reports regarding the functional impact of PPS maculopathy.[13] The VFQ questions were scored based on a 5-point Likert scale, with 1 as "very poor"/"stopped doing this because of eyesight" and 5 as "excellent"/"no difficulty at all" with eyesight and a particular functional task, respectively. Respondents who reported that they stopped performing at least one task due to reasons other than vision were excluded from analyses. A composite VFQ score summed the individual scores across the 4 VFQ items. The fifth definition of the American Association for Public Opinion Research (AAPOR5) was used to calculate the survey response rate, calculated as the number of respondents divided by the number of eligible individuals.[18] A participant was eligible for the survey if they accessed the e-mail. Subscribers who did not access the e-mail were determined to have unknown eligibility and were removed from the survey analysis.

There were 3 primary outcome measures that were compared amongst PPS exposure groups: proportion of respondents seen by a retina specialist, proportion with a diagnosis of any pigmentary macular disease, and proportion with a score of less than 3 out of 5 on VFQ questions. Respondents were categorized into four PPS exposure groups: a PPS naïve group and 3 groups of PPS-exposed respondents based on tertile of cumulative exposure. We chose to group subjects by cumulative exposure given emerging evidence that high cumulative PPS exposure is a primary risk factor for development of PPS maculopathy.[14,19] Tertiles were formed by taking the distribution of reported cumulative PPS exposures and dividing the sample into 3 groups based on cumulative exposure. Covariates included age, sex, race,

height, weight, BMI, history of smoking tobacco in the past year, other medication exposures, and history of kidney, liver, or splenic dysfunction. A separate analysis evaluated rates of macular disease in respondents with atypical dosing regimens of 100mg or 500mg daily.

Descriptive statistics were used to summarize participant characteristics using Microsoft Excel (Microsoft, Redmond, WA). These variables were compared across PPS exposure groups with analysis of variance (ANOVA) if they were continuous, Pearson's chi squared test if they were categorical with non-zero values, and Fisher's exact test if they were categorical and included zero values. Analyses were conducted on XLSTAT for Microsoft Excel (Addinsoft, Paris, France). The impact of each covariate on the outcomes of interest was assessed using univariate and multivariate logistic regression analysis across groups of known PPS exposure using GraphPad Prism v8.4 (GraphPad, San Diego, CA). Each multivariate model was adjusted for age, gender, race, tobacco use, and any covariate associated with the outcomes of interest with a p-value of <0.2 in the univariate analysis.

Results:

The survey invitation email was delivered to 26,141 unique email addresses, and 5734 users accessed the email (21.9%). A total of 912 individuals completed the survey, representing an AAPOR5 response rate of 15.9%. The median survey completion time was 3 minutes (IQR, 2-5 minutes). Eight hundred and sixty-one (96.4%) were female, with a median age of 55 (IQR, 45-64 years). Eight hundred and forty-six (93.0%) identified as white. Respondents were from the United States (n=807, 88.5%), Canada (n=61, 7%), United Kingdom (n=18, 2%), Australia (n=11, 1%), and New Zealand (n=5, 0.5%).

Of all respondents, 772 (84.7%) reported complete PPS exposure data. Three-hundred and seventeen (34.5%) had no PPS exposure. Respondents with PPS-exposure were grouped into tertiles, with exposures 3.65-≤328.5g for the 1st tertile (T1), 328.5g-1031.0g for the 2nd tertile (T2), and ≥1031.0-5110.0 for the 3rd tertile (T3). The cutoffs of 328.5g and 1031.0g would be equivalent to 3 years and 9.4 years, respectively, of PPS use at a standard daily dose of 300mg. There was an unequal number of subjects in each tertile because multiple subjects reported 328.5 g cumulative exposure, which fell on the cutoff exposure value separating tertiles 1 and 2. The mean (SD) PPS exposure, in grams, was 161.8 (93.8), 636.7 (204.4), and 1903.3 (787.7) for the T1, T2, and T3 groups, respectively (p<0.001). An unknown exposure group was created for patients who did not report complete PPS exposure information or who used intravesicular PPS.

The daily dose of PPS users ranged from 100mg to 500mg, with 237 out of 455 (52.1%) respondents in the known PPS exposure groups indicating the standard daily dose of 300mg. The median overall duration of PPS use was 5.0 years (IQR, 1.4-12.0 years), with a median duration of 2.0 years (IQR, 1.0-3.0 years) in T1, 7.0 years (IQR, 5.0-8.3 years) in T2, and 15.0 years (IQR, 12.0-20.0 years) in T3. Two (0.2%) respondents reported taking a non-oral PPS formulation delivered intravesically.

Clinical and demographic characteristics for the PPS-naïve and PPS-exposed groups were balanced with the exception of age (Table 2). The mean (SD) ages, in years, were 53.7 (14.7), 47.6 (12.9), 54.0 (12.7), 57.0 (11.4) and 54.4 (13.6) for the unexposed, T1, T2, T3, and unknown PPS exposure groups, respectively ($p<0.001$). The unknown exposure group was balanced in terms of clinical and demographic characteristics compared to those with known exposures.

Among those with known PPS exposure, 710 out of 762 (93.2%) respondents reported having an exam with an ophthalmologist or optometrist in the prior 5 years. One hundred and sixty-seven (22.9%) respondents were referred to a retina specialist in the prior 5 years. The retina evaluation multivariate model was adjusted for age, sex, race, and smoking status only (see Table, Supplemental Digital Content 1, which shows univariate analysis). Respondents from the highest exposure tertile were more likely to have had a referral to a retina specialist compared to the unexposed group, with an adjusted odds ratio of 1.99 (95%CI 1.26-3.14) (Table 3).

One hundred and sixteen (18.6%) individuals with PPS exposure reported receiving at least one diagnosis of macular disease, including AMD (n=85), retinal spots (n=45), drusen (n=26), retinal pigment epithelium changes (n=24), pattern dystrophy (n=8), macular dystrophy (n=7), atypical macular degeneration (n=3), Stargardt Disease (n=2), and rod and cone dystrophy (n=1). Forty-three (4.7%) respondents reported having multiple diagnoses. The macular disease multivariate model was adjusted for age, sex, race, and smoking status only (see Table, Supplemental Digital Content 2, which shows univariate analysis). Participants from the highest exposure tertile were at increased odds of being diagnosed with macular disease as compared to the unexposed group, with an adjusted odds ratio of 2.41 (95%CI 1.44-4.03) (Table 3).

Among questions related to visual function, few respondents (6.4%) reported having poor or very poor eyesight when using both eyes, and this general measure of eyesight was not significantly different among exposure groups (Table 2). Respondents in the highest exposure tertile were more likely to report greater difficulty reading newspaper or magazine print, as compared to unexposed individuals (adjusted OR 2.29, 95%CI 1.15-4.57). Respondents in the higher exposure tertiles trended towards having more difficulty driving at night and reading menus in dimly lit restaurants, although the difference did not meet statistical significance for either endpoint. Higher PPS exposure was associated with a trend for increased odds of a poor VFQ composite score (<12), although this did not meet statistical significance in the adjusted analysis (Table 3). In addition to age, race, gender, and smoking status, the overall eyesight, reading small print, and VFQ multivariate models were adjusted for history of splenic disease; the driving at night multivariate model was adjusted for history of kidney disease; and the reading menus in dim lighting model was adjusted for BMI and history of splenic disease (see Table, Supplemental Digital Content 2, which shows univariate analysis for visual function outcomes). A total of 25 (2.7%) respondents stopped performing a visual task due to other reasons. Three stated they do not read newspapers or magazines, 20 stopped driving before taking PPS, and 2 reported they do not go to restaurants.

Among 57 respondents with atypical dosing regimens, there were 47 with a daily dose of 100mg, and 10 with a daily dose of 500mg. Six respondents reported at least 15 years exposure to a 100mg daily dose, with a cumulative dose range of 620.5-1241.0 g. One of these 6 (17%), a 64-year-old white individual with 1241g cumulative dosage, reported having a maculopathy. Among those with a daily dose of 500mg, the median duration of intake was 5 years (range, 0.1-22 years), with cumulative dosage of 18.3-4015.0 g. Six of these (60%) high daily dose PPS users reported a prior diagnosis of AMD or another pigmentary maculopathy. The median age of these respondents was 57.0 years (IQR, 43.0-65.8 years) and all identified as white except for the 39-year-old user.

Discussion:

This study provides an assessment of patient reported visual outcomes in a large, international group of individuals with interstitial cystitis treated with PPS. Respondents with high cumulative PPS exposure had significantly increased odds of having a prior diagnosis of AMD or another pigmentary maculopathy. Further, there was a trend for worsening visual function with increasing PPS exposure for most subjective visual outcomes. Given the widespread use of PPS for interstitial cystitis, these findings of a dose-response relationship between PPS use and visual dysfunction deepen our concerns regarding this patient safety issue.

By querying a large population of PPS users, we were able to rapidly evaluate a broad range of PPS exposures. For instance, this study included 152 respondents in the highest exposure tertile, equivalent to >9.4 years at a standard 300mg daily dose. Nearly one third (32.3%) of individuals in this exposure group reported having age-related macular degeneration or another pigmentary maculopathy, with significantly greater odds than those in the unexposed group (15.2%). As a reference, a study using the National Health and Nutrition Examination Survey reported a 3.0% AMD prevalence among 1,368 demographically similar (non-Hispanic white patients aged 40-59) individuals.[20]

With regard to the functional impact of PPS use, this study found trends for worsening function with greater exposure, although this was not statistically significant for every outcome. Respondents in the highest exposure tertile were significantly more likely to report difficulty reading small print compared to unexposed respondents. Among three other questions regarding visual function and for the composite visual function score, there were similar but nonsignificant trends.

Among the other covariates evaluated, age had the greatest impact on presence of macular disease and retina specialist referral. This is not surprising, as most acquired maculopathies are age-related. History of smoking was associated with increased odds of patient-reported visual dysfunction. Tobacco use is a significant modifiable risk factor for AMD,[21] although it is unclear if tobacco use exacerbates PPS maculopathy. Of note, 32.9% of respondents in the present study stated current or past history of daily tobacco use, which is higher than the percentage of women older than 18 years of age who reported daily tobacco use in 2018 in the U.S. (13.7%).[22]

This study also allowed us to explore atypical dosing regimens, gaining preliminary insights into the relative impact of duration of PPS use versus the mean daily dose. For instance, only 1 of 6 respondents with at least 15 years on a small daily dose of 100mg reported having a maculopathy. In contrast, 60% of those with a relatively high 500mg daily dose reported having a maculopathy, despite relatively low exposure durations in this group. These findings in small numbers of patients warrant further exploration.

A primary limitation of this study is that there is no way to verify accuracy of responses in this anonymous online survey. The lack of clinical data such as visual acuity, lens status, posterior segment exam findings, and retinal imaging limit our ability to correlate subjective findings and PPS use to objective information. The vast majority of our respondents were white, limiting the generalizability of our findings. A recent study of insurance claims data reported that non-white individuals comprised 29% of PPS users in the database.[23] Additionally, although IC is known to be more prevalent in whites, a recent study suggests it may be underdiagnosed in non-white populations.[24] Recall bias may have also influenced responses, given the retrospective nature of the study and that one third of the entire respondent population had used PPS for over 5 years.

The use of an online platform for this survey may also limit generalizability of our findings by selecting for participants with access to and familiarity with modern information technology. The response rate of 15.9%, calculated per AAPOR5 guidelines, may be an overestimate. A low response rate can lead to nonresponse bias. However, our calculated response rate is considered typical for external online surveys, which target an average response rate of 10-15%.[25] Importantly, our survey was conducted prior to broad dissemination of warnings regarding PPS-associated maculopathy. The survey structure and title were designed to limit the impact of nonresponse bias on the critical questions regarding the impact of PPS use on our outcomes of interest. For instance, there was no mention of PPS in the title or survey questions until after completing questions regarding outcomes of interest.

In spite of limitations inherent to survey studies, our findings provide additional support from a large, international group of respondents that long term PPS use is associated with macular disease and a worsening in some measures of subjective visual function. By rapidly reaching this broad audience, this study provides an early snapshot of the scale of this international patient safety issue and complements findings from smaller case series performed at tertiary referral centers.

Ophthalmologists and prescribers of PPS should be aware of the potential impact of long-term PPS use on visual function. Prescribers should use the lowest dose and duration of therapy necessary for disease control and consider alternative therapies where possible. Further prospective study with comprehensive visual function testing is needed to fully gauge the impact of this condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement:

Jill Osborne, The Interstitial Cystitis Network

This work was supported by an unrestricted departmental grant to the Emory Eye Center from Research to Prevent Blindness (New York, NY).

OEU is supported in part by the Alpha Omega Alpha Carolyn L. Kuckein Student Research Fellowship and an Emory Eye Center Trainee Research Award.

MKS is supported in part by the National Center for Advancing Translational Sciences of the NIH under Award Number UL1TR002378 and KL2TR002381.

NJ is supported in part by the Foundation Fighting Blindness under Award Number CD-C-0918-0748-EEC

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Table 1.

Survey questions

No.	Interstitial Cystitis and Vision Questionnaire
1	How old were you (in years) when first diagnosed with interstitial cystitis?
2	Have you ever smoked tobacco products on a daily basis for longer than one year? If yes, please include for how long.
3	Do you have any medical conditions involving your kidneys? If yes, please explain.
4	Do you have any medical conditions involving your liver? If yes, please explain.
5	Do you have any medical conditions involving your spleen? If yes, please explain.
6	What is your height in feet and inches? For example, if you are 5 feet and 4 inches, please write 5'4".
7	Please indicate your weight in pounds (lbs) or kilograms (kg).
8	At this time, what is your eyesight when using both eyes (with glasses or contact lenses, if you wear them)? Choices: Very Poor, Poor, Fair, Good, Excellent
9	How much difficulty do you have when reading ordinary print in newspapers and/or magazines (with glasses or contact lenses, if you wear them)? Choices: Stopped doing this for another reason (please specify), Stopped doing this because of your eyesight, extreme difficulty, moderate difficulty, a little difficulty, no difficulty at all.
10	How much difficulty do you have when driving at night (with glasses or contact lenses, if you wear them)? Choices: Stopped doing this for another reason (please specify), Stopped doing this because of your eyesight, extreme difficulty, moderate difficulty, a little difficulty, no difficulty at all.
11	How much difficulty do you have reading menus in dimly lit restaurants (with glasses or contact lenses, if you wear them)? Choices: Stopped doing this for another reason (please specify), Stopped doing this because of your eyesight, extreme difficulty, moderate difficulty, a little difficulty, no difficulty at all.
12	Have you seen an ophthalmologist or optometrist in the past 5 years? Choices: Yes, No, Don’t know
13	Have you seen a retina specialist in the past 5 years? Choices: Yes, No, Don’t know
14	Have you ever been diagnosed by an eye doctor with any of the following? Choices: Macular degeneration, drusen, pattern dystrophy, retinal pigment changes, retinal spots, other retina or macular problems, don’t know, no.
15	If you have any of the conditions listed in the previous question, at what age (in years) were you first diagnosed?
16	Which of these medications have you ever taken by mouth for 1 year or longer, 5 years or longer? Choices: Hydroxyzine, amitriptyline, gabapentin, hydroxychloroquine, hyoscyamine, carisoprodol, cyclobenzaprine, cystaMD, uribel, none
17	Have you ever taken, or are you currently taking pentosan polysulfate sodium, also known as Elmiron?
18	Which form of pentosan polysulfate sodium have you taken? Choices: Brand name (Elmiron), Generic form (pentosan polysulfate sodium), Both, Neither
19	What is/was your total daily dose of pentosan polysulfate sodium (Elmiron)? For example, if you have taken a 100 mg tablet three times daily, select 300 mg. If your prescription has been modified over time, please explain.
20	For how many years have you taken, or did you take pentosan polysulfate sodium (Elmiron)?
21	To your best recollection, how many years after you started taking pentosan polysulfate sodium (Elmiron) did your retina or macular problems begin?
22	What is your birth sex?
23	What is your current age?
24	What is your current country of residence?
25	How would you describe yourself? Choices: Hispanic/Latino, White, Black or African American, American Indian/Alaska Native, East or Southeast Asian, South Asian, Native Hawaiian or other Pacific Islander, Other

Table 2.

Demographic and clinical characteristics of all respondents by exposure group

Characteristic		Total population (n=912)	No PPS exposure (n=317)	T1 (n=163)	T2 (n=140)	T3 (n=152)	Unknown Exposure (n=140)	p-value
Mean Age- yr (SD)		53.6 (13.7)	53.7 (14.7)	47.6 (12.9)	54.0 (12.7)	57.0 (11.4)	54.4 (13.6)	<0.001
Female sex- no./total no. (%)		861/893 (96.4)	301/317 (95.0)	152/163 (93.3)	132/140 (94.3)	146/149 (98.0)	130/135 (96.3)	0.49‡
Race- White no./total no. (%)		846/910 (93.0)	290/317 (91.5)	150/163 (92.0)	130/140 (92.9)	143/151 (94.7)	133/139 (95.7)	0.47‡
≥1-year tobacco use history – no./total no. (%)		297/904 (32.9)	112/313 (35.8)	50/162 (30.9)	40/139 (28.8)	55/151 (36.4)	40/139 (28.8)	0.35‡
Height- m (SD)		1.64 (0.09)	1.64 (0.08)	1.65 (0.07)	1.64 (0.08)	1.64 (0.07)	1.64 (0.11)	0.82
Weight- kg (SD)		76.7 (25.6)	78.8 (28.7)	75.7 (23.3)	76.3 (27.6)	73.4 (21.0)	77.5 (23.6)	0.29
Body Mass Index- kg/m^2 (SD)		28.7 (10.2)	29.5 (11.3)	27.9 (8.4)	28.7 (11.3)	27.6 (8.8)	29.1 (9.8)	0.33
Medical history- no./ total no. (%)	Kidney-related	46/907 (5.1)	18/315 (5.7)	6/162 (3.7)	7/140 (5.0)	7/152 (4.6)	8/140 (5.8)	0.90‡
	Liver-related	7/905 (0.8)	5/314 (1.6)	0/161 (0)	0/140 (0)	1/151 (0.7)	1/139 (0.7)	0.34**
	Spleen-related	3/903 (0.3)	2/313 (0.6)	0/162 (0)	0/139 (0)	1/149 (0.7)	0/140 (0)	0.81**
Mean PPS exposure in exposed participants- g (SD)		889.7 (881.0)	NA	161.8 (93.8)	636.7 (204.4)	1903.3 (787.7)	NA	<0.001
Proportion of respondents with score <3- no/total no. (%)	Overall eyesight *	61/902 (6.8)	19/313 (6.0)	10/161 (6.2)	6/140 (4.3)	14/151 (9.3)	12/137 (8.8)	0.40
	Reading small print †	69/901 (7.7)	20/311 (6.4)	6/161 (3.7)	11/140 (7.9)	20/152 (13.2)	12/137 (8.8)	0.03
	Driving at night †	196/879 (22.3)	62/301 (20.6)	35/158 (22.2)	28/137 (20.0)	38/147 (25.8)	33/136 (24.3)	0.71
	Reading in dim lighting †	127/901 (14.1)	40/311 (12.9)	15/161 (9.3)	28/140 (20.0)	29/152 (19.1)	15/137 (10.9)	0.02

NA: Not applicable. T: tertile. PPS: pentosan polysulfate. SD: standard deviation

*Scoring based on a 5-point Likert scale: 1=Very poor, 2=Poor, 3=Fair, 4=Good, 5=Excellent.

†Scoring based on a 5-point Likert scale: 1= Stopped doing this due to eyesight, 2= Extreme difficulty, 3=Moderate difficulty, 4= A little difficulty, 5= No difficulty at all.

Comparison with ANOVA across all exposure groups unless otherwise specified.

‡Comparison with Pearson's chi-squared test across all exposure groups.

**Comparison with Fisher's exact test across all exposure groups.

Table 3.

Multivariate analyses of outcomes

Group	Total	Outcomes	OR (95%CI)	P value
	(n=730)	**Recent evaluation by retina specialist (n=167; 22.9%)** *		
No PPS	299	66 (22.1%)	Reference	
T1	158	23 (14.6%)	0.70 (0.39, 1.20)	0.21
T2	131	23 (17.6%)	0.70 (0.40, 1.18)	0.20
T3	142	55 (38.7%)	1.99 (1.26, 3.14)	0.003
	(n=623)	**AMD+ (n=116, 18.6%)** *		
No PPS	243	37 (15.2%)	Reference	
T1	138	19 (13.8%)	1.37 (0.73, 2.51)	0.32
T2	118	20 (16.9%)	1.14 (0.62, 2.05)	0.68
T3	124	40 (32.3%)	2.41 (1.44, 4.03)	<0.001
	(n=765)	**Overall eyesight score <3 (n=49; 6.4%)** †		
No PPS	313	19 (6.0%)	Reference	
T1	161	10 (6.2%)	1.00 (0.42, 2.27)	0.98
T2	140	6 (4.3%)	0.75 (0.29, 1.78)	0.54
T3	151	14 (9.3%)	1.85 (0.87, 3.87)	0.10
	(n=764)	**Reading small print score <3 (n=57; 7.5%)** †		
No PPS	311	20 (6.4%)	Reference	
T1	161	6 (3.7%)	0.71 (0.25, 1.75)	0.48
T2	140	11 (7.9%)	1.23 (0.55, 2.64)	0.60
T3	152	20 (13.2%)	2.29 (1.15, 4.57)	0.02
	(n=743)	**Driving at night score <3 (n=160; 21.5%)**		
No PPS	301	62 (20.6%)	Reference	
T1	158	32 (22.2%)	1.02 (0.61, 1.69)	0.94
T2	137	28 (20.0%)	1.25 (0.77, 2.01)	0.37
T3	147	38 (25.9%)	1.33 (0.82, 2.15)	0.24
	(n=764)	**Reading menus in dim lighting score <3 (n=112, 14.7%)** ‡		
No PPS	311	40 (12.9%)	Reference	
T1	161	15 (9.3%)	0.90 (0.46, 1.69)	0.75
T2	140	28 (20.0%)	1.67 (0.97, 2.87)	0.06
T3	152	29 (19.1%)	1.48 (0.84, 2.58)	0.16
	(n=737)	**VFQ <12 (n=113; 15.3%)** †		
No PPS	298	43 (14.4%)	Reference	
T1	156	13 (8.3%)	0.65 (0.32, 1.22)	0.20
T2	137	24 (17.5%)	1.16 (0.66, 2.00)	0.59
T3	146	33 (22.6%)	1.66 (0.98, 2.80)	0.06

AMD+: Age-related macular degeneration and any pigmentary maculopathy.

*Adjusted for age, race, gender, and smoking status.

[†]Adjusted for age, race, gender, smoking status, and history of splenic disease.

Adjusted for age, race, gender, smoking status, and history of kidney disease.

[≠]Adjusted for age, race, gender, smoking status, BMI, and history of splenic disease.