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Commentary

Ocular Pseudoexfoliation Syndrome and Life Span: Act 2

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A R T I C L E   I N F O

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A hundred years after its description in 1917 by John Lindberg, a Finnish ophthalmologist (Tarkkanen and Kivelä, 2002) pseudoexfoliation syndrome (PES) – an eye abnormality estimated to affect 80 million people and to be associated with a significantly increased risk of cataract and secondary open-angle glaucoma, both of which may compromise vision – continues to be shrouded in mysteries (Ritch, 2014; Anastasopoulos et al., 2015). Why is PES so often unilateral? Why does not everyone with PES develop secondary glaucoma? Why do lysyl oxidase like-1 gene polymorphisms that are strongly associated with hyperhomocystinemia in PES-positive subjects (for references see Slettedal et al., 2015). Such claims have independently been challenged by data from other centers, which also has spoken against a clinically significant, true association between PES, vascular disease and, indirectly, excess mortality (Tarkkanen, 2008; Anastasopoulos et al., 2015).

Although one tends to agree with the main conclusion of Slettedal et al. (2015) in that PES is unlikely to be a life threatening condition – an important message to millions of people – one has to address potential bias in their statistics.

A notable confounding factor that the authors mention — and one that they cannot adjust for — is that although several PES-negative subjects most likely later converted to PES-positive ones they were still all counted as PES-negative. One can roughly estimate the magnitude of this bias as follows. First, the prevalence of PES by age group given in Table 1 of Slettedal et al. (2015) can be plotted to provide prevalence estimates for other ages (Fig. 1). Second, the eventual median age of PES-negative subjects by age group can be read from Fig. 1 of Slettedal et al. (2015). One can then read the corresponding predicted prevalence of PES from the plot (Fig. 1) and calculate the number of PES-positive

![Fig. 1. Estimated conversion of subjects from pseudoexfoliation syndrome (PES)-negative to positive status before the end of the study of Slettedal et al. (2015). The line graph is based on the reported prevalence of PES by age group plotted at the midpoint of the age range and the dashed arrows extend to the reported eventual median ages of the subjects for each age group in their study. The prevalence of PES by the end of the follow-up for each age group can be estimated from the plotted line graph as shown for the age group 65–69 years with the dotted bent arrow. Numbers on the left hand side of the dashed arrows are the PES-positive subjects as reported in the study and those on the right hand side are the corresponding estimates by the end of the study, obtained by multiplying the total number of subjects in each age group by the estimated prevalence at the end of the study.](http://dx.doi.org/10.1016/j.ebiom.2015.06.006)
subjects at the end of the study for each age group. For example, the eventual median age for the 65–69 years old is 85 years, prevalence of PES 28.5%, and number of PES-positive subjects 143 (as compared to 67 years, 11.0% and 55 at baseline — an increase of 88 subjects). Repeating this across all age groups returns a total number of 575 rather than 319 PES-positive subjects. If those who converted to PES-positive had similar survival than those who were PES-positive at baseline, the median life length of the PES-negative subjects would have been somewhat higher, but not much; for example, the estimated median life span for those 65–69 years old would be 4 months longer. This bias is unlikely to change the main results.

However, another source of bias that the authors acknowledge, namely analyzing only all-cause mortality, cannot be dismissed as potentially hiding clinically meaningful differences in cause-specific mortality. PES has only been suspected of increasing cardio- and cerebrovascular mortality (Anastasopoulos et al., 2015). It has not been implicated in cancer, another major cause of death. Moreover, PES has often been less common among diabetic patients (for references see Tarkkanen et al., 2008). Because cardiovascular complications of diabetes shorten survival, this diminishes chances of detecting any mortality excess from PES. Luckily, this bias can still be addressed by Slettedal et al. (2015), because causes of death are generally obtainable for valid research purposes. There is, consequently, scope for Act 3 before excluding shortened life spans in a subset of PES-positive subjects.

Disclosure

I declare that I have no conflict of interest.

References


