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Field-wide meta-analyses of observational associations can map selective availability of risk factors and the impact of model specifications

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Abstract

Objectives—Instead of evaluating one risk factor at a time, we illustrate the utility of “field-wide meta-analyses” in considering all available data on all putative risk factors of a disease simultaneously.

Study Design and Setting—We identified studies on putative risk factors of pterygium (surfer's eye) in PubMed, EMBASE, and Web of Science. We mapped which factors were considered, reported, and adjusted for in each study. For each putative risk factor, four meta-analyses were done using univariate only, multivariate only, preferentially univariate, or preferentially multivariate estimates.

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Supplementary data

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Results—A total of 2052 records were screened to identify 60 eligible studies reporting on 65 putative risk factors. Only 4 of 60 studies reported both multivariate and univariate regression analyses. None of the 32 studies using multivariate analysis adjusted for the same set of risk factors. Effect sizes from different types of regression analyses led to significantly different summary effect sizes (P -value < 0.001). Observed heterogeneity was very high for both multivariate (median I^2 , 76.1%) and univariate (median I^2 , 85.8%) estimates. No single study investigated all 11 risk factors that were statistically significant in at least one of our meta-analyses.

Conclusion—Field-wide meta-analyses can map availability of risk factors and trends in modeling, adjustments and reporting, as well as the impact of differences in model specification.

Keywords

Meta-analysis; Exposome-wide association study; Observational study; Risk factor epidemiology; Statistical modeling; Big data

1. Introduction

Meta-analyses of observational studies on putative risk factors [1–3] are popular, and thousands of such meta-analyses have been published. Although useful in combining large numbers of relevant studies into a summary effect size, these quantitative syntheses suffer from significant limitations [4–6].

Most meta-analysis publications focus on studying the association of one or at most a few putative risk factors to a particular outcome. However, given the massive volume of published studies on risk factor epidemiology, there is typically a large number of risk factors that have been studied for any given outcome. Different investigators may have evaluated different risk factors and may have only reported subsets of them in their published articles. Moreover, there is often lack of consensus about whether risk factors should be analyzed and reported in univariate or multivariate models or both [7], and sometimes this can have a substantial effect on the results [5,8]. When multivariate models are used, there is a large diversity in terms of what other variables should be included for standard adjustments [9–11]. The pool of such variables can be very large, and it depends on what has been measured and what the investigators of each study consider essential for adjustments.

Finally, the reporting of an observational study may select only a few of the many models that have been assessed, and the choice may be based not only on *a priori* considerations about which model is the best, but also on the results [12]. Selective reporting bias can be a major threat to the validity of the available published information [13]. Meta-analyses that try to synthesize the selectively reported results, despite the advent of *post hoc* bias correction [14], may simply reinforce these biases by averaging the impact of diverse biases on the strength of the assessed associations [7,15].

Here, we propose that instead of merely assessing one putative risk factor at a time and synthesizing a limited set of potentially biased results, a meta-analytic approach to such

observational data should assess the entire field (defined by an outcome of interest) and its putative risk factors. We call this approach a field-wide meta-analysis of putative risk factors. A field-wide meta-analysis aims to (1) consider all data on all assessed risk factors for the outcome of interest and to compare the relative availability of data for each of the putative risk factors across the respective studies; (2) map systematically whether univariate analyses, multivariate analyses, or both have been reported; (3) map systematically what adjustments have been made in multivariate analyses; (4) examine systematically whether the results of meta-analyses are consistent when different estimates from different models (univariate or multivariate) are synthesized; and (5) assess whether the results across the entire field have evidence of selective biases [16,17]. We exemplify this approach by applying it to data on putative risk factors of pterygium (a conjunctival growth over the cornea), a topic with a substantial number of observational studies.

2. Materials and methods

2.1. Systematic review

For a detailed overview of Methods please refer to Appendix A at www.jclinepi.com. Briefly, all studies quantitatively exploring the association of any putative risk factor to the presence of pterygium and providing (or allowing the calculation of) the effect size and 95% confidence interval (CI) were eligible. We systematically reviewed EMBASE Classic and EMBASE (1947 to October 15, 2013), ISI Web of Science (1900 to October 15, 2013), PubMed (1950 to October 15, 2013) and Cochrane Central Register of Controlled Trials (up to October 15, 2013). We customized our search strategy to every database and selected for studies where the main outcome measure was the presence of pterygium. Data were collected by two reviewers (S.S. and Y.Y.T.), who also extracted the following data items: type of modeling (multivariate, univariate or both), adjustment variables (in multivariate models), high-level risk factor domain (e.g., sunlight exposure), more granular risk factor specification (e.g., sunlight exposure for >5 hours/d vs. not), metric type (e.g., odds ratio [OR] and relative risk [RR]), metric value (e.g., OR = 0.78), and 95% CI or standard error (whichever was available). Whenever the same study population was used more than once to study the same risk factors, we only extracted data from the latest article reporting on that study population. In studies where two multivariate models were used (e.g., a small model adjusting for age and gender and a large model adjusting for all statistically significant factors), we extracted the multivariate data from the largest model for which these were available. Metrics specific to continuous variables (e.g., Cohen's d) were transformed into ORs using an online tool [18] and standard formulae [19]. Only one study reported RR [20]; given that the incidence of the outcome of interest (pterygium) in that study was less than 10%, the RRs were considered to adequately approximate ORs [21]. On the basis of what is known regarding the pathogenesis of pterygium [22,23], we denoted a priori interest in the following 10 risk factors: sunlight exposure, occupation type, educational attainment, income, area of residence, use of sunglasses, use of spectacles, use of hat, dry eyes, and latitude. Our complete database can be found here: <https://goo.gl/9Ti1oG>.

2.2. Mapping of risk factors, type of analysis, and adjustments

R [24] was used to format and analyze our database. The figures illustrating the results of this analysis were color coded using the “Conditional Formatting” function of Microsoft Excel (Redmond, Washington; USA). As noted above, all recorded risk factors were categorized into high-level domains and more granular risk factor specifications (thus, each domain includes several risk factor specifications). For convenience, whenever we use the term “risk factors,” we refer to risk factor domains.

2.3. Meta-analyses for four modeling scenarios

Standard errors were calculated using: $\ln(\text{upper limit of CI}/\text{lower limit of CI})/(2 \times 1.96)$. We meta-analyzed only domains/specifications for which three or more estimates were available. All estimates were synthesized using a random-effects model due to evident between-study heterogeneity. The summary OR was estimated using the restricted maximum-likelihood ratio method. Four meta-analyses were done, one for each of: (1) multivariate data, (2) univariate data, (3) multivariate data combined with univariate data, whenever multivariate data were unavailable (henceforth called preferentially multivariate), and (4) univariate data combined with multivariate data, whenever univariate data were available (henceforth called preferentially univariate). We decided *a priori* to use $\alpha = 0.01$ for claiming nominal statistical significance. Given the multiple meta-analyses performed, $\alpha = 0.05$ would be too lenient, whereas a Bonferroni correction ($\alpha = 0.05/76 = 0.0006$) would be too stringent, given that many factors are correlated.

The nonparametric Friedman test was used to identify whether any of the four matched pairs of modeling differs from at least one of the rest. *Post hoc* multiple comparison after Nemenyi was then used to delineate which specific groups were significantly different from each other, as per the R package “PMCMR” [25]. Where both domains and risk factor specifications were eligible, only domains were included to avoid bias. Meta-analyses were done using the “metafor” 1.9-1 package [26].

2.4. Heterogeneity metrics

Between-study heterogeneity was assessed using the Q statistic and the I^2 metric, which we calculated using the “metafor” package.

2.5. Excess significance testing

Publication bias, outcome bias, and selective analyses may lead to an excess of statistically significant results, for which we tested by applying the excess significance test to factors reported by at least three studies [16]. Briefly, for every meta-analyzed risk factor, we compare the amount of observed significant results (O) at $\alpha = 0.05$ to the amount of expected significant results (E), where $E = \text{sum of power of each study within a specific meta-analysis}$. Power was calculated using simulations on R, taking as plausible effect for the risk factor the effect seen in the most precise study (lowest standard error). The difference between O and E was assessed using the binomial test, with $\alpha = 0.1$, as previously suggested [17].

3. Results

3.1. Literature search and study description

We initially identified 2,052 records, from which 1,992 were excluded (Fig. 1) leaving 60 eligible studies (Table 1; Appendix B at www.jclinepi.com). No new studies were imported through reference checking. In two of the eligible articles, not all the mentioned risk factors were analyzable because not enough information was available to obtain ORs [27,28].

There were 32 cross-sectional, 22 case-control, 3 prospective cohort, and 3 retrospective cohort studies. Twenty-one of 32 cross-sectional, 8 of 22 case-control, and 3 of 3 prospective cohort studies used multivariate analyses. The following population types were used, with the proportion of those reporting multivariate analyses in parentheses: general (18 of 24), hospital based (3 of 12), work specific (0 of 10), rural (6 of 7), and ethnically specified (5 of 7); the differences reflect the tendency of earlier studies (before 1990) to use case-control studies to investigate specific occupations using univariate analysis. Most studies emanated from Asia (34 of 60), followed by America (10 of 60), Oceania (9 of 60), Africa (5 of 60), and Europe (3 of 60)—one study took place both in America and Asia [29]. The most commonly studied age groups were those aged 40 years old or older (23 of 60). Eligible studies involved 362,548 participants, including 20,094 with at least unilateral pterygium (excluding a study not providing adequate sample size information [30]).

3.2. Mapping of risk factors

A total of 65 risk factors (Fig. 2A) have been studied within 183 different risk factor specifications (Fig. 2B; Supplementary Fig. 1 at www.jclinepi.com). Each risk factor was only studied in a median of one article (interquartile range [IQR], 1–4), and the 10 risk factors of *a priori*-specified interest were studied in a median of eight articles (IQR, 6–13). Although each of our *a priori*-determined risk factors have been reported at least five times, only 6 of 60 studies investigated at least half of these 10 factors and the maximum number of these risk factors investigated was 6 of 10.

A total of 25 risk factors were studied at least 3 times, and 17 were studied at least 5 times. Age, occupation type, level of education, sunlight exposure, dry eye, and ethnicity were studied in at least five different risk factor specifications (range, 5–34).

3.3. Mapping of univariate or multivariate modeling and their adjustments

A total of 32 of 60 studies reported a multivariate model to adjust for potential confounders; the rest (28 of 60) only used univariate analysis. Of the studies using multivariate modeling, 5 studies only reported multivariate data; 17 studies reported only multivariate data for some risk factors, whereas for others they either reported both multivariate and univariate data, only univariate data, or raw data from which univariate data could be extracted; 5 studies reported only univariate data for some risk factors but both univariate and multivariate data for the rest; and 1 only reported univariate data, merely indicating that multivariate data were not significant. Seven of 32 studies did not report the multivariate data for risk factors that were found to be significant in univariate but not significant in multivariate analysis. Only 4 of 60 studies reported both univariate and multivariate data for all risk factors that were

reported. The 32 studies using multivariate analysis adjusted for a total of 38 risk factors. Among these studies, we did not find a single pair considering exactly the same variables (Fig. 3). However, almost all these studies adjusted for gender (30 of 32) and age (29 of 32). Ten of 32 studies (31.3%) did not adjust for outdoor occupation or sunlight exposure.

3.4. Meta-analyses for four modeling scenarios

A meta-analysis was done for all four types of modeling for 19 risk factors (Fig. 4; Supplementary Table 1 at www.jclinepi.com) and 10 risk factor specifications. Ten factors were significantly associated with pterygium in multivariate meta-analysis (old age, male gender, high sunlight exposure, outdoor occupation, rural area of residence, low level of education, low income, latitude of residence $> 30^\circ$, use of spectacles, and use of sunglasses). Use of sunglasses lost its significance in all other modes of analysis, male gender lost significance in univariate analysis, and dry eyes gained significance in univariate analysis. No single study investigated all 11 risk factors found to be significant in at least one meta-analysis.

Considering risk factor domains, the summary estimate for different types of analysis was statistically significantly different ($F_{\chi^2} = 27.1$; P -value < 0.0001) because of differences between multivariate vs. univariate and preferentially multivariate vs. univariate analyses ($P < 0.0005$ for both). Univariate analyses displayed a tendency toward higher effect sizes; specifically, in 13 of 19 cases, the univariate analysis yielded larger effect sizes than the multivariate analysis. (When taking risk factor specifications into account, this ratio became 19 of 28—for one of the risk factors, the OR for multivariate was equal to that for univariate analysis).

3.5. Heterogeneity metrics and excess significance

Heterogeneity between all summary effect sizes was consistently very high, with median heterogeneity $I^2 = 76.1\%$ (IQR, 59.9–88.0%) for multivariate/preferentially multivariate meta-analyses, against $I^2 = 81.2\%$ (IQR, 80.8–94.3%) for univariate/preferentially univariate meta-analyses; excluding risk factor domains led to a small nonsignificant decrease. In 18 of 29 risk factors, heterogeneity was larger for univariate than multivariate models (binomial P -value = 0.18). The O exceeded the E number of studies with statistically significant results at $\alpha = 0.1$ in 21 of 116 meta-analyses.

4. Discussion

We have presented and implemented the concept of field-wide meta-analyses of risk factors using data from pterygium risk factor epidemiology. Our example illustrates what is likely to be common in many fields where efforts are made to identify risk factors for a given outcome of interest: a large number of studies evaluate a large number of risk factors, most of which are reported in the minority of studies. It is unclear if this means that these factors were not studied or studied but not reported. Moreover, there is a large diversity in modeling and adjustments—in our case study of pterygium, not a single multivariate model specification was identical between at least two studies. Different combinations of data emanating from either univariate or multivariate analyses yield different meta-analytical

effect size estimates. However, differences in combinations did not seem to affect whether our summary estimates reach statistical significance or not. Large heterogeneity, small-study effects, and excess significance signals are suggestive of reporting biases, although they probably have modest specificity in that regard. Such examples of between-study differences probably are the norm rather than the exception and have been previously shown to affect meta-analyses [7,31,32].

The observed variability in model specification in observational epidemiology may be related to a combination of different reasons and motives. Researchers perhaps do not actively try to align their research to previously published models, and editors/referees do not actively promote this practice. Perhaps, they do not see a need in doing so or even explicitly try to do things differently, using a different model specification and consideration of different risk factors as a means to claim innovation [33]. Furthermore, there are often many valid ways to define a putative risk factor, unless there is a generally accepted consensus. Even when there is consensus, reporting of models may still be sketchy and selective, despite efforts for standardization of reporting [34,35]. Eventually, there is substantial room for flexible analyses and for bias because of conflict of interest or prior beliefs that may result in selective reporting and partial interpretation of the results.

The phenomenon whereby effect size estimates change with alternative data approaches has been called “vibration of effects” [36,37]. Vibration can be generated from alternative choices, not only in adjustments for covariates in model specification [37, 38], but also from different definitions of variables, eligibility criteria, and statistical methods of analysis. Sometimes, analytical choices [36,37] may be aimed at facilitating the identification of as strong an effect as possible [39], leading to potentially inflated or widely different estimates [40].

As we show, multivariate models tend to give weaker effects than univariate ones, but this is not always the case. Nevertheless, the optimal choice of model may be difficult to identify. For example, adjusting for confounders is appropriate, whereas adjusting for variables that may be in the path that explains the effect of a risk factor may inappropriately diminish the adjusted effect size. Often it is difficult to understand which variables are confounders and which are not.

Despite our comprehensive and systematic approach to gathering and evaluating all the literature related to pterygium risk factor epidemiology, limitations exist. First, although we went at great length to ensure that all relevant articles were identified by creating a sensitive literature search strategy, translating articles published in languages other than English, and having two researchers going through and validating our database, we cannot exclude the possibility that some articles were overlooked. Second, we focused on what is reported, but it is quite likely that additional unreported risk factors and models were measured and fit. However, if something is not reported, it does not inform the research literature. Third, it is possible that in some studies, some risk factors may not have been relevant to model, for example, if all participants had the same value (e.g., if a study only enrolled women, gender would not be relevant to adjust for). Fourth, outcomes of interest other than pterygium may exhibit different field-wide profiles with more (or even less) consistency. Routine application

of this approach across diverse fields of risk factor epidemiology will inform the extent to which these analytical choices make a difference. Fifth, although our meta-analyses have identified summary estimates for all risk factors ever studied in the context of pterygium and these have been duly reported, the quality of the data available cannot be necessarily trusted to permit firm conclusions based on those results.

Approaches similar to our field-wide meta-analysis have been used in genetic epidemiology to generate field synopses, where databases are dedicated to collecting all genetic association studies on specific outcomes (phenotypes) [41–43]. However, in the case of genetics, adjustments for covariates are not an issue and human-genome epidemiology has made tremendous progress with the advent of platforms that allow covering the entire genome. Exposure-wide assessments, such as “Exposome/Environment-wide Association Studies” (EWAS), are similarly being proposed in nongenetic variables [44–49], to not only facilitate discovery, but also standardize variable adjustments and variables. However, until EWAS-like approaches become more commonplace and widely accepted, single studies are likely to continue covering very different aspects of the putative risk factors’ space. Field-wide evaluations provide a way of recognizing the quality of current data and selective availability of evidence and aid to characterize how susceptible to potential bias entire fields of risk factor epidemiology may be. They also provide visual tabulation of the gaps in a field, thus guiding further research in the field. To enhance field-wide analyses, we recommend executing EWAS to standardize, use of reproducible methods to identify covariates [11], estimating and reporting required power before commencing data collection and calibrating *P*-values with a database of gold standard negative controls [8,50].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is new?**Key findings**

- Field-wide meta-analyses can map the selective availability of risk factors as well as the patterns of modeling, adjustments and reporting, of risk factors across studies.

What this adds to what was known?

- Across all 60 studies on the risk factor epidemiology of pterygium, 32 used multivariate analyses, but no two studies used identical variables in their multivariate models.
- Differences in model specification can confer differences in summary effect sizes.

What is the implication and what should change now?

- We propose that instead of assessing one putative risk factor at a time, a meta-analysis of observational data should assess the entire field of putative risk factors—we call this approach a field-wide meta-analysis.

Fig. 1.

A flow diagram demonstrating the study selection process. Of the ineligible articles, nine could not be used because they did not provide their results in a metric that could be transformed into an odds ratio (e.g., provided means without any additional information) or did not provide enough information to interpret their results (e.g., use of unclear comparison groups) or results that seemed to have logical errors.

Fig. 2. (A) A “data microarray” illustrating what studies investigated which putative risk factors, for all risk factors studied three or more times. Risk factors are ordered based on how many times they were studied. Risk factors in light gray are the *a priori* factors of interest. Each row represents a separate article in the order these were presented in Table 1. (B) A “datamicroarray” illustrating the risk factor specifications for the “sunlight” risk factor domain. It shows that although many domains have been investigated extensively, they have been specified very differently across studies. Refer to Supplementary Fig. 1 at

www.jclinepi.com for the data microarray illustrating all specifications for all risk factor domains. Light gray risk factor, a priori factor of interest; light gray, not analyzed; medium gray, univariate analysis; dark gray, multivariate analysis; black, both multivariate and univariate analysis; AMD, age-related macular degeneration; UVA, ultraviolet A; UVB, ultraviolet B.

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Author	Occupation	Education	Area of residence	Income	Use of hat	Sunlight	Dry eyes	Use of spectacles	Latitude	Use of sunglasses	Total
Rim et al., 2013											5
Lu et al., 2007											4
Nemesure et al., 2008											4
Yan et al., 2006											4
Zhao et al., 2013											4
Marmamula et al., 2013											3
Mackenzie et al., 1992											3
Shiroma et al., 2009											2
Zhong et al., 2012											2
Cajucom-Uy et al., 2010											2
West and Munoz, 2009											2
Ang et al., 2012											2
Sun et al., 2013											2
Saw et al., 2000											2
Asokan et al., 2012											2
Khoo et al., 1998											2
McCarty et al., 2000											2
Twelker and Bailey, 2002											2
Xie et al., 2009											2
Taylor et al., 2006											1
Anguria et al., 2012											1
Durkin et al., 2008											1
Gazzard et al., 2002											1
Li and Cui, 2013											1
Sherwin et al., 2013											1
Tano et al., 2013											1
Lin et al., 2008											1
Viso et al., 2011											1
Wong et al., 2001											1
Fotouhi et al., 2009											0
Threlfall and English, 1999											0
Hayashida and Kitaoka, 2003											0
Total	19	9	7	7	5	4	3	3	2	2	

Fig. 3.

A “data microarray” illustrating what putative risk factors were adjusted for by each article. Only *a priori*-determined risk factors of interest are shown for convenience. Articles are ordered in descending order based on how many putative risk factors they adjusted for (this order only holds true for the risk factors shown). No two articles adjusted for the same putative risk factors. Refer to Supplementary Fig. 2 at www.jclinepi.com for a data microarray illustrating all risk factor domains for which adjustments were made. Black, adjusted for; gray, not adjusted for.

Fig. 4.

A panel of forest plots illustrating summary effect sizes and respective 95% confidence intervals for all 19 meta-analyzed risk factor domains for each type of analysis. The following factors were statistically significant at $\alpha = 0.01$ for all four types of analysis: old age, high sunlight exposure, outdoor occupation, rural area of residence, low level of education, low income, latitude of residence $> 30^\circ$, and use of spectacles. Refer to Supplementary Table 1 at www.jclinepi.com for a table illustrating all our results, alongside tests of heterogeneity and excess significance. OR, odds ratio.

Table 1

Studies meeting the eligibility criteria (numbers within [] refer to full references in Appendix B at www.jclinepi.com)

Authors	Year	Journal	Design	N	n
Li and Cui [1]	2013	Cornea	Prospective cohort	5,057	323
Liu et al. [2]	2013	Intern Eye Sci	Cross-sectional	3,067	280
Marmamula et al. [3]	2013	Invest Ophthalmol Vis Sci	Cross-sectional	5,586	655
Rim et al. [4]	2013	Cornea	Cross-sectional	14,920	4,307
Sherwin et al. [5]	2013	Acta Ophthalmol	Cross-sectional	641	70
Sun et al. [6]	2013	Ophthalmic Epidemiol	Cross-sectional	6,685	401
Tano et al. [7]	2013	Acta Ophthalmol	Cross-sectional	2,312	101
Zhao et al. [8]	2013	Invest Ophthalmol Vis Sci	Prospective cohort	2,628	129
Ang et al. [9]	2012	Ophthalmology	Cross-sectional	8,906	900
Anguria et al. [10]	2012	S Afr Med J	Case-control	150	150
Asokan et al. [11]	2012	Ophthalmic Physiol Opt	Cross-sectional	3,924	740
Rezvan et al. [12]	2012	Acta Med Iran	Cross-sectional	5,190	489
Sarac et al. [13]	2012	Turk J Med Sci	Retrospective cohort	6,470	196
Sudhalkar [14]	2012	Eye (lond)	Case-control	107	310
Zhong et al. [15]	2012	Invest Ophthalmol Vis Sci	Cross-sectional	2,133	832
Viso et al. [16]	2011	Eye (lond)	Cross-sectional	619	42
Cajucum-Uy et al. [17]	2010	Br J Ophthalmol	Cross-sectional	3,280	508
Peiretti et al. [18]	2010	Invest Ophthalmol Vis Sci	Case-control	112	123
Fotouhi et al. [19]	2009	Eye (lond)	Cross-sectional	4,565	59
Shiroma et al. [20]	2009	Am J Ophthalmol	Cross-sectional	3,747	1,154
West and Munoz [21]	2009	Br J Ophthalmol	Cross-sectional	4,774	772
Xie et al. [22]	2009	Graefes Arch Clin Exp Ophthalmol	Cross-sectional	3,214	–
Demirok et al. [23]	2008	Ann Ophthalmol (skokie)	Case-control	60	102
Durkin et al. [24]	2008	Br J Ophthalmol	Cross-sectional	2,076	407
Lin et al. [25]	2008	Environ Health Perspect	Case-control	383	134
Nemesure et al. [26]	2008	Ophthalmology	Prospective cohort	1,888	219
Omoti et al. [27]	2008	Eye (lond)	Case-control	154	174
Davies et al. [28]	2007	Niger J Physiol Sci	Case-control	110	85
Lu et al. [29]	2007	Clin Exp Ophthalmol	Cross-sectional	2,229	323
Ukponmwan et al. [30]	2007	East Afr Med J	Case-control	123	162
Paula et al. [31]	2006	Eye (lond)	Case-control	624	115
Tan et al. [32]	2006	Eye (lond)	Cross-sectional	477	81
Taylor et al. [33]	2006	Arch Environ Occup Health	Cross-sectional	304	68
Yan et al. [34]	2006	Chinese Med J-peking	Case-control	100	100
Balachandra [35]	2005	Pac Health Dialogue	Cross-sectional	753	109
Mathur et al. [36]	2005	Int Ophthalmol	Cross-sectional	1,169	148
Hayashida and Kitaoka [37]	2003	Acta Med Nagasaki	Cross-sectional	1,558	164
Gazzard et al. [38]	2002	Br J Ophthalmol	Cross-sectional	1,210	113

Authors	Year	Journal	Design	N	n
Twelker and Bailey [39]	2002	Invest Ophthalmol Vis Sci	Case-control	90	90
Wong et al. [40]	2001	Am J Ophthalmol	Cross-sectional	1,232	120
McCarty et al. [41]	2000	Br J Ophthalmol	Cross-sectional	5,147	141
Saw et al. [42]	2000	Acta Ophthalmol Scand	Case-control	125	61
Threlfall and English [43]	1999	Am J Ophthalmol	Case-control	135	150
Kadayifçilar et al. [44]	1998	Acta Ophthalmol Scand	Case-control	70	70
Khoo et al. [45]	1998	Int Ophthalmol	Case-control	125	61
Panchapakesan et al. [46]	1998	Aust N Z J Ophthalmol	Cross-sectional	3,629	266
Corzo-Alvarez and Urribarri-Delgado [47]	1997	Invest Clin	Case-control	143	143
Mackenzie et al. [48]	1992	Ophthalmology	Case-control	278	278
Taylor et al. [49]	1992	Arch Ophthalmol	Cross-sectional	838	140
Ibechukwu [50]	1990	East Afr Med J	Case-control	1	98
Taylor et al. [51]	1989	Arch Ophthalmol	Cross-sectional	838	140
Spierer et al. [52]	1985	Metab Pediatr Syst Ophthalmol	Retrospective cohort	600	93
Karai and Horiguchi [53]	1984	Br J Ophthalmol	Case-control	191	214
Moran and Hollows [54]	1984	Br J Ophthalmol	Cross-sectional	64,314	2,194
Taylor [55]	1980	Br J Ophthalmol	Cross-sectional	350	67
Biedner et al. [56]	1979	Ann Ophthalmol	Case-control	0	60
Detels and Dhir [57]	1967	Arch Ophthalmol	Case-control	1,252	151
Darrell and Bachrach [58]	1963	Arch Ophthalmol	Case-control	1,904	463
Kerkenezov [59]	1956	Trans Ophthalmol Soc Aust	Cross-sectional	3,000	287
Ten Doesschate and Fischer [60]	1949	Ophthalmologica	Retrospective cohort	180,000	147