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The association between fruit and vegetable consumption and physical activity with the risk of glaucoma: a retrospective cohort study

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Abstract

Objectives: This study aimed to examine whether physical activity and consumption of fruits and vegetables were associated with the risk of developing glaucoma.

Methods: The Household, Longitudinal component of the Canadian National Population Health Survey database was used. Weighted crude and adjusted Cox proportional hazards models were fitted with time-dependent covariates. The adjusted models were controlled for age, sex, BMI, cigarette smoking, alcohol consumption, diabetes mellitus, arterial hypertension, heart disease, education, and income.

Results: A total of 9,950 respondents were included, of which 190 developed glaucoma within the 10-year follow-up period. The adjusted hazards ratios for physical activity and fruit and vegetable consumption were 0.99 [95% CI: 0.87, 1.12] and 1.03 [95% CI: 0.93, 1.14], respectively.

Conclusion: The results suggest that physical activity and consumption of fruit and vegetable are not associated with the risk of developing glaucoma. Future studies should consider including other aspects of diet and physical fitness.

Keywords: physical activity, fruit and vegetable consumption, NPHS, glaucoma.

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List of Abbreviations

BMI – Body Mass Index

CI – Confidence Interval

FV – Fruits and Vegetables

HR – Hazard Ratio

MCMC – Markov Chain Monte Carlo

NPHS – National Population Health Survey

OR – Odds Ratio

PACG – Primary Angle-Closure Glaucoma

POAG – Primary Open-Angle Glaucoma

SES – Socioeconomic Status

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Chapter 1

1. Introduction

Glaucoma is a disease defined as "optic neuropathy that is characterized by specific structural findings in the optic disc and specific functional deficits" (Cook & Foster, 2012). It manifests as an optic neuropathy with a cupped nerve characterized by retinal ganglion cell apoptosis, and its greatest risk factor is high intraocular pressure (Zhu et al., 2018). Glaucoma affects approximately 67 million people globally (Rouland, Berdeaux, & Lafuma, 2005), with 5.2 million visually impaired as a result of this disease (Thylefors & Négrel, 1994). It is the second leading cause of blindness in the world, contributing to approximately 15% of cases of blindness (Leske, 1983; Thylefors & Négrel, 1994). Visual impairment caused by glaucoma is irreversible; therefore, prevention is crucial in controlling the burden of this disease. Disability from advanced glaucoma is the most severe amongst the major blinding diseases, as both peripheral and central vision are affected. Lastly, glaucoma – a chronic disease that can begin as early as 40 years of age and requires constant monitoring, medications, lasers and surgery – is the largest visually-related health economic burden.

Living a healthy lifestyle, through healthy eating and physical activity, has been known to be associated with a decreased risk of numerous chronic diseases, including coronary artery disease, hypertension, and diabetes (Roberts & Barnard, 2005). Along with the many benefits of exercise, it may also be beneficial in reducing the risk of glaucoma. Findings have suggested that exercise aids in the outflow from eye channels by blocking obstruction, which may occur in some outflow canals (Coleman & Kodjebacheva, 2009). In addition, many studies have shown that physical activity has a positive effect on intraocular pressure (Chiotoroiu, Popa, Ştefãniu, Secureanu, & Purcărea, 2013; Dane, Koçer, Demirel, Ucok, & Tan, 2006; Katz & Sommer, 1987; Marcus, Edelhauser, Maksud, & Wiley, 1974; Risner et al., 2009; Schacknow & Samples, 2010). Since intraocular pressure is a major risk factor for glaucoma, the association between physical activity and the risk of developing glaucoma appears quite plausible and warrants investigation.

Certain antioxidants found in fruits and vegetables (FV) have been found to decrease oxidative stress which has been shown to be linked to optic nerve deterioration (Parikh & Parikh, 2011). Furthermore, there is a possibility that certain diets rich in vitamins, found in FVs, can improve the function of the trabecular meshwork, which in turn would protect the optic nerve from damage (Kang et al., 2003). Therefore, an association between FV and glaucoma should be examined.

The purpose of this study was to examine whether lifestyle factors, namely FV intake and physical activity, influence the risk of developing glaucoma. The National Population Health Survey (NPHS) from Statistics Canada was utilized for this study.

Chapter 2

2. Background

This chapter explores the types, treatment and diagnosis of glaucoma (2.1). Following this, both the public health burden (2.2) and economic burden (2.3) of this condition are described.

2.1 Overview of Glaucoma

Glaucoma is a chronic, progressive eye disease defined by the presence of optic neuropathy (Casson, Chidlow, Wood, Crowston, & Goldberg, 2012). The presence of optic neuropathy is indicated by the developing changes occurring in the optic nerve head "comprising focal or generalized thinning of the neuroretinal rim with excavation and enlargement of the optic cup" (Casson et al., 2012). The lamina cribrosa, a fibrous tissue which forms the lower portion of the optic cup and allows for the passage of the optic nerve and associated vessels through the scleral layer, is known to be the structure primarily affected by glaucoma (Schacknow & Samples, 2010, p. 83). This occurs when the trabecular meshwork, a mesh-like structure present at the angle where the iris and cornea meet, is compromised. This causes the intraocular pressure to rise and push on the lamina cribrosa, resulting in permanent damage to the fibrous tissue. Although visual field loss may not be observed in the early stages of this disease, the progression of glaucoma can lead to complete blindness when untreated (Casson et al., 2012). A fully labeled diagram of the eye may be viewed in Figure 2.1.

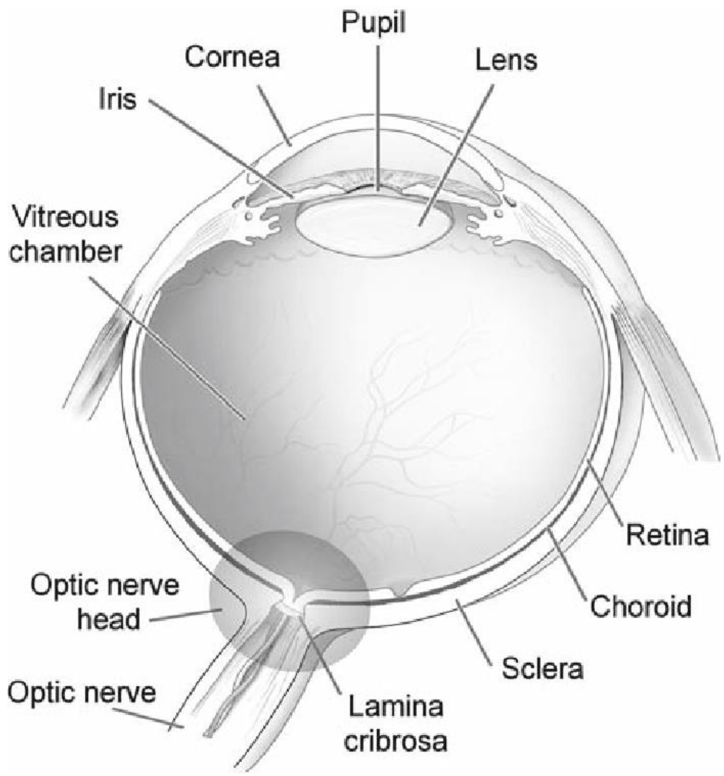

Figure 2.1 Fully labelled diagram of the cross-section of a human eye.

**Retrieved from https://www.researchgate.net/profile/Ian_Sigal/publication/5541908/figure/fig1/AS:394710666498057 @1471117764327/Fig-1-Schematic-cross-section-through-a-human-eye-Light-enters-the-eye-through-the.png*

2.1.1 Types of Glaucoma

There are two major types of primary glaucoma: primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG). The primary and secondary types of glaucoma are discussed in further detail in the following sections.

Primary Open-Angle Glaucoma

Approximately 75% of glaucoma patients are diagnosed with POAG (Quigley & Broman, 2006). POAG is determined by the angle at which the fluid drains from the eye (Schacknow & Samples, 2010, p. 400). Patients with POAG have a wide anterior chamber angle, which is always open regardless of the disease's stage (Grant & Chandler, 2013, p.

186). Anatomically, an open angle is greater than 20 degrees, and is located where the iris plane and posterior cornea meet the ciliary body face, also known as the drainage canal (Schacknow & Samples, 2010, p. 400). The progression of POAG is rather slow and can result in the development of symptoms without notice.

Normal tension glaucoma is a type of POAG characterized by normal intraocular pressure (i.e., less than 22 mmHg) (Schacknow & Samples, 2010, p. 421). As a result of the normal intraocular pressure levels, normal tension glaucoma can easily go undiagnosed during the early stages, at which point the central visual functions are affected (Grant & Chandler, 2013, p. 207). This condition is difficult to treat because most glaucoma treatments target intraocular pressure (Grant & Chandler, 2013, p. 207).

Primary Angle-Closure Glaucoma

PACG is characterized by a narrowing anterior chamber angle located where fluid outflow occurs. PACG is the second most common type of glaucoma; however, it is the most devastating. Although not as prevalent as POAG, PACG contributes to the largest proportion of blindness among glaucoma patients (Quigley & Broman, 2006). People with PACG typically have eyes that are shorter in length, and smaller in anterior chamber depth (Quigley, 1996). In comparison with POAG, this type of glaucoma develops more quickly, and its symptoms are much more prominent.

Secondary Types of Glaucoma

Secondary types of glaucoma occur when there is an identifiable pathological cause for the optic nerve deterioration, such as eye trauma (Casson et al., 2012). Some other causes include surgery, advanced cataract, certain eye tumors, uveitis (uvea inflammation), diabetes, and the use of corticosteroid drugs (Access Economics, 2008). Common secondary types of glaucoma include exfoliative, neovascular, pigmentary, traumatic, uveitic, and congenital. Both secondary open-angle and secondary closed-angle types of glaucoma exist.

2.1.2 Diagnosis and Treatment

Glaucoma is primarily diagnosed using ocular computerized tomography. This is a new diagnostic technique that takes only about 5 minutes and uses x-rays, magnetic resonance imaging, or B-scan ultrasounds to produce cross-sectional images of the entire eye (Schuman et al., 1995). This technique also allows possible early detection of glaucoma and glaucomatous progression (Schuman et al., 1995). As visual field testing takes approximately 30 minutes, it is used as a supporting test. Automated visual field testing helps to observe any optic disc irregularities (Cook & Foster, 2012; Foster, Buhrmann, Quigley, & Johnson, 2002). However, visual field loss occurs at later stages of the disease (Thylefors & Négrel, 1994).

Since blindness resulting from glaucoma is irreversible, treatments for glaucoma specifically focus on delaying or stopping progression (Marquis & Whitson, 2005). Treatment usually starts with eye drops, drugs, or laser, with some incisional surgeries needed in severe cases (Lee & Higginbotham, 2005; Marquis & Whitson, 2005). Most glaucoma treatments aim to protect the optic nerve from damage because neuroprotection is crucial in delaying the progression of this condition (Marquis & Whitson, 2005).

2.2 Public Health Burden

Glaucoma is a major disease that needs to be addressed in tackling the issue of worldwide blindness (World Health Organization, 1985). It is expected that by the year of 2020, the number of worldwide glaucoma cases will increase to 79.6 million, of which 11.2 million are expected to eventually go blind as a result (Cook & Foster, 2012; Quigley & Broman, 2006). In Canada, the estimated prevalence of glaucoma was found to be approximately 1.8% (Perruccio, Badley, & Trope, 2007). It is important to note that prevalence increases with age.

Vision loss increases aging patients' vulnerability to daily living struggles, clinical depression, and social dependence. In addition, vision loss victims are prone to higher rates of car accidents and falls, hip fractures, premature admission to nursing homes, and premature death (Access Economics, 2008; Ramulu, 2009). Many of these issues are a result of the mobility issues associated with vision loss. The next section discusses the economic burden associated with this chronic eye disease.

2.3 Economic Burden

Glaucoma is a very costly disease, mostly due to treatment and disability. Vision loss in Canada accounts for approximately 8% of the economic burden of all illnesses and has the highest direct costs associated with it, ranking even higher than diabetes. (Access Economics, 2008). The total financial burden of vision loss in Canada in 2007 was estimated to be approximately $15.8 billion; in other words, $19,370 was spent for each visually impaired individual (Cruess, Gordon, Bellan, Mitchell, & Pezzullo, 2011). If vision loss is not controlled, the economic burden of this disability could increase to a total annual cost of approximately $30.3 billion in Canada by the year 2032 (Access Economics, 2008). With an estimated total of $54.7 million in 1998, costs associated with glaucoma treatment increase with the severity of the condition (Rouland et al., 2005) and are expected to be much higher now (Access Economics, 2008).

An Ontario-based cost analysis reported the treatment cost associated with glaucoma (inclusive of the procedure and physician, assistant, and anesthetist/anesthesiologist's fees) ranged from $344 to $511 per person, varying based on the severity of the condition

(Iskedjian et al., 2003). An example of experience of a glaucoma patient, diagnosed in his/her early 40s, is as follows. Once a patient is diagnosed with the disease, he/she would be required to visit the ophthalmologist twice a year with testing to monitor his/her condition. Then he/she is prescribed drops, which gradually increase in dosage. Now this patient (in his/her 50s) uses laser treatments and even more drops, with more visits. In his/her early 60s, he/she has trabeculectomy surgery, and in his/her late 60s – valve surgery. As he/she continues aging into his/her 70s, he/she is now visually impaired and needs increased assistance in the activities of daily living. As his/her vision deteriorates further into blindness, even more help is required. Looking back at the path of this patient, he/she has undergone 45 years of treatments and tests, with enormous associated financial costs.

The actual economic burden of glaucoma may be even greater than estimated because although approximately a quarter of a million Canadians have glaucoma, in reality only about half of these people are aware that they have this disease, and therefore may not seek out treatment (Access Economics, 2008; Anraku et al., 2011; Quigley, 1996). Some eye professionals may fail to diagnose glaucoma in the early stages, which is why most diagnoses occur in the later stages, when the condition becomes more severe (Access Economics, 2008). In fact, a 2004 population-based study which aimed to examine features of undiagnosed OAG showed that approximately 59% of all glaucoma cases from a cluster-stratified random sample of 4744 respondents were undiagnosed by eye care providers (E. Y. H. Wong et al., 2004). Therefore, the burden of glaucoma is much greater than estimated by many studies.

Chapter 3

3. Literature Review

In this chapter, the literature on risk factors of glaucoma is explored. A comprehensive search was undertaken, using PubMed, Embase, MEDLINE, CINAHL, and the Cochrane Library. Both published and unpublished articles were reviewed. Additionally, hand-searching was done to further identify any studies which may have been missed through the search of the databases listed above. A detailed list of keywords and MeSH terms is provided in Appendix A, Table 1.

3.1 Risk Factors

3.1.1 Intraocular Pressure

Intraocular pressure is defined as the pressure within the eye and is used to predict the risk of developing glaucoma as well as the rate of progression (Cook & Foster, 2012). As a matter of fact, intraocular pressure has repeatedly been implicated as a risk factor for presence of glaucoma (Medeiros, 2014), but is not necessary for the disease to occur (Foster et al., 2002; Gupta, 2005, p. 7). People can have vision loss indicative of glaucoma with a low intraocular pressure, and people with high intraocular pressure may not have glaucoma (Drance, 1999). In fact, one study showed that only 54% persons with incident cases of glaucoma had an elevated intraocular pressure (Leske, Wu, Hennis, Honkanen, & Nemesure, 2008). In addition, normal tension glaucoma patients develop glaucoma regardless of having low intraocular pressure.

3.1.2 Age

Age has been established as a risk factor for glaucoma. Numerous studies have found an association between age and the incidence and/or prevalence of glaucoma (Cook & Foster, 2012; Gupta, 2005). For example, the Beaver Dam Eye study showed that the prevalence of POAG in subjects between the ages of 43 and 54 was approximately a quarter of that found in subjects older than 75 (Klein et al., 1992). The association between age and the occurrence of glaucoma may be a result of ocular tissue deterioration, specifically the deterioration of the trabecular meshwork and the lamina cribrosa, the crowding of the anterior chamber due to an increase in crystalline lens thickness, and poor medication adherence (Boland & Quigley, 2007; Gupta, 2005).

3.1.3 Sex

In some studies, women have been found to be more likely to develop glaucoma in comparison to men (Amerasinghe & Aung, 2008; Cedrone, Mancino, Cerulli, Cesareo, & Nucci, 2008; Mitchell, Smith, Attebo, & Healey, 1996; Quigley & Broman, 2006; Vajaranant, Nayak, Wilensky, & Joslin, 2010). These findings are consistent with the fact that women are predisposed to having a shorter eye as well as a shallower anterior chamber than men (Gupta, 2005; Mark, 2005). However, in the Rotterdam study the age-adjusted prevalence of glaucoma was found to be higher among men than women (Dielemans et al., 1994). Overall, the literature association between sex and glaucoma seems to indicate that females are at higher risk of developing glaucoma than males.

3.1.4 Ethnicity/Race

Ethnicity has been implicated as a risk factor for glaucoma. The occurrence of POAG has been found to be higher among Africans than among Chinese, Indians, Europeans and Japanese people (Cedrone et al., 2008; Quigley & Broman, 2006). The age-adjusted prevalence rates of POAG among black respondents was found to be four to five times as high as among white respondents in the Baltimore Eye Survey (Tielsch et al., 1991). Further, the average age of onset of glaucoma was also much lower for black people (49.5 years of age), compared with white people (at 59.5 years) (R. Wilson, Richardson, Hertzmark, & Grant, 1985). Black people may be at a higher risk of developing glaucoma due to an increased disc area and therefore increased mechanical stress in the eye leading to damage (Gupta, 2005). The disease severity has also been found to be greater among blacks, with worse disk damage and visual field loss, and a faster rate of progression (Racette, Wilson, Zangwill, Weinreb, & Sample, 2003; R. Wilson et al., 1985).

3.1.5 Family History

Family history of glaucoma is an important risk factor for occurrence of glaucoma (Coleman & Miglior, 2008; Hulsman et al., 2002; Tielsch, Katz, Sommer, Quigley, & Javitt, 1994). According to findings, approximately half of POAG patients had a family history of glaucoma (Leske, Connell, Wu, Hyman, & Schachat, 1995; Shin, Becker, & Kolker, 1977). Glaucoma was found to occur more often when members from the maternal side also had the condition in comparison to the paternal side (Shin et al., 1977). Furthermore, the odds of having glaucoma were higher when glaucoma was also present in siblings compared to in parents (Tielsch et al., 1994). The association between family history and glaucoma was found to become weaker in older persons (Budde & Jonas, 1999).

3.1.6 Cigarette Smoking

Cigarette smoking is a major risk factor for the development and progression of glaucoma (Bonovas, Filioussi, Tsantes, & Peponis, 2004; Chiotoroiu, De Popa, Stefaniu, Secureanu, & Purcarea, 2013). The risk of having glaucoma has been found to be almost three times as high in current smokers as in non-smokers (M. R. Wilson, Hertzmark, Walker, Childs-Shaw, & Epstein, 1987). Additionally, a meta-analysis showed that current smokers had 37% higher odds of having POAG compared to non-smokers (Bonovas, Filioussi, et al., 2004). Vasoconstriction, which occurs as a consequence of smoking, may be the mechanism behind the increased risk associated with smoking, which may lead to a more vulnerable optic nerve (Chiotoroiu, De Popa, et al., 2013).

3.1.7 Alcohol Consumption

There was found to be an association between alcohol consumption and glaucoma, with alcohol use leading to a higher odds of glaucoma occurrence (Chiotoroiu, De Popa, et al., 2013; Katz & Sommer, 1987). Interestingly, drinking alcohol was shown to decrease intraocular pressure within the glaucomatous eye (Houle & Grant, 1967). The prevailing explanation for this association is the diuretic properties of alcohol, which may lead to increased circulation of water within the eye and therefore cause perfusion problems (Chiotoroiu, De Popa, et al., 2013).

3.1.8 Corticosteroid Use

Corticosteroids have been implicated as a risk factor of glaucoma for many years (Jones & Rhee, 2006; Tripathi, Parapuram, Tripathi, Zhong, & Chalam, 1999). One of the adverse effects of corticosteroid use is the increase in intraocular pressure levels (Kersey & Broadway, 2005). The reasoning behind this association is that the use of corticosteroids changes the trabecular meshwork cells in multiple ways, some of which include the cell shape and function (Clark, 1995).

3.1.9 Myopia

Myopia, also known as nearsightedness or short-sightedness, has been shown to be a risk factor for glaucoma, specifically POAG (M. W. Marcus, de Vries, Montolio, & Jansonius, 2011). A recent meta-analysis based on 11 original studies reported that the odds of having glaucoma were 88% higher in subjects with any type of myopia than in those with no myopia (M. W. Marcus et al., 2011). A proposed explanation between this association is that individuals with myopia may have optic nerve heads which are more prone to damage as a result of increased intraocular pressure in comparison to those without myopia (Chihara et al., 1997; Jonas, Gusek, & Naumann, 1988; Lotufo, Ritch, Szmyd, & Burris, 1989; Perkins & Phelps, 1982). The explanation behind this can be because of the large myopic eyes, structures like the lamina cribrosa and trabecular meshwork are also larger and therefore endure more strain.

3.1.10 Cardiovascular Disease

Cardiovascular disease may be a key player in influencing the development and progression of glaucoma, independent of the effects of intraocular pressure (Hayreh, 1999). Cardiovascular disease history was found to considerably increase the progression of the disease among patients who had a high intraocular pressure (Leske et al., 2007). Moreover, results from a study on ocular hypertension treatment suggest that cardiovascular disease is an important factor in predicting the development of POAG (Gordon et al., 2002).

3.1.11 Diabetes

Diabetes has been implicated as a risk factor for glaucoma (V. H. Wong, Bui, & Vingrys, 2011). According to findings from the Blue Mountains Eye Study, the prevalence of glaucoma was higher among subjects who had diabetes than among those who did not (Mitchell, Smith, Chey, & Healey, 1997). A meta-analysis also showed that there was an increased risk of POAG associated with diabetes (Bonovas, Peponis, & Filioussi, 2004). Furthermore, ocular hypertension patients who have diabetes are at an increased risk of having visual field defects or disc change which can result in glaucoma (Morgan & Drance, 1975). The possible explanation behind this relationship is thought to be the decrease in blood flow to the capillaries surrounding the optic nerve as a consequence of diabetes (Gupta, 2005, p. 12).

3.1.12 Body Mass Index

Body mass index (BMI) is a commonly used measure of adiposity, with high BMI being a risk factor for numerous chronic diseases. Surprisingly, research done using the Barbados Eye Study showed that the probability of having POAG was higher when BMI was lower (Gasser, Stümpfig, Schötzau, Ackermann-Liebrich, & Flammer, 1999; Leske et al., 1995). In contrast, in a large sample of hospitalized patients, there was an increased risk of glaucoma associated with an increase in BMI (Zang & Wynder, 1994). Therefore, it appears that both extremes of BMI may result in an increased risk of glaucoma.

3.1.13 Hypertension

A positive association was found between hypertension and POAG (Bonomi et al., 2000). There were many common mechanisms found between systemic hypertension and glaucoma (Langman, Lancashire, Cheng, & Stewart, 2005). Among patients who had glaucoma, the odds of having hypertension were 30% higher compared with patients who did not have glaucoma (Langman et al., 2005). A case-control study examining risk factors for POAG showed that (untreated) hypertension was associated with glaucoma (M. R. Wilson et al., 1987). Finally, findings from the Blue Mountains eye study also showed that hypertension was associated with an increase in risk of POAG, independently of the effects of intraocular pressure (Mitchell, Lee, Rochtchina, & Wang, 2004). The relationship between glaucoma and hypertension may be a result of the association of the vascular effects of systemic hypertension on ocular hypertension (Mitchell et al., 2004).

3.1.14 Socioeconomic Status

Socioeconomic status (SES) is an indicator of an individual's social and economic status, which is calculated by combining information on income, education, and occupation. SES has been found to be associated with many unhealthy behaviours (D. R. Williams, 1999). Recent findings showed that those who came from lower SES backgrounds were more likely to be diagnosed with advanced or moderate stage glaucoma compared to those with higher SES (Buys & Jin, 2013; Fraser, Bunce, Wormald, & Brunner, 2001). Interestingly, the association between late-stage glaucoma and SES was stronger among adults over the age of 65 (Buys & Jin, 2013). This association may be due, in part, to unhealthy behaviours associated with low SES.

3.2 Physical Activity

Physical activity has been implicated as a risk factor for intraocular pressure in multiple studies. Leighton et al (1970) carried out a study among young adults and found that walking lowered ocular tension compared to sitting. One study demonstrated that exercise decreases intraocular pressure temporarily in subjects with and without glaucoma (Qureshi, 1995). Additional studies have suggested that vigorous physical activity and static, aerobic and anaerobic exercise may decrease intraocular pressure levels (Ashkenazi, Melamed, & Blumenthal, 1992; Bakke, Hisdal, & Semb, 2009; Dane et al., 2006; Kielar, Teraslinna, Rowe, & Jackson, 1975; D. F. Marcus et al., 1974; Orgül & Flammer, 1994; P. T. Williams, 2009)(Ashkenazi, Melamed, & Blumenthal, 1992; Bakke, Hisdal, & Semb, 2009; Dane, Koçer, Demirel, Ucok, & Tan, 2006; Kielar, Teraslinna, Rowe, & Jackson, 1975; D. F. Marcus, Edelhauser, Maksud, & Wiley, 1974; Orgül & Flammer, 1994; P. T. Williams, 2009).

Interestingly, some studies have shown a relationship between increasing intensity of physical activity and decrease in intraocular pressure, (Kiuchi et al., 1994; Rowe, Teraslinna, Kielar, & Jackson, 1976) whereas other studies found no statistically significant association between physical fitness and intraocular pressure (Sargent et al., 1981). Qureshi (1996) showed that among sedentary and physically fit young adults, walking decreased intraocular pressure. In addition, Qureshi (1997) found that intraocular pressure was lower among subjects who participated in moderate or intense exercises compared to sedentary subjects. Finally, Qureshi et al. (1996) also demonstrated that among young adult men intensity of exercise was related to the magnitude of intraocular pressure reduction. An additional study done among 67 subjects aged 23-40, showed that both isometric and isokinetic exercises were associated with a lower intraocular pressure depending on exercise intensity and total energy consumption (Avunduk, Yilmaz, Sahin, Kapicioglu, & Dayanir, 1999). In contrast, breath holding, or the Valsalva maneuver during exercise may lead to an intraocular pressure increase (Vieira, Oliveira, de Andrade, Bottaro, & Ritch, 2006). Finally, only one longitudinal study was conducted to investigate the relationship between exercise and glaucoma. Using data on 5,650 adults from the EPIC population study, Yip et al (2011) found that physical activity was associated with a low mean ocular perfusion pressure (OR=0.75; 95% confidence interval (CI): 0.60, 0.93) and diastolic ocular perfusion pressure (OR=0.73; 95% CI: 0.58, 0.93) among people who had a previously active lifestyle. Although this study showed that these findings were not a direct result of the association with intraocular pressure, the effects were directly mediated by diastolic blood pressure (Yip et al., 2011).

3.2.1 Summary of Previous Physical Activity Research

To our knowledge, no study has been done to produce direct evidence on the association between physical activity and glaucoma. Nevertheless, there have been many studies done examining the association between physical activity and intraocular pressure in the short-term. However, most of these studies used one-time measures of intraocular pressure as a surrogate measure of glaucoma. Intraocular pressure changes throughout the day, and after certain activities analogous to blood pressure (Gupta, 2005, p. 7), therefore a one-time measure of intraocular pressure - which is what most clinicians do - is imprecise and may not be valid. Nevertheless, intraocular pressure is by far the most important risk factor for glaucoma.

However, it is important to address the current knowledge gap on the potential effects of physical activity on the risk of development of glaucoma. To date, only one large prospective study was conducted to analyze the association between physical activity and ocular perfusion pressure, another surrogate outcome of glaucoma, over a 10-year period (Yip et al., 2011). Although this was the largest study done in this area, Yip et al. failed to adjust for many of the risk factors of glaucoma, such as diabetes, heart disease, ethnicity, corticosteroid use, cigarette smoking and alcohol use. Therefore, further research is needed in order to achieve a greater understanding on whether physical activity has an effect on the risk of glaucoma.

3.3 Diet

Many FV are known to be abundant in antioxidants, and have been implicated as a protective factor against coronary heart disease, stroke, diabetes and cancer (Dauchet, Amouyel, Hercberg, & Dallongeville, 2006; Ford & Mokdad, 2001; He, Nowson, & MacGregor, 2006; Pérez, 2002). It is thought that the antioxidants found in FVs may decrease oxidative stress and protect the retinal ganglion cells from damage, which has been found to be associated with optic nerve deterioration (Maher & Hanneken, 2008;

Parikh & Parikh, 2011). Thus, it seems reasonable to hypothesize that that certain diets rich in antioxidants can improve the function of the trabecular meshwork, which would in turn protect the optic nerve from damage (Kang et al., 2003; Veach, 2004).

Coleman et al. (2008) conducted a cross-sectional study among 1,155 women over the age of 65. This study examined the association of canned/dried peaches, raw/cooked spinach, orange juice, green salad, fresh apples, bananas, oranges, green collards and kale, and carrots with glaucoma. All fruits, fruit juices, and vegetables were categorized as follows: less than one serving per day, 1 serving per day, 2 servings per day, and 3 servings or more per day. Through adjusted logistic regression models, this study showed that increased consumption of green collards and kale, carrots, and canned or dried peaches was associated with decreased odds of glaucoma by 69% (OR=0.31; 95% CI: 0.11, 0.91), 64% (OR=0.36; 95% CI: 0.17, 0.77), and 47% (OR=0.53; 95% CI: 0.29, 0.97), respectively.

Giaconi et al. (2012) conducted a cross-sectional study in 584 African-American women. This study showed that women who had more than one serving of collard green or kale per week had approximately 57% lower prevalence-odds of having glaucoma (OR=0.43; 95% CI: 0.21, 0.85) compared to women who had less than one serving per month. In addition, this study showed that women who had 3 or more servings of fruit and/or fruit juice per day were 79% (OR=0.21; 95% CI: 0.08, 0.60) less likely to have glaucoma compared to women who had less than 1 serving per day.

Kang et al. (2003) examined the associations of antioxidant intake and FV consumption with POAG using the Nurses' Health Study and Health Professionals Follow-up Study in a sample of approximately 474 self-reported POAG cases. This study used data from 1980 to 1986 for the Nurse's Health study and 1986 to 1996 for the Health Professionals Follow-up Study. The mean ages of women and men in this study were 48 to 50 and 53 to 57, respectively. This study controlled for age, African-American heritage, BMI, alcohol, smoking, physical activity, hypertension and diabetes. Diet was averaged over a four-year period and used to predict the risk of developing glaucoma in next 4-year period, 4 years later. For example, the risk for 1988-1990 was based on the average of 1980 and 1984 diets. No statistically significant associations were found between the antioxidants and the risk of developing glaucoma using the Cox proportional hazards model (Kang et al., 2003). Specifically, the pooled rate ratios for α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein/zeaxanthin, vitamin C, vitamin E and vitamin A were 1.17 (95% CI: 0.87, 1.58), 1.10 (95% CI: 0.82, 1.48), 0.95 (95% CI: 0.70, 1.29), 0.82 (95% CI: 0.60, 1.12), 0.92 (95% CI: 0.69, 1.24), 1.05 (95% CI: 0.59, 1.89), 0.97 (95% CI: 0.62, 1.52), 1.11 (95% CI: 0.82, 1.51), respectively when comparing the highest quintile of cumulative updated intake versus the lowest quintile.

Finally, a prospective longitudinal population-based study, using data from the Rotterdam Study, examined nutrient intake and the risk of OAG among women older than 55, with nutrients assessed at baseline. The Rotterdam Study data were collected from 1991 to 2006. The following potential confounders were adjusted for: age, gender, intraocular pressure, intraocular pressure-lowering treatment, and BMI, all of which were measured at baseline. The hazard of having glaucoma was 55% lower (HR=0.45; 95% CI: 0.23, 0.90) in participants who had a high intake of retinol equivalents compared to a low intake. In comparison, the hazard of having glaucoma was 50% lower (HR=0.50; 95% CI: 0.25, 0.98) in participants who had a high intake of vitamin B1 compared to a low intake. The hazard of having glaucoma was 2 times higher (HR=2.25; 95% CI: 1.16, 4.38) for participants who had a high intake of magnesium compared to a low intake (Ramdas et al., 2012).

3.3.1 Summary of Previous Diet Research

There is evidence of an association between FV consumption with glaucoma, although the literature is sparse and inconclusive. The four previously done studies, two cross-sectional and two prospective, showed some support of the association. The studies by Coleman et al. (2008) and Giaconi et al. (2012) were both cross-sectional, which limited the utility of the evidence produced by them as the basis for potential inferring of a causal association, as the temporal relation between FV consumption and glaucoma was unknown. Nonetheless Kang et al (2003) and Ramdas et al. (2012) conducted longitudinal studies, but each had important limitations. Notably, Kang et al. (2003) dealt with missing data in a suboptimal manner, and Ramdas et al (2012) documented both nutrient intake and potential confounders at cohort baseline only. However, many personal characteristics, such as, for example, body weight and eating habits may change – possibly quite dramatically – over the years. In closing, more research is needed to reach a deeper understanding on whether there is an effect on glaucoma through FV consumption.

Chapter 4

4. Study Rationale and Objectives

The preceding chapter presented an overview of the current body of knowledge which is presently available on the risk factors of glaucoma. In this chapter, the rationale for the study carried out for this thesis (4.1) is presented, followed by the study objectives (4.2).

4.1 Rationale

The previous chapter provided an overview of the previous research which has been conducted to investigate the association between lifestyle factors, namely, physical activity and FV consumption, with glaucoma. There has been some evidence supporting the existence of associations between these factors and glaucoma, but the associations have yet to be established. This study will contribute to the current body of evidence by using a national longitudinal survey to conduct a study specifically designed to address the topics at issue.

4.2 Study Objectives and Hypotheses

The objectives are:

1. To examine if physical activity is associated with the risk of glaucoma.

   Hypothesis: It is hypothesized that physical activity lowers the risk of glaucoma.

2. To examine if FV consumption is associated with the risk of glaucoma.

Hypothesis: It is hypothesized that consumption of FV lowers the risk of glaucoma.

Chapter 5

5. Methods

In this section, the methodology used to execute this thesis project is explained. Sections 5.1 and 5.2 describe the data source which was utilized and the study population. The following sections (5.3-5.5) describe the variables which were used and the statistical analyses.

5.1 Data Source

The data source used for this thesis was the National Population Health Survey (NPHS) – Household - Longitudinal component, confidential data files. This survey was carried out in response to the need for an ongoing national survey for population health requested by the National Health Information Council. The NPHS began in 1994, with the surveys being conducted every two years until 2012. This survey targeted Canadian household residents aged 12 years or older and aimed to gather self-reported health related and socio-demographic information. Canadians living on Indian reserves, Crown lands, and in health-institutions, or remote areas of Ontario or Quebec were excluded, as well as full-time members of the Canadian Forces who lived on the Canadian Forces bases (Statistics Canada, 2000). The NPHS sample design was based off three factors: national and provincial sample sizes, only one member of each household as a longitudinal survey respondent, and the Labour Force Survey as the basis for the selection of the sample (Statistics Canada, 2000). Similarly to the Labour Force Survey, the NPHS also utilized a multistage stratified method for sampling where provinces were first divided into the following categories: major cities, urban towns and rural areas. These categories were further used to select six independent samples of clusters from Census Enumeration areas; small areas used by Statistics Canada for Census distribution. Next, one respondent was chosen from each household at random from the dwelling list prepared for each of the chosen clusters (Statistics Canada, 2000).

This survey was distributed to a total of 17,276 respondents, with a response rate ranging between 70% and 93% across the survey cycles. The NPHS was completed using computer-assisted interviewing, which allowed participants’ responses to questions to follow a logical flow. An exemption was cycle 9, in which data collection was performed through interviewers who were employed at calling centers as part of Statistics Canada. Data quality was ensured by reducing loss to follow-up and by performing extensive tests with the computer-assisted interviewing in-house. Loss to follow up was reduced in the following way: when a person did not respond in the survey, every effort was made to reach them through contacting the participant at the last known address, as well as through local telephone directories. Furthermore, all deaths were confirmed using the Canadian Vital Statistics Database, and all drug coding was established using the Anatomical Therapeutic Chemical classification developed by the World Health Organization.

A proposal was written in order to access data through the Statistics Canada Research Data Centre at Western University (Appendix C).

5.2 Study Population

For the current study, data from cycles 5 through 9 (2002-2011) were used since information regarding nutrition began to be collected in cycle 5. We limited the study population to white respondents over the age of 18, who did not report using corticosteroids or having glaucoma at baseline (cycle 5). The restrictions based on race and corticosteroid use were done for the purpose of preventing possible confounding by these characteristics. Finally, only those who did not report having glaucoma at baseline were included to ensure that only incidence cases of glaucoma served as the outcome, because the purpose of this study was to assess the effect of FV consumption and physical activity on the risk of development of glaucoma. The final study population size of 9,950 was used for the analysis. Figure 5.1 shows a flow chart according to the study inclusion/exclusion criteria.

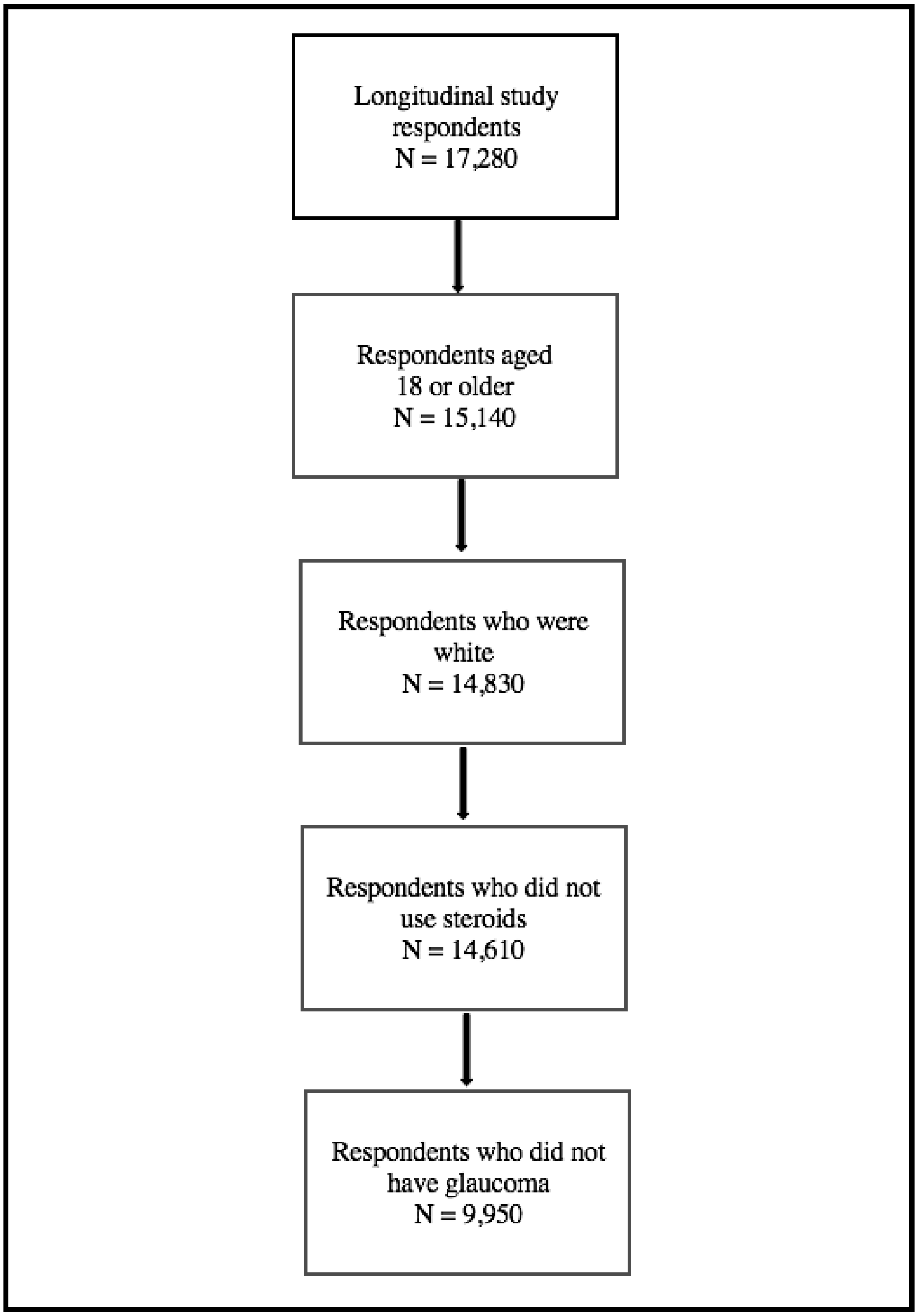

Figure 5.1 Study population flowchart.
**All values have been rounded to the base of 10 as per RDC at Western's requirements for confidentiality.*

5.3 Variables

This section will describe the variables which were used in the analysis.

5.3.1 Outcome

In this section the outcome which was used for this study, glaucoma, is described.

Glaucoma: The outcome of interest was glaucoma, which assessed by asking study participants over the age of 18 if they were diagnosed with glaucoma in the past 12 months. This variable was kept binary with a yes or no response.

5.3.2 Exposures

In this section both exposures of interest, physical activity and FV consumption are described in detail.

Physical Activity: To measure physical activity, a derived variable, provided by Statistics Canada was used. First, respondents were asked if they participated in the following activities: walking for exercise, gardening or yard work, swimming, bicycling, popular or social dance, home exercises, ice hockey, ice skating, downhill skiing or snowboarding, jogging or running, golfing, exercise class or aerobics, bowling, baseball or softball, tennis, weight-training, fishing, Based on their response, they were asked the number of times they participated in each activity and the amount of time they spent doing each activity in the past three months. Metabolic Equivalent (MET) values which were analogous to the low intensity values of the physical activity were utilized, as stated by the Canadian Fitness and Lifestyle Research Institute (provided in Appendix B). Next, data on all these activities were used to derive the energy expended during physical activity. Energy expenditure was calculated using the following equation (Statistics Canada, 2012):

$$\text{Energy Expenditure (kcal/kg/day)} = \text{Sum of } ((N_i * D_i * \text{MET value}) / 365$$

N_i = the number of times a respondent engaged in an activity (i) over a 12-month period

D_i = the average duration (in hours) of the activity (i)

MET = the energy cost of the activity expressed as kilocalories expended per kilogram of body weight per hour of activity (kcal/kg/hour)/ 365 (to convert yearly data into daily data)

FV Consumption: Participants were asked to think back about all the meals and snacks that usually eat and drink daily. They were then required to report the number of times they drink fruit juices (such as orange, grapefruit, or tomato), and ate fruit. To report vegetable consumption, respondents were asked to report how often they ate green salad, potatoes (not including French fries, fried potatoes or potato chips), carrots, and other vegetables not including the previously stated. Participants had to specify their reporting period as daily, weekly, monthly, or yearly which was later converted into daily for each respondent.

For our analyses, the derived variable created in the NPHS for fruit and vegetable was used. The derived variable was created using the sum of the annual FV consumption variables and then divided by 365 'to derive an aggregate of the daily frequency of fruit and vegetables consumed'. This variable represents the number of times in one day that a person ate fruits and vegetables.

5.3.3 Confounders

After a thorough literature review, a directed acyclic graph was drawn (Figure 5.2) to identify potential confounders and guide the conceptualization of this study. The following potential confounders were adjusted for in the analyses: age, sex, education, income, alcohol use, smoking status, BMI, blood pressure, diabetes, and heart disease.

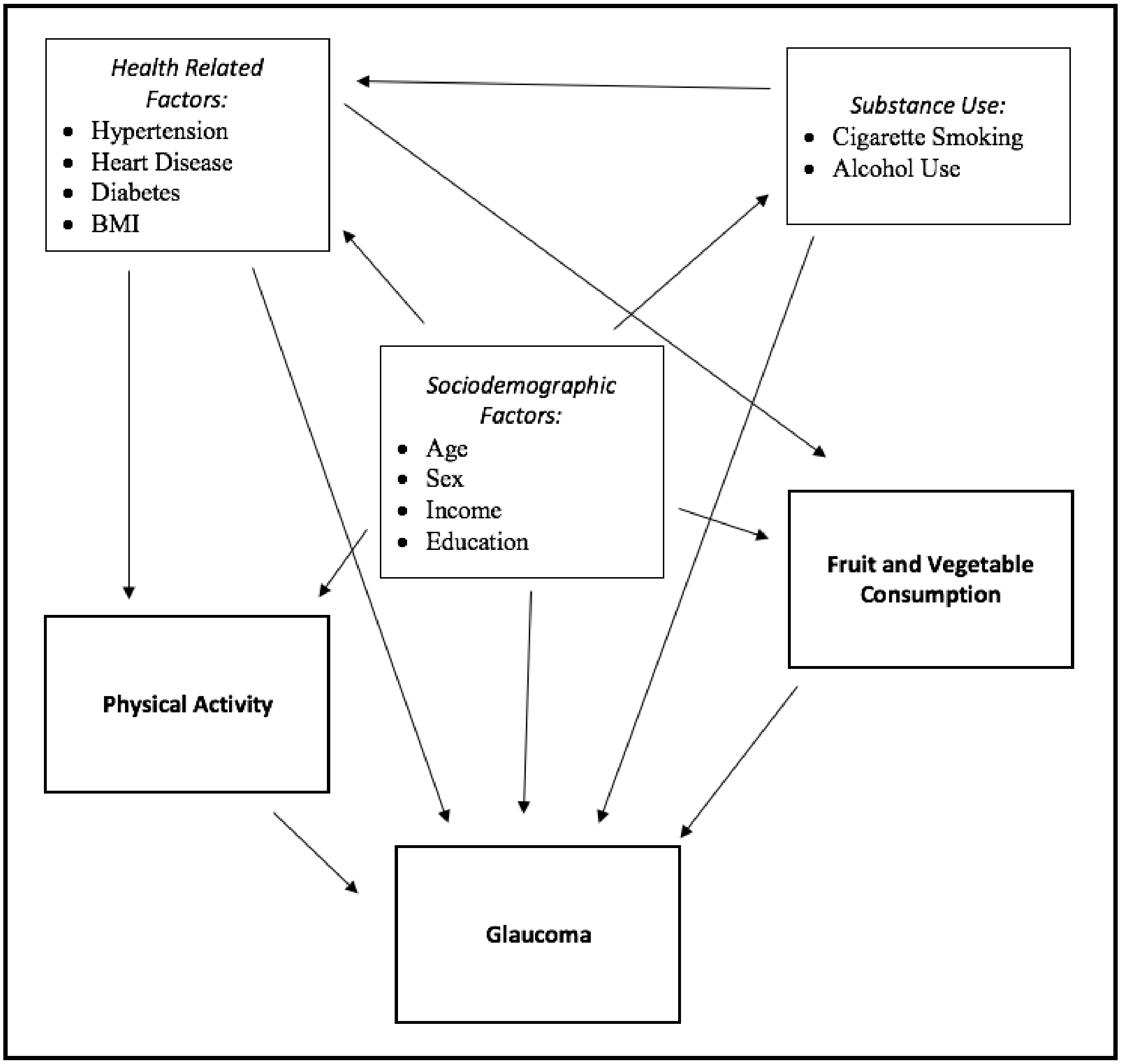

Figure 5.2 Directed acyclic graph depicting the associations between the exposures of interest (physical activity and fruit and vegetable consumption) and the outcome (glaucoma) with confounders.

Age: All respondents were asked to report their date of birth, which was then used in the survey to calculate age in each cycle of the survey. For this study, age was treated as a continuous variable.

Sex: Sex was a binary variable, with male as the reference category.

Education: Highest level of education was reported by study participants using the following four categories: 'less than secondary school graduation', 'secondary school graduation', 'some post-secondary', and 'post-secondary graduation'.

Income**:** The questionnaire item for income inquired about the respondent's "best estimate" of total personal income, before taxes and deductions from all sources, in the past 12 months. This variable was kept as a continuous.

Alcohol Use: Alcohol use was documented by asking the survey participants if they drank alcohol (beer, wine, liquor or any other alcoholic beverage) in the past 12 months. This variable was kept as binary, with a 'yes' or 'no' response.

Smoking Status*:* Smoking status was documented through a derived variable describing the type of smoker the respondent was. For the purposes of the analysis, smoking status was kept binary, with 'non-smoker' and 'smoker'.

BMI: BMI was calculated by dividing weight (kg) by the square of height (m). The derived variable for BMI was used. This BMI was an imputed variable found in the survey, which used sex, imputed height, weight and pregnancy. Subjects were asked about their height and weight independently in each cycle of the survey. Imputation was performed by the NPHS for values where the data was missing or incoherent. An incoherent measure for height was someone who had a decrease or extreme increase in height at a certain age. The detailed process for the imputations can be viewed in Appendix B.

Chronic conditions: Participants were asked if they had high blood pressure, diabetes and heart disease in each survey cycle. For each of these three conditions, response was kept as a ‘yes’ or ‘no’.

5.4 Missing Values

A variable which was used to indicate the response patterns of each participant throughout the duration of the survey, was used to delete data from participants who were deceased or had non-response for each cycle. In other words, the cycles were aggregated and participants who did not respond to the survey or had died during that survey were then deleted from the dataset for that cycle and following cycles, but not prior. Data from participants who responded to the relevant questions with “don’t know”, “not applicable”,” refusal” or “not stated” were recoded into missing values. The percentage of missingness was also checked.

5.5 Statistical Analysis

All statistical analyses were done on SAS version 9.4. All statistical analyses complied with the RDC at Western’s rules for confidentiality.

5.5.1 Descriptive Analysis

First, an incidence rate was calculated using the cycle-specific numbers of new cases of glaucoma and the corresponding amounts of population-time of follow-up of the study cohort. Next, tables presenting frequency distributions for all of the relevant variables were produced. First the total number of respondents was calculated for each category for each of the categorical variables, including sex, education, alcohol use, cigarette smoking, diabetes, high blood pressure and heart disease. For the continuous variables, including age, and BMI, the mean and standard deviations were provided, for income median and interquartile range was provided. In addition, the same descriptive statistics were provided for each quartile category of physical activity and FV consumption. FV consumption and physical activity were divided into the following categories based on quartiles values: low, low-intermediate, high-intermediate, high.

5.5.2 Cox Proportional Hazards Regression Analysis

To address the research objectives, crude and adjusted Cox proportional hazards models were fitted. In these analyses, cohort time served as the time axis. Crude models included only the exposure of interest and the outcome. All adjusted Cox proportional hazard models were adjusted for age (years), sex (male/female), BMI (kg/m^2), smoking status (yes/no), alcohol use (yes/no), diabetes (yes/no), hypertension (yes/no) and heart disease (yes/no), total personal income and education. First Cox proportional hazards models with time-independent covariates were fitted, followed by models including time-varying covariates. Time-varying covariates allow for changes in covariate values between cycles across study participants. For example, as people age, their BMI generally changes. By treating BMI as a time-varying covariate, we were able to account for these changes in the statistical analysis. In the Cox models with time-varying covariates, values of theses covariates were lagged by one cycle (i.e., the occurrence of the outcome at any given cycle was represented as a function of covariate values from a previous cycle). List-wise deletion was used for the main analyses. The equation representing the main Cox proportional hazards regression analysis is shown below:

$$\log h(t) = a(t) + B_1 x_1(t-1) + B_2 x_2(t-1) + B_3 x_3(t-1) + B_4 x_4 + B_5 x_5(t-1)$$
$$+ B_6 x_6(t-1) + B_7 x_7(t-1) + B_8 x_8(t-1) + B_9 x_9(t-1)$$
$$+ B_{10} x_{10}(t-1) + B_{11} x_{11}(t-1) + B_{12} x_{12}(t-1) + B_{13} x_{13}(t-1)$$
$$+ B_{14} x_{14}(t-1)$$

Where: t = time;
x_1 = FV consumption
x_2 =Physical activity
x_3 =Age
x_4 =Sex (where male=0, female=1)
x_5 = BMI
x_6 =Smoking status (where yes=0, no=1)
x_7 =Alcohol use (where yes=0, no=1)
x_8 =Diabetes (where yes=0, no=1)
x_9 =Hypertension (where yes=0, no=1)
x_{10} = Heart disease (where yes=0, no=1)
x_{11} =Total personal income
x_{12} = Education (where less than secondary school graduation=0, secondary school graduation=1, some post-secondary=2, post-secondary graduation=3

5.5.3 Weighting

All analyses were done using the survey weight variable, which was a variable that incorporated each participant's associated sampling weight. The purpose of sampling weights was to allow for the ability to estimate population parameters based on sample data. The weight variable was calculated using all participant records and was not adjusted for non-response. Since our sample had some restrictions on the inclusion and the entire NPHS population was not utilized, the weight variable had to be rescaled. This was done by dividing the weight variable by the mean to consider the 'stratification the unequal probabilities of selection' (Statistics Canada, 2000).

5.5.4 Sensitivity Analysis

For sensitivity analysis, we conducted the analyses using multiple imputation to deal with missing values. The method we used was Markov Chain Monte Carlo (MCMC), with multiple chains. The reason behind choosing the MCMC method was because we assumed that missing was arbitrary (Berglund & Heeringa, 2014). MCMC acquires new parameter estimates to predict the missing values through Bayesian estimation of the mean vector and covariance matrix (Schunk, 2008; Zhang, 2003). A total of 50 imputed data sets were created, for which the following auxiliary variables were included: type of alcohol drinker, current smoking status, number of consultations with an eye specialist, presence of cataracts, type of dwelling, self-perceived eating habits and self-perceived health. Auxiliary variables were variables which were correlated with the analysis variables and included in order to make the imputation less biased (Berglund & Heeringa, 2014).

5.5.5 Additional Analyses

Further analyses were done to ensure age was not a moderator of the relationship between FV consumption and physical activity with glaucoma. First the interaction between FV consumption with age was assessed, followed by the interaction between physical activity and age. An additional analysis was also done through sub-group analysis. Age was divided into younger than or equal to 50 years of age and older than 50 years of age.

5.5.6 Assumptions

The Cox proportional hazards regression analysis assumes that the hazard ratios of interest were constant over time. We assessed the proportionality-of-hazards assumption by using interaction terms, specifically the “one-at-a-time” strategy (Kleinbaum & Klein, 2010, pp. 154–155). This was done by introducing an interaction term for time*exposure and examining whether this term was statistically significant. We performed this test for both FV consumption and physical activity and found that these terms were not statistically significant. The use of time-varying covariates would also have minimized the likelihood of violating the proportionality-of-hazards assumption.

Chapter 6

6. Results

The results chapter begins with a description of the overall sample, which is then described by categories for the physical activity and FV consumption. Next, the incidence rate of glaucoma through the duration of the study is reported as well as the results of the crude and multivariable Cox proportional hazards models for both physical activity and nutrition. Finally, the results of the sensitivity analyses and additional analyses are presented.

6.1 Incidence of Glaucoma

Throughout the duration of the study, a total of 190 individuals developed glaucoma, with an overall incidence rate of 6 cases per 1000 person-years (Table 6.1). The incident cases of glaucoma were highest in the last cycle of the survey (60 cases), resulting in an incidence rate of 14 cases per 1000 person-years.

6.2 Descriptive Statistics

Total Sample

A total of 9,950 adults over the age of 18 were included at baseline (2002-2003). The study population consisted of white respondents who did not use corticosteroids throughout the study and did not have the outcome, glaucoma, at baseline.

All study population characteristics at baseline were reported in Tables 6.2 through 6.4. In Table 6.2 the overall descriptive statistics of the study population can be seen. The mean age for the study population was 46. Of the 9,950 survey respondents, approximately half were male (48.3%) and more than a third of the sample had the highest education level (38.5%). The median yearly personal income before taxes and deductions over the past year for the population was approximately $30,000. Most of the subjects reported drinking alcohol in the past year (86.2%) and smoking at some point (68.8%). The mean BMI for the sample was 26 kg/m^2. In addition, a small portion of subjects had diabetes (4.8%) or heart disease (5.1%), with high blood pressure (15.1%) being the most common chronic condition. The mean energy expenditure and FV consumption were 2.0 kcal/kg/day and 4.2 times daily, respectively.

Physical Activity Categories

After dividing the sample into categories based on the physical activity quartiles of the sample distribution at baseline, the characteristics among each category were explored (Table 6.3). A lower mean age was observed as individuals become more physically active, with mean age decreasing from 50 at the lowest physical activity category to 42 at the highest physical activity category. There were more men in the highest physical activity category (55.4%) compared to women. In terms of educational attainment, in the low category of physical activity, the frequencies for educational attainment were mostly similar. However, in the following categories of physical activity, a majority of the sample had at least some post-secondary education (27.8-29.9%), and even more of the sample had post-secondary graduation (40.7%-42.9%). Median personal income also remained relatively similar throughout the last three categories ($30,000), with the lowest median income in the least physically active category ($24,000). Alcohol use percentages were higher as individuals were more physically active, increasing from 79.7% to 90.9%. In comparison, however, frequency of reported smoking was quite similar across the physical activity categories, with the majority of people smoking at some point (67.4%-70.9%). Surprisingly, BMI also remained relatively similar throughout each physical activity category around 26 kg/m^2. There was a decrease in the frequency for all three chronic diseases (diabetes, blood pressure, heart disease) as people were more physically active.

The proportion of those with diabetes, high blood pressure and heart disease lowered from 7.3% to 3.0%, 19.9% to 10.8% and 8.0% to 3.0%, respectively.

Fruit and Vegetable Quartiles

The study population was divided into FV consumption categories and the distribution were explored (Table 6.4). Mean age became higher as category of FV consumption increased, 44 years old at low FV consumption to 48 at high FV consumption. A higher percentage of females (64.1%) reported consuming more FV compared to men. The first two categories of educational attainment decreased as people ate more FVs, with the opposite effect shown in those who were in the last two categories of education. Income was highest in the low-intermediate category, followed by the high category of FV consumption ($30,000 and $29,000). Alcohol use was the highest in the low-intermediate consumption category (89.3%) and lowest in the low category (84.2%). The frequency of smoking decreased as respondents ate more FVs (74.9% to 63.8%). BMI remained relatively similar, hovering at overweight, or 26 kg/m^2. Diabetes rate was highest in the high-intermediate FV consumption category at 6.2%. However, high blood pressure was highest in the two higher FV consumption categories at 17.1% and 17.0%. Heart disease was highest in the low (6.1%) and high (5.2%) categories of FV consumption.

6.3 The Association between Fruit and Vegetable Consumption and Physical Activity with Glaucoma

Table 6.5 shows the crude and adjusted Cox proportional hazards models for the association between physical activity and FV consumption with glaucoma with time-independent covariates. The results showed that for every time a fruit or vegetable was consumed daily, the hazard of glaucoma increased by 3% (HR: 1.03 [95% CI: 0.96-1.10]). The hazard of glaucoma decreased by 10% (HR: 0.90 [95% CI: 0.82-0.98]) for every one unit increase in daily energy expenditure. However, when adjusting for potential confounders, the following was found: for every time a fruit or vegetable was consumed daily, the hazard of glaucoma decreased by 23% (HR: 0.77 [95% CI: 0.57-1.04]), and for every one unit increase in daily energy expenditure, the hazard increased by 5% (HR: 1.05 [95% CI: 0.92-1.21]).

Table 6.6 shows the crude and adjusted Cox proportional hazards models for the association between physical activity and FV consumption with glaucoma using time-varying covariates. The results showed that for every one time FVs were consumed daily, the hazard of glaucoma increased by 3% (HR: 1.03 [95% CI: 0.96-1.10]). Furthermore, for every one unit increase in daily energy expenditure the hazard of glaucoma decreased by 3% (HR: 0.97 [95% CI: 0.90-1.05]). However, when adjusting for potential confounders, the following was found: for every one-time FVs were consumed daily, the hazard of glaucoma increased by 3% (HR: 1.03 [95% CI: 0.93-1.14]), and for every one unit increase in daily energy expenditure the hazard of glaucoma decreased by 1% (HR: 0.99 [95% CI: 0.87-1.12]).

Finally, Table 6.7 shows the crude and adjusted Cox proportional hazards models for the association between physical activity and FV consumption with glaucoma using time-varying covariates, but with FVs separated in six different categories. It was shown that for every one-time a fruit, fruit juice, potato, green salad, or other vegetable was consumed daily, the hazard of glaucoma increased by 3% (HR: 1.03 [95% CI: 0.96-1.10]). Every one-time a carrot was consumed daily the hazard of glaucoma increased by 36% (HR: 1.03 [95% CI: 1.00-1.86). After adjusting for potential confounders, the hazard of glaucoma decreased by 27% (HR: 0.77 [95% CI: 0.57-1.04]) for every time a fruit was consumed, but the hazard increased by 20% (HR: 1.20 [95% CI: 0.85-1.68]) every time a fruit juice was consumed. The hazard also increased for every time a carrot, potato, green salad, or other vegetable was consumed by 21%, 76%, 21% and 12%, respectively (HR: 1.21 [95% CI: 0.63-2.31]; HR: 1.76 [95% CI: 1.11-2.79]; HR: 1.21 [95% CI: 0.68-2.16]; HR: 1.12 [95% CI: 0.86-1.46]).

6.4 Sensitivity Analysis

Table 6.8 shows the crude and adjusted Cox proportional hazards models for the association between physical activity and FV consumption with glaucoma with time-independent covariates and multiple imputations. The crude model results based on multiple imputation were the same as the corresponding results that did not involve multiple imputation. However, the results for the adjusted models varied slightly, with narrower 95% CIs for hazard ratios quantifying the associations of both FV consumption and physical activity with glaucoma.

In Table 6.9, the crude and adjusted Cox proportional hazards models for the association between physical activity and FV consumption and glaucoma using MCMC multiple imputations with time-varying covariates is shown. The point estimates for all models were very similar, with the only difference between the two sets of results being slightly narrower 95% CIs around the hazard ratio estimates compared with results based on the list-wise deletion approach.

Finally, Table 6.10 displays the crude and adjusted Cox proportional hazards models for the association between physical activity and separated FV consumption with glaucoma using multiple imputations. For the crude models, the hazard ratios and CIs estimated upon multiple imputation were identical to their counterparts from the corresponding non-imputed models, aside from carrot consumption (HR:1.45 [95% CI: 1.11-1.90]). The adjusted models upon multiple imputation, however, had similar estimated hazard ratios (but with narrower 95% CIs) than the non-imputed models.

6.5 Additional Analysis

Table 6.11 and 6.12 display the results of the interaction analyses for the interaction (on the hazard ratio scale) between FV consumption and age, followed by the interaction between physical activity and age. The next two tables, 6.13 and 6.14 showed the subgroup analyses results. Lastly, tables 6.15 through 6.18 showed all the previous results with imputation. There was found to be no statistically significant interaction (on the hazard ratio scale) between age and either of the exposures of interest.

Table 6.1 Overall and per cycle incidence rate of glaucoma.

Cycle (Years)	Incident Cases of Glaucoma*	Incidence Rate (per 1000 person-years)
6 (2004-2005)	50	5.2
7 (2006-2007)	30	3.5
8 (2008-2009)	50	6.4
9 (2010-2011)	60	14.2
Overall	190	6.0

* Incident cases were rounded to the base of ten as required by the Research Data Center at Western University, Statistics Canada.

Table 6.2 Descriptive statistics for study population characteristics at baseline (cycle 5, n=9,950).

Characteristic (Units[1,2])	Frequency (%)*
Age (years)	46 (17.5)
Sex (male)	4810 (48.3%)
Educational attainment (highest level attained)	
Less than secondary school graduation	1890 (19.1%)
Secondary school graduation	1430 (14.4%)
Some post-secondary	2770 (28.0%)
Post-secondary graduation	3810 (38.5%)
Income (yearly personal income in dollars)	28,000 (31,000)
Alcohol Use (yes)	8560 (86.2%)
Smoking (yes)	6820 (68.8%)
BMI (kg/m^2)	26 (4.8)
Diabetes (yes)	480 (4.8%)
High Blood Pressure (yes)	1500 (15.1%)
Heart Disease (yes)	510 (5.1%)
Physical Activity (kcal/kg/day)[3]	2.0 (2.0)
Fruit and Vegetable Consumption (times consumed daily)[4]	4.2 (2.1)

*Frequency counts for all categorical and binary variables were rounded to the base of ten as required by the Research Data Center at Western University, Statistics Canada.

1. For all binary variables, the 'yes' response frequencies were reported and for sex, the male category was reported.
2. For all continuous variables (age, BMI, physical activity, and fruit and vegetable consumption) the mean (standard deviation) was reported, apart from income, where median (interquartile range) was reported.
3. Physical activity was calculated using metabolic equivalent values for each activity respondents reported participating in, the number of times they participated and the amount of time they spent participating in each bout.
4. Fruit and vegetable consumption was calculated through respondents' daily reported consumption of fruit, fruit juices, green salad, potatoes, carrots, and other vegetables.

Table 6.3 Descriptive statistics across physical activity categories for all covariates at baseline (cycle 5).

	Physical Activity Category			
Characteristic (Units[1,2])	**Low**	**Low-Intermediate**	**High-Intermediate**	**High**
Age (years)	50 (18.3)	46 (16.6)	46 (16.6)	42 (17.4)
Sex (male)	1410 (49.0%)	980 (42.6%)	1140 (46.3%)	1280 (55.4%)
Educational attainment (highest level attained)				
Less than secondary school graduation	800 (28.2%)	390 (17.0%)	390 (15.9%)	310 (13.4%)
Secondary school graduation	430 (15.1%)	310 (13.5%)	330 (13.5%)	360 (15.6%)
Some post-secondary	770 (27.1%)	640 (27.8%)	670 (27.4%)	690 (29.9%)
Post-secondary graduation	850 (29.9%)	970 (42.2%)	1050 (42.9%)	940 (40.7%)
Income (yearly personal income in dollars)	24,000 (28,000)	30,000 (31,000)	30,000 (35,000)	30,000 (35,000)
Alcohol Use (yes)	2280 (79.7%)	2010 (87.0%)	2170 (88.6%)	2100 (90.9%)
Smoking (yes)	2020 (70.9%)	1550 (67.4%)	1660 (67.8%)	1590 (68.8%)
BMI, (kg/m^2)	26.6 (5.3)	26.1 (4.8)	26.0 (4.5)	25.5 (4.3)
Diabetes (yes)	210 (7.3%)	100 (4.4%)	100 (4.1%)	70 (3.0%)
High Blood Pressure (yes)	570 (19.9%)	360 (15.7%)	320 (13.1%)	250 (10.8%)
Heart Disease (yes)	230 (8.0%)	120 (5.2%)	90 (3.7%)	70 (3.0%)

*Frequency counts for all categorical and binary variables were rounded to the base of ten as required by the Research Data Center at Western University, Statistics Canada.

1. For all binary variables, the 'yes' response frequencies were reported and for sex, the male category was reported.
2. For all continuous variables (age, BMI, physical activity, and fruit and vegetable consumption) the mean (standard deviation) was reported, apart from income, where median (interquartile range) was reported.

Table 6.4 Descriptive statistics across fruit and vegetable consumption categories for all covariates at baseline (cycle 5).

	Fruit and Vegetable Consumption Category			
Characteristic (Units)	**Low**	**Low-Intermediate**	**High-Intermediate**	**High**
Age (years)	44 (17.7)	45 (16.5)	48 (17.9)	48 (17.6)
Sex (male)	1690 (60.4%)	1290 (53.1%)	1000 (41.5%)	830 (35.9%)
Educational attainment (highest level attained)				
Less than secondary school graduation	680 (24.6%)	430 (17.8%)	420 (17.4%)	360 (15.7%)
Secondary school graduation	460 (16.6%)	370 (15.3%)	330 (13.7%)	270 (11.7%)
Some post-secondary	760 (27.4%)	660 (27.3%)	660 (27.4%)	690 (30.00%)
Post-secondary graduation	890 (32.1%)	950 (39.3%)	990 (41.1%)	980 (42.6%)
Income (yearly personal income in dollars)	25,000 (33,000)	30,000 (35,000)	26,000 (31,000)	29,000 (31,500)
Alcohol Use (yes)	2350 (84.2%)	2160 (89.3%)	2080 (86.3%)	1970 (85.3%)
Smoking (yes)	2090 (74.9%)	1660 (68.6%)	1610 (66.8%)	1460 (63.8%)
BMI (kg/m^2)	26.2 (4.8)	26.2 (4.9)	26.0 (4.8)	25.9 (4.8)
Diabetes (yes)	120 (4.3%)	100 (4.1%)	150 (6.2%)	110 (4.8%)
High Blood Pressure (yes)	390 (14.0%)	310 (12.8%)	410 (17.1%)	390 (17.0%)
Heart Disease (yes)	170 (6.1%)	100 (4.1%)	120 (5.0%)	120 (5.2%)

*Frequency counts for all categorical and binary variables were rounded to the base of ten as required by the Research Data Center at Western University, Statistics Canada.

1. For all binary variables, the 'yes' response frequencies were reported and for sex, the male category was reported.
2. For all continuous variables (age, BMI, physical activity, and fruit and vegetable consumption) the mean (standard deviation) was reported, apart from income, where median (interquartile range) was reported.
3. Physical activity was calculated using metabolic equivalent values for each activity respondents reported participating in, the number of times they participated and the amount of time they spent participating in each bout.
4. Fruit and vegetable consumption was calculated through respondents' daily reported consumption of fruit, fruit juices, green salad, potatoes, carrots, and other vegetables.

Table 6.5 Crude and adjusted Cox proportional hazards models of fruit and vegetable consumption and physical activity in relation to the risk of glaucoma for National Population Health Survey respondents from 2002-2011 with time-independent covariates.

Variable (units)	**Crude Model** Hazard Ratio (95% CI)	**Adjusted Model*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)	1.03 (0.96-1.10)	0.77 (0.57-1.04)
Physical Activity (kcal/kg/day)	0.90 (0.82-0.98)	1.05 (0.92-1.21)
Age (years)		1.07 (1.05-1.09)
Sex (male/female)		1.29 (0.72-2.30)
Educational attainment (highest level attained)		0.99 (0.78-1.25)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		1.04 (0.48-2.25)
Smoking (yes/no)		1.02 (0.59-1.77)
BMI (kg/m^2)		1.00 (0.94-1.06)
Diabetes (yes/no)		0.68 (0.21-2.18)
High Blood Pressure (yes/no)		0.78 (0.42-1.46)
Heart Disease (yes/no)		0.89 (0.33-2.40)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.6 Crude and adjusted Cox proportional hazards models of fruit and vegetable consumption and physical activity in relation to the risk of glaucoma for National Population Health Survey respondents from 2002-2011 using time-varying covariates with a lag-time of one cycle.

Variable (units)	**Crude Model** Hazard Ratio (95% CI)	**Adjusted Model*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)	1.03 (0.96-1.10)	1.03 (0.93-1.14)
Physical Activity (kcal/kg/day)	0.97 (0.90-1.05)	0.99 (0.87-1.12)
Age (years)		1.07 (1.05-1.09)
Sex (male/female)		1.07 (0.66-1.75)
Educational attainment (highest level attained)		1.10 (0.89-1.35)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		1.08 (0.55-2.10)
Smoking (yes/no)		1.16 (0.71-1.89)
BMI (kg/m^2)		0.98 (0.93-1.03)
Diabetes (yes/no)		0.46 (0.16-1.34)
High Blood Pressure (yes/no)		1.23 (0.73-2.06)
Heart Disease (yes/no)		1.15 (0.55-2.43)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.7 Crude and adjusted Cox proportional hazards models of separated fruits and vegetables consumption and physical activity in relation to the risk of glaucoma for National Population Health Survey respondents from 2002-2011 using time-varying covariates with a lag-time of one cycle.

Variable (units)	**Crude Model** Hazard Ratio (95% CI)	**Adjusted Model*** Hazard Ratio (95% CI)
Fruits (times consumed daily)	1.03 (0.96-1.10)	0.77 (0.57-1.04)
Fruit Juices (times consumed daily)	1.03 (0.96-1.10)	1.20 (0.85-1.68)
Carrots (times consumed daily)	1.36 (1.00-1.86)	1.21 (0.63-2.31)
Potatoes (times consumed daily)	1.03 (0.96-1.10)	1.76 (1.11-2.79)
Green Salad (times consumed daily)	1.03 (0.96-1.10)	1.21 (0.68-2.16)
Other vegetables (times consumed daily)	1.03 (0.96-1.10)	1.12 (0.86-1.46)
Physical Activity (kcal/kg/day)		1.05 (0.92-1.21)
Age (years)		1.07 (1.05-1.09)
Sex (male/female)		1.29 (0.72-2.30)
Educational attainment (highest level attained)		0.99 (0.78-1.25)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		1.04 (0.48-2.25)
Smoking (yes/no)		1.02 (0.59-1.77)
BMI (kg/m^2)		1.00 (0.94-1.06)
Diabetes (yes/no)		0.68 (0.21-2.18)
High Blood Pressure (yes/no)		0.78 (0.42-1.46)
Heart Disease (yes/no)		0.89 (0.33-2.40)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.8 Crude and adjusted Cox proportional hazards models of fruit and vegetable consumption and physical activity in relation to the risk of glaucoma for National Population Health Survey respondents from 2002-2011 with time-independent covariates using Markov Chain Monte Carlo multiple imputation (50 imputations).

Variable (units)	**Crude Model** Hazard Ratio (95% CI)	**Adjusted Model*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)	1.03 (0.96-1.10)	0.98 (0.91-1.05)
Physical Activity (kcal/kg/day)	0.90 (0.82-0.98)	0.96 (0.88-1.05)
Age (years)		1.05 (1.04-1.06)
Sex (male/female)		1.06 (0.77-1.46)
Educational attainment (highest level attained)		1.08 (0.95-1.23)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		0.85 (0.59-1.23)
Smoking (yes/no)		1.09 (0.80-1.49)
BMI (kg/m^2)		0.97 (0.93-1.00)
Diabetes (yes/no)		0.94 (0.53-1.66)
High Blood Pressure (yes/no)		0.96 (0.67-1.38)
Heart Disease (yes/no)		1.55 (0.98-2.43)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.9 Crude and adjusted Cox proportional hazards models of fruit and vegetable consumption and physical activity in relation to the risk of glaucoma for National Population Health Survey respondents from 2002-2011 using time-varying covariates with a lag-time of one cycle using Markov Chain Monte Carlo multiple imputation (50 imputations).

Variable (units)	**Crude Model** Hazard Ratio (95% CI)	**Adjusted Model*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)	1.04 (0.98-1.11)	1.00 (0.94-1.08)
Physical Activity (kcal/kg/day)	0.96 (0.89-1.04)	1.02 (0.94-1.11)
Age (years)		1.05 (1.04-10.6)
Sex (male/female)		1.11 (0.80-1.53)
Educational attainment (highest level attained)		1.05 (0.92-1.20)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		0.95 (0.65-1.39)
Smoking (yes/no)		1.19 (0.86-1.64)
BMI (kg/m^2)		0.96 (0.93-0.99)
Diabetes (yes/no)		1.06 (0.64-1.74)
High Blood Pressure (yes/no)		1.16 (0.82-1.63)
Heart Disease (yes/no)		2.01 (1.34-3.00)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.10 Crude and adjusted Cox proportional hazards models of separated fruits and vegetables consumption and physical activity in relation to the risk of glaucoma for National Population Health Survey respondents from 2002-2011 using time-varying covariates with a lag-time of one cycle using Markov Chain Monte Carlo multiple imputation (50 imputations).

Variable (units)	**Crude Model** Hazard Ratio (95% CI)	**Adjusted Model*** Hazard Ratio (95% CI)
Fruits (times consumed daily)	1.03 (0.96-1.10)	0.87 (0.73-1.03)
Fruit Juices (times consumed daily)	1.03 (0.96-1.10)	1.13 (0.94-1.36)
Carrots (times consumed daily)	1.45 (1.11-1.90)	1.07 (0.74-1.54)
Potatoes (times consumed daily)	1.03 (0.96-1.10)	1.14 (0.80-1.63)
Green Salad (times consumed daily)	1.03 (0.96-1.10)	1.16 (0.86-1.58)
Other vegetables (times consumed daily)	1.03 (0.96-1.10)	1.03 (0.87-1.22)
Physical Activity (kcal/kg/day)		1.02 (0.94-1.11)
Age (years)		1.05 (1.04-1.06)
Sex (male/female)		1.16 (0.84-1.62)
Educational attainment (highest level attained)		1.06 (0.93-1.21)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		0.96 (0.66-1.42)
Smoking (yes/no)		1.18 (0.86-1.63)
BMI (kg/m^2)		0.96 (0.93-0.99)
Diabetes (yes/no)		1.08 (0.66-1.78)
High Blood Pressure (yes/no)		1.15 (0.82-1.62)
Heart Disease (yes/no)		2.02 (1.35-3.03)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.11 Crude and adjusted Cox proportional hazards models of interaction between fruit and vegetable consumption and age in relation to the risk of glaucoma for National Population Health Survey respondents from 2002-2011 using time-varying covariates with a lag-time of one cycle.

Variable (units)	**Crude Model (a)** Hazard Ratio (95% CI)	**Adjusted Model (b)*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)	0.81 (0.61-1.07)	1.25 (0.84-1.87)
Physical Activity (kcal/kg/day)		0.98 (0.87-1.12)
Interaction term	1.00 (1.00-1.01)	1.00 (0.99-1.00)
Age (years)	1.03 (1.01-1.06)	1.09 (1.05-1.13)
Sex (male/female)		1.07 (0.66-1.75)
Educational attainment (highest level attained)		1.10 (0.89-1.35)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		1.09 (0.56-2.11)
Smoking (yes/no)		1.15 (0.71-1.88)
BMI (kg/m^2)		0.98 (0.93-1.03)
Diabetes (yes/no)		0.46 (0.16-1.34)
High Blood Pressure (yes/no)		1.23 (0.73-2.07)
Heart Disease (yes/no)		1.15 (0.55-2.43)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.12 Crude and adjusted Cox proportional hazards models of interaction between physical activity and age in relation to the risk of glaucoma for National Population Health Survey respondents from 2002-2011 using time-varying covariates with a lag-time of one cycle.

Variable (units)	**Crude Model (a)** Hazard Ratio (95% CI)	**Adjusted Model (b)*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)		1.03 (0.93-1.14)
Physical Activity (kcal/kg/day)	1.10 (0.84-1.45)	0.81 (0.46-1.44)
Interaction term	1.00 (0.99-1.00)	1.00 (0.99-1.01)
Age (years)	1.05 (1.04-1.07)	1.06 (1.03-1.09)
Sex (male/female)		1.09 (0.67-1.77)
Educational attainment (highest level attained)		1.09 (0.88-1.35)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		1.07 (0.55-2.08)
Smoking (yes/no)		1.16 (0.71-1.89)
BMI (kg/m^2)		0.98 (0.93-1.03)
Diabetes (yes/no)		0.47 (0.16-1.37)
High Blood Pressure (yes/no)		1.24 (0.74-2.07)
Heart Disease (yes/no)		1.16 (0.55-2.45)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.13 Crude and adjusted Cox proportional hazards models of fruit and vegetable consumption and physical activity in relation to the risk of glaucoma for National Population Health Survey respondents younger than or equal to 50 years of age from 2002-2011 using time-varying covariate with a lag-time of one cycle.

Variable (units)	**Crude Model (a)** Hazard Ratio (95% CI)	**Adjusted Model (b)*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)	0.95 (0.83-1.09)	1.11 (0.94-1.31)
Physical Activity (kcal/kg/day)	1.01 (0.88-1.16)	1.00 (0.80-1.26)
Age (years)		1.14 (1.06-1.23)
Sex (male/female)		1.04 (0.40-2.70)
Educational attainment (highest level attained)		1.45 (0.84-2.51)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		1.25 (0.25-6.33)
Smoking (yes/no)		2.18 (0.68-7.02)
BMI (kg/m^2)		1.04 (0.96-1.12)
Diabetes (yes/no)		0.76 (0.08-7.29)
High Blood Pressure (yes/no)		0.86 (0.21-3.60)
Heart Disease (yes/no)		2.08 (0.24-18.02)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.14 Crude and adjusted Cox proportional hazards models of fruit and vegetable consumption and physical activity in relation to the risk of glaucoma for National Population Health Survey respondents older than 50 years of age from 2002-2011 using time-varying covariate with a lag-time of one cycle.

Variable (units)	**Crude Model (a)** Hazard Ratio (95% CI)	**Adjusted Model (b)*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)	1.02 (0.95-1.11)	0.99 (0.87-1.12)
Physical Activity (kcal/kg/day)	0.99 (0.90-1.10)	0.97 (0.83-1.13)
Age (years)		1.04 (1.01-1.07)
Sex (male/female)		1.03 (0.57-1.84)
Educational attainment (highest level attained)		1.10 (0.89-1.35)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		1.06 (0.51-2.21)
Smoking (yes/no)		0.91 (0.53-1.59)
BMI (kg/m^2)		0.92 (0.86-0.99)
Diabetes (yes/no)		0.46 (0.13-1.56)
High Blood Pressure (yes/no)		1.41 (0.81-2.47)
Heart Disease (yes/no)		1.21 (0.55-2.68)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.15 Crude and adjusted Cox proportional hazards models of interaction between fruit and vegetable consumption and age in relation to the risk of glaucoma for National Population Health Survey respondents from 2002-2011 using time-varying covariates with a lag-time of one cycle using Markov Chain Monte Carlo multiple imputation (50 imputations).

Variable (units)	**Crude Model (a)** Hazard Ratio (95% CI)	**Adjusted Model (b)*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)	0.83 (0.64-1.08)	0.82 (0.63-1.07)
Physical Activity (kcal/kg/day)		1.02 (0.94-1.11)
Interaction term	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Age (years)	1.04 (1.02-1.06)	1.03 (1.01-1.05)
Sex (male/female)		1.12 (0.81-1.55)
Educational attainment (highest level attained)		1.05 (0.92-1.20)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		0.96 (0.65-1.41)
Smoking (yes/no)		1.20 (0.87-1.66)
BMI (kg/m^2)		0.96 (0.93-0.99)
Diabetes (yes/no)		1.05 (0.64-1.73)
High Blood Pressure (yes/no)		1.16 (0.82-1.62)
Heart Disease (yes/no)		2.00 (1.34-3.00)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.16 Crude and adjusted Cox proportional hazards models of interaction between physical activity and age in relation to the risk of glaucoma for National Population Health Survey respondents from 2002-2011 using time-varying covariates with a lag-time of one cycle using Markov Chain Monte Carlo multiple imputation (50 imputations).

Variable (units)	**Crude Model (a)** Hazard Ratio (95% CI)	**Adjusted Model (b)*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)		1.01 (0.94-1.08)
Physical Activity (kcal/kg/day)	1.09 (0.83-1.44)	1.06 (0.80-1.39)
Interaction term	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Age (years)	1.05 (1.04-1.07)	1.05 (1.03-1.06)
Sex (male/female)		1.11 (0.80-1.53)
Educational attainment (highest level attained)		1.05 (0.92-1.20)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		0.96 (0.66-1.41)
Smoking (yes/no)		1.19 (0.86-1.64)
BMI (kg/m^2)		0.96 (0.93-0.99)
Diabetes (yes/no)		1.05 (0.64-1.73)
High Blood Pressure (yes/no)		1.15 (0.82-1.62)
Heart Disease (yes/no)		2.00 (1.34-3.00)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.17 Crude and adjusted Cox proportional hazards models of fruit and vegetable consumption and physical activity in relation to the risk of glaucoma for National Population Health Survey respondents younger than or equal to 50 years of age from 2002-2011 using time-varying covariate with a lag-time of one cycle using Markov Chain Monte Carlo multiple imputation (50 imputations).

Variable (units)	**Crude Model (a)** Hazard Ratio (95% CI)	**Adjusted Model (b)*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)	0.96 (0.84-1.10)	0.93 (0.80-1.07)
Physical Activity (kcal/kg/day)	1.01 (0.88-1.15)	1.04 (0.90-1.19)
Age (years)		1.01 (0.98-1.05)
Sex (male/female)		3.19 (1.58-6.43)
Educational attainment (highest level attained)		0.86 (0.65-1.16)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		2.14 (0.53-8.74)
Smoking (yes/no)		2.69 (1.17-6.18)
BMI (kg/m^2)		0.94 (0.88-1.01)
Diabetes (yes/no)		0.92 (0.12-6.99)
High Blood Pressure (yes/no)		0.96 (0.30-3.12)
Heart Disease (yes/no)		5.71 (1.87-17.43)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Table 6.18 Crude and adjusted Cox proportional hazards models of fruit and vegetable consumption and physical activity in relation to the risk of glaucoma for National Population Health Survey respondents older than 50 years of age from 2002-2011 using time-varying covariate with a lag-time of one cycle using Markov Chain Monte Carlo multiple imputation (50 imputations).

Variable (units)	**Crude Model (a)** Hazard Ratio (95% CI)	**Adjusted Model (b)*** Hazard Ratio (95% CI)
Fruit and Vegetable Consumption (times consumed daily)	1.04 (0.96-1.12)	1.03 (0.95-1.12)
Physical Activity (kcal/kg/day)	0.98 (0.88-1.09)	1.00 (0.89-1.11)
Age (years)		1.04 (1.02-1.06)
Sex (male/female)		0.76 (0.52-1.11)
Educational attainment (highest level attained)		1.10 (0.95-1.28)
Income (yearly personal income in dollars)		1.00 (1.00-1.00)
Alcohol Use (yes/no)		0.85 (0.57-1.28)
Smoking (yes/no)		0.89 (0.62-1.28)
BMI (kg/m^2)		0.97 (0.93-1.01)
Diabetes (yes/no)		1.02 (0.61-1.71)
High Blood Pressure (yes/no)		1.13 (0.79-1.61)
Heart Disease (yes/no)		1.74 (1.14-2.66)

*Adjusted models all included fruit and vegetable consumption (times consumed daily), physical activity (daily energy expenditure), age (years), sex (male/female), education (highest level of education attained), income, alcohol use, smoking status, BMI, blood pressure, diabetes and heart disease.

Chapter 7

7. Discussion

In this chapter, the findings from this study are summarized and interpreted (7.1), followed by the discussion of the study's strengths (7.2) and limitations (7.3). The conclusion includes closing remarks and future directions (7.4).

7.1 Thesis Summary

The purpose of this thesis was to examine whether FV consumption and/or physical activity affect the risk of glaucoma. The NPHS, a nationally representative survey that collected self-reported health-related and sociodemographic information from Canadians, was the data source utilized for this study. Although there were nine survey cycles of data collection in the NPHS, some restrictions had to be applied due to availability of specific data. Our study began at cycle 5 (which thus served as the baseline) because this is when nutritional data began to be collected. At baseline (cycle 5), white individuals over the age of 18 who did not report using corticosteroids and did not report having had a prior diagnosis of glaucoma were included. Using a conceptual causal model, which was created through a systematic literature search, Cox proportional hazards models were used to investigate the associations of interest in this thesis. Overall, the results of this study do not support an association between either of the factors of interest with glaucoma.

7.1.1 Association between Glaucoma and Fruit and Vegetable Consumption

The first objective of this study was to assess whether FV consumption lowers the risk of glaucoma. Although time-independent and time-varying adjusted models both produced hazard ratio estimates in opposite directions of each other, the pair of results are not inconsistent with each other, as evidenced by the overlapping of 95% CIs around the point estimates. Methodologically, the Cox model with time-varying covariates provides a more meaningful estimate of the effect measure, as it allows for the intra-individual changes over time in both the exposures of interest and the potential confounders (namely, socio-demographic and health-related characteristics) to be accounted for. However, the results for the associations between FV consumption and glaucoma were not statistically significant. These findings did not support our first study hypothesis. Additional analyses were conducted for the six FV food items separately; fruits, fruit juices, carrots, potatoes, green salad, and other vegetables. All the FV items were found to have no statistically significant association with glaucoma, except from potatoes, consumption of which was found to be positively, statistically significantly associated with glaucoma.

A study done by Kang et al. (2003) which also examined the relationship between FV consumption as well as antioxidant intake and the use of multivitamins or supplements with risk of POAG, found that there was no statistically significant association between any of the exposures and the outcome. This was the only longitudinal study which investigated the association between FV consumption with glaucoma. Giaconi et al. (2012) carried out a cross-sectional study, which produced findings of a non-statistically significant association between FV consumption and glaucoma. Both of these studies produced results which were consistent with the findings in our study, suggesting no association between FV consumption and glaucoma.

However, contrary to our findings, Coleman et al. (2008) reported results suggesting an association between consumption of certain FV with glaucoma among elderly women. Particularly, carrots, green collards and kale, and canned or dried peaches were found to be negatively associated with glaucoma in that study. However, it is important to note that the study by Coleman et al. (2008) was cross-sectional, therefore the temporality of the exposures and outcome cannot be assessed. In addition, our study population was slightly different from the study population used for this study. Coleman et al. only assessed glaucoma among the elderly women from the Study of Osteoporotic Fractures in the

United States. The major difference with our study was the methodology, namely the longitudinal nature and the statistical analyses which were conducted.

Measurement error may also have been a key player in the results which were produced in our study. Notably, respondents may not have accurately reported their intake of fruits and vegetables. Only frequency of consumption was utilized as a measure of intake. This would consequently result in suboptimal findings, because accurate serving sizes were not recorded. For instance, an individual could consume one cherry or an entire bowl of mixed fruits in one sitting and report that fruits were consumed one time in that day. Both of these scenarios would provide different amounts of antioxidants to the body. In addition, it would have been useful to actually have the exact food item which was consumed so nutritional values could further be computed.

Fruit was shown to have a point estimate which suggested a protective effect on glaucoma. This may have been a result of the fact that fruits are eaten raw, they are not cooked, seasoned, or dressed. In contrast, fruit juice consumption was a poor measure of fruit consumption because it is well established that many fruit juices are highly concentrated in sugar and packed with artificial flavours. Individuals may be consuming fruit juices while unaware of the nutrition content. For example, Sunny Delight and freshly squeezed apple juice from a juicer would both fall under this category, even though they would both impact the body differently. It is important to understand that highly sugar concentrated drinks are also a risk factor for many other conditions such as diabetes, heart disease and obesity (Malik et al., 2010; Schulze et al., 2004), all of which are also noted risk factors of glaucoma.

Potatoes were the only food item consumption of which was statistically significantly associated with glaucoma in our study and appeared to be harmful in respect to glaucoma occurrence. Carrots, green salad and other vegetables were also found to have a point estimate of the hazard ratio indicating that they increase the risk of glaucoma; however these point estimates were not statistically significant. The apparent negative effect may have been due to food preparation, as the amount of antioxidant found in FV dramatically decreases when these foods are prepared as opposed to eaten raw (Blasa, Gennari, Angelino, & Ninfali, 2010).

However, there is a strong possibility that there is truly no effect of fruit and vegetable consumption on the risk of developing glaucoma. In fact, evidence suggests that an association between fruit and vegetable consumption with other major chronic diseases is not statistically significant (Hung et al., 2004). A plausible explanation may be that the antioxidant dosage consumed through fruits and vegetables is too small to truly have an effect.

Other possible reasons behind the results may have been chance or residual confounding, which we could not control for. For example, we did not have two risk factors for glaucoma, including intraocular pressure and family history. Intraocular pressure has been used as a surrogate measure in many studies where glaucoma was not recorded, and family history is difficult to document and is therefore rarely available in glaucoma studies.

7.1.2 Association between Glaucoma and Physical Activity

The second objective of this study was to assess whether physical activity was associated with the development of glaucoma. All the Cox proportional hazards models assessing the association between physical activity and risk of glaucoma suggest there to be no association between them.

Although no previous studies were conducted to produce direct evidence on the association between physical activity and glaucoma, many studies used a surrogate measure, intraocular pressure to investigate this association. Intraocular pressure was used as a surrogate measure to assess the short-term effects of physical activity on glaucoma. Generally, most studies suggested an association between physical activity and intraocular pressure, suggesting a possibly protective effect of the former on the latter. However, our study found a statistically significant association between physical activity and glaucoma per se. It is thus possible that although intraocular pressure may be reduced by physical activity, this reduction would not necessarily result in the reduction of the risk of glaucoma (Pasquale & Kang, 2009).

The lack of a statistically significant association between physical activity and glaucoma may have been due to measurement error. People are generally prone to over-reporting their duration of physical activity, which was used to calculate energy expenditure. In addition, physical activity was only to be reported for the previous three months, and not the entire year, which is another limiting factor for this measurement. A better measurement of physical activity, perhaps with heart rate also being monitored, would have resulted in more accurate results.

7.2 Strengths

To our knowledge, this study was the first study to produce direct evidence on the association between FV consumption and physical activity with glaucoma. We used a retrospective cohort study design based on a database containing longitudinal data on a large, national sample of Canadians. The longitudinal nature of the study and the sample size of the study were both key strengths of this study. Further, the NPHS had a high response rate because of the many steps were taken to reduce loss to follow-up and attrition rates. The use of computer assisted interviewing also minimized interviewer error and allowed respondents to reply to questions more openly. By using this survey, we were able to have a large sample size, and therefore increasing power.

Another major strength of our study in comparison to current literature was that when assessing the relationship particularly between physical activity and glaucoma, we had data on the actual outcome of interest, glaucoma. In many studies, intraocular pressure was used as a surrogate measure, which although a major risk factor for the condition, is not necessary for the development of glaucoma. A prime example of an instance where glaucoma develops regardless of intraocular pressure is normal tension glaucoma.

In terms of the methodological strengths of this study, it relied on survival-analytic methodology – specifically, multivariable Cox proportional hazards regression models with time-varying covariates. The time variation allowed for changes in values of the covariates as time passed. In addition, using the Cox proportional hazards model also allowed us to go further than a basic logistic regression model because we were able to use time-varying covariates while also accounting for censoring. We also did age interaction analyses to assess whether age was moderating the relationships. Finally, multiple imputation using the MCMC method was also done to examine whether there was a difference in the findings after the missing values were imputed and thereby assess the robustness of our main analytic approach. There were little to no changes in the results after imputation was done, which provided support for the findings.

7.3 Limitations

Due to RDC restrictions, we were not able to control for ethnicity and corticosteroid use in the statistical analyses, so we chose to prevent confounding by these factors by restriction, which decreased our study sample. In addition, the self-reporting nature of the survey which was used for this study lead to many possible limitations. For one, there is a high possibility that glaucoma diagnosis was underreported, as not many people were visiting their ophthalmologists. This could have been a direct result of some Canadian health insurance plans not covering glaucoma screening costs (Einarson et al., 2006). Our study population also was low income as seen in the median income for the descriptive tables. This would have further reduced detection of glaucoma, because low income individuals were less likely to visit the doctor/ophthalmologist (Chou et al., 2012; Flores, Bauchner, Feinstein, & Nguyen, 1999).

Further, due to self-reporting, there may have been errors in the reporting of most variables used in this study, namely the exposures, which required respondents to reflect on the last three months' physical activity habits. There may have also been non-differential misclassification of the exposures of interest. We assume it is non-differential because although there may have been misreporting of values for many of the variables, we presume it is similar throughout for those who had glaucoma or those who did not. For example, those who had glaucoma would not have had different eating or physical activity habits than those with glaucoma prior to the development of the outcome. This misclassification of the exposures would have caused the results to be closer to the null, therefore possibly masking an association.

7.4 Conclusion

The findings from this study indicate no association between the exposures and glaucoma, suggesting that further research should be done. As next steps, a follow-up study should be done using food diaries so accurate measurements of food are recorded. In addition, it is important for participants in the study to have food literacy, meaning a knowledge of foods. This is necessary because as previously mentioned not everyone knows what proper serving sizes may look like in regard to different food items. Becoming food literate will help to improve the quality of the food diaries kept as well. To build upon this, it would also be interesting to see how preparing foods in different ways might impact the risk of glaucoma.

With regards to assessing the association between physical activity and glaucoma, the use of heart rate monitors may help produce higher quality results. With current technology advances, it would not be difficult to get heart rates or even estimated caloric output with the use of Fitbits and smartphones. If researchers wanted to go even further, they may also consider measures of VO_2max, although this would not be feasible to do in the long term.

In conclusion, the findings of our study suggest no association between either FV consumption or physical activity and glaucoma. The results of this study can be used as a stepping stone for future research projects.

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Appendix A

Table 1: Database search strategy

Concept	Cochrane*	MEDLINE/ PubMed	Embase	CINAHL	Keywords**
Fruit and Vegetable Consumption	Food Habits, Eating, Feeding Behaviour (this term only), Diet, Food, Vitamins, Fruit, Citrus, Vegetable, antioxidants	Diet/, eating/, feeding behaviour/, vitamin D/, vitamin/, vitamin intake/, fruit/, vegetable/	Diet/, eating/, feeding behaviour/, vitamin D/, vitamin/, vitamin intake/, fruit/, vegetable/	MH "Diet+", MH "Nutrition", MH "Food Intake", MH "Eating Behaviour", MH "Food Habits", MH "Vitamins", MH "Vitamin K", MH "Vitamin E", MH "Fruit", MH "Vegetable"	Diet*, nutri*, feeding behavi*, food intake, food habit, food habits, eat*, feed*, food*, vitamin*, fruit*, vegetable*
Physical Activity	Exercise, Fitness, Physical Fitness, Cardiorespiratory Fitness	Fitness/, exercise/, activity/, physical activity/	Fitness/, exercise/, activity/, physical activity/	MH "Fitness", MH "Physical Fitness", MH "Physical Activity", MH "Exercise"	Exercise*, aerobics, physical activity, fitness, run*, swim*, walk*, active*
Glaucoma	Low Tension Glaucoma, Ocular Hypertension, Intraocular pressure, Open-Angle Glaucoma	Ocular hypertension/, intraocular pressure/, open-angle glaucoma/, low tension glaucoma/	Ocular hypertension/, intraocular pressure/, open-angle glaucoma/, low tension glaucoma/	MH "intraocular pressure", MH "ocular hypertension+",	Low tension glaucoma, low pressure glaucoma, normal tension glaucoma, normal angle glaucoma, normal pressure glaucoma, open-angle glaucoma, open angle glaucoma,

					ocular hypertension, intraocular pressure, intra-ocular pressure, secondary open-angle glaucoma, primary open angle glaucoma
Limits	None	English & Human	English & Human	None	

*All terms exploded, unless mentioned as single term
*Keywords were used for all databases along with MeSH terms

Appendix B

Activity	MET value Cycle 1	MET value Cycle 2	MET value Cycle 3 to Cycle 8
PACn_1A - Walking for exercise	3	3	3
PACn_1B - Gardening, yard work	3	3	3
PACn_1C - Swimming	3	3	3
PACn_1D - Bicycling	4	4	4
PACn_1E - Popular or social dance	3	3	3
PACn_1F - Home exercises	3	3	3
PACn_1G - Ice hockey	6	6	6
PACn_1H - Ice-skating ("Skating" in Cycle 1)	4	4	4
PACn_1I - Downhill skiing or snowboarding ("Downhill skiing" in cycles 1 to 4)	4	4	4
PACn_1J - Jogging or running	9.5	9.5	9.5
PACn_1K - Golfing	4	4	4
PACn_1L - Exercise class or aerobics	4	4	4
PACn_1M - Cross-country skiing (Dropped in Cycle 3)	5	5	N/A
PACn_1N - Bowling	2	2	2
PACn_1O - Baseball or softball	3	3	3
PACn_1P - Tennis	4	4	4
PACn_1Q - Weight-training	3	3	3
PACn_1R - Fishing	3	3	3
PACn_1S - Volleyball	5	5	5
PACn_1T - Basketball (New in Cycle 2)	N/A	6	6
PACn_1Y - In-line skating or roller-blading (New in Cycle 3)	N/A	N/A	5
PACn_1Z - Yoga or tai-chi (Dropped in Cycle 2)	2	N/A	N/A
PACn_1U , PACn_1W, PACn_1X - Other activities (see Note (2))	4.2	4	4

Body Mass Index (BMI)

The BMI (variables HWCcDBMI, HWCcDCOL and HWCcDISW) is calculated by dividing the weight in kilogram (kg) by the square height in meters. A healthy BMI is between 18.5 and 25; a respondent with a BMI over 30 is classified as obese, and a BMI over 40 is classified in the extremely obese category.

Some studies found that survey respondents tend to underestimate their weight and overestimate their height, which has an impact on their BMI. This impact could be reduced by applying a correction factor (see Sheilds (2008) – "Estimates of obesity based on self-reported versus direct measures", Health Reports (Statistics Canada), vol.19, no.3, September 2008).

The method preferred for this survey is to impute the height and the weight variables first and then recalculate the BMI based on the imputed values.

Height

This variable (HWCn_HT) is in inches (or by category if reported in metric scale). For example, the value "3" was assigned to anyone with a height of 1'1" (13 inches) (31.8 to 34.2 cm). Height should increase for children, but be stable for adults until they reach 65. After 65, a height decrease of 1 to 3 inches over time could occur. A height decrease or an extreme height increase is considered as incoherent height according to the respondent's age.

Strategy for height

Since height fluctuates differently depending on the respondent's age, an imputation strategy was selected according to the respondent's age in cycle 1. Instead of using the age collected in cycle 1 (variable DHC4_AGE), the value of the cycle 1 age was updated using the most recent birthday date available. Therefore, for a few cases, the age used for imputation differs from DHC4_AGE. This new value (referred as cycle 1 age below) was used to create the imputation classes.

Before proceeding with imputation, all incoherent data were set to missing for respondents aged 12 and older.

<u>0 to 11 years old (in cycle 1)</u>

The imputation study showed poor results for this age group; height varies significantly from one year to the next; for more details, see Shields 2011 – "*Obesity estimates for children based on parent-reported versus direct measures*", Health Reports (Statistics Canada), vol. 22, no 3, September 2011.

Conclusion: No imputation to height of children 0 to 11 years old.

<u>12 to 19 years old (in cycle 1)</u>

1-Regression by age-gender using t-1 and t+1 height to impute missing t height. (If cycle 1, use t+1 and t+2; if cycle 9, use t-1 and t-2)

2-Regression by age-gender using t-1 height to impute missing t height. (If cycle 1, use t+1)

3-Impute height by mode from the cycle when respondent older than 20 years.

For step 2 and 3, the assumption is that imputed values from previous steps are accurate (used as reported values).

<u>Height imputation rates for respondents aged 12 to 19 in cycle 1</u>

The following table contains the imputation rates by cycle for the respondents aged 12 to 19 in cycle 1. Imputation was performed for missing data in the case of partial and full questionnaire with item non-response for the height and when incoherent data was observed (example, height decrease).

<u>20 to 64 years old (in cycle 1)</u>

1-Height imputed by the mode

2-When more than one mode is available for a given respondent, cycle 1's value is selected as the mode (if included in one of the modes). Most of the interviews were personal in cycle 1, so we believe this answer was the most accurate. After cycle 1, most interviews were done by phone.

3-As for the cases for which no mode was available or cycle 1's value is not include in one of the mode if many modes, the height is imputed by the median when the difference between the minimum and the maximum reported height is less than 5 inches.

4-Cycle 1's value was used for the remaining cases when available (if not available, cycle's 2 height was used – only 4 respondents were in that situation when cycle's 8 data was used to do analyzes).

<u>65 years old and over (in cycle 1)</u>

Instead of using the mode, the height of previous cycle is used to take into account the possibility of height decrease. The previous height is the most recent height available prior to the cycle of interest (for cycle 1, the mode is used as previous cycle value). The same strategy is applied when respondent reach the age of 65 after cycle 1.

1-Height imputed by previous height.

2-For the remaining cases, the height is imputed by the median of all reported heights when the difference between the minimum and the maximum is less than 5 inches.

3-Cycle 1's value was used for the remaining cases when available (if not available, cycle's 2 height was used).

<u>Height imputation rates for respondents aged 20 years or older in cycle 1</u>

The following table contains the imputation rates by cycle for the respondents aged 20 or older in cycle 1. Imputation was performed for missing data in the case of partial and full questionnaire with item non-response for the height and when incoherent data was observed (example, height differences greater than 2 inches).

<u>Weight</u>

The weight variable (HWCn_3KG or HWCn_3LB) was captured in kilograms (kg)or in pounds (lbs) for all NPHS cycles. The respondent's answer was then converted into the non-reported scale. For example, a respondent who reported a weight of 60 kg was assigned a weight of 132 lbs. As a reminder, 1 kilogram (kg) is equivalent to 2.2 pounds (lbs).

Two main types of errors were detected:

- Scale error or inversion error - Instances where pounds were captured as kilograms (the reverse error also occurred).
- Keying error – Incorrect value was entered. For example, a weight of 5 kg is entered for a respondent older than 18 years old. The keying errors are more difficult to detect, since they could only be found if an extreme value was captured.

In this section, the method used to adjust the weights when they are incoherent is described.

Strategy for weight

Adjust the weight when incoherent. Imputation performed on kilogram weights (HWCn_3KG). The weights are converted in pounds (HWCn_3LB) at the end of the imputation process. Instead of using the age collected in cycle 1 (variable DHC4_AGE), the value of the cycle 1 age was updated using the most recent birthday date available. Therefore, for a few cases, the age used for imputation differs from DHC4_AGE. This new value (referred as cycle 1 age below) was used to create the imputation classes.

In order to regroup similar respondents in the same category, a weight category variable (WGT_CAT) was created. These categories were based on the median weight derived from the collected weights and the number of reported values.

0 to 11 years old (in cycle 1)

The imputation study showed poor results for this age group; weight varies significantly from one year to the next; for more details, see Shields 2011 – "*Obesity estimates for children based on parent-reported versus direct measures*", Health Reports (Statistics Canada), vol. 22, no 3, September 2011.

Conclusion: No correction or imputation to the weight of children in this age group. Their weight may be imputed once they reach 12 years old, using the strategy described below.

12 to 17 years old (in cycle 1)

Imputation class: SEX DHC4_AGE

Imputation Steps (BANFF used):

1-Outlier detection

2-Regression using t-1 and t+1 weight (in C1, use t+1 & t+2; in C9, use t-1 & t-2)

3-Donor imputation (must match variables initial available weight, final weight available and number of available weight)

Weight imputation rates for respondents aged 12 to 17 in cycle 1

The following table contains the imputation rates by cycle for the respondents aged 12 to 17 in cycle 1. Imputation was performed for missing data in the case of partial and full questionnaire with item non-response for the weight and when incoherent data was observed (example, weight in kilograms instead of pounds).

18 years old and over (in cycle 1)

Imputation class: WGT_CAT SEX AGEGR

Imputation Steps (BANFF used):

0-Correction of scale errors (kg/lbs)

1-Outlier detection

2-Regression using t-1 and t+1 weight (in C1,use t+1 & t+2; in C9, use t-1 & t-2)

3-Donor imputation (must match variables initial available weight, final weight available and number of available weight)

4-Ratio imputation

Weight imputation rates for respondents aged 18 years or older in cycle 1

The following table contains the imputation rates by cycle for the respondents aged 18 and more in cycle 1. Imputation was performed for missing data in the case of partial and full questionnaire with item non-response for the weight and when incoherent data was observed (example, weight in kilograms instead of pounds).

Appendix C

<u>Title of the project:</u> The effect of fruit and vegetable consumption and physical activity on the risk of glaucoma: a cohort study

Requesting access to the **Western University RDC**.

<u>Rationale and objectives of the study</u>

Background. Glaucoma is defined by "optic neuropathy that is characterized by specific structural findings in the optic disc and specific functional deficits" (Cook & Foster, 2012). This condition is detected by automated visual field testing (Cook & Foster, 2012) and can lead to blindness when it is chronic (Leske, 1983; Ramdas et al., 2012). In fact, it is known to be the second leading cause of blindness in the world (Leske, 1983). The prevalence estimates of this condition range from 1.8% to 7.5% in Canada (Anraku et al., 2011; Harasymowycz, Papamatheakis, Fansi, Gresset, & Lesk, 2005; Perruccio et al., 2007; Shenken, 1966). The worldwide prevalence of glaucoma continues to increase with estimated cases of glaucoma expected to increase to 79.6 million by 2020 (Quigley & Broman, 2006), of which 11.2 million are expected to go blind as a result (Cook & Foster, 2012). Prevention is the first step in controlling the burden of this disease. Known risk factors for glaucoma include age, sex, ethnicity, family history, intraocular pressure, cataracts, hypertension, diabetes, and cardiovascular disease (Cook & Foster, 2012; Leske et al., 2008). Of the above-listed risk factors, only intraocular pressure, and some chronic diseases are modifiable, therefore controlling the risk of developing this condition may be considered difficult.

Rationale. Healthy eating and physical activity have been known to be associated with improved overall health and a decreased risk of numerous chronic diseases, including coronary artery disease, hypertension and diabetes (Roberts & Barnard, 2005). Diet and physical activity are lifestyle factors which are modifiable and relatively easy to control. It is thought that certain antioxidants may decrease oxidative stress, which has been found to be associated with optic nerve deterioration (Parikh & Parikh, 2011). There is a possibility that certain diets rich in vitamins can improve the function of the trabecular meshwork, which in turn would protect the optic nerve from damage (Kang et al., 2003). Additionally, it has been established that physical activity has a positive effect on intraocular pressure.

Two previous studies were conducted to examine the association between fruit and vegetable consumption and glaucoma (Coleman et al., 2008; Giaconi et al., 2012). Both of these studies were cross-sectional with a sample of women older than 55. A third study examined the association between antioxidant intake and primary open-angle glaucoma but found no statistically significant association. The most recent study was a longitudinal study on nutrient intake and the risk of open-angle glaucoma also among women greater than 55, with nutrients only assessed at baseline. The evidence produced from these studies was not high quality, and may be viewed as imprecise. There is still great uncertainty, therefore there is a need for more studies in this area in order to reach a conclusion.

To our knowledge, no study has been done to examine the association between physical activity and glaucoma. Although there have been no studies done on glaucoma as an outcome, there have been many studies to examine the association between physical activity and intraocular pressure in the short-term. In addition, one large study was done to examine the relationship between physical activity and ocular perfusion pressure, another surrogate outcome of glaucoma, over a 10-year period (Yip et al., 2011). Intraocular pressure is a surrogate measure of glaucoma (Medeiros, 2014). Although intraocular pressure is a known modifiable risk factor of glaucoma, people can have vision loss indicative of glaucoma with a low intraocular pressure, and people with high intraocular pressure may not have glaucoma (Drance, 1999; Kass MA et al., 2002). In fact, one study showed that only 54% of incident cases of glaucoma had an elevated intraocular pressure (Leske et al., 2008), therefore concluding that intraocular pressure was not a strong surrogate measure of glaucoma. Lastly, there have been no studies to examine whether diet, specifically fruit and vegetable consumption and physical activity interact to have a joint effect on the risk of glaucoma.

Objectives. The purpose of this study is to examine whether lifestyle factors have an effect on the risk of glaucoma in adults.

The primary objectives are:

1. To examine if fruit consumption has an effect on the risk of glaucoma
2. To examine if vegetable consumption has an effect on the risk of glaucoma
3. To examine if physical activity has an effect on the risk of glaucoma

The secondary objectives are:

4. To examine if fruit and vegetable consumption interact in effecting the risk of glaucoma
5. To examine whether physical activity and vegetable consumption interact in effecting the risk of glaucoma.
6. To examine whether physical activity and fruit consumption interact in effecting the risk of glaucoma.

<u>Proposed data analysis and software requirements</u>

Study Variables. The main exposures will be physical activity, and fruit and vegetable consumption. Both fruit and vegetable consumption will be kept as continuous variables, by reported frequency of consumption, for the analyses. Physical activity will be represented using metabolic equivalents of the task (METs). Glaucoma status will be the dependent variable. In addition, the following risk factors will be included in the analyses: age, sex, BMI, ethnicity, smoking status, alcohol use, diabetes, hypertension, heart disease, and cataracts. Age will be kept as a continuous variable. BMI and ethnicity will be kept as categorical variables. Sex, smoking status, alcohol use, diabetes, hypertension, heart disease and cataracts will all be kept as binary variables for our study.

Data Analysis. The first step in our analysis will be to clean the data and examine the distributions of all the potential variables. Next, we will produce descriptive statistics (mean, median, range for continuous variables and relative frequencies for categorical variables) first for the overall sample, then for exposed/unexposed for each of the main exposure variables using frequency tables. Since our exposure variables are continuous, for the sake of presentation, we will be dichotomizing the variables on the basis of the sample medians for each of the main exposure variables.

We will pool observations for every 2 years of the repeated surveys across individuals in order to change the structure of the dataset so we can fit our pooled logistic regression models (D'Agostino et al., 1990).The pooled logistic model is known to emulate the Cox Proportional Hazard Model (D'Agostino et al., 1990). By using a pooled logistic regression model, we are able to use time-dependent covariates while still using a logistic regression model, which is necessary to account for the change in exposures over time. In order to address each objective, we will fit crude and multivariable pooled logistic regression models. All multivariable logistic will be adjusted for age, sex, BMI, ethnicity, smoking status, alcohol use, diabetes, hypertension, heart disease, and cataracts.

To address objectives 4,5 and 6, we will introduce two-way interaction terms between the three exposure variables.

All data analyses will be done using SAS v. 9.4 (SAS Institute Inc., Cary, NC, USA).

Data requirements

For this project we are requesting to use the National Population Health Survey-Household- Longitudinal component, cycles 1 through 9 confidential data files. The confidential data is necessary as my project will be looking at a long-term relationship between the effect of specific lifestyle factors on the risk of glaucoma. In addition, the diet component of the questionnaire does not begin until cycle 5.

Population of Interest. The entire cohort over the age of 19 will be our study population.

Variables. The variables required for this analysis include: age, sex, BMI, ethnicity, smoking status, alcohol use, diabetes, hypertension, heart disease, eye specialist visit, physical activities and fruit and vegetable consumption, person ID, income, education. A detailed list of these variables may be found in **Table 1**.

Sample Size/Power Analysis. According to NPHS longitudinal documentation, the sample size of participants who provided full response from cycle 1 through 8 was approximately 9,982. When taking into account the individual response rate in cycle 9 (69.7%), the Canadian population over the age of 19 (Government of Canada, 2015), the size of the analytic sample is approximately 5,427. Based on the prevalence of the exposure being 50% (defined according to the sample median), we estimated the approximate power. Presuming a 1.2% incidence of the outcome among the exposed, and 0.6% incidence among the unexposed with an alpha level of 0.05, we can obtain a power of 0.91 with the sample size above.

Expected project start and end dates

This project is expected to begin in August 2016 and end in August 2019.

Expected products

A peer-reviewed journal article as well as a graduate level thesis are expected as a result of this study. For publication, we will consider epidemiology and ophthalmology journals.

Table 1: Variables requested

Variable Code	Variable Name	Question
DHCD_AGE	Age	Age (age is calculated and confirmed with the respondent)
SEX	Sex	Sex (male/female)
SD_Q4	Ethnicity	To which ethnic or cultural group(s) did %your/FNAME's% ancestors belong? (For example: French, Scottish, Chinese)
HWQ2	Height	
HWQ3	Weight	
HWCnDBMI	BMI	Body Mass Index
ALCnDDLY	Alcohol	Average daily alcohol consumption
SMCnDTYP	Smoking	Type of smoker
All FV regular All FV derived	Fruit and Vegetable Consumption	
HC_Q02A HCCD_2B	Eye specialist Visit	(Not counting when [you/FNAME] [were/was] an overnight patient,) In the past 12 HCCD_2A months, how many times [have/has] [you/FNAME/he/she] seen or talked on the telephone about [your/his/her] physical, emotional or mental health with: . an eye specialist (such as an ophthalmologist or optometrist)?
CC_Q071	High Blood Pressure	[Do/Does] [you/FNAME] have high blood pressure?
CC_Q101	Diabetes	[Do/Does] [you/FNAME] have diabetes?
CC_Q121	Heart Disease	[Do/Does] [you/FNAME] have heart disease?
CC_Q191	Cataracts	[Do/Does] [you/FNAME] have cataracts?
CC_Q201	Glaucoma	[Do/Does] [you/FNAME] have glaucoma?
All PA All PA derived	Physical Activities	
INCnDHH INCnDPER	Income	Total Household Income Total Personal Income
EDCnD1	Education	Highest level of education
	Person ID	
GE	Geographic indicators	

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Presentations:

Poster Presentation: **Brar R.,** Hodge W., Karp I. Are Physical Activity and Consumption of Fruits and Vegetables Associated with Glaucoma? Canadian Society of Epidemiology and Biostatistics Annual Conference; Banff, AB. June 2, 2017.

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