Type 2 diabetes mellitus and the prevalence of age-related cataract in a clinic population.

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Purpose: The prevalence of diabetes (DM) is increasing globally with type 2 diabetes (T2DM) being primarily responsible for this alarming trend. Age and DM have been associated with an increased prevalence of AR cataract in earlier studies but T2DM has not been considered separately from type 1 diabetes. Furthermore, study results have been inconsistent in terms of whether nuclear sclerosis (NS), cortical cataract (CC) or posterior subcapsular (PSC) are specifically associated with DM. The purpose of this thesis was to provide Canadian data on these issues while considering the limitations found in earlier studies in terms of variable age group selection and cataract definition. Logistic regression analysis was extended beyond risk analysis to model the prevalence of AR cataract across the human age range. Finally, as statins are commonly prescribed for patients with T2DM, the impact of using this pharmaceutical on AR cataract prevalence was investigated.

Methods: A file review of over 6397 clinic files was performed to create the Waterloo Eye Study (WatES) database. Abstracted data included patient age and sex, the presence of early to late AR cataract (NS, CC, PSC or related lens extraction-LE), systemic health diagnoses including a diagnosis of T2DM or type 1 diabetes, and any medication used. Data quality was looked at through repeatability with double-entry of files and calculation of missing data rates. Comparisons were done between the study population demographics (age and sex) and those available on the general population and representative Canadian optometric patients. Prevalence of AR cataract was determined for the entire study group and for yearly age-groups. The probability of AR cataract generated from logistic regression analysis was used to model the prevalence of AR cataract over the entire age range of patients. Similar functions were determined for T2DM and non-diabetic (ND) subgroups and then again after further subdividing them into patients who did and did not use statins. The age of 50% prevalence of AR cataract were determined for each of these functions. Distribution rates of mixed and uniform cataract were calculated and compared for the T2DM and ND subgroups. Age of first lens extraction and differences in LE rates were also determined for these groups. Multivariable logistic

regression analysis was done to determine odds ratios (OR) for associations between variables (patient age, being female, having a diagnosis of T2DM, smoking, systemic hypertension, and statin use) and the outcome of AR cataracts or its subtypes.

Results: Data abstraction repeatability was found to be high and missing data rates were found to be low. While significant differences existed between the demographics of the general population and this clinic population, the sex and age distributions were comparable to optometric practices in Canada. The overall prevalence of AR cataract, NS, CC,and PSC in this population was 35.3%, 28.8%, 9.9%, and 3.6% respectively. The yearly prevalence of AR cataract in this population was found to increase in a sigmoid trend over the course of the human age span that began to rise after 38 years of age and approached 100% by 75 years of age. When modelled into a probability of cataract function, 50% prevalence of AR cataract occurred at 56.6 years of age. T2DM was reported in 452 WatES patients; 97% of whom were over 38 years of age. The probability of 50% AR cataract, NS, and CC prevalence occurred almost four years earlier in the T2DM subgroup compared to those without diabetes. PSC was much less prevalent and did not reach 50% levels, but the age of 10% prevalence was eight year earlier in the T2DM group compared to the ND group. Patients with T2DM had more mixed cataract, a higher rate of LE and an earlier age of first LE than non-diabetics. Statin use was reported in 761 patients; 96% who were over 38 years of age. Statin use was 3.5 times more common in patients with T2DM compared to non-diabetics. When the diabetic subgroups were further subdivided by those who do and do not use statins, the age of 50% probability of AR cataracts was now almost eight years earlier in the T2DM patients using statins compared to the ND patients who did not. The probability functions were similar between T2DM patients not using statins and ND patients who did report statin use. Having a diagnosis of T2DM was significantly associated with early to late NS and CC when controlling for statin use, whereas statin use was significantly associated with NS and PSC when controlling for a diagnosis of T2DM.

Conclusions: AR cataract, T2DM and statin use were prevalent conditions in this clinic population, especially over 38 years of age. Modelling the prevalence of AR

cataract over a broad age range could assist predicting cataract in Canadian optometric patients. A diagnosis of T2DM resulted in an earlier development of all three cataract subtypes, resulting in increased rates of LE and mixed cataract. However, the association was only significant for NS and CC when controlling for statin use. Given the frequent use of statins in patients with T2DM, the significant association found between statin use and increased risk of AR cataract warrants further study.

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Dedication

To my mother, Grace

A woman so aptly named, who always believed in me.

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Chapter 1

Introduction and literature summary

1.1 Type 2 diabetes

Diabetes mellitus (DM) is a chronic metabolic disease involving hyperglycemia.[1,2] The Institute for Clinical Evaluative Sciences (ICES) reports that as of 2003, over 2 million Canadians had DM at a estimated cost to healthcare of over $9 billion annually.[3] The prevalence of the disease has been increasing worldwide such that it has now labelled a pandemic and this will pose a significant challenge to health care in the 21st century .[4,5] Traditionally, diabetes is diagnosed by a fasting blood plasma glucose level of $\geq$ 126 mg/dL or less commonly, a two hour plasma glucose level of $\geq$ 200 mg/dL after an oral glucose tolerance test.[1] These thresholds were determined from studies on the associated risk of microvascular changes, namely retinopathy.[5] A glycosylated hemoglobin (Hgb A_{1C}) level of $\geq$ 6.5% is also suggestive for diagnosis if repeatable or found in combination with hyperglycemic symptoms (e.g. polyuria, polydipsia, weight loss), as is a casual plasma glucose of $\geq$ 200mg/dL if hyperglycemic symptoms exist.[1] Glycosylated hemoglobin levels indicate the amount of glucose a red blood cell has been exposed to over the previous 120 days. The goal of diabetic therapy is an A_{1C} of 7% or less.[5] Impaired fasting glucose (100 to 125 mg/dL) and impaired glucose tolerance (140 to 199 mg/dL) are identified as transitional stages in the progression towards DM.[1,5]

Type 2 diabetes (T2DM) accounts for approximately 90% of all cases of DM.[1,5] It is characterized by insulin resistance and relative insulin deficiency.[1,2] Insulin

facilitates the entry of glucose into cells and inhibits the release of glucose from the liver. Insulin resistance in T2DM affects both of these mechanisms.[5] As insulin and blood sugar levels rise, kidney function is altered resulting in lipid abnormalities including increased triglycerides.[2] Exogenous insulin is only required for treatment of T2DM when blood glucose levels cannot be adequately controlled with dietary changes, increased activity levels, and/or oral hypoglycemic agents.[1] T2DM is thought to be the result of genetic predisposition and lifestyle choices as age, obesity and family history are significant risk factors. Unfortunately, there has been a shift in the demographics towards a younger median age with the rising rate in childhood obesity.[2,5]

1.2 Type 2 Diabetes and use of statins

Metabolic syndrome is a combination of medical disorders that occur together and increase the risk of cardiovascular disease and T2DM. The requirements for diagnosis vary somewhat among health groups but most often include central obesity, hypertension, dyslipidemia, and insulin resistance.[5,6] The Centre for Disease Control and Prevention in the USA estimated the age-adjusted prevalence of metabolic syndrome to be 23.7% in their large nationally representative sample over 20 years of age.[6] As a result, many patients with T2DM have concurrent high blood pressure, lipid abnormalities and increased risk of stroke or coronary arteryhe disease.[5,7]

Statins are one of the most widely prescribed drugs worldwide.[8] Introduced in the early 1980's, this pharmaceutical group of 3-hydroxy-3-methyl-glutaryl-CoA

reductase inhibitors can lower low-density lipoprotein (LDL) cholesterol in those with pre-existing cardio-vascular disease (CVD) or at high risk of heart disease. Neutel et al reported that between 1994 and 2002, overall age-adjusted statin use in Canada increased from 1.6% to 7.8%.[9] The main atherogenic components in patients with T2DM include a preponderance of small, dense LDL's, elevation in tri-glyceride-rich lipoprotein particles and low high-density (HDL) levels. Lowering LDL levels is considered the first priority in cholesterol control in T2DM.[10] Recognizing the risks of dyslipidemia in patients with T2DM, studies were conducted to look at the benefit of statin use in patients with T2DM. For example, the Collaborative Atorvastatin Diabetes Study (CARDS) (2004) [11] was a multicentre randomised placebo-controlled trial in the UK looking at the role of statins for primary prevention of CVD in T2DM. Results involving 2838 patients between 40 and 75 years of age from their 132 centres were published in 2004. The researched concluded that Atorvastatin, significantly reduced the risk of CVD and stroke in patients with T2DM even in those without high LDL-cholesterol. They deemed no particular LDL threshold was required to recommend statin use for this disease. The trial was halted two years early because the benefit was so overwhelming. Therefore, the American College of Physicians is among many groups that advocate the use of statins not only for the secondary prevention in patients with coronary artery disease and T2DM, but also for primary prevention against macrovascular complications in patients with T2DM and any other cardiovascular risk factors.[12]

Paradoxically, a recent study has shown that statin therapy is associated with a slightly increased risk (9%) of developing incident diabetes (OR= 1.09, 1.02-1.17).

The research group performed a meta-analysis on 13 earlier statin trials comprising over 91,000 participants.[13] However, the researchers did not expect this finding to change the clinical practice of prescribing statins in patients because the benefit of the pharmaceutical agent greatly outweighs the risk.

1.3 Age-related cataract and type 2 diabetes

Diabetes can affect most ocular tissues and epidemiological studies have shown repeatedly that DM is a risk factor for age-related (AR) cataracts.[14, 15, 16, 17] Some of this information has come out of prevalence studies of diabetic retinopathy (DR). The Wisconsin Eidemiologic Study of Diabetic Retinopathy[18] found the severity of DR and proteinuria were associated with increased risk of cataract surgery in type 1 diabetes, whereas age and use of insulin predicted surgical intervention in T2DM. Janghorbani et al [19], followed 3606 DM patients in Scotland initially free of cataract and found that besides age, any retinopathy was a significant independent predictor of cataract for both DM types. Additionally, poor metabolic control and duration of diabetes were significant independent predictors of cataract in T1D patients.

Three distinct morphological subtypes of AR cataracts are recognized. Nuclear sclerosis (NS), the gradual yellowing of the lens, typically causes reduced acuity, color vision change and loss of contrast sensitivity.[20,21] Cortical cataracts (CC) start as vacuoles or spokes in the lens periphery and cause a gradual decrease in vision, glare at night, changes in astigmatism and a risk of monocular diplopia.[20,21] Posterior sub-capsular cataracts (PSC) develop centrally and cause glare and acuity

loss early on.[20,21] Investigations have varied on which morphological types of age-related (AR) cataracts are associated with DM but CC and/or PSC have most commonly been linked compared to NS. The National Health and Nutrition Examination Survey (1986) was one of the earlier cross-sectional studies of a large population (aged 45-74). The researchers found a significant association between DM and PSC. Their definition of cataract was acuity based (≤6/9).[22] In 1990, the Lens Opacities Case-Control Study (LOCS) attempted to standardize cataract grading in studies by introducing comparative lens photographs for evaluation. Diabetes in this clinic population was associated with greater than grade one CC (OR= 1.98 (1.25, 3.13) and mixed cataract (OR= 1.96 (1.28, 3.00).[14] Klein et al (1998) carried out a five year follow up of the Beaver Dam Eye Study cohort (>42 years of age) and defined CC and PSC as opacities >5% of the lens surface. They found that the use of insulin was associated with CC (OR= 3.3, 95% CI 1.61, 7.08). Additionally, increased levels of glycosylated hemoglobin were shown to be associated with increased risk of NS (> grade 3 Wisconsin scale) and CC.[23] The Barbados Eye Studies (1998) looked at the relationship between diabetes and the prevalence of cataract in their large black population. They reported that a history of diabetes was related to cortical cataract only (whether mixed or uniform) in their patients, using a definition of grade 2 or greater on the LOCS II scale. The associated risk was higher in their young patients (40 to < 60 yrs.: OR=2.30, 95% CI 1.63, 3.24) than in their older group (60 to 84 yrs.: OR=1.42, 95% CI 1.03, 1.96).[24] At the Barbados Eye Studies four year follow-up (2004), having diabetes increased the risk of incident CC (RR= 2.4 (1.8, 3.2) and PSC (RR= 2.9 (1.9, 4.5).[17] The Pola

study (2000) was a cross-sectional study of a large population in France (> 60 years of age). Cataract was designated as ≥ 2 CC or NS and ≥ 1 PSC opacity using the LOCSIII system. The investigators found known diabetes of long duration (≥ 10 years) had a 2.7 times increased risk of PSC, CC and lens extraction but not NS.[16] The Visual Impairment Project looked at the prevalence of age-related cataract in a large Australian population (> 40 years of age) and defined cataract as ≥ 2 NS (Wilmer scale), CC >1/4 of the pupil circumference and PSC ≥ 1mm^2. They found a significant association with having diabetes > 5 years and an increased risk of NS and CC, but not PSC.[25] However, at the five year follow up of their cohort, they found having diabetes as a significant univariate risk factor for developing PSC only (RR, 1.80; 95% CI, 1.10, 3.00).[15] The Blue Mountains Eye Study (2008) assessed their large cohort (≥49 years of age at baseline) after a ten year period. Result of multivariate analysis indicated that having an impaired fasting glucose level at baseline (RR= 3.77; 95% CI, 171, 8.30) or a diagnosis of diabetes (RR= 2.49; 95% CI, 1.40, 4.45) was significantly associated with CC, but not other AR types. Interestingly, diabetes duration was not associated with incident cataract or extraction.[26] Raman et al (2010) used a cross-sectional study of a clinic population in India to look at risk factors for cataracts in patients with diabetes. They found high serum triglycerides increased the risk of NS (OR=8.83), poor glycemic control increased the risk of CC (OR=2.43) and duration of diabetes increased the risk of PSC (OR=1.11).[27] Very recently, the Malay Eye Study (2011) found diabetes in their 40-80 year old population to be associated with CC (>5% of the lens) (OR=2.28, 95%CI, 1.83, 2.83) and any PSC (OR= 1.39, 95% CI, 1.09-1.77).[28] It is

likely that NS, CC and PSC have different pathogenic processes. Identifying any risk factors for NS, CC and PSC may help to illuminate the pathogenesis of each cataract subtype.

The pathogenesis of diabetic age-related lens changes has not been studied in as much detail as diabetic retinopathy or neuropathy. Unlike vascular tissue, the crystalline lens is not insulin dependent and instead utilizes anaerobic glucose metabolism such as glycolysis and the pentose phosphate pathway.[29] However, as with vascular tissue, an overloading of glucose in these pathways still results in sorbitol accumulation and consequential lens cell swelling from osmotic stress. Aldose-reductase inhibitors prevent the conversion of glucose to sorbitol, and are being investigated as a possible anti-cataract treatment.[30] Additionally, an increase in glycation end products (AGE's) have also been identified in the cataractous lenses of people with diabetes.[29] Ultrasound evaluation of type 2 diabetic crystalline lenses reveals decreased epithelial cell density compared to non-diabetics.[30] Fiber cells that make up the rest of the lens are derived from this single layer of epithelial cells. During development, the epithelial cells that grow, and elongate into fiber cells lose their nucleus, mitochondria, endoplasmic reticulum and other organelles. As a result, the mature lens is completely dependent on the metabolism of this epithelial cell layer for transparency.[31] Fiber cells have a high concentration of soluble proteins, primarily crystallins, essential to lens optical properties.[32] Certain crystallins are thought to suppress unfolding and cross-linking of proteins. The oxidative stress and AGE's that occur with diabetes cause insolubilization of these crystallins followed by lens opacification. Recent research has shown unregulated proteolysis of

crystallins by calpains, and now calpain inhibitors are being investigated as possible way to stop or slow down lens opacification.[32] Finding therapeutic cataract treatment is important as people with diabetes have higher complication rates from lens extraction. These include an increased risk of retinopathy acceleration, rubeosis, diabetic macular edema, cystoids macular edema and inflammation from impaired blood-aqueous barrier post-operatively.[30]

1.4 Age-related cataract, type 2 diabetes and statin use

Results from epidemiological studies on the relationship between statin use and AR cataracts have been inconclusive. Clinical trials on the ocular drug-safety of Pravastatin and Simvastatin began to be published around 1990 from Germany, Sweden, England and the USA.[33,34,35,36,37,38] These studies involved sample sizes that ranged from less than 20 participants to just over 400 and ranged from 6 months to 3 year follow up periods. No evidence was found for pathological lens changes induced by the drug treatment. Based on these findings, no adverse side effects on the human lens are listed in current drug compendiums and manufacturers do not recommend any specific monitoring of the crystalline lens. And because short-term use of statins was not found to be associated with lens opacities in early clinical trials, statin-use was generally not a controlled factor in studies on T2DM and its associations to AR cataract.

In contrast to these clinical trials, animal studies have since shown a correlation with cataract development with chronic statin treatment. Cataracts were among the

observed changes in beagles caused by fluvastatin at ≥ 8mg/kg/day doses for less than a year.[39] Statins have been isolated from the lenses of study dogs (and later humans) taking statins indicating the drug does enter its tissues.[40] Cataractogenic activity was also seen in atorvastatin-treated white rats and the drug dose corresponded directly to the increase in the number and duration of cataract episodes.[41]

One of the earliest observational investigations on cataract and the use of statins was a case-control study in UK by Smeeth et al (2003).[42] There were over 15,000 people in both the cataract group and the control group and they were matched for age, sex, practice location and observation period. Looking at an "ever" or "never" criteria for statin use, the association between risk of cataract and statin use did not reach significance after a short exposure time (mean = <2 years). Then, Tan et al (2006)[43] looked at the risk of incident cataract in their Blue Mountain Eye Study (BMES) cohort survivors at five years and ten years post-baseline. Statin use was protective for overall cataract (hazard ratio (HR) = 0.52, (95% CI) 0.29-0.93) but there was no significant associations for reduced incidence of NS, CC or PSC individually. Their definition of cataract was ≥ grade 4 NS on the Wisconsin Cataract Grading System, > 5% of the total lens surface of CC, or the presence any PSC. However, Smeeth et al[42] point out that incident cataract at these levels is relatively uncommon and that many studies involving humans lack adequate power to exlude clinically important effects. In the BMES follow up, out of the 1044 survivors free of AR cataracts at baseline, 63 used statins and only 22 of these developed cataracts by the ten-year mark. Klein et al (2007)[44] also looked at the impact of statin use on incident cataract

in their Beaver Dam Eye Study cohort at five years post-baseline. Again, they used a definition of clinically significant lens opacity for cataract similar to the BMES group. No significant difference in incident CC or PSC were found between users of statins and non-users in patients free of those opacities at baseline. However, statin-use was associated with a lower risk of NS (OR= 0.55, (95% CI) 0.36-0.84). There were 270 participants who used statins and were free of NS at baseline; 33 of these developed NS by the five-year mark. They hypothesized a reduction in oxidative stress in the lens with the use of statins for the reduced NS risk.

Based on the reduced oxidative stress theory, a population-based historical cohort study was conducted in Israel between 1998 and 2007on the persistent use of statins and incident cataract. In this investigation, Chodick et al[45] looked at over 180,00 new statin users in a large health organization and concluded that persistent statin use for this time period was associated with a reduced risk of cataract in participants ages 45 to 74 years but paradoxically a higher risk in female participants over 74. No explanations for the age-dependent effects were offered. This study depended on a diagnosis of AR cataract as recorded by a practitioner in computerized medical records without the ability to verify this information. However, Ruigomez et al[46] had previously shown a high degree of validity (94%) for a recorded diagnosis of cataract in a large UK medical database compared to an independent consultant in their study.

In contrast, a recent study by Hippisley-Cox and Coupland (2010)[47] found statin use increased the risk of cataract. This investigation involved a prospective cohort of over two million patients in the UK , ages 30-84 from 368 general practices in the

QResearch database. Over 200,000 of the patients were new statin users and Cox proportional hazard models were used to estimate effects of statin type, dose and duration of use. Based on the 20% threshold for cardiovascular risk, the number to harm (NNH) for an additional case of cataract over five years was 33 (95% CI, 28 to 38). Interestingly, after stopping statin treatment, the risk of cataract returned to normal within a year.

A very recent case-control study (2011)[48] looked at the impact of recent statin use on cataract surgery rates. Close to 14,000 patients who had lens extraction were compared to over 34,000 controls who were part of a prepaid healthcare community in the USA. After adjusting for age, sex, race, smoking status, diabetes, and coronary artery disease, logistic regression analysis showed that statin use of ≥ 5 years or more was protective against cataract surgery in the younger age group (50-64 yrs.), while shorter-term use of < 5 years was associated with an increased risk of surgery in both the younger and older age groups (> 59 yrs.).

There is bio-plausibility for statin use being associated with an increase in AR cataracts. In 1996, Cendella[49] stated that the human lens contains one of the highest cholesterol levels of any known membrane, and that the crystalline lens' epithelial cell layer requires on-site synthesis of cholesterol for proper lens cell development and transparency. Increased cataract formation has been seen in both animals and humans with hereditary cholesterol deficiency.[50] For example, the Smith-Lemli-Opitz Syndrome is a common inherited human disease that is accompanied by a mutated enzyme in the sterol synthetic pathway that converts 7-dehydrocholesterol

(7DHC) to cholesterol. Cholesterol is important in cell membranes, serves as the precursor for steroid hormones and bile acids, and is a major component in myelin.[51] Commonly, fetuses with Smith-Lemli-Opitz syndrome abort spontaneously, but for those who survive, cataracts can acutely occur in the postnatal period.[52] Statins inhibit an early enzyme of cholesterol production and the risk exists that statins can inhibit cholesterol biosynthesis in the human lens.[49] Once a patient has been prescribed a statin, these drugs are generally intended for life-long use.[50] Cenedella suggests that the impact of statin use requires study periods of between10 to 20 years due to the slow life-long growth of the lens.[49] Beri et al. published a literature review of studies between 1950 and 2008 involving the non-arteroprotective effects of statins. They concluded there was inadequate and conflicting evidence for statin benefit in any condition (including cataract) beyond hyperlipidemia and atherosclerosis.[53]

Up to now, most studies on the risk factors for AR cataract have involved DM but it is also important to consider T2DM separate from type 1 diabetes as the epidemiological trends of the two processes are different. Also, little work has been done specifically on the wide use of statins in patients with T2DM and their combined impact on cataract development. Recently, Hermans and Rousseau (2011)[54] did a cross-sectional analysis of 780 T2DM outpatients in Belgium. After equalizing groups for mean age, statin type and diabetes duration, overall cataract prevalence was not significantly higher in statin users versus non-users. Analysis involved the Fisher's exact test for differences in proportions. What remains to be investigated is the impact of statins on cataract development, utilizing a large sample

size of participants with and without diabetes controlling for T2DM. The definition of cataracts should include all levels of lens opacity to ensure an outcome condition of adequate frequency. A study with a wide age span would provide information on the age of onset of AR cataract valuable for monitoring future therapeutical treatment effects. Logistic regression analysis with the aforementioned criteria is useful both in terms of risk analysis but also for modeling the prevalence of AR cataract across the entire human age range which is absent in the current literature. Since T2DM, and now the use of statins, are increasing in prevalence in Canada and around the world, epidemiological studies on their impact must be ongoing if health care planners are to access the most up to date information. Patient education about associated risks with statin use may encourage dietary and other life style changes to avoid developing statin-requiring conditions such as CVD and DM.

Chapter 2

Waterloo Eye Study: data abstraction and population representation

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This article was written by Carolyn Machan with guidance, editing and suggestions given by Elizabeth Irving and Patricia Hrynchak. The concept for the database was formulated by Elizabeth Irving and the database content was determined by Elizabeth Irving, Patricia Hrynchak and Carolyn Machan. Data entry for the database was done by Carolyn Machan except for the double-entered data for inter-abstractor repeatability which was done by Patricia Hrynchak and Elizabeth Irving. Analysis was done by Carolyn Machan with input from Elizabeth Irving. The data for Figure 2-2 was provided by Patricia Hrynchak.

2.1 INTRODUCTION

There is a wealth of data contained within patient records and as such these records are a relatively inexpensive and readily available source of information. For example, no patient participation is required beyond consent to access their files, and little is required in terms of equipment beyond an adequate vehicle for data entry. This makes large sample sizes feasible. The data retrieved provide a snapshot of the conditions within the study groups for the selected slice in time. Consequentially, cross-sectional studies based on file review are the foundation of quality assurance programs and the planning of future health care services.[1] In addition, the prevalence findings in these studies aid differential diagnosis in the clinical setting. Large clinic and hospital chart reviews are available from various parts of the world but no comparable Canadian studies using optometric files are known. The Waterloo Eye Study (WatES) database was created for cross-sectional studies of refraction, binocular vision and disease within an optometric clinic population.

There are limitations to this type of study design. For example, clinic populations are not necessarily representative of the general population,[1] and there are inherent difficulties with using retrospective rather than prospective data. The intent for which the clinical information was originally collected is not the same as that of the subsequent study. File data are abstracted from the patient records via an intermediary clinician(s) who did not collect the initial information.[2,3] As such, the potential for abstraction errors and reviewer interpretation/bias exists. Finally, as Zadnik et al[4] point out, there is also potential for missing data in file reviews.

A review of the literature offers several guidelines for ensuring data quality in file review studies. Research groups[2,3] point to the benefit of a trial launch of the abstraction tool within a pilot study. Review of a sample of files allows clarification of inclusion criteria and reassurance that all category options are mutually exclusive.[2,3] Cassidy et al[5] recommend carefully defining the data elements to be collected and monitoring data quality through reliability testing. The latter can be achieved through inter-abstractor repeatability measures. The Cohen's kappa statistic is often employed for categorical data as it corrects for chance agreement, unlike percentage agreement rates.[6] Numerical data lend themselves to intra-class correlation coefficient analysis as a reliability index.[7]

The purpose of this study is to determine the quality of the WatES database, generated from a large scale file review of optometric patient charts with regard to data abstraction, missing data and representation of the population at large in terms of age and sex distribution.

2.2 METHODS

The WatES database was created from a retrospective review of 6,397 clinical files from the University of Waterloo, School of Optometry Clinic. Virtually all clinical testing at the School of Optometry Clinic is done by optometry interns in either their third or fourth year of study. These interns are supervised by registered optometrists who are ultimately responsible for all information within the record. The files reviewed represented patients of all ages seen over a one year period (January 2007 to January 2008) from the Primary Care and Pediatric Service areas exclusively.

Special needs patients (defined as those having insufficient intellectual, visual or communicative capabilities or patient co-operation issues for their age, so as to limit testing or require adaptive testing) were not included. In cases where patients were seen more than once in the given time frame, the record that contained the most current data was used. The study was approved by the Office of Research Ethics at the University of Waterloo. The clinic has a procedure whereby implied consent is in place for all patients to have information from their clinic record reviewed for research purposes. Patients may withdraw their consent and files of persons having done so would not have been reviewed.

An experienced optometric practitioner who was familiar with the clinic files abstracted the data, over a period of one and a half years. Before file review began, a specific list of data to be abstracted was determined. In compiling the list, consideration was given to the information normally gathered in a full eye examination at the clinic and thus generally available. A pilot test of the database template was done on 62 files (approximately 1%) for refinement of the list.

The Primary Care and Pediatric service areas each have a standardized form for recording vision assessment results. For patient history, there is space provided for patient-specific information as well as checklist word prompts for routine vision and medical questions (see Table 2-1). The rest of the clinic record is divided into sections for recording visual acuities, binocular vision test results, refractive testing, ocular health evaluation, and a final section for recording diagnoses or ocular problems and recommended management.

Table 2-1: Case history word prompts on the University of Waterloo, School of Optometry examination records for the pediatric and primary care services.

Date of visual assessment		
Reason for visit		
Developmental delays*		
School concerns*		
Pertinent birth history*		
	Pediatric & Primary Care	**Primary Care Only**
Visual symptoms	Blur Diplopia	Flashes / floaters Halos in vision Asthenopia Ocular itch or pain
Ocular history	History of eye surgery Presence of strabismus Use of spectacles Use of contact lenses	History of eye infection History of eye injury
Medical history	Allergies Current medications/supplements Serious health concerns*	Hypertension Heart disease Thyroid disease Cancer Smoking currently Diabetes Headaches

* Pediatric service only

Table 2-2: Clinical data collected in file review for Waterloo Eye Study database.

1.	Patient date of birth (day/month/year)
2.	Assessment date (day/month/year)
3.	Patient sex (M or F)
4	Chief complaint and/or motivation for having an assessment
5.	Additional ocular or visual symptoms elicited in the case history
6.	Lens extraction(s) date(s) if applicable (year)
7.	Systemic disease diagnoses
8.	Current medications
9.	Entering prescription and final prescription (sphere, cylinder, axis, addition, and prismatic correction for right and left eyes)
10.	Refractive error
11.	Binocular vision data
12.	Best corrected monocular distance and near visual acuities

The data elements were abstracted directly from the files into an Excel spreadsheet to create the WatES database. Ocular and systemic health were each given a cell for listing diagnoses. Twenty ocular and nineteen systemic diagnoses were screened in the files. There were a total of 80 variables abstracted in the entire database. The presence of disease only, rather than the severity or grade was abstracted in an attempt to exclude potential judgment variability between clinical practitioners and to avoid inconsistency in classification standards. The types of data reviewed are listed in Table 2-2. All variables were categorical except for age and refractive components, which were continuous data. Patient age was calculated from the difference between the examination date and the date of birth. This was done with a preprogrammed formula to avoid computation error. Race is not identified in the

clinic files, and therefore could not be included in the database. Refractive error was taken from subjective refraction testing results (sphere and cylinder in 0.25 dioptre units). Usually, a balancing technique is used in pre-presbyopes to achieve equal accommodation between eyes during refractive testing. If this had been done, then these results were abstracted, otherwise, the refractive results achieved through monocular testing were used. Retinoscopy results were entered into the database in cases where the file indicated the subjective refraction could not be done (e.g., very young children). The method of refraction was included, as well as the amount, test distance and method used to determine the near addition when applicable. The use of a cycloplegic agent was noted. Abstracted visual acuities were rounded to the nearest full optotype size (metric Snellen for distance and M notation for near). Binocular vision data included the presence (yes or no), direction (hypertropia, extotropia, or esotropia), test distance (6m or 0.4m), and frequency (constant versus intermittent) of strabismus. Near phoria measurements were categorized as being within (0–6 exophoria) or outside (esophoria or greater than 6 exophoria) Morgan's "normal" values, and entered as either 1,2 or 3 designations respectively. Accommodative amplitudes in pre-presbyopes as measured in dioptres by the push-up method were recorded. Vertical Maddox rod findings at near were recorded as ≤ 1 or >1 prism dioptres and any Broad H ocular motility restrictions were recorded as present or absent. All numbers abstracted were entered into the database with a precision clinically appropriate for the type of data.

From the data, age and sex distributions for the clinic population were determined. Patients were binned in five year intervals to allow easier comparison to Statistics

Canada data reports which employ these age groups. However, as there were significantly fewer subjects over 84 years of age in WatES, all individuals ≥ 85 years of age were combined into one group. These age and sex distributions were compared to national population statistics for the closest available time period.[8]

Once abstraction of the clinic files was completed, re-abstraction of fifty (0.8%) randomly selected files was done by the original practitioner to look at intra-abstractor repeatability. In addition, four hundred and twenty five of the original clinic files (6.6%) were randomly selected and independently abstracted by two other experienced practitioners to determine inter-abstractor repeatability. Cohen's kappa statistic was used to examine agreement for the following categorical data: sex, near phoria grouping, chief complaint, systemic disease, ocular disease, and medication. Dichotomous grouping was used for all variables except near phoria which had three categories. Chief complaint was sorted into either presenting for the purpose of a routine eye examination (ree) only or presenting with symptoms as well. For the disease categories, samples of diagnoses were picked from the inclusion list based on anticipated cross-sectional analysis. The database cells were sorted and then screened for each of the diagnoses. A match was the inclusion or exclusion of the diagnoses in both entries for each file. For the "smoker" variable, patients were coded as current or not current smokers at the time of the assessment. To assess repeatability of medication data abstracted, a match required inclusion of all medications listed in both entries. Frequency of occurrence was determined since some categorical data, do not occur frequently, and this can have significant impact on kappa statistic repeatability measures. Higher kappa values are hard to achieve if the distribution of

the factor is extreme. Although there are no universally accepted benchmarks for interpreting the magnitude of kappa, the standards often referred to in the literature are those proposed by Landis and Koch in 1977.[9] The following values for the kappa values were used: 0=no agreement; 0–0.2=slight agreement; 0.21–0.4=fair agreement; 0.41–0.6=moderate agreement; 0.61–0.80=substantial (or good) agreement; 0.81–0.99=almost perfect (or very good); and 1.00=perfect agreement. For continuous numerical data, repeatability was evaluated using the intra-class correlation coefficient.

Missing information in the original patient file could be the result of illegible hand writing, failure to record clinical findings, inability to perform the test on the patient, or unavailable information at the time of the visual assessment (e.g., patient could not recall the name of their medication). Missing information rates were determined for clinic file information or measurements that would be expected to be available in all files. These included patient age and sex, chief or presenting complaint, screening for strabismus, near phoria measurements, refraction, and best corrected visual acuity. Information for other categories including ocular health, systemic diagnoses, medications, use of cycloplegic agent or prismatic correction, should have been recorded in the file when applicable, and a blank clinic file entry in these cases was taken to indicate an absence of the diagnoses, no use of medications or cycloplegic agent or no prismatic correction as opposed to missing data. However, it is not possible to verify these assumptions and classification of missing data in these categories is not possible.

2.3 RESULTS

WatES patient ages ranged from 0.2 to 93.9 years. The mean and median ages of this clinical population were 42.5 and 45.1 years respectively. With the exception of the oldest group, all age groups are reasonably represented with between 3.6 and 7.4% of the study population. Age distribution rates were relatively stable averaging approximately 6.6% through childhood to age 24 years. The rate decreased after 24 years of age and was lowest between 25 and 40 years (3.8% average). The rate rose again after 39 years to 5.3% and remained around 6.4% between 50 and 80 years of age. This was followed by a rapid decline in patient numbers after 79 years of age (2.8% average). Figure 2-1 shows the study distribution relative to federal census statistics. It can be seen that the WatES database over-represents individuals less than 10 years of age and over 65 years of age relative to the general population and it under-represents the population between 10 and 20 and 25 to 50 years of age. When compared to a cross-sectional study with a stratified random sampling of 133 Canadian optometric practices[10] the age distributions were generally similar in the two studies. However, the WatES database had 14.50% of its population 9 years of age or under compared to 8.58% in the Robinson[10] study. Conversely there were more 35–54 year olds in the Robinson data[10] than the WatES.

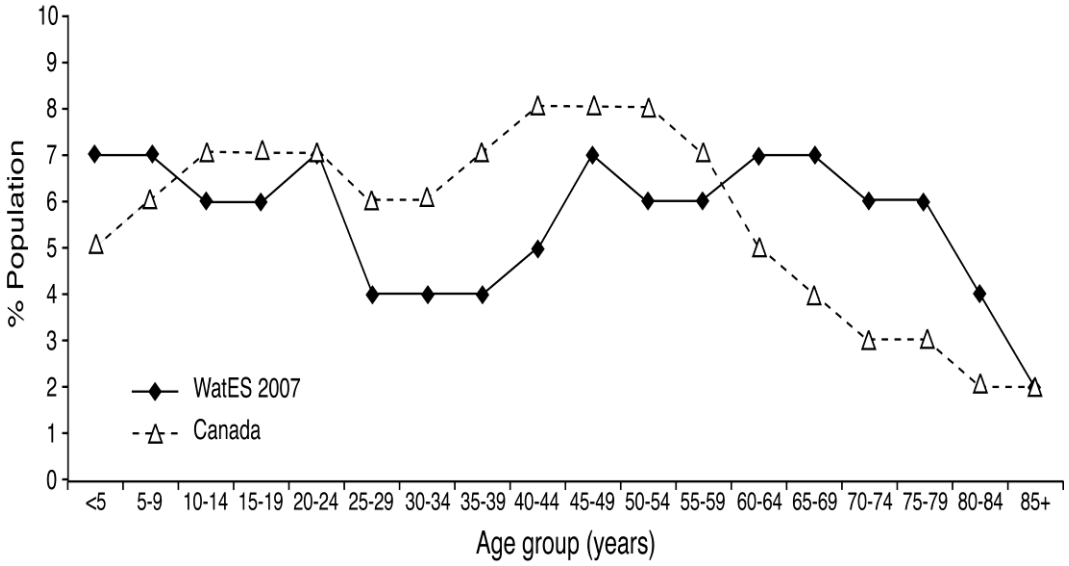

Figure 2-1. Comparison of Waterloo Eye Study patients to national numbers from Stats Canada Census (2006).[8]

There were 3458 female patients representing 54.1% of the clinic population and 2939 male patients, or 45.9%. The mean age of WatES females was 42.6 years and 42.3 years for males. The median ages were 45.1 and 45.5 years for female and male patients respectively. Although there were 8.2% more females than males in the clinic population, the overall distribution profile was similar between sexes. The exceptions were a slightly greater number of male pediatric patients than female, and a greater number of females creating a peak at ages 20–25 years. In comparison, Canada reportedly had 51.0% females compared to 49.0% males.[8]

Repeatability of file data abstraction, determined from double-entry analysis of the same abstractor (intra-abstractor) and different observers (inter-abstractor) are summarized in Tables 2-3 and 2-4. For categorical data, the kappa (K) values were above 0.80 (very good agreement) for all but 5 inter-abstractor categories (Table 2-3). Of these 3 were above 0.60 (good agreement). The migraine and smoking

categories had low frequency of occurrence values and agreement rates of 0.41 and 0.26 respectively. Intra-abstractor kappa values were generally high with all but two values above 0.80 and both of those above 0.74 (Table 2-3). Intra-class correlation co-efficients for continuous data were very high for both intra- (>0.95; Table 2-4) and inter-abstractor (>0.90; Table 2-4) comparisons. One notable exception was best corrected distance acuity of the left eye (0.83; Table 2-4). Although noticeably lower than the rest, it is still quite high.

Table 2-3. Intra-abstractor (N=50 files) and inter-abstractor (N=425 files) repeatability for nominal data from double entered files: frequency of occurrence (% of N files double entered), disagreement rate (%), and kappa (K) value (95% CI–truncated at 0 and 1.00).

	Intra-abstractor		Inter-abstractor	
Categorical Data Type	**% of N, % Dis-agreement**	**Kappa (CI)**	**% of N, % Dis-agreement**	**Kappa (CI)**
Sex	100%, 2%	K=0.96 (0.87–1.00)	100%, 2%	K=0.96 (0.93–0.99)
Near Phoria	92%, 0%	K= 1.00	88%, 2%	K=0.94 (0.89-0.98)
Chief complaint	100%, 8%	K=0.82 (0.65–0.99)	100%, 4%	K=0.91 (0.87–0.95)
Ocular disease/diagnosis				
Cataract	52%, 8%	K=0.84 (0.69-0.99)	30%, 4%	K=0.90 (0.86-0.95)
Intra-ocular lenses	11%, 0%	K= 1.00	6.1%, <1%	K=0.92 (0.84–1.00)
Diabetic retinopathy	6%, 0%	K= 1.00	1.8%, <1%	K=0.93 (0.80–1.00)
Macular degeneration	11%, 2%	K=0.90 (0.70–1.00)	6.4%, 2%	K=0.85 (0.74–0.96)
Glaucoma	9%, 2%	K=0.88 (0.64–1.00)	4.2%, 1%	K=0.88 (0.77–0.99)
Amblyopia	9%, 2%	K=0.88 (0.64–1.00)	3.3%, 2%	K=0.70 (0.50–0.90)
Systemic disease/condition				
Diabetes	7%, 2%	K=0.85 (0.55–1.00)	14.5%, <1%	K=0.99 (0.98–1.00)
Hypertension	43%, 2%	K=0.96 (0.88–1.00)	21.9%, 7%	K=0.99 (0.98–1.00)
Hyperlipidemia	20%, 8%	K=0.75 (0.51–0.99)	8.1%, 5%	K=0.70 (0.57–0.83)
Heart disease	14%, 0%	K= 1.00	5.8%, <1%	K=0.94 (0.87–1.00)
Smoker	0%, NA	K=NA	2.6%, 4%	K=0.26 (0.00–0.62)
Thyroid disease	18%, 0%	K= 1.00	5.7%, 7%	K=0.79 (0.72–0.86)
Arthritis	21%, 6%	K=0.82 (0.62–1.00)	6.4%, 1%	K=0.88 (0.79–0.87)
Migraine	11%, 2%	K=0.85 (0.55–1.00)	2.2%, 1%	K=0.41 (0.07–0.75)
Medication	75%, 10%	K=0.78 (0.60–0.96)	52.2%,8.2%	K=0.84 (0.78–0.89)

Table 2-4. Intra-abstractor (50 files) and inter-abstractor (425 files) repeatability for continuous data from double entered files: Disagreement rates (%) and correlation coefficient (ICC) (95% CI).

Quantitative Data Type	Intra-abstractor	Inter-abstractor
Age	4%, ICC=1.00	6%, ICC=1.00
Refraction–right sphere	4%, ICC=1.00	3% ICC=1.00
Refraction–right cylinder	2%, ICC=1.00	2% ICC=1.00
Refraction–left sphere	4%, ICC=1.00	5%, ICC=0.99 (0.99-0.99)
Refraction–left cylinder	4%, ICC=1.00	2%, ICC=0.99 (0.99-0.99)
Refraction–addition	16%, ICC=0.98 (0.96-0.99)	10%, ICC=0.91 (0.88-0.93)
Best corrected right distance acuity	2%, ICC=0.96 (0.93-0.98)	4%, ICC=0.99 (0.99-0.99)
Best corrected left distance acuity	8%, ICC=0.98 (0.96-0.99)	5%, ICC=0.83 (0.79-0.86)

Missing data rates are summarized in Table 2-5. Our review of the WatES database yielded low rates (<1%) for most of the applicable variables. There were only 3 files without the sex recorded and only 14 with no chief complaint recorded (including presenting for a routine eye examination). There were 11 patients who were monocular or used eccentric viewing and therefore screening for the presence of strabismus would not have been appropriate. Of the remaining 6386 file entries, there were 44 that did not have distance and near strabismus screening results in their files (<1.0% missing data rate). There were 6165 file entries of the 6386 that did not have strabismus at near for which near phoria testing was appropriate. However, 457 did not have near phoria testing results (7.4% missing data rate). The majority of these were younger patients, for whom accurate fixation required for alternating

cover test would be difficult and/or the child may not have understood the instructions for the test. Refractive testing results were available for both eyes in close to 98.8% of the patient files. Best corrected distance visual acuity measurements were available for at least one eye per patient in all but 31 files.

Table 2-5. Percentage of missing data elements from the 6397 records in the Waterloo Eye Study database.

Data type	Files with missing data (actual #)	Files with missing data (%)
Age	0	0
Sex	3	<1
Chief complaint	14	<1
Presence of strabismus*	44*	<1
Near phoria**	457**	7.4
Refraction	75	1.2%
Best corrected visual acuity	31	<1

* 44 of 6386 patients who do not have eccentric viewing or monocular vision
** 457 of 6165 patients without near strabismus

2.4 DISCUSSION

The strength of the WatES database lies in its sample size and an age range that spans from infancy to the geriatric years. A full year of clinic visits should approach the cross-section of patients generally seen in the clinic. Based on the analysis performed here, this database should provide valuable information about the prevalence of and associations between many ocular conditions within this population.

The median age of the WatES population was higher than the median age for residents in Canada, which has been estimated at 39.5 years.[8] Overall, the clinic

population under-represents 25 to 50 year olds, and over-represents children and seniors compared to the general population. Steady clinic visit rates in childhood may point to public awareness and education on the importance of early vision screening. The decreased rate of ocular assessments after 25 years of age until 39 years of age is likely attributable to the relative stability of refraction and ocular health during that time. The rise after 39 years of age coincides with the onset of presbyopia. The fact that in 2007, provincial health insurance (OHIP) only covered eye exams for all residents under the age of 20 and over the age of 64 could influence examination frequency for certain age groups. However, records of earlier clinic visits when OHIP insured all age groups show similar trends with regard to age distribution to that of the WatES population (Figure 2-2).

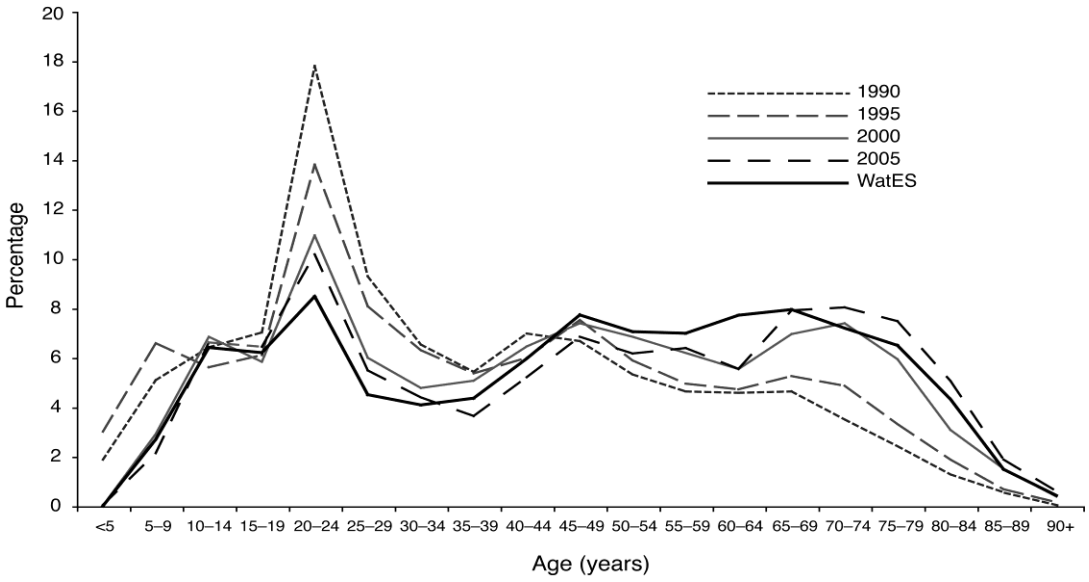

Figure 2-2. Comparison of the age distributions of patients seen at the the University of Waterloo School of Optometry Primary Care Clinic from 1990 to 2007 including the Waterloo Eye Study. (Data prior to 2007 were obtain from Primary Care Clinic billing records by P. Hrynchak and patients seen in the Pediatric Service have been removed from the WatES data for the purpose of this comparison.)

The WatES age distribution is fairly similar to nationally representative optometric practice with the exception of the youngest ages. This is presumably because the University of Waterloo, School of Optometry clinic has a dedicated clinic for pediatric vision assessments. The high level of ocular assessments at ages 20–25 (Figure 2-1), may be representative of frequent refractive changes and increased use of contact lenses in those age groups. However, the City of Waterloo population is higher than the national and provincial averages for this age group and this may also be a contributing factor.[8] The age distribution for the national population is not skewed downwards in early adulthood, but instead remains evenly distributed from the teen years into the middle ages. There is a steady decline in age distribution of Canadians older than 59. The result is lower median ages for the general population

compared to the clinic group. In 2004, the Canadian Centre for Health Information conducted a survey on behalf of Statistics Canada to determine the prevalence of vision problems among Canadian seniors. Their report, the Canadian Community Health Survey (CCHS) found 82% of seniors (ages 65 and over) had some form of vision problem in 2003.[11] This included any functional visual concerns experienced such as reading difficulties, inability to see the television and being visually excluded from driving a car. However, 78% were correctable through proper management.[11] This along with increasing risk of ocular disease could explain the higher percentage of the 65 to 84 year old WatES patients seeking eye exams than other age groups in the national population. The oldest group (over 84) comprised approximately 2% of the study population, which matches the age distribution countrywide (Stats Can Census 2006).[8]

Overall there were more females than males in the clinic population with a peak at ages 20–24 years. The sex difference in the peak may in part result from the fact that optometry students are predominately female (70%) and optometry students are strongly encouraged to have an eye examination in the clinic at the outset of their training. In comparison the national population more closely approached 50% for each sex. The Robinson study[10] also had a somewhat skewed sex distribution of 57.2% females and 42.8% males. Possible reasons for a higher percentage of females in optometric populations than the general population include females seeking routine optometric care in general and/or more females having visual concerns than males. The aforementioned CCHS results indicate that there were a higher proportion of women surveyed who reported vision problems than men.[11] However,

of those experiencing vision problems, there was no difference in consultation rates between men and women. A consultation was an office visit to either an optometrist or ophthalmologist in the past year.[11]

The quality of the database depends on the consistency in the abstraction methods used and how the file information was interpreted by the reviewer. The abstractor for this study had used the files for many years. While the abstraction process was aided by this familiarity, there was a potential for assumption that needed to be avoided. The fact that the data were entered manually over an eighteen month period does not appear to be a major factor as the intra-abstractor analysis shows very high agreement. Since the double-entered files were re-entered after the initial data collection any abstraction changes over time should be reflected in this analysis.[3]

According to Rozewski,[12] data are only considered reliable if similar results would be obtained if other experienced and/or trained observers had entered it. Allison et al[3] looked at techniques to improve data quality during chart review. Their literature review revealed higher disagreement rates when abstractors were required to use any clinical judgment or analysis during file reviews. Likewise, Yawn et al[13] studied inter-rater reliability and found that free-text rather than numeric variables was very challenging for abstractors. Thus, one could expect categorical data that required some interpretation (e.g., ocular disease) to be less repeatable than data that did not (e.g., sex) or continuous data that involved simply copying numerical results (e.g., refraction data). For our database, disease diagnoses required searching the record's case history, clinical findings and the diagnostic summary at the end, whereas, the numerical data were generally found in designated areas of the file. Numerical data

generally require less interpretation, but are more prone to accidental transposition when entering. Intraclass correlation coefficient (ICC) values were all high for the continuous data. This suggests that even when values were not agreeing exactly, they are not significantly different. The Cohen's kappa statistic values suggest very good agreement for most categories but span a range from "fair" to "perfect". Most of the categorical variables selected were dichotomous, and higher Kappa values can be found when using only two coding classifications compared to many. Kappa coefficient values do not indicate why there is a lack of agreement and in the case of low kappa values, this must be determined though data examination. Systematic differences in the case of inter-abstractor file review are often the result of ambiguity in the definition of a diagnosis not clarified ahead of time.[6] Zadnik et al[4] looked at the inter-clinician agreement for two observers when data were abstracted retrospectively from patients' optometric charts. They found good repeatability between the two trained but inexperienced collectors reviewing 100 patient records over five visits. Their results suggested that a large retrospective database of at least 1000 patients would benefit from double entry of demographic information (e.g., gender or age) in 2% of the files. Our double-entry file numbers exceed that recommendation. Statistically, the minimum calculated sample size required for data abstraction repeatability measures for this study is 276 files.[14] With 425 double entries we also exceed this.

Rozewski[12] found agreement rates between 70 and 75% or more for the majority of categorical data. Zadnik et al[4] found disagreement rates for demographic variables (e.g., sex or age) were relatively small (between 0 and 12%). For clinical ocular data

(e.g., case history specifics or ocular disease) disagreements rates were still reasonable but somewhat larger (3 to 26%)[4]. In 2008, looking at intra-rater agreement for 10 abstractors, six data categories and 110 randomly selected files out of 1,433, the Asthma Care Program in Ontario, found an overall kappa of 0.81 for intra-rater abstraction and an inter-rater agreement of 88% and inter-rater kappa statistic of 0.75.[15] Our results have the same or better agreement rates than previous studies, since agreement rates were 83% or greater for all information analyzed and the mean intra-rater and inter-rater kappa statistics were 0.90 and 0.82 respectively. Similar to previous studies, agreement rates were higher for categorical demographic variables than for categorical clinical data and repeatability was high for numerical clinical data.

2.5 CONCLUSIONS

It is possible with retrospective clinic file review for both qualitative and quantitative data to be reliably abstracted providing a wealth of pertinent information for studying health care needs. However, care must be taken to consider how the data were initially recorded, specifically what is to be abstracted, and how it should be entered. As healthcare records move from written to electronic files, the ease of abstraction, rate of abstraction and reliability of the abstracted data should improve, which is encouraging for the undertaking of any similar studies in the future. The WatES includes patients across the entire age spectrum providing a reasonable distribution of all age groups. The sex distribution is skewed somewhat towards females compared to the general population, but again there is fair representation of

both males and females. The sample size and good inter-abstractor repeatability of this database provides the statistical power and quality necessary for subsequent cross-sectional observation and analytical studies of prevalence and associations.

Chapter 3

Modeling the prevalence of age-related cataract: Waterloo Eye Study

This chapter is published as follows:

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This article was written by Carolyn Machan. Guidance, editing and suggestions were given by Elizabeth Irving and Patricia Hrynchak.

3.1 INTRODUCTION

Cataract is any opacity of the natural crystalline lens that degrades the optical quality.[1,2] The World Health Organization (WHO) identifies cataract as the cause of approximately 50% of the world's blindness; blindness being defined as best corrected visual acuity of less than 3/60 or a visual field loss to less than 10 degrees.[3-5] This number drops to 5% in North America, primarily due to accessibility of cataract extraction surgery and its restoration of visual function.[3] Unfortunately, increasing the availability of surgery globally can be cost prohibitive and logistically challenging.[5,6]

Only age-related cataracts contribute significantly to these public health concerns, as congenital and other types are rare in comparison.[7] Age-related (AR) lens changes are typically described as three distinct morphological entities: nuclear sclerosis (NS), cortical cataracts (CC) and posterior sub-capsular cataracts (PSC) [2,5,7] For those who cannot access surgery, the resultant visual disability from AR cataract can result in job loss and increased financial strife.[5] In many places, it is women who suffer these fates as they are particularly susceptible to surgical care barriers.[3,5,8]

With increasing life expectancy worldwide, the overall burden of AR cataract is expected to climb. Identifying the onset and prevalence of any AR lens opacity is important as non-surgical treatments and preventative measures are investigated. It has been suggested that delaying the onset of cataracts could have significant financial consequences for public health. For example, by delaying the onset by ten years, it has estimated that there would be a 45% reduction in cataract extraction rates and a 50 % decrease in the prevalence of cataract in USA.[5,7,9] Similar results

could be expected in Ontario, Canada where there has been a significant increase in lens extractions rates.[10] Hatch et al[11] found that the number of extractions in Ontario more than doubled between 1994 and 2005 in patients over 65. While cataract prevalence studies exist outside of Canada, Canadian data are limited. Robinson[12] used a large scale cross-sectional clinical study to look at eye disease prevalence in representative optometric practices across Canada between mid-October 2000 and the end of January 2001. Based on reports from optometrists, she found an overall cataract prevalence of 12.85% +/- 0.42 (CI 95%) in a study population of 24,570 patients (ages ≥9 to ≤85 years). However, the authors are unaware of Canadian data on the frequency of each AR lens opacity type separately and of differences in prevalence between males and females.

The paper has several objectives. The first is to provide Canadian clinical optometric data on AR, NS, CC and PSC cataract prevalence to assist in public health planning. Comparison of these results to optometric populations elsewhere may reflect differences in our health care delivery. The second objective is to offer additional information on sex difference as results have varied somewhat in previous studies warranting further investigation. Thirdly, to model age related prevalence over the entire lifespan through logistic regression analysis to demonstrate the onset of AR cataract which is not found in the current literature. Finally, when preparing for this investigation, the literature review revealed inherent difficulties in comparing previous cataract studies in terms of different definitions of cataracts and age groups involved. Thus, this manuscript will highlight those difficulties and offer methods to address those concerns for future investigations with its unique approach.

3.2 METHODS

The Waterloo Eye Study database (WatES) was developed from a retrospective review of 6397 clinical records from the University of Waterloo, School of Optometry. The collection methods, abstraction repeatability rates and patient distribution profile have been detailed in an earlier report.[13] Various types of visual and ocular variables were abstracted on patients (ages 0 to 93 years) seen over a one year period (January 2007- January 2008) in the Primary Care and Pediatric services. Ocular disease data collected included the presence and type of any clinically apparent cataract, and any history of aphakia or pseudophakia. For patients that had had cataract extraction in either one or both eyes, surgical dates (year) were recorded. For the WatES database, clinically apparent cataract was defined as a recording of grade one or greater NS, and any PSC, CC, anterior sub-capsular, traumatic, inflammatory, metabolic or congenital cataract. For this investigation, NS, CC, and PSC or their associated lens extraction (LE) were considered AR cataract regardless of patient age. In 2007, crystalline lens evaluation was part of the routine ocular assessment at the University of Waterloo, School of Optometry. Pupil dilation with 1% tropicamide was the routine practice for adult patients. In younger patients, mydriatic drops were used when non-dilated pupil size did not allow sufficient evaluation of posterior segment ocular health. Crystalline lenses were examined by biomicroscopy using direct and retro-illumination. Lens opacity type and subjective severity grade were recorded with text in a designated area on the clinic record. A common clinical five point grading system similar to the LOCS II was utilized.[14]

Typically the word ‘clear’ or a designated grade and type of cataract were written. Blank textual references to the crystalline lens existed in less than 1% of the files and were taken to mean an absence of cataract. Rarely, only the words “trace” or “slight” in association with nuclear sclerosis were given and were interpreted as less than grade 1 and not included as a diagnosis. A report of lens opacity in either eye was accepted as a diagnosis for this investigation. Patient age was electronically calculated in the spreadsheet from the date of assessment and the patient’s birthday, and this information was available for all database files.

The overall prevalence (%) of any AR cataract was determined for this optometric clinic population and for male and female subgroups. All WatES patients were then sorted by age (years) into those without AR cataracts and into the following AR categories: 1) patients with any AR cataract but no LE, 2) patients with unilateral LE and AR cataract in the other eye, and 3) patients who had bilateral LE due to AR cataract. The percentage of the sample size by age was calculated for each category. As there were few subjects over eighty-eight years of age, those subjects were combined into one age group (>88years). Logistic regression analysis was done to determine a prevalence probability function for the total of the three AR cataract groups. From this function, the age for 50% prevalence was estimated. A similar analysis was then done to compare male and female subgroups.

Further investigation looked at the prevalence (%) of each AR cataract type (NS, CC, PSC or applicable LE) independent of whether they were mixed presentation. Patients that had undergone unilateral LE were categorized by the type of lens

opacities in the other eye. After age adjusting, sex differences were reviewed for statistical significance for each cataract category through logistic regression analysis.

Next, patients with AR cataract were sorted by the following categories for males and females: NS only, CC only, PSC only, mixed cataract (any combination of the three), and bilateral LE. Again, patients that had undergone monocular LE were categorized by the type of lens opacities in the other eye. The percentages of male and female AR cataract patients were determined for each category and distribution differences between men and women were obtained. Finally, the age at first lens extraction was calculated for applicable patients from patient age and reported surgical dates. The mean age at initial cataract surgery was determined and compared for the male and female subgroups.

3.3 RESULTS

Repeatability rates for entering WatES variables in the database were determined and found to be high.[13] Cohen Kappa was calculated for the following categorical data: NS, 0.88; CC, 0.80; PSC, 0.85; LE, 0.92 and patient sex, 0.96. Intra-class correlation coefficient, used for continuous data, was 0.95 for patient age.

Males (n=2939) accounted for 45.9% of the population with a mean age of 42.3 years, and females (n= 3458) comprised 54.1% of the population with a mean age of 42.6 years. After 24 years of age, age distribution profiles were similar for both sex subgroups.[13]

Clinically apparent cataract was identified in 2332 patients (36.5% of this optometric population). Of those, only 75 patients (or 1.2%) had lens opacities attributed to etiologies other than age and were included in the group without age-related cataracts. Thus, 2257, or 35.3% of the study population, had AR crystalline lens changes or had prior LE for NS, CC or PSC. The prevalence was somewhat higher for males (n=1058 or 36.0%) than females (n= 1199 or 34.7%) but the difference was not statistically significant once age matched. Looking strictly at the occurrence of AR cataract at the time of assessment, and excluding those with bilateral LE, the prevalence of WatES patients with existing AR changes was 1940 out of the 6397 patients, or 30.3%. In this case, the sex difference in prevalence shows a slight increase with males at 31.7% and females at 28.4%, suggesting more female patients had undergone bilateral LE than males.

Fig. 3-1 illustrates the age distribution of WatES patients grouped by year with no AR cataract and the three AR subgroups. The rate of bilateral lens extraction progressed steadily from 70 years of age onward. The logistic regression line is shown for the prevalence of AR cataracts as a function of age. The prevalence increased in a sigmoid manner after age thirty-eight approaching 100% by 75 years. From this function, 50% prevalence can be estimated at age 56.6 years (56.3- 56.9, 95% CI) in this population.

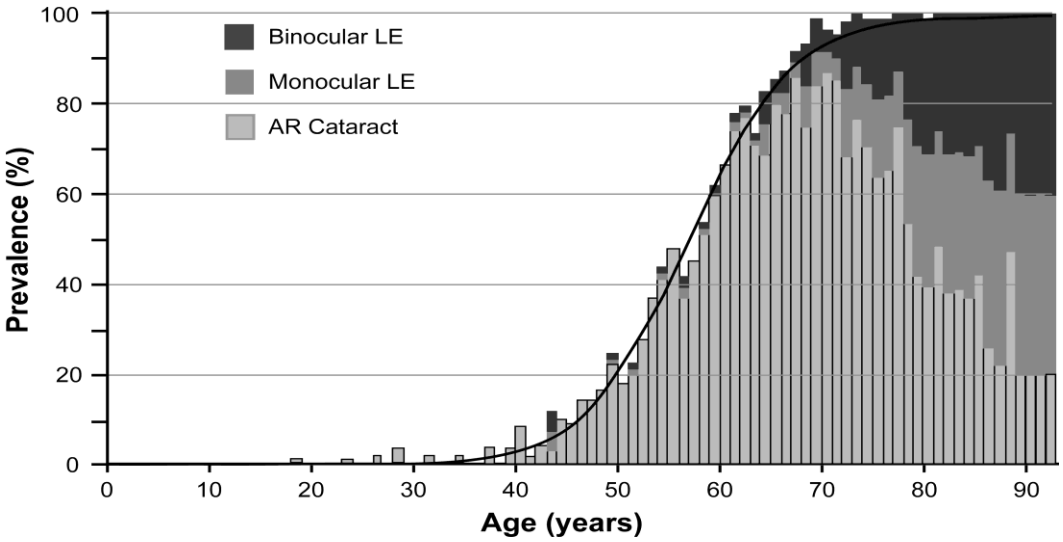


Figure 3-1. The prevalence of age-related (AR) cataract as a function of age in all Waterloo Eye Study (WatES) patients. The predicted prevalence from logistic regression analysis is shown.

Examining each type of age-related cataract individually, 28.8% of all WatES patients had NS, 9.9% had CC, 3.6% had PSC and 14.0% had bilateral LE. Nuclear sclerosis occurred progressively after age 38 for both male and female WatES patients and there was no significant sex difference in its prevalence. Fifty percent prevalence NS is estimated at 57.9 years of age in the WatES population. Being female in this population was associated with an increased prevalence of cortical cataract (Odds Ratio; OR= 1.54, 95% CI 1.27 to 1.88). This association was even greater for females over 59 year of age (OR=1.66, 95% CI 1.35 to2.05). Fig. 3-2 A) shows the predicted prevalence of CC in female and male WatES patients as a function of age using regression analysis. From this, the age of 50% prevalence for CC can be estimated at 76.7 years of age for females compared to 82.6 years of age for males. In general, CC prevalence increased at a later age than NS, only rising

appreciably after age 50 compared to 38 for NS. Posterior subcapsular cataract was the least prevalent type of cataract. Males had a higher prevalence of PSC than females in this population, but this difference fell slightly short of statistical significance, in part due to the low frequency of this opacity. Ten percent prevalence of PSC, determined by regression analysis, was estimated at 69.7 years of age for males and 72.1 years of age for females. Fig. 3-2 B) shows the predicted prevalence of bilateral lens extraction for both subgroups. Although males in this population appear to have a slightly greater rate of bilateral LE than females before 67 years of age, females past this age have an increasingly higher rate of LE than men. A 50% predicted prevalence of bilateral LE is reached at 84.6 years for females and at 90.5 years for males. The odds of having bilateral lens extraction in females was 1.41 (95% CI, 1.09–1.84) times that of males. The mean age of first cataract extraction in this population was 72.0 years +/- 10.3 (SD) of age. Females had a significantly higher mean age of first LE at 73.2 years compared to 70.4 years for males (p= 0.002).

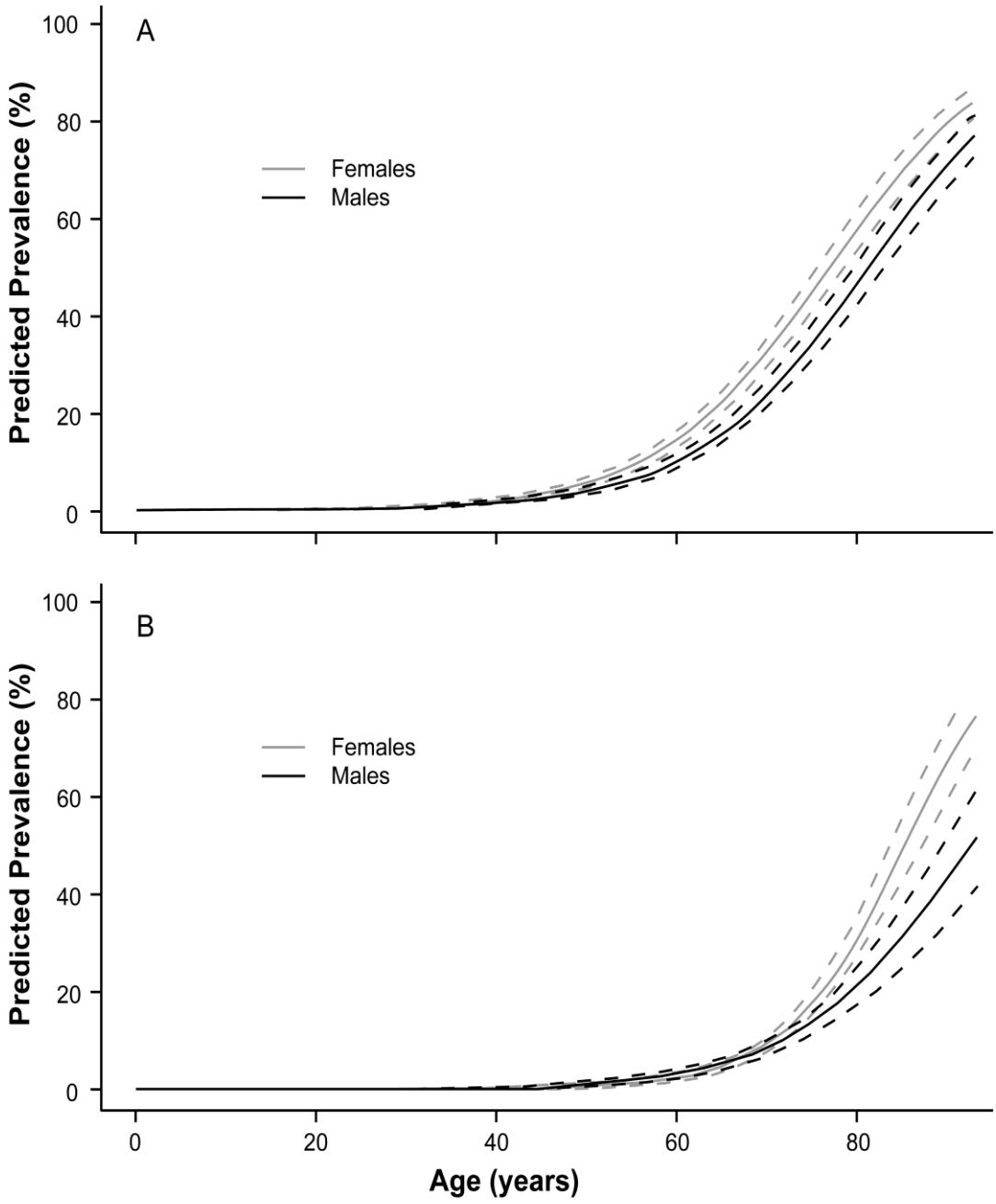


Figure 3-2. The predicted prevalence (%) of cortical cataract (A) and bilateral lens extraction (B) in female (light grey) and male (dark grey) Waterloo Eye Study (WatES) patients as a logistic regression function of age.

Fig. 3-3 shows the distribution of AR cataract for male and female subgroups when separated into mixed and homogenous types. Female patients with AR cataracts had a higher rate of bilateral LE (15.9% versus 11.9%) and a higher rate of mixed cataract (31.6% versus 29.3%) than males. Consequentially, there were more male cataract patients with NS only (55.1%) than females (48.2%). Due to the considerable predominance of NS in patients with AR cataracts, over 99% of mixed cataracts had NS as one of the components for both sexes. Whereas, CC occurred in 87.1% of mixed cataracts in females, it attributed to only 76.5% in males. Conversely, PSC was reported for 35.2% of mixed cataracts in males and only 25.9% in females.

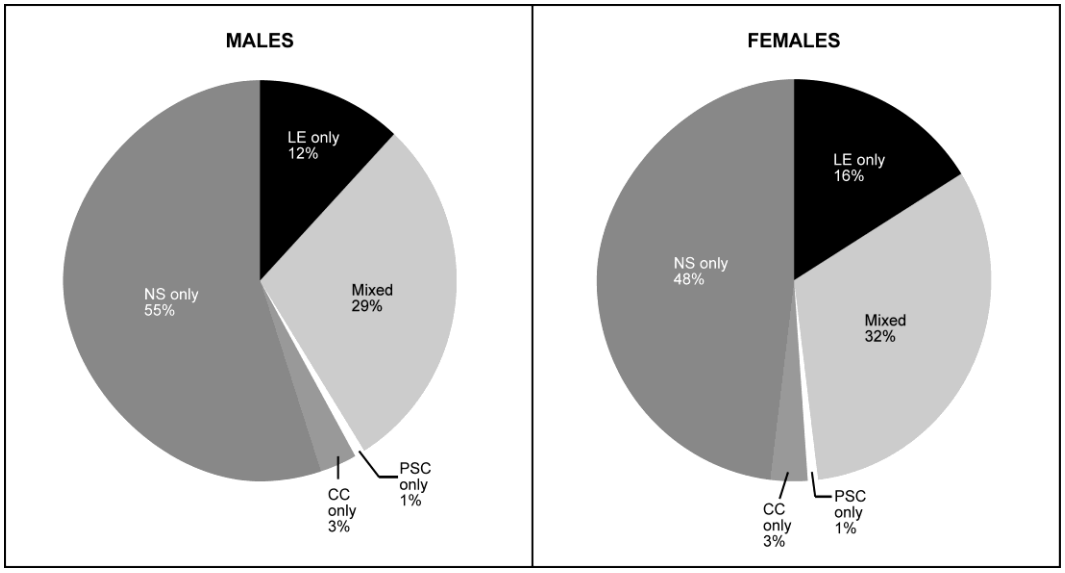


Figure 3-3. The distribution of mixed and homogeneous cataract types in male and female Waterloo Eye Study (WatES) patients with age related (AR) cataracts.

3.4 DISCUSSION

Although retrospective file reviews can be useful in determining associations between factors and suggesting potential disease etiologies,[15] they are not without limitations. They cannot demonstrate causation since the temporal precedence of the cause occurring before the effect cannot be ascertained in studies that measures both factors at the same time. Additionally, confounding variables may not be equally distributed within the groups when doing risk analysis. As discussed in the methods paper for the WatES database (see Machan et al 2011[13]) data from clinic populations are not necessarily representative of the general population and prevalence or demographic data from clinic populations must be viewed in light of the population from which they were obtained. Finally, the intent for collecting the file information originally is not the same as that of the subsequent study.

In all cataract studies, disease definition is important. First, lens opacity progresses continuously with age and a threshold of sufficient optical degradation to be called "cataract" for each opacity type must be decided.[16] Second, the detection and grading of lens opacity requires clinical judgment. Several large studies employed well recognized grading systems, such as the LOC III or the Wisconsin Cataract Grading System[16-18] that use coloured photographs to match density, colour, and/or area covered by lens opacities. Unfortunately many investigators have chosen different grading points on these scales, especially for nuclear sclerosis, making comparison between studies difficult.[5] Demonstrating standardization between examiners in retrospective file review is even more difficult. However, unlike the fore-mentioned studies, we were interested in the onset of clinically apparent cataract rather than

when cataracts become visually significant. There should be greater inter-clinician agreement in whether lens opacity is seen or not seen (grade one at least), than in determining the actual severity of the opacity. Within the clinic files, failure to detect opacities may result from incomplete or declined dilation on the part of the patient. As a result, analysis of the collected data is more likely to yield a conservative estimate of the prevalence of age-related lens opacities in this clinic population. The term "cataract" is often reserved for opacities associated with vision loss and earlier studies included acuity determinants of visual significance as an indicator of cataract progression.[1,5,19] This was not required based on our goal to include any clinically apparent lens opacities and would become imprecise in the presence of any other eye disease.

Previous studies have reported cataract prevalence for discreet age categories causing comparison difficulties of odds ratios with studies using different age groupings. Our study approach is unique in that it takes in the entire lifespan. Through logistic regression analysis a prevalence functions can be generated, allowing prevalence estimates and odds ratio values for any age group, facilitating study comparison. We can also determine age estimates for any specified prevalence levels. Furthermore, since we include all levels of lens opacity, we can determine the age of onset for AR cataract.

One could expect the prevalence of cataract to be somewhat higher in a clinic population than the general population, as patients with previously detected cataracts have been encouraged to maintain regular ocular health assessments to monitor progression of the lens opacity. Visual symptoms resulting from lens opacity may be

[1]a motivation to seek an eye examination.[9] This may explain the lower prevalence rates for age-related lens changes or extraction in the Framingham Eye Study cohort compared to our study.[19] The Framingham Eye Study (1973–1975) was one of the earliest large scale American studies to report prevalence rates for cataract (defined as any early to later age-related lens changes or aphakia). The authors reported prevalence rates of 41.7% in persons 52–64 years of age rising to 91.1% in persons 75–85 years.* Comparatively, prevalence values of 58.3% and 99.5% were found for the same age groups in our study. The Robinson Study had a much lower prevalence of cataract than in our study, but it is important to note that the decision of inclusion was left to the discretion of the reporting private practice optometrists in their study.[12] A diagnosis of "cataract" in private practice may apply to more advanced lens opacity levels than in our study, which aimed to report from a threshold of early monitoring. The Beaver Dam Eye Study was done as an American population-based study with a cohort of 4926 patients examined initially between 1988 and 1990. At the baseline examination, their patients between ages 43 and 84 had a 16.3% prevalence of any CC, and a 6.0% prevalence of any PSC.[18] When our data was similarly sorted, the prevalence of CC and PSC was again comparable at 18.1% and 6.8% respectively.

Interestingly, the Framingham Eye Study was done over 25 years ago before phaco-emulsification technique for intra-ocular lenses became the standard for cataract

* These numbers came from a recalculation of the original Framingham Eye Study data including all early to late lens changes regardless of visual acuity and ignoring the original calculation criterion of including only those with a reduced visual acuity of 6/9 or worse. (Sperduto RD, Seigel D. Senile lens and senile macular changes in a population-based sample. *Am J. Ophthalmol* 1980; 90:86-91.)

surgery. Erie et al[20] used the Rochester Epidemiology Project databases to show when phaco-emulsification replaced extracapsular extraction methods, the rate of cataract surgery increased linearly over time in their study group. Only 72 of the 2631 Framingham cohort being followed were designated as aphakes (2.7%) whereas 368 out of 2535 WatES patients between 52 and 85 (14.5%) had had cataract surgery in one or both eyes.[1]

Some studies have shown an associated risk for NS with being female;[18,21,22] others have not found this association.[16,17,23,24] However, the sex difference for CC found in our study has been consistently shown in other investigations. The POLA study found an increased odds of cortical cataracts for females (OR= 1.67), as did the Visual Impairment Project (age-adjusted relative risk of 1.8; 95% CI, 1.3-2.6) and the Lens Opacities Case-Control Study (OR= 1.51).[16,23,24] The Blue Mountains Eye Study looked at sex differences for ten-year person-specific incidences. After adjusting for age, women had a significantly higher incidence than men of cortical cataract (30.8% versus 24.4%, p=0.007).[21] Hormones have been implicated in female cortical cataractogenesis[24-26] but this has not yet been sufficiently substantiated. Literature review finds less evidence for sex differences in the prevalence of PSC.[8]

The higher occurrence of CC in women and a slightly higher PSC prevalence in men may explain the observation that women in the WatES population have a greater overall prevalence of bilateral cataract extraction but a later mean age of first lens extraction. Initially, cortical cataracts are associated with a gradual decrease in vision until the opacity reaches the visual axis of the crystalline lens. Consequential lens extraction from this type of cataract comes at a more advanced stage of development

than posterior subcapsular cataract which rapidly causes visual impairment. This was reported in both the Blue Mountains Eye Study and the Beaver Dam Eye Study, which found that the presence of PSC was associated with the greatest rate of incident cataract surgery over NS or CC.[27,28] There may be differences in the type of cortical change that occurs in women as well. The Framingham Eye Study noted that of the 2631 patients they screened, cortical vacuoles were slightly more prevalent than spokes among men while spokes were observed substantially more frequently than vacuoles in women's lenses.[1]

Our result that males had an earlier mean age of first lens extraction than females is comparable to other studies. In a retrospective review conducted from the operating records of 8256 cataract surgeries performed at the Waterford Regional Hospital, Republic of Ireland, O'Reilly et al found the mean age at surgery between 1986 and 2003 to be 72.32 years +/- 12.21 (SD) years for males and 74.89 +/- 11.03 (SD) for females**.** The age profile did not change significantly over the 18 year study period; however there was a significant increase in the proportion of women having lens extraction.[29] Bilinska et al, in a Polish study of surgical records between 1997 and 2002, found that for their 4385 patients, women were operated on at a mean age of 71.1 years whereas the mean age for men was 69.1 years. A statistically significant increase in these ages was occurring over time.[30] The prospective POLA Study in France, found an increased risk of having had bilateral cataract surgery for the female sex (OR= 3.03).[16] Comparatively, the Blue Mountains study (2008) found a mean age at cataract surgery to be 75.8 years with no significant sex difference.

However, they did find women had a significantly higher incidence than men for cataract surgery ($p=0.03$).[21]

Investigations on age-related cataracts will continue to be important. Crystalline lens changes are responsible for many visual concerns including refractive changes, decreasing acuity, loss of contrast sensitivity and glare concerns.[2] In mature patients, a significant amount of their eye examination is dedicated to dealing with these issues. This along with overall increasing surgical costs for lens extraction will continue to drive the search for therapeutic or preventative measures for this prevalent disease.[16] Interestingly, several studies have suggested that the presence of cataracts is a commanding predictor of mortality.[31,32] Therefore the prevalence of cataract in a population may be a marker for the overall health of its members.

3.5 CONCLUSIONS

Our results confirmed the well known risk of age for cataract development in both males and females. Within this optometric clinical population, age-related cataract was a common finding in patients over fifty-six years of age with nuclear sclerosis being the predominant type of cataract. Being female was associated with an increased prevalence of cortical cataract, and consequently mixed cataracts, and an increased rate of surgical intervention. Despite this, females had a greater average age of first cataract extraction than males. The prevalence of cataract increased in a sigmoid progression as a function of age that could be modeled through logistic regression. This novel way of presenting prevalence data is recommended as an improved way to compare results between studies and for predicting prevalence at any age for the reported population.

Chapter 4

Type 2 diabetes and statin use associated with age-related cataract: Waterloo Eye Study.

This chapter is submitted as follows:

Machan CM, Hrynchak PK, Irving EL. (2011). Type 2 diabetes and statin use associated with age- related cataract: Waterloo Eye Study.

This article was written by Carolyn Machan. Guidance, editing and suggestions were given by Elizabeth Irving and Patricia Hrynchak.

4.1 INTRODUCTION

Age-related cataracts have been identified as a prevalent ocular disease in patients over 39 years of age.[1–5] The financial and functional burdens of this inevitable aging process are known, both in terms of surgical costs and visual impairment when surgery is inaccessible or pending.[6–10] Accordingly, it is important to identify factors that accelerate cataract development and to minimize exposure to them through public health measures. Several large population studies have identified the diagnosis of diabetes mellitus (DM) as a risk factor for age-related (AR) cataracts.[11–17] However, which types of AR lens opacities are involved varies between studies, namely, whether it is nuclear sclerosis (NS), cortical cataract (CC) and/or posterior subcapsular (PSC) that is associated with DM. Health care planners are concerned that the prevalence of DM is rising at a pandemic rate, with over 300 million people predicted to be affected globally by the year 2025.[18] The Canadian Diabetes Association[19] (CDA) reports that the number of people diagnosed with DM in Canada grew by 70% between 1998 and 2005 and that more than 10% of Canadian healthcare costs are spent on dealing with DM and its complications. Type 2 diabetes mellitus (T2DM), predominantly insulin resistant with relative insulin deficiency, accounts for 90% of all cases of DM in North America.[18] Contributing to the high number of people with DM are an aging population, people living longer with diabetes, increased immigration of high-risk populations, growth of high-risk aboriginal populations and rising obesity rates.[19] Many people with T2DM have concurrent dyslipidemia and are at higher risk of cardiovascular disease and stroke. The results of several studies from around the globe have provided evidence that

taking statins (HMG-CoA reductase inhibitors) reduces cardiovascular risks in patients with DM.[20–22] Consequently, statins are a class of pharmaceuticals commonly prescribed for patients with DM to lower cholesterol.

Early clinical trials did not find significant lenticular changes with statin use of less than five years.[23–26] However, a very large recent cohort study from the UK reported an association between statin use and increased risk of cataracts, suggesting that further study is warranted.[27] Furthermore, the morphological types of AR cataract associated with statin use have not yet been investigated.

The authors are unaware of any Canadian studies investigating the impact of DM on the prevalence of age-related cataract. In this study we compare the prevalence of all clinically apparent age-related lens opacities in non-diabetic (ND) and T2DM subgroups from a large clinic population at the University of Waterloo, School of Optometry. We also look for any age-matched differences in the subgroups for NS, CC, and PSC separately. The impact of these differences are investigated through distribution comparison of homogeneous and mixed form cataracts, and/or resultant lens extraction (LE) in the T2DM and ND subgroups. Unlike many earlier investigations, this study considers the association between cataract and T2DM only, and not DM in general, as the epidemiological trends for type 1 DM (T1DM) and T2DM are different. Our study approach is unique in that it considers the entire lifespan and defines cataracts to include early changes as well as visually significant ones. Thus, the age of AR cataract onset can be observed in a prevalence function generated though logistic regression that considers all ages. This approach also allows easier comparison to other studies that vary in the age groups reported.

Finally, the prevalence of statin use and any associations between statin use and AR cataract prevalence is determined for patients with T2DM and ND.

4.3 METHODS

The Waterloo Eye Study (WatES) database was developed from a retrospective file review of 6397 patient visits from January 2007 to January 2008 at the University of Waterloo, School of Optometry. Data was abstracted for several variables for cross-sectional analysis. Abstraction methods, data quality analysis, study limitations and population representation of the database have been detailed in an earlier paper.[28] Furthermore, overall cataract prevalence and the modelling technique have been reported previously for this data set including a comparison between male and female patients.[1] The abstracted ocular health data in the current investigation included the presence of any clinically apparent AR cataract (NS ≥ grade I, LOCS II,[29] any CC, any PSC or any history of related LE) and surgical dates from LE. A report of lens opacity in either eye was accepted as a diagnosis. The systemic health information included a diagnosis of T1DM or T2DM, and any medication being taken. Patient age was electronically calculated in the database from the date of assessment and the patients' birthday, and this information was available for all patient files.

The repeatability of data abstraction was determined through inter-abstractor agreement rates of 425 double-entered clinic files.[28] As previously reported, Cohen Kappa statistic values were high for patient sex and the presence of NS, CC, PSC, and LE as was the intra-class coefficient value for patient age.[1] The Kappa value for the presence of DM was very high at 0.99 with less than a 1% disagreement rate

between abstractors. The Kappa value was somewhat lower for overall medications (K=0.84); however when considered on its own, the inter-abstractor agreement for statin use was high at K=0.95 with a disagreement rate of less than 1%.

Patients with T1DM were excluded from the analysis. The remaining patients (n=6336) were separated into subgroups of patients having T2DM or being ND and then further sorted into patients having any or no AR lens opacity. The age and sex distributions of the T2DM group were compared to provincially available data on DM rates in Ontario.[19] The overall prevalence (%) of any AR cataract was determined for T2DM and ND subgroups. Multivariable logistic regression analysis was done to determine prevalence probability functions for AR cataract in the two subgroups. We have previously shown a sex difference in AR cataracts in this population, with being female associated with an increased risk of CC.[1] Smoking is known to be associated with nuclear sclerosis.[8,12,13] Recently the Malay Study looked at the components of metabolic syndrome and their relationship to AR cataracts. Besides DM, the presence of hypertension (HTN) was associated with increased odds of having cataract.[30] Therefore, sex, smoking and HTN were also controlled for in this analysis. The odds ratio (OR) for a diagnosis of T2DM and AR cataract prevalence was calculated. The ages at which there was a 50% prevalence of AR cataracts for ND and T2DM patients were determined from these functions.

The prevalence of NS, CC and PSC was determined separately independent of whether they occurred in a mixed-type presentation or as homogeneous opacities. There were a significant number of patients with CC or PSC that also had NS. For this reason, an insufficient number of patients with CC or PSC only were available to

consider only patients with a single type of opacity in our analysis. Instead, we chose to do a multivariable logistic regression analysis controlling for the aforementioned variables as well as the other lens opacity types when looking at NS, CC and then PSC. Patients with monocular LE were categorized by the cataract type in the other eye. Patients who had undergone bilateral LE (n= 312) were excluded as it was not possible to determine which type of AR cataract existed pre-surgically. For the remaining patients (n=6024), OR's for any association between a diagnosis of T2DM and cataract subtype prevalence were calculated. The ages at which they had a 50% prevalence of NS or CC or 10% prevalence of PSC were compared for each subgroup.

Next, considering patients over 38 years with AR cataracts, the proportion of total AR cataract patients with mixed and homogeneous cataract was compared for patients with T2DM and ND. The AR cataract subgroups were sorted into 1) NS only, 2) CC only, 3) PSC only, 4) mixed with NS and CC, 5) mixed with NS and PSC, 6) mixed with CC and PSC and finally 7) mixed with all three types. Categories 4) to 7) were totalled to determine the proportion of each diabetic subgroup with mixed cataract.

The prevalence of LE and odds of having LE in patients with T2DM compared to ND was determined. Subsequently, the age at first LE was calculated from patient age and surgical dates (nearest year) for patients with any monocular or binocular LE. From this, mean ages of first LE were determined for applicable patients with T2DM and ND and compared for a significant difference.

Finally, the prevalence of reported statin use was determined for the T2DM and ND subgroups. A multivariable analysis was performed to control for age, sex, smoking, HTN and DM status, to determine any associations between statin use and overall AR cataract prevalence and then each AR cataract subtype. Prevalence probability functions for AR cataract were determined for each of the following groups: 1) T2DM patients not taking statins, 2) T2DM patients taking statins, 3) ND patients not taking statins, and 4) ND patients taking statins.

4.3 RESULTS

There were 452 T2DM, 5884 ND and 61 T1DM patients, representing 7.0%, 91.9% and 0.9% of the study population respectively. The mean age for the T2DM subgroup was 64.3 ±12.4 (SD) years compared to 40.8 ± 25.4 (SD) years for ND. Whereas the ND subgroup had a slightly higher proportion of female patients (n=3236 or 55.0%) compared to male patients (n= 2648 or 45.0%), the sex distribution of T2DM subgroup was skewed towards more male patients. There were only 194 female compared to 258 male T2DM patients, representing 42.9% and 57.1% of the T2DM group respectively. The Canadian Diabetic Association (CDA) used algorithms applied to health care administrative data from 1995 to 1999 to look at prevalence rates of diagnosed DM in Ontario and create the Ontario Diabetes Database (ODD). The CDA could not separate T1DM from T2DM from their available data, so reported results include all cases of DM.[19] Figure 4-1 compares the age distribution of WatES patients with DM (T1DM and T2DM) to the 1999 ODD numbers using their age grouping. The overall rate of DM in people >19 years of age

was 10.5% for the WatES database in 2007 and 6.2% for the ODD in 1999. For both databases, women in the 20 to 34 year age group had a slightly higher prevalence of DM than men, but a lower prevalence in all remaining age groups. However, WatES has a lower proportion of patients with DM who are senior than the ODD study group and a slightly higher proportion of patients with DM in the 35 to 64 year range.

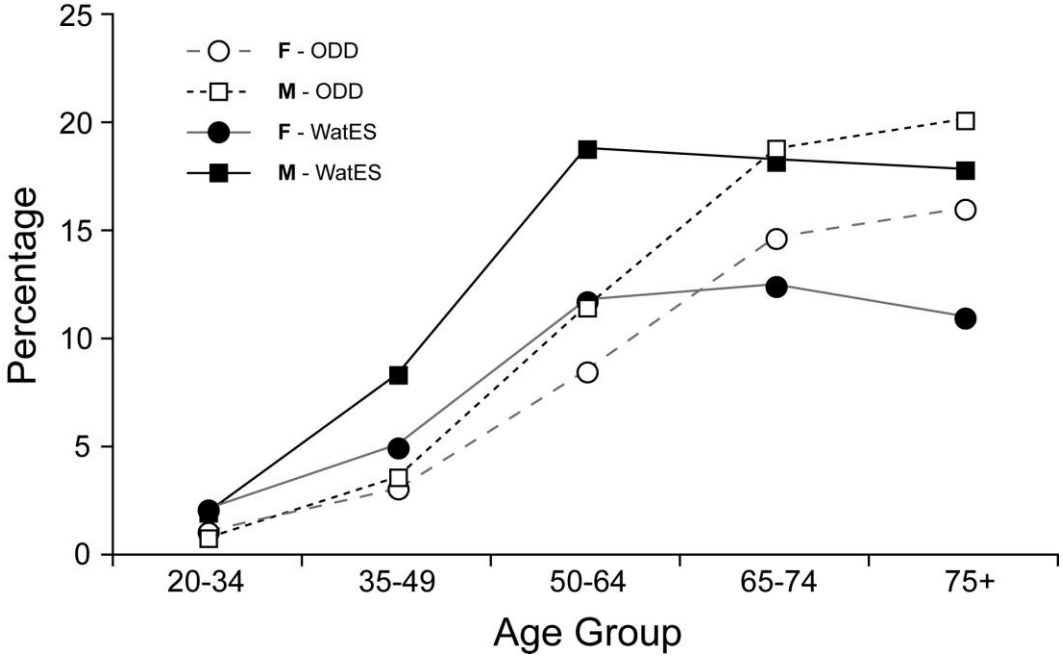


Figure 4-1. Prevalence of Diabetes Mellitus (DM) as a function of age group (% per age group) for males (M) and females (F), in the Waterloo eye study 2007 (WatES) and the Ontario Diabetes Database 1999 (ODD).

The relatively older WatES T2DM subgroup had 348 of its 452 patients (77.0%) with some clinically apparent age-related cataract whereas the proportionately younger ND group only had 1882 out of 5887 with age-related cataract (32.0%). Figure 4-2 shows the prevalence of AR cataract in the T2DM and ND groups in

yearly age groups to control for the age disparity between T2DM and ND patients. Prevalence probability functions were determined and also shown in the figure. Cataracts occurred earlier in the T2DM subgroup, with the probability of 50% prevalence reached by age 53.2 (95% CI, 52.3–54.0) years compared to 57.0 (95% CI, 56.7–57.2) in the non-diabetic (3.8 year difference) patients. There was no statistically significant difference in the slope value of these two functions, indicating that once the prevalence of age-related cataracts begins to rise, the rate of increase in prevalence appears similar for the two subgroups. For this population, a diagnosis of T2DM was associated with an increased odds of having AR cataracts (OR=1.86, 95% CI, 1.34–2.59) across the lifespan when controlling for age, being female, smoking and hypertension.

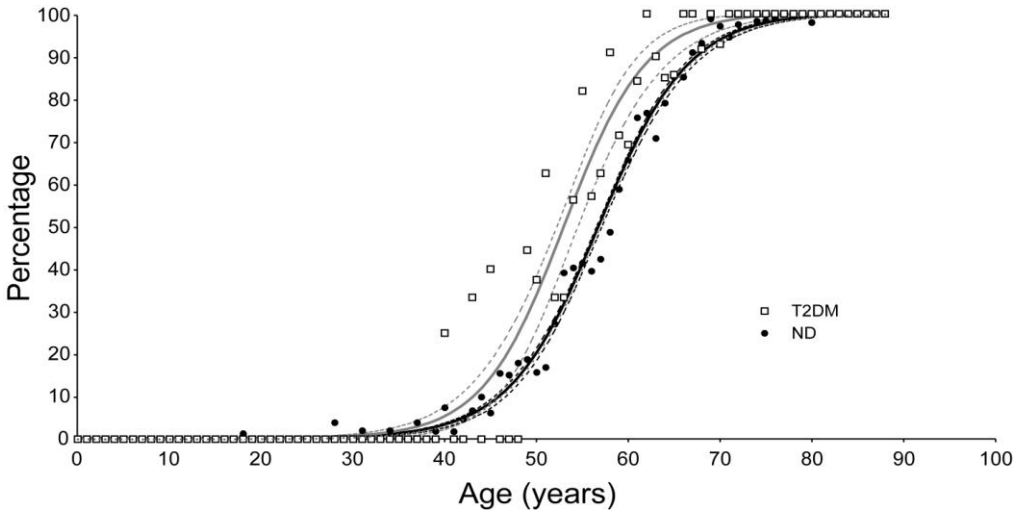


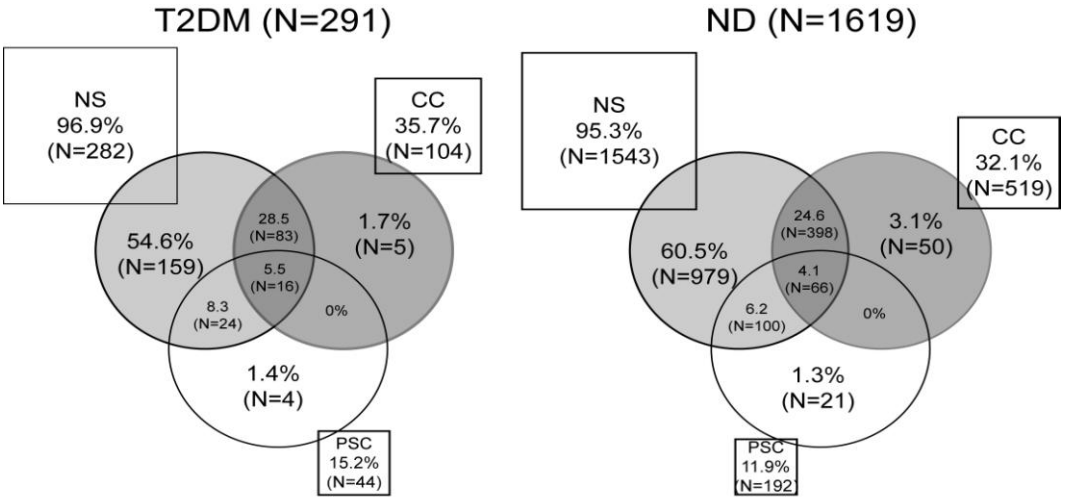
Figure 4-2. The prevalence of age-related cataract (AR) in WatES patients with type 2 diabetes (T2DM) (n=452) and patients that do not have diabetes (ND) (n=5884) over the entire lifespan in yearly age groups. The probability function of AR cataract using logistic regression has been included with 95% confidence intervals.

Table 4-1 presents the results from logistic regression analysis for each morphological AR cataract subtype. Fifty percent prevalence occurred about four years earlier for both NS and CC in T2DM compared to ND patients. As PSC was significantly less prevalent, the age of 10% prevalence of PSC is shown which occurred close to eight years earlier in the patients with T2DM. After multivariable analysis, a diagnosis of T2DM in this study group was associated with increased odds of having NS (OR=1.84, 1.32–2.56), CC (OR=1.38, 1.04–1.82) and PSC (OR=1.52, 1.04–2.19) compared to ND patients.

Table 4-1. Predicted ages for specified prevalence amounts from multivariable logistic regression analysis of each AR cataract subtype. WatES patients were grouped as having type 2 diabetes (T2DM) (n=452) or not having diabetes (ND) (n=5884).

Cataract type	Prevalence	T2DM age (yrs)	ND age (yrs)	Difference (yrs)
NS	50%	54.4	58.4	4.0
CC	50%	75.5	79.8	4.3
PSC	10%	64.2	71.9	7.7

There were 291 T2DM and 1619 ND AR cataract patients over 38 years of age. Figure 4-3 demonstrates an increased proportion of mixed AR cataract in the patients with T2DM compared to ND. Whereas 42.3% of AR cataracts in T2DM patients over 38 years had a combination of two or more components, only 35.2% of the AR cataracts in ND patients over 38 were mixed. Only patients over 38 years of age were included as 99% of patients with AR cataracts are older than this age.



% Cataract	T2DM	ND
Mixed	42.3%	35.2%
Homogeneous	57.7%	65.8%

Figure 4-3. Frequency distribution of homongeneous and mixed lens opacities in WatES patients with type 2 diabetes (T2DM) and patients that do not have diabetes (ND) over 38 yrs with age-related cataract (excluding those with bilateral LE).

There were 72 T2DM patients and 345 ND patients who had either monocular or binocular LE for AR cataracts. A higher percentage of T2DM patients with AR cataracts had already had bilateral LE (16.0%) compared to the ND cataract group (13.0%). Also, the T2DM subgroup had their first LE at a mean age of 70.3 yrs. compared to 72.9 yrs for the ND subgroup (2.6 year difference, $p<0.05$, t-test). There were four ND patients with unknown surgical dates and they were excluded from this analysis. Controlling for the same variables as before, the T2DM subgroup had an increased odds (OR=1.60, 1.15–2.22) of having LE compared to the ND subgroup.

The mean age of patients taking statins was 68.5 years (± 11.1). Statin use increased with age such that 0.4% of WatES patients under 39 years of age, 9.2% of patients between 39 and 59, and 30.5 % of patients over 60 were taking statins. Considering diabetic status, statin use was reported in 56% of T2DM patients but only 16% of ND patients over 38 years. As shown in Table 4-2, after controlling for age, sex, smoking, HTN and diabetic status, statin use was significantly associated with AR cataract (OR=1.57, 1.15–2.13), NS (OR=1.48, 1.09–2.00) and PSC (OR=1.48, 1.07–2.04) but not CC (OR= 1.02, 0.80–1.30). Interestingly, PSC was no longer significantly associated with T2DM when controlling for statin use. CC was still associated with being female (OR=1.59, 1.30-1.94) and in this analysis, HTN (OR=1.24, 1.00-1.53). Agreeing with results from other studies, NS was associated with smoking (OR= 1.62, 1.08-2.42).

Table 4-2. Odds ratio (95% CI) for AR cataracts and cataract subtypes in WatES patients using multivariable logistic regression analysis (patients with type 1 diabetes mellitius were excluded).

	Age	Female	Smoking	HTN	T2DM	Statin use
AR	1.22 (1.20–1.23)	1.01 (0.82–1.24)	1.52 (1.03–2.24)	1.21 (0.95–1.55)	1.60 (1.13–2.27)	1.57 (1.15–2.13)
NS	1.21 (1.19–1.23)	0.97 (0.79–1.19)	1.62 (1.08–2.42)	1.21 (0.95–1.55)	1.62 (1.14–2.29	1.48 (1.09–2.00)
CC	1.08 (1.07–1.10)	1.59 (1.30–1.94)	0.99 (0.63–1.55)	1.24 (1.00–1.53)	1.37 (1.02–1.83)	1.02 (0.80–1.30)
PSC	1.06 (1.05–1.08)	0.93 (0.71–1.23)	1.06 (0.57–1.98)	0.95 (0.70–1.28)	1.33 (0.90–1.96)	1.48 (1.07–2.04)

As shown in Figure 4-4, the probability of AR cataract in patients who use statins reached 50% at age 51.7 and 54.9 years in T2DM and ND patients respectively. In

patients who did not use statins, it was later at 55.1 and 57.3 years for T2DM and ND patients respectively.

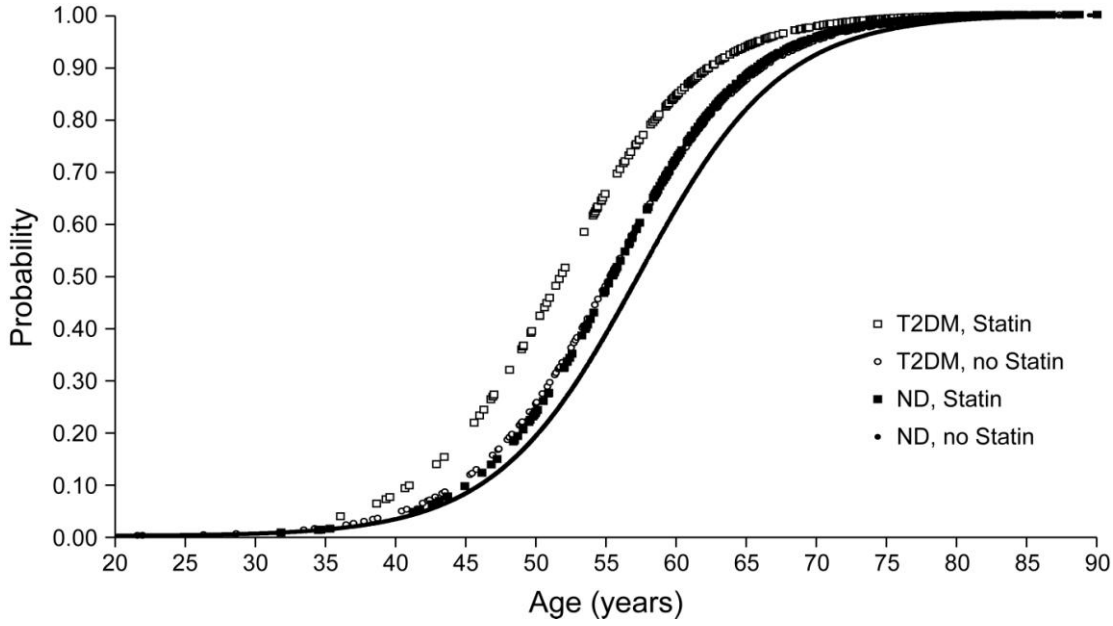


Figure 4-4. Comparsion of age-related cataract using logistic regression analysis in WatES in four patient groups: having type 2 diabetes (T2DM) and using statins, type 2 diabetes and not using statins, no diabetes (ND) and using statins, and no diabetes and not using statins.

4.4 DISCUSSION

WatES is a cross-sectional database and therefore cannot determine causation of disease. Retrospective file reviews can identify associations between factors and are useful for directing further study. In this clinic population, a strong association between age and T2DM was confirmed, as the age distribution of these patients with DM was skewed toward the senior years compared to ND patients. It is also important to identify potential biases and to recognize what type of population your sample represents.

Previously, the age distribution of the WatES clinic population was shown to be comparable to that from a study of representative optometric practices across Canada.[5,28] This investigation shows that the age and sex distribution of WatES patients with DM approximated the provincial distributions given by the ODD. The CDA reports that the age and sex-adjusted prevalence of DM per 100 Ontarians over 19 years of age rose from 4.72% in 1995 to 6.19% in 1999 (0.29% increase/year on average).[19] If the increasing trend continued, one could expect that in 2007 the provincial prevalence of DM would have been around 8.51% which approaches the 10.48 % overall rate of DM found in the WatES.

Patients with DM are encouraged to get routine eye assessments because of the increased risk of ocular disease in DM, and therefore, we could expect a clinical eye care population to have a somewhat higher percentage of patients with DM than the general population.[8] The fact that vision assessment costs are covered by the provincial health insurance plan for patients with DM but not non-diabetics between the ages 20 to 64 years of age, could also increase the prevalence of DM in the WatES clinic population. This may explain the slightly higher percentage of 35–64 year old WatES patients with DM compared to ODD. However, WatES also had a lower percentage of patients with DM over 65 years of age compared to ODD. It is possible that proportionately more mature patients with DM are exclusively under ophthalmologic care for advanced disease or are in residential care where they cannot access optometric care as readily.[31] We relied on patient reporting for a diagnosis of DM, unlike other studies that utilized glycosylated haemoglobin (GHb) testing. This may result in a less reliable number of patients with DM in this study.

However, Leske et al.[32] in the Barbados Eye Study (BES) also relied on patient reports of diabetes. They compared results using GHb measurements taken for the study and found consistency in associations for cataracts whether a reported diabetic history or GHb measurements were used. Finally, selection bias in clinic-based population studies can occur as patients with symptoms from maturing cataracts may be more likely to seek out vision care than those without. However, our inclusion of pre-symptomatic levels of cataract helps minimize this bias.

In this study, T2DM was found to be significantly associated with AR cataract. DM has been previously shown to be a risk factor for AR cataracts but the strength of this association has varied among studies.[11–17] Comparison to other studies can be hindered by the differing cataract grading scales and the age-groups chosen by various investigators. Therefore, investigators must conduct literature reviews carefully. In 1998, the BES looked at the relationship between DM and the prevalence of cataract using the LOCS II scale. They reported that a history of DM was related to any age-related lens changes (including lens extraction) in their 4313 patients between 40 and 84 years of age (OR=1.89; 95% CI: 1.52–2.34).[32] As we have generated an AR cataract prevalence function over the entire lifespan, we can extract WatES prevalence values for any specified age group. Considering patients 40 to 84 years only, comparable AR cataract prevalence values to BES are found (OR=2.00, 1.44–2.78).

In addition to overall AR cataract, T2DM was associated with all three morphological cataract subtypes in this population when statins were not considered. However, when controlling for statin use, PSC was no longer associated with T2DM. Previous studies

have varied on which morphological types are at greater risk of developing in patients with DM, but CC and/or PSC are generally identified.[11–13,15, 30,32] Fewer studies have found DM to be a risk factor for NS development. Klein et al.[16] in their five year follow up of the Beaver Dam Eye Study cohort (n=3684) did find that increased levels of GHb were shown to be associated with increased risk of NS and CC. Similarly, at the 10 year follow up of the Blue Mountain Eye Study, Tan et al.[14] found that baseline DM predicted NS and impaired fasting glucose predicted CC when controlling for age and sex. However, most studies looked at much higher grades of nuclear sclerosis than WatES resulting in weak associations between DM and NS. NS at these levels tends to occur at fairly advanced ages where the prevalence of severe DM also diminishes due to increased mortality in patients with DM.[33] Our inclusion of all levels of cataract is less specific to visual significance but is more sensitive to differences in onset and prevalence of cataracts in patients with DM.

A higher rate and earlier age of AR cataract surgery was also found for patients with DM in this population. Presumably, an increased amount of PSC would translate into an increased risk of LE, as it is centrally placed causing debilitating visual symptoms fairly quickly.[34] However, differences in mean age of surgery may reflect differences in surgical criteria by ophthalmologists. Historically, surgeons may have had a higher treatment threshold for cataract removal in patients with DM as they are known to have poorer visual outcomes than non-diabetics which include an increased risk of complications.[35] On the other hand, Pollreisz et al.[36] report that there has been a recent shift towards earlier cataract extraction in patients with DM so lens opacity does not prohibit detailed fundus examination.

Our data cannot suggest causation of AR cataract with statin use but an undeniable association was found in this population after controlling for age, sex and diabetic status. In early clinical trials with statins, researchers did not report significant lenticular changes in patients observed for relatively short periods of less than five years.[23–26,37,38] Several animal studies have clearly shown a correlation between cataract development and chronic statin treatment, although drug dosages have been generally higher than the clinical levels given to humans.[39–41] A few human population studies have even suggested a protective effect with statins use and cataract risk,[42–44] hypothesizing an anti-inflammatory/antioxidant mechanism for the effect.[44] However, Smeeth et al.[45] point out that lens opacities are a gradual process making incident cataracts rare and that many human studies involving statins and cataracts lack adequate power as a result. Cenedella[46] suggests that the long term impact of statin use requires study periods of between10 to 20 years. Beri et al.[47] published a literature review of studies between 1950 and 2008 involving the non-arteroprotective effects of statins. They concluded there was inadequate and conflicting evidence for statin benefit in any condition (including cataract) beyond hyperlipidemia and atherosclerosis. Recently, Hippilsley-Cox and Coupland[27] looked at data for over 2 million patients (ages 30-84) in a prospective cohort study involving 368 general practices in the UK. Over 10% of the patients were new statin users and the effects of statin type, dose and duration of use were estimated by Cox proportional hazard models. Refuting earlier findings, statin use was associated with an increased risk of cataract.

The bio-plausibility of these results lies in the fact that the crystalline lens membrane requires high cholesterol for proper epithelial cell development and lens transparency. Increased cataract formation has been seen in both animals and humans with hereditary cholesterol deficiency[46,48] and the risk exists that statins can inhibit cholesterol biosynthesis in the human lens.

Our study benefits from the statistical power associated with its large sample size. As this is a later study, there also could be more patients with longer exposure to statin use than earlier population studies when statins were first being recommended. Further study is warranted to recommend close monitoring of crystalline lenses in patients benefiting from statins, especially those with T2DM.

4.5 CONCLUSIONS

Given the aging population and the expected increase in the number of people affected by age-related cataract, it is important to identify associated risk factors. In this Canadian clinic population, having a diagnosis of T2DM was significantly associated with an increased prevalence of age-related cataract overall and an earlier onset of NS and CC when statin use is considered. This resulted in a greater proportion of mixed cataract development in this subgroup and an earlier mean age of surgical intervention. Furthermore, in this population, reported statin use was strongly associated with an earlier development of NS and increased risk of PSC. This information can serve Canadian public health efforts to educate people on the risks of DM and promote efforts to curtail current DM prevalence trends.

Chapter 5

General Discussion and Conclusions

This investigation demonstrated how information contained in optometric files at a large clinic can provide epidemiological data. The risk of interpretational bias existed as the file information was coming to the researchers indirectly. However, repeatability analysis done on double-entered files and missing data calculations verified that the study variables could be reliably abstracted and were without significant bias from file omissions. Like other cross-sectional studies, this research described population demographics and the distribution patterns of selected variables while examining associations between these variables without the concern of subject drop out as in cohort studies.[1] Over 6000 patient visits contributed to the information in the WatES database providing significant statistical power for all analysis. The sex and age distribution of this clinic population differed in some aspects compared to that of available statistics on the general Canadian population.[2] This clinic population was not a randomly selected group and was subject to bias in terms the type of individuals seeking out eye care. However, there was sufficient similarity to the demographic profile of Canadian optometric practices in the Robinson study, for clinicians to estimate the chance of AR lens opacity within their patients with these data. By using the criterion of clinically apparent AR cataract as opposed to the more commonly chosen advanced levels of lens opacity, yearly prevalence levels for overall AR cataract approached 100% by the late seventies. Earlier investigations reported on the prevalence of AR cataract in discreet varying age groups making

study comparisons challenging. The WatES database included data for all yearly age groups, and as such the onset of overall AR cataract prevalence was demonstrated as patients reached their late thirties with a sigmoid increase in cataract frequency after that. The probability of AR cataract function, generated through logistic regression analysis allowed predictive prevalence levels at a chosen patient age. Thus, in a similar population, it is likely that half the patients in their mid-fifties would have some AR lens opacity. Early to late NS was the most prevalent lens opacity subtype occurring in 28.8% of the population, and contributed significantly to the probability function. The prevalence of CC was 9.9% in this population followed by PSC at 3.6% which are comparable proportions to a study with similar cataract definitions once age matched.[4] Being female was associated with CC specifically. Despite any differences in our health care system, this Canadian data yielded a similar age of first lens extraction at 72 years compared to European studies.[5,6] Again, consistent with these studies, women had a greater overall rate of bilateral lens extraction but approximately a three year later age of first lens extraction compared to men.

AR cataracts, T2DM and statin use were found to be prevalent conditions, especially after 38 years of age, which made them more appropriate factors for cross-sectional analysis than rarer conditions.[1] Previous work clearly demonstrated associations between diabetes mellitus (DM) and AR cataracts, and this study confirmed a similar association existed when T2DM is considered independently (without type 1 DM) while controlling for age, being female, smoking and hypertension. The impact of this association has not been quantified in the literature in terms of age differences in cataract development between patients with T2DM and those without diabetes.

Applying our probability of AR cataract model to T2DM and non-diabetic subgroups, the age of 50% probability of AR cataract in patients with T2DM was close to four years earlier than patients without DM. As with other studies, significantly more CC was seen in the T2DM subgroup compared to those without DM.[7,8,9,10] However, a clear association with NS and T2DM in this investigation demonstrated how the degree of opacity chosen in these studies can effect associations. The consequences of NS, CC and PSC being associated with T2DM in this population included 7% more mixed cataracts and almost a three year earlier age of first lens extraction in patients with T2DM compared to patients without DM.

Reported statin use was almost 3.5 times higher in patients with T2DM than patients without DM over 38 years of age. Statin use was significantly associated with AR cataract such that the probability of cataract for patients with T2DM who did not use statins was similar to patients without DM who did use statins. Statin use was specifically associated with NS and PSC in this population, which has not found to have been reported previously in the literature. One of the most compelling findings was that PSC, long associated with DM, was no longer significantly associated with T2DM when controlling for statin use. The cross-sectional nature and limitations in available file information did not allow analysis of statin type, dosage, or duration of use and their relationships to lens opacity. However, the strong association found between statin use and AR cataract in this study, validates the need for a more complex study design to investigate these more specific aspects of statin use. Also, cross-sectional studies such as this often become the baseline for future cohort

studies on associations of interest.[1] It is likely that some of the associations found in this study but not in previous investigations, reflect the additional years of potential statin use compared to earlier studies. Statins are intended for long-term use and Neutal et al, in their report on statin use in Canada, found that approximately 75% of users continue to take statins for at least two years once they have started.[11] It is important to point out that statin use does not necessary reflect pre-medication dyslipidemia in this population as use of the pharmaceutical has moved away from only patients with high cholesterol to be recommended for all patients with heart disease and diabetes.[11] A future study that controls for both statin use and blood cholesterol levels and looks at AR cataract frequency while controlling for sex, T2DM, smoking and hypertension would be particularly valuable. Given the high cost of lens extraction to the health care system, further work on the impact of statin use on cataract surgery rates is also recommended.

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References

References for Chapter 1

1. American Optometric Association, Care of the Patient with Diabetes Mellitus, Optometric Clinical Practice Guideline, available at: www.aoa.org/x4813.xml accessed May 2009.
2. Stenson S. Healthy Sight Counseling: Diabetes and the eye. *Clinical and Refractive Optometry* 2009; **20**(11/12): 248–258.
3. Institute for Clinical Evaluative Sciences. Diabetes in Ontario: An ICES Practice Atlas. 2003 [accessed January 2010] available online at: www.ices.on.ca.
4. Amos AF, McCarty DJ, Zimmet P. The Rising Global Burden of Diabetes and its Complications: Estimates and Projections to the Year 2010. *Diabetic Medicine* 1997; **14**: S7–S14.
5. Whitaker NA. Diabetes Mellitus: A Systemic Review and Update. *Clinical and Refractive Optometry* 2006; **17**(11): 408–18.
6. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey.Centre for Disease Control and Prevention. *Jama* 2002; **287**(3): 356–9.
7. Ginsberg HN, Tuck C. Diabetes and Dyslipidemia. *Heart Fail Monit* 2001; **2**(1): 14–20.
8. Fernandez G, Spatz ES, Jablecki C, Phillips PS. Statin myopathy: A common dilemma not reflected in clinical trials. *Cleveland Clinic Journal of Medicine* 2011; **78**(6): 393–403.

9. Neutel CI, Morrison H, Campbell NRC, de Groh M. Statin Use in Canadians: Trends, Determinants and Persistence. *Revue Canadienne de Sante Publique* 2007; **98**(5): 412–6.

10. Carmena R, Betteridge DJ. Statins and diabetes. *Semin Vasc Med.* 2004; **4**(4): 321–32.

11. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364** (9435): 685–696.

12. Gottlieb S. Patients with type 2 diabetes should take statins. *BMJ* 2004; **328**: 1095.

13. Sattar N. Preiss D, Murray HM, Welsh P. Buckley BM et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. *Lancet* 2010: **375**(9716): 735–42.

14. Leske MC, Chylack LT Jr, Wu SY. The Lens Opacities Case-Control Study. Risk factors for cataract. *Arch Ophthalmol* 1991; **109**(2): 244–251.

15. Mukesh BN, Anhchuong L, Dimitrov P; et al. Development of cataract and associated risk factors; The Visual Impairment Project. *Arch Ophthalmol* 2006; **124**(1): 79–85.

16. Delcourt C, Cristol J-P, Tessier F, Leger CL, Michel F, Papoz L. Risk factors for cortical, nuclear and posterior subcapsular cataract: The Pola Study. *American Journal of Epidemiology* 2000; **151**(5): 497–504.

17. Hennis A, Wu SY, Nemesure B, Leske MC. Risk factors for incident cortical and posterior subcapsular lens opacities in the Barbados Eye Studies. *Arch Ophthalmol* 2004; **122**: 525–30.

18. Klein B E K, Klein R, Moss S E. Incidence of cataract surgery in the Wisconsin epidemiologic study of diabetic retinopathy. *American Journal of Ophthalmology* 1995; **119**(3): 295–300.

19. Janghorbani MB, Jones RB, Allison SP. Incidence of and risk factors for cataract among diabetes clinic attenders. *Ophthalmic Epidemiol* 2000; **7**(1): 13–25.

20. Cataract in the adult eye. American Academy of Ophthalmology. Preferred practice patterns. 2008 [accessed October 8, 2008] available from: http://one.aao.org/CE/PracticeGuidelines.

21. Hodge WG, Whitcher JP, Satariano W. Risk Factors for age-related cataracts. *Epidemiol Rev* 1995; **17**: 336–46.

22. Hiller R, Sperduto RD, Ederer F. Epidemiologic associations with nuclear, cortical, and posterior subcapsular cataracts. *Am J Epidemiol* 1986; **124**(6): 917–925.

23. Klein BE, Klein R, Lee KE. Diabetes, cardiovascular disease, selected cardiovascular disease risk factors, and the 5-year incidence of age-related cataract and progression of lens opacities: the Beaver Dam Eye Study. *Am J Ophthalmol* 1998; **126**: 782–90.

24. Leske M. C, Wu S-Y, Hennis A, Connell A M, Hyman L, Schachat A. Diabetes, hypertenstion, and central obesity as cataract risk factors in a black population. The Barbados Eye Study. *Ophthalmology* 1999; **106**(1): 36–41.

25. McCarty CA, Nanjan MB, Taylor HR. Attributable risk estimates for cataract to prioritize medical and public health action. *IOVS* 2000; **41**(12): 3720–3725.

26. Tan JSL, Wang JJ, Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: The Blue Mountains Eye Study. *Ophthalmic Epidemiology* 2008; **15**: 317–327.

27. Raman R, Pal SS, Adams JS, Rani PK, Vaithesswaran K, Sharma T. Prevalence and risk factors for cataract in diabetes: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study, report no. 17. *IOVS* 2010; **51**(12): 6253–61.

28. Sabanayagam C, Wang JJ, Mitchell P, Tan AG, Shyong Tai E. Metabolic syndrome components and age-related cataract: the Singapore Malay Eye Study. *Invest Ophtholmol Vis Sci* 2011; **52**: 2397–2404.

29. Obrosova IG, Chung SSM, Kador PF. Diabetic cataracts: mechanisms and management. *Diabetes Metab Res Rev* 2010; **26**: 172–180.

30. Pollreisz A, Schmidt-Erfurth U. Diabetic cataract- pathogenesis, epidemiology and treatment. *Journal of Ophthalmology* 2010: 1–8.

31. Shichi H. Cataract formation and prevention. *Expert Opin Investig Drugs* 2004; **13**(6): 691–701.

32. Biswas S, Harris F, Singh J, Phoenix D. Role of calpains in diabetes mellitus-induced cataractogenesis: a mini review. *Molecular and Cellular Biochemistry* 2004; **13**(46): 1–9.

33. Behrens-Baumann W, Thiery J, Fieseler HG, Seidel D. Pravastatin-ocular side effects after a two year follow-up? *Lens Eye Toxic Res* 1990; **7**: 311–318.

34. Schmitt C, Schmidt J, Hockwin O. Ocular drug-safety study with the HMG-CoA reductase inhibitor pravastatin. *Lens Eye Toxic Res* 1990; **7**: 631–642.

35. Harris ML, Bron AJ, Brown NA, et al. Absence of effect of simvastatin on the progression of lens opacities in a randomised placebo controlled study. Br J Ophthalmol. 1995; **79**: 996–1002.

36. Lundh BL, Nilsson SE. Lens changes in matched normals and hyperlipidaemic patients treated with simvastatin for 2 years. *Acta Ophthalmol*. 1990; **68**: 658–660.

37. Behrens-Baumann W, Thiery J, Wieland E, Fieseler HG, Seidel D. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor simvastatin and the human lens. Clinical results of a 3-year follow up. *Arzneimittelforschung* 1992; **42**(8): 1023–4.

38. Schmidt J, Schitt C, Hockwin O. No lens changes caused by simvastatin results from a prospective drug safety study. *Lens Eye Toxic Res* 1990; **7**(3-4): 643–50.

39. Hartman HA, Myers LA, Evans M, Robison RL, Engstrom RG, Tse FL. The safety evaluation of fluvastatin, an HMG-CoA reductase inhibitor, in beagle dogs and rhesus monkeys. *Fundam Appl Toxicol* 1996; **29**(1): 48–62.

40. Gerson RJ, MacDonald JS, Alberts AW, et al. On the etiology of subcapsular lenticular opacities produced in dogs receiving HMG-CoA reductase inhibitors. *Exp Eye Res* 1990; **50**(1): 65–76.

41. Zakrzewski P, Milewska J, Czerny K. The eye lens evaluation of the atorvastatin-treated white rat. *Ann Univ Mariae Curie Sklodowska Med* 2002; **57**(2): 165-71.

42. Smeeth L, Hubbard R Fletcher AE. Cataract and the use of statins: a case-control study. *Medicine* 2003; **96**(5): 337–343.

43. Tan JS, Mitchell P, Rochtchina E, Wang JJ. Statin use and the long-term risk of incident cataract: the Blue Mountains Eye Study. *Am J Ophthalmol* 2007; **143**(4): 687–9.

44. Klein BEK, Klein R, Lee KE, Grady LM. Statin use and incident nuclear cataract. *Arch Ophthalmol* 2007; **125**(3): 401–402.

45. Chodick G, Heymann AD, Flash S, Kokia E, Shalev V. Persistance with statins and incident cataract: A population-based historical cohort study. *Annals of Epidemiology* 2010; **20**(2): 136–142.

46. Ruigomez A, Rodriguez LAG, Dev VJ, Arellano F, Raniwala J. Are Schizophrenia or Antipsychotic Drugs a Risk Factor for Cataracts? *Epidemiology* 2000; **11**(6): 620–23.

47. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* 2010; **340**: c2197.

48. Fong DS, Poon KY. Recent Statin Use and Cataract Surgery. *Am J Ophthalmol* 2011; (Epub ahead of print).
49. Cenedella RJ. Cholesterol and cataracts. *Surv Ophthalmol* 1996; **40**(4): 320–37.
50. Mori J, Guixin Li, Abe I, et al. Lanosterol synthase mutations cause cholesterol deficiency-associated cataracts in the Shumiya cataract rat. The Journal of Clinical Investigation 2006; **116**(2): 395–404.
51. Malgorzata JM, Nowaczyk MJM, Whelan DT, Heshka TW, Hill RE. Smith-Lemli-Opitz syndrome: a treatable inherited error of metabolism causing mental retardation. *CMAJ* 1999; **161**(2): 165–70.
52. Goodwin H, Brooks BP, Porter FD. Acute postnatal cataract formation in Smith-Lemli-Opitz syndrome. *Am J Med Genet A* 2008; **146A**(2): 208–11.
53. Beri A, Sural N, Mahahan SB. Non-atheroprotective effects of statins: a systemic review. *American Journal of Cardiovascular Drugs* 2009; **9**(6): 361–70.
54. Hermans MP. Statin therapy and cataract in type 2 diabetes. *Diabetes and Metabolism* 2010; **37**(2): 139–43.

References for Chapter 2

1. Fletcher RW, Fletcher SW. *Clinical Epidemiology; The Essentials*. Baltimore: Lippincott, Williams and Wilkins; 2005.
2. Jansen AC, van Aalst-Cohen ES, Hutten BA, Büller HR, Kastelein JJP, Prins MH. Guidelines were developed for data collection from medical records for use in retrospective analyses. *J Clin Epidemiol* 2005; **58**: 269–74.
3. Allison JJ, Wall TC, Spettell CM, Calhoun J, Fargason CA Jr, Kobylinski RW, Farmer R, Kiefe C. The art and science of chart review. *Jt Comm J Qual Improv* 2000; **26**: 115–36.
4. Zadnik K, Mannis MJ, Kim HS, Miller M, Marquez M. Inter-clinician agreement on clinical data abstracted from patients' medical charts. Optom Vis Sci 1998; **75**: 813–6.
5. Cassidy LD, Marsh GM, Holleran M, Ruhl LS. Methodology to improve data quality from chart review in the managed care setting. *Am J Manag Care* 2002; **8**: 787–93.
6. Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. *Phys Ther* 2005; **85**; 257–68.
7. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979; **86**: 420–8.
8. Statistics Canada. 2006 census of population Canada. Ottawa, Ont, 2007 [accessed November 19, 2008] available from: http://www12.statcan.ca/census-recensement/2006/rt-td/pd-pl-eng.cfm

9. Landis J, Koch G. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**: 159–74.

10. Robinson BE. Prevalence of asymptomatic eye disease. *Can J Optom* 2003; **65**; 175–80.

11. Millar WJ. Vision problems among seniors. *Health Rep* 2004; **16**: 45–9.

12. Rozewski CM. A method for measuring and reporting manual data extraction reliability. *Comput Methods Programs Biomed* 1993; **41**: 17–31.

13. Yawn BP, Wollan P. Interrater Reliability: Completing the Methods Description in Medical Records Review Studies. *Am J Epidemiol* 2005; **161**: 974–7.

14. Stat Trek; Teach yourself statistics. Statistics Tutorial: Sample Size. [accessed November 09, 2009] available from: http://stattrek.com/Lesson6/SampleSize.aspx

15. To T, Estrabillo E, Wang C, Cicutto L. Examining intra-rater and inter-rater response agreement: a medical chart abstraction study of a community-based asthma care program. *BMC Med Res Methodol* 2008; **8**: 29.

References for Chapter 3

1. Leibowitz HM; et al. Framingham Eye Study III. *Cataract. Surv Ophthalmol* 1980; **24**(suppl): 350–65.
2. Cataract in the adult eye. American Academy of Ophthalmology. Preferred practice patterns. 2008 [accessed October 8, 2008] available from: http://one.aao.org/CE/PracticeGuidelines
3. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP. Global data on visual impairment in the year 2002. *Bull World Health Organ* 2004; **82**: 844–51.
4. Thylefors B. The World Health Organization's programme for the prevention of blindness. *Int Ophthalmol* 1990; **14**: 211–19.
5. Javitt JC, Wang F, West SK. Blindness due to cataract: epidemiology and prevention. *Annu Rev Public Health* 1996; **17**: 159–77.
6. Foster A. Who will operate on Africa's 3 million curable blind people? *Lancet* 1991; **337**: 1267–69.
7. Hodge WG, Whitcher JP, Satariano W. Risk Factors for age-related cataracts. *Epidemiol Rev* 1995; **17**: 336–46.
8. West, S. Epidemiology of cataract: Accomplishments over 25 years and future directions. *Ophthalmic Epidemiol* 2007; **14**: 173–8.
9. Sperduto RD. Age-related cataracts: Scope of problem and prospects for prevention. *Prev Med* 1994; **23**: 735–9.

10. Rachmiel R, Trope GE, Chipman ML, Buys YM. Cataract surgery rates in Ontario, Canada, from 1992 to 2004: more surgeries with fewer ophthalmologists. *Can J Ophthalmol* 2007; **42**: 539–42.
11. Hatch WV, Cernat G, Singer S, Bell C M, A 10-year population-based cohort analysis of cataract surgery rates in Ontario. *Can J Ophthalmol* 2007; **42**: 552–6.
12. Robinson BE. Prevalence of Asymptomatic Eye Disease. *Can J Optom* 2003; 65: 175–80.
13. Machan CM, Hrynchak PK, Irving EL. Waterloo Eye Study: data abstraction and population representation. *Optom Vis Sci* 2011; **88**: 613–620.
14. Chylack LT Jr, Leske MC, McCarthy D, Khu P, Kashiwagi T, Sperduto R. Lens opacities classification system II (LOCS II). *Arch Ophthalmol* 1989; **107**: 991–7.
15. Fletcher RW, Fletcher SW. Clinical Epidemiology; The Essentials. Lippincott Williams & Wilkins; 2005.
16. Delcourt C, Cristol J-P, Tessier F, Leger CL, Michel F, Papoz L, and the POLA study group. Risk factors for cortical, nuclear and posterior subcapsular cataracts: The POLA Study. *Am J Epidemiol* 2000; **151**: 497–504.
17. Tan AG, Wang JJ, Rochtchina E, Mitchell P. Comparison of age-specific cataract prevalence in two population-based surveys 6 years apart. *BMC Ophthalmol* 2006; **20**: 17–21.
18. Klein BE, Klein R, Linton KL. Prevalence of age-related lens opacities in a population. The Beaver Dam Eye Study. *Ophthalmology* 1992; **99**: 546–52.

19. Kahn HA, Leibowitz HM, Ganley JP, Kini MM, Colton T, Nickerson RS, Dawber TR. The Framingham Eye Study I. Outline and major prevalence findings. *Am J Epidemiol* 1977; **106**: 17–32.
20. Erie JC, Baratz KH, Hodge DO, Schleck CD, Burke JP. Incidence of cataract surgery from 1980 through 2004: 25-year population-based study. *J Cataract Refract Surg* 2007; **33**: 1273–7.
21. Kathan GL, Wang JJ, Rochtcina E; Ten-year incidence of age-related cataract and cataract surgery in an older Australian population. The Blue Mountains Eye Study. *Ophthalmology* 2008; **115**: 808–14.
22. McCarty CA, Nanjan MB, Taylor HR. Attributable risk estimates for cataract to prioritize medical and public health action. *Invest Ophthalmol Vis Sci* 2000; **41**: 3720–5.
23. Leske MC, Chylack LT Jr, Wu SY. The Lens Opacities Case-Control Study. Risk factors for cataract. *Arch Ophthalmol* 1991; **109**: 244–51.
24. Mukesh BN, Le A, Dimitrov PN, Ahmed S, Taylor HR, McCarty CA. Development of cataract and associated risk factors; The Visual Impairment Project. *Arch Ophthalmol.* 2006; 124: 79–85.
25. Worzala K Worzala K, Hiller R, Sperduto RD, Mutalik K, Murabito JM, Moskowitz M, D'Agostino RB, Wilson PW. Postmenopausal estrogen use, type of menopause, and lens opacities in the Framingham studies. *Arch Intern Med.* 2001; **161**: 1448–54.
26. Cumming R G, Mitchell P. Hormone replacement therapy, reproductive factors, and cataract: the Blue Mountain Eye Study. *Am J Epidemiol* 1997; **145**: 242–9.

27. Panchapakesan J, Mitchell P, Tumuluri K, Rochtchina E, Foran S, Cumming RG.. Five year incidence of cataract surgery: the Blue Mountains Eye Study. *Br J Ophthalmol* 2003; **87**: 168–72.

28. Klein BEK, Klein R, Moss SE. Incident cataract surgery. The Beaver Dam Eye Study. *Ophthalmology* 1997; **104**: 573–80.

29. O'Reilly P, Mahmoud U, Hayes P, Tormey P, Beatty S. Age and sex profile of patients having cataract surgery between 1986 and 2003. *J Cataract Refract Surg* 2005; **31**: 2162–6.

30. Bilinska E, Moll A, Kowalczyk G, Omulecki W. Epidemiology of cataract in clinical material of Department of Ophthalmology, Medical University of Lodz. *Klin Oczna* 2004; **106**: 450–2 (English - abstract only).

31. Cugati S, Cumming RG, Smith W, Burlutsky G, Mitchell P, Wang JJ. Visual impairment, age-related macular degeneration, cataract and long-term mortality. The Blue Mountains Eye Study. *Arch Ophthalmol* 2007; **125**: 917–24.

32. Hennis A, Wu SY, Li X, Nemesure B, Leske MC; Barbados Eye Study Group. Lens opacities and mortality: the Barbados Eye Studies. *Ophthalmology* 2001; **108**: 498–504.

References for Chapter 4

1. Machan CM, Hrynchak PK, Irving IL. Modeling the prevalence of age-related cataract: Waterloo Eye Study. *OVS* 2011; **89**(2): 1-7.
2. Leibowitz HM, Krueger DE, Maunder LR, et al. The Framingham Eye Study monograph: An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973–1975 **.** Framingham Eye Study III. Cataract. *Surv Ophthalmol* 1980; **24**(suppl): 350–365.
3. Tan AG, Wang JJ, Rochtchina E, Mitchell P. Comparison of age-specific cataract prevalence in two population-based surveys 6 years apart. *BMC Ophthalmol* 2006; **6**: 17.
4. Klein BE, Klein R, Linton KL. Prevalence of age-related lens opacities in a population. The Beaver Dam Eye Study. *Ophthalmology* 1992; **99**: 546–552.
5. Robinson BE. Prevalence of Asymptomatic Eye Disease. *Can J Optom* 2003; **65**: 175–180.
6. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ* 2004; **82**: 844–851.
7. Javitt JC, Wang F, West SK. Blindness due to cataract: epidemiology and prevention. *Annu Rev Public Health* 1996; **17**: 159–177.
8. Hodge WG, Whitcher JP, Satariano W. Risk Factors for age-related cataracts. *Epidemiol Rev* 1995; **17**: 336–346.

9. American Academy of Ophthalmology. Cataract in the Adult Eye, Preferred practice patterns. 2008 [accessed October 8, 2008] available at: http://www.aao.org/CE/PracticeGuidelines.

10. American Optometric Association, Care of the Adult Patient with Cataract, Optometric Clinical Practice Guideline [accessed May 2009] available at: www.aoa.org/x4813.xml.

11. Delcourt C, Cristol JP, Tessier F, Léger CL, Michel F, Papoz L. Risk factors for cortical, nuclear and posterior subcapsular cataract: The POLA Study. *Am J Epidemiol* 2000; **151**: 497–504.

12. Leske MC, Chylack LT Jr, Wu SY. The Lens Opacities Case-Control Study. Risk factors for cataract. *Arch Ophthalmol* 1991; **109**: 244–251.

13. Mukesh BN, Le A, Dimitrov PN, Ahmed S, Taylor HR, McCarty CA. Development of cataract and associated risk factors; The Visual Impairment Project. *Arch Ophthalmol* 2006; **124**: 79–85.

14. Tan JSL, Wang JJ, Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: The Blue Mountains Eye Study. *Ophthalmic Epidemiol* 2008; 15: 317–327.

15. Hennis A, Wu SY, Nemesure B, Leske MC; Barbados Eye Studies Group. Risk factors for incident cortical and posterior subcapsular lens opacities in the Barbados Eye Studies. *Arch Ophthalmol* 2004; **122**: 525–530.

16. Klein BE, Klein R, Lee KE. Diabetes, cardiovascular disease, selected cardiovascular disease risk factors, and the 5-year incidence of age-related

cataract and progression of lens opacities: the Beaver Dam Eye Study. *Am J Ophthalmol* 1998; **126**: 782–790.

17. West S. Epidemiology of cataract: Accomplishments over 25 years and future directions. *Ophthalmic Epidemiol* 2007; **14**: 173–178.
18. Stenson S. Healthy sight counseling: Diabetes and the eye. *Clinical Refractive Optometry* 2009; **20**: 248–258.
19. Institute for Clinical Evaluative Sciences. Diabetes in Ontario: An ICES Practice Atlas. 2003 [accessed January 2010] available online at: www.ices.on.ca.
20. Carmena R, Betteridge DJ. Statins and diabetes. *Semin Vasc Med* 2004; **4** :321–332.
21. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**: 685–696.
22. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. *Clin Diabetes* 2008; **26**: 77–82.
23. Behrens-Baumann W, Thiery J, Fieseler HG, Seidel D. Pravastatin-ocular side effects after a two year follow-up? *Lens Eye Toxic Res* 1990; **7**: 311–318.
24. Schmitt C, Schmidt J, Hockwin O. Ocular drug-safety study with the HMG-CoA reductase inhibitor pravastatin. *Lens Eye Toxic Res* 1990; **7**: 631–642.
25. Harris ML, Bron AJ, Brown NA, et al. Absence of effect of simvastatin on the progression of lens opacities in a randomised placebo controlled study. *Br J Ophthalmol* 1995; **79**: 996–1002.

26. Lundh BL, Nilsson SE. Lens changes in matched normals and hyperlipidaemic patients treated with simvastatin for 2 years. *Acta Ophthalmol* 1990; **68**: 658–660.

27. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ*. 2010; **340**: c2197.

28. Machan CM, Hrynchak PK, Irving EL. Waterloo Eye Study: data abstraction and population representation. *Optom Vis Sci* 2011; **88**: 613–620.

29. Chylack LT Jr, Leske MC, McCarthy D, Khu P, Kashiwagi T, Sperduto R. Lens opacities classification system II (LOCS II). *Arch Ophthalmol* 1989; **107**: 991–997.

30. Sabanayagam C, Wang JJ, Mitchell P, Tan AG, Shyong Tai E. Metabolic syndrome components and age-related cataract: the Singapore Malay Eye Study. *Invest Ophtholmol Vis Sci* 2011; **52**: 2397–2404.

31. Centers for Disease Control and Prevention (CDC). National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2005. [Accessed February 12, 2011] available at: http://www.cdc.gov/diabetes/pubs/pd/ndfs_2005.

32. Leske M. C, Wu S-Y, Hennis A, Connell A M, Hyman L, Schachat A. Diabetes, hypertenstion, and central obesity as cataract risk factors in a black population. The Barbados Eye Study. *Ophthalmology* 1999; **106**: 36–41.

33. Ederer F, Hiller R, Taylor HR. Senile lens changes and diabetes in two population studies. *Am J Ophthalmol* 1981; 91: 381–395.

34. Panchapakesan J, Mitchell P, Tumuluri K, Rochtchina E, Foran S, Cumming RG. Five year incidence of cataract surgery: the Blue Mountains Eye Study. *Br J Ophthalmol* 2003; **87**: 168–172.

35. Sadiq SA, Chatterjee, Vernon SA. Progresion of diabetic retinopathy and rubeotic glaucoma following cataract surgery. *Eye* 1995; **9**: 728–738.

36. Pollreisz A, Schmidt-Erfurth U. Review Article. Diabetic cataract—pathogenesis, epidemiology and treatment. *J Ophthalmol* 2010: ID 608751.

37. Behrens-Baumann W, Thiery J, Wieland E, Fieseler HG, Seidel D. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor simvastatin and the human lens. Clinical results of a 3-year follow up. *Arzneimittelforschung* 1992; **42**: 1023–1024.

38. Schmidt J, Schmitt C, Hockwin O. No lens changes caused by simvastatin results from a prospective drug safety study. *Lens Eye Toxic Res* 1990; **7**: 643–650.

39. Hartman HA, Myers LA, Evans M, Robison RL, Engstrom RG, Tse FL. The safety evaluation of fluvastatin, an HMG-CoA reductase inhibitor, in beagle dogs and rhesus monkeys. *Fundam Appl Toxicol* 1996; **29**: 48–62.

40. Zakrzewski P, Milewska J, Czerny K. The eye lens evaluation of the atorvastatin-treated white rat. *Ann Univ Mariae Curie Sklodowska Med* 2002; **57**: 165–171.

41. Gerson RJ, MacDonald JS, Alberts AW, et al. On the etiology of subcapsular lenticular opacities produced in dogs receiving HMG-CoA reductase inhibitors. *Exp Eye Res* 1990; **50**: 65–78.

42. Chodick G, Heymann AD, Flash S, Kokia E, Shalev V. Persistance with statins and incident cataract: A population-based historical cohort study. *Ann Epidemiol* 2010; **20**: 136–142.

43. Tan JS, Mitchell P, Rochtchina E, Wang JJ. Statin use and the long-term risk of incident cataract: the Blue Mountains Eye Study. *Am J Ophthalmol* 2007; **143**: 687–689.

44. Klein BEK, Klein R, Lee KE, Grady LM. Statin use and incident nuclear cataract. *JAMA* 2006; **125**: 401–402.

45. Smeeth L, Hubbard R, Fletcher AE. Cataract and the use of statins: a case-control study. *QJM* 2003; **96**: 337–343.

46. Cenedella RJ. Cholesterol and cataracts. *Surv Ophthalmol* 1996; **40**: 320–337.

47. Beri A, Sural N, Mahahan SB. Non-atheroprotective effects of statins: a systemic review. *Am J Cardiovasc Drugs* 2009; **9**: 361–370.

48. Mori J, Li G, Abe I, et al. Lanosterol synthase mutations cause cholesterol deficiency-associated cataracts in the Shumiya cataract rat. *J Clin Invest* 2006; **116**: 395–404.

References for Chapter 5

1. Hulley SB, Dummings SR. *Designing Clinical Research*. 1988, Baltimore, Williams and Wilkins.
2. Statistics Canada. 2006 census of population Canada. Ottawa, Ont, 2007 [accessed November 19, 2008] available from: http://www12.statcan.ca/census-recensement/2006/rt-td/pd-pl-eng.cfm
3. Robinson BE. Prevalence of Asymptomatic Eye Disease. *Can J Optom* 2003; **65**: 175–180.
4. Klein BE, Klein R, Linton KL. Prevalence of age-related lens opacities in a population. The Beaver Dam Eye Study. *Ophthalmology* 1992; **99**: 546–52.
5. O'Reilly P, Mahmoud U, Hayes P, Tormey P, Beatty S. Age and sex profile of patients having cataract surgery between 1986 and 2003. *J Cataract Refract Surg* 2005; **31**: 2162–6.
6. Bilinska E, Moll A, Kowalczyk G, Omulecki W. Epidemiology of cataract in clinical material of Department of Ophthalmology, Medical University of Lodz. *Klin Oczna* 2004; **106**: 450–2(English - abstract only).
7. Delcourt C, Cristol JP, Tessier F, Léger CL, Michel F, Papoz L. Risk factors for cortical, nuclear and posterior subcapsular cataract: The POLA Study. *Am J Epidemiol*. 2000; **151**: 497–504.
8. Leske MC, Chylack LT Jr, Wu SY. The Lens Opacities Case-Control Study. Risk factors for cataract. *Arch Ophthalmol*. 1991; **109**: 244–251.

9. Mukesh BN, Le A, Dimitrov PN, Ahmed S, Taylor HR, McCarty CA. Development of cataract and associated risk factors; The Visual Impairment Project. *Arch Ophthalmol*. 2006; **124**: 79–85.
10. Hennis A, Wu SY, Nemesure B, Leske MC; Barbados Eye Studies Group. Risk factors for incident cortical and posterior subcapsular lens opacities in the Barbados Eye Studies. *Arch Ophthalmol*. 2004; **122**: 525–530.
11. Neutel CI, Morrison H, Campbell NRC, de Groh M. Statin Use in Canadians: Trends, Determinants and Persistence. *Revue Canadienne de Sante Publique* 2007; **98**(5): 412–6.

Appendix

Additional Table for Chapter 2

Table 2-6 Distribution of Waterloo Vision Study patients in five-year increments

Age group	Number of patients	% study population
<5	460	7.2
5-9	465	7.3
10-14	373	5.8
15-19	350	5.5
20-24	474	7.4
25-29	252	3.9
30-34	228	3.6
35-39	244	3.8
40-44	337	5.3
45-49	431	6.7
50-54	395	6.2
55-59	398	6.2
60-64	432	6.8
65-69	444	6.9
70-74	404	6.3
75-79	362	5.7
80-84	242	3.8
85+	106	1.7
Total	6397	100

Additional Figures for Chapter 2

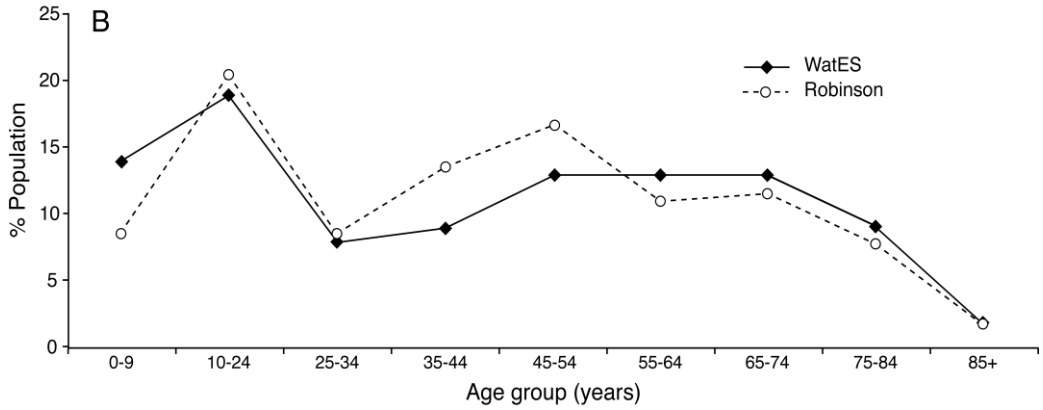

Figure 2-3 Distribution of WatES patients and representative optometric private practice patients from the Robinson Study (2003) in ten year increments.

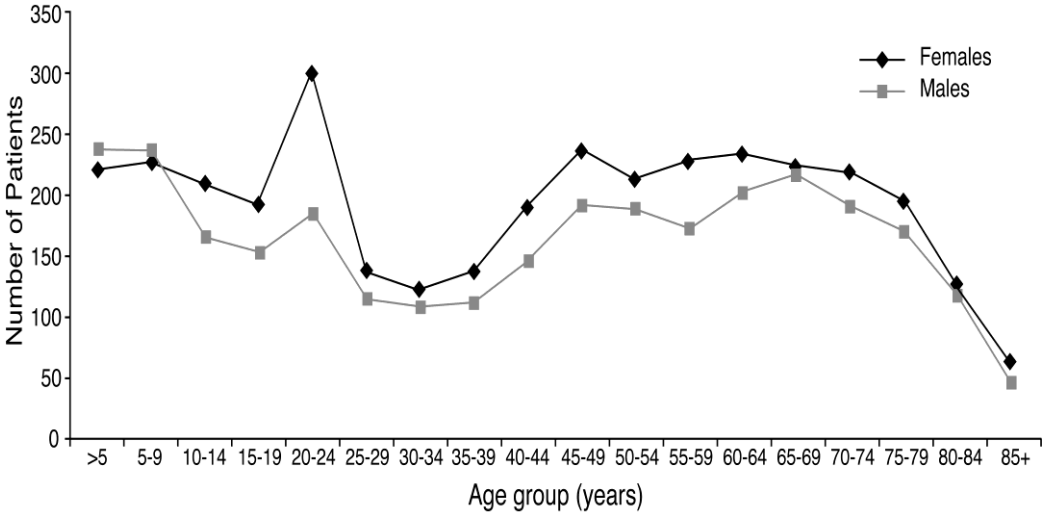

Figure 2-4 Age distribution of male and female WatES patients in five year increments.