MODERN BAYESIAN MODELING
TO SOLVE COMMON BUT COMPLEX CLINICAL AND EPIDEMIOLOGICAL PROBLEMS IN OPHTHALMOLOGY

WONG WAN LING

(MBiostat, University of Melbourne)

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DECLARATION

I hereby declare that the thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.

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Wong Wan Ling

12th May 2014

THESIS COMMITTEE AND SUPERVISORS

Thesis Advisory Committee (TAC):

Saw Seang Mei, M.B.,B.S., M.P.H., Ph.D., Professor, Saw Swee Hock School of Public Health, National University of Singapore (Chairman)

Cheung Yim Lui Carol, Ph.D, Senior Research Scientist, Singapore Eye Research Institute (Member)

Wong Tien Yin, M.B.,B.S., M.P.H., Ph.D., Professor, Department of Ophthalmology, National University of Singapore (Member)

Thesis Supervisors:

Wong Tien Yin, M.B.,B.S., M.P.H., Ph.D., Professor, Department of Ophthalmology, National University of Singapore (Main supervisor)

Cheng Ching-Yu, M.D., M.P.H, Ph.D., , Assistant Professor, Department of Ophthalmology and Saw Swee Hock School of Public Health National University of Singapore (Co-supervisor)

Li Jialiang, Ph.D., Associate Professor, Department of Statistics and Applied Probability, National University of Singapore (Co-supervisor)

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CHAPTERS

SUMMARY

The use of advanced and newly developed biostatistical methods usually lag behind their initial discovery by a period ranging from a few years to decades. Most clinical research use well-established "classical" statistics to make statistical inference, for example, presence of association. However, when analyzing research data with complex study designs or data structure, simply relying on "classical" statistical methods such as *t*-tests or standard procedures from generalized linear model may be inappropriate as the data do not satisfy the underlying model's assumptions. This thesis will introduce and focus on the use of modern Bayesian methods to address research questions encountered in different areas of clinical and epidemiological research with a focus on eye diseases. The thesis will analyze data with questions that may be difficult to address using "classical" statistics. The application of Bayesian analysis using modern Bayesian computation techniques may pose a challenge for clinical researchers and hence a documented "step-by-step" R codes to help clinical researchers to perform their own Bayesian analysis for similar research conditions are proposed.

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LIST OF ABBREVIATIONS

AMD	Age-related macular degeneration
AJO	American Journal of Ophthalmology
ATT	Anti-TB therapy
ETDRS	Early Treatment Diabetic Retinopathy Study
GLM	Generalized Linear Model
GA	Geographic atrophy
HB	Hierarchical Bayesian
IGRAs	Interferon-gamma Release Assays
JAGS	Just Another Gibbs Sampler (http://mcmc-jags.sourceforge.net/)
LOCS	Lens Opacities Classification System
MCMC	Markov chain Monte Carlo
nvAMD	neovascular Age-related macular degeneration
PSC	Posterior subcapuslar cataract
TST	Tuberculin skin test
QFT	QuantiFERON-TB Gold In-Tube
SEED	Singapore Epidemiology of Eye Disease
SERI	Singapore Eye Research Institute
SICC	Singapore Indian Chinese Cohort Study
SNEC	Singapore National Eye Center
TBU	Tuberculous uveitis
UN	United Nations
VF-14	Visual function-14 questionnaire
winBUGs	Bayesian inference Using Gibbs Sampling (Windows operating system)

LIST OF PUBLICATIONS FOR THESIS

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1. **Wong WL**, Li X, Li J, Cheng CY, Lamoureux EL, Wang JJ, Cheung CY, Wong TY. Cataract Conversion assessment using Lens Opacity Classification System III and Wisconsin Cataract Grading System. Invest Ophthalmol Vis Sci. 2013 Jan 9;54(1):280-7. doi: 10.1167/iovs.12-10657.

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3. **Wong WL***, Su X*, Li X, Cheung CM, Klein R, Cheng CY, Tien W. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health 2014 Jan 3. http://dx.doi.org/10.1016/S2214-109X(13)70145-1.

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* Equal contributions

CHAPTER 1

Introduction, Bayesian Framework and Literature reviews

1.1 INTRODUCTION

Uncertainty plays a very important role in clinical medicine and research as the translation of scientific discoveries and clinical diagnoses are usually not straightforward. Statistical modeling enables various sources of uncertainty (e.g. sampling or measurement errors) to be accounted for in biomedical research, to improve scientific inference and predictions, aiding clinicians make better diagnostic, prognostic and therapeutic decisions.

In research fields such as ophthalmic epidemiology, analyzing research data relying only on "classical" or conventional statistical methods presents severe bottleneck for today's science. A recent article by Nuzzo (2014) in *Nature*, titled *"P-values, the 'gold standard' of statistical validity, are not as reliable as many scientists assume"* have likened *P-values* to "mosquitoes, the emperor's new clothes or a tool of sterile intellectual rake" and *'fishing'* practices have the effect of "turning discoveries from exploratory studies, what look like sound confirmations but vanish on replication".[1] Statistical thinking in the Bayesian way was suggested as a possible solution, which offers a flexible alternative approach to data analyses.

1.1.1 Bayesian Perspectives on Some Common Problems of the "classical" Statistics

Concerns in Meta-analysis (refer Bayesian application in Chapter 5)

Meta-analysis methods used to synthesize evidence from related research studies to provide an overall pooled effect, were frequently formulated in the "classical" approach using random effects model. The random effects model assumes that each individual observed study result is estimating its own unknown underlying effect that originates from a common population mean, and hence allows for both within and between study variability. Inference based on asymptotic properties from "classical" approach usually requires large sample sizes. Bayesian models mirrored the "classical" formulation, but provides a number of specific advantages performed in the Bayesian framework.[2]

We illustrate using an example of a previous systematic review and meta-analysis to summarize the prevalence of age-related macular degeneration in Asian populations and investigate ethnic differences with reported prevalence in white populations. This work was conducted by Kawasaki et al. (2010)[3] and they had used the random effects model. Their analyses could have benefited from the flexibility in Bayesian's approach. Firstly, the data manipulation and exclusion of studies could be avoided in the analysis step to fully utilize all data in eligible studies. Four of the nine eligible papers reviewed containing potential information for the meta-analysis were excluded because of the different age range or unavailable age-specific prevalence data. Analysis was further restricted to include data only for age range from 40 to 79, due to small numbers for data for age ≥ 80. Furthermore, data was manipulated in the form of re-classifying some reported prevalence (up to ≥ 5 years in age ranges for each age category), e.g. prevalence for ages 43-54 years to be counted in the "40-49 years" age category. Bayesian approach allows layers of specifications for all model parameters to overcome the above issues, particularly useful for units of analysis with small sample sizes by borrowing strength from other units, and has the ability to include other pertinent information that would otherwise be excluded. Secondly, a separate meta-regression was performed to test for difference in prevalence of disease between Asians and whites, restricted to include only (white populations) studies with ≥ 1000 study subjects. It would be more desirable to model for ethnic-specific (Asian and whites) prevalence of disease, accounting for all sources of uncertainty within a single comprehensive Bayesian model. Ethnicity effect can then be examined by computing the Bayes factors. Thirdly, intuitive interpretations on probability statements (from Bayesian analyses) can be made directly on the pooled prevalence, e.g. there is 95% probability that prevalence of age-related macular degeneration in Asian populations is from 4.6% to 8.9%. Lastly, our simulation study results in **Study 3 (Appendix 2, Supplementary Figure 5.2)**

showed that estimated prevalence from Bayesian model is more accurate than random effects model, especially for small sample sizes < 100.

Multiple Comparisons Issue

Researchers often have a set of hypotheses that they wish to test simultaneously, such as the evaluation of relationships between several potential risk factors and disease outcomes. Such practice will lead to an increase (with each additional test) in the likelihood of the researcher wrongly conclude that there is at least one statistically significant effect across a set of tests, even if there is no real effect at all. For example, if we performed 20 null tests each at a 5% significance level, there will be a 64% chance that at least one them will be statistically significant resulting in a false positive finding.

"Classical" procedures such as the popular Bonferroni correction[4] accounts for multiple comparisons by adjusting the p-values to maintain the overall significance level at 5%, which is very conservative and may lead to a high rate of false negatives (reduces power to detect an important effect). Other "classical" corrections include controlling for family-wise error rate or false discovery rate. [5]

However, the multiple comparison issue can be accounted for in the Bayesian model. Multilevel models naturally incorporate all relevant research questions as parameters in one coherent model, and hence addresses multiple comparisons problem faced with "classical" statistics.[6-7] Once we work within a Bayesian multilevel modeling framework and model these relationships appropriately, we are able to get more reliable and effective estimates, especially in settings with low group-level variation which is where multiple comparisons are a particular concern.

No Gold Standards Problem (refer to Bayesian application in Chapter 4)

"Classical" approach assess newly developed diagnostic tests or classifiers using calculated measures such as sensitivity, specificity, positive and negative predictive values and overall accuracy, require a reference or gold standard test to establish the disease

outcome of a patient.[8] Conditional on disease state, the tests are assumed to be independent. The assumption may not be reasonable when the biological basis of the tests is the same and ignoring it may lead to biased sensitivity and specificity estimates. Furthermore, in the absence of a reference test, the true disease status is unknown. Statistical modeling in Bayesian framework can better handle these issues by allowing for conditional dependence of tests and the incorporation of informative priors based on expert opinion.[9-10]

Bayesian perspective offers flexibility to craft useful solutions tailored for specific research conditions. Above are some specific advantages described to overcome difficulties faced by using common statistical techniques.

1.1.2 Advantages of Bayesian Approach in Epidemiological Research

We often have some or partial information of what we wonder about, re-think or adjust our beliefs as we acquire new information but we all hope to predict something based on our past experiences. Such logic reasoning is reflected in Bayes' rule, a simple and intuitive theorem on updating our initial belief about an event of interest with new objective information. Bayesian methodology is a promising field of statistics, increasingly adopted across the disciplines of science and leading medical journals.[11-14] Its applications are particularly useful in clinical and epidemiological research.[15]

Firstly, research data structure can be complex, such as repeated measurements or multiple observations nested within subjects, or subjects may be clustered according to treatment sites with random effects model. Similarly, the hierarchical Bayesian (HB) approach is naturally suited to the modeling of various layers of conditional data, i.e. first level describes multiple measurements per subject, second level describes subjects within sites etc. Furthermore, even well-designed research data may be subjected to multiple sources of uncertainty. Bayesian methods allow for the modeling of complex data structures and the attachment of uncertainty to parameters to account for all the uncertainties at play. Such reflection of uncertainty is important in honest assessment of

post-data knowledge, especially in facing new treatments that affect clinician's inferential advice to patients in their course of actions. Lastly, in epidemiology, we often have partial knowledge of many exposure-outcome relationships from past experiences, previous literature and various limitations of measurements from data collection, implies that not all relevant parameters can be estimated consistently from the data. Past information are useful for cumulative scientific knowledge and for leveraging inference. Bayesian approach allows for accumulated results (as priors) to be integrated into analysis of subsequent research data, to update our previous beliefs and refine conclusions.

This thesis will focus on the application of modern Bayesian methodology in context to several areas of clinical and epidemiological problems faced in ophthalmology (where the above described advantages prevail).

1.2 BAYESIAN FRAMEWORK

1.2.1 Defining the Bayesian Approach

The Bayesian approach quantifies a measure of belief that lies in the gray areas between absolute truth and total uncertainty, derived from new evidence and approximations from other sources of information. Bayesian statistics considers unknown parameters as random variables and computes probability distributions (i.e. posteriors) – by updating prior knowledge with new data, expressed formally by integrating the likelihood function (study data) and the prior distribution (previous information), to which probabilistic statements about parameters of interest can be made from the posterior distribution. For example, 95% credible intervals are the 2.5^{th} to 97.5^{th} percentile of the posterior distribution of interest.

1.2.2 Bayesian versus "classical" Statistics

It is important to recognise that both Bayesian and "classical" statistics have their respective strengths and limitations. The thesis focused on the application of Bayesian modeling in complex research scenarios to one's advantage, when it is difficult to resolve

using the "classical" approach or common statistical techniques. "Classical" and Bayesian statistics are analysis tools and can be thought of as complementary statistical approaches.

"Classical" approach considers inference problem in a repeated sampling framework, where experiments are repeatable and research data represents one of the many possible random samples from the population. Model parameters are treated as fixed quantities (unknown parameters but not random variables) and inference are based on hypothetical replications of the experiments. For example, *P-value* describes how likely it would be to find an observation as large as or larger than our observed (from current experiment data), if we were to repeat the experiment many times, assuming the null hypothesis was in fact true. Its interpretation is often confused to correspond to the probability of false positives. On the other hand, Bayesian offers an intuitive statistical philosophy that allows us to make probability statements of the underlying reality. Its statistics framework allows for proper adjustments to work around limitations faced in "classical" methods, such as when our data violates common model assumptions that may be due to imperfections in data collection procedure or the complexity of study design, and in keeping other sources of variation under control. **Table 1.1** summarizes the advantages and disadvantages of the two approaches.

However, the application of Bayesian analysis using modern Bayesian computation techniques[16] (such as *Markov chain Monte Carlo* methods) may pose a challenge for non-quantitative researchers. The Bayesian implementation procedures, to implement a MCMC algorithm to simulate draws from the posterior distribution of the unobserved quantities given what is observed may seem daunting for beginners. WinBUGS and JAGs are special software available (free and good start) to perform automated computations for complex Bayesian modeling.[17-18] While well-known "classical" statistics have long-established guidelines for specialized techniques to correspond with data types, straightforward implementations and remains acceptable in practice, there is increasing trend of

computational intensive needs to handle large and increasing complexity of datasets. On-going developments of new and modern statistics improves efficiency and reliability of data analysis and its applications should be embraced to advance science – using statistical techniques that is closer to being right given the structure of the problem, together with good scientific judgement.

1.2.3 Prior Information

Objectivity and precision are expected of science but Bayesian analysis framework incorporates prior knowledge deemed as subjective beliefs, naturally became the main target of criticism from scientists uncomfortable with the approach. Prior knowledge varies from different people may lead to different answers and hence the concern on objectivity. The current practice to evaluate the properties or effect of prior distributions on our analysis model is to conduct sensitivity analyses, i.e. to perform cross-validation on multiple trial / mock data, or to test on a range possible / reasonable informative (and non-informative) priors to validate our model results. Varying posterior distributions should be observed with the application of multiple trial data (i.e. changing likelihood functions) to suggest that posterior distribution was driven by the likelihood (i.e. data) incorporated with prior information rather than prior distribution over-influencing the results. Similarly, consistency in inferences based on a range of reasonable priors will boost confidence in results. Serious disagreement between prior beliefs and the calculated posterior signals the need to re-evaluate your model, where the real challenge comes in constructing realistic models and in assessing their fit. Relevant sections of textbooks "Bayesian approach Bayesian Data Analysis" by Gelman et al. (2004) and "Statistical Decision Theory and Bayesian Analysis" by Berger (1985) provided in-depth discussion to handle criticisms of Bayesian methods.

1.3 GENERALIZATION FROM LITERATURE REVIEWS

Statistics Used in Ophthalmic Journals

"Statistical Techniques in Ophthalmic Journals" published in 1992 at JAMA Ophthalmology (formerly Archives of Ophthalmology) was the only article found to have reviewed and examined the frequency of statistical methods previously used in ophthalmic literature.[19] In total, 947 articles were reviewed from the ARCHIVES for years 1970, 1980, and 1990; American Journal of Ophthalmology (AJO) for 1990; and Ophthalmology for 1990. It was found that readers familiar with "classical" statistical techniques would have "statistical accessibility" to 88.9% of 1990 articles. Measures of central tendency (65.0%) was the most common technique, followed by dispersion (50.3%), *t*-test (20.3%), and contingency tables (16.6%). Nonparametric tests (8.3%) and survival analysis (5.4%) were considered advanced statistics then.

Recently, an article revealed on the current "Use of Statistical Analyses in the Ophthalmic Literature" (2014), based on 780 peer-reviewed articles for the type of statistical methods used in AJO, Ophthalmology and Archives of Ophthalmology, from January 2012 through December 2012.[20] A variety of statistical methods were currently used in analysis in ophthalmic research, moving beyond merely descriptive statistics observed two decades ago. More applications of specific techniques such as reliability tests, generalized estimating equations and Rasch analysis were used. However, only 0.5% of the 780 reviewed articles employed the Bayesian approach for analysis shows the unfamiliarity of Bayesian methods to eye-researchers. **Table 1.2** shows the distribution and ranks of current statistical methods used.

Biostatistics Research

Generalized linear models (GLMs), survival analysis, categorical data analysis, spatial statistics, and Bayesian methods (in diagnostic, epidemiological and clinical trials contexts) as well as meta-analysis (as a tool for evidence-based medicine) were popular areas of statistics used in medical research during mid-1990s, observed by Armitage in his book "Statistical Methods in Medical Research".

In 1994, Altman and Goodman[21] suggested that the following new statistical methods will play a key role in biomedical research over coming years: (i) bootstrap (and other computer-intensive methods); (ii) Gibbs sampler (and other Bayesian methods); (iii) generalized additive models; (iv) classification and regression trees (CART); (v) models for longitudinal data (general estimating equations); (vi) models for hierarchical data; and (vii) neural networks.

In 1997, Houwelingen[22] likewise suggested that the future would be marked by new biomedical applications (in epidemiology, historical data on oncological patients and their families; in ecology, spatial data); by new philosophies (causal models instead of randomized clinical trials; prediction versus prognostic modeling); new models (graphical chain models, random effects models); new computational facilities (with an impact on the other aspects); new techniques (graphic techniques, exact methods, pseudo-likelihood); and new forms of collaboration (databases for meta-analysis, Internet software, Internet publications).

A recent review on current research in biostatistics was conducted in 2009 by Abdelmonem A. Afifi and Fei Yu and was published in AJO.[23] **Table 1.3** below shows the list of leading biostatistical journals and issued reviewed and **Table 1.4**, the frequency of statistical methods used. Briefly, the category with the highest frequency covers *nonparametric and semi-parametric* approaches to inference techniques, GLM, regression models, and variable selection. Following category is *regression analysis*, including survival analysis and parametric approaches to GLM. Next is the *high-dimensional data* category, which includes handling time series data, spatial temporal data, data mining, discrimination and classification models and neural networks. The next category includes general *Bayesian analysis* methodology as well as Bayesian approaches to genetics/ ecology, stochastic processes, model selection, nonparametric analysis, and experimental design. *Post hoc analysis* includes missing data analysis and parametric model and variable

selection, as well as multiple comparisons. *Study design* encompasses experimental design research, design of clinical trials, and survey sampling. The *general inference* category includes "classical" statistical inference methods, such as hypothesis testing and confidence intervals. *Genetic analysis* contains statistical methodology and applications to genetic data, such as gene sequence, population genomic data, and gene expression microarry data. *Causal inference* encompasses methods that aim to uncover whether observed phenomena reflect statistical association or a true causal relationship, such as the propensity score methods discussed in this series. Lastly, "*other*" category consists methods that does not fit into the above categories, such as quality control, meta-analysis, and graphical theory, stochastic processes.

Conclusions

The tremendous breadth of modern and new methods appearing in biostatistics research is at a greater speed than its application into biomedical research.[16] The advantages and flexibility of Bayesian approach to customize statistical models for specific data structure is particularly useful in clinical and epidemiology research. Bayesian methods are among the popular and promising fields of current biostatistics research.[7, 24-30] However, Bayesian methods are yet to be widely utilized to solve ophthalmic research problems. This may be due to the inclination to stay with known methods and the ease of "classical" methods application while they remain acceptable in practice, or the lack of communication between statisticians and clinician scientists resulting in an unappealing alternative due to limited statistical knowledge. Also, the application of Bayesian analysis using modern Bayesian computation techniques (such as *MCMC* methods) may pose a challenge for non-quantitative researchers. Hence, the need for the role of an effective interdisciplinary biostatistician, to facilitate communication of modern statistical techniques (being able to explain difficult concepts to non-quantitative researchers or clinician scientists) and its applications into health research projects.

The purpose of this thesis is to develop Bayesian models to address some common but complex research problems (where the above described advantages prevail) encountered in different areas of clinical and epidemiology research in ophthalmology, and to advocate the use of Bayesian methods when handling complex research scenarios with documented "step-by-step" R codes to help researchers to perform their own Bayesian analysis for similar research settings.

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1.5 Chapter 1 Tables

Table 1.1 Comparison of Bayesian versus "classical" Approach

Bayes	**"Classical"**
Advantages	***Disadvantages***
Able to formally incorporate prior information	Unable to include external information
Inferences are conditional on observed data	Inferences are based on repeated sampling framework, on data conditional on fixed but unknown parameters
Intuitive interpretation e.g. 95% probability that the true value is in the credible interval	Awkward interpretation e.g. in hypothetical repetition of the same experiment, 95% of confidence intervals contain the true value. e.g. p-value is the long-term probability of obtaining data at least as unusual as what was actually observed.
Reasons for stopping experiment does not affect inference	Stopping conditions statistical test results/decisions e.g. two experiments with identical likelihoods could result in different p-values if the experiments were designed differently.
Analyses follow directly from the posterior. e.g. no separate theories of estimation, testing, multiple comparisons etc. are needed.	Strict rules and assumptions to follow. e.g. hypothesis testing applicable only for nested hypotheses and can only offer evidence against the null hypothesis. e.g. multiple testing inflates Type I error (false positives)
Procedures are consistent and estimators are optimal, even for small samples and complex models	Require large samples for asymptotic properties.
Disadvantages	***Advantages***
Less efficient	Fully efficient when samples are large
MCMC methods may be time-consuming	For standard applications, present closed-form solutions (i.e. fast)

Table 1.2 Distribution of Statistical Methods used in Selected Ophthalmic Journals during 2012

	Statistical Method	Articles containing the method	
		Number*	%
0	No statistical methods or descriptive statistics only	162	20.8
1	*t*-test	246	31.5
2	Contingency tables	266	34.1
3	Nonparametric tests	170	21.8
4	Epidemiologic statistics	42	5.4
5	Adjustments for epidemiologic statistics	15	1.9
6	Diagnostic proportions	40	5.1
7	Multiple comparison	49	6.3
8	Pearson's correlation	67	8.6
9	Spearman's correlation	49	6.3
10	Kappa statistics for agreement	25	3.2
11	Bland-Altman	17	2.2
12	Analysis of covariance	99	12.7
13	Analysis of covariance	25	3.2
14	Transformation	51	6.5
15	Simple linear regression	64	8.2
16	Multiple linear regression	66	8.5
17	Multi-way tables	6	0.8
18	Simple logistic regression	77	9.9
19	Multiple logistic regression	89	11.4
20	Survival methods	85	10.9
21	Power analyses and sample size calculations	58	7.4
22	Cost-benefit analysis	15	1.9
23	Sensitivity analysis	21	2.7
24	Repeated-measures analysis	18	2.3
25	Missing-data methods	23	2.9
26	Receiver operating characteristic	27	3.5
27	Resampling	17	2.2
28	Generalized estimating equations	41	5.3
29	Linear mixed models	58	7.4
30	Bayesian analysis	4	0.5
31	Meta-analysis	8	1
32	Rasch analysis and item response theory	3	0.4
33	Generalized linear models (excluding linear and logistic)	10	1.3
34	Other methods	25	3.2
	Totals	2038	

*Multiple statistical methods may be used in some articles (total 780 articles reviewed)

Table 1.3 List of Statistical Journals and Issues Reviewed

Journal Title	Impact Factor	Journals Issues Reviewed	No. of Articles
Biostatistics	3.394	October 2008 - April 2009	45
Journal of the Royal Statistical Society,	2.835	November 2008 - September 2009	47
Annals of Applied Statistics	2.448	September 2008 - June 2009	55
Journal of the American Statistical Association	2.394	September 2008 - March 2009	92
Annals of Statistics	2.307	February 2009 - June 2009	52
Statistical Methods in Medical Research	2.177	October 2008 - August 2009	33
Statistical Science	2.135	November 2007 - September 2008	17
Statistics in Medicine	2.111	January 2009 - May 2009	89
Biometrics	1.97	September 2008 - March 2009	100
Biometrika	1.405	September 2008 - March 2009	53
Total			583

Table 1.4 Categories of Statistical Research and Their Frequencies in Reviewed Journals

Category of Statistical Research	Number (%) of Articles
Nonparametric/semiparametric analysis	83 (14.2%)
Regression analysis	81 (13.9%)*
High-dimensional data	73 (12.5%)
Bayesian analysis	71 (12.2%)
Post hoc analysis	58 (9.9%)
Study design	46 (7.9%)
General inference	45 (7.7%)
Casual inference	33 (5.7%)
Genetic analysis	25 (4.3%)
Other	68 (11.7%)
Total	583 (100%)

*Including 29 GLM (5.0%) and 52 survival regression analyses (8.9%)

CHAPTER 2

Thesis structure, Study populations, design and methods

2.1 SPECIFIC AIMS

The goal of the thesis is to develop solutions via statistical models in the Bayesian perspective for four research problems that may face difficulty or limitations when using the "classical" approach, with focus in eye diseases. The specific aims are:

1. To develop a conversion algorithm based on Bayes' principal for the conversion of cataract prevalence between any two cataract grading systems, illustrated with the LOCS III and Wisconsin system.

   Current limitations: Direct comparisons of cataract prevalence estimates across epidemiological studies from current literature limit meaningful inferences due to substantial variability in the various grading protocols adopted (grading methods, definitions of lens opacities and examination techniques).

2. To develop Bayesian model for evaluation and comparison of diagnostic tests for tuberculous uveitis, tuberculin skin test and two (dependent) interferon γ release assay tests in the absence of a gold standard.

   Current limitations: The estimations of sensitivity and specificity of diagnostic tests from the "classical" approach assume independence of tests and requires a reference or gold standard for true disease status.

3. To perform systematic review and develop Bayesian model to perform meta-analysis for the global prevalence and burden projection of age-related macular degeneration for 2020 and 2040.

   Current limitations: To perform global meta-analysis using "classical" approach may face many limitations and restrictions in handling and combining numerous studies, such as small samples studies, differences in age range and age-group specific breakdowns across studies and various sources of heterogeneity etc.

4. To develop hierarchical Bayesian one-stage "joint analysis" approach to account for measurement errors of vision-specific latent trait in regression models.

   Current limitations: Rasch analysis and linear regression results and inferences are fine on its own, but naïve combination / integration of statistical methods lacking proper statistical considerations may lead to biased inferences.

2.2 STRUCTURE OF THESIS

The thesis is organized as follows. **Chapter 1** introduces the concept, advantages and flexibility of Bayesian approach in handling complex research scenarios, lending motivation in advocating Bayesian analysis methods in ophthalmic research. Analyses performed in the thesis included data from the Singapore Malay Eye Study (SiMES), prospective cohort of patients presented with uveitis to a tertiary institution and data extracted when conducting meta-analysis. Specific aims, study design, methods and data details were documented in **Chapter 2**.

Chapter 3 (Study 1) begins with an intuitive application of Bayes' principal to develop a conversion algorithm and applied to two cataract classification systems to enable fairer comparison of cataract prevalence from the diversity of grading systems implemented across epidemiological studies.

In many areas of medicine, gold standard diagnostic techniques are rare, yet accurate diagnosis of infectious diseases is essential in primary health care. In particular, the diagnosis of uveitis associated with tuberculosis is controversial and there is no established "gold standard" to diagnose tuberculous uveitis which makes it difficult to evaluate new medical diagnostic tests. **Chapter 4 (Study 2)** uses Bayesian Latent Class modeling to evaluate three diagnostic tests available in the absence of a gold standard and incorporating prior information obtained from previous meta-analysis literature. As two of the diagnostic tests are not independent (both are whole-blood tests), our model also accounted for their

dependency and further investigated the optimal choice of diagnostic test to be used, which is more interest to ophthalmologists.

Chapter 5 (study 3) is a study on Bayesian approach in the meta-analysis of population-based studies of age related macular degeneration worldwide. Various sources of heterogeneity and uncertainty (e.g. ethnicity, geographic regions etc.) were accounted for and tested in our statistical model. Pooled prevalence and to projections would provide useful guide for global strategies.

Vision functioning is one of the key latent traits for vision-specific instruments / questionnaires and its data were commonly evaluated using Rasch analysis. Subsequent applications using "classical" statistics (e.g. linear regressions) for association analysis of latent data without accounting for its measurement error may lead to biased estimations and statistical inferences. **Chapter 6 (study 4)** demonstrates the effectiveness of a modeling framework that integrates Rasch and regression models using hierarchical Bayesian approach that accounts for latent trait measurement errors to produce more accurate estimation of association effects.

The above studies elucidate some Bayesian modeling techniques that are useful to resolve hypotheses / questions with complex settings in various areas of ophthalmic research. Finally, **Chapter 7** summarizes the key findings of this thesis and discuss possible extensions and recommendations for future research work. Instructions for "step-by-step" R codes to help researchers to perform their own Bayesian analysis for similar research settings were documented in **Appendix 1**.

2.3 STUDY POPULATIONS, DESIGN AND METHODS

Many interesting research questions differing in complexity in data structures / study deigns were encountered in the years of experience working in Singapore Eye Research Institute. However, some cannot be easily resolved with "classical" statistics. To improve and advance ophthalmic research, this thesis advocate the advantages and flexibility of

modern Bayesian approach in different areas of clinical and epidemiology research. **Study 1 and 4** are research questions / issues based on data from the Singapore Epidemiology of Eye Disease (SEED) program, mainly using the Singapore Malay Eye Study (SiMES) data. **Study 2** is a clinical question that is of direct relevance to ophthalmologists, a diagnostic accuracy study based on data collected from a prospective cohort of patients presented with uveitis to a tertiary eye institution. **Study 3** is a systematic review and meta-analysis and hence analysis was based on data extracted from published literature identified from our systematic review.

2.3.1 Singapore Malay Eye Study (SiMES)

The Singapore Epidemiology of Eye Disease (SEED) is a program that consists the Singapore Malay Eye Study (SiMES)[1] and Singapore Indian Chinese Cohort (SICC) Eye Study,[2] with aims to investigate the prevalence, risk factors, and impact of major eye diseases in Chinese, Indians and Malays in Singapore. The SEED program includes database from three population-based, cross-sectional studies, conducted between 2004 and 2011 for Malays, Indian and Chinese adults aged 40 and older in the south-western Singapore (**Figure 1**).

Using an age-stratified random sampling strategy, 5,600 Malay names, 6,350 Indian names, and 6,752 Chinese names were selected from the Ministry of Home Affairs. A total of 4,168 Malays, 4,497 Indians, and 4,605 Chinese were deemed eligible to participate.[1-2] "Ineligible" persons were those who had moved from the residential address, had not lived there in the past six months, or were deceased or terminally ill. In total, 3,280 Malays, 3,400 Indians and 3,353 Chinese participated in the SEED program, giving a response rate of 78.7%, 75.6%, and 72.8% respectively (**Figure 2**).[1-2]

The study adhered to the Declaration of Helsinki, and ethics approval was obtained from the Singapore Eye Research Institute (SERI) Institutional Review Board with written informed consent obtained from all subjects before participation. All participants

underwent a comprehensive ocular examination that was carried out at SERI. A detailed interviewer-administered questionnaire was used to collect relevant information such as socioeconomic status, lifestyle data and medical history of eye diseases.

Recruitment

Participants were invited to attend a comprehensive eye and physical exam at the SERI via telephone, by mail, and/or by home visit. A booklet outlining the overall eye study findings and an invitation letter (reply-paid postage) were sent to all baseline participants to elicit a strong spirit of cooperation.

Questionnaire

A questionnaire based interview was administrated by trained interviewers. These questionnaires, listed below, were either validated in the Blue Mountains Eye Study (BMES), a landmark population-based eye study in Australia) or other studies:

- Contact and demographic information
- Socioeconomic characteristics (education, income level, occupation)
- Family and medical history
- Smoking status
- Questionnaire on access and barriers to use of general health and eye care services,
- Vision-related quality of life, including the modified visual function-14 questionnaire (VF-14).

Systemic and ophthalmologic examinations

- Blood pressure, height, weight
- Presenting and best-corrected distance visual acuity using the Early Treatment Diabetic Retinopathy Study (ETDRS) Logarithm of the Minimum Angle of Resolution (LogMAR) chart
- Auto-refraction, keratometry and lensometry.

- Axial length was measured using the IOL-Master®.
- Central corneal thickness, anterior chamber and angle parameters were measured with anterior-segment Visante™ OCT (Carl Zeiss Meditec, Dublin, CA)
- Gonioscopy and automated perimetry (Humphrey Visual Field Analyzer II, 24-2 SITA, Carl Zeiss Meditec, Dublin, CA, USA) for all glaucoma suspects
- Slitlamp biomicroscopy for anterior eye abnormalities and applanation intraocular pressure
- After pupil dilation, slit-lamp based lens photographs were taken to measure nuclear cataract. Retroillumination photos of the anterior and posterior lens were taken on a Neitz digital cataract camera to measure cortical and posterior subcapsular cataract. The clinical grading of cataract was based on the Lens Opacities Classification System (LOCS III)[3]
- ETDRS standard fundus fields 1 (optic disc) and 2 (macula) were taken using a digital retinal camera (Canon CR-1 Mark -II Nonmydriatic Digital Retinal Camera, Canon, Japan). Photographs then were graded using the BMES and Wisconsin protocols
- Blood collection for assessment of HbA1c, serum glucose, lipid and CRP levels

Imaging data

- Signs of DR were graded from fundus photographs using the modified Airlie House classification system and a modification of the ETDRS severity system for DR. Graders assessed the presence/severity of diabetic macular edema, and sign of laser treatment scar.[4-5]
- Presence of AMD was graded using the Wisconsin AMD grading system[6]

- Photography of lens through the dilated pupil for assessment of nuclear, cortical, and posterior subcapsular cataract were graded using the Wisconsin cataract grading system.[7]
- Retinal vascular caliber are measured by using a semiautomatic computer-assisted program (Singapore I Vessel Assessment), according to standardized protocol.[8]

Contributions

My main contribution in the SEED program is in the management, consolidation and maintaining integrity of the database for the SiMES and SICC study (10,033 subjects) that includes questionnaire, clinic, imaging data and other sub-datasets. I have helped to organize and standardize definitions and codebooks across the studies, created data request forms for documentation of data sharing between collaborators, to ensure consistency of variables and that project topics do not overlap between researchers to avoid unnecessary conflicts.

2.3.2 Diagnostic Accuracy Study

We conducted a prospective study of all new consecutive patients with uveitis presenting to the Singapore National Eye Centre (SNEC) Ocular Inflammation and Immunology Service from 2008 to 2010. Ethics approval was obtained from our local institutional review board, and our research adhered to the tenets of the Declaration of Helsinki. Patients were enrolled if they had clinical ocular signs indicative of tuberculous uveitis (TBU) and consented to participate in the study.

All of the study subjects underwent a full systemic review, ocular examination, and standard baseline investigations. Blood was taken for diagnostic tests T-SPOT.TB (Oxford Immunotec, Oxford, United Kingdom) before the tuberculin skin test (TST) was performed. Patients were excluded if they had (1) any other possible infectious or noninfectious cause that could account for the uveitis or (2) a T-SPOT.TB result that was "indeterminate"[9] as these tests cannot be interpreted. Those suspected TBU were referred to infectious diseases

physician at Singapore General Hospital for evaluation. Anti-TB therapy (ATT) was prescribed if required. Patients' treatment response and recurrence were monitored for six months after completion of ATT, if given, or 1 year if no ATT was given.

From 1st January 2009, in addition to diagnostic tests T-SPOT.TB and TST, QuantiFERON-TB Gold In-Tube (Cellestis Incorporated, Carnegie, Australia) [QFT] was also performed for incoming patients. Blood was taken for QFT and T-SPOT.TB testing before the TST was performed to avoid any boosting effect (although it has been shown that this is unlikely to be significant).[10-11]

Investigations

- Complete blood count
- Erythrocyte sedimentation rate analysis
- Liver enzyme panel analysis
- Infectious disease screen (which included Venereal Disease Research Laboratory test for syphilis, TST, urine microscopy)
- Chest X ray
- T-SPOT.TB was performed according to the manufacturer's instructions,[12] where two readers quantified the number of Interferon-gamma spot-forming T-cells visually and a third reader was consulted if the results were disparate.
- TST was performed using the standard Mantoux method[13]
- QFT was performed according to the recommended guidelines[14]

Definitions

- T-SPOT.TB considered positive if there were >8 spots compared to the negative control well; negative if there were <4 spots compared to the control well; or equivocal if the test wells had 5–7 spots more than the control.[9] If the negative

control well had >10 spots and/or <20 spots in the mitogen positive control wells, the result was considered to be 'indeterminate'.

- TST induration was measured at 72 h with a ruler and considered positive if it was more than or equal to 15 mm, as validated in our population.[15]
- QFT considered positive if the response to the specific antigens was ≥0.35 IU/mL, regardless of the level of the positive control; negative if the response to the specific antigens was <0.35 IU/mL and the Interferon-gamma level of the positive control was ≥0.5 IU/mL; and indeterminate if both antigen-stimulated samples were <0.35 IU/mL and the level of the positive control was <0.5 IU/mL.[14]

2.3.3 Data for Meta-analysis

In Study 3, we performed a systematic literature review to identify all population-based studies of age-related macular degeneration (AMD) published before May, 2013 by searching the electronic databases of PubMed, Web of Science, and Embase.

Inclusion criteria

- Population-based study from a defined geographic area with response rate >50%
- Studies with standardized photographic assessment of AMD, i.e. using grading classifications according to the Wisconsin age-related maculopathy grading system[16], the international classification for age-related macular degeneration[17], or the Rotterdam staging system[18].

Definitions

- Early AMD defined as either any soft drusen (distinct or indistinct) and pigmentary abnormalities or large soft drusen 125 μm or more in diameter with a large drusen area (>500 μm diameter circle) or large soft indistinct drusen in the absence of signs of late-stage disease

- Late AMD defined as the presence of any of the following: geographic atrophy or pigment epithelial detachment, subretinal haemorrhage or visible subretinal new vessel, or subretinal fibrous scar or laser treatment scar.

Data Extraction from each Study

- Age-gender specific prevalence for early and late AMD (total number of subjects and number of cases recorded)
- Study name
- Age
- Gender
- Ethnicity
- Geographical region
- Publication year
- Response rate

Meta-analysis was performed according to the Meta analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[19]

2.4 Chapter 2 References

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2.5 Chapter 2 Figures

Figure 2.1 Study sampling areas in Singapore

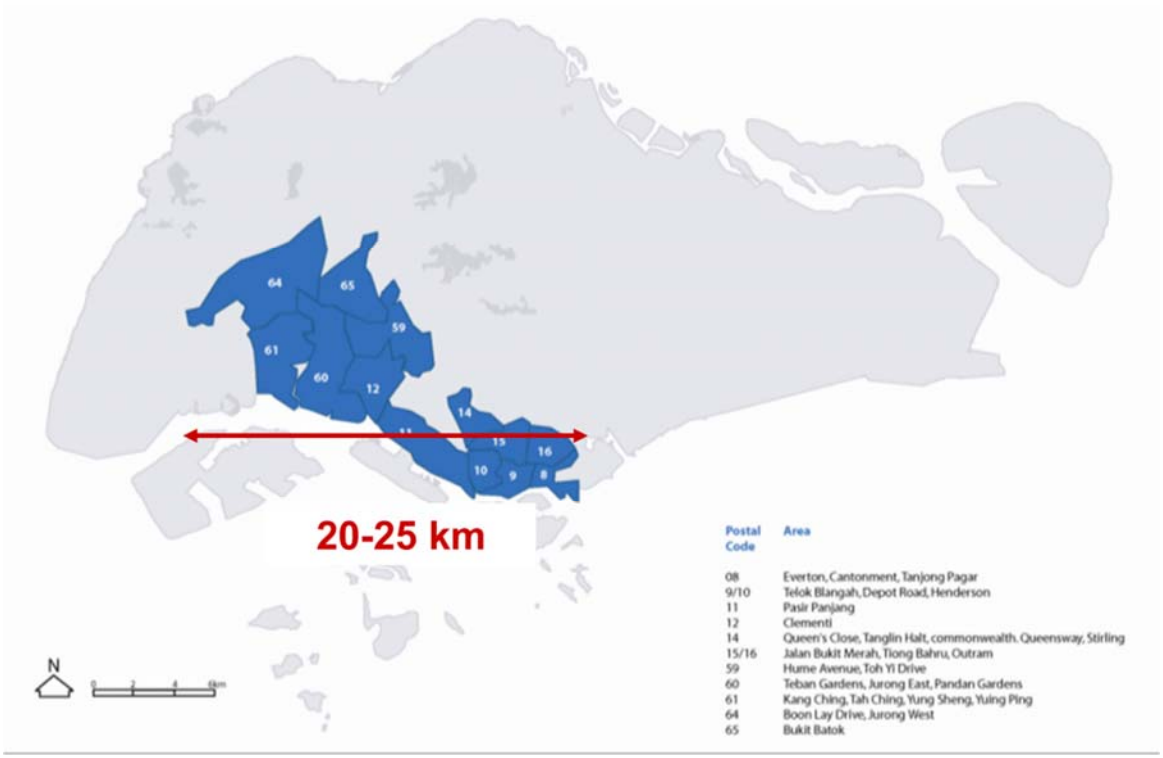
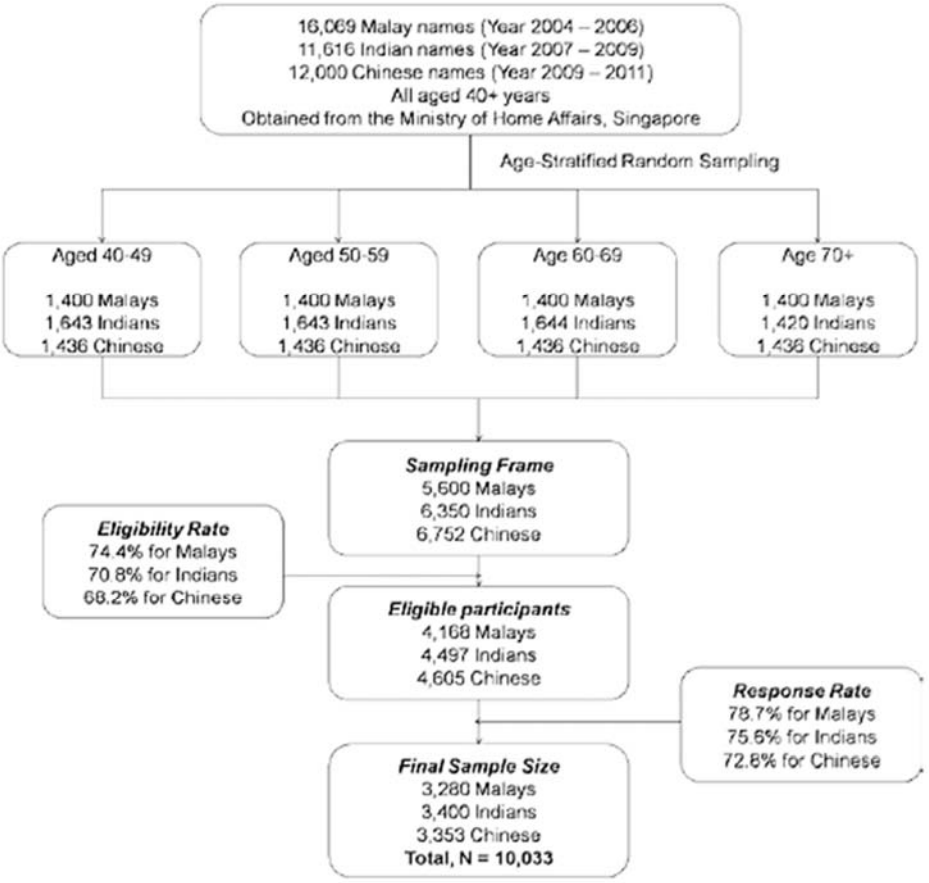


Figure 2.2 Enrolment of subjects into the study



CHAPTER 3

Intuitive Application of Bayes' Principle

Study 1: Cataract Conversion assessment using Lens Opacity Classification System III and Wisconsin Cataract Grading System

Publication:

Wong WL, Li X, Li J, Cheng CY, Lamoureux EL, Wang JJ, Cheung CY, Wong TY. Cataract Conversion assessment using Lens Opacity Classification System III and Wisconsin Cataract Grading System. Invest Ophthalmol Vis Sci. 2013 Jan 9;54(1):280-7. doi: 10.1167/iovs.12-10657.

3.1 RESEARCH MOTIVATION and CONTRIBUTIONS

Literature review on the prevalence of cataract across epidemiological studies varied substantially with the different prevailing grading protocols. Differences in grading methods, definitions of lens opacities and examination techniques limit meaningful inferences from the comparisons across studies conducted using different assessment methods. Conclusions based on naïve pooling of estimates without consideration of the differences in classification systems may not be accurate. Hence to fill this gap, we developed a conversion algorithm to determine the equivalence of construct measurements performed on different scales that would be especially useful for diseases where there is yet to be global consensus for the adoption of a simple definition and classification system (e.g. cataract, chronic kidney disease).

Bayes' theorem is a result that is of importance in the mathematical manipulation of conditional probabilities. Conditional probability which represents the likelihood of one system's grading score category (A) given another (B), can be easily transformed to the other direction (i.e. the likelihood of B given A). This relationship described in Bayes' theorem links and converts between two conditional probabilities, i.e. P(A|B) to P(B|A) provides a natural solution for the transformation between scales. Hence, we developed a general algorithm that approximates conversion between any two cataract systems and illustrated its application in two major cataract classification systems, LOCS III and Wisconsin system. Our conversion algorithm was validated by using cross-validation and can be extended for use in the conversion between any two scales. We also provided step by step instructions to facilitate the use of our conversion codes that automates the iterations of our collapsing algorithm using R, a free statistical computing software (refer to **Appendix 1**).

3.2 INTRODUCTION

Age-related cataracts remain the leading cause of blindness worldwide, posing a big challenge to rapidly aging populations.[1-3] Prevalence and incidence of cataracts have been well examined in many population-based epidemiologic studies.[4-31] Understanding the burden of cataracts from these prevalence and incidence data is important in the planning of eye care services, particularly health service delivery for cataract surgery.[32]

Several cataract classification systems have been developed and used to measure the presence and extent of cataracts including Lens Opacities Classification System (LOCS),[6, 8, 10, 11, 13-21, 27, 30] Wisconsin Cataract Grading System (Wisconsin system),[7, 9, 23-26] Wilmer,[12, 33] Age-Related Eye Disease Study Grading System (AREDS),[22, 31] World Health Organization Simplified Cataract Grading System (WHOSCGS),[4] and Oxford Clinical Cataract Classification System (OCCGS)[5] resulting in several arbitrary cut-offs derived within and across the various systems (**Tables 3.1 and 3.2**). It is important to note that direct comparison of prevalence of cataracts between different studies is hampered by the diversity of classification systems using various assessment methods.[34] In fact, some studies adopted more than one classification system simultaneously to assess different cataract subtypes.[13] Some other studies attempted to pool or compare prevalence of cataracts between studies despite having used different grading systems.[19, 35] Few studies have developed conversion scores between cataract classification systems, such as the calibration performed for LOCS III and OCCGS.[36] There is a gap in general formulas or conversion algorithm that enables one system's grading to be converted into another to allow for reasonable comparison across centers or studies.

In this study, we aim to develop a general algorithm that approximates conversion between any two cataract systems and illustrate the application in two major cataract classification systems, LOCS III and Wisconsin system.

3.3 METHODS

Study Population

The Singapore Malay Eye Study (SiMES) investigated the prevalence, causes and risk factors of blindness and visual impairment in the urban Malay community. SiMES is a population-based, cross-sectional epidemiological study of Asian Malays aged between 40 and 80 years old living in south western Singapore. Comprehensive details of the study have been reported and published elsewhere.[37-39] . Between August 2004 and June 2006, 3280 (78.7% participation rate from a total of 4168 eligible) Malays were examined in our study clinic. In total, 6530 eyes from 3265 SiMES participants were graded for cataract using the LOCS III and Wisconsin system; data we used to derive the conversion algorithm. The SiMES study conducted adhered to the Declaration of Helsinki and ethics approval was obtained by the Singapore Eye Research Institute Institutional Review Board. The conversion algorithm was further validated in the Singapore Indian Eye Study[40] (SINDI); a population-based cross-sectional study of 3400 (75.6% participation rate) Indian adults aged 40 and above using the same study protocol as in SiMES.

Cataract Classification Systems and Grading Procedures

Lens opacity was assessed using both LOCS III and Wisconsin system , as described previously.[34] **Table 3** summarizes the main characteristics of the LOCS III[41] and Wisconsin grading system[42]. Five study ophthalmologists examined all participants for cataract using slit lamp bio-microscopy with a Haag-Streit slit-lamp microscope (model BQ-900; Haag-Streit, K¨oniz, Switzerland) in accordance to the LOCS III[41], comparing with standard photographic slides for nuclear opalescence, nuclear colour, cortical and posterior subcapsular (PSC) cataract. Prior to the study, all study ophthalmologists were trained for

the standardized examination that includes documentation of clinical diseases according to written protocol (e.g., corneal pathology, diabetic retinopathy, etc), measurement of intraocular pressure and assessment of lens opacity using LOCSIII grading scale. Inter-rate reliability was assessed in a set of 30 patients with moderately high inter-rater reliability with intra-class correlation coefficients ranging from 0.70 to 0.85 between the study ophthalmologists.

Additionally, lens photographs were taken by digital slit-lamp (Topcon model DC-1 with FD-21 flash attachment; Topcon, Tokyo, Japan) and retro-illumination (Nidek EAS-1000, Nidek, Gamagori, Japan) cameras during the examination, and lens opacity was assessed using the Wisconsin system. The slit beam was adjusted to completely fill the pupil and to vertically bisect the lens at a 45^{o} angle focusing on the sulcus of the lens. All photographs were graded by a single trained grader at the University of Sydney who also graded cataract for the Blue Mountains Eye Study. 14,378 photos were taken in total with at least two photos for each eye and only the best quality photo based on grader's judgment was evaluated. These photographs were compared against a set of four standards to determine degree of nuclear opacity. Cortical and PSC cataracts were assessed from retro-illumination photographs using an overlying grid to determine the location and percentage of lens involved by the opacity. Percentage of lens area involvement by cortical and PSC cataract were estimated for each segment of the grid in order to calculate the total percentage area of involvement. Adjudication was provided for images with positive nuclear cataract by a senior researcher and PSC cases were confirmed by a senior ophthalmologist. The intra-grader reliability was high, with an intra-class correlation coefficient of 0.95 (95% confidence interval: 0.93-0.97) in a random sample of 100 photographs re-graded by the same grader.

Statistical Analyses

All statistical analyses were performed using R version 2.14.2 (http://www.R-project.org/, provided in the public domain by R Development Core Team, 2012).[43] Box plots were provided for graphical display of relationship between LOCS III and Wisconsin system for each cataract subtype.

Conversion algorithm

A contingency table was used to record and analyze the multivariate frequency distribution of modified categorical LOCS III and Wisconsin system. In order to increase the power and also the counts in each cell of the contingency table, a collapsing method was performed as in the following algorithm:

1) Calculate the conditional frequency distribution;

2) Compare conditional frequency distribution of any two contiguous categories;

3) Collapse the two contiguous categories with smallest distance or similar distribution;

4) Repeat the first three steps until desired number of contiguous categories is achieved.

In this algorithm, the smallest distance was defined as the least absolute shrinkage in terms of L1-norm.

Conversion Application using LOCS III and Wisconsin System

For nuclear opalescence score, LOCS III ranged from 0.1 to 6.9 with one decimal, while Wisconsin system used a five-point scale by comparing participant photographs of the eye with the set of four Wisconsin standard photographs. Also, a decimalized system of nuclear grading of one decimal place was estimated on a continuous scale between each standard by the grader (e.g., 3.8). We first start by collapsing the grading scheme used for LOCS III to encompass only half-unit steps: 0.1 to 0.4, 0.5 to 0.9, 1.0 to 1.4, 1.5 to 1.9 … 6.5 to 6.9 before applying our algorithm in the contingency table with Wisconsin system using five-point scale. LOCS III cortical and PSC scores ranged from 0.1 to 5.9, while

Wisconsin system measured the percentage of area involved. LOCS III cortical and PSC grading schemes were collapsed similarly as for nuclear score into half-unit steps. Continuous Wisconsin system for cortical was re-coded into fewer categories of 5% incremental steps from 0 to 100 while PSC was initially collapsed as 0 (since 0 may potentially be used as cut-offs), 1 to 4, and 5% increment steps thereafter from 5 to 100. Conversion algorithm was then applied to collapse LOCS III and Wisconsin system for all three cataract subtypes until we obtain five contiguous categories (i.e., 5 by 5 contingency table). The order of collapsing has little influence on the results.

The final collapsed contingency tables of nuclear opalescence, cortical, and PSC cataract were used as guidelines for conversion between LOCS III and Wisconsin system. This method works as a classification approach that tries to minimize the difference within each category and at the same time maximize the variability between any categories. We attempted to maximize the likelihood of the multivariate frequency distribution while restricting to five categories for each classification system. The conversion between LOCS III and Wisconsin system was based on conditional probabilities which reflect the likelihood of falling into corresponding LOCS III or Wisconsin system categories.

Data cleaning

We started with the initial contingency table having maximal contiguous categories collapsed arbitrarily. Data points in any cells of the final collapsed contingency table that have conditional probabilities of lesser than 10% were regarded as noise data (may be due to measurement errors) and were removed. Conditional probabilities were then standardized to ensure they summed up to one.

Validation

The conversion was validated using the cross-validation method.[44] Our data was randomly divided into 10 subsets. Nine subsets of data were used to construct the collapsed contingency table to propose the conversion guideline. The remaining subset of data was

used to test the conversion trained by the nine parts of data. We further validated our conversion algorithm with the SINDI population.

3.4 RESULTS

Figure 3.1 shows the distributions of individual cataract subtypes in SiMES. We observed possible quadratic or non-linear relationship.

As the relationship between LOCS III and Wisconsin system is not one-to-one due to the differences in score ranges and interval sizes, the conversion from LOCS III to Wisconsin system was different from the reverse direction of Wisconsin system to LOCS III (i.e. not vice versa). We therefore performed collapsed algorithm for the conversion between the two systems, and the results of our final collapsed contingency table was tabulated in **Appendix 2, Supplementary Table 3.1**. **Figure 3.2** illustrates our proposed conversion approximation results for nuclear, cortical, and PSC cataracts individually from LOCS III to Wisconsin system and the reverse order of Wisconsin system to LOCS III. **Figure 3.3** shows our validation analysis performed in 10% test SiMES data and in SINDI data. Relative frequencies of subjects in corresponding collapsed categories after conversion is almost identical to that of original scale for moderate to severe cataract.

The guide to use **Figure 3.2** is as follows: for example, to find the corresponding LOCS III score from Wisconsin system scale for nuclear opalescence, refer to the top left graph in **Figure 3.2**. Assuming the scale in Wisconsin system is 1, **Figure 3.2** shows that two corresponding LOCS III categories, “0.1-2.9” and “3.0-3.9” are most likely to match this Wisconsin system scale of 1 with conditional probability of 0.65 and 0.35, respectively. We may infer that it is 65% likely to be in the “0.1-2.9” category and 35% likely to be in the “3.0-3.9” category. Hence, in the consideration of prevalence, this subject with Wisconsin scale 1 reading contributes 0.65 headcount to “0.1-2.9” and 0.35 headcount to “3.0-3.9”.

3.5 DISCUSSION

We applied our proposed algorithm to approximate the conversion between two major cataract grading systems, LOCS III and Wisconsin system by collapsing the multivariate frequency distribution contingency table. Our conversion algorithm can be extended and applied to other cataract grading systems. There is a need for such method of conversion, as prevalence and incidence of cataract cannot be compared directly between studies that were assessed using different classification systems.

The estimation of prevalence of cataract varies substantially with different grading protocols,[34] which may be often neglected in the pooling and comparison of estimates seen in a few studies.[19, 35] The lack of universal epidemiologic definition of cataract cut-offs added to the inaccurate comparison of cataract prevalence even within studies using common grading systems. Pooling of cataract prevalence in the United States[35] was performed to include Barbados Eye Study (BES) with LOCS II,[8] Beaver Dam Eye Study (BDES) with Wisconsin,[7] Blue Mountain Eye Study (BMES) with Wisconsin,[9] Salisbury Eye Evaluation Project with Wilmer,[12] and Melbourne Visual Impairment Project with Wilmer.[45] Differences in grading methods, definitions of lens opacities and examination techniques limit the accuracy of conclusion with regards to pooled prevalence of cataract.

The application of our proposed conversion method provided a conversion approximation to transform between LOCS III and Wisconsin system. For example, converting nuclear opalescence from Wisconsin system to LOCS III in our data gave estimated prevalence of 24.8% (based on the "classical" or optimal cut-off of ≥ 4) compared with prevalence of 26.7% from direct use of LOCS III with the same cut-off. The reverse conversion of nuclear opalescence from LOCS III to Wisconsin system gave estimated prevalence of 17.8% (based on the "classical" or optimal cut-off of ≥ 4) compared to prevalence of 16.8% from direct use of Wisconsin system. The small difference in the converted prevalence and original prevalence on the same scale suggests

good approximation derived from our conversion algorithm. Conversion for cortical and PSC had similar performance. Our conversion algorithm allows fairer and more accurate inferences based on the same scale than current naïve comparisons of prevalence and pooling analysis performed directly across studies using different systems. In addition, the cross-validation analysis (**Figure 3**) demonstrated that our method was very robust and that our conversion algorithm may be extended to other population data for all three cataract subtypes.

Our findings have important insights and implications. We provided a general conversion algorithm and its application to approximate the conversion between LOCS III and Wisconsin system to improve the pooling or comparison of prevalence of cataracts. Wisconsin system for assessment of cataracts was also used in BMES and BDES, the two landmark epidemiological studies in eye research. At present, there continues to be important new papers on epidemiology of cataract from these two studies using the Wisconsin system,[46, 47] while more recent studies have used LOCS III. Our study is therefore important by being the first study to directly compare the two systems.

Large overlaps observed in early cataract scores between grading systems suggests difficulty in the discrimination of subtle lens opacity changes and the detection of early cataract. Newer methods under development such as Quasielastic or Dynamic Light Scattering (QELS or DLS) with Scheimpflug imaging system may be more objective and promising as such methods in clinical use have shown that a growing cataract can be detected at the molecular level using the technique of dynamic light scattering[48].

The strengths of our study include a large sample size from two population-based samples, and having performed two standardized cataract grading protocols in the same population. Our main limitation in the study application is the grading variability between clinical grading at the slit-lamp compared to grading lens photos. However, in many clinical and epidemiological studies and multi-center trials, clinical grading at the slit-lamp

may be the only feasible (and less expensive and complex) approach, particularly when cataract is important but of secondary interest (e.g., many landmark trials on anti-VEGF injection treatment for age-related macular degeneration (AMD) had clinical LOCS grading for cataract such as [CATT][49], Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in AMD [ANCHOR][50], Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD [MARINA],[51] and a Study of rhuFAB V2 [Ranibizumab] in Subjects with Subfoveal Choroidal Neovascularization Secondary to AMD [PIER][52, 53]). Our conversion algorithm application is therefore more practically relevant and allows comparison and conversion of clinical LOCS III grading performed at the slit lamp with grading of photographs using Wisconsin system. Further investigation needs to be conducted to ensure our conversion algorithm is widely applicable in other population data. Conversion based on original protocols of grading systems or lens images should be further explored.

In conclusion, we proposed a general algorithm that approximates conversion between any two cataract systems and illustrated its application in two major cataract classification systems, LOCS III and Wisconsin system. The transformation is not one-to-one and is validated by using cross-validation. The results of our study suggest that prevalence rates of cataract need to be converted to the same scale before comparison between different grading systems, and ideally with standardized universal epidemiologic definition of cut-offs for cataract subtypes.

3.6 Chapter 3 References

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3.7 Chapter 3 Tables and Figures

Table 3.1 Prevalence of Nuclear Opalescence, Cortical, and PSC with Various Cut-offs used from Population-based Studies

Study	Conduct Years	Country/City	Ethnicity	Rural/Urban	Age range	Grading Method	Nuclear (cut-off)	Cortical (cut-off)	PSC (cut-off)
Beaver Dam Eye Study[7]	1988-1990	Wisconsin, US	Caucasians (non-Hispanic)	Rural	43-84	Wisconsin	17.3% (≥ 4)	16.3% (≥ 5%)	6% (≥ 5%)
Blue Mountains Eye Study[9]	1992-1994	Sydney, Australia	Caucasians	Urban	49-96	Wisconsin	51.7% (≥ 4)	23.8% (≥ 5%)	6.3% (≥ 5%)
Tanjong Pagar Survey[11]	1997-1998	Singapore	Chinese	Urban	40-79	LOCS III	40.11% (≥ 4)	38.55% (≥ 2)	12.13% (≥ 2)
Aravind Comprehensive Eye Study[10]	1995-1997	South India	Indian	Rural	40+	LOCS III	44.7% (≥ 3)	27.1% (≥ 3)	22.9% (≥ 2)
Shihpai Eye Study[19]	1999-2000	Taiwan	Chinese	Urban	65+	LOCS III	38.9% (≥ 2)	21.9% (≥ 2)	9.2% (≥ 2)
Indonesia Eye Study[17]	2003	Indonesia	Malay	Rural	21+	LOCS III	16.89% (≥ 4)	15.68% (≥ 2)	7.35% (≥ 2)
Skovde Cataract Study[18]	2001	Sweden	Caucasians	Urban	70-84	LOCS III	14.37% (≥ 4)	6.69% (> 3)	9.74% (> 1)
Meiktila Eye Study[14]	2005	Myanmar	Burmese	Rural	40+	LOCS III	27.35% (≥ 4)	20.91% (≥ 2)	11.34% (≥ 2)
Kandy Eye Study[15]	2006-2007	Sri Lanka	Sinhalese, Tamils, Moors	Rural	40+	LOCS III	4.5% (≥ 4)	26.0% (≥ 2)	7.9% (≥ 2)
India Study of Age-related Eye Disease[21]	2005-2007	North India	Indian	Rural and Urban	60+	LOCS III	48% (≥ 4)	7.6% (≥ 3)	21% (≥ 2)
India Study of Age-related Eye Disease[21]	2005-2007	South India	Indian	Rural and Urban	60+	LOCS III	38% (≥ 4)	10.2% (≥ 3)	17% (≥ 2)
Handan Eye Study[16]	2006-2007	Hebei, China	Chinese	Rural	30+	LOCS III	5.1% (≥ 4)	18.3% (≥ 2)	1.5% (≥ 2)
Casteldaccia Eye Study[6]	1992	Italy	Caucasians	Rural	40-99	LOCS II	18.5% (≥ 2)	12.9% (≥ 2)	10.8% (≥ 2)
Barbados Eye Study[8]	1987-1992	Barbados	Blacks	Urban	40-84	LOCS II	19% (≥ 2)	34% (≥ 2)	4% (≥ 2)
			Mixed (Blacks and Whites)			LOCS II	20% (≥ 2)	30% (≥ 2)	5% (≥ 2)
			Whites			LOCS II	23% (≥ 2)	15% (≥ 2)	5% (≥ 2)

Los Angeles Latino Eye Study[20]	2000-2003	California, US	Latinos (Hispanics)	Urban	40+	LOCS II	9.0% (≥ 2)	13.4% (≥ 2)	3.1% (≥ 2)
Andhra Pradesh Eye Disease Study[13]	1996-2000	South India	Indian	Rural and Urban	16+	LOCS III & Wilmer*	12.4% (≥ 3)	7.4% (≥ 2)	8.1% (≥ 1)
Salisbury Eye Evaluation Project[12]	1993-1995	Maryland, US	Blacks	Rural and Urban	65-84	Wilmer	31.0% (≥ 2)	54.5% (≥ 1/8)	2.6% (Present)
			Caucasians		65-84	Wilmer	46.3% (≥ 2)	23.9% (≥ 1/8)	5.4% (Present)
Beijing Eye Study[22]	2001	Beijing, China	Chinese	Rural and Urban	40-101	AREDS	82% (≥ 2)	10.3% (≥ 5%)	4.3% (≥ 1%)
Kongwa Eye Project[4]	1996	Tanzania	Blacks	Rural	40+	WHOSCGS	15.6% (≥ 1)	8.8% (≥ 1)	1.9% (≥ 1)

*LOCS III was used for nuclear opalescence while Wilmer was used for cortical and PSC cataract.

Table 3.2 Incidence Rate of Nuclear Opalescence, Cortical, and PSC with Various Cut-offs used from Population-based Studies

Study	Start Year (Duration Years)	Country/City	Ethnicity	Rural/Urban	Age	Grading Method	Nuclear (cut-off)	Cortical (cut-off)	PSC (cut-off)
Blue Mountains Eye Study[23]	1992 (10)	Sydney, Australia	Caucasians	Urban	49-97	Wisconsin	36% (≥ 4)	28% (≥ 25%)	9.1% (> 0%)
Beaver Dam Eye Study[25]	1988 (15)	Wisconsin, US	non-Hispanic Caucasian Americans	Rural and Urban	43-84	Wisconsin	29.7% (≥ 4)	22.9% (≥ 5%)	8.4% (≥ 5%)
Barbados Eye Study[27]	1987 (9)	Barbados	African Barbadian	Urban	40-84	LOCS II	42% (≥ 2)	33.8% (≥ 2)	6.3% (≥ 2)
			Mixed (Black and White)		40-84	LOCS II	42.2% (≥ 2)	22.4% (≥ 2)	3.6% (≥ 2)
			White Barbadian		40-84	LOCS II	36.5% (≥ 2)	14.2% (≥ 2)	7.1% (≥ 2)
Los Angeles Latino Eye Study[30]	2000 (4)	California, US	Latinos (Hispanics)	Urban	40+	LOCS II	10.2% (≥ 2)	7.5% (≥ 2)	2.5% (≥ 2)
Beijing Eye Study[31]	2001 (5)	Beijing, China	Chinese	Rural and Urban	40-101	AREDS	5.98% (≥ 4)	11.14% (≥ 5%)	5.47% (≥ 1%)

LOCS III: Lens Opacity Classification III; Wisconsin system: Wisconsin Cataract Grading System; AREDS: Age-Related Eye Disease Study Grading System; PSC: posterior subcapsular cataract; Nuclear: nuclear opalescence.

Table 3.3 Characteristics of LOCS III and Wisconsin Cataract Grading System, WHOSCGS

System	LOCS III [40]		Wisconsin system [41]	
Method	Clinical assessment with slit lamp or grading performed on retro-illumination photographs		Slit lamp photos for nuclear cataract; Retro-illumination photographs for cortical and PSC cataract	
Category	NC	0-6.9	NO	0-5
	NO	0-6.9	Cortical	% involved
	Cortical	0-5.9	PSC	% involved
	PSC	0-5.9		
Decimal	Yes		No	

NO: nuclear opalescence, NC: nuclear colour, PSC: posterior subcapsular cataract

Figure 3.1 Scatter plots and box plots for each cataract subtypes (nuclear opalescence, cortical and PSC) using Wisconsin System (Wisconsin) and LOCS III

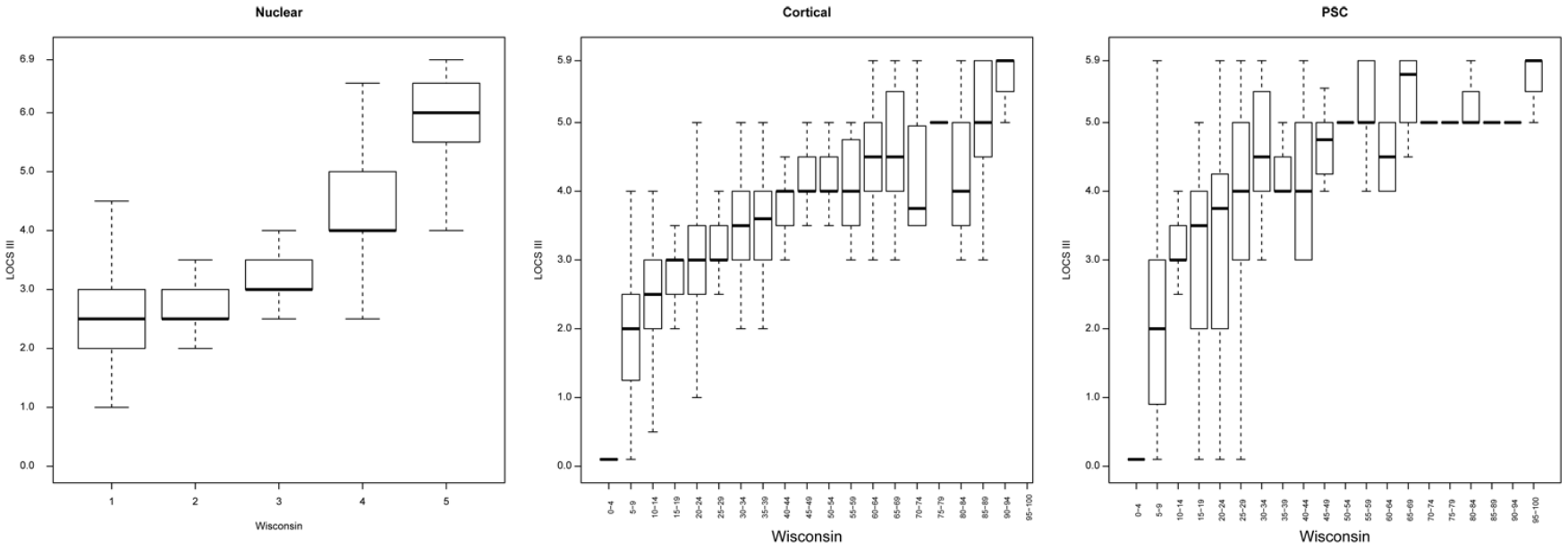


Figure 3.2 Conversion between LOCS III and Wisconsin system. Nuclear: nuclear opalescence; *bold lines and numbers* in plots were estimated from the conditional probabilities given either LOCS III or Wisconsin (conditional on the grading system to be converted).

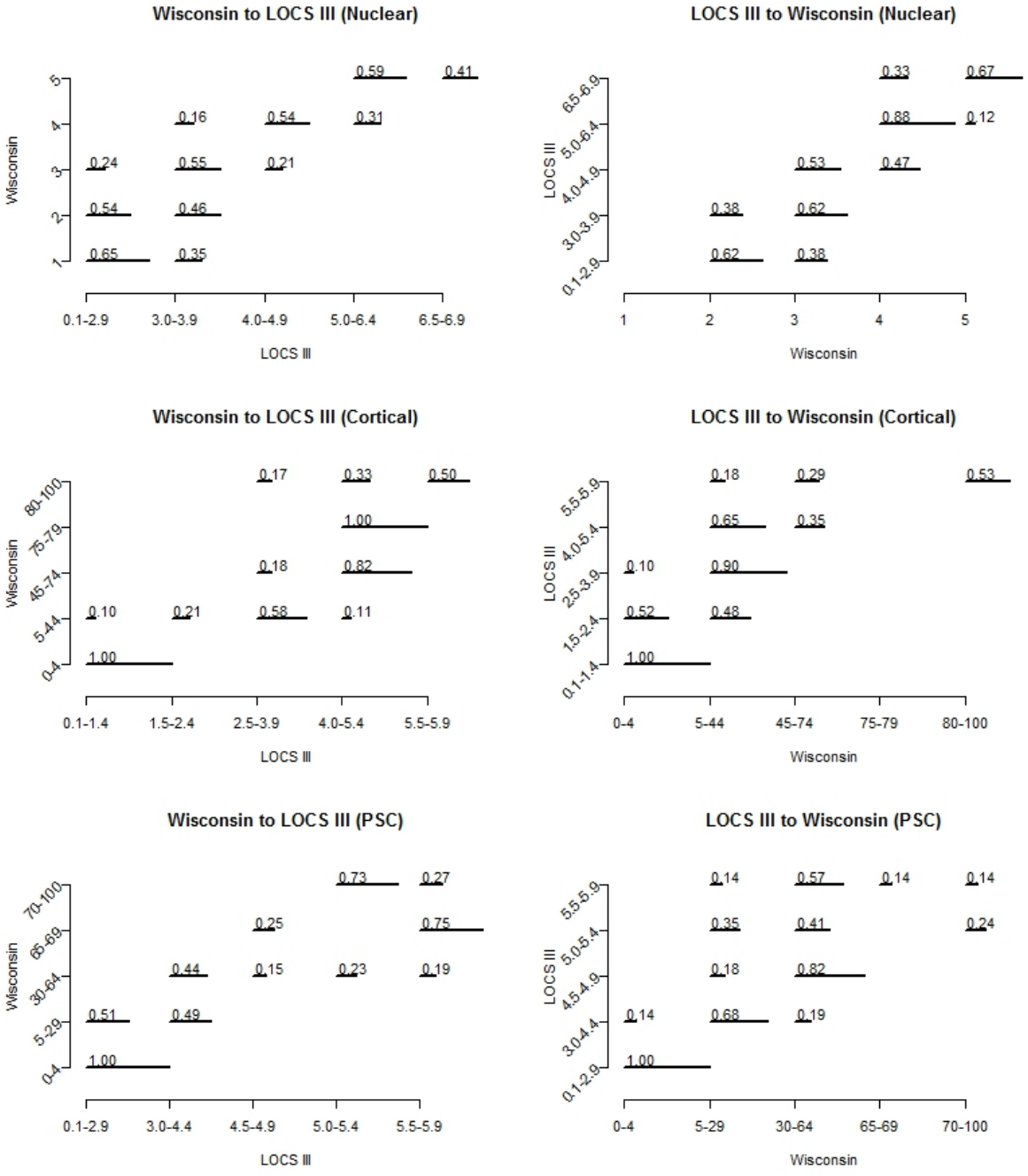
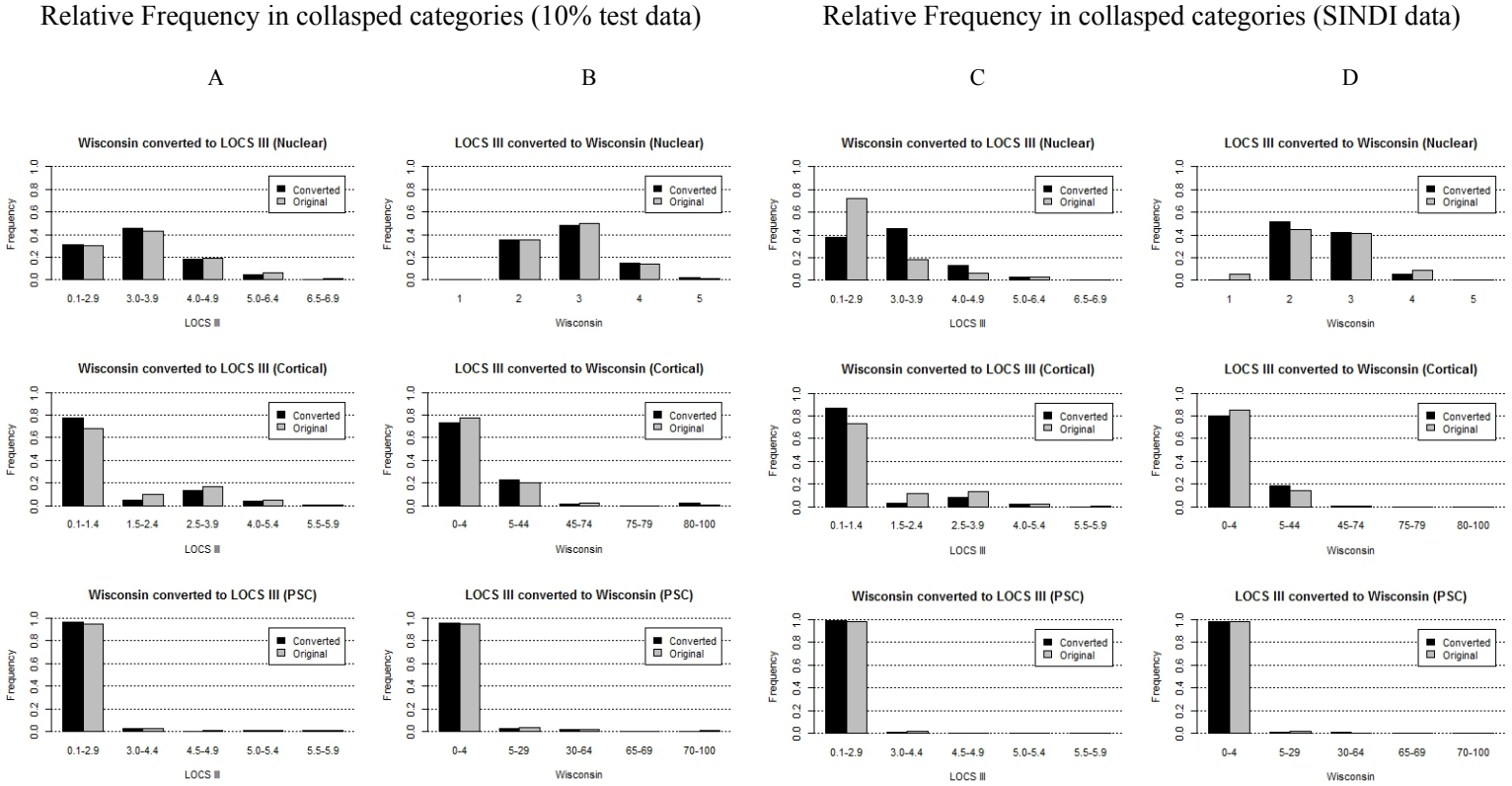


Figure 3.3 Validation of Conversion Algorithm on Relative Subject Frequency in 10% Test data and SINDI data. *Columns A, C*: Original: percent of subjects in original LOCS III grade; Converted: percent of subjects using converted LOCS III grade (i.e. after conversion from Wisconsin to LOCS III scale). *Columns B, D*: Original: percent of subjects in original Wisconsin grade; Converted: percent of subjects using converted Wisconsin grade (i.e. after conversion from LOCS III to Wisconsin scale).



CHAPTER 4

Bayesian Approach in Diagnostic Classification

Study 2: Comparison of Tuberculin Skin Test and two Interferon γ release assay for the diagnosis of Tuberculous Uveitis: Bayesian evaluation in the absence of a gold standard.

Publications:

Ang M*, **Wong WL***, Li X, Chee SP. Interferon γ release assay for the diagnosis of uveitis associated with tuberculosis: a Bayesian evaluation in the absence of a gold standard. Br J Ophthalmol. 2013 Aug;97(8):1062-7. doi: 10.1136/bjophthalmol-2012-302199. Epub 2013 May 30

Ang M*, **Wong WL***, Kiew SY, Li X, Chee SP. Prospective Head-to-Head Study Comparing Two Commercial Interferon-gamma Release Assays for the Diagnosis of Tuberculous Uveitis. Am J Ophthalmol. 2014 Feb 4. pii: S0002-9394(14)00061-0. doi: 10.1016/j.ajo.2014.01.031.

*Equal contributions

4.1 RESEARCH MOTIVATION and CONTRIBUTIONS

It is important and essential for infectious diseases to be accurately diagnosed in the primary healthcare setting for the timely management of patient's disease. However, gold standard diagnostic techniques are rare in many areas of medicine. Furthermore, the lack of established gold standards makes it harder to evaluate new diagnostic tests. In our area of research interest, the diagnosis of tuberculous uveitis is controversial. The widely used Mantoux test (TST) has a low specificity due to a false-positive response in patients infected with nontuberculous mycobacterium (NTM) or vaccinated with Bacille CalmetteeGuérin (BCG). Interferon-gamma (IFN-g)-release assays (IGRAs) are newer diagnostic tests based on in vitro detection of IFN-g released by T-cells in response to antigens specific to Mycobacterium tuberculosis (MTB). Clinicians may face diagnostic and therapeutic dilemma, especially with the availability of various tests. Diagnostic test comparisons and criteria guidelines would be useful information to aid ophthalmologists in interpretation of test results and advise course of actions for patients, such as the need and sequence of performing additional diagnostic tests or treatments.

Our analysis approach is to use latent class model via Bayesian methods (avoids computational restrictions in "classical" approach), to model the relationship between results of several diagnostic tests and latent disease status to estimate the diagnostic accuracy (in terms of sensitivity and specificity) of all tests under consideration without explicitly using any of the tests as gold standard. This approach is increasingly used in the analysis of diagnostic accuracy studies without gold standards but yet to be commonly adopted in the field of ophthalmology, probably due to the statistical and programing complexity in modeling and implementation. We developed and described our models for the type and structure of our study data to estimate sensitivity and specificity of each diagnostic test, prevalence of disease and proposed sequential testing guidelines based on decision theory. We also provided step by step instructions to guide the implementation of

our model analyses in R (a free statistical computing software), that can be easily used by researchers without advanced statistical training (refer to **Appendix 1**).

4.2 INTRODUCTION

Tuberculosis (TB) remains one of the leading causes of morbidity and mortality worldwide, with 8.7 million incident cases in 2011.[1] Currently, the diagnosis of TB still depends on the century-old *Mantoux* or tuberculin skin test (TST).[2] However, TST has poor specificity due to false-positives in persons infected with *non-tuberculous mycobacterium* or vaccinated with *Bacille Calmette–Guérin* (BCG).[3,4] Interferon-gamma (IFN-γ) release assays (IGRAs) are based on in-vitro detection of IFN-γ released by T-cells, in response to antigens specific to *Mycobacterium tuberculosis* (MTB);[5] as opposed to TST which uses a crude extract of proteins from MTB i.e. purified protein derivative.[6, 7] Commercially available IGRAs include the T-SPOT.TB (Oxford Immunotec, Oxford, United Kingdom) and QuantiFERON-TB Gold In-tube [QFT] (Cellestis Incorporated, Carnegie, Australia).[8]

The main advantage of IGRA is that it is an objective, reproducible blood test that requires only one visit.[8] However, its main disadvantages are higher cost, logistical issues as the samples are time and temperature sensitive, and the need for trained personnel to analyze the results. Though similar, there are some key differences between T-SPOT.TB and QFT. In T-SPOT.TB the number of IFN-γ producing T-cells are counted, after stimulating isolated peripheral blood mononuclear cells with early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10), using an enzyme-linked *immunospot* assay.[9] On the other hand, QFT is a whole blood assay that quantifies IFN-γ produced by T-cells in response to ESAT-6, CFP-10 and TB7.7 using an enzyme-linked *immuno-sorbent* assay.[10]

Today, TB-associated uveitis is essentially a presumptive diagnosis. It is diagnosed when uveitis is present with a positive TST or IGRA and chest x-ray (CXR) findings suggestive of pulmonary TB and/or evidence of associated systemic TB infections in the

absence of other underlying disease.[11] Few ocular biopsies[3] are positive on culture, acid-fast bacilli (AFB) smear or polymerase chain reaction (PCR) analysis.[11] Thus, the impact of IGRAs in the diagnosis of TBU has become increasingly important as these may potentially affect treatment and prognosis.[12] While the role of IGRAs in diagnosing tubercular uveitis has been studied, to our knowledge,[13-15] there is currently no head-to-head comparison between QFT and T-SPOT.TB specifically for the diagnosis of TBU. Thus, we conducted a prospective, direct comparative study to compare these two commercially available IGRAs to diagnose TBU in our population.

4.3 METHODS

Overview of Management

We conducted a prospective study of consecutive patients presenting with new onset of uveitis to the Singapore National Eye Centre Ocular Inflammation and Immunology Service from 2008 – 2010 and added the QFT diagnostic test from 1st January 2009 onwards. Ethical approval was obtained from our Singapore Health Services Centralized Institutional Review Board, and our study adhered to the tenets of the Declaration of Helsinki. After obtaining informed consent, all patients underwent a full systemic review, ocular examination, and standard baseline investigations as previously described.[13] We included all patients who were undergoing systemic review for acute uveitis and gave informed consent to be enrolled in the study. We excluded patients who did not consent to the minimum follow-up period of 1 year after completion of ocular and/or systemic therapy.

Investigations

At presentation, all patients were tested with a standard panel of investigations as described,[13] essentially: a complete blood count, erythrocyte sedimentation rate analysis, liver enzyme panel analysis, and infectious disease screening, which included a venereal disease research laboratory (VDRL) test for syphilis, TST, urine microscopy, and a CXR. Other tests such as HLA-B27 screen, an AFB smear from throat swabs, and PCR assays

for TB DNA from ocular samples were performed if the patient consented to the procedure. Blood was taken for QFT and T-SPOT.TB testing before the TST was performed, to avoid any boosting effect (albeit shown that this is unlikely to be significant).[16, 17] The TST was performed with the standard Mantoux method: intradermal injection of 0.1 ml (2 tuberculin units) purified protein derivative (PPD) (RT23 SSI – 2T.U./0.1 ml Statens Serum Institut, Copenhagen, Denmark).[18] Induration was measured at 72 hours with a ruler and considered positive if it was more than or equal to 15 mm (as validated in our population).[13]

T-SPOT.TB was performed according to the manufacturer's instructions.[19] For each patient, 8 ml of blood was collected in Lithium Heparin tubes and processed within 8 hours of sampling. Peripheral blood mononuclear cells were prepared by density gradient centrifugation over Ficoll Paque™Plus (GE Healthcare). 250 000 cells were seeded in each of four wells of the assay plate. The cells were stimulated for 16–20 h (under 5% carbon dioxide at 37°C) with GIBCO AIM-V™ medium (nil control), phytohaemagglutinin (mitogen-positive control) or the TB-specific peptide antigens (peptide pools for ESAT-6 and CFP-10 in separate wells) in a total volume of 150 µL per well. Two readers quantified the number of IFN-γ spot forming T-cells visually, and a third reader was consulted if the results were disparate. The T-SPOT.TB test was considered positive if there were >8 spots compared to the negative control well; negative if there were <4 spots compared to the control well; or equivocal if the test wells had 5–7 spots more than the control.[14] If the negative control well had >10 spots and/or <20 spots in the mitogen positive control wells, the result was considered to be 'indeterminate'.

QFT was performed according to the recommended guidelines.[10] Whole blood from each patient was divided into three tubes of 1 ml each (nil control, positive control and TB specific antigens [ESAT-6, CFP-10 and TB7.7]). Samples were incubated with the stimulating antigens for 16–24 h at 37°C. Afterwards, plasma samples were harvested and the amount of IFN-γ released was measured via ELISA. The result obtained in the nil

control was subtracted from the mitogen control and the antigen-stimulated samples. The result was considered positive if the response to the specific antigens was ≥0.35 IU/mL, regardless of the level of the positive control; negative if the response to the specific antigens was <0.35 IU/mL and the IFN-γ level of the positive control was ≥0.5 IU/mL; and indeterminate if both antigen-stimulated samples were <0.35 IU/mL and the level of the positive control was <0.5 IU/mL.

Treatment and Management of patients

The infectious diseases physicians at the Singapore General Hospital independently evaluated all patients with a high clinical index of suspicion for TB. Those found to have associated systemic or pulmonary TB infection received anti-tuberculosis therapy (ATT), while uveitis patients with latent TB were advised on the risk-benefit ratio of ATT.[20] Patients consenting to treatment received standard ATT according to CDC guidelines (isoniazid 5 mg/kg daily, rifampicin 450-600 mg daily, pyrazinamide 30 mg/kg daily and ethambutol 15 mg/kg daily for 2 months, followed by 2 drugs for a 4 month continuation phase, for a total minimum of 6 months duration).[20, 21] In patients with posterior segment inflammation where ATT was not indicated, oral prednisolone was used at a starting dose of 1mg/kg body weight, tapering slowly over the clinical course. Any anterior segment inflammation was treated with topical corticosteroids. The therapeutic response was monitored by one ophthalmologist (SPC), where a two-step decrease in inflammation (SUN working group activity score) was considered an improvement in clinical activity and a positive response to treatment.[22]

Statistical Analysis

In the diagnosis of tubercular uveitis, there is currently no gold standard, i.e. a diagnostic test with 100 percent sensitivity and specificity.[23, 24] Bayesian statistics are used to compute probability distributions (i.e. posteriors) for parameters of interest in our

statistical models by updating prior knowledge with new data, expressed formally by integrating the prior distribution and the likelihood function. We used Bayesian latent class models to evaluate the frequencies of true positives derived from diagnostic tests as well as their sensitivities and specificities. As the 'true' numbers of patients with tuberculous uveitis are unknown, these were termed as 'latent data'. In the first part of the study, we performed analysis for TST and T-SPOT.TB data.[25] In the second part where we collected data for another diagnostic test, QFT in addition to TST and T-SPOT.TB for a new group of uveitis patients where T-SPOT.TB and QFT are IGRAs and hence closely related tests, we modified our model to take into consideration their dependency in the estimation of sensitivities and specificities. Furthermore, in addition to using non-informative prior for the prevalence of tuberculous uveitis in our model, we have conducted a separate meta-analysis to estimate pooled prevalence, to incorporate informed prior knowledge as part of our sensitivity analysis.

In summary, we performed the analysis in four major parts: (A) Estimation of Prevalence, Sensitivity, Specificity, Negative, and Positive Predictive Value; (B) Analysis of the tuberculin skin test, T-SPOT.TB and QFT in combination; (C) Optimal choice of diagnostic test; and (D) Sensitivity Analysis, where technical details are described below.[26, 27] The Gibbs sampler algorithm, an iterative Markov-chain Monte Carlo technique, was used for estimations using the R and JAGS program.[28, 29] We used the JAGS software (version 3.3.0), running from R version 3.0.2 (R Development Core Team, 2013) to implement the Gibbs sampler, using specific marginal posterior densities.[28, 29] Convergence of estimation was checked and confirmed using the Gelman–Rubin convergence diagnostic.[28, 29]

The sensitivity (S) and specificity (C) of each test, as well as the prevalence of tuberculous uveitis (π), were the proposed model parameters to be estimated. Positive predictive value (PPV) and negative predictive value (NPV) can then be calculated with

the three estimated parameters using Bayes' formula. Prior information for sensitivity and specificity of T-SPOT.TB, QFT and TST were obtained from a previous meta-analysis of tests for latent tuberculosis infection.[23] To obtain relevant prior information from similar studies on the prevalence of tuberculous uveitis for patients with uveitis, we performed a meta-analysis of published literature using a similar Bayesian approach (**Appendix 2, Supplementary Table 4.1 and Figure 4.1**) and updated the information in the model as part of our sensitivity analysis.

A. Estimation of Prevalence, Sensitivity, Specificity, Negative, and Positive Predictive Value

Our Bayesian latent model describes the number of patients screened with tuberculin skin test (independent from IRGA tests) having tuberculous uveitis (y_{tst}) as distributed binomially: $y_{tst} \sim Binomial(n_{tst}, p_{tst})$ where n_{tst} is the number of patients and p_{tst} is the probability of a positive tuberculin skin test result. We calculate $p_{tst} = \pi * S_{tst} + (1 - \pi) * (1 - C_{tst})$ where S and C represents the sensitivity and specificity of each test, and π is the prevalence of disease, i.e. tuberculous uveitis.

IGRAs T-SPOT.TB and QFT tests are closely related and our interest lies in estimation of sensitivities of T-SPOT.TB (S_2) and QFT test (S_3) and their respective specificities (C_2 *and* C_3) while accounting for the correlation between test outcomes for a given patient. The cross-classified test results for T-SPOT.TB and QFT tests are assumed to follow a multinomial distribution: $y \sim Multinomial(n, (p_{11}, p_{12}, p_{21}, p_{22}))$, and the multinomial cell probability of test-outcome combination ij is given by $p_{ij} = \pi_{ij} * S_{ij} + (1 - \pi_{ij}) * C_{ij}$, for i, j = 1, 2. y_{11} (y_{22}) is the number of patients that test positive (negative) on both tests and y_{12} (y_{21}) is the number of patients that test positive (negative) on 1 test and negative (positive) on the other test. We account for the correlation between diagnostic tests by incorporating covariance terms for sensitivity and specificity, i.e. S_{11},

the sensitivity for cell with positive result on both is given by $S_1 * S_2 + covariance\_S$ and C_{22} is given by $C_1 * C_2 + covariance\_C$. Note that the two sensitivities and specificities are functions of the model parameters: $S_2 = S_{11} + S_{12}$, $S_3 = S_{11} + S_{21}$, $C_2 = C_{22} + C_{21}$ and $C_3 = C_{22} + C_{12}$.

As the "true" numbers of patients with tuberculous uveitis are unknown, y is the latent variable of interest in our analysis. The sensitivity (S) and specificity (C) of each test, as well as the prevalence of tuberculous uveitis (π), were the proposed model parameters to be estimated. Positive predictive value (PPV) and negative predictive value (NPV) for individual tests can then be calculated as $PPV = \frac{\pi * S}{S*\pi + (1-C)*(1-\pi)}$ and $NPV = \frac{(1-\pi)*C}{\pi*(1-S) + C*(1-\pi)}$. Correlations between sensitivities and specificities were also investigated in the construction of our final statistical model.

Beta distribution is a very flexible distribution family that applies to an unknown quantity that takes values between 0 and 1 (i.e. proportions). Hence it is appropriate to be used as the prior distribution for the prevalence of tuberculous uveitis, sensitivity and specificity of each test. The shape of the beta distribution is determined by two parameter specification, α and β . Based on the obtained prior information, α and β were calculated to be 219.84 and 90.01 for prior distribution of sensitivity of tuberculin skin test; 22.14 and 10.27 for specificity of tuberculin skin test; 17.64 and 17.64 for sensitivity of T-SPOT.TB; 560.31 and 58.48 for specificity of T-SPOT.TB; 245.18 and 136.72 for sensitivity of QFT and 718.30 and 3.97 for specificity for QFT. Prior information for sensitivity and specificity of T-SPOT.TB, QFT TST were obtained from a previous meta-analysis of tests for latent tuberculosis infection.[23] Uniform prior distributions were used for the two covariances.[27]

B. Analysis of the TST and T-SPOT.TB and QFT in combination

With the model described above, we also estimated the number of "true positives" in the multinomial cells for pair-wise diagnostic tests and reported the results as median with 95% Bayesian credible interval (Crl). The multinomial cell probability of disease given joint test results can be derived using Bayes' formula. The posterior distributions of "true positives" for discordant pair-wise diagnostic test results were also examined.

C. Optimal Choice of Diagnostic test

The choice of the diagnostic test sequence was analyzed using statistical decision theory by choosing the smallest risk of the decision rules.[26] A "0-1 loss function" was used to calculate the risk of performing a diagnostic test where a loss or a risk was calculated for misclassification, i.e. false positive or false negative. The formulae used to calculate the risk of a diagnostic test, i.e. the misclassification rate is given by $Risk = \pi * (1 - S) + (1 - \pi) * (1 - C)$.

D. Sensitivity Analysis

Sensitivity analyses were performed to validate our model results. Multiple trial or mock data were applied into our Bayesian model to investigate if our data or the priors are driving model results. Varying posterior distributions should be observed with the application of multiple trial data (i.e. changing likelihood functions) to suggest that posterior distribution was calculated by the likelihood (i.e. data) incorporated with prior information rather than prior distribution alone influencing the results. Analysis using non-informative prior was also perform. Also, we have performed meta-analysis using similar Bayesian approach on similar published studies for prevalence of tuberculous uveitis amongst patients with uveitis to be used as prior information for π (Supplementary Table 1 and Figure 1). The model results updated with prior knowledge from our meta-analysis was compared to that using non-informative prior for prevalence of tuberculous uveitis.

4.4 RESULTS

Based on data in the second part of our prospective study, we enrolled 120 patients (of whom 106 patients completed follow-up) with valid QFT and T-SPOT.TB test results. Mean age of our patients was 48 ± 17 years, with an equal gender ratio (1:1, n = 52 males). Majority of the patients in our study were of Chinese ethnicity (65/106, 61.3%), followed by Indian (22/106, 20.8%) and Malay (7/106, 6.6%) - reflective of the racial distribution in our South-East Asian population. Of the 106 patients (152 eyes), 46 patients (43.4%) presented with bilateral uveitis. Uveitis was predominantly anterior (91/152, 59.9%), intermediate (4/152, 2.6%), or posterior (23/152, 15.1%); while 34 eyes (22.4%) presented with panuveitis. Suggestive clinical features of a tubercular cause such as granulomatous inflammation (38 eyes, 25.0%), extensive posterior synechiae (29 eyes, 19.1%), vasculitis (19 eyes, 12.5%), single nodular or serpinginous choroiditis (1 eye, 0.7%) were observed in our study cohort. We found no significant differences in terms of age, gender, race or anatomical classification of uveitis when we compared the different QFT, T-SPOT.TB and TST test results for the patients. We also did not have any definite cases of ocular TB infection i.e. culture-positive TB from ocular samples, in this study cohort. One patient (0.9%) had *Mycobacterium tuberculosis* smear-positive sputum samples, and 1 patient (0.9%) had positive PCR results for *Mycobacterium fortuitum* from the urine sample. The majority of patients (n=90, 84.9%) had CXR findings that were not suggestive of pulmonary TB infection. None of the study subjects were found to be immunocompromised nor had BCG vaccinations within 10 years from the study enrolment.

Using all diagnostic tests results, we had more data to improve estimations for individual tests (**Table 4.1**) and found that the QFT was estimated to be more specific (QFT: 0.995, 0.988-0.999) than T-SPOT.TB (0.905, 0.879–0.926); and slightly less sensitive (QFT: 0.64, 0.60-0.69) compared to T-SPOT.TB (0.67, 0.60–0.74). TST, as a reference has sensitivity (0.69, 0.64–0.74) and specificity (0.74, 0.60–0.85). The correlations for

sensitivities between QFT and T-SPOT.TB was estimated to be 0.62 (0.43-0.77) but specificities was not found be correlated. The pooled prevalence of tuberculous uveitis from our meta-analysis of similar studies was 1.62 (95% CrI: 0.88, 2.81) (**Appendix 2, Supplementary Figure 4.1**). Comparisons between estimations for our final model and the model updated with prior knowledge from our meta-analysis for prevalence of tuberculous uveitis were also shown in **Table 4.1**. Sensitivity and specificity estimates were similar. Predictive values differ greatly but was not surprising as they are dependent on the prevalence of disease.

Table 4.2 shows the estimated number of "true positives" corresponding to each of the four possible outcomes of the diagnostic tests. All tested QFT and T-SPOT.TB positive in our study were estimated to be 'true positive'. However, amongst discordant results, QFT was significantly more accurate compared to T-SPOT.TB (QFT positive 98% versus T-SPOT.TB positive 76% with ratio 1.28, 95%Crl: 1.11-1.72 i.e. 95%Crl > 1.0, strong statistically evidence). Similarly, both QFT (0.99 95%Crl 0.98-1.00) and T-SPOT.TB (0.90 95%Crl 0.82-0.96) were more accurate than the tuberculin skin test amongst the discordant results. Using the estimated sensitivity and the specificity of each diagnostic test (TST, T-SPOT.TB and QFT), we then calculated the risk of each test expressed as the function of probability of tuberculous uveitis (**Figure 4.1**). Based on statistical decision theory, QFT is the first-line test and should be performed ahead of T-SPOT.TB and the TST for diagnosis of tuberculous uveitis. Our sensitivity analysis confirmed that posterior distribution of parameters with mock data varied appreciably with the changing likelihood functions suggesting that our results are data driven and were not overly influenced by priors. Furthermore, the optimal choice of diagnostic test is QFT as seen in **Figure 4.1**, regardless of influence from choice of prior for prevalence of tuberculous uveitis.

4.5 DISCUSSION

There is increasing evidence that suggests that Interferon-gamma release assays are more specific and/or accurate for the diagnosis of TB compared to the TST.[30-33] The improved specificity of Interferon-gamma release assays over tuberculin skin testing has been shown to reduce unnecessary ATT.[34] There have also been several studies which suggest that Interferon-gamma release assays are more useful than tuberculin skin test in the diagnosis and management of patients with uveitis and TB infection.[13, 15, 25, 35-37] However, there have been no direct comparative studies between QFT and T-SPOT.TB for the diagnosis of tuberculous uveitis. In the first part of our study data, we found that T-SPOT.TB is more specific but less sensitive than TST and should be used in preference to TST in low TB-prevalence populations. When used in conjunction, the likelihood of tuberculous uveitis is greatest if both T-SPOT.TB and TST are positive.[25] Based on new patient data in the second part of data collection, QFT was estimated to be more specific than T-SPOT.TB in diagnosing tuberculous uveitis. A recent meta-analysis suggested that QFT was more specific but less sensitive as compared to T-SPOT.TB, albeit for diagnosis of active TB instead of tuberculous uveitis.[38] Our final model incorporates the covariances between related estimates QFT to be more specific than T-SPOT.TB; while the sensitivity of T-SPOT.TB was better in diagnosing tuberculous uveitis compared to previous studies (0.50 to 0.67). We then derived the optimal risk of using either the QFT or the T-SPOT.TB, while varying the prevalence or probability of tuberculous uveitis. Our analysis using statistical decision theory suggested that whether the prevalence of tubercular uveitis in TB endemic subpopulations is low or relatively high, the QFT remains superior and should be used as a first-line test.

Of note and more important to clinician, is the fact that the QFT has a high PPV with a moderate NPV, i.e., a positive QFT assures you that the result of the test is reliable. The estimated sensitivity and specificity for each diagnostic test (final model seen in **Table 4.1**)

is particularly useful in the calculation of PPV, NPV and post-test odds for a new patient to aid the clinician in advising their patient. For example, if a new patient in a low TB endemic population (e.g. prevalence of tuberculous uveitis is assumed to be 2%) is positive for QuantiFERON-TB Gold In-Tube, using the estimated sensitivities and specificities in **Table 4.1**, the PPV of the patient is calculated to be 0.72 and the post-test odds is 2.62. This suggests that given positive QFT result, the patient has a 72% probability of having disease and is about thrice as likely to have the disease than not. Predictive values are influenced by the prevalence of disease in the population being screened,[39] and for low disease prevalence, diagostic tests have low sensitivities as there would be fewer "affected" or "diseased" subjects. Predictive values of Interferon-gamma release assays can be increased by performing these diagnostic tests only in patients with a high clinical index of suspicion - for example, if they have clinical signs consistent with tuberculous uveitis.[40]

We also studied the usefulness of performing both tests in combination, QFT and the T-SPOT.TB. If both were positive, it increased the likelihood of a tubercular cause in our patients who present with suggestive clinical signs to 100% in our data. However, if both tests were negative, there is still the possibility of excluding a tubercular cause, i.e. there was a 46% chance that the patient may have tuberculous uveitis. For discordant results, QFT was more accurate than T-SPOT.TB; of note, both QuantiFERON-TB Gold In-Tube and T-SPOT.TB were more accurate than the tuberculin skin test. These results suggest that performing QFT and T-SPOT.TB tests increases the accuracy of diagnosing tuberculous uveitis, although discordant or negative results are less useful.

Both the QFT and T-SPOT.TB provide an objective, single-visit blood test that detects and quantify Interferon-gamma release from T-cells in persons infected with TB. However, the QFT uses more peptide-simulating specific TB antigens: ESAT-6, CFP-10, and TB7.7 (p4), as opposed to T-SPOT.TB which only uses ESAT-6 and CFP-10. This may explain the higher specificity in QFT as compared to T-SPOT.TB.[38] Nonetheless, as these antigens

are absent from all BCG strains and most NTM, both QFT and T-SPOT.TB impart greater specificity than tests using PPD, which is reflected in most studies including ours.[33] T-SPOT.TB also differs from QFT in that the former involves harvesting and counting viable peripheral mononuclear blood cells (PMBCs) that release Interferon-gamma; while the latter uses an enzyme-linked immuno-sorbent assay (ELISA) to study Interferon-gamma release from T-cells in whole blood. The technique used in T-SPOT.TB may provide better resolution of blood samples with reduced T-cell numbers (e.g. samples from immunocompromised individuals) that would usually give indeterminate QFT results.[8] However, in individuals undergoing immunosuppressive therapy, both QFT and T-SPOT.TB appear to have comparable efficacy. [41-43]

The main aim of this current study is to compare QFT and T-SPOT.TB. However, TST results were also included as a reference and to allow comparisons with previous studies. Our results confirm that both QFT and T-SPOT.TB have lower sensitivity compared to the tuberculin skin test. This means that a negative or indeterminate result is difficult to interpret, and may not be useful in diagnosing tuberculous uveitis. Indeterminate QFT or T-SPOT.TB results can occur, due to low mitogen levels, heterophile antibodies or high background IFN- Interferon-gamma levels; while equivocal T-SPOT.TB results are likely to be negative but require repeat testing.[14] The other setback of Interferon-gamma release assays is the high cost and technical difficulty. Cost-effectiveness studies have thus affected clinical practice and guidelines: the UK-based National Institute for Health and Care Excellence (NICE) guidelines advocate a two-step approach using tuberculin skin testing and chest radiography as first line investigations, with subsequent confirmatory Interferon-gamma release assays testing in cases with positive tuberculin skin test results. These guidelines have been widely accepted in the rest of Europe. In contrast, the USA Centers for Disease Control and Prevention (CDC) guidance recommends one-step Interferon-gamma release assays testing for screening of latent TB infection. This lack

of agreement likely reflects the current areas of uncertainty with regards to Interferon-gamma release assays and will continue to evolve as ongoing research rapidly fills the gaps in our current knowledge. [44, 45]

The limitation with all studies involving extrapulmonary TB, including "ocular TB," is the small number of patients who actually have a positive TB culture from ocular samples, which is the 'gold standard' for diagnosis.[46] Thus, most studies use a diagnosis of "presumed" tubercular uveitis or employ meta-analysis to evaluate new diagnostic tests such as T-SPOT.TB. We used the Bayesian technique, which has also been employed in a variety of studies of other infectious diseases that face the same diagnostic dilemmas as tubercular uveitis.[47-53] We had previously compared the tuberculin skin test and T-SPOT.TB using a similar Bayesian analysis, in patients with clinical signs suggestive of tuberculous uveitis;[25] as opposed to the current study where we included all patients who presented with uveitis for the first time. Due to small numbers of patients who are culture-positive or have evidence of AFB on smears or MTB DNA using PCR from ocular biopsies, it is difficult to evaluate the QFT or T-SPOT.TB as a diagnostic test using 'classical' hypothesis testing. Our Bayesian analysis using the established latent class model considered estimation of the accuracy of two correlated tests and a third test that is conditionally independent of the two tests of interest, allowed contemporary comparison of the T-SPOT.TB and QFT accuracy without a gold standard. We recognize the limitation of applying prior information into our model with relatively limited data as priors are subjective and may influence the final results. However, our choice of prior distribution used was based on prior information derived from a recent meta-analysis performed on published studies [23, 24]. Moreover, our sensitivity analyses confirmed that our results and models were robust, and not overly influenced by prior information. However, we recognize that these results may only apply to patients who present with uveitis to a tertiary eye centre.

In conclusion, this head-to-head comparison of two commercially available Interferon-gamma release assays suggests that QFT is the optimal choice test to diagnose patients with tuberculous uveitis. This analysis was consistent after performing sensitivity analyses and varying the prevalence or probability of tuberculous uveitis. In the absence of a gold standard test, our study confirms that a combination of any two Interferon-gamma release assays or "classical" tests such as tuberculin skin testing can improve the diagnostic accuracy using Bayesian modeling. However, further study into the most optimal or cost-effective combination and sequence of tests to diagnose tuberculous uveitis is required.

4.6 Chapter 4 References

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4.7 Chapter 4 Tables and Figures

Table 4.1 Estimated sensitivity and specificity and the positive and negative predictive values for the TST, T-SPOT.TB and QFT

Data presented as median (95% Bayesian Credible Interval) using data from all diagnostic tests
*Prior distribution and data derived from meta-analysis (Reference 23)
†Final model, accounted only for correlated sensitivities between tests
Model 1 considers correlated sensitivities and specificities between tests; Model 2 accounted only for correlated specificities between tests
S = sensitivity, C = specificity, PPV = positive predictive value, NPV = negative predictive value

		Prior information for S and C*	Informative Prior for Prevalence 0.0162 (0.0088-0.0281)		Non-Informative Prior for Prevalence	
			Model 1	Model 2	Model 1	Model 3†
	Prevalence		0.048 (0.028-0.078)	0.042 (0.025-0.067)	0.750 (0.638-0.860)	0.750 (0.642-0.867)
TST	S	0.709 (0.658-0.761)	0.711 (0.658-0.758)	0.710 (0.657-0.760)	0.690 (0.638-0.739)	0.689 (0.639-0.739)
	C	0.683 (0.522-0.844)	0.531 (0.451-0.609)	0.528 (0.453-0.604)	0.743 (0.596-0.861)	0.739 (0.597-0.853)
	PPV		0.070 (0.040-0.118)	0.062 (0.035-0.102)	0.893 (0.795-0.955)	0.890 (0.798-0.953)
	NPV		0.973 (0.955-0.986)	0.976 (0.960-0.986)	0.442 (0.261-0.590)	0.443 (0.252-0.589)
T-SPOT.TB	S	0.500 (0.334-0.666)	0.603 (0.452-0.738)	0.613 (0.437-0.759)	0.669 (0.593-0.741)	0.670 (0.595-0.743)
	C	0.906 (0.882-0.929)	0.880 (0.856-0.902)	0.879 (0.853-0.901)	0.905 (0.881-0.927)	0.905 (0.879-0.926)
	PPV		0.199 (0.103-0.336)	0.180 (0.094-0.311)	0.955 (0.920-0.978)	0.955 (0.924-0.978)
	NPV		0.978 (0.964-0.988)	0.981 (0.970-0.989)	0.480 (0.289-0.631)	0.481 (0.289-0.634)
QFT	S	0.642 (0.593-0.691)	0.661 (0.614-0.704)	0.658 (0.610-0.704)	0.643 (0.595-0.686)	0.643 (0.597-0.687)
	C	0.996 (0.989-1.000)	0.945 (0.924-0.967)	0.940 (0.921-0.958)	0.995 (0.988-0.998)	0.995 (0.988-0.999)

	PPV		0.372 (0.216-0.618)	0.326 (0.190-0.508)	0.997 (0.993-0.999)	0.998 (0.993-0.999)
	NPV		0.982 (0.972-0.990)	0.984 (0.975-0.991)	0.480 (0.299-0.622)	0.482 (0.294-0.617)
Correlations between related tests	S		0.527 (-0.266, 0.890)		0.619 (0.420-0.761)	0.621 (0.426-0.765)
	C		0.596 (0.398-0.730)	0.645 (0.527-0.759)	0.091 (-0.017, 0.272)	

Table 4.2 Estimated "true positives" in our study data

*Study data are counts
†Estimated counts from Final Model, Bayesian median (95% Crl)

Study Data*				Estimated "true positive" Counts†			
T-SPOT.TB	QFT +	QFT -	Total	T-SPOT.TB	QFT +	QFT -	Total
+	72	16	88	+	72 (1.00 ,1.00-1.00)	12 (0.76 ,0.57-0.88)	84
-	7	57	64	-	7 (0.98 ,0.93-1.00)	27 (0.46 ,0.30-0.67)	34
Total	79	73	152	Total	79	39	118

T-SPOT.TB	TST +	TST -	Total	T-SPOT.TB	TST +	TST -	Total
+	57	27	84	+	56 (0.98 ,0.96-0.99)	24 (0.90 ,0.82-0.96)	80
-	18	43	61	-	14 (0.75 ,0.56-0.89)	14 (0.32 ,0.18-0.54)	28
Total	75	70	145	Total	70	38	108

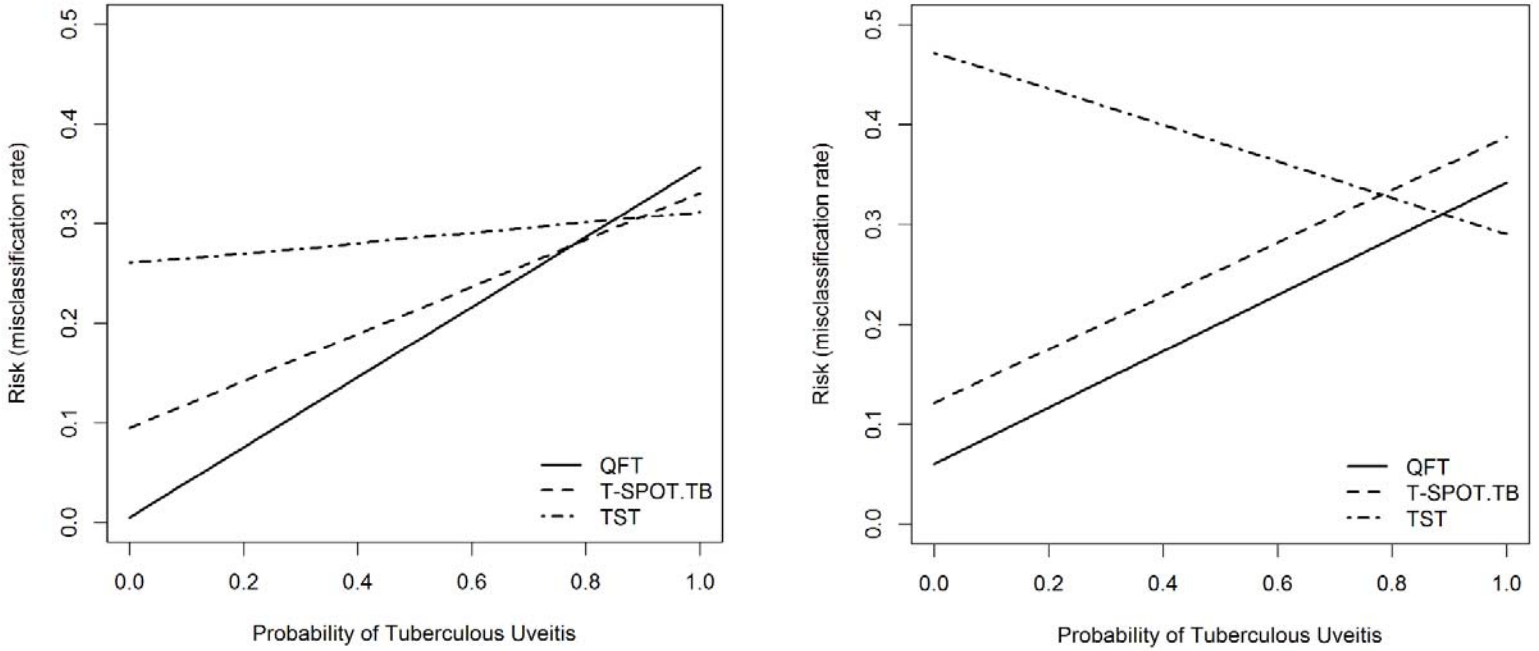
QFT	TST +	TST -	Total	QFT	TST +	TST -	Total
+	55	20	75	+	55 (1.00 ,1.00-1.00)	20 (0.99 ,0.98-1.00)	75
-	20	50	70	-	15 (0.75 ,0.56-0.88)	16 (0.31 ,0.19-0.53)	31
Total	75	70	145	Total	70	36	106

Figure 4.1 Optimal Choice of Diagnostic Test, QFT or T-SPOT.TB?

The risk (misclassification rate) of all tests increases with the prevalence of tuberculous uveitis. In our study, the risk of QFT was the lower than T-SPOT.TB even as the prevalence of tuberculous uveitis varied, suggesting that QFT should be performed ahead of T-SPOT.TB. Risk for tuberculin skin test was included as for reference.

Non-informative Prior for Prevalence†

Informative Prior for Prevalence
0.0162 (0.0088-0.0281)



†Final model

CHAPTER 5

Bayesian Approach in Systematic Review and Meta-analysis

Study 3: Global Prevalence and Burden of Age-Related Macular Degeneration,

A Meta-Analysis and Disease Burden Projection for 2020 and 2040.

Publications:

Wong WL*, Su XY*, Li X, Cheung CM G, Klein R, Cheung CY[#], Wong TY[#]. Global Prevalence and Burden of Age-Related Macular Degeneration: A Meta-Analysis and Disease Burden Projection for 2020 and 2040. Invest Ophthalmol Vis Sci. 2013 Jan 9;54(1):280-7. doi: 10.1167/iovs.12-10657.

*Equal contributions

5.1 RESEARCH MOTIVATION and CONTRIBUTIONS

It is desirable and useful to have available updated summarized evidence of diseases, be it treatment or exposure relationships consolidated from the many related but independent health research studies of various design types (i.e. randomized controlled trials, cross-sectional studies, cohort studies and case-control studies) provides better confidence and guidance in clinical decisions and future research directions. However, the key challenge faced in integrating results across studies conducted by investigators worldwide is the involvement of multiple sources of uncertainty, such as the variability in clinical practices between multi-centers, measurement uncertainties of exposures and differences in patient populations such as social-demographics like ethnicities and geographical regions. In epidemiology, pooled prevalence of diseases and effect sizes is essential information for the healthcare planning of disease burden.

We conducted a literature review to incorporate recently published population based studies data to provide an updated pooled global prevalence and projections (to the UN data) of age-related macular degeneration (AMD) for years 2014 to 2040 by ethnicity and geographical regions using the Hierarchical Bayesian approach. Ethnicity, geographical regions, gender and publication year effects were assessed with Bayes factor. Our model carefully took into account the various levels of uncertainty and pulls strength across studies in estimating both the study specific effects and population effect, giving robust estimation to study prevalence especially for studies with small sample sizes. We also compared and evaluated our model of AMD prevalence estimation with "classical" random-effect model in a simulation study. Detailed instructions to run our model analyses in R (free statistical computing software) were given in **Appendix 1** (requires some perseverance for researchers with little statistical and computing experience). Our codes can be expanded to perform similar meta-analyses.

5.2 INTRODUCTION

Age-related macular degeneration (AMD) is responsible for 8.7% of all global blindness and is the most common cause of blindness in developed countries,[1-5] particularly in elderly people above 60 years. The prevalence of AMD is likely to increase globally as a consequence of exponential population ageing. There have been significant advances in the management of exudative or "wet" AMD with the introduction of anti-angiogenesis therapy and patients now have effective treatment options that can prevent blindness, and in many cases, even restore vision.[6-10] However, these treatments are expensive, and not available to all patients in many countries.[11-14] Thus, understanding the prevalence, burden and population impact of AMD is essential for adequate health care planning and provision, and this requires both precise and contemporary estimates of disease prevalence.

Although there have been many population-based studies of AMD around the world, there are no summarized data to guide global strategies. Furthermore, studies have suggested substantial racial/ethnic differences in prevalence of AMD. In the Baltimore Eye Study, persons of European (white) ancestry were more likely to have early and late AMD than those of African ancestry.[15, 16] Two meta-analyses conducted in populations of European [17] and Asian ancestry[4] suggest that among persons ages 40-79, age-specific prevalence of late AMD in Asians (0.56%) appears comparable to Europeans (0.59%), but early AMD signs were less common among Asians (6.8%) than Europeans (8.8%). There are no studies that have systematically compared the prevalence of AMD amongst Europeans or Asians with Africans or Hispanics, nor across geographical regions.

To address this gap, we performed a systematic review of the literature on AMD to estimate the prevalence of AMD, to determine differences by ethnicity, region and gender, and to project the number of individuals affected with AMD globally in 2020 and 2040.

5.3 METHODS

Sources and Methods of Literature Search

We systematically reviewed publications that reported prevalence of AMD by searching the electronic databases of PubMed, Web of Science and EMBASE for relevant papers published up to May, 2013, with the following search terms (formatted for PubMed search):

1. ("Macular Degeneration"[Mesh] AND ("Prevalence"[Mesh] OR "Epidemiology"[Mesh] OR "Cross-Sectional Studies" [Mesh] OR "Cohort Studies"[Mesh]))

2. (("age-related maculopathy"[All Fields] OR "age-related maculopathy"[All Fields] OR "age-related macular degeneration"[All Fields] OR "age related macular degeneration"[All Fields] OR "macular degeneration"[All Fields]) AND ("prevalence"[All Fields] OR "incidence"[All Fields] OR "epidemiology"[All Fields] OR "risk factors"[All Fields]))

The strategy identified all articles used in previous reviews.[4, 17] In addition, reference lists of identified reports were scanned to identify other relevant studies. Initial search was scrutinized in detail by clinician scientist XYS and reviewed by senior clinician scientist CYC. Data checks were conducted by statisticians (WLW, XL). Disagreements were resolved by discussion.

Inclusion and Exclusion Criteria

Our meta-analysis was conducted according to the meta-analysis of observational studies in epidemiology (MOOSE) guideline.[18] The full texts of potentially relevant articles were reviewed to identify studies which met the inclusion and exclusion criteria. The 2 criteria for inclusion were (I) population-based study from a defined geographic area and (II) standardized photographic assessment of AMD.

For (I), studies were included if they quantified the prevalence of AMD (including early, late and exudative or neovascular AMD [nvAMD], and geographic atrophy [GA]) in population-based samples, with clearly defined methods of sampling. A response rate of

50% or higher is considered adequate for the purpose of this meta-analysis[19] with the exception of the European Eye Study (EUREYE) study[20] as it was a large population study but sensitivity analysis showed almost no effect on our robust model estimates (**Appendix 2, Supplementary Table 5.2**). Surveys or audits of hospital eye departments or clinics were excluded. Studies inviting nonspecific volunteers or particular professions were excluded, as were studies that relied on self-reported diagnoses or carried out fundus examinations only in those with reduced vision.

For (II), we included studies that had used retinal photography and standardized grading methods to diagnose and classify AMD lesions (i.e., grading of retinal photographs following either the Wisconsin Age-Related Maculopathy Grading System [WARMGS],[21] the International AMD classification[22] or the Rotterdam Staging System[23]) with reproducible grading results.

Studies fulfilling any one of the following were excluded: (1) used only clinical examination by ophthalmoscopy or slit-lamp biomicroscopy for diagnosis of AMD (i.e. lack of any grading reproducibility assessment), (2) reports of number of eyes with AMD as opposed to the number of individuals, (3) studies in which determination of AMD prevalence was not one of the primary study objectives (e.g. studies determining AMD risk factors) and (4) not population based, but were interview based or audits of hospital eye departments. Although we did not specifically exclude non-English literature, studies included in the final analysis were all written in English.

Appendix 2, Supplementary Figure 5.1 shows the flow chart of the selection process to identify relevant studies. A total of 2,751 published original research articles, letters, abstracts, and review articles based on abstracts and titles were identified as of May 2013 from our literature search. After initial abstract review, 54 potentially eligible articles were retrieved for evaluation. Of these, we applied the inclusion and exclusion criteria and

identified 39 eligible articles reporting on 39 population-based studies (12,727 any AMD cases in 129,664 participants) (**Appendix 2, Supplementary Figure 5.1**).

Definition of Early, Late and Any AMD

The classification systems used to define those with early, late and any AMD (GA and NVAMD) in each study was recorded, that is, the Wisconsin Age-Related Maculopathy Grading System [WARMGS][21] or the International AMD classification[22]. Early AMD was defined by either any soft drusen (distinct or indistinct) and pigmentary abnormalities or large soft drusen 125μm or more in diameter with a large drusen area (> 500μm diameter circle) or large soft indistinct drusen in the absence of signs of late AMD. Late AMD was defined by the presence of any of the following: geographic atrophy or pigment epithelial detachment, subretinal hemorrhage or visible subretinal new vessel, or subretinal fibrous scar or laser treatment scar for AMD. Any AMD was defined by presence of either Early or Late AMD.

Modeling and Hierarchical Bayesian Approach

Because intrinsic difficulties exist when conducting meta-analysis to summarize the overall prevalence of data from varied studies with differing characteristics such as disease definition, age distribution of the sample, and prevalence estimates stratified by age and gender versus single prevalence estimates, we constructed statistical models to best describe and fit our extracted data in this study. Heterogeneity issues were addressed in our pooled meta-analysis using a Hierarchical Bayesian (HB) approach to determine the prevalence of AMD globally. The HB approach models the hierarchical structure of data extracted, taking into account the difference in age distribution across studies and effects of ethnicity, gender and region to ensure greater precision in AMD estimates.

Meta-analysis can be naturally described in a hierarchical structure in a HB model. The number of people with AMD (y_{ij}) can be specified as binomially distributed:

$y_{ij} \sim Binomial(n_{ij}, p_{ij})$, where n_{ij} is the total number of participants and p_{ij} is the prevalence of AMD in the i^{th} study of the j^{th} category of the varying covariate (e.g. each study may consist of more than one ethnicity).

In the Bayesian approach, prevalence of AMD, p_{ij} is considered as a random variable (that has a probability density distribution) in contrast to a fixed unknown parameter (an unknown value) in the "classical" approach. Hence, the logit transformation of p_{ij} follows a Normal distribution: $logit(p_{ij}) = u_{ij}$ and $u_{ij} \sim Normal(\mu_{ij}, \sigma^2)$, where $\sigma^2 = 1/\tau$.

To investigate and account for the heterogeneity within and between studies, we modeled μ_{ij} as a linear combination of covariates that varies across studies (i.e. age, gender, ethnicity, regions). Hence, our base model to pool the overall prevalence of AMD was: $\mu_{ij} = \beta_0 + \beta_1 * agel_{ij} + \beta_2 * ageu_{ij} + \beta_3 * ageui_{ij}$, where $agel_{ij}$ and $ageu_{ij}$ are the centered and standardized lower and upper bounds of the age group range for participants of each study and $ageui_{ij}$ is a right censoring indicator for studies with right-censored age range data for the upper bound, i.e. 80+ years. The lower and upper bounds of age range was centered to 45 and 85 years respectively and then standardized by dividing by their respective standard deviations to ensure that pooled estimates are comparable as they were being mapped onto the same age range, i.e. 45 to 85 years. Gender, ethnicity and regions covariates were then individually added to the base model to determine their impact and for covariate-specific pooled prevalence. The percentage of variability in prevalence estimates due to various sources of heterogeneity compared to chance alone were examined (refer to heterogeneity analysis described in **Appendix 2, Supplementary text 5.1**).

Finally, non-informative prior (to represent ignorance) was specified for residual variability τ using the conjugate gamma distribution: $Gamma(0.01,0.01)$. Gamma distribution is applicable to unknown quantities that take values between 0 and ∞. All age

coefficients and intercept in the model were specified with non-informative Normal priors, i.e. $\beta \sim Normal(0,0.0001)$.

The Gibbs sampler algorithm, an iterative Markov-chain Monte Carlo technique, was used to estimate the posterior distributions of our random variables using the R and JAGS program.[24, 25] We used the JAGS software (version 3.3.0), running from R version 3.0.2 (R Development Core Team, 2013) to implement the Gibbs sampler, using specific marginal posterior densities.[24, 25] Convergence estimation was assessed by calculating the Gelman–Rubin convergence statistics.[24, 25]

Ethnicity, Region and Gender Effects

Bayesian hypothesis testing was performed to examine the effect of ethnicity, geographic regions and gender on the prevalence of any, early and late AMD using Bayes factors (BF) to compare hypotheses of differences between groups, implementing the Gibbs variable selection as proposed by Dellaportas et al.[26] using the JAGS software. The comparison of the posterior probabilities of hypothesis is given by:

$$\mathrm{P}(\mathrm{H}_1|data)/\mathrm{P}(\mathrm{H}_0|data) = \mathrm{P}(data|\mathrm{H}_1)/\mathrm{P}(data|\mathrm{H}_0) * \mathrm{P}(\mathrm{H}_1)/\mathrm{P}(\mathrm{H}_0)$$

(posterior odds) (Bayes factor) (prior odds)

where H_0 is the null hypothesis and H_1 is the alternative hypothesis. Jeffreys[27] proposed an interpretation scheme for the magnitude of BF in terms of weak (BF 1-3), substantial (BF 3-10), strong (BF 10-30), very strong (BF 30-100), and decisive (BF > 100) for H_1, while BF < 1 suggests support for H_0.

We evaluated four major ethnic groups (European ancestry populations [Europeans], African ancestry populations [Africans], Asian, and Hispanics) and six geographic regions (Africa, Asia, Europe, Latin America and the Caribbean, Northern America and Oceania). Publication year was also tested to assess the trend of prevalence over the years for consideration in projection estimates.

Simulation Study to Compare Hierarchical Bayesian and Random-Effect Methods

Because the random effect (RE) model is the most frequently used meta-analytic method to account for the heterogeneity between the studies by incorporating a random effect estimate of between-study variation in the weighting, we performed simulation study to assess and compare HB and RE methods. This analysis is presented in **Appendix 2, Supplementary text 5.2 and Figure 5.2**.

Projection Estimates

Model $\mu_{ijk} = \beta_{0k} + \beta_{1k} * age_{ij} + \beta_2 * ageui_{ij} + \beta_3 * study_i$ was used to estimate the prevalence for each year increase in age for the k^{th} region. Global and region effects were incorporated as fixed and random effects in β_{0k} and β_{1k}. Age-specific prevalence was often reported as interval (e.g. 40-49) or censored (e.g. 80+) age range in the published papers and hence the median of interval was used to represent the age interval while censored age range was taken as the age with a censoring indicator in the analysis model. The estimated prevalence were used to calculate the global and region specific total number of individuals with AMD in 2020 and 2040 by multiplying the age- and region-specific estimated prevalence rates to the population projection data in World Population Prospects of the United Nations.[28] Age group-specific prevalence rates were assumed to be constant over the next 27 years for our global projection to year 2040 as Bayesian hypothesis testing of publication year covariate suggests no evidence to support any trend for prevalence from year 1989 to 2013 in our reviewed literature data.

5.4 RESULTS

Our meta-analysis included 129,664 individuals in 39 published articles from 39 population-based studies comprising of 5 ethnic ancestry groups with details listed in **Appendix 2, Supplementary Table 5.1**. Any, early and late AMD were pooled separately. Of the study participants, 43.5% were of European ancestry, 12.4% were of African ancestry, 33.1% were Asian, 9.7% Hispanic and 1.3% were others.

Forest plots in **Figure 5.1** show the overall and ethnic-specific pooled prevalence of AMD. The lack of overlaps in credible intervals from graphical inspection of forest plots suggest presence of heterogeneity. Further analysis showed that heterogeneity in ethnicity and geographic regions for any AMD were 99.5% (95% CrI: 99.2%, 99.8%) and 99.7% (95% CrI: 99.5%, 99.9%) respectively (**Appendix 2, Supplementary Table 5.4**). The pooled global prevalence (accounting for various sources of heterogeneity) of early and late AMD in adult populations were 8.01% (95% CrI: 3.95%, 15.49%) and 0.37% (95% CrI: 0.18%, 0.77%), respectively. The overall prevalence of any AMD was 8.69% (95% CrI: 4.26%, 17.40%). Detailed estimated prevalence by AMD subtypes, ethnicity and age groups from meta-analysis using HB approach are provided in **Appendix 2, Supplementary Table 5.5**. **Appendix 2, Supplementary Table 5.6** provides further detailed prevalence estimates stratified by geographic regions.

Early AMD was found to be more prevalent in populations of European ancestry (11.2%) than in Asians (6.8%), with a BF of 3.9, suggesting substantial evidence for the difference between groups (**Figure 5.2A and Appendix 2, Supplementary Table 5.3**). Likewise, any AMD was more prevalent in populations of European ancestry compared to Asians (12.3% vs. 7.4%; BF = 4.3). Compared to African ancestry populations, European ancestry populations had higher prevalence of early, late or any AMD (late AMD: 12.3% vs. 7.5%; BF = 31.3, suggesting very strong evidence). Geographically, early and any AMD were less prevalent in Asia, compared to Europe and Northern America (all BFs > 2) (**Figure 5.2B and Appendix 2, Supplementary Table 5.3**). There was no evidence of difference in the prevalence of early, late, or any AMD between gender (all BFs < 0.05, **Appendix 2, Supplementary Table 5.3**). 8 (21%) out of the 39 studies examined provided information on GA and nvAMD subtypes. Sub-group analysis showed similar overall prevalence of GA and nvAMD, 0.44% (95% CrI: 0.15%, 1.36%) and 0.46% (95% CrI: 0.18%, 1.08%) respectively. European has evidence of higher prevalence of GA as

compared to African, Asian and Hispanic (1.11 [95% CrI: 0.53%, 2.08%] compared to 0.14% [95% CrI: 0.04%, 0.45%], 0.21% [95% CrI: 0.04%, 0.87%] and 0.16% [95% CrI: 0.05%, 0.46%] respectively). There was no difference in prevalence of nvAMD between ethnicities.

The prevalence of early and late AMD increased with age in each of the ethnic groups and regions (**Figure 5.3**). Prevalence of late AMD in European ancestry populations increased most rapidly after age 75 and similar trend was observed in Europe and Oceania regions.

The projected number of people with AMD by regions in years 2014, 2020 and 2040 are provided in **Figure 5.4**. In year 2040, projected AMD cases globally are 288 million (95% CrI: 205, 399). Asia will have the largest number of people with AMD. **Appendix 2, Supplementary Table 5.7** provides more detailed data on the projected number of people with AMD from 2012 to 2040. Pairwise comparison between geographical regions were presented in **Appendix 2, Supplementary Table 5.8** and showed statistical evidence for the larger projected number of people with any AMD in 2040 in Asia compared to Latin America and the Caribbean, Northern America and Oceania and up to 2038 for Africa.

5.5 DISCUSSION

This systematic review and meta-analysis provided comprehensive and up-to-date pooled estimates of early, late and any AMD prevalence in the four major ethnic groups pooled from 39 studies and nearly 130,000 persons conducted in the six geographic regions around the world. Estimated prevalence were also projected for these geographically regions and worldwide to obtain number of people with AMD in years 2014 to 2040. We showed that 8.7% of the population globally have AMD, and the projected number of people with AMD is 196 million in 2020, increasing to 288 million in 2040. We describe ethnic and regional variations. Our study provides data that reflect the substantial burden of AMD which can be used for planning health care services around the world.

Our meta-analysis updates two earlier reviews focused on single ethnicities, one carried out in Europeans by Rudnicka et al[17] and one in Asians by Kawasaki et al[4]. In our study, compared to the Asian meta-analysis, we included four additional Asian studies published after 2010, including the Handan Eye Study[29], the Central India Eye and Medical Study[30], one multiethnic Asian cohort study in Singapore[31] and one study in Thailand[32]. In comparison to Rudnicka et al, six studies published earlier in the 1970s to 1990s were excluded as they relied only on eye examinations without taking fundus photos and on study-specific definitions.[33-38] In our current study, we included only those with internationally recognized definitions of AMD[21, 22] confirmed using retinal photographs.

Our study provides estimates on ethnic differences in AMD prevalence. First, we found substantial evidence that early AMD was more prevalent in Europeans than Asians but that late AMD was similar. This results confirms the previous meta-analysis[4] and multi-ethnic population-based studies.[15] It has been suggested that Asians (Chinese) may be more likely to develop exudative or nvAMD than whites,[15, 33] but our sub-group analysis suggest no evidence for ethnicity difference. Also, most population-based studies were unable to reliably diagnose polypoidal choroidal vasculopathy (PCV), which often manifests like exudative AMD. Taking into consideration that PCV is markedly more common in Asians compared to Europeans, we may be overestimating the true prevalence of late AMD in Asians.[39-41] Second, our study provided substantial to very strong evidence that early, late and any AMD are more prevalent in people of European ancestry than those of African ancestry, which validates observations derived from previous individual studies, such as the Baltimore Eye Study.[15, 16] These patterns are in line with a previous multi-ethnic population-based study in the US, whereby the prevalence of early AMD was highest in the people of European ancestry, compared to Hispanics, Asians (Chinese) and African Americans.[15]

Analysis of pooled prevalence by geographical regions showed greater variability, indicated by the larger 95% credible intervals as compared to prevalence pooled by ethnic ancestry groups. This could be due to heterogeneity contributed by various ethnic groups within each region. This lends further support to the hypothesis that inherited genetic factors determined by ethnic ancestry play a substantial role in AMD,[42-44] in addition to established environmental risk factors such as smoking. Northern America and Europe were found to have higher pooled prevalence of early and any AMD as compared to Asia, in accordance with the higher prevalence of AMD in people of European ancestry compared to Asians as reported both in the literature and substantiated in our meta-analysis study.

Female gender was considered a weak risk factor with inconsistent association for late AMD.[45, 46] In our meta-analysis, there was no evidence of gender difference in both early and late AMD prevalence. This is consistent with previous reviews in people of European ancestry, where no significant gender difference was found in the prevalence of nvAMD or GA[47]. Similarly in Asians, men do not have a higher prevalence of late AMD compared to women after adjusting for risk factors such as smoking.[48-50]

Asia is the most populous continent, accounting for over 60% of the world population and hence will see the largest projected number of AMD cases (113 million [95%CrI: 60, 203] in 2040, a third of AMD cases globally) and is expected to increase more rapidly than other regions over the years, despite having the lowest estimated prevalence. Europe, being the third most populous region (11%) with the highest AMD prevalence, follows after Asia in the number of projected AMD cases (69 million [95%CrI: 40, 109] in 2040), with moderate increase over the years. Our models project that in 2040 there will be 39 million [95%CrI: 12, 93] people with AMD in Africa, 39 million [95%CrI: 15, 82] in Latin America and the Caribbean, 25 million [95%CrI: 15, 38] in the North America and 2 million [95%CrI: 1, 5] in Oceania. The trends and differences are mainly influenced by the

demographic progression in population structure (e.g. aging population) of the regions based on the population projection data by the United Nations.[28] These data are important as more than 2/3 of the AMD patients in Asia, Africa and Latin America may not have access to expensive anti-angiogenesis therapies now widely used in North America and Europe

Our study has a number of strengths. First, we pooled data that used fundus photography and standardized protocols to assess AMD. Our study was limited by the fact that despite the large number of studies included in this meta-analysis, our sub-group analysis on the prevalence of late AMD subtypes (i.e nvAMD vs. GA) with ethnicity was based on data from only 8 studies. Moreover, there is evidence that without harmonization of classification systems and definitions of AMD lesions, estimates of early AMD may substantially vary due to a variety of factors. These include varying definitions used for grading AMD and inconsistencies in quality of images.[51] Although there are inherent disadvantages in performing a meta-analysis based on data sets pooled together from disparate population studies, we have attempted to circumvent this issue by only including studies in which standard protocols are used to grade fundus photos.

In conclusion, our study estimates reflect the significant present and future burden of AMD globally. There is substantial evidence for higher prevalence of early AMD in people of European ancestry than in Asians, and early and late AMD in people of European ancestry than those of African ancestry. We observed that late AMD prevalence increases rapidly after age 75, especially in people of European ethnicity and in Europe and Oceania regions, but Asia will see the largest number of people with AMD despite having the lowest prevalence. These data provide important information for the design and implementation of eye care programs for both specific ethnic groups and geographical regions, as well as worldwide.

5.6 Chapter 5 References

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5.7 Chapter 5 Tables and Figures

Figure 5.1 Forest Plots of Overall and Race-specified Pooled Prevalence of AMD: (**A**) Early AMD, (**B**) Late AMD and (**C**) Any AMD. Dashed line refers to the overall pooled prevalence estimate presented in bold.

Figure 5.1A

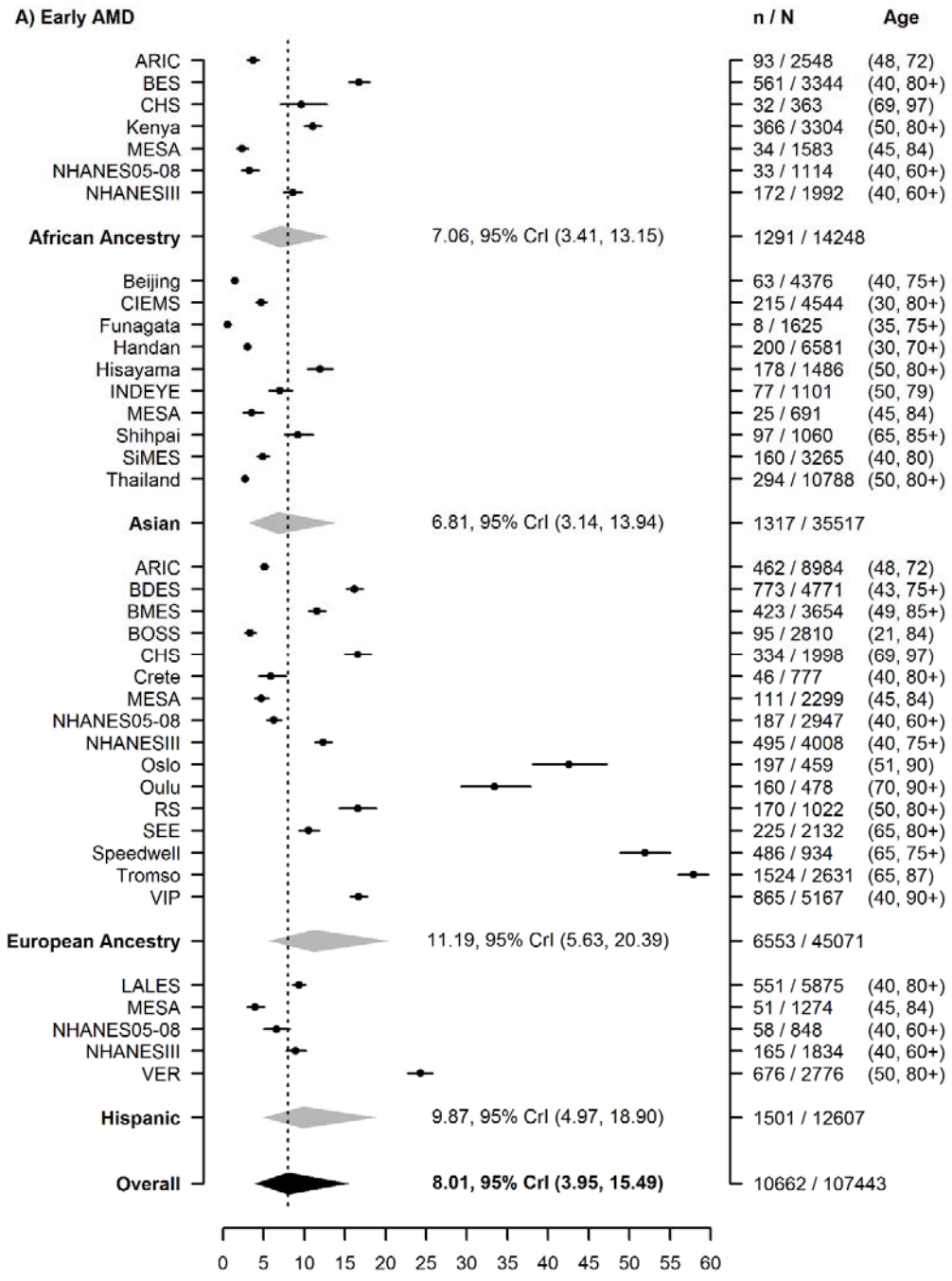


Figure 5.1B

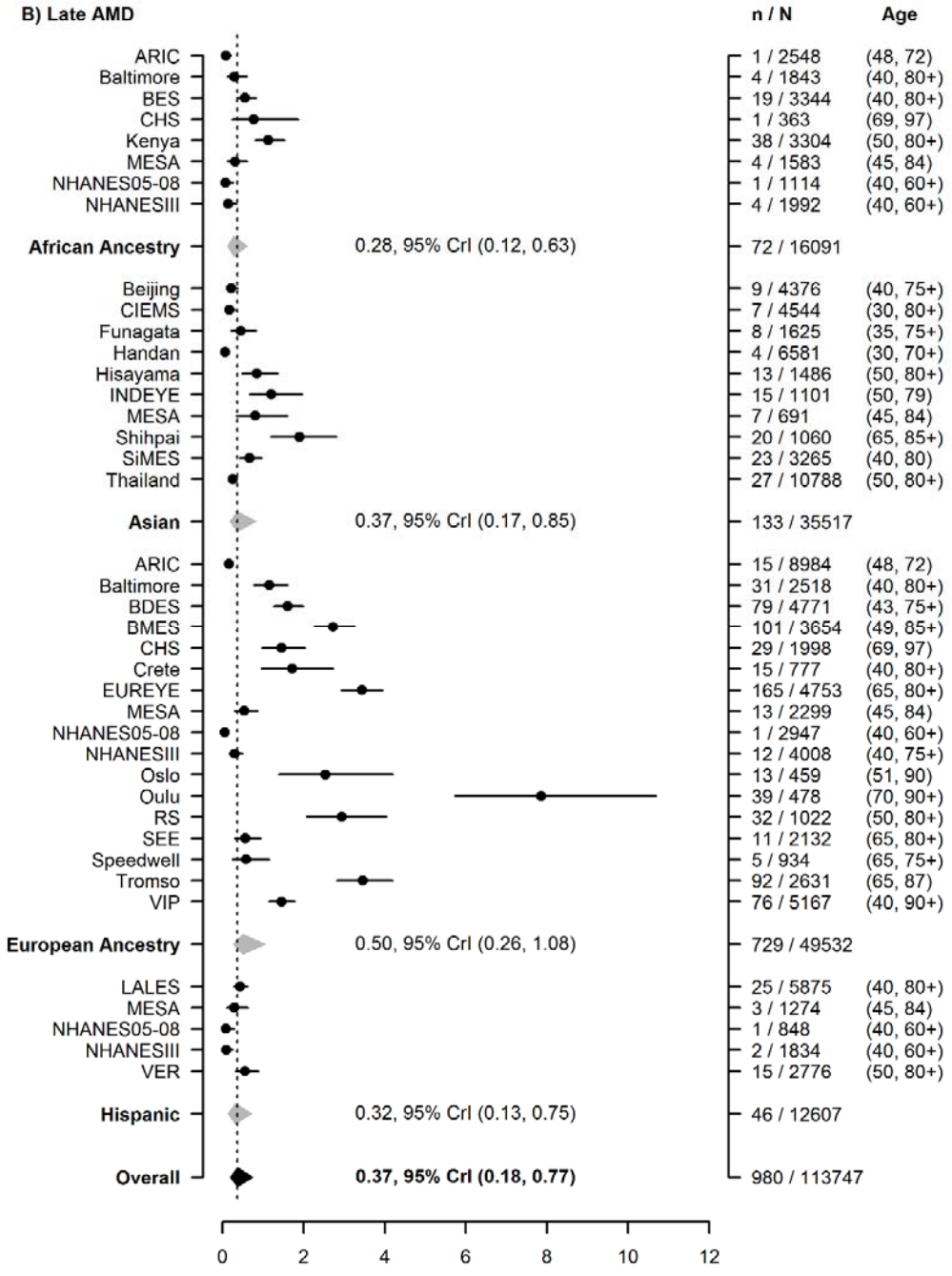

B) Late AMD
n / N
Age
ARIC 1 / 2548 (48, 72)
Baltimore 4 / 1843 (40, 80+)
BES 19 / 3344 (40, 80+)
CHS 1 / 363 (69, 97)
Kenya 38 / 3304 (50, 80+)
MESA 4 / 1583 (45, 84)
NHANES05-08 1 / 1114 (40, 60+)
NHANESIII 4 / 1992 (40, 60+)
African Ancestry 0.28, 95% CrI (0.12, 0.63) 72 / 16091
Beijing 9 / 4376 (40, 75+)
CIEMS 7 / 4544 (30, 80+)
Funagata 8 / 1625 (35, 75+)
Handan 4 / 6581 (30, 70+)
Hisayama 13 / 1486 (50, 80+)
INDEYE 15 / 1101 (50, 79)
MESA 7 / 691 (45, 84)
Shihpai 20 / 1060 (65, 85+)
SiMES 23 / 3265 (40, 80)
Thailand 27 / 10788 (50, 80+)
Asian 0.37, 95% CrI (0.17, 0.85) 133 / 35517
ARIC 15 / 8984 (48, 72)
Baltimore 31 / 2518 (40, 80+)
BDES 79 / 4771 (43, 75+)
BMES 101 / 3654 (49, 85+)
CHS 29 / 1998 (69, 97)
Crete 15 / 777 (40, 80+)
EUREYE 165 / 4753 (65, 80+)
MESA 13 / 2299 (45, 84)
NHANES05-08 1 / 2947 (40, 60+)
NHANESIII 12 / 4008 (40, 75+)
Oslo 13 / 459 (51, 90)
Oulu 39 / 478 (70, 90+)
RS 32 / 1022 (50, 80+)
SEE 11 / 2132 (65, 80+)
Speedwell 5 / 934 (65, 75+)
Tromso 92 / 2631 (65, 87)
VIP 76 / 5167 (40, 90+)
European Ancestry 0.50, 95% CrI (0.26, 1.08) 729 / 49532
LALES 25 / 5875 (40, 80+)
MESA 3 / 1274 (45, 84)
NHANES05-08 1 / 848 (40, 60+)
NHANESIII 2 / 1834 (40, 60+)
VER 15 / 2776 (50, 80+)
Hispanic 0.32, 95% CrI (0.13, 0.75) 46 / 12607
Overall 0.37, 95% CrI (0.18, 0.77) 980 / 113747
0
2
4
6
8
10
12

Figure 5.1C

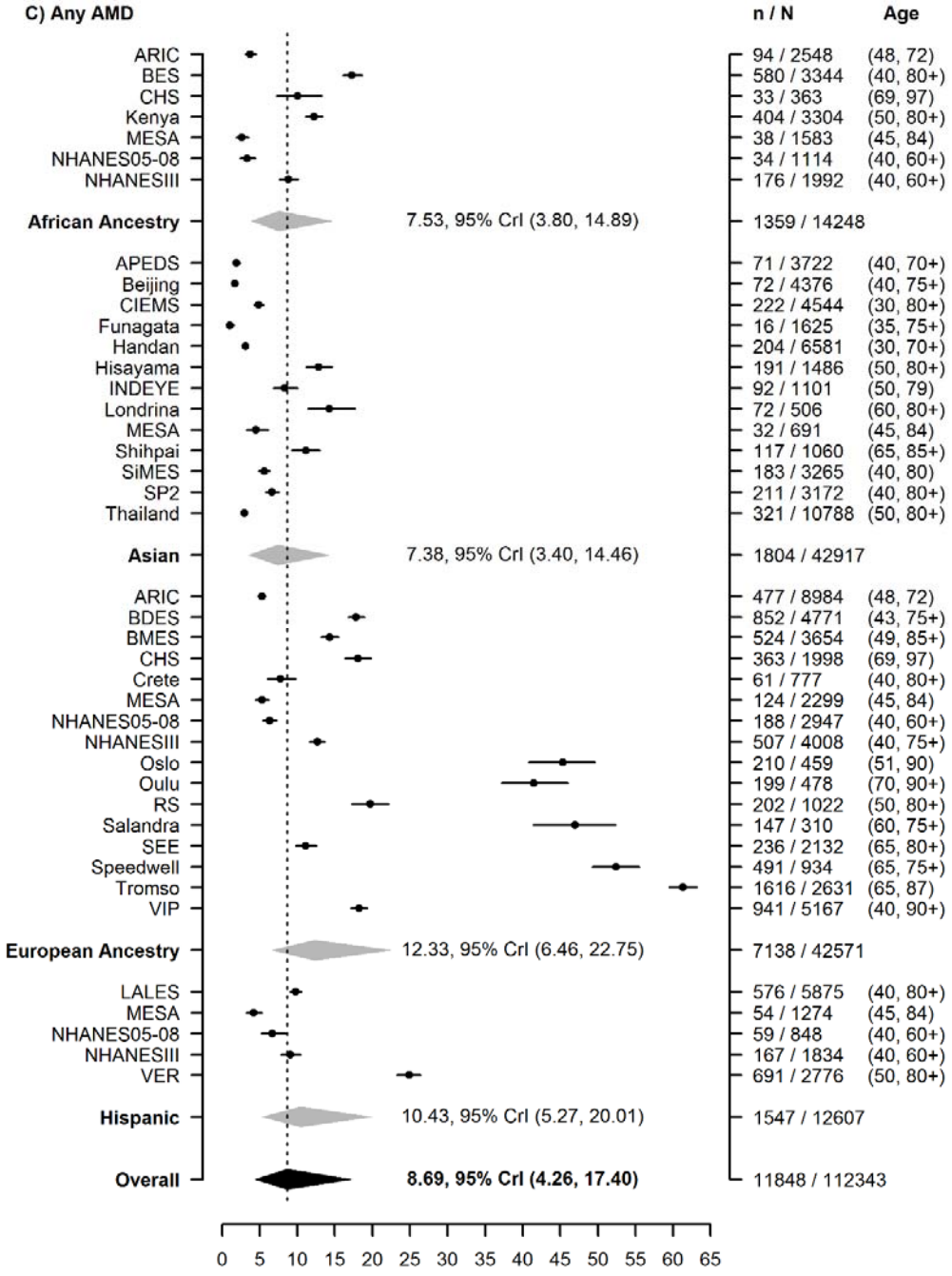

C) Any AMD
n / N
Age
ARIC 94 / 2548 (48, 72)
BES 580 / 3344 (40, 80+)
CHS 33 / 363 (69, 97)
Kenya 404 / 3304 (50, 80+)
MESA 38 / 1583 (45, 84)
NHANES05-08 34 / 1114 (40, 60+)
NHANESIII 176 / 1992 (40, 60+)
African Ancestry 7.53, 95% CrI (3.80, 14.89) 1359 / 14248
APEDS 71 / 3722 (40, 70+)
Beijing 72 / 4376 (40, 75+)
CIEMS 222 / 4544 (30, 80+)
Funagata 16 / 1625 (35, 75+)
Handan 204 / 6581 (30, 70+)
Hisayama 191 / 1486 (50, 80+)
INDEYE 92 / 1101 (50, 79)
Londrina 72 / 506 (60, 80+)
MESA 32 / 691 (45, 84)
Shihpai 117 / 1060 (65, 85+)
SiMES 183 / 3265 (40, 80)
SP2 211 / 3172 (40, 80+)
Thailand 321 / 10788 (50, 80+)
Asian 7.38, 95% CrI (3.40, 14.46) 1804 / 42917
ARIC 477 / 8984 (48, 72)
BDES 852 / 4771 (43, 75+)
BMES 524 / 3654 (49, 85+)
CHS 363 / 1998 (69, 97)
Crete 61 / 777 (40, 80+)
MESA 124 / 2299 (45, 84)
NHANES05-08 188 / 2947 (40, 60+)
NHANESIII 507 / 4008 (40, 75+)
Oslo 210 / 459 (51, 90)
Oulu 199 / 478 (70, 90+)
RS 202 / 1022 (50, 80+)
Salandra 147 / 310 (60, 75+)
SEE 236 / 2132 (65, 80+)
Speedwell 491 / 934 (65, 75+)
Tromso 1616 / 2631 (65, 87)
VIP 941 / 5167 (40, 90+)
European Ancestry 12.33, 95% CrI (6.46, 22.75) 7138 / 42571
LALES 576 / 5875 (40, 80+)
MESA 54 / 1274 (45, 84)
NHANES05-08 59 / 848 (40, 60+)
NHANESIII 167 / 1834 (40, 60+)
VER 691 / 2776 (50, 80+)
Hispanic 10.43, 95% CrI (5.27, 20.01) 1547 / 12607
Overall 8.69, 95% CrI (4.26, 17.40) 11848 / 112343
0 5 10 15 20 25 30 35 40 45 50 55 60 65

Figure 5.2 Prevalence of AMD by Ethnic Groups (A) and (B) Geographic Regions

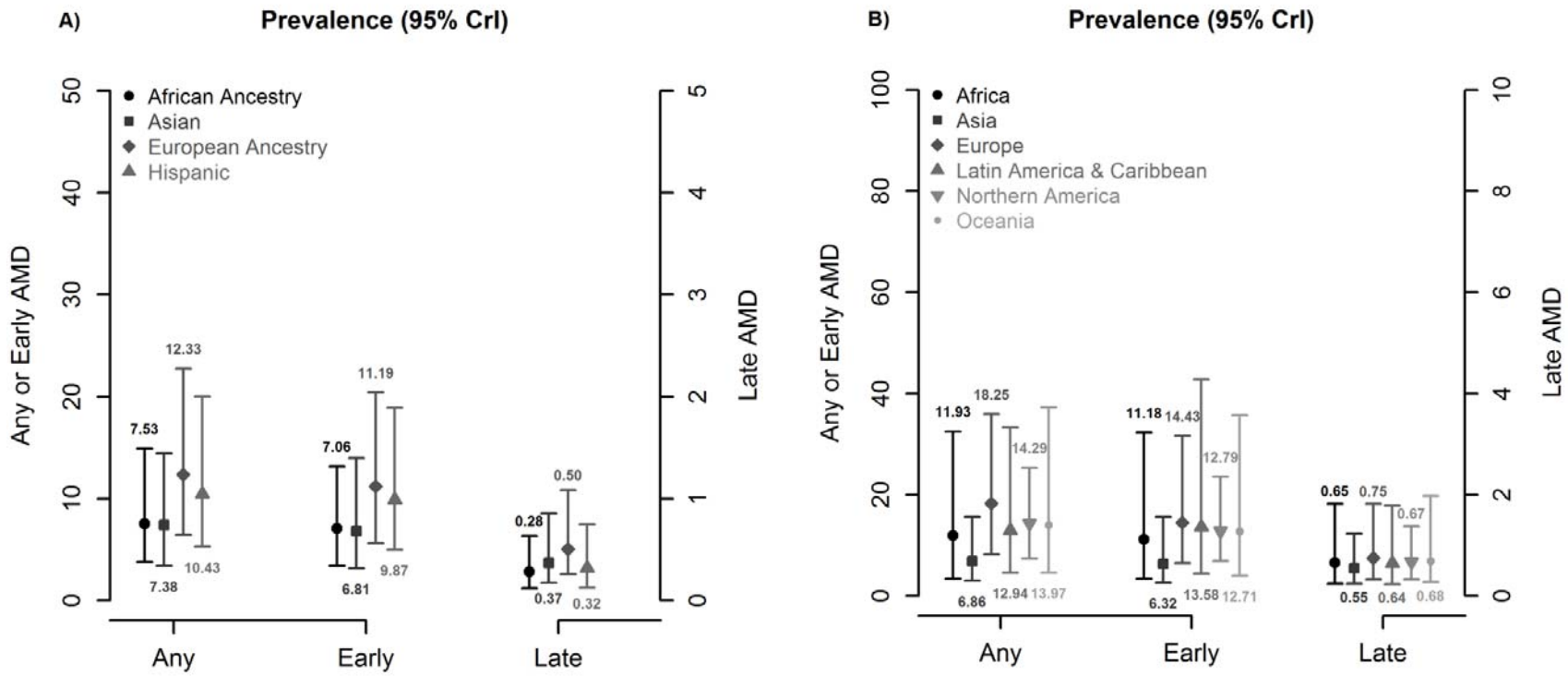


Figure 5.3 Age Trends of AMD Prevalence by Ethnicity (A & B) & Regions (C & D)

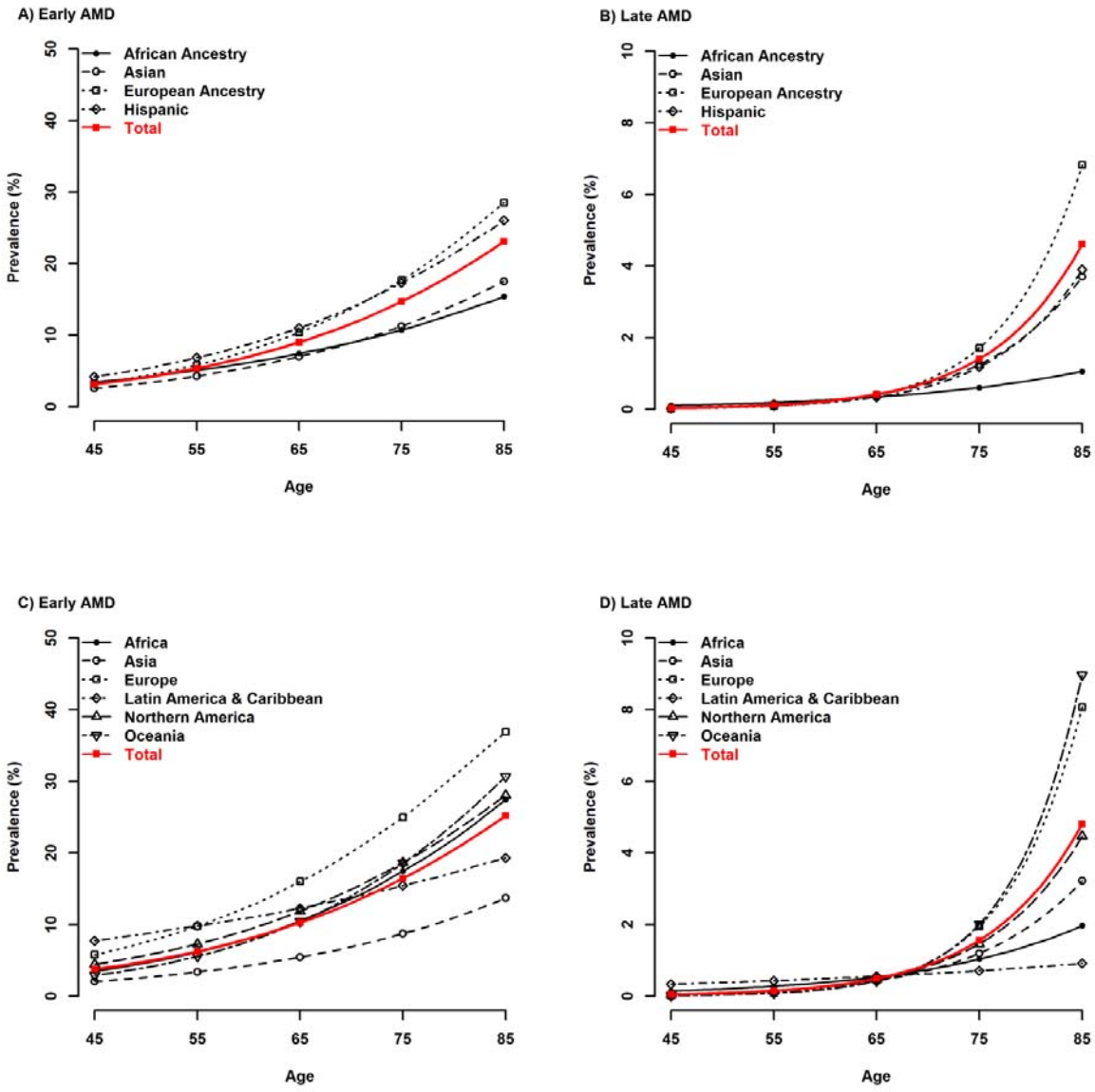
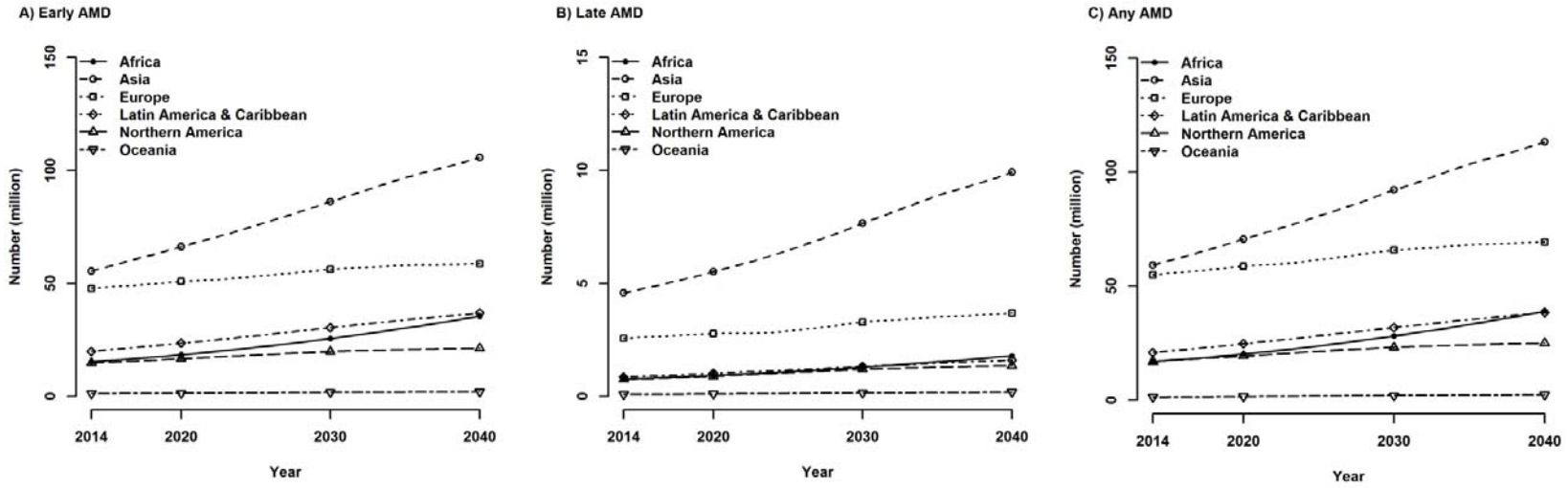


Figure 5.4 Projection of Number of People with Early and Late AMD by Regions in 2014, 2020 and 2040



World Region	Early AMD (million)				Late AMD (million)				Any AMD (million)			
	2014	**2020**	**2030**	**2040**	**2014**	**2020**	**2030**	**2040**	**2014**	**2020**	**2030**	**2040**
Africa	15.36	18.47	25.67	35.53	0.77	0.93	1.30	1.80	16.87	20.29	28.20	39.06
Asia	55.51	66.29	86.22	105.76	4.59	5.52	7.66	9.92	59.16	70.68	92.14	113.21
Europe	47.81	50.87	56.28	58.65	2.57	2.79	3.29	3.69	54.98	58.78	65.82	69.32
Latin America & Caribbean	19.87	23.59	30.47	36.95	0.86	1.02	1.32	1.61	20.93	24.80	31.90	38.53
Northern America	14.77	16.70	19.80	21.30	0.76	0.90	1.20	1.36	17.07	19.41	23.25	25.08
Oceania	1.21	1.43	1.79	2.07	0.09	0.11	0.15	0.19	1.37	1.62	2.06	2.40
Total	154.55	177.35	220.22	260.26	9.64	11.26	14.92	18.57	170.38	195.58	243.38	287.59

CHAPTER 6

Bayesian Approach in Vision and Quality of Life Research

Study 4: Accounting for Measurement Errors of Vision-specific Latent Trait

In Regression Models

Manuscript Submitted to IOVS:

Wong WL, Li X, Li JL, Wong TY, Cheng CY, Lamoureux EL. Accounting for Measurement Errors of Vision-specific Latent Trait In Regression Models.

6.1 RESEARCH MOTIVATION and CONTRIBUTIONS

Objective means of measuring frequency of disease, magnitude of associations between exposure and disease and the collective impact on public health are the building blocks of epidemiologic research. Assessing whether observed study results represent valid associations that reflect the true relationships between the exposures and the disease, is a matter of determining the likelihood that alternative explanations such as chance, bias, measurement errors, or confounding could account for the findings. Vision-specific functioning is an intangible aspect of visual impairment. Vision-specific quality-of-life questionnaires are designed to assess the impact of vision impairment in patients. However, the statistical modeling and estimation of association effects are not straightforward when dealing with quality-of-life survey with many questions, collectively measuring a single latent construct. Our literature review of association analyses involving vision-specific instruments revealed current inappropriate handling of measurement errors of vision functioning, one of the key latent traits using Rasch analysis.

Hence in this study, we developed a statistical model that is appropriate for the assessment of association effects related to vision-specific latent trait, with proper treatment of its associated measurement error to produce accurate and contemporary estimates of association effects. We demonstrated the effectiveness this modeling framework that integrates Rasch and regression models using Hierarchical Bayesian approach and documented the model codes in **Appendix 1** which can be altered to conform to other instruments.

6.2 INTRODUCTION

There is increasing recognition that patient-reported outcomes [PRO] (commonly referred as questionnaires or instruments) is important to assess the impact of vision loss in ophthalmic research.[1-9] For vision-specific instruments, vision functioning is one of the key latent traits. Recently, Rasch analysis has been used to estimate and evaluate latent traits, producing Rasch-scaled scores in preference to raw scores from questionnaire data. Numerous vision-specific instruments have been rigorously validated using Rasch analysis for daily living activities dependent on vision[10, 11] and for a spectrum of eye conditions such cataract,[8, 12, 13] diabetic retinopathy,[6] age-related macular degeneration,[4, 14] and glaucoma.[7, 15, 16] A literature review for instruments for the assessment of vision-specific quality of life identified 22 instruments.[17]

However, the handling of latent variables and their interpretation can be challenging as they are not observed scores and so estimation of latent variables comes with uncertainty commonly termed as measurement error. Subsequent applications of "classical" statistics such as *t-tests* and linear regressions are not strictly appropriate for association analysis of latent data as they require dependent/outcome variables to be known. The analysis of latent variables requires the associated measurement error to be accounted for as failure to do so may lead to biased estimates of correlations, associations and statistical inferences.[18, 19] Multilevel item response theory (MLIRT) models have been shown to allow for a better estimation of relationships between predictor variables and MLIRT latent traits.[20, 21] However, appropriate handling of measurement errors of latent dependent variable in multilevel models are only more often practiced in some fields, such as in educational[22, 23] and psychometric[24, 25] research.

The purpose of our study was to demonstrate the effectiveness of a modeling framework that integrates Rasch and regression models using Hierarchical Bayesian (HB) approach that accounts for latent trait measurement errors. This modeling is appropriate

for the assessment of association effects related to vision-specific latent trait, with proper treatment of its associated measurement error for a more accurate and contemporary estimates of association effects. We compared the one-stage "joint analysis" and two-stage "separate analysis" model results using real data and assessed the performance of the methods in a simulation study based on the frequently used Andrich rating scale model[26].

6.3 MATERIALS AND METHODS

Literature Review

We systematically reviewed publications that used Rasch analysis by searching the electronic databases of PubMed in the top four Ophthalmic journals (Ophthalmology, American Journal of Ophthalmology [AJO], British Journal of Ophthalmology [BJO] and Investigative Ophthalmology & Visual Science [IOVS]) for relevant papers published up to July, 2013, with the following search terms (formatted for PubMed search):

1. (rasch[All Fields] AND ("analysis"[Subheading] OR "analysis"[All Fields])) AND "Ophthalmology"[Journal]
2. (rasch[All Fields] AND ("analysis"[Subheading] OR "analysis"[All Fields])) AND ("Am J Ophthalmol"[Journal] OR "american journal of ophthalmology"[All Fields])
3. (rasch[All Fields] AND ("analysis"[Subheading] OR "analysis"[All Fields])) AND ("Br J Ophthalmol"[Journal] OR "british journal of ophthalmology"[All Fields])
4. (rasch[All Fields] AND ("analysis"[Subheading] OR "analysis"[All Fields])) AND ("Invest Ophthalmol Vis Sci"[Journal] OR "investigative ophthalmology and visual science"[All Fields])

The strategy identified 70 articles and the full texts were reviewed (by WLW and XL) to identify studies having performed Rasch analysis on visual functioning questionnaire data. Of the 70 articles identified, two were letters,[27, 28] one study applied Rasch model to investigate inter-reader agreement,[29] and another focused on the genetic components of the optic nerve head[30] were excluded. The remaining 66 articles related to visual functioning

data were reviewed for choice of Rasch model, implementation software and sample size of studies (**Table 6.1**).

Pitfalls in Observed Analysis Framework (two-stage "separate analysis" procedure)

All 66 articles reviewed performed Rasch analysis to evaluate the validity, reliability and measurement characteristics of instruments (i.e. visual functioning) for their population sample data. Most (86.4%) performed further statistical analysis on the Rasch-scaled score (i.e. vision-specific latent trait), such as performing correlations or linear regressions with visual acuity, demographic or clinical data to assess the impact of visual impairment and other patients' characteristics or factors on visual functioning .

However, none of the articles mentioned or discussed the potential bias in estimation of association effects and the underestimation of their standard errors[31] having ignored the associated uncertainties involved in the estimation of the latent trait when used naively in subsequent association analysis. In the first stage, the vision-specific latent trait (i.e vision functioning) was modeled and estimated given a set of item responses using a polytomous Rasch model (e.g. Andrich rating scale model when item response options are more than dichotomous i.e. three or more). In the second stage, relationships between the estimated Rasch-scaled data (treated as known outcome variable) and risk factors were analyzed using regression techniques. Ignoring the uncertainty regarding the abilities within the regression model may lead to biased estimation of association effects. Underestimation of standard errors may also result in false identified positive factors and hence mislead statistical inferences.

Moreover, a key assumption in Rasch model states that a change in the latent variable is completely described by the item characteristic functions (the relationship of the latent trait and responses of the items) and hence any association analysis on the latent trait with other covariates performed in the second stage can violate and contradict the key assumptions in the first stage of Rasch analysis (having assumed that vision-specific latent

trait only dependents on item response data). Such estimation procedure can cause serious underestimation of the standard errors of the model parameters.

Our literature review also observed that studies assessing visual functioning traits were often conducted for moderately small sample sizes (median 240 with interquartile range of 497) and together with response data (and Rasch-scaled scores) that are typically non-normally distributed; it is precarious to rely on asymptotic approximations and the properties of conditional maximum likelihood estimates obtained from analysis software without showing them to be accurate.[32] Similarly, validation inference based on correlations may not be accurate.

Our study analysis and discussion will focus on the Andrich rating scale[26] because it is the most frequently used polytomous Rasch model for vision-specific instruments.

Andrich Rating Scale Model

The Andrich rating scale[26] model is an extension of the Rasch model[33] for polychotomous responses (i.e. three or more categories). The natural log of the likelihood ratio of adjacent response category probabilities is given by

$$\ln(P_{ik,y}/P_{ik,(y-1)}) = \theta_i - \eta_k - \gamma_y$$

where $P_{ik,y}$ is the probability of person i on encountering item k would be observed in category y. θ_i is ability trait for the i^{th} person (i.e. i = 1, …, n) , η_k is the item k difficulty parameter (i.e. k items means k = 1, …, k) and γ_y is the threshold for category y (e.g. items with 5 categories means y is in the range of integers 1 to 5), which is constant across items.

Proposed Analysis Framework (one-stage "joint analysis")

A rigorous alternative is to combine the observed two-stage analysis procedure to overcome the problematic issues described above. Item response data structure are hierarchical since item responses are nested within respondents and respondents may also be nested (e.g. patients nested in hospitals). Such relationships can be adequately explained

by the multilevel Rasch model using the Hierarchical Bayesian (HB) approach. Model parameters can also be incorporated and estimated from the item response data without having to condition on estimated person ability parameter (i.e. latent trait). In **Appendix 2, Supplementary Figure 6.1**, a path diagram of this multilevel Rasch model is depicted and explained.

For example, the combined model for linear regression (i.e. continuous latent trait outcome) can be written as

$$\begin{cases} \ln(P_{ik,y}/P_{ik,(y-1)}) = \theta_i - \eta_k - \gamma_y \\ \theta_i = \beta \times X_i + \varepsilon_i \end{cases}.$$

where β is the beta coefficient from linear regression, X_i is the observed covariates of person i and ε_i is the residual random error. The HB approach provides an elegant execution of the multilevel Rasch modeling framework that allows the incorporation of explanatory variables or covariates at different levels of hierarchy by specifying parameters to come from a specific distribution with parameters and possibly hyper-parameters that are, themselves, estimated prior information.[31] All model parameters can then be estimated simultaneously using the Monte Carlo Markov Chain method with the JAGS software.[34, 35] The proposed procedure enables direct estimation of beta coefficients for association effects without having to explicitly know the latent trait measurements, i.e. personal ability. The JAGS codes used to fit our example model in one-stage "joint analysis" HB approach is provided in the **Appendix 1**, can be altered readily to conform to different data structure.

Comparison of Methods Using Real Data

Both the HB one-stage "joint analysis" and the two-stage "separate analysis" methods were performed to assess the relationship of reading and writing literacy on visual functioning (measured by a modified VF-9 questionnaire) using data from the Singapore Malay Eye Study (SiMES)[36], a population-based cross-sectional study of 3,280 Singaporean Malays aged above 40. Previous studies suggest an association of inadequate

literacy with systemic health and hence the influence of literacy on vision functioning (in addition to visual impairment), another aspect contributing to vision-specific quality of life is important.[37, 38] Association of reading and writing literacy with visual functioning were adjusted for age, gender, language of interview, body mass index, occupation, marital status, income, housing type, education, smoking status and presenting visual acuity in the better-seeing eye.

Simulation Study

As there is no "gold standard" in the comparison of methods using real data, we conducted a simulation study to demonstrate the performance of our proposed HB one-stage "joint analysis" approach as compared to the observed two-stage "separate analysis" procedure. Two independent covariates (X_{i1}, X_{i2}), a continuous variable data such as standardized age and a binary variable such as gender were simulated with pre-specified association effects (β_1, β_2) for the impact of these two covariates with the latent visual functioning ability parameter and hence, these were considered as the "true" association effects or "gold standard" for reference when we re-run analysis on our simulated data using both analytical methods. Association estimates and their standard errors from both approaches were computed to assess their performance, where estimates closer to the "gold standard" indicate higher accuracy and smaller standard errors suggest greater precision. The calibration of nine item difficulty parameters, η_k was fixed according to Table 3 of a study conducted by *Ecosse L. Lamoureux et. al.*,[39] that performed a systematic evaluation of the reliability and validity of the visual functioning questionnaire (VF-11) using Rasch analysis that was later modified to nine items (VF-9) to tailor fit to the Asian population. We also investigated the empirical power for both approaches. We provided detailed description of our simulation study in **Appendix 2, Supplementary text 6.1**.

6.4 RESULTS

Table 6.1 shows the summary of articles reviewed in the four major ophthalmic journals that have performed Rasch analysis for visual functioning related instrument data. The majority (65.1%) performed Rasch analysis using Andrich rating scale model and most (68.2%) conducted Rasch analysis using Winsteps software. The median sample size of these studies was 240 with interquartile range of 497.

Associations of inadequate reading and writing literacy with visual functioning adjusted for potential confounding variables (model 1 and 2 respectively) derived from both approaches analyzed on our simulated data were shown in **Table 6.2**. Comparison of both approaches for Model 1 assessing reading literacy showed no difference in terms of statistical evidence for factors identified but results were not consistent for writing literacy in Model 2. Inadequate writing was statistically significant based on the HB one-stage "joint analysis" but was not significant in the two-stage "separate analysis" approach. Smaller association effects were also estimated in the two-stage "separate analysis" approach which is consistent with the attenuation bias observed in simulation study.

Simulation results on the association effects and their standard errors of a continuous measurement such as standardized age (β_1) and that for a binary factor such as gender (β_2) with the vision-specific latent trait compared to the "gold standards" for both approaches are depicted in **Figure 6.1**. There is greater inaccuracy (average of 5 folds increase in bias) in effect size estimations from the frequently used two-stage "separate analysis" procedure compared to the proposed HB one-stage "joint analysis" approach. We also observed an attenuation bias in estimations (shrunk towards zero) from the two-stage procedure. Smaller standard errors for estimates were expected for the two-stage procedure having assumed no uncertainty in the latent trait measurements but the slightly larger standard errors (average of one-tenth fold difference) from the HB approach suggest comparable precision for a more accurate estimation of associations. Furthermore, similar power (no

difference for beta ≥ 0.5 at 5% significance level and less than one-twelfth fold difference for beta at 0.2 for both continuous and categorical variables) in our proposed HB approach despite taking into account uncertainty in the latent trait (**Appendix 2, Supplementary Table 6.1**).

6.5 DISCUSSION

This is the first study to assess the performance of two regression models for visual functioning, comparing the frequently used two-stage "separate analysis" method (ignoring measurement error of the dependent latent trait) and our proposed one-stage "joint analysis" approach in terms of estimation accuracy of association effects, precision of their standard errors and power. Association effect sizes from our real data analysis were observed to be smaller in the two-stage "separate analysis" approach with slightly tighter intervals and the identification of significant factors between approaches were different. Our simulation study results (assessing methods performance) provided support for these observations. Attenuation bias, the shrinking of estimations towards zero, was found using the two-stage procedure (a phenomenon expected from ordinary least squares regression of *explanatory* variables with measurement errors) that explains the (artificial) smaller association effects observed in our real data analysis.

One-stage "joint analysis" approach allows the estimation of all models parameters simultaneously and hence integrates visual functioning in the regression model accounting for its measurement errors. Simulation results also showed that the one-stage "joint analysis" method produced highly accurate estimations (average of 5 folds decrease in bias) with comparable precisions and power as compared to the commonly used two-stage "separate analysis" procedure. The magnitude of measurement error also affects the size of attenuation bias. Accurate estimation of effect size and its variance are both critical to statistical significance testing results that directly influence our interpretation of risk factors. Hence moving forward, the one-stage "joint analysis" approach is preferred when we

perform regression analysis with dependent outcome that is essentially a latent variable being derived from some prior analyses.

Our model codes provided in the **Appendix 1** can be altered readily to analyze data from any instruments/questionnaires with any choice of Rasch or item response theory models (e.g. Partial Credit model, Graded Response model etc.) and complexity of multilevel regression models as depicted in **Appendix 2, Supplementary Figure 6.1** to adequately describe the hierarchical data structure, incorporate different sources of uncertainty and inclusion of explanatory covariates at different levels. Furthermore, latent variable can also be analyzed as independent covariate (as required) instead of an outcome variable used in our simulation example.

In our literature review, visual functioning rating scale instruments/questionnaires were mainly validated using Rasch analysis for their well-known scaling and measurement properties. Without a realist interpretation of latent variables, actual Rasch-scaled scores do not have straightforward meaning and its interpretations are based on relative comparisons of the scaled scores (i.e. relative difference tells us how much more of persons' visual functioning ability compared to another). Many reviewed articles provide ready-to-use spread sheets that convert raw scores entered to Rasch-scaled scores for their respective instruments to benefit clinicians and researchers unfamiliar with Rasch analysis who may wish to use its scoring benefits. It is important to note that the population of respondents plays an important part in the probability model for each response and so the personal ability and item parameters will always be estimated with respect to a population. Hence, ready-to-use spread sheets should only be used on different samples of individuals from the same population as validated for in the article and that Rasch-scaled scores are not comparable between studies from different populations unless it happens (rarely) that both populations have identical item characteristic functions. Researchers were also unaware of the measurement errors associated with Rasch-scaled scores and performed further analysis

directly with simple statistical tests such as independent t-tests to examine between group differences in the instrument scores across various socio-demographic variables and levels of vision impairment.

The strength of our study includes the simulating datasets with various pre-specified association effects that acts as "ground truth" to enable the comparison between methods. The simulating conditions in our study were however, limited to only the Andrich Rating Scale model with linear regression analysis for covariates at the respondents' level. Statistical computations are necessary for applying our proposed analysis using the HB approach and some background in statistics and programming skills are needed to alter codes to conform to other conditions.

In conclusion, there is a need to account for measurement error associated with vision-specific latent trait in association analysis. We demonstrated that our HB one-stage "joint analysis" approach is a better method that produces greater accuracy with comparable power and precision in estimation of association effects compared to the frequently used two-stage procedure, despite taking into account greater uncertainty due to the latent trait. The study finding has direct implications in our inference drawn from statistical significance of risk factors.

6.6 Chapter 6 References

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6.7 Chapter 6 Tables and Figures

Table 6.1 Summary of Articles Reviewed (N=66)

AJO: American Journal of Ophthalmology; BJO: British Journal of Ophthalmology; IOVS: Investigative Ophthalmology & Visual Science; PCM: partial credit model.

	Major Ophthalmic Journals				Total
	Ophthalmology	AJO	BJO	IOVS	
No. of Articles	8 (12.1%)	3 (4.6%)	8 (12.1%)	47 (71.2%)	66 (100.0%)
Method					
Andrich	6 (75.0%)	1 (33.3%)	5 (62.5%)	31 (66.0%)	43 (65.1%)
PCM	0 (0.0%)	0 (0.0%)	1 (12.5%)	4 (8.5%)	5 (7.6%)
Not indicated	2 (25.0%)	2 (66.7%)	2 (25.0%)	12 (25.5%)	18 (27.3%)
Software					
Winsteps	5 (62.5%)	2 (66.7%)	5 (62.5%)	33 (70.2%)	45 (68.2%)
RUMM2020	3 37.5%)	0 (0.0%)	1 (12.5%)	10 (21.3%)	14 (21.3%)
BIGSTEPS	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (6.4%)	3 (4.5%)
Facets	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (1.5%)
Not indicated	0 (0.0%)	1 (33.3%)	1 (12.5%)	1 (2.1%)	3 (4.5%)
Sample size					
Median	1992	411	360	192	240
Range	108 - 14817	135 - 3400	16 - 3280	22 - 7363	16 - 14817

Table 6.2 Comparison between Approaches Using Real Data*

*Based on SiMES data

Model 1 adjusted for factors in table (excluding writing literacy);

Model 2 adjusted for factors in table (excluding reading literacy)

Data represented are difference in Rasch-scaled score with 95% Credible interval in parentheses

P-value < 0.05 suggests evidence of associations in 2-stage "separate-analysis" approach

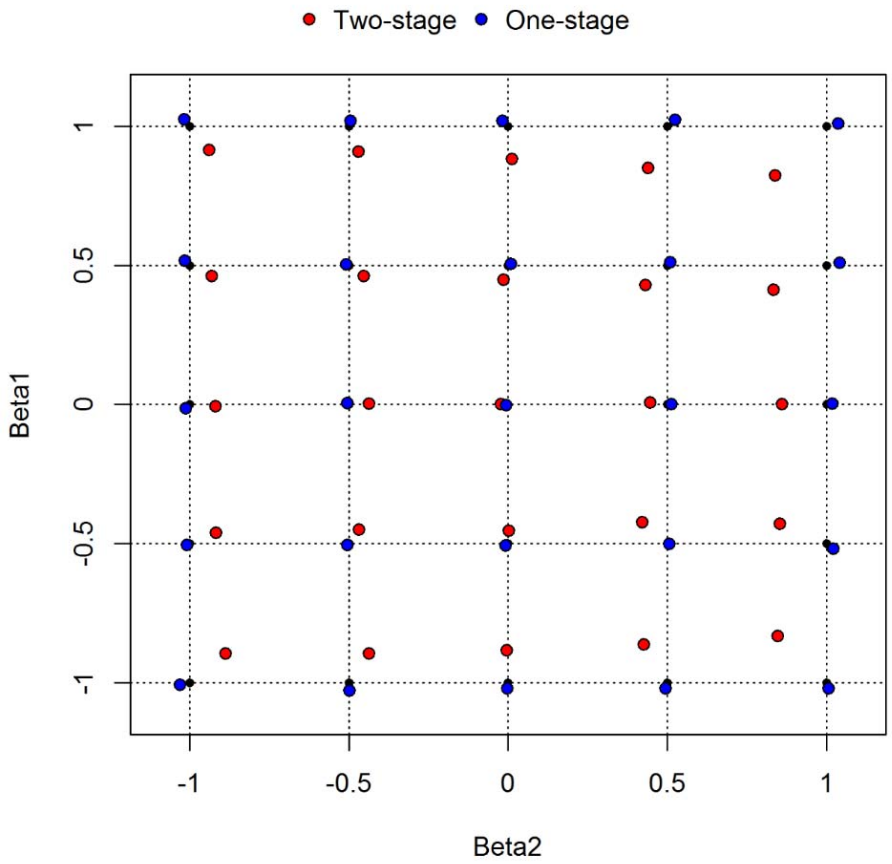
95%Credible Intervals not including 0 suggests evidence of associations in 1-stage "joint-analysis" approach

	Model 1 (reading literacy)			**Model 2 (writing literacy)**		
Approach	**2-Stage**	**P**	**1-Stage**	**2-Stage**	**P**	**1-Stage Approach**
Age, years	0.000 (-0.008, 0.008)	0.906	-0.001 (-0.020, 0.014)	0.001 (-0.007, 0.009)	0.892	-0.002 (-0.018, 0.014)
Gender						
Male vs. Female	0.012 (-0.161, 0.184)	0.894	0.073 (-0.330, 0.474)	0.010 (-0.163, 0.182)	0.913	0.053 (-0.265, 0.399)
Language of interview						
English vs. Malay	-0.227 (-0.501, 0.046)	0.103	-0.442 (-1.026, 0.142)	-0.229 (-0.502, 0.045)	0.101	-0.482 (-1.001, 0.027)
Others vs. Malay	0.659 (-0.685, 2.002)	0.336	6.389 (-0.604, 26.143)	0.649 (-0.696,1.994)	0.343	5.657 (-0.515, 17.086)
BMI	0.002 (-0.010, 0.014)	0.739	0.003 (-0.021, 0.027)	0.002 (-0.010, 0.014)	0.733	0.005 (-0.021, 0.028)
Occupation						
Office work	Reference		Reference	Reference		Reference
Service work	-0.060 (-0.263, 0.143)	0.559	-0.127 (-0.633, 0.380)	-0.062 (-0.265, 0.141)	0.549	-0.133 (-0.655, 0.343)
Factory work	-0.186 (-0.451, 0.078)	0.166	-0.402 (-1.013, 0.226)	-0.181 (-0.446, 0.083)	0.178	-0.396 (-0.890, 0.212)
Homemaking	-0.118 (-0.376, 0.141)	0.371	-0.210 (-0.809, 0.420)	-0.104 (-0.363, 0.155)	0.431	-0.273 (-0.797, 0.304)
Unemployed/others	-0.091 (-0.334, 0.152)	0.463	-0.197 (-0.750, 0.424)	-0.090 (-0.333, 0.153)	0.468	-0.227 (-0.775, 0.339)
Maratial Status						
Never married	Reference		Reference	Reference		Reference
Married	0.072 (-0.165,0.309)	0.552	0.227 (-0.304, 0.772)	0.074 (-0.164, 0.311)	0.543	0.232 (-0.216, 0.727)
Separate/divorced	-0.218 (-0.527,0.091)	0.167	-0.305 (-0.866, 0.304)	-0.213 (-0.522, 0.097)	0.177	-0.272 (-0.828, 0.283)
Widowed	0.082 (-0.237,0.400)	0.615	0.307 (-0.348, 0.990)	0.093 (-0.227, 0.414)	0.568	0.324 (-0.253, 0.929)
Income						
> SGD$1000/month	Reference		Reference	Reference		Reference
< SGD$1000/month	0.049 (-0.114, 0.212)	0.556	0.106 (-0.219, 0.475)	0.049 (-0.115, 0.212)	0.557	0.082 (-0.257, 0.406)
Retirement income	0.065 (-0.127, 0.256)	0.508	0.105 (-0.338, 0.570)	0.067 (-0.125, 0.259)	0.495	0.135 (-0.278, 0.491)
Current housing status						

1/2 room flat	Reference		Reference	Reference		Reference
3/4 room flat	-0.259 (-0.416, -0.101)	0.001	-0.580 (-0.944, -0.182)	-0.255 (-0.413, -0.098)	0.002	-0.526 (-0.843, -0.214)
5 room/private house	-0.281 (-0.477,-0.085)	0.005	-0.617 (-1.147, -0.194)	-0.278 (-0.474, -0.082)	0.006	-0.547 (-0.926, -0.192)
Education						
No formal education	Reference		Reference	Reference		Reference
Primary education	-0.164 (-0.394,0.066)	0.162	-0.360 (-0.930, 0.135)	-0.160 (-0.393, 0.074)	0.180	-0.342 (-0.789, 0.115)
Secondary education	-0.152 (-0.411,0.107)	0.249	-0.318 (-0.976, 0.237)	-0.151 (-0.414, 0.112)	0.261	-0.297 (-0.794, 0.201)
Poly/University	-0.124 (-0.427,0.180)	0.424	-0.178 (-0.965, 0.508)	-0.120 (-0.426, 0.187)	0.443	-0.147 (-0.75, 0.506)
Smoking status						
Past or never	Reference		Reference	Reference		Reference
Current	-0.203 (-0.359,-0.048)	0.010	-0.461 (-0.802, -0.141)	-0.201 (-0.356, -0.045)	0.012	-0.411 (-0.706, -0.159)
PVA of better eye	-0.934 (-1.165,-0.703)	0.000	-1.568 (-2.112, -1.085)	-0.950 (-1.180, -0.720)	0.000	-1.468 (-1.999, -1.022)
Read						
Yes vs. No	0.297 (0.026,0.568)	0.032	0.578 (0.051, 1.193)			
Write						
Yes vs. No				0.245 (-0.010, 0.500)	0.060	0.462 (0.0496, 0.966)

Figure 6.1 Association Effects and Standard Errors: Comparison of Proposed One-Stage HB and Observed Two-Stage Analysis Framework from Simulation Results

Attenuation Bias: red dots were shrunk towards zero and greater bias observed from the greater distance away from the black dots, the true value as compared to blue dots from one-stage approach



Bias of Beta1 (Beta 2 constant) ↕		Beta2				
		-1	**-0.5**	**0**	**0.5**	**1**
		Two-stage; One-stage	**Two-stage; One-stage**	**Two-stage; One-stage**	**Two-stage; One-stage**	**Two-stage; One-stage**
Beta1	**-1**	0.105 (0.075); -0.008 (0.084)	0.104 (0.076); -0.028 (0.093)	0.116 (0.077); -0.022 (0.094)	0.137 (0.080); -0.021 (0.087)	0.167 (0.074); -0.022 (0.091)
	-0.5	0.038 (0.056); -0.006 (0.068)	0.050 (0.053); -0.005 (0.075)	0.045 (0.052); -0.008 (0.073)	0.076 (0.058); -0.001 (0.076)	0.070 (0.062); -0.018 (0.065)
	0	-0.007 (0.056); -0.013 (0.059)	0.003 (0.049); 0.005 (0.057)	0.001 (0.053); -0.002 (0.059)	0.007 (0.059); 0.001 (0.058)	0.001 (0.054); 0.003 (0.062)
	0.5	-0.038 (0.059); 0.017 (0.067)	-0.039 (0.058); 0.004 (0.067)	-0.052 (0.064); 0.005 (0.062)	-0.071 (0.063); 0.012 (0.073)	-0.087 (0.060) ; 0.009 (0.076)
	1	-0.085 (0.081); 0.025 (0.089)	-0.091 (0.076); 0.020 (0.095)	-0.118 (0.080); 0.020 (0.092)	-0.150 (0.076); 0.022 (0.102)	-0.176 (0.081); 0.010 (0.092)

Bias of Beta2 (Beta 1 constant) ↔		Beta2				
		-1	**-0.5**	**0**	**0.5**	**1**
		Two-stage; One-stage	**Two-stage; One-stage**	**Two-stage; One-stage**	**Two-stage; One-stage**	**Two-stage; One-stage**
Beta1	**-1**	0.112 (0.122); -0.031 (0.132)	0.063 (0.117); 0.001 (0.128)	-0.005 (0.122); -0.003 (0.121)	-0.073 (0.117); -0.006 (0.122)	-0.153 (0.140); 0.007 (0.151)
	-0.5	0.082 (0.131); -0.008 (0.133)	0.031 (0.121); -0.006 (0.131)	0.002 (0.107); -0.007 (0.126)	-0.078 (0.116); 0.007 (0.131)	-0.145 (0.108); 0.022 (0.129)
	0	0.081 (0.133); -0.013 (0.116)	0.063 (0.116); -0.005 (0.110)	-0.022 (0.103); -0.005 (0.129)	-0.054 (0.116); 0.013 (0.126)	-0.140 (0.129); 0.019 (0.121)
	0.5	0.069 (0.132); -0.015 (0.131)	0.047 (0.122); -0.009 (0.133)	-0.014 (0.099); 0.010 (0.126)	-0.068 (0.115); 0.010 (0.138)	-0.165 (0.116); 0.042 (0.139)
	1	0.061 (0.130); -0.018 (0.147)	0.030 (0.136); 0.004 (0.137)	0.012 (0.134); -0.018 (0.138)	-0.059 (0.108); 0.024 (0.138)	-0.160 (0.128); 0.038 (0.144)

Based on 100 simulations using N=300; K=9; C=5
Data represented as average bias of Two-stage and One-stage estimates of Beta1 (holding Beta2 constant) and Beta2 (holding Beta1 constant), with standard error of Betas in the parentheses (true model is given by Beta1*Continuous variable + Beta2*Binary variable).

CHAPTER 7

Summary, Extensions and Future Research

7.1 SUMMARY

In the first chapter (**Chapter 1**), we reviewed published literature on the types of statistics used in ophthalmic journals and the major areas of developments in biostatistics research in recent years. New statistics and advanced methods improve efficiency and reliability of analysis results, in which its developments are driven by dynamic clinical and research questions, where study designs and nature of data collected can be complex due to limited resources, restrictions and factors not within control. Mathematical statistics uses two major paradigms, "classical" and Bayesian approach. This thesis focuses on the Bayesian methods, which is less understood and not commonly applied in ophthalmic research as observed from a current literature review but offers an alternative solution to solve many of the difficulties faced by conventional methods. Bayesian approach is fundamentally sound, flexible, provides clear and direct inferences and makes use of all available information and the main criticism of using priors was also discussed. We developed statistical models and used Bayesian inference to resolve different areas of common but complex clinical and epidemiologic research questions in the thesis. Contributions were highlighted in each study chapter.

The study design, methods and data details for analyses performed in the thesis were documented in **Chapter 2**. Clinical and epidemiologic research questions were encountered in my work experience with clinicians and scientists in the Singapore Eye Research Institute, and hence the study data were from the Singapore Malay Eye Study (SiMES), a prospective cohort of patients presented with uveitis to Singapore National Eye Center and also data extracted from literature review to conduct meta-analysis.

Study 1 (Chapter 3)

Few studies have developed conversion scores between cataract classification systems. There is a need for such a method of conversion, as prevalence and incidence of cataract cannot be compared directly between studies that were assessed using different

classification systems. In this study, we developed a conversion algorithm and applied our algorithm to transform between the LOCS III and Wisconsin system. The conversion between the two cataract classification systems is affected by the direction of transformation. The conversion algorithm was validated and R program codes to automate the collapsing iterations of the conversion algorithm was provided in **Appendix 1**.

Extensions and future research

Our conversion algorithm can be applied to other cataract grading systems and be extended for use in other diseases that requires harmonizing of classification systems and definitions of lesions such as for age-related macular degeneration, or chronic kidney disease where the classification system may lack coherence[1]. The usefulness of our conversion algorithm should be further investigated in its application to other research areas or improved/modified to overcome limitations.

Chapter 4 (Study 2)

The clinical diagnosis of infectious disease such as tuberculous uveitis is controversial, and without an established "gold standard" diagnostic test, it is difficult to evaluate current and new diagnostic tests results using "classical" statistics without knowing the correct disease status. Furthermore, IGRAs tests are not independent which complicates modeling. Our study have shown how analysis can be performed using Bayesian approach to estimate parameters (sensitivity and specificity of diagnostic tests) of latent class model for tuberculous uveitis, accounting for tests dependency and considering all available information. We have also investigated the optimal choice of diagnostic test to be used.

Extensions and future research

Our statistical model can be extended or made to confirm to other situations or limitations for analysis of other diagnostic tests or screening programs, such as dilated ophthalmoscopy or retina image grading for screening of diabetic retinopathy[2], or in assessment of rapid tests for dengue diagnosis[3]. Correct classification rate, validity, cost,

urgency and invasiveness of tests are some of the many factors to be considered in the in-depth evaluation of diagnostic or screening tests. Further research can be done in the sequence of multiple tests to be performed, whether sequentially or simultaneously; and the reproducibility, repeatability and reliability of tests.

Chapter 5 (study 3)

Numerous population-based studies of age-related macular degeneration have been reported around the world, with the results of some studies suggesting racial or ethnic differences in disease prevalence. Integrating these resources to provide summarized data to establish worldwide prevalence and to project the number of people with age-related macular degeneration from 2020 to 2040 would be a useful guide for global strategies. In this study, we conducted a systematic literature review to identify all population-based studies of age-related macular degeneration published before May, 2013 and included only studies using retinal photographs and standardized grading classifications (the Wisconsin age-related maculopathy grading system, the international classification for age-related macular degeneration, or the Rotterdam staging system).

Various sources of heterogeneity and uncertainty (e.g. ethnicity, geographic regions etc.) were accounted for and tested in our statistical model using Hierarchical Bayesian approach; and to estimate the pooled prevalence, the 95% credible intervals (CrI), and examine the difference in prevalence by ethnicity (European, African, Hispanic, Asian) and region (Africa, Asia, Europe, Latin America and the Caribbean, North America, and Oceania). We then projected the number of people affected in 2014 and 2040 based on the UN World Population Prospects. These estimates indicate the substantial global burden of age-related macular degeneration. Our study provided summarized evidence for understanding the effect of the condition and provide data towards designing eye-care strategies and health services around the world.

Extensions and future research

Further research should be done in addressing the overall disease burden such as on visual acuity or the effect of vision loss on quality of vision and quality of life as suggested in commentary article by Jost B Jonas.[4] Our study provided the first step in examination of the overall prevalence of age-related degeneration; the next step would require further investigation on the factors associated with age-related macular degeneration, whether the factors and its influence differs between countries or ethnicities or caused the prevalence varies between regions. The answers to these questions could help in the prevention of the disease, in elucidating the pathogenesis, and could give hints for the development of new therapeutic procedures.

Chapter 6 (study 4)

Numerous vision-specific instruments have been rigorously validated using Rasch analysis for daily living activities dependent on vision and for a spectrum of eye conditions such as cataract, diabetic retinopathy, age-related macular degeneration, and glaucoma. Vision functioning is one of the key latent traits for vision-specific instruments and Rasch analysis has been used to estimate and evaluate latent traits, producing Rasch-scaled scores in preference to raw scores from questionnaire data. Subsequent applications of "classical" statistics such as t-tests and linear regressions are not strictly appropriate for association analysis of latent data as they require dependent/outcome variables to be known. The analysis of latent variables requires the associated measurement error to be accounted for as failure to do so may lead to biased estimates of correlations, associations and statistical inferences.

In this study, we demonstrated the effectiveness of a modeling framework that integrates Rasch and regression models using HB approach that accounts for latent trait measurement errors, producing accurate estimation of association effects in our simulation study compared to the frequently used approach. Both methods applied on real data showed different identification of significant factors between approaches. HB one-stage "joint

analysis" is a better approach, producing accurate effect size estimations and information about the independent association of exposure variables with vision-specific latent traits.

Extensions and future research

Our model codes could be further improved and made into a simple graphical user interface program with easy implementation, to reach out to more researchers. The application of advanced/improved bio-statistical methodology should be encouraged to advance analysis of research data.

7.1.1 Significance and Impact on Health Research

The discipline of biostatistics is clearly a fundamental scientific component of biomedical, public health and health services research.[5] In particular, epidemiology and clinical trials are two major fields of medical research that depends on statistics as a fundamental tool in the achievement of their goals. The focus of this thesis is on epidemiologic research - the study of how often diseases occur, and reasons for differences in different groups of people.

Epidemiological information is used to plan and evaluate strategies to prevent illness, and serves as a guide for the management of patients in whom disease has already developed. The involvement of biostatisticians contribute in advising on the conditions for valid inference, from the design of the study to concerns on various sources of uncertainty and bias due to possible confounding factors in the evaluation of effects of potential risk factors for diseases. These effects are quantified by measures of association such as the odds ratio or relative risk, involving probabilistic concepts to be estimated appropriately according to the type of study (e.g. case-control, cross-sectional, cohort) and specific conditions for individual research project. The variety of statistical methods required in epidemiology is immense, where the increase in diversity of new research questions has led to significant contributions of biostatistics to the ongoing advancement in epidemiological research.

It is important for researchers to communicate with biostatisticians to take full advantage of newly developed and advanced statistical methods to advance cutting edge research and knowledge. This thesis contributes in the development of modern Bayesian models applied to different areas of clinical and epidemiology research, to bridge the transfer of advanced statistical methods into the mainstream of ophthalmic research. Bayesian approached is useful to resolve research questions that may be difficult with conventional statistics. A documented "step-by-step" R codes to help researchers to perform their own Bayesian analysis for similar research settings was proposed.

7.1.2 Bayes Methods and Other Modern Statistics

The thesis is limited to development of mainly hierarchical Bayesian models focusing on eye research topics in clinical and epidemiological settings. There are many other Bayesian techniques and its applications in other disciplines that were not discussed, such as Bayesian approach in handling missing data, in the analyses of longitudinal data, clinical trials, health economics, model selection methods or survival analysis.[6-7] The empirical Bayes is another approach to Bayesian that uses observed data to estimate final-stage prior (e.g. hyper-parameters) and proceed as though the priors were known (as in our usual Bayesian approach), that may produce superior estimates of parameters.[6-11] Continual explorations in Bayes applications provides potential analytic benefits to advance research.

Because research questions health research are diverse, biostatistics has expanded its domain to include any quantitative methods that may be used to answer these questions. This thesis focused on Bayesian approach as an alternative to the "classical" approach. Literature review on current research in biostatistics in **Chapter 2** revealed other current popular research to be in the area of nonparametric and semi-parametric approaches to inference techniques and variable selection. The management of high-dimensional data, data mining techniques, discrimination and classification models and neural networks are other important and useful modern statistics applicable to epidemiology research.

7.1.3 Conclusions

Restricting ourselves to the use of a single specific data analysis method may impede the progress of research. When various statistical methods come up with different answers, efforts in figuring out why would lead to a better understanding of the underlying reality. The arising diversity of clinical questions, new research problems with increasingly complex study designs require both continual development of "classical" techniques and the creation of new statistical methods crafted for specific research scenarios.[12]

In summary, efficient methodological and modeling tools should be used, especially in cases where the usual modeling assumptions are not applicable to the data under consideration. Simulation studies and data analyses of research projects provided in this thesis illustrate the practical utility of the Bayesian approach helps to improve and advance ophthalmic research. These statistical models and analyses procedures formulated (and codes provided) may be emulated and further improved for other research studies.

7.2 Chapter 7 References

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APPENDICES

APPENDIX 1: R programming Codes

Points to take note:

*Comments are in **green**.*

*Variable names to be used according to own research data are in **blue**.*

*Data specifications to be changed according to own research preference are in **red**.*

R Codes for Chapter 3

General steps to perform conversion algorithm:

1) Organize data spreadsheet and read into R

2) Recode/Categorize continuous scales

3) Run collapsed algorithm to obtain collapsed frequency table to required categories (run twice if both scales needs to be collapsed)

4) Data Cleaning (any cells with conditional probabilities of < 10% were regarded as noise) and calculation of conditional probabilities

Step 1: Data input for R

Data spreadsheet should be arranged in the below manner and saved as .csv file type, e.g. "locs_w.csv".

	A	B	C	D	E	F	G	H
1	sno	eye	nl	nw	cl	cw	pl	pw
2	MS10060	L	3.5	3	0.1	0.0	0.1	0.0
3	MS10060	R	3.5	2	0.1	0.0	0.1	0.0
4	MS10061	L	4	3	4.5		0.5	
5	MS10061	R	4	3	5.0		0.5	
6	MS10062	L	2.5	2	0.1		0.1	
7	MS10062	R	2.5	2	0.1		0.1	
8	MS10064	L	4.5	2	0.1		0.5	
9	MS10064	R	4.5	2	0.1		2.0	
10	MS10065	L	3.5	2	0.1	0.0	0.1	0.0
11	MS10065	R	3.5	2	0.1	0.0	0.1	0.0

Data Legend: sno = unique subject identifier, i.e. study number; nl = LOCS nuclear score; nw = Wisconsin nuclear score; cl = LOCS cortical score; cw = Wisconsin cortical score; pl = LOCS PSC score; pw = Wisconsin PSC score.

Step 2: R programming codes to convert scores between scales

Converting Nuclear cataract

```
### R to read "locs_w.csv" spreadsheet data saved on C drive
data<-read.csv("C:/locs_1.csv",header=T)

## Step 2a) Recode LOCS (range 0-6.9) into half unit steps (14 categories), i.e. 0-0.4
coded as 1, 0.5-0.9 coded as 2 etc.
library(car)
nl_cg<-recode(nl,"0:0.4=1;0.5:0.9=2;1:1.4=3;1.5:1.9=4;2:2.4=5;2.5:2.9=6;3:3.4=7;
3.5:3.9=8;4:4.4=9;4.5:4.9=10;5:5.4=11;5.5:5.9=12;6:6.4=13;6.5:6.9=14")
## Display nuclear Wisconsin and LOCS 14 by 5 frequency table
u<-!is.na(nl)&!is.na(nw)
lik<-matrix(0,ncol=5,nrow=14)
for(i in 1:14){
for(j in 1:5){
lik[i,j]<-sum(nl_cg==i&nw==j&u)
}}
lik

## Step 2b) Collapsed algorithm to obtain collapsed frequency table
library(gmodels)
i<-1
nl_cg->nl_cb
while(i<=9){        # Have to collapse 9 times to get 5 categories from 14 categories
i<-i+1              (Reduce number of iterations for rows with complete zero counts)
CrossTable(nl_cb,nw,prop.c=F,prop.t=F,prop.chisq=F)->ct
ct$prop.row->cpr
nrow(cpr)->nr
cprd<-numeric(nr-1)
for(j in 1:(nr-1)){
sum(abs(cpr[j,]-cpr[j+1,]))->cprd[j]
}
which(cprd==min(cprd))->ij
as.numeric(row.names(cpr)[ij])->ij1
```

```
as.numeric(row.names(cpr)[ij+1])->ij2
nl_cb2<-nl_cb
nl_cb2[nl_cb==ij1&!is.na(nl)]<-ij2
nl_cb<-nl_cb2
}
table(nl_cb,nw)->xt;
xt   # Collapsed results (frequency counts)
```

Step 2c) Data Cleaning – any cells with conditional probabilities of < 10% were regarded as noise

```
## Convert Wisconsin to LOCS
## (To convert from LOCS to Wisconsin, swap the row and column variables)
tem1<-nl_cb   # To convert LOCS to Wisconsin, replace tem1 with variable nw,
i.e.“tem1<-nw”
tem2<-nw    # To convert LOCS to Wisconsin, replace tem2 with variable nl_cb, i.e.
“tem2<-nl_cb”
table(tem1,tem2)->ct    # Rows are LOCS, columns are Wisconsin
result<-matrix(0,ncol=5,nrow=5)
for(i in 1:5){
sum(ct[,i])->si
result[,i]<-ct[,i]/si
(result[,i]>=0.1)->indi    # <10% were regarded as noise
sum(result[indi,i])->s2
result[indi,i]<-result[indi,i]/s2
result[!indi,i]<-0
}
round(result,2)    # Conversion results (conditional probabilities)
write.csv(round(result,2),"R_conver.csv",row.names=F)    # Output results into MS excel
```

Converting Cortical cataract

Step 2a) Recode/Categorize both scales

```
## Recode LOCS (range 0-5.9) into half unit steps (12 categories), i.e. 0-0.4 coded as 1,
0.5-0.9 coded as 2 etc.
library(car)
```

```
cl_cg<-
recode(cl,"0:0.4=1;0.5:0.9=2;1:1.4=3;1.5:1.9=4;2:2.4=5;2.5:2.9=6;3:3.4=7;3.5:3.9=8;
4:4.4=9;4.5:4.9=10;5:5.4=11;5.5:5.9=12")
## Recode Wisconsin (range 0-100%) into 5% unit steps (20 categories), i.e. 0-4.99
coded as 1, 5-9.99 coded as 2 etc.
cw_cg<-recode(cw,"0:4.99=1;5:9.99=2;10:14.99=3;15:19.99=4;20:24.99=5;
25:29.99=6;30:34.99=7;35:39.99=8;40:44.99=9;45:49.99=10;50:54.99=11;55:59.99=12;
60:64.99=13;65:69.99=14;70:74.99=15;75:79.99=16;80:84.99=17;85:89.99=18;90:94.99
=19;95:100=20")
## Display cortical LOCS and Wisconsin 12 by 20 frequency table
u<-!is.na(cl)&!is.na(cw)
lik<-matrix(0,ncol=20,nrow=12)
for(i in 1:12){
for(j in 1:20){
lik[i,j]<-sum(cl_cg==i&cw_cg==j&u)
}}
lik
```

Step 2b) Collapsed algorithm to obtain collapsed frequency table

```
library(gmodels)
# Collapse LOCS
i<-1
cl_cg->cl_cb
cw_cg->cw_cb
while(i<=7){    # Have to collapse 7 times to get 5 categories from 12 categories
i<-i+1
CrossTable(cl_cb,cw_cb,prop.c=F,prop.t=F,prop.chisq=F)->ct    # 12 rows (LOCS) by 20
columns (Wisconsin)
ct$prop.row->cpr
nrow(cpr)->nr
cprd<-numeric(nr-1)
for(j in 1:(nr-1)){
sum(abs(cpr[j,]-cpr[j+1,]))->cprd[j]
}
```

```
which(cprd==min(cprd))->ij
as.numeric(row.names(cpr)[ij])->ij1
as.numeric(row.names(cpr)[ij+1])->ij2
cl_cb2<-cl_cb
cl_cb2[cl_cb==ij1&!is.na(cl)]<-ij2
cl_cb<-cl_cb2
}
table(cl_cb,cw_cb)->xt;
xt    # Collapsed results (frequency counts)

## Collapse Wisconsin
i<-1
while(i<=15){    # Have to collapse 15 times to get 5 categories from 20 categories
i<-i+1
CrossTable(cw_cb,cl_cb,prop.c=F,prop.t=F,prop.chisq=F)->ct    # 20 rows (Wisconsin)
by 5 columns (LOCS)
ct$prop.row->cpr
nrow(cpr)->nr
cprd<-numeric(nr-1)
for(j in 1:(nr-1)){
sum(abs(cpr[j,]-cpr[j+1,]))->cprd[j]
}
which(cprd==min(cprd))->ij
as.numeric(row.names(cpr)[ij])->ij1
as.numeric(row.names(cpr)[ij+1])->ij2
cw_cb2<-cw_cb
cw_cb2[cw_cb==ij1&!is.na(cw)]<-ij2
cw_cb<-cw_cb2
}
table(cw_cb,cl_cb)->xt;
xt    # Collapsed results (frequency counts)
```

Step 2c) Data Cleaning – any cells with conditional probabilities of < 10% were regarded as noise

```
## Convert Wisconsin to LOCS
## (To convert from LOCS to Wisconsin, swap the row and column variables)
tem1<-cl_cb    # To convert LOCS to Wisconsin, replace tem1 with variable nw, i.e. "tem1<-cw_cb"
tem2<-cw_cb    # To convert LOCS to Wisconsin, replace tem2 with variable nl_cb, i.e. "tem2<-cl_cb"
table(tem1,tem2)->ct    # Rows are LOCS, columns are Wisconsin
result<-matrix(0,ncol=5,nrow=5)
for(i in 1:5){
sum(ct[,i])->si
result[,i]<-ct[,i]/si
(result[,i]>=0.1)->indi
sum(result[indi,i])->s2
result[indi,i]<-result[indi,i]/s2
result[!indi,i]<-0
}
round(result,2)    # Conversion results (conditional probabilities)
write.csv(round(result,2),"R_conver.csv",row.names=F)    # Output results into MS excel
```

Converting PSC cataract

```
## Step 2a) Recode/Categorize both scales
## Recode LOCS (range 0-5.9) into half unit steps (12 categories), i.e. 0-0.4 coded as 1, 0.5-0.9 coded as 2 etc.
library(car)
pl_cg<-recode(pl,"0:0.4=1;0.5:0.9=2;1:1.4=3;1.5:1.9=4;2:2.4=5;2.5:2.9=6;3:3.4=7;3.5:3.9=8;4:4.4=9;4.5:4.9=10;5:5.4=11;5.5:5.9=12")
## Recode Wisconsin (range 0-100%) into 0%, 1-4%, then 5% unit steps (21 categories), i.e. 0 coded as 1, 0.01-4.99 coded as 2, 5-9.99 coded as 3, 10-14.99 coded as 4 etc.
pw_cg<-recode(pw,"0=1;0.01:4.99=2;5:9.99=3;10:14.99=4;15:19.99=5;20:24.99=6;25:29.99=7;30:34.99=8;35:39.99=9;40:44.99=10;45:49.99=11;50:54.99=12;55:59.99=13;60:64.99=14;65:69.99=15;70:74.99=16;75:79.99=17;80:84.99=18;85:89.99=19;90:94.99=20;95:100=21")
## Display PSC LOCS and Wisconsin 12 by 21 frequency table
u<-!is.na(pl)&!is.na(pw)
```

```
lik<-matrix(0,ncol=21,nrow=12)
for(i in 1:12){
for(j in 1:21){
lik[i,j]<-sum(pl_cg==i&pw_cg==j&u)
}}
lik

## Step 2b) Collapsed algorithm to obtain collapsed frequency table
library(gmodels)
# Collapse LOCS
i<-1
pl_cg->pl_cb
pw_cg->pw_cb
while(i<=7){    # Have to collapse 7 times to get 5 categories from 12 categories
i<-i+1
CrossTable(pl_cb,pw_cb,prop.c=F,prop.t=F,prop.chisq=F)->ct    # 12 rows (LOCS) by
21 columns (Wisconsin)
ct$prop.row->cpr
nrow(cpr)->nr
cprd<-numeric(nr-1)
for(j in 1:(nr-1)){
sum(abs(cpr[j,]-cpr[j+1,]))->cprd[j]
}
which(cprd==min(cprd))->ij
as.numeric(row.names(cpr)[ij])->ij1
as.numeric(row.names(cpr)[ij+1])->ij2
pl_cb2<-pl_cb
pl_cb2[pl_cb==ij1&!is.na(pl)]<-ij2
pl_cb<-pl_cb2
}
table(pl_cb,pw_cb)->xt;
xt    # Collapsed results (frequency counts)

## Collapse Wisconsin
```

```
i<-1
while(i<=16){    # Have to collapse 16 times to get 5 categories from 21 categories
i<-i+1
CrossTable(pw_cb,pl_cb,prop.c=F,prop.t=F,prop.chisq=F)->ct    # 20 rows (Wisconsin)
by 5 columns (LOCS)
ct$prop.row->cpr
 nrow(cpr)->nr
 cprd<-numeric(nr-1)
 for(j in 1:(nr-1)){
  sum(abs(cpr[j,]-cpr[j+1,]))->cprd[j]
 }
 which(cprd==min(cprd))->ij
 as.numeric(row.names(cpr)[ij])->ij1
 as.numeric(row.names(cpr)[ij+1])->ij2
 pw_cb2<-pw_cb
 for(k in 1:length(ij1)){    #  For more than 2 adjacent rows to be collapsed at a time
  pw_cb2[pw_cb==ij1[k]&!is.na(pw)]<-ij2[k]
  pw_cb<-pw_cb2
 }
 i=i+(length(ij1)-1)
}
table(pw_cb,pl_cb)->xt;
xt    # Collapsed results (frequency counts)
```

Step 2c) Data Cleaning – any cells with conditional probabilities of < 10% were regarded as noise

```
## Convert Wisconsin to LOCS
## (To convert from LOCS to Wisconsin, swap the row and column variables)
tem1<-pl_cb    # To convert LOCS to Wisconsin, replace tem1 with variable nw, i.e.
“tem1<-cw_cb”
tem2<-pw_cb    # To convert LOCS to Wisconsin, replace tem2 with variable nl_cb, i.e.
“tem2<-cl_cb”
table(tem1,tem2)->ct    # Rows are LOCS, columns are Wisconsin
result<-matrix(0,ncol=5,nrow=5)
```

```
for(i in 1:5){
sum(ct[,i])->si
result[,i]<-ct[,i]/si
(result[,i]>=0.1)->indi    # <10% were regarded as noise
sum(result[indi,i])->s2
result[indi,i]<-result[indi,i]/s2
result[!indi,i]<-0
}
round(result,2)    # Conversion results (conditional probabilities)
write.csv(round(result,2),"R_conver.csv",row.names=F)    # Output results into MS excel
```

R Programming Codes for Chapter 4

General steps in analyses:

a) Organize data spreadsheet and read into R

b) Building our Bayesian Latent model *(QFT, TspotTB correlated, TST independent)* to:

i. Estimate prevalence of disease, sensitivity and specificity of diagnostic tests and calculate their PPV and NPV

ii. To predict "true" cell counts and analyze discordant results

iii. Develop decision rules to evaluate optimal choice of diagnostic tests

c) Perform sensitivity analysis

Step 1: Data input for R

Data spreadsheet should be arranged in the below manner and saved as .csv file type, e.g. "data.csv".

	A	B	C	D
1	id	TST	QFT	TspotTB
2	1	1	0	0
3	2	1	0	0
4	3	1	1	1
5	4	1	0	0
6	5	1	0	0
7	6	0	0	0
8	7	1	1	1
9	8	1	0	0
10	9	1	0	1

Data Legend: id = patient identifier; Diagnostic tests were coded as 1 for positive result and 0 for negative result.

```
### R to read "tb_data.csv" spreadsheet data saved on C drive
data<-read.csv("C:/data.csv",header=T)
```

Step 2, part bi): R programming codes for Parameter Estimations

```
### Step 2a) Building/Setting up model and save as "model.txt" in your R working directory
model{
```

```
## Correlated test
y[1:4]~dmulti(p[1:4],n[1])  # multinomial distribution
p[1]<-P*Se11+(1-P)*Sp11  # ++
p[2]<-P*Se12+(1-P)*Sp12  # +-
p[3]<-P*Se21+(1-P)*Sp21  # -+
p[4]<-P*Se22+(1-P)*Sp22  # --
## Sensitivity
Se11<-Se[1]*Se[2]+covSe;Se12<-Se[1]-Se11;
Se21<-Se[2]-Se11;Se22<-1-Se11-Se12-Se21
## covSe (covariance of sensitivity between related diagnostic tests)
lSe<-(Se[1]-1)*(1-Se[2]);uSe<-min(Se[1],Se[2])-Se[1]*Se[2]
covSe~dunif(lSe,uSe);rhoSe<-covSe/sqrt(Se[1]*(1-Se[1])*Se[2]*(1-Se[2]))
## Specificity
Sp22<-Sp[1]*Sp[2]+covSp;Sp12<-Sp[2]-Sp22;Sp21<-Sp[1]-Sp22;Sp11<-1-Sp22-Sp12-
Sp21
## covSp (covariance of specificity between related diagnostic tests)
lSp<-(Sp[1]-1)*(1-Sp[2]);uSp<-min(Sp[1],Sp[2])-Sp[1]*Sp[2]
covSp~dunif(lSp,uSp);rhoSp<-covSp/sqrt(Sp[1]*(1-Sp[1])*Sp[2]*(1-Sp[2]))
##  Independent diagnostic test
y[5]~dbin(p[5],n[2])  # binomial distribution
p[5]<-P*Se[3]+(1-P)*(1-Sp[3])

##  Input of Prior specifications
for(k in 1:3){
Se[k]~dbeta(beta_Se[k,1],beta_Se[k,2])  # informative beta prior distribution for
sensitivity
Sp[k]~dbeta(beta_Sp[k,1],beta_Sp[k,2])  # informative beta prior distribution for
specificity
PPV[k]<-Se[k]*P/(Se[k]*P+(1-Sp[k])*(1-P))  # calculation of PPV
NPV[k]<-Sp[k]*(1-P)/(Sp[k]*(1-P)+(1-Se[k])*P)  # calculation of NPV
}
P~dbeta(beta_P[1],beta_P[2])  # non-informative beta prior distribution for prevalence

}
```

		QFT +	QFT -
TSpotTB	+	+ +	+ -
	-	- +	- -

```
### Step 2b) Execute Bayesian model
## Load library
source("rounds.R")
library(R2jags)
library(car)
## Specification of informative beta priors for Sensitivity & Specificity of all 3
diagnostic tests (in the order of TST, TspotTB, QFT) derived from previous literature
mm=c(709,683,500,906,642,996)/1000  # prior – mean
ml=c(658,522,334,882,593,989)/1000  # prior – lower limit
mu=c(761,844,666,929,691,1000)/1000  # prior – upper limit
mu0=(mu+ml)/2;sd0=(mu-ml)/4
beta_Se0=t(apply(cbind(mu0[c(1,3,5)],sd0[c(1,3,5)]),1,ab))
beta_Sp0=t(apply(cbind(mu0[c(2,4,6)],sd0[c(2,4,6)]),1,ab))
beta_Se=matrix(beta_Se0[c(2,3,1),],nrow=3)
beta_Sp=matrix(beta_Sp0[c(2,3,1),],nrow=3)
beta_P=c(1,1)  # non-informative beta prior distribution for prevalence

tem_data=data[,c("TspotTB","QFT")]
y=table(tem_data);y=y[c(2,1),c(2,1)];y=c(y[1,],y[2,])  # cell counts for TspotTB & QFT
n=sum(y)  # total counts, i.e. sample size
tem_data=data[,"TST"]
tem_data=tem_data[!is.na(tem_data)]
y=c(y,sum(tem_data))  # to include positive counts for TST
n=c(n,length(tem_data))  # to include sample size of TST

dat=list("y","n","beta_Se","beta_Sp","beta_P")
parameters=c("P","Se","Sp","PPV","NPV","rhoSe","rhoSp")  # parameters to be tracked
for their posterior distributions
inits=function(){list(P=0.5,Se=c(0.5,0.5,0.5),Sp=c(0.5,0.5,0.5))}  # initial values
set.seed(1213)  # set seed number
## R to launch JAGS software and load and run "model.txt"
corr2ind1=jags.parallel(dat,inits,parameters,model.file="model.txt",n.chains=2,n.iter=25
000,n.burnin=5000,DIC=F,digits = 5,working.directory=getwd())
corr2ind1$BUGSoutput$summary[,c("2.5%", "50%", "97.5%")]  # display results
```

Step 2, part bii): To predict "true" cell counts and analyze discordant results

```
###To include the below into model.txt in Step 2a above & re-run analyses

###  TSpotTB & QFT (correlated tests)
P_pred[1,1]<-P*Se11/p[1]  # ++
P_pred[1,2]<-P*Se12/p[2]  # +-
P_pred[1,3]<-P*Se21/p[3]  # -+
P_pred[1,4]<-P*Se22/p[4]  # --
for(i in 1:4){N_pred[1,i]~dbin(P_pred[1,i],Y[1,i])}

###  T-SPOT.TB & TST (independent tests)
P_pred[2,1]<-(Se[1]*Se[3]*P)/(Se[1]*Se[3]*P+(1-Sp[1])*(1-Sp[3])*(1-P))  # ++
P_pred[2,2]<-(Se[1]*(1-Se[3])*P)/(Se[1]*(1-Se[3])*P+(1-Sp[1])*Sp[3]*(1-P))  # +-
P_pred[2,3]<-(Se[3]*(1-Se[1])*P)/(Se[3]*(1-Se[1])*P+(1-Sp[3])*Sp[1]*(1-P))  # -+
P_pred[2,4]<-((1-Se[1])*(1-Se[3])*P)/((1-Se[1])*(1-Se[3])*P+Sp[1]*Sp[3]*(1-P))  # --
for(i in 1:4){N_pred[2,i]~dbin(P_pred[2,i],Y[2,i])}

###  QFT & TST (independent tests)
P_pred[3,1]<-(Se[2]*Se[3]*P)/(Se[2]*Se[3]*P+(1-Sp[2])*(1-Sp[3])*(1-P)) # ++
P_pred[3,2]<-(Se[2]*(1-Se[3])*P)/(Se[2]*(1-Se[3])*P+(1-Sp[2])*Sp[3]*(1-P)) # +-
P_pred[3,3]<-(Se[3]*(1-Se[2])*P)/(Se[3]*(1-Se[2])*P+(1-Sp[3])*Sp[2]*(1-P)) # -+
P_pred[3,4]<-((1-Se[2])*(1-Se[3])*P)/((1-Se[2])*(1-Se[3])*P+Sp[2]*Sp[3]*(1-P)) # --
for(i in 1:4){N_pred[3,i]~dbin(P_pred[3,i],Y[3,i])}

for(i in 1:3){Ratio[i]<-P_pred[i,2]/P_pred[i,3]}
```

Step 2, part biii): Optimal choice of diagnostic test

```
###To include the below into model.txt in Step 2a above & re-run analyses
for(i in 1:NP){
for(k in 1:3){risk[k,i]<-(1-Se[k])*PP[i]+(1-Sp[k])*(1-PP[i])}
}
## Plot to illustrate sequential testing of QFT, TSpot.TB and TST
## To first plot risk line for QFT
i=1;temi=model$BUGSoutput$summary[paste("risk[",i,",",1:NP,"]",sep=""),"50%"]
```

```
plot(PP,temi,type="l",ylim=c(0,0.5),ylab="Risk (misclassification
rate)",xlab="Probability of Tuberculous Uveitis",lwd=2,lty=2)
## To add risk line for TspotTB in plot
i=2;temi=model$BUGSoutput$summary[paste("risk[",i,",",1:NP,"]",sep=""),"50%"]
lines(PP,temi,lty=1,lwd=2)
## To add risk line for TST in plot
i=3;temi=model$BUGSoutput$summary[paste("risk[",i,",",1:NP,"]",sep=""),"50%"]
lines(PP,temi,lty=4,lwd=2)
legend("bottomright",c("QFT","T-SPOT.TB","TST"),lty=c(1,2,4),bty="n",lwd=2)
```

Part c) Step 3: Sensitivity analysis

```
## Generate multiple trial or mock data, "0s" and "1s" data.
mockdata1<-cbind(sample(0:1,152,replace=T),sample(0:1,152,replace=T),
sample(0:1,152,replace=T))
mockdata1<-data.frame(mockdata1)
names(mockdata1)<-c("QFT","TspotTB","TST")

## Repeat model analysis documented above to investigate if our data or priors are
driving model results. Varying posterior distributions should be observed with the
application of multiple trial or mock data.

## To re-run analyses using informative prior based on information obtained previous
literature if available to compare with model results using non-informative priors.
```

R Programming Codes for Chapter 5

General steps in analyses:

a) Build Hierarchical Bayesian model to pool overall and subgroup prevalence estimates:

i. Ethnicity

ii. Geographic regions

b) Projection of number of people with AMD by regions

c) Bayesian hypothesis testing to examine ethnicity effect

(codes can be expanded/modified for analysis of gender, region, publication year effects)

Step 1: Data input for R

Data spreadsheet should be arranged in the below manner and saved as .csv file type, e.g. "amd_data.csv".

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	study	year	response_rate	country	ethnicity	agegp	gender	n	ye	yl	yb	region_wl	race_wl
2	APEDS	2005	86.7	India	Indian	60 - 69	3	899	NA	NA	31	2	2
3	APEDS	2005	86.7	India	Indian	> 70	3	353	NA	NA	13	2	2
4	APEDS	2005	86.7	India	Indian	40 - 49	3	1423	NA	NA	13	2	2
5	APEDS	2005	86.7	India	Indian	50 - 59	3	1047	NA	NA	14	2	2
6	ARIC	1999	55.5	USA	Black	55 - 59	2	495	20	0	20	5	1
7	ARIC	1999	55.5	USA	Black	60 - 64	2	361	14	1	15	5	1
8	ARIC	1999	55.5	USA	Black	65 - 72	2	277	10	0	10	5	1
9	ARIC	1999	55.5	USA	Black	60 - 64	1	191	12	0	12	5	1
10	ARIC	1999	55.5	USA	Black	48 - 54	1	283	5	0	5	5	1
11	ARIC	1999	55.5	USA	Black	65 - 72	1	195	13	0	13	5	1
12	ARIC	1999	55.5	USA	Black	48 - 54	2	480	14	0	14	5	1

Data Legend: study = study name abbreviation; year = publication year; gender coded as 1 for male, 2 for female and 3 for both; n = study sample size; ye = number of subjects with early amd; yl = number of subjects with late amd; yb = number of subjects with any amd; region_wl = geographical region coded as 1 for Africa, 2 for Asia, 3 for Europe, 4 for Altin America & Caribbean, 5 for Northern America, 6 for Oceania; race_wl = ethnicity coded as 1 for African, 2 for Asian, 3 for European, 4 for Hispanic, 5 for Others.

```
### R to read "amd_data.csv" spreadsheet data saved on C drive
data_amd<-read.csv("C:/amd_data.csv",header=T)
```

Step 2, part a): R programming codes for Meta-analysis

```
## Load library
source("rounds.R")
```

```
library(car)
library(R2jags)
library(coda)
library(dummies)
library(metafor)

## Data manipulation
# Create agel variable – lower bound of age group
tem=sapply(strsplit(as.character(data_amd$agegp),split=" - ",fixed=T),function(x){x[1]})
tem1=sapply(strsplit(as.character(tem),split="> ",fixed=T),function(x){x[2]})
tem[!is.na(tem1)]=tem1[!is.na(tem1)]
data_amd$agel=as.numeric(tem)
# Create ageu variable – upper bound of age group
tem=sapply(strsplit(as.character(data_amd$agegp),split=" - ",fixed=T),function(x){x[1]})
tem1=sapply(strsplit(as.character(tem),split="> ",fixed=T),function(x){x[2]})
tem0=sapply(strsplit(as.character(data_amd$agegp),split=" -
",fixed=T),function(x){x[2]})
tem0[!is.na(tem1)]=tem1[!is.na(tem1)]
data_amd$ageu=as.numeric(tem0)
# Create ageuid variable – indicator variable if upper bound is not deterministic, e.g. 80+
data_amd$ageuid=as.numeric(sapply(strsplit(as.character(data_amd$agegp),split="",
fixed=T),function(x){sum(x==">")>0}))

### Prepare/collapse subgroups data, e.g. data3 Region, data4 for Ethnicity
tem_data=data_amd
studyu=unique(tem_data$study);Ns=length(studyu)

data3=NULL;data4=NULL
for(i in 1:Ns){
  studyi=studyu[i]
  ## Region
  regioni=unique(tem_data$region_wl[tem_data$study==studyi])
  temi=tem_data[tem_data$study==studyi & tem_data$region_wl==regioni,]
  if(sum(temi$gender==3)>0){   # Need to drop male only studies
```

```
    temi=temi[temi$gender==3,]
    ybi=sum(temi$yb);yei=sum(temi$ye);yli=sum(temi$yl);ni=sum(temi$n)
    ageuidi=max(temi$ageuid);ageui=max(temi$ageu);ageli=min(temi$agel)
datai=data.frame(sname=studyi,n=ni,ye=yei,yl=yli,yb=ybi,agel=ageli,ageu=ageui,ageuid
=ageuidi,region=regioni)
    data3=rbind(data3,datai)
  }else if(sum(temi$gender==1)>0 & sum(temi$gender==2)>0){
    temi=temi[temi$gender==1 | temi$gender==2,]
    ybi=sum(temi$yb);yei=sum(temi$ye);yli=sum(temi$yl);ni=sum(temi$n)
    ageuidi=max(temi$ageuid);ageui=max(temi$ageu);ageli=min(temi$agel)
datai=data.frame(sname=studyi,n=ni,ye=yei,yl=yli,yb=ybi,agel=ageli,ageu=ageui,ageuid
=ageuidi,region=regioni)
    temi1=temi[temi$gender==1,];temi1=temi1[order(temi1$agegp),]
    temi2=temi[temi$gender==2,];temi2=temi2[order(temi2$agegp),]
    data3=rbind(data3,datai)
  }

  ## Ethnicity
  racei=unique(tem_data$race_wl[tem_data$study==studyi])
  for(j in 1:length(racei)){
    temi=tem_data[tem_data$study==studyi & tem_data$race_wl==racei[j],]
    if(sum(temi$gender==3)>0){   # Need to drop male only studies
      temi=temi[temi$gender==3,]
      ybi=sum(temi$yb);yei=sum(temi$ye);yli=sum(temi$yl);ni=sum(temi$n)
      ageuidi=max(temi$ageuid);ageui=max(temi$ageu);ageli=min(temi$agel)
datai=data.frame(sname=studyi,n=ni,ye=yei,yl=yli,yb=ybi,agel=ageli,ageu=ageui,ageuid
=ageuidi,race=racei[j])
      data4=rbind(data4,datai)
      check4=c(check4,0)
    }else if(sum(temi$gender==1)>0 & sum(temi$gender==2)>0){
      ybi=sum(temi$yb);yei=sum(temi$ye);yli=sum(temi$yl);ni=sum(temi$n)
      ageuidi=max(temi$ageuid);ageui=max(temi$ageu);ageli=min(temi$agel)
datai=data.frame(sname=studyi,n=ni,ye=yei,yl=yli,yb=ybi,agel=ageli,ageu=ageui,ageuid
=ageuidi,race=racei[j])
```

```
    temi1=temi[temi$gender==1,];temi1=temi1[order(temi1$agegp),]
    temi2=temi[temi$gender==2,];temi2=temi2[order(temi2$agegp),]
    data4=rbind(data4,datai)
   }
  } # j
} # i

## Create agedl and agedu variables to map age to (45, 85)
data2$agedl=data2$agel-45;data2$agedu=data2$ageu-85
data3$agedl=data3$agel-45;data3$agedu=data3$ageu-85
data4$agedl=data4$agel-45;data4$agedu=data4$ageu-85

### Step 2a) Building/Setting up model and save as text file in your R working directory
## Prevalence estimation
## Part a, i) By ethnicity (to use data4)
## Model for overall pooled prevalence – saved as "pooledS_map.txt"
model{
for (i in 1:N){
y[i]~dbin(p[i],n[i])
logit(p[i])<-u[i]
u[i]~dnorm(mu[i],tau)
mu[i]<-inprod(Z[i,],Zbeta[])+inprod(S[i,],Sbeta[])
}
# Non-informative gamma prior distribution specified for tau
tau~dgamma(0.01,0.01);sigma<-pow(tau,-1/2)
# Non-informative normal prior distribution for regression coefficients
for(i in 1:NZ){Zbeta[i]~dnorm(0,0.0001)}
for(i in 1:NS){Sbeta[i]~dnorm(0,Stau)}
# Non-informative gamma prior distribution specified for tau (between study variability)
Stau~dgamma(0.01,0.01);Ssigma<-pow(Stau,-1/2)

logit(P)<-Zbeta[1]
}
```

```
## Model for pooled prevalence by ethnicity – saved as "pooledXS_map.txt"
model{
for (i in 1:N){
y[i]~dbin(p[i],n[i])
logit(p[i])<-u[i]
u[i]~dnorm(mu[i],tau)
mu[i]<-inprod(Z[i,],Zbeta[])+inprod(S[i,],Sbeta[])+inprod(X[i,],Xbeta[])
}
# Non-informative gamma prior distribution specified for tau (residual variability)
tau~dgamma(0.01,0.01);sigma<-pow(tau,-1/2)
# Non-informative normal prior distribution for regression coefficients
for(i in 1:NZ){Zbeta[i]~dnorm(0,0.0001)}
for(i in 1:NS){Sbeta[i]~dnorm(0,Stau)}
# Non-informative gamma prior distribution specified for Stau & Xtau (between study &
between race variability)
Stau~dgamma(0.01,0.01);Ssigma<-pow(Stau,-1/2)
for(i in 1:NX){Xbeta[i]~dnorm(0,Xtau)}
Xtau~dgamma(0.01,0.01);Xsigma<-pow(Xtau,-1/2)

for(i in 1:NX){logit(P[i])<-Zbeta[1]+Xbeta[i]}
}
```

Part a, ii) By regions *(to use data3)*

```
## Model for overall pooled prevalence – saved as "pooled_map.txt"
model{
for (i in 1:N){
y[i]~dbin(p[i],n[i])
logit(p[i])<-u[i]
u[i]~dnorm(mu[i],tau)
mu[i]<-inprod(Z[i,],Zbeta[])
}
# Non-informative gamma prior distribution specified for tau
tau~dgamma(0.01,0.01);sigma<-pow(tau,-1/2)
# Non-informative normal prior distribution for regression coefficients
```

```
for(i in 1:NZ){Zbeta[i]~dnorm(0,0.0001)}

logit(P[1])<-Zbeta[1]
}

## Model for pooled prevalence by regions – saved as "pooledX_map.txt"
model{
for (i in 1:N){
y[i]~dbin(p[i],n[i])
logit(p[i])<-u[i]
u[i]~dnorm(mu[i],tau)
mu[i]<-inprod(Z[i,],Zbeta[])+inprod(X[i,],Xbeta[])
}
# Non-informative gamma prior distribution specified for tau (residual variability)
tau~dgamma(0.01,0.01);sigma<-pow(tau,-1/2)
# Non-informative normal prior distribution for regression coefficients
for(i in 1:NZ){Zbeta[i]~dnorm(0,0.0001)}
for(i in 1:NX){Xbeta[i]~dnorm(0,Xtau)}
# Non-informative gamma prior distribution specified for Xtau (between region
variability)
Xtau~dgamma(0.01,0.01);Xsigma<-pow(Xtau,-1/2)

for(i in 1:NX){logit(P[i])<-Zbeta[1]+Xbeta[i]}
}

### Step 2b) Execute HB model
## Part b, i) By ethnicity
data42=data4[data4$race!=5,]   # Drop "others" race data
set.seed(1213)
pools=list();pools_race=list()
for(i in 3:5){
  cat(paste("\n\n...",i,"...",sep=""))
  tem_data=data42[!(is.na(data42[,i])),]
  y=tem_data[,i];n=tem_data$n;N=nrow(tem_data);study<-tem_data$study
```

```
  map=cbind((tem_data$agedl-mean(tem_data$agedl))/sd(tem_data$agedl),
(tem_data$agedu-mean(tem_data$agedu))/sd(tem_data$agedu),tem_data$ageuid)

  Z=cbind(1,map);NZ=ncol(Z);S<-dummy(study);NS<-ncol(S)
  dat<-list("n","y","N","Z","NZ","S","NS")
  parameters<-c("p","P")
  inits<-function(){list(tau=1,Stau=1)}
  pools[[i-2]]<-jags.parallel(dat, inits, parameters,
model.file = "pooledS_map.txt",n.chains=2,n.iter=50000,n.burnin=5000,DIC=F,
digits = 5,working.directory=getwd())

  X=dummy(tem_data$race);NX=ncol(X)
  dat<-list("n","y","N","Z","NZ","S","NS","X","NX")
  parameters<-c("P")
  inits<-function(){list(tau=1,Stau=1,Xtau=1)}
  pools_race[[i-2]]<-jags.parallel(dat, inits, parameters,
model.file = "pooledXS_map.txt",n.chains=2,n.iter=80000,n.burnin=8000,DIC=F,digits
= 5,working.directory=getwd())
}

## By ethnicity
# Display overall pooled early amd prevalence
pools[[1]]$BUGSoutput$summary["P", c("2.5%","50%","97.5%")]*100
# Display overall pooled late amd prevalence
pools[[2]]$BUGSoutput$summary["P", c("2.5%","50%","97.5%")]*100
# Display overall pooled any amd prevalence
pools[[3]]$BUGSoutput$summary["P", c("2.5%","50%","97.5%")]*100

# Display pooled early amd prevalence by race
pools_race[[1]]$BUGSoutput$summary[, c("2.5%","50%","97.5%")]*100
# Display overall pooled late amd prevalence by race
pools_race[[2]]$BUGSoutput$summary[, c("2.5%","50%","97.5%")]*100
# Display overall pooled any amd prevalence by race
```

```
pools_race[[3]]$BUGSoutput$summary[, c("2.5%","50%","97.5%")]*100

## Part b, i) By regions
data32=data3
set.seed(1213)
pools=list();pools_region=list()
for(i in 3:5){
  cat(paste("\n\n...",i,"...",sep=""))
  tem_data=data32[!(is.na(data32[,i])),]
  y=tem_data[,i];n=tem_data$n;N=nrow(tem_data)

  map=cbind((tem_data$agedl-mean(tem_data$agedl))/sd(tem_data$agedl),
(tem_data$agedu-mean(tem_data$agedu))/sd(tem_data$agedu),tem_data$ageuid)

  Z=cbind(1,map);NZ=ncol(Z)
  dat<-list("n","y","N","Z","NZ")
  parameters<-c("p","P")
  inits<-function(){list(tau=1)}
  pools[[i-2]]<-jags.parallel(dat, inits, parameters, model.file = "pooled_map.txt",
n.chains=2,n.iter=50000,n.burnin=5000,DIC=F,digits = 5,working.directory=getwd())

  X=dummy(tem_data$region);NX=ncol(X)
  dat<-list("n","y","N","Z","NZ","X","NX")
  parameters<-c("P")
  inits<-function(){list(tau=1,Xtau=1)}
  pools_region[[i-2]]<-jags.parallel(dat, inits, parameters,
 model.file = "pooledX_map.txt",n.chains=2,n.iter=80000,n.burnin=8000,DIC=F,digits =
5,working.directory=getwd())
}
# Display overall pooled early amd prevalence
pools[[1]]$BUGSoutput$summary["P", c("2.5%","50%","97.5%")]*100
# Display overall pooled late amd prevalence
pools[[2]]$BUGSoutput$summary["P", c("2.5%","50%","97.5%")]*100
# Display overall pooled any amd prevalence
```

```
pools[[3]]$BUGSoutput$summary["P", c("2.5%","50%","97.5%")]*100

# Display pooled early amd prevalence by region
pools_region[[1]]$BUGSoutput$summary[, c("2.5%","50%","97.5%")]*100
# Display overall pooled late amd prevalence by region
pools_region[[2]]$BUGSoutput$summary[, c("2.5%","50%","97.5%")]*100
# Display overall pooled any amd prevalence by region
pools_region[[3]]$BUGSoutput$summary[, c("2.5%","50%","97.5%")]*100
```

Step 3, part b: Projection of Number of People with AMD by Regions

```
## Region-specific estimated prevalence rates obtained in part a) were multiplied to the
population projection data in World Population Prospects of the United Nations.

projs=read.csv("WPP2010.csv",header=T)
years=seq(2011,2050)
regions=c("AFRICA","ASIA","EUROPE","LATIN AMERICA AND THE
CARIBBEAN","NORTHERN AMERICA","OCEANIA","WORLD")

output_mid=matrix(0,ncol=length(years),nrow=7)
output_low=matrix(0,ncol=length(years),nrow=7)
output_upper=matrix(0,ncol=length(years),nrow=7)

for(j in 1:6){
  for(i in 1:length(years)){
output_low[j,i]=sum(pools_region[[3]]$BUGSoutput$summary[j,c("2.5%")]*projs[whic
h(projs$year==years[i] & projs$region==regions[j]),c(8:14,16)])
output_mid[j,i]=sum(pools_region[[3]]$BUGSoutput$summary[j,c("50%")]*projs[which
(projs$year==years[i] & projs$region==regions[j]),c(8:14,16)])
output_upper[j,i]=sum(pools_region[[3]]$BUGSoutput$summary[j,c("97.5%")]*projs[w
hich(projs$year==years[i] & projs$region==regions[j]),c(8:14,16)])
  } #i
} #j
j=7
for(i in 1:length(years)){
```

```
output_low[j,i]=sum(pools[[3]]$BUGSoutput$summary["P",c("2.5%")]*projs[which(pro
js$year==years[i] & projs$region==regions[j]),c(8:14,16)])
output_mid[j,i]=sum(pools [[3]]$BUGSoutput$summary["P",c("50%")]*
projs[which(projs$year==years[i] & projs$region==regions[j]),c(8:14,16)])
output_upper[j,i]=sum(pools [[3]]$BUGSoutput$summary["P",c("97.5%")]*
projs[which(projs$year==years[i] & projs$region==regions[j]),c(8:14,16)])
  } #i
} #j

## Per Million
output_mid=output_mid/1000
output_low=output_low/1000
output_upper=output_upper/1000

## To repeat for early and late AMD projections, i.e. "[[1]]" for early, "[[2]]" for late
```

Step 4, part c: Bayesian hypothesis testing to examine effects

Step 4a) Building/Setting up model and save as text file in your R working directory

By ethnicity *(to use data4)*

```
## Model – saved as "VSS.txt"
model{
for (i in 1:N){
y[i]~dbin(p[i],n[i])
logit(p[i])<-u[i]
u[i]~dnorm(gmu[i],tau)
gmu[i]<-inprod(S[i,],Sbeta[])+inprod(X[i,],gbeta[])
}
tau~dgamma(0.001,0.001);sigma<-pow(tau,-1/2)

for(i in 1:NS){Sbeta[i]~dnorm(0,Stau)}
Stau~dgamma(0.001,0.001);Ssigma<-pow(Stau,-1/2)

for(i in 1:(NX+1)){gbeta[i]<-g[i]*Xbeta[i]}
```

```
g[1]<-1;for(i in 2:(NX+1)){g[i]~dbern(0.5)}

Xbeta[1:(NX+1)]~dmnorm(mb[1:(NX+1)],T[1:(NX+1),1:(NX+1)])
#Mu for Xbeta
for(i in 1:(NX+1)){mb[i]<- (1-g[i])*prop.mean[i]}  # g[] is the variable selection variable
#Tau for Xbeta
for(i in 1:(NX+1)){
for(j in 1:(NX+1)){
T[i,j]<- g[i]*g[j]*Tt[i,j]+(1-g[i]*g[j])*equals(i,j)*pow(prop.sd[i],-2)
}}

for(j in 1:NX){mindex[j]<-pow(2,j)}
mm<-g[1]+inprod(g[2:(NX+1)],mindex[])
}
```

Step 4b) Execute HB model

```
## Execute model in similar manner as Step 2b above
inits<-function(){list(tau=1,Stau=1)}
parameters<-c("Xbeta","sigma","g","mm")
vs<-jags.parallel(dat, inits, parameters, model.file =
"VSS.txt",n.chains=2,n.iter=100000,n.burnin=10000,DIC=F,digits = 5,
working.directory=getwd())

## Bayesian hypothesis testing can be similarly done for region, gender and publication
year.
```

R Programming Codes for Chapter 6

Steps to perform "one-stage" HB association analysis:

a) Organize data spreadsheet and read into R

b) Perform association analysis:

i. Build the "one-stage" HB model

ii. Execute the "one-stage" HB model

(note that the validity of instrument should be determined before association analysis)

Step 1: Data input for R

Data spreadsheet should be arranged in the below manner and saved as .csv file type, e.g. "eg_data.csv".

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	sno	age_rec	gender	bmi	smks_curr	read	write	vfstair_rev	vfsign_rev	vfrecog_rev	vftv_rev	vfcook_rev	vfgame_rev	vfpaper_rev	vftoto_rev	vftelbk_rev
2	1	51	1	21.90311	1	1	1	3	3	4	4	NA	NA	4	NA	4
3	2	66	0	25.12539	0	1	1	3	2	2	2	4	NA	NA	NA	NA
4	3	40	0	17.69531	0	1	1	4	4	4	4	4	4	4	4	4
5	4	71	1	24.20526	0	1	1	4	4	4	4	4	4	4	4	4
6	5	41	0	23.27571	0	1	1	4	4	4	4	4	4	4	4	4
7	6	62	0	26.57778	0	1	1	4	4	4	4	4	NA	4	4	4
8	7	50	1	24.48617	1	1	1	4	4	4	4	4	4	4	4	4
9	8	46	0	27.44982	0	1	1	4	4	4	4	4	4	4	NA	4
10	9	42	1	25.62342	0	1	1	4	4	4	4	4	NA	3	3	3
11	10	51	1	21.93684	1	1	1	4	4	4	4	NA	NA	4	4	4
12	11	46	1	27.39592	0	1	1	4	4	4	4	4	4	4	4	4

Data Legend: sno = patient number; age_rec = age; gender coded as 0 for male, 1 for female; bmi = body mass index; smks_curr coded as 1 for current smoker and 0 for past or non-smoker; read coded as 1 for can read and 0 for can't read; write coded as 1 for can write and 0 for can't write; vfstair_rev to vftelbk_rev are the 9 items in modified VF-9 questionnaire, each item graded on level of difficulty on scale of 1 to 4 where 4 = a little, 3 = moderate, 2 = a great deal, 1 = unable to do activity.

Step 2: R programming codes for Association analysis

Step 2a) Building/Setting up model and save as "model.txt" in your R working directory

```
model {
for (i in 1:N) {
```

```
for (k in 1:K) {
for (c in 1:C) { q[i,k,c]<-exp(1.7*(c-1)*(theta[i]-eta[k])-sum(gamma[1:c])) }   ##
Andrich model
for (c in 1:C) { p[i,k,c]<-q[i,k,c]/sum(q[i,k,1:C]) }
Y[i,k]~dcat(p[i,k,1:C])
}
mutheta[i]<-inprod(X[i,],beta[])   ## Regression model
theta[i]~dnorm(mutheta[i],tau)
}
## Difficulty or location parameter
for (k in 1:(K-1)) { eta[k]~dnorm(0,etau) }
etau~dgamma(0.01,0.01);esigma<-pow(etau,-1/2)
eta[K]<-(-sum(eta[1:(K-1)]))
## Threshold
gamma[1]<-0
for (c in 2:C) { gamma[c]~dnorm(0,1) }
## Beta and Sigma for Theta
for (i in 1:Q) { beta[i]~dnorm(0,0.01) }
tau~dgamma(0.01,0.01);sigma<-pow(tau,-1/2)
}
```

Step 2b) Execute "one-stage" HB model

```
## Load library
library(R2jags)
library(coda)
library(dummies)

N=3280  # specify the sample size of data
K=9  # specify number of items in instrument/questionnaire
C=4  ## specify number of categories in each item

set.seed(1213)  # set seed number
gamma=rnorm(C-1);gamma=c(0,gamma)
```

```
data_gamma=NULL
data_eta=NULL
data_beta=NULL

## Analysis to investigate factor “read” (creating tem_data to exclude “write” variable)
tem_data=eg_data[,c(2:6,8:16)]
indexy=apply(tem_data,1,function(x){sum(is.na(x))})
tem_data=tem_data[indexy==0,]

###  ONE - Stage  ###
X=tem_data[,1:12]  # X: risk factors
Y=tem_data[,13:21]  # Y: instrument items
colnames(X)  # display variable names
cats=c(1:2,4:15)  # variables that are categorical

tem_X=NULL;name_X=NULL
for(i in 1:ncol(X)){
 if(i %in% cats){
   tem_X=cbind(tem_X,dummy(X[,i])[,-1])
   name_X=c(name_X,paste(colnames(X)[i],2:length(unique(X[,i])),sep=""))
 }else{
   tem_X=cbind(tem_X,X[,i])
   name_X=c(name_X,colnames(X)[i])
 }
}
colnames(tem_X)=name_X;name_X

X=tem_X
X=cbind(1,X)
Q=ncol(X);N=nrow(X)
dat=list("N","K","C","Y","X","Q")
inits=function(){list(etau=1,tau=1,beta=rep(0,Q))}
parameters=c("eta","gamma","beta")
```

```
model=jags.parallel(dat,inits,parameters,model.file="Andrich_X.txt",n.chains=2,n.iter=3
00,n.burnin=30,DIC=F,digits=5,working.directory=getwd())

data_beta=model$BUGSoutput$summary[paste("beta[",2:Q,"]",sep=""),c("2.5%","50%",
"97.5%","Rhat")]
row.names(data_beta)=colnames(X)[-1]

sigs=!(data_beta[,1]<0 & data_beta[,3]>0)
(colnames(X)[-1])[sigs]
data_beta[sigs,]

## Output estimations of association effects (of latent trait) and its 95% credible intervals
into Excel
write.csv(data_beta,paste("Date_beta.csv"))
```

APPENDIX 2: Additional Tables and Figures

Chapter 3

Supplementary Table 3.1 Collapsed contingency table between LOCS III and Wisconsin system for nuclear opalescence, cortical and posterior subcapsular cataract (PSC).

LOCS III	**Wisconsin system**				
Nuclear					
	1	**2**	**3**	**4**	**5**
0.1-2.9	64	1038	635	26	0
3.0-3.9	34	867	1431	146	0
4.0-4.9	4	93	559	493	5
5.0-6.4	0	2	34	281	38
6.5-6.9	0	0	0	13	26
Cortical					
	0-4	**5-44**	**45-74**	**75-79**	**80-100**
0.1-1.4	3750	134	0	0	0
1.5-2.4	307	280	2	0	0
2.5-3.9	89	764	17	0	3
4.0-5.4	5	143	77	1	6
5.5-5.9	0	3	5	0	9
PSC					
	0-4	**5-29**	**30-64**	**65-69**	**70-100**
0.1-2.9	5246	100	0	0	0
3.0-4.4	20	98	27	0	0
4.5-4.9	0	2	9	1	0
5.0-5.4	1	12	14	0	8
5.5-5.9	0	3	12	3	3

LOCS III: Lens Opacity Classification III; Wisconsin system: Wisconsin Cataract Grading System.

Chapter 4

Supplementary Table 4.1 Data for Meta-analysis for prevalence of tuberculous uveitis

Year	Author	Country	Total no of patients	No. of TBU	Prevalence of TBU
2008	Kazokoglu et al. [1]	Turkey	761	3	0.3%
2008	Pathanapithoon et al. [2]	Thailand	200	3	2.2%
2007	Khairallah et al. [3]	Tunisia	472	5	1.1%
2007	Rathinam and Namperumalsamy[4]	India	8759	488	5.6%
2005	Yang et al. [5]	China	1752	13	0.7%
2005	Sengun et al. [6]	Turkey	300	4	1.3%
2004	Soheilian et al. [7]	Iran	544	8	1.5%
2004	Singh et al. [8]	India	1233	125	10.1%
2003	Wakabayashi et al. [9]	Japan	189	13	6.9%
2002	Islam and Tabbara[10]	Saudi Arabia	200	21	10.5%
2002	Morimura[11]	Japan	126	10	7.9%
2001	Mercanti et al. [12]	Italy	655	46	7.02%
1998	Kaimbo wa Kimbo et al. [13]	Congo	336	30	6%
1997	Kotake et al. [14]	Japan	551	1	0.2%
1997	Merrill et al. [15]	USA	385	2	0.5%
1996	Rodriguez et al. [16]	USA	1273	8	0.06%
1996	Thean et al. [17]	UK	712	2	0.28%
1995	Das et al. [18]	India	465	3	0.6%
1993	Smit et al.[19]	Netherland	750	20	2.7%
1992	Rothova et al. [20]	Netherland	865	12	1.4%
1991	Weiner and BenEzra[21]	Israel	400	3	0.7%
1990	Palmares et al. [22]	Portugal	450	10	2.2%
1987	Henderly et al. [23]	USA	600	1	0.2%

TBU: Tuberculosis-associated uveitis

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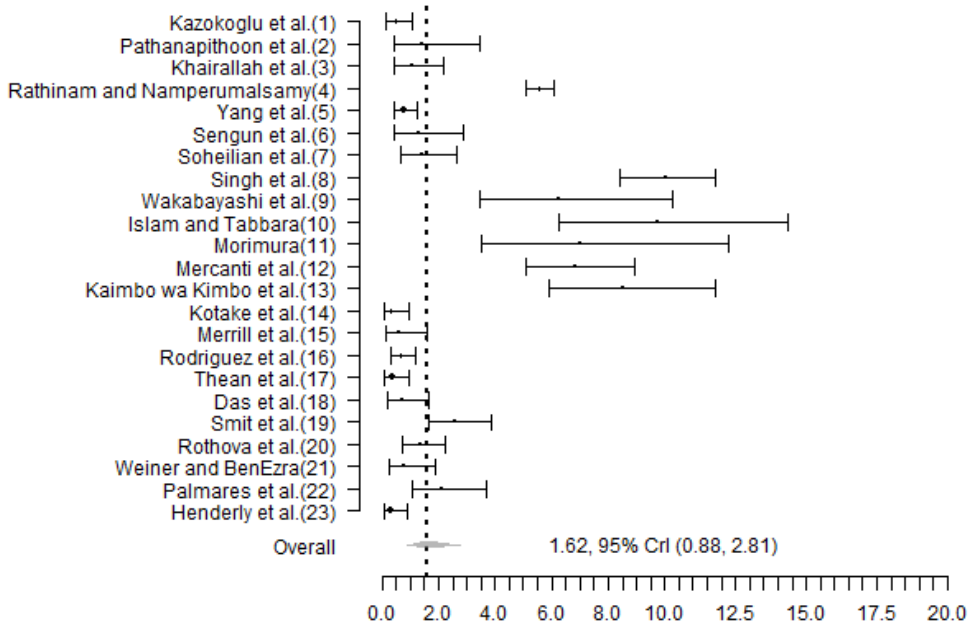
Supplementary Figure 4.1 Meta-analysis for prevalence of tuberculous uveitis



Chapter 5

Supplementary Table 5.1 Global Population-Based Studies included in Meta-analysis

* '-' represents prevalence data were not published and thus unavailable.

† (1), International classification and grading system for age-related maculopathy and age-related macular degeneration; (2), Wisconsin Age-related Maculopathy Grading System; and (3), Rotterdam Staging System.

World Region	Study/ Location	Study Abbreviation	Year	Age Group	Early AMD*	Late AMD*	Any AMD*	Response Rate	Sample Size	AMD Grading†	Ethnic Ancestry
Asia	Andhra Pradesh Eye Disease Study[1] (Andhra Pradesh, India)	APEDS	2005	40-70+	-	-	71	86.7%	3723	(1)	Asian
	Beijing Eye Study (Beijing, China)[2]	Beijing	2006	40-75+	63	9	-	83.4%	4376	(2)	Asian
	Funagata Study (Funagata, Japan)[3]	Funagata	2008	35-75+	58	8	-	53.3%	1625	(1), (2)	Asian
	Hisayama Study (Fukuoka, Japan)[4]	Hisayama	2001	50-80+	178	13	-	60.7%	1486	(1), (2)	Asian
	INDEYE Study (Haryana, North India)[5]	INDEYE	2007	50-80	77	15	-	87.6%	1260	(2)	Asian
	Shihpai Eye Study (Taipei, Taiwan)[6]	Shihpai	2008	50-80+	97	20	-	66.6%	1361	(2)	Asian
	Singapore Malay Eye Study (Singapore)[7]	SiMES	2008	40-80	160	23	-	78.7%	3280	(2)	Asian
	Handan Eye Study (Hebei Province, China)[8]	Handan	2011	30-70+	241	4	-	90.3%	6830	(2)	Asian
	Central India Eye and Medical Study[9] (Nagpur, India)	CIEMS	2011	30-80+	215	7	-	80.1%	4711	(2)	Asian
	Thailand (7 regions: central, north, northeast, south, east, west, and Bangkok metropolitan area)[10]	Thailand	2011	50-80+	294	27	-	66.7%	21711	(1)	Asian
	Singapore Prospective Study Program (Singapore)[11]	SP2	2012	40-80+	-	-	211	72.0%	5157	(2)	Asian
Europe	EUREYE study (Norway, Estonia, United Kingdom, France, Italy, Greece, Spain)[12]	EUREYE	2006	65-75+	-	-	165	45.0%	4753	(1), (3)	European ancestry

	Reykjavik Eye Study (Reykjavik, Iceland)[13]	RS	2003	50-80+	338	32		75.8%	1045	(1), (2)	European ancestry
	Crete, Greece[14]	Crete	1999	40-80+	76	15	-	70.6%	777	(2), (3)	European ancestry
	Oslo Macular Study (Oslo, Norway)[15]	Oslo	2006	51-90+	197	13	-	59.6%	770	(1)	European ancestry
	Oulu Country, Finland[16]	Oulu	1995	70-90+	160	39	-	89%	500	(1)	European ancestry
	Salandra, Southern Italy[17]	Salandra	1997	60-75+	-	-	147	63.5%	366	(1)	European ancestry
	Copenhagen City Eye Study (Copenhagen, Denmark)[18]	Copenhagen	1995	60-80+	151	112	-	75%	946	(2)	European ancestry
	Tromso Eye Study (Tromso, Norway)[19]	Tromso	2012	65-87+	892	92	-	87%	3025	(1)	European ancestry
	Spanish Eyes Epidemiological Study (Spain)[20]	SEE	2010	65-80+	225	10	-	70.9%	2132	(1)	European ancestry
	Speedwell Eye Study (Bristol, UK)[21]	Speedwell	2011	65-75+	86	8	-	68.9%	949	(2)	European ancestry
Latin America and the Caribbean	Londrina, Brazil[22]	Londrina	2008	60-80+	66	6		80.5%	483	(1)	Asian
	Barbados Eye Study (Barbados, West Indies)[23]	BES	1995	40-80+	561	19	-	83.4%	3444	(1)	African ancestry
Africa	Nakura, Kenya[24]	Kenya	2013	50-80+	366	38	-	88.1%	4414	(1)	African ancestry
Northern America	Greenland Inuit Study (Greenland)[25]	GIES	2008	60-80+	328	61	-	74.8%	695	(2)	Others
	National Health and Nutrition Examination Survey III (USA)[26]	NHANESIII	1999	40-60+	832	18	-	79.1%	8270	(2)	European/ African ancestry Hispanics
	Atherosclerosis Risk in Communities Study (North Carolina, Minneapolis, Maryland, USA)[27]	ARIC	1999	48-72+	555	16	-	55.5%	11532	(2)	European/ African ancestry
	Beaver Dam Eye Study (Wisconsin, USA)[28]	BDES	1992	43-75+	773	79	-	83.1%	4771	(2)	European ancestry

	Baltimore Eye Survey (East Baltimore, US)[29]	Baltimore	1999	40-80+	1133	63	-	73.0%	5308	(1)	European/ African ancestry
	Cardiovascular Health Study (Pennsylvania, North Carolina, California and Maryland, USA)[30]	CHS	2002	69-97	366	30	-	57.3	2361	(2)	European/ African ancestry
	Los Angeles Latino Eye Study (California, USA)[31]	LALES	2004	40-80+	551	25	-	88.0%	6870	(2)	Hispanic
	Multi-ethnic Study of Atherosclerosis (Maryland, Illinois, North Carolina, California, New York and Minnesota, USA)[32]	MESA	2006	45-85+	236	27	-	59.5%	6167	(2)	European/ African ancestry Hispanic/ Asian
	Proyecto VER (Arizona, USA)[33]	VER	2005	50-80+	676	15	-	72%	4774	(2)	Hispanic
	Chesapeake Bay Watermen (Maryland, USA)[34]	Chesapeake Bay	1989	30-79	-	8	-	70%	755	(2)	European ancestry
	Vision Keepers Study (Oklahoma, USA)[35]	VKS	2011	48-82+	339	21	-	66.7%	1019	(2)	Others (Indian)
	National Health and Nutrition Examination Survey (USA)[36]	NHANES05-08	2011	40-60+	375	59	-	95.9%	5553	(2)	European/ African ancestry /Hispanic
	Beaver Dam Offspring Study (Wisconsin, USA)[37]	BOSS	2010	21-84+	95	0	-	66.2%	3285	(2)	European ancestry
Oceania	Blue Mountains Eye Study (Sydney, Australia)[38]	BMES	1995	49-85+	423	101	-	82.4%	3654	(2)	European ancestry
	Visual Impairment Project (Melbourne, Australia)[39]	VIP	1999	40-90+	865	76	-	82.0%	5147	(2)	European ancestry

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Supplementary Table 5.2 Sensitivity Analysis

Data are % (95% credible intervals)

	Any AMD	Early AMD	Late AMD
All (39 studies)	8.69 (4.26, 17.40)	8.01 (3.95, 15.49)	0.37 (0.18, 0.77)
≥50% (38 studies)	8.69 (4.26, 17.40)	8.01 (3.95, 15.49)	0.36 (0.18, 0.73)

Supplementary Table 5.3 Bayesian Hypothesis Testing of Gender, Ethnicity, Region and Publication Year Effect on the Prevalence of AMD subtypes

*Bayes factor describes level of statistical evidence: negative evidence (BF <1), weak (BF 1-3), substantial (BF 3-10), strong (BF 10-30), very strong (BF 30-100), and decisive (BF > 100). BFs of >1 are in bold.

	Bayes Factor*		
	Early AMD	Late AMD	Any AMD
Gender			
Male vs. Female	0.03	0.04	0.03
Ethnicity groups			
European vs. African	**12.16**	**3.74**	**31.26**
European vs. Asian	**3.94**	0.20	**4.31**
European vs. Hispanic	0.06	0.34	0.08
African vs. Asian	0.15	0.41	0.10
African vs. Hispanic	0.24	0.11	0.19
Asian vs. Hispanic	0.33	0.18	0.26
Geographic regions			
Africa vs. Asia	0.24	0.17	0.20
Africa vs. Europe	0.28	0.20	0.30
Africa vs. Latin America & Caribbean	0.44	0.62	0.20
Africa vs. Northern America	0.14	0.16	0.15
Africa vs. Oceania	0.14	0.29	0.19
Asia vs. Europe	**2.32**	0.80	**7.55**
Asia vs. Latin America & Caribbean	0.52	0.12	0.76
Asia vs. Northern America	**3.02**	0.14	**3.75**
Asia vs. Oceania	0.24	0.62	0.14
Europe vs. Latin America & Caribbean	0.24	0.36	0.24
Europe vs. Northern America	0.12	0.26	0.16
Europe vs. Oceania	0.19	0.17	0.20
Latin America & Caribbean vs. Northern America	0.13	0.18	0.11
Latin America & Caribbean vs. Oceania	0.12	0.91	0.05
Northern America vs. Oceania	0.15	0.21	0.15
Publication Year			
1989 to 2013	0.12	0.47	0.12

Supplementary Table 5.4 Heterogeneity Analysis of Ethnicity and Geographical Regions Effects

Data presented as mean (95% CrI) of percentage of total variability; posterior mean is used instead of median to ensure the sum of total between and within study equal to one

*Variability between ethnic groups in the same study

Percentage of total variability	AMD		
	Early	Late	Any
Ethnicity			
Total between-study	99.5 (99.2, 99.8)	95.2 (91.6, 98.5)	99.5 (99.2, 99.8)
Ethnicity covariate (within ethnicity)	18.5 (1.7, 68.8)	23.1 (1.1, 73.7)	21.0 (2.2, 70.9)
Between ethnicity*	74.9 (23.3, 95.5)	32.6 (0.9, 81.1)	69.7 (15.4, 94.1)
Residual	6.2 (0.7, 25.6)	39.5 (2.0, 86.6)	8.8 (0.8, 37.5)
Total within-study	0.5 (0.2, 0.8)	4.8 (1.5, 8.4)	0.5 (0.2, 0.8)
Region			
Total between-study	99.7 (99.5, 99.9)	96.6 (94.3, 98.4)	99.7 (99.5, 99.9)
Region covariate (within region)	27.3 (1.4, 72.9)	11.6 (0.6, 50.4)	30.0 (2.2, 74.8)
Residual	72.4 (27.0, 98.2)	85.0 (47.0, 96.7)	69.7 (25.1, 97.5)
Total within-study	0.3 (0.1, 0.5)	3.4 (1.6, 5.7)	0.3 (0.1, 0.5)

Supplementary Table 5.5 Age-group Specific Prevalence Estimates of Any, Early and Late AMD by Ethnic Ancestry Groups

Data in parentheses are 95% credible intervals.

Age Group	Early AMD				
	African	Asian	European	Hispanic	Total
45-49	3.73 (2.25, 6.04)	2.89 (1.67, 4.80)	3.67 (2.28, 5.76)	4.63 (2.82, 7.70)	3.53 (2.34, 5.25)
50-59	5.10 (3.24, 7.83)	4.29 (2.60, 6.98)	5.86 (3.83, 8.83)	6.87 (4.29, 10.77)	5.39 (3.64, 7.93)
60-69	7.45 (4.84, 11.14)	7.01 (4.36, 11.12)	10.40 (7.06, 14.95)	11.01 (7.05, 16.93)	9.04 (6.20, 12.92)
70-79	10.73 (6.93, 16.45)	11.27 (6.97, 17.46)	17.68 (12.32, 24.42)	17.31 (10.77, 26.45)	14.71 (10.18, 20.83)
80-84	13.88 (8.62, 21.52)	15.44 (9.43, 23.56)	24.91 (17.58, 33.65)	23.20 (14.22, 35.59)	20.26 (14.10, 28.33)
Total	7.06 (3.41, 13.15)	6.81 (3.14, 13.94)	11.19 (5.63, 20.39)	9.87 (4.97, 18.90)	8.01 (3.95, 15.49)
			Late AMD		
45-49	0.13 (0.06, 0.25)	0.06 (0.03, 0.11)	0.03 (0.02, 0.06)	0.04 (0.02, 0.09)	0.05 (0.03, 0.08)
50-59	0.20 (0.10, 0.34)	0.14 (0.08, 0.24)	0.10 (0.06, 0.16)	0.10 (0.05, 0.20)	0.13 (0.08, 0.18)
60-69	0.35 (0.20, 0.55)	0.41 (0.27, 0.63)	0.41 (0.27, 0.60)	0.35 (0.19, 0.58)	0.42 (0.30, 0.57)
70-79	0.61 (0.31, 1.08)	1.26 (0.79, 1.96)	1.71 (1.17, 2.44)	1.19 (0.61, 2.12)	1.41 (1.00, 1.92)
80-84	0.90 (0.42, 1.84)	2.69 (1.56, 4.61)	4.56 (2.96, 6.73)	2.75 (1.23, 5.69)	3.25 (2.21, 4.60)
Total	0.28 (0.12, 0.63)	0.37 (0.17, 0.85)	0.50 (0.26, 1.08)	0.32 (0.13, 0.75)	0.37 (0.18, 0.77)
			Any AMD		
45-49	4.06 (2.39, 6.47)	3.21 (1.98, 5.20)	3.10 (1.99, 4.79)	4.80 (2.90, 7.81)	3.49 (2.32, 5.23)
50-59	5.65 (3.58, 8.35)	4.92 (3.14, 7.60)	5.66 (3.74, 8.41)	7.28 (4.62, 11.28)	5.66 (3.83, 8.26)
60-69	8.41 (5.53, 12.21)	8.28 (5.35, 12.27)	11.63 (7.95, 16.36)	12.08 (7.73, 18.01)	10.19 (7.10, 14.29)
70-79	12.35 (8.12, 18.14)	13.61 (8.96, 19.73)	22.50 (15.83, 29.93)	19.24 (12.37, 28.71)	17.61 (12.53, 23.87)
80-84	16.06 (10.15, 24.09)	18.87 (12.27, 27.22)	33.57 (24.17, 42.86)	25.84 (16.25, 38.64)	24.96 (18.01, 33.25)
Total	7.53 (3.80, 14.89)	7.38 (3.40, 14.46)	12.33 (6.46, 22.75)	10.43 (5.27, 20.01)	8.69 (4.26, 17.40)

Supplementary Table 5.6 Age-group Specific Prevalence Estimates of Early, Late and Any AMD by Geographic Regions

Data in parentheses are 95% credible intervals.

Age Group	Africa	Asia	Europe	Latin America & Caribbean	Northern America	Oceania	Total
				Early AMD			
45-49	3.92 (1.08, 14.22)	2.29 (1.16, 4.74)	6.47 (2.86, 14.81)	8.14 (2.51, 26.63)	4.93 (2.82, 8.93)	3.32 (1.20, 9.18)	4.18 (2.77, 6.51)
50-59	6.14 (1.78, 19.48)	3.37 (1.71, 6.89)	9.81 (4.65, 20.40)	9.84 (3.15, 29.22)	7.30 (4.35, 12.59)	5.57 (2.06, 14.25)	6.26 (4.24, 9.51)
60-69	10.53 (3.32, 30.42)	5.47 (2.83, 10.76)	16.00 (8.18, 28.98)	12.27 (4.15, 33.90)	11.88 (7.32, 19.33)	10.46 (3.98, 23.79)	10.31 (6.96, 15.22)
70-79	17.43 (5.93, 43.78)	8.75 (4.49, 16.85)	24.99 (13.63, 40.77)	15.46 (5.30, 41.51)	18.65 (11.65, 29.19)	18.58 (7.57, 37.90)	16.45 (11.29, 23.63)
80-84	24.04 (8.38, 55.42)	12.01 (6.16, 22.94)	33.19 (18.65, 51.17)	18.14 (5.99, 45.71)	24.92 (15.99, 37.83)	26.60 (11.46, 49.87)	22.29 (15.41, 31.24)
Total	11.18 (3.41, 32.28)	6.32 (2.58, 15.60)	14.43 (6.48, 31.59)	13.58 (4.37, 42.75)	12.79 (6.83, 23.52)	12.71 (4.00, 35.77)	11.33 (5.93, 20.87)
				Late AMD			
45-49	0.17 (0.05, 0.61)	0.07 (0.03, 0.14)	0.03 (0.01, 0.08)	0.36 (0.11, 1.11)	0.06 (0.03, 0.11)	0.03 (0.01, 0.07)	0.06 (0.04, 0.10)
50-59	0.28 (0.12, 0.76)	0.16 (0.09, 0.28)	0.10 (0.05, 0.22)	0.44 (0.18, 1.01)	0.15 (0.09, 0.26)	0.09 (0.04, 0.19)	0.15 (0.10, 0.23)
60-69	0.54 (0.28, 1.12)	0.44 (0.27, 0.68)	0.45 (0.27, 0.75)	0.56 (0.28, 1.11)	0.47 (0.30, 0.74)	0.43 (0.23, 0.83)	0.49 (0.35, 0.68)
70-79	1.04 (0.50, 2.26)	1.20 (0.69, 1.87)	1.95 (1.18, 3.15)	0.71 (0.32, 1.53)	1.46 (0.89, 2.30)	2.01 (1.08, 4.02)	1.56 (1.07, 2.17)
80-84	1.62 (0.63, 4.19)	2.41 (1.29, 4.19)	5.33 (3.07, 9.18)	0.85 (0.31, 2.25)	3.21 (1.82, 5.35)	5.76 (2.88, 11.82)	3.44 (2.24, 4.98)
Total	0.65 (0.24, 1.82)	0.55 (0.24, 1.23)	0.75 (0.32, 1.81)	0.64 (0.23, 1.79)	0.67 (0.32, 1.37)	0.68 (0.27, 1.97)	0.64 (0.32, 1.27)
				Any AMD			
45-49	4.28 (1.17, 14.42)	2.38 (1.29, 4.76)	5.47 (2.45, 11.62)	9.32 (3.39, 26.18)	5.05 (2.84, 9.14)	2.88 (1.06, 7.83)	4.17 (2.71, 6.27)
50-59	6.81 (2.09, 20.53)	3.59 (1.99, 7.02)	9.64 (4.74, 18.56)	11.01 (4.36, 27.28)	8.02 (4.68, 13.78)	5.45 (2.16, 14.00)	6.65 (4.43, 9.68)
60-69	11.90 (3.95, 30.70)	5.88 (3.29, 11.34)	18.48 (10.21, 32.06)	13.23 (5.69, 30.38)	13.88 (8.30, 22.40)	11.62 (4.99, 27.47)	11.61 (7.99, 16.30)

70-79	19.61 (6.96, 44.58)	9.59 (5.35, 17.78)	32.52 (19.77, 49.89)	15.88 (6.76, 35.15)	23.05 (14.10, 34.95)	23.06 (10.46, 46.42)	19.55 (13.75, 26.36)
80-84	27.14 (9.49, 56.37)	13.25 (7.32, 24.25)	45.33 (28.95, 63.31)	17.93 (7.44, 40.87)	31.59 (19.69, 45.65)	34.86 (17.31, 60.89)	27.17 (19.46, 35.82)
Total	11.93 (3.42, 32.48)	6.86 (2.95, 15.61)	18.25 (8.18, 35.90)	12.94 (4.55, 33.30)	14.29 (7.39, 25.28)	13.97 (4.58, 37.23)	12.34 (5.99, 22.78)

Supplementary Table 5.7 Projection of Number of People with Early, Late and Any AMD by Regions

97.5% Upper bound = Upper limit of 95% Credible Interval; 2.5% Lower bound = Lower limit of 95% Credible Interval

Year	2014	2016	2018	2020	2022	2024	2026	2028	2030	2032	2034	2036	2038	2040
							Early AMD (millions)							
97.5% Upper bound														
Africa	39.72	42.14	44.73	47.67	50.69	54.10	57.81	61.76	66.15	70.56	75.40	80.42	85.60	91.30
Asia	102.04	108.39	114.83	121.63	127.95	134.66	141.92	149.48	157.71	165.37	173.28	180.40	186.78	193.78
Europe	82.08	83.76	85.41	87.16	88.25	89.70	91.54	93.42	95.28	96.42	97.57	98.34	98.59	98.88
Latin America & Caribbean	48.69	51.54	54.42	57.52	60.61	63.93	67.24	70.60	74.10	77.32	80.61	83.72	86.64	89.63
Northern America	23.06	23.98	24.95	26.10	27.02	28.01	28.96	29.88	30.75	31.29	31.83	32.28	32.65	33.01
Oceania	2.51	2.64	2.78	2.94	3.07	3.22	3.35	3.49	3.63	3.73	3.84	3.95	4.06	4.18
Total	221.19	231.43	242.29	255.12	266.88	279.60	292.31	305.48	320.45	333.56	346.57	359.16	370.22	381.98
Mean														
Africa	15.36	16.31	17.32	18.47	19.65	20.98	22.42	23.96	25.67	27.38	29.27	31.24	33.29	35.53
Asia	55.51	58.98	62.52	66.29	69.84	73.64	77.66	81.76	86.22	90.37	94.67	98.53	101.98	105.76
Europe	47.81	48.79	49.80	50.87	51.52	52.44	53.66	54.97	56.28	56.96	57.65	58.13	58.37	58.65
Latin America & Caribbean	19.87	21.05	22.27	23.59	24.86	26.22	27.61	29.01	30.47	31.81	33.18	34.48	35.69	36.95
Northern America	14.77	15.37	16.00	16.70	17.32	17.99	18.63	19.23	19.80	20.16	20.51	20.81	21.06	21.30
Oceania	1.21	1.28	1.35	1.43	1.50	1.57	1.65	1.72	1.79	1.84	1.90	1.96	2.01	2.07
Total	154.55	161.79	169.27	177.35	184.69	192.84	201.63	210.64	220.22	228.53	237.18	245.14	252.40	260.26
2.5% Lower bound														
Africa	4.29	4.56	4.85	5.17	5.50	5.87	6.27	6.70	7.18	7.66	8.19	8.74	9.30	9.92
Asia	26.87	28.55	30.26	32.07	33.78	35.63	37.69	39.76	41.95	43.99	46.09	47.99	49.68	51.54
Europe	24.07	24.60	25.16	25.75	26.08	26.59	27.26	27.93	28.59	28.95	29.36	29.72	29.85	29.93
Latin America & Caribbean	5.78	6.10	6.42	6.79	7.18	7.60	8.04	8.48	8.95	9.40	9.83	10.25	10.63	10.98
Northern America	8.89	9.26	9.65	10.10	10.50	10.91	11.31	11.69	12.04	12.27	12.48	12.66	12.81	12.95
Oceania	0.44	0.47	0.49	0.52	0.55	0.58	0.61	0.64	0.66	0.68	0.70	0.73	0.75	0.77
Total	104.97	110.11	115.35	120.35	125.01	130.35	136.01	142.13	148.27	153.50	159.04	164.13	168.77	173.52
							Late AMD (millions)							

97.5% Upper bound														
Africa	1.57	1.67	1.77	1.89	2.01	2.14	2.29	2.45	2.62	2.80	2.99	3.18	3.39	3.60
Asia	6.93	7.37	7.82	8.34	8.85	9.44	10.11	10.82	11.59	12.33	13.06	13.72	14.30	14.98
Europe	4.03	4.13	4.25	4.36	4.37	4.43	4.63	4.89	5.15	5.29	5.44	5.58	5.69	5.82
Latin America & Caribbean	1.71	1.80	1.89	2.00	2.11	2.22	2.34	2.44	2.55	2.65	2.76	2.86	2.96	3.05
Northern America	1.16	1.21	1.28	1.36	1.45	1.55	1.64	1.73	1.82	1.88	1.95	2.00	2.04	2.08
Oceania	0.17	0.18	0.19	0.21	0.22	0.24	0.25	0.27	0.29	0.30	0.31	0.32	0.34	0.35
World	13.45	14.13	14.87	15.70	16.45	17.33	18.38	19.58	20.83	22.06	23.24	24.25	25.18	26.23
Mean														
Africa	0.77	0.82	0.87	0.93	0.99	1.06	1.13	1.21	1.30	1.38	1.48	1.58	1.68	1.80
Asia	4.59	4.88	5.18	5.52	5.86	6.25	6.69	7.15	7.66	8.15	8.64	9.08	9.46	9.92
Europe	2.57	2.64	2.72	2.79	2.79	2.84	2.96	3.13	3.29	3.38	3.46	3.55	3.61	3.69
Latin America & Caribbean	0.86	0.91	0.97	1.02	1.08	1.14	1.20	1.26	1.32	1.38	1.44	1.50	1.55	1.61
Northern America	0.76	0.80	0.84	0.90	0.95	1.02	1.08	1.14	1.20	1.24	1.28	1.31	1.34	1.36
Oceania	0.09	0.10	0.10	0.11	0.12	0.13	0.14	0.15	0.15	0.16	0.17	0.17	0.18	0.19
World	9.64	10.14	10.68	11.26	11.79	12.42	13.19	14.03	14.92	15.69	16.47	17.19	17.83	18.57
2.5% Lower bound														
Africa	0.37	0.39	0.42	0.45	0.48	0.51	0.55	0.58	0.63	0.67	0.72	0.77	0.82	0.87
Asia	2.76	2.93	3.11	3.31	3.51	3.73	3.99	4.25	4.55	4.82	5.11	5.37	5.60	5.87
Europe	1.51	1.55	1.60	1.64	1.64	1.67	1.74	1.84	1.93	1.98	2.03	2.08	2.11	2.16
Latin America & Caribbean	0.39	0.41	0.44	0.47	0.50	0.53	0.56	0.59	0.62	0.65	0.68	0.71	0.73	0.76
Northern America	0.46	0.48	0.51	0.54	0.57	0.61	0.65	0.68	0.72	0.74	0.76	0.78	0.80	0.81
Oceania	0.05	0.05	0.05	0.06	0.06	0.06	0.07	0.07	0.08	0.08	0.08	0.09	0.09	0.09
World	6.46	6.80	7.15	7.54	7.91	8.33	8.85	9.41	10.02	10.52	11.06	11.53	11.98	12.46
							Any AMD (millions)							
97.5% Upper bound														
Africa	40.50	42.98	45.63	48.63	51.72	55.20	58.98	63.01	67.48	71.99	76.93	82.08	87.41	93.21
Asia	106.65	113.33	120.17	127.49	134.41	141.59	149.43	157.37	165.91	173.86	182.07	189.46	196.09	203.32
Europe	88.76	90.61	92.51	94.55	95.82	97.58	99.86	102.26	104.64	105.89	107.15	107.93	108.31	108.99
Latin America & Caribbean	45.80	48.39	51.12	54.05	56.77	59.54	62.43	65.38	68.31	71.12	74.19	77.07	79.49	82.03
Northern America	26.57	27.68	28.86	30.08	31.17	32.33	33.50	34.47	35.43	36.05	36.65	37.16	37.58	38.00

Oceania	2.85	3.00	3.17	3.34	3.50	3.66	3.83	4.01	4.18	4.30	4.43	4.56	4.69	4.83
World	233.30	244.54	256.30	269.51	280.91	293.52	307.15	321.43	336.52	349.14	362.66	374.95	386.61	399.38
Mean														
Africa	16.87	17.92	19.03	20.29	21.59	23.05	24.64	26.32	28.20	30.09	32.16	34.33	36.58	39.06
Asia	59.16	62.87	66.65	70.68	74.50	78.58	82.92	87.33	92.14	96.62	101.24	105.40	109.13	113.21
Europe	54.98	56.18	57.43	58.78	59.58	60.75	62.35	64.10	65.82	66.75	67.67	68.37	68.80	69.32
Latin America & Caribbean	20.93	22.16	23.43	24.80	26.12	27.53	28.96	30.40	31.90	33.28	34.68	36.01	37.26	38.53
Northern America	17.07	17.79	18.55	19.41	20.18	21.01	21.81	22.55	23.25	23.70	24.13	24.50	24.79	25.08
Oceania	1.37	1.45	1.53	1.62	1.71	1.80	1.89	1.98	2.06	2.13	2.19	2.26	2.33	2.40
World	170.38	178.36	186.62	195.58	203.67	212.72	222.56	232.68	243.38	252.55	262.08	270.87	278.88	287.59
2.5% Lower bound														
Africa	5.02	5.34	5.67	6.05	6.44	6.88	7.36	7.86	8.43	8.99	9.62	10.27	10.96	11.71
Asia	31.31	33.26	35.24	37.33	39.28	41.39	43.71	46.08	48.66	51.08	53.56	55.79	57.79	60.00
Europe	31.09	31.78	32.51	33.27	33.71	34.38	35.35	36.41	37.59	38.23	38.82	39.27	39.56	39.86
Latin America & Caribbean	7.98	8.46	8.96	9.48	10.02	10.57	11.14	11.73	12.29	12.82	13.40	13.94	14.46	14.97
Northern America	10.10	10.55	11.04	11.60	12.06	12.59	13.08	13.54	13.96	14.23	14.49	14.72	14.90	15.08
Oceania	0.56	0.59	0.63	0.67	0.71	0.74	0.78	0.82	0.86	0.89	0.92	0.95	0.98	1.01
World	121.89	127.56	133.61	140.36	146.10	152.38	159.61	167.00	174.64	181.09	187.77	193.90	199.44	205.49

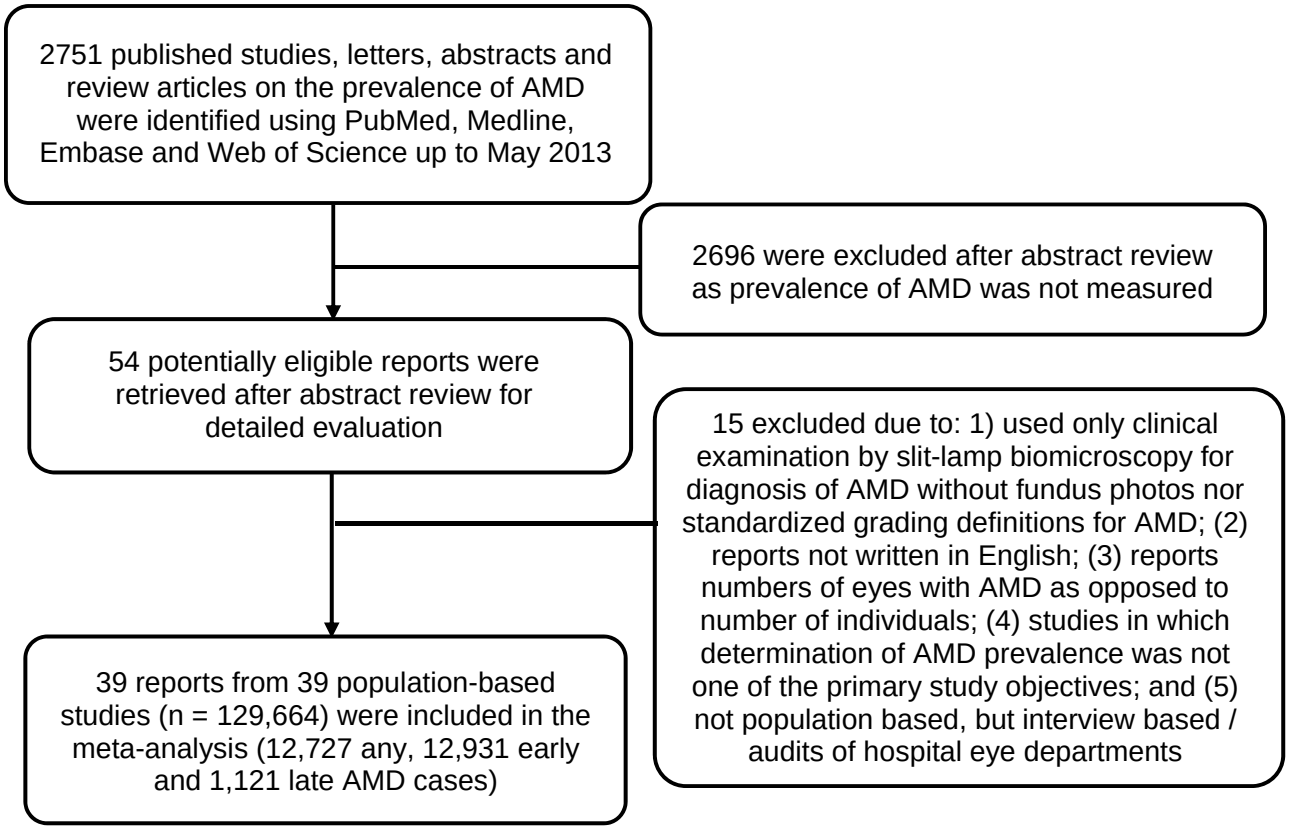
Supplementary Table 5.8 Pairwise Comparison of Projected Number of People with Early, Late and Any AMD by Regions

Data represented as indicator of whether 95% credible interval contains zero. If A-B=1, A>B; if A-B=0, A=B; if A-B=-1, A<B.

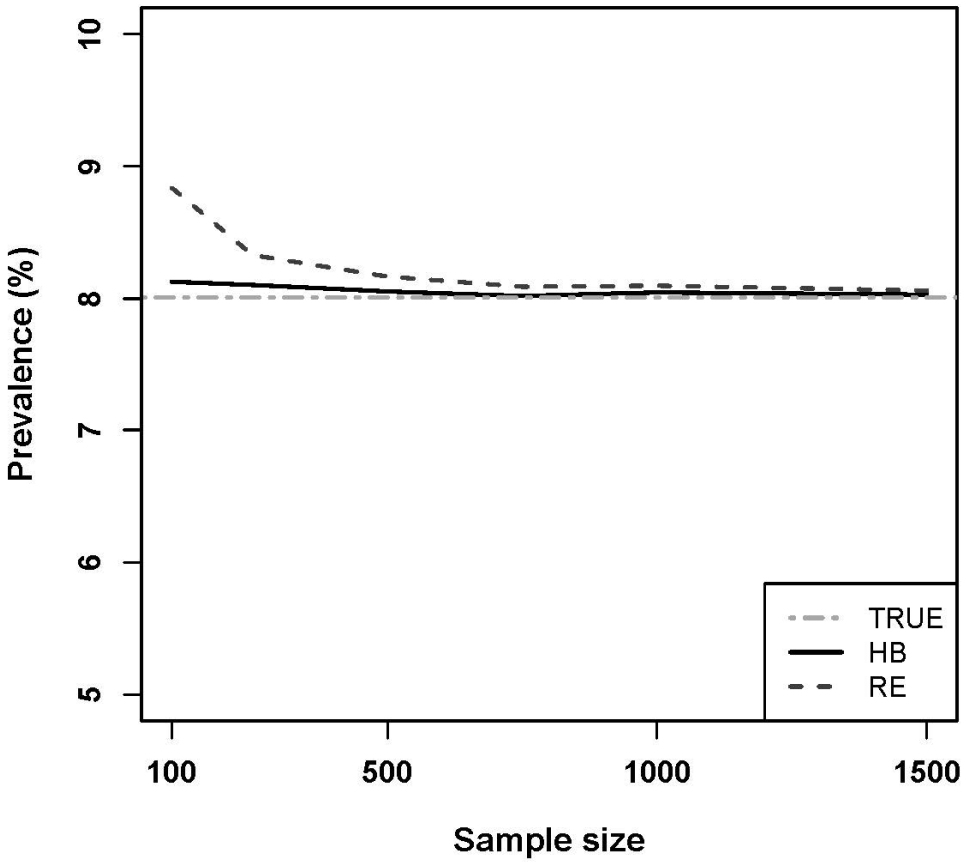
Pairwise Comparisons, (A) – (B)	2014	2016	2018	2020	2022	2024	2026	2028	2030	2032	2034	2036	2038	2040
							Early AMD							
Africa - Asia	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	0	0	0	0
Africa - Europe	-1	-1	-1	-1	0	0	0	0	0	0	0	0	0	0
Africa - Latin America & Caribbean	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Africa - Northern America	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Africa - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Asia - Europe	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Asia - Latin America & Caribbean	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Asia - Northern America	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Asia - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Europe - Latin America & Caribbean	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Europe - Northern America	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Europe - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Latin America & Caribbean - Northern America	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Latin America & Caribbean - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Northern America - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
							Late AMD							
Africa - Asia	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1
Africa - Europe	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	0
Africa - Latin America & Caribbean	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Africa - Northern America	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Africa - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Asia - Europe	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Asia - Latin America & Caribbean	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Asia - Northern America	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Asia - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Europe - Latin America & Caribbean	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Europe - Northern America	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Europe - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Latin America & Caribbean - Northern America	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Latin America & Caribbean - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Northern America - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
							Any AMD							
Africa - Asia	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	0
Africa - Europe	-1	-1	-1	-1	-1	-1	-1	0	0	0	0	0	0	0
Africa - Latin America & Caribbean	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Africa - Northern America	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Africa - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Asia - Europe	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Asia - Latin America & Caribbean	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Asia - Northern America	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Asia - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Europe - Latin America & Caribbean	1	1	1	1	0	0	0	0	0	0	0	0	0	0
Europe - Northern America	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Europe - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Latin America & Caribbean - Northern America	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Latin America & Caribbean - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Northern America - Oceania	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Supplementary Figure 5.1 Flowchart of the Article Selection Process



Supplementary Figure 5.2 Simulation Study Results



Supplementary text 5.1 Heterogeneity Analysis

Age groups, gender, ethnicity, geographic regions-specific data for early and late AMD types were the only information available from all 39 published studies and hence we were only able to investigate and account for heterogeneity derived from these sources in our statistical models.

Some studies may comprise of more than one ethnic group, which may result in between-ethnicity heterogeneity in the study. Hence, the between-ethnicity variance σ_e^2 in the same study was accounted as random effects with Normal distribution, i.e. $Normal(0, \sigma_e^2)$, to describe this correlation. Conditioning on these random effects, ethnicity groups within the same study are considered independent. Similarly, for ethnicity covariate, its variability σ_x^2 was accounted for as random effects with Normal distribution, i.e. $Normal(0, \sigma_x^2)$. Other residual variability encompassing between study variance (after accounting for other sources of uncertainty) was explained by σ^2. The total between-study variability can be calculated as the sum of the above three variances, denoted by σ_T^2. When analyzing ethnicity effect, the between-study variability is $\sigma_e^2 + \sigma_x^2 + \sigma^2$ if the two ethnic groups are from the same study; is $\sigma_x^2 + \sigma^2$ if the two studies are in the same ethnic group; and is σ^2 if the two studies are in different ethnic groups. These random effects were useful in pooling information together for sub-groups with small sample sizes or with few number of available studies, by borrowing strength from other covariate-specific groups.

Each population-based study would originate from only one region, hence in performing analysis of region effect, there is no need for parameter σ_e^2 in the model. As with ethnicity covariate, region effect was accounted as random effects with σ_x^2 and the residual variance was explained by σ^2. The total between-study variability can be calculated as the sum of the above two variances, denoted by σ_T^2. When analyzing region effect, the between-study variability is $\sigma_x^2 + \sigma^2$ if the two studies are in the same region group; and is σ^2 if the two studies are from different region groups.

As described by Higgins and Thompson (2002), within-study variance can be estimated by $s^2 = \frac{\sum \omega_i(k-1)}{(\sum \omega_i)^2 - \sum \omega_i^2}$, where ω_i is the reciprocal of the estimate's variance and k is the number of study. As logit link function was used in our model, variance of the logit prevalence estimate can be obtained by using delta method, given by $\frac{1}{p(1-p)n}$, where p and n are the sample prevalence estimate and sample size respectively. Then the total variability is the sum of between and within study variance, $\sigma_T^2 + s^2$. $I^2 = \frac{\sigma_T^2}{\sigma_T^2 + s^2}$ (Higgins

and Thompson, 2002) was calculated to describe the proportion of total variability explained by the heterogeneity. Separate sources of heterogeneity (e.g. ethnicity and region) can be calculated accordingly.

Fixed effect was used for age and gender. Age is a well-known risk factor for AMD and is strongly associated with AMD (Bayes factor > 100). Whereas for gender, Bayes factors were all < 1 (**Supplementary Table 5.3**), suggesting strong statistical evidence of no gender effect.

Supplementary text 5.2 Simulation Study

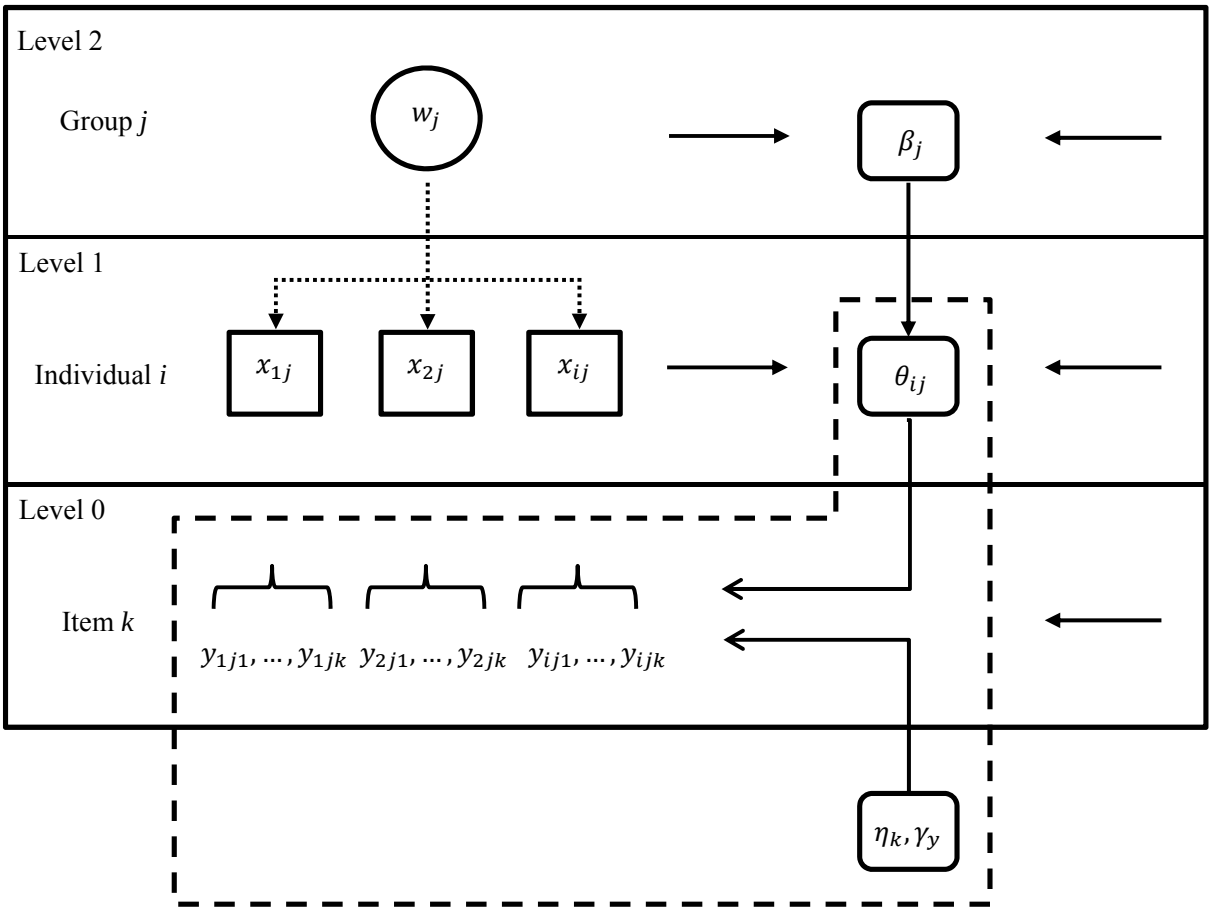
Simulation data was derived from our estimated global prevalence of early AMD (pooled by region data) of 11.40% and the between and within study variations obtained from our meta-analysis. We generated 39 distributions with their own prevalence (p_i) and within study variance (σ_i^2) with the between study variance obtained from our meta-analysis. Binary AMD data was then created for a sample size of 100, with the probability of AMD for each data point (pseudo-subject) as p_i for the i^{th} pseudo-study (total 39 pseudo-studies) to form our pseudo-global population data (i.e. generated 3,900 data points from the 39 pseudo-studies, representing the individual data for our pseudo-populations). Analysis of the pseudo-population data was performed with our HB model and the frequently used RE model. We perform such simulation 100 times to obtain the pooled prevalence estimates for both models and for a range of sample sizes (i.e. 100, 250, 500, 750, 1000 and 1500).

Our simulation results showed that based on simulated sample size of 1000, the prevalence of overall any AMD was estimated as 11.5% (95% CrI: 8.1, 15.9) by HB and 15.1% (95% CI: 12.1, 18.1) by RE methods (**Supplementary Figure 5.2**). Estimation from HB model was always more accurate than RE model but the difference decreases as sample size increased. This result was expected because the inference made from RE model was based on asymptotic properties which requires very large sample sizes while HB model depends on the posterior distribution. Hence HB model would be preferred especially for small sample sizes.

Chapter 6

Supplementary Figure 6.1 Path Diagram for the Multilevel Rasch Model

Path diagram for multilevel Rasch model: Item response data can be considered as level 0, nested within respondents with covariate information such as demographic or clinical data considered in level 1 that can be further nested in groups considered in level 2. Higher levels may be needed to model complex data structure which is common in survey research. The levels in the rectangular box illustrate the nesting of item observations in individuals and individuals in groups. Levels 1 and 2 constitute the multilevel model for θ_{ij}. There are uncertainties involved at each level, i.e. at the level of observations, at the individual level and at the group level. Explanatory information x_{ij} and w_j at levels 1 and 2 explain variability in the latent abilities between individuals within groups and across groups respectively. The dotted inverse L-box describes the Rasch model where item parameters, η_k, γ_y are not influenced by the nested data structure.



Supplementary Table 6.1 Power Analysis: Comparison of Proposed One-Stage HB and Observed Two-Stage Analysis Framework from Simulation Results

Based on 200 simulations using K=9; C=5

Data represented as empirical power of Two-stage and One-stage estimates of Beta, where the true model is given by Beta*Continuous or Beta*Categorical

	Continuous Variable					Categorical Variable					
	Effect Size					Effect Size					
	Beta=0.2		Beta=0.5			Beta=0.2		Beta=0.5		Beta=1.0	
	N=100					N=100					
alpha level	One-stage	Two-stage	One-stage	Two-stage	alpha level	One-stage	Two-stage	One-stage	Two-stage	One-stage	Two-stage
1%	0.245	0.250	0.970	0.970	1%	0.045	0.045	0.440	0.445	0.950	0.955
5%	0.490	0.505	0.995	0.995	5%	0.150	0.135	0.670	0.675	0.990	0.990
10%	0.610	0.605	1	1	10%	0.225	0.225	0.780	0.775	0.995	1
	N=300					N=300					
1%	0.755	0.74	1	1	1%	0.130	0.145	0.900	0.910	1	1
5%	0.915	0.905	1	1	5%	0.315	0.320	0.985	0.985	1	1
10%	0.960	0.950	1	1	10%	0.475	0.470	0.995	1	1	1

Supplementary text 6.1 Simulation Study

We simulated our data as follows: two independent covariates (X_{i1}, X_{i2}), a continuous variable data such as standardized age was drawn from standard normal distribution and a binary variable such as gender drawn from binomial distribution with equal probability of being male or female gender (i.e. probability 0.5). The association effects (β_1, β_2) of these two covariates with the latent visual functioning ability parameter were fixed for a range from -1 to 1 by steps of 0.5 (i.e. β_s = -1, -0.5, 0, 0.5, 1) and hence, these were considered as the "true" association effects for our simulated datasets. The calibration of nine item difficulty parameters, η_k was fixed according to Table 3 of a study conducted by *Ecosse L. Lamoureux et. al.*,[36] that performed a systematic evaluation of the reliability and validity of the visual functioning questionnaire (VF-11) using Rasch analysis that was later modified to nine items (VF-9) to tailor fit to the Asian population. The threshold parameters were specified with normal distribution of mean 0 and standard deviation 1. Hence, multinomial response data for each of the nine items with five response categories were then generated for a sample size of 300 with probability of response determined by the Andrich rating scale model with the model parameters specifications described above, to form our pseudo-visual functioning questionnaire (modified VF-9) data (i.e. n = 300, k= 9 and y in the range of integers 1 to 5 for five response categories for each item resulted in 2,700 response data generated).

Analysis of the generated pseudo-visual functioning sample data was performed with our one-stage HB approach and the frequently used two-stage procedure. Based on 100 replicates for each pair of our specified "true" association effects (25 pairs of "β_1, β_2"), average association estimates and their standard errors from the one and two-stage approach were computed to assess their performance in comparison to our pre-specified "true" effects. Finally, we performed another 200 simulations for continuous and categorical variable separately to investigate and compare the empirical power between one and two-stage approach.

APPENDIX 3: Publications during Candidature (2011-2014)

1. Narayanaswamy A, Chung RS, Wu RY, Park J, **Wong WL**, Saw SM, Wong TY, Aung T. Determinants of Corneal Biomechanical Properties in an Adult Chinese Population. Ophthalmology. 2011 Jul;118(7):1253-9. Epub 2011 Feb 18.

2. Zheng Y, Lavanya R, Wu R, **Wong WL**, Wang JJ, Mitchell P, Cheung N, Cajucom-Uy H, Lamoureux E, Aung T, Saw SM, Wong TY. Prevalence and Causes of Visual Impairment and Blindness in an Urban Indian Population: The Singapore Indian Eye (SINDI) Study Ophthalmology. 2011 Sep;118(9):1798-804.

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