Immigrants & Secondary Cardiac Prevention Therapy Adherence

THE ASSOCIATION OF IMMIGRATION AND ETHNICITY WITH ADHERENCE TO STATINS AND CARDIAC REHABILITATION POST-MYOCARDIAL INFARCTION: A SUB-STUDY OF THE ISLAND RANDOMIZED CONTROLLED TRIAL

By SHAUN G SHEPHERD, BSc. Hon.

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Department of Health Research Methods, Evaluation and Impact

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TITLE: The Association of Immigration and Ethnicity with Adherence to Statins and Cardiac Rehabilitation Post-Myocardial Infarction: A sub-study of the ISLAND Randomized Controlled Trial

AUTHOR: Shaun Shepherd, BSc. Hons. (University of Toronto, 2013)

SUPERVISORS: J-D Schwalm, MD, MSc, FRCPC; Noah Ivers, MD, PhD, CCFP

COMIMITTEE: Madhu Natarajan, MD, FRCPC, FACC; Robby Nieuwlaat, MSc, PhD; Philip Joseph, MD, BASC, FRCPC

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Lay Abstract

The primary purpose of this research project was to assess whether immigrants, individuals who reside in Canada but were born outside of the country, who have experienced a previous heart attack were adhere to heart health therapies better than Canadian-born patients. The heart health therapies of interest to our investigation are two guideline-recommended heart attack prevention therapies, statins and cardiac rehabilitation.

The study design of our research project was a cohort sub-study of the ISLAND randomized control trial which investigated adherence to heart health therapies in patients residing in Ontario, Canada.

Our major finding was that immigrants who lived in Canada for >10 years were more adherent to statin therapy for a previous heart attack compared to Canadian-born participants. Our findings support the hypothesis that immigrants tend to demonstrate behaviours associated with improved outcomes compared to their Canadian-born counterparts.

Abstract

Adherence to guideline-recommended secondary cardiovascular prevention therapy (statins and cardiac rehabilitation) has been demonstrated to reduce the risk of all-cause mortality (Statins RRR 0.25, 95% CI 0.19-0.30; Cardiac Rehabilitation RRR 0.26, 95% CI 0.14-0.36) and secondary events.[1,2] Yet, ≥50% of patients discontinue statin use within 12-month after an initial prescription and completion of cardiac rehabilitation is ≤20% in Ontario.[3,4] Low statin adherence and cardiac rehab completion limits patients from realizing the full benefits of therapy.

A meta-analysis of randomized controlled trials of adherence to statins for secondary prevention reported that nonadherence to statins was greater in non-white ethnicities compared to white ethnicities (OR 1.28, 95% CI 1.04-1.59) with geographical variation in outcomes.[5] In respect to cardiac rehabilitation, the literature suggests that non-white ethnicities are less likely to complete cardiac rehabilitation compared to white participants.[6,7] However, a gap remains in our knowledge of cardiac rehabilitation completion among immigrants due to lack of outcome reporting across clinical trials. The literature suggests that immigrants have improved health profiles relative to Canadian-born patients. Specifically, immigrants with ≤10 years of Canadian residency have greater medication adherence than immigrants with >10 of Canadian residency when compared to Canadian-born participants.[6-9]

This thesis was a planned sub-study of the *Interventions Supporting Long-Term Adherence and Decreasing Cardiovascular Events* (ISLAND) randomized control trial.

The ISLAND study was a pragmatic, randomized controlled trial investigating the effect of educational reminders on adherence to guideline-recommended therapy post-myocardial infarction. Study participants were allocated in a 1:1:1 ratio to one of three groups: i) usual care, ii) educational reminders sent via post, or iii) combination post and interactive voice response educational reminders. Investigators were blinded to the allocation sequence, participant allocation, and outcome assessment. Medication adherence and completion of cardiac rehabilitation were assessed 12-months from baseline. This sub-study of ISLAND focused on participants who completed a 12-month outcome assessment with a recorded response to the following question, “Were you born a Canadian citizen?”.

Immigrants experienced greater odds of statin adherence at 7-days (OR 1.36, 95% CI 1.00-1.85) and 30 days (OR 1.36, 95% CI 0.96-1.94) at one-year post-myocardial infarction, after adjusting for age, diabetes, sex, and smoking status. We found no evidence that immigration status was associated with cardiac rehabilitation completion (OR 0.91, 95% CI 0.72-1.14) after adjusting for age, diabetes, sex, smoking status, average neighborhood income quintile, education, and marital status. The odds of statin adherence at 7-days (OR 1.33, 95% CI 0.89-2.18) and 30-days (OR 1.39, 95% CI 0.89-2.18) was greater in visual minorities than white patients, however the difference was not statistically significant. We found no evidence of an association between ethnicity and cardiac rehabilitation completion (OR 0.98, 95% CI 0.75-1.29). Our analysis could not fully evaluate the healthy immigrant effect due to an insufficient sample size of immigrants with <10 years of Canadian residency exposure (n=29).

In conclusion, we report a statistically significant 36% increase in the odds of 7-day and 30-day statin adherence in immigrants compared to Canadian-born patients. We also report that the odds of cardiac rehabilitation decreased by 9% in immigrants

compared to Canadian-born patients at 12-months post-myocardial infarction but this was not statistically significant. Our findings offer support for the "healthy immigrant effect" continuing in immigrants with >10 years of Canadian residency exposure. We were unable to evaluate outcomes in immigrants with <10 years Canadian residency exposure due to a lack of sample size (n=29).

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To my family, thank you for your patience and understanding in giving me the time and space to write this manuscript.

Abbreviations

Name	Abbreviation
Coronary artery disease	CAD
Acute coronary syndrome	ACS
ST-segment elevation Acute Coronary Syndrome	STEACS
Non-ST-segment elevation Acute Coronary Syndrome	NSTEACS
Unstable angina	UA
Odds ratio	OR
Hazard ratio	HR
Confidence interval	CI
Randomized controlled trial	RCT
Acute myocardial infarction	AMI

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CHAPTER 1: INTRODUCTION AND REVIEW OF THE LITERATURE

Ischemic cardiovascular disease burden

Coronary artery disease (CAD) is the leading cause of premature death worldwide.[10] In 2016, the total deaths from CAD increased by 19% to 9.48 million deaths (95% confidence interval (CI), 9.28 million to 9.76 million).[10] In 2012, there were 578,040 reported acute myocardial infarctions (AMI) associated with CAD in Canada which accounted for an age standardized prevalence rate of 2.88 and 1.12 per 1,000 for men and women, respectively.[11] Globally, CAD was ranked the number one cause of disability-adjusted life years (DALYs) in 2010, increasing 13.7% from 1990.[12]

CAD has been demonstrated to be a leading cause of all-age DALYs in females within the following global regions: South Asia, North Africa and the Middle East, Southeast Asia, East Asia, Latin America (with the exception of Andean Latin America and Central America) and the Caribbean, Central Europe, Eastern Europe, Central Asia, Southern Latin America, Western Europe, North America, and Asia Pacific. For males, the regional trends were similar, with the exception that CADs were not a leading cause of DALYs in Andean Latin America, Central America, tropical Latin America, and high-income Asia Pacific. [3]

Acute myocardial Infarction definition

Acute myocardial infarction is defined as a clinical evidence of myocardial necrosis caused by acute cardiac ischemia. A clinical diagnosis of myocardial infarction requires the detection of a change in cardiac biomarkers, such as cardiac

troponin, with at least one of the following: symptoms of ischemia; significant ST-segment-T wave changes; assessment of pathological Q waves by ECG; presence of intracoronary thrombus; or evidence of the loss of viable myocardium or cardiac wall motion abnormality.[13]

Acute myocardial infarction can be organized by the identification of either ST-segment elevation or lack of ST-segment elevation by ECG.[13] Patients who present with an ST-segment elevation in two adjacent leads are categorized as having ST-segment elevation acute coronary syndrome or STEACS. Patients who present without ST-elevation are categorized as non-ST-elevation acute coronary syndrome (NSTEACS)".

Secondary cardiovascular prevention

Current guidelines recommend lifestyle modifications, combination medication therapy, and cardiac rehabilitation for patients who have experienced a previous AMI.[14,15] Lifestyle modifications include regular exercise, stress reduction, smoking cessation, and a diet low in saturated fats and sodium. Participation in and completion of a cardiac rehabilitation program is a key component in reducing the risk of a secondary cardiac event. Cardiac rehabilitation programs educate patients on their modifiable risks, train patients to exercise regularly, and offer counseling services.[16]

Combination therapy with statins, angiotensin-agents, beta-blockers, and blood thinners is a preferred therapy for patients without contraindications. In particular, statins have been demonstrated in the literature to be effective at

reducing the risk of secondary cardiac events and cardiac mortality after STEACS. The average relative risk reduction in patients who use statins for over 5 years is 20-30%.[17-19]. However, there are reports in the literature of differential uptake of statins by immigrant status and ethnicity[5,20-22].

Lewey *et al*[5] conducted a systematic review and meta-analysis of 53 studies (n=2,663,638) that reported adherence to statins. The authors concluded that the odds of statin nonadherence in non-white patients was 53% more likely (OR 1.53, 95% CI 1.25-1.87) compared to white patients. The reported outcomes were consistent among studies that adjusted for socioeconomic status, and health insurance coverage.

Mochari-Greenberger *et al*[23] reported that black and hispanic patients with coronary artery disease who were prescribed statins had a 23% greater odds (OR 1.23; 95% CI 1.06-1.43) of rehospitlization or death within one year of initial hospitalization compared to white and Asian patients. Blacks and hispanics were less likely to have health insurance (22% with no insurance) compared to whites and Asians (7% with no insurance). The authors concluded that ethnic disparities in outcomes may be partially attributed to disparities in statin adherence.

Mulder *et al*[24] and The SEARCH Collaborative Group[25] have reported that genetic predispositions are associated with patient tolerability for statin therapy. The findings from these studies suggest that disparity in statin adherence between ethnicities and immigrants is plausible.

Canadian residency time: "The healthy immigrant effect"

The literature suggests that foreign-born individuals who take up residency in a host country have superior health profiles compared to individuals born in the host country.[8] This 'healthy immigrant effect' is attributed to positive selection pressure from national immigration policies and socioeconomic forces.[26] The superior health profiles have been assessed in individuals who have <10 years of residency in the host country. The healthy immigrant effect is an inadequate descriptor of the health profiles of individuals with >10 years of residency in the host country.[20,27,28]

Overtime, the favourable health profile of individuals with <10 years of residency declines and converges towards the health profile of individuals with >10 years of residency.[9,29-33] Increased acculturation exposure with the host country and the tendency for immigrants to experience a reduction in social status, among other stressors, are attributable factors to the reduction in overall health.[30,34] Acculturation can be understood as the process whereby new residents adapt to the sociocultural norms and institutions of the new country of residence.

Cohort studies have demonstrated that with increased residency time within the receiving country, the average health of immigrant communities can deteriorate to be worse than that of the receiving society. Known as the overshoot effect, this reduction in immigrant health has been demonstrated in diabetes and cardiovascular studies of foreign-born immigrants.[29,30,35,36] Whether an overshoot effect will be observed among individuals with <10 years of

Canadian residency who receive reminder interventions to improve persistence and adherence to cardiac secondary prevention therapies is of interest to the proposed investigation.

Secondary Prevention Therapy and Risk Reduction: Statins

There is a considerable evidence in the literature for the efficacy of statins and cardiac rehabilitation for secondary prevention. Adherence to guideline-recommended secondary statin therapy has been demonstrated to reduce the risk of symptomatic cardiovascular disease (HR 0.71; 95% CI 0.62-0.82) and mortality (HR 0.78, 95% CI 0.69-0.87).[37] Optimal medication adherence is required for patients to benefit completely from statin therapy.

Spertus *et al* (n=1,521)) reported hazard ratios statin discontinuation at 1-month from a prospective, multisite cohort study. Statin discontinuation at 1-month resulted in lower 12-month survival compared to patients who continued statins at 12-months (HR 2.86; 95% CI 1.47-5.55).[38]

Three landmark statin randomized control trials have provided evidence that optimal statin adherence can reduce the risk of mortality and morbidity at 5 years by 20-30%.[17-19]

Secondary Prevention Therapy and Risk Reduction: Cardiac Rehabilitation

Cardiac rehabilitation is indicated for patients who have experienced a previous acute coronary event or coronary revascularisation.[39] Cardiac rehabilitation is a programmatic intervention where participants receive lifestyle and behavioural counselling to reduce the risk of all-cause mortality (OR 0.80; 95% CI 0.68-0.93), cardiac mortality (OR 0.74; 95% CI 0.61-0.96), and nonfatal myocardial infarction (OR 0.79; 95% CI 0.59-1.09).[40] However, low initiation and attendance to cardiac rehabilitation are barriers to patients achieving the full benefits of therapy. Participation in cardiac rehabilitation ranges from 9% to 50%.[41-43]

Secondary Prevention Therapy and Patient Adherence

Although, guideline-recommended cardiovascular therapies have demonstrated a high effectiveness in the management of cardiovascular disease, patient nonadherence reduces limits the full-benefits of therapy in a real-world application.[44] The World Health Organization defines adherence as "the extent to which a person's behaviour – taking medications, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".[45] Understanding patient non-adherence is critical to improving health system effectiveness. The benefits achieved in randomized controlled trials for secondary cardiovascular prevention may be unrealized in clinical practice.

Patients with poor adherence are unable to fully benefit from the gains of therapy. 15-61% of patients are non-adherent to preventative cardiovascular

therapies.[45] Several studies have demonstrated that adherence outcomes are modified by the number of concurrent prescription medications, duration of residency, ethnicity, sex, socioeconomic status, diabetes, and level of acculturation.[29-31,35,45-47]

Possible factors for low adherence to statins and completion of cardiac rehabilitation include accessibility, psychosocial, and socioeconomic factors. A systematic review of cardiac rehabilitation studies found that ethnicity was rarely reported by authors.[48] When women were compared to men, women were less likely to withdraw from cardiac rehabilitation (35% to 29%, $p<0.001$) but more likely to be nonadherent to statins (OR 1.07; 95% 1.04-1.11). When patients with a history of diabetes were compared to those without, diabetic patients were less likely to be non-adherent to statins (OR 0.92; 95% CI 0.88-0.95) and less likely to complete cardiac rehabilitation (OR 0.69; 95% CI 0.69-0.80).[22,49,50] There is a gap in our knowledge on cardiac rehabilitation completion and statin adherence rates among ethnic minorities in a Canadian context.

Reminder interventions are hypothesized to improve adherence to guideline-recommended secondary preventative therapies by enhancing patient social support networks, improving patient knowledge of CVD risk factors, and mediating persistence in care.[34,36] A systematic review suggests there is weak evidence that structured telephone calls and motivational letters improve patient uptake to cardiac rehabilitation.[51] Several studies suggest that interventions

which overcome barriers to accessing health care services and improving knowledge of cardiovascular risk factors would be beneficial.[48] These interventions are hypothesized to be most effective at reducing nonadherence in immigrants < 75 years old or immigrants with Canadian residence of < 10 years. Similar effects in age and acculturation time have been demonstrated in CVD studies involving foreign-born immigrants.[31]

Rationale

In summary, despite evidence for the use of statins and cardiac rehab post AMI, there are significant concerns regarding patient adherence to these therapies. This non-adherence is also relevant in immigrants. A gap in our knowledge exists in respect to adherence to secondary prevention therapies post-AMI among immigrants residing in Canada. Furthermore, there exists a substantial body of evidence that suggests that there is a positive correlation between duration of national residency and improved health outcomes. We hypothesize that this effect may be associated with improved medication adherence and attendance to cardiac rehabilitation among individuals with < 10 years national residency. A similar effect has been demonstrated in the in high-income countries.[20,28,31] The mechanism for this effect may be attributed to self-selection of healthier people with higher levels of education, who are motivated to immigrate.[31,32]

Research questions

1. Is immigration to Canada associated with medication adherence to statins and completion of cardiac rehabilitation at one-year post-AMI?
2. Is ethnicity associated with statin adherence or completion of cardiac rehabilitation at one-year post-AMI?
3. Is the duration of Canadian residency associated with statin adherence or completion of cardiac rehabilitation at one-year post-AMI?
4. Does immigration status modify the effects of the ISLAND educational reminder interventions (i. standard care, ii. educational reminders via post, iii. educational reminders via post plus interactive voice response educational reminders)?

Thesis objectives

The main objective of this thesis is to investigate whether immigration status is associated with adherence to secondary therapy post-AMI. Knowledge gained from ths study may help to inform future translational research in secondary prevention.

CHAPTER 2: THE ISLAND AMI RANDOMIZED CONTROL TRIAL

Summary of the ISLAND AMI RCT

This chapter describes the study design, methods, and participants of the ISLAND AMI randomized control trial. A description of limitations of the methods and methodology of the ISLAND AMI study will follow.

Objective

The ISLAND clinical trial is an investigation of health system interventions to improve adherence to guideline-recommended secondary preventative cardiac therapies (statins, beta-blockers, ACE-inhibitors & ARBs, blood thinners) and completion of cardiac rehabilitation programs among patients post-MI.

Methods: Study design, allocation, and enrollment

The ISLAND study is a registered, multi-centre, pragmatic, randomized controlled clinical trial.[52] Allocation sequence generation was conducted by a statistician at the Population Health Research Institute in Hamilton, ON independent of the study. Allocation randomization used a permuted block design with block sizes varying at random. Investigators, study centres, and study staff were blinded. Participants unblinded due to the nature of the interventions. However, the investigators designed the interventions such that participants would believe the interventions were standard care in order to reduce potential bias from the Hawthorne Effect.

Eligible patients were identified through a secondary assessment of the CorHealth Registry (CHR) database. The CHR maintains a registry of all patients who have received coronary angiography in Ontario. This database has been used to evaluate and plan for health inequities among high-risk patients.[39]

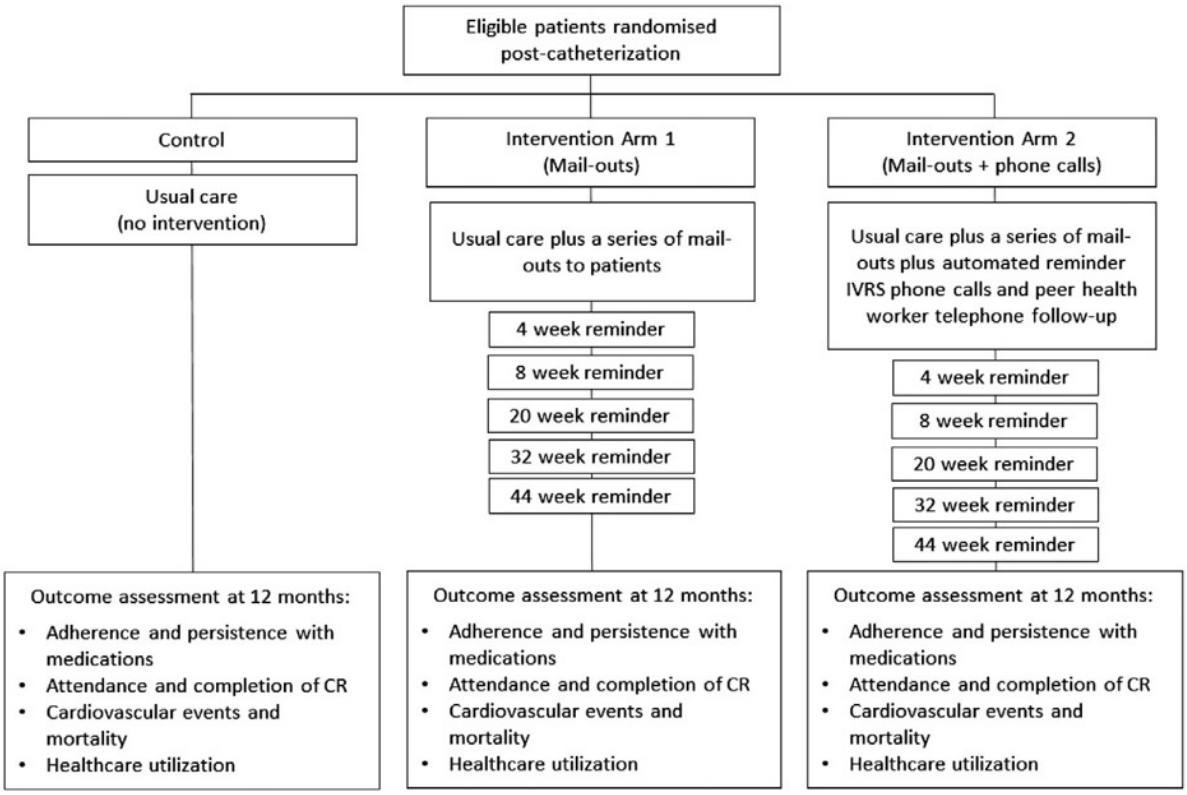
Furthermore, the ISLAND investigators conducted a single-centre pilot study of the ISLAND trial using the CHR database to identify eligible patients.[53]

Allocation concealment was limited to investigators, statisticians, and some study staff. Staff responsible for delivering the interventions will require access to participants' allocation. Staff who have been unblinded were not involved in outcome adjudication. The ISLAND study did not permit unblinding.

Methods: interventions and participants

Participants were allocated in a 1:1:1 ratio to one of three intervention groups: (i) a control group which will received usual care with no intervention, (ii) a group that receives educational reminders via postal delivery, (iii) a group that receives usual care plus educational reminders via postal delivery, and (iii) a group that receives usual care and educational reminders via postal delivery plus the support of a trained health worker via telephone for patients identified to be at risk of non-adherence by automated reminder interactive voice response phone calls **(Figure 1)**.[53]

Figure 1 - *ISLAND trial design diagram*[53]



The ISLAND study's recruitment goal was 2,742 participants with 914 participants in each study arm. The sample size was determined based on a minimum power of 80% for detecting a minimally important difference in either adherence to guideline-recommended medication classes at 12-months or completion of cardiac rehabilitation. Power calculations maintained a used the step-down Šidák procedure to maintain an alpha level of 5% after accounting for multiple testing of two co-primary outcomes and a three-arm trial design.[53] Participants were excluded if they required translation services to receive communication in English. A table of the ISLAND inclusion and exclusion criteria is included **(Table 1)**.

Table 1 - ISLAND study eligibility criteria

Inclusion Criteria	Exclusion Criteria
• ≤ 18 years of age with current Ontario health card number • Recieved a coronary angiography after an AMI (ST-elevation or non–ST-elevation), • Evidence of coronary artery disease (50% blockage of left main and/or 70% blockage of ≥1 major coronary artery [vessels ≥2 mm]) as assessed by a coronary angiography post-AMI • **Discharged alive after coronary angiography**	• Categorized as Kilip class IV as determined by the diagnosis of cardiogenic shock at the time of post-MI coronary angiography • Translation services are required to receive information in English, as captured in the CHR referral form • CHR data is incomplete

Limitations of the ISLAND AMI RCT

Limitations in the study methods and methodology should be mentioned. First, generalization of the results may be limited due to the presence of language bias. Eligibility was restricted to English speakers. The language bias may result in an effect size overestimation in favour of adherence and underrepresentation of recent immigrants. However, Canada's immigration point system favours immigrants proficient in either English or French.[54] We expect the effect of language bias to be minimal: the 2016 census data report that 86% of Ontario residents can conduct a conversation in English.[55]

Second, patient self-reported outcomes may lead to imprecision in outcome measurements. Patient self-reports may be at a high risk of bias from social desirability, inaccuracies in memory recall, or a misunderstanding of the response question. The effect of patient response bias is likely to overestimate outcomes.[56] However, the primary measure of adherence, an adapted version of

the Brief Medication Questionnaire, was found to have 80%-90% and 90% sensitivity for assessing major dosage errors and minor dosage errors, respectively. The Brief Medication Questionnaire was verified in a population prescribed the angiotensin-converting enzyme inhibitors, enalapril and captopril.[57]

Chapter summary

This chapter provides detailed background of the methods and methodology used in the ISLAND clinical trial. The ISLAND study design establishes the framework of strengths and limitations for subsequent retrospective analysis conducted with the ISLAND cohort. In comprehending the study design, we can design a retrospective study with due consideration to the restrictions and advantages inherent to the dataset.

The next chapter introduces readers to the study design methods and methodology of the proposed investigation.

CHAPTER 3: RETROSPECTIVE COHORT ANALYSIS METHODS AND METHODOLOGY

Review of retrospective cohort study methodology

Introduction:

A cohort study is a specific study design where a sample population is followed through time to assess associations between exposure variables and measured outcomes. Cohort studies typically enroll participants by their presence or absence of baseline exposure variables.[58] The enrollment methodology permits between-group comparisons of outcomes by exposure status. An advantage of cohort studies is that their temporal framework permits assessment of relative risk and incidence. Cohort studies are differentiated by whether participants are followed prospectively or retrospectively in time.[58]

A retrospective cohort study enrolls a sample population where the outcome of interest was assessed retroactively. Comparatively, a prospective cohort study follows a sample population forwards in time to assess the response outcome. Both retrospective and prospective cohorts are popular methodologies in secondary prevention research.

Retrospective cohort studies often use less time and financial resources to conduct compared to prospective cohort studies. However, the prospective study design can better control for known mediators and moderators through their ability to control measurement of the response outcome.

A major disadvantage of the retrospective cohort methodology is the lack of control researchers have over measurement. The accuracy of the available data and the validity of the measurement methods can restrict introduce considerable bias to a retrospective outcome assessment.[58] However, the retrospective design offers a significant cost and time advantage due to the availability of data, compared to prospective assessments.

Analysis implications

Multiple logistic regression will be used for the statistical analysis. This method is widely used in the literature to assess associations when multiple predictors are defined *a priori*. Unlike linear regression, logistic regression produces a binary response variable. Multiple logistic regression permits the analysis of associations between multiple predictor variables with a single outcome. Odds ratios can be deduced from the antilog of logistic model coefficients, where each odds ratio represents the independent association of the coefficient to the outcome while holding all other variables constant. The null hypothesis of logistic regression is defined as each covariate having an odds ratio equal to 1.00. [59] In retrospective analysis, multiple regression is permissive of adjusting for continuous, ordinal, and dichotomous outcomes simultaneously. Furthermore, post-hoc estimation techniques can be used to control for multiple testing associated with having co-primary outcomes and multiple primary research questions.

Multiple logistic regression is not without limitations. First, the odds that are reported in a logistic analysis are not readily interpretable. Odds ratios are ratios between probabilities rather than probabilities in themselves. The result is that odds tend to approximate risk as risk decreases with odds closely matching risk when risk is ≤10%.[60] Second, regression assumes that the relationship between predictor variables and the outcome is identical in the direction and magnitude throughout all values of the predictor. However, this assumption may not be true for all predictors. For example, the association between a predictor and an outcome may change in direction or magnitude depending on the level of the predictor variable.[61]

Study methods for the ISLAND substudy

Methods: Studies characteristics and Population

The subject database for the ISLAND randomized control trial[53] was collected and maintained by the Population Health Research Institute and will be used to assess the research questions.

Participants with an Ontario Health Insurance Plan number and who completed a 12-month outcome assessment as a part of the ISLAND randomized control trial protocol were included in the analysis. Participants who failed to provide a response to question 7 of the ISLAND RCT's 12-month outcome assessment, "Were you born a Canadian citizen?" were excluded due to an inability to determine their immigration status.

Exposure considerations

Assessment of the *a priori* exposure of interest, ethnicity, was determined to be unsuitable for analysis. There was a significant disparity between the counts of individuals who self-identified as white compared to all other ethnic categories. 9 out of 14 ethnic categories had counts of ≤ 5 when grouped by immigration status (**Table 3.1**). As an alternative, the *ad hoc* binary exposure outcome of ethnic was determined for analysis. Ethnicity was determined to be a dichotomous proxy variable where non-European ethnicities were pooled into a *visual minority* category and all European ethnicities were pooled into a *White* category.

The second *a priori* exposure of interest, duration of Canadian residency was defined as the length of time spent living in Canada. Canadian residency time was calculated for foreign-born individuals by subtracting the outcome assessment completion year from the self-reported year of immigration into Canada[i]

Chiu et al[31] used duration of residency as an exposure. Similarly, multiple publications [62] dichotomized immigrant residency time as recent immigrants (<10 years of residency) and long-term residents (≥10 years of residency).[9,29-32]

[i] **Appendix 3.1** Statistical code for the calculation of Canadian residency duration using Stata version 13.1

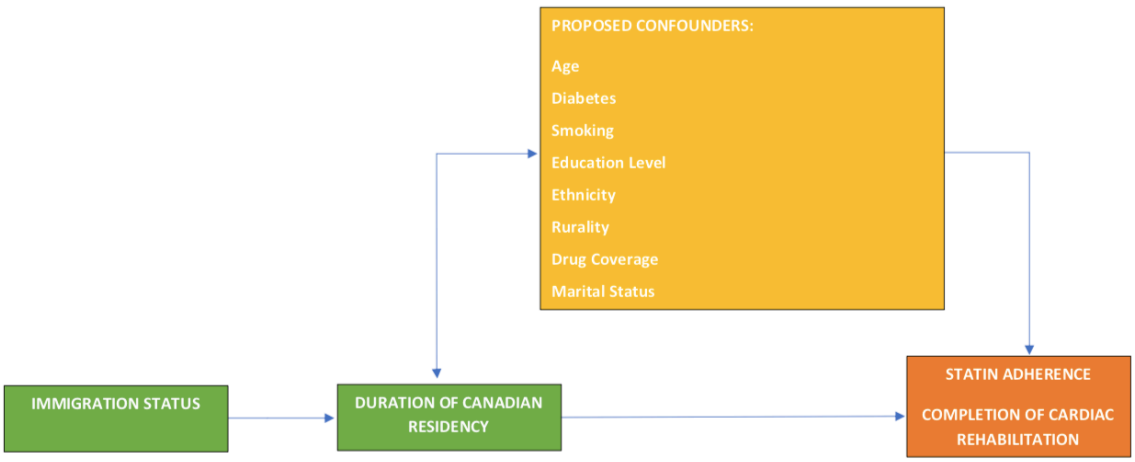


Figure 2 - Simplified Theoretical framework for ISLAND subgroup analysis
Yellow: proposed potential confounders, Green: exposures, Orange: outcomes

A theoretical framework was developed for all explanatory variables (**Figure 2**). Explanatory variables are exposures identified by a literature review to be proposed confounders of statin adherence outcomes. The theoretical framework conceptualizes the direction of effects associated with explanatory variables. Reported below for each explanatory variable are the following: (i) the hypothesized exposure effect size on our proposed retrospective analysis on statin adherence, (ii) the estimated exposure effect magnitude found in our literature review, and (iii) a summary of outcome data collection methods used in the ISLAND study. A review of the data collection methods and estimated effect size for each explanatory variable was conducted and is reported below.

- ***Immigration status:*** We expect that recent immigrants (<10 years of Canadian residency exposure) will display greater statin adherence

compared separately to immigrants who have lived in Canada for ≥10 and Canadian-born participants.[9,29,31] An estimated exposure effect was not identified in our literature review. We expect that the difference in treatment effect is attributable to differences in acculturation exposure, that is exposure to factors which align individuals with societal practices and cultural norms. Non-recent immigrants would have greater acculturation exposure compared to recent immigrants.[30,31,63] Differences in acculturation exposure, are correlated with inequities in access to care and comparatively lower socioeconomic status among foreign-born individuals.[64] Immigration status and length of Canadian residency was assessed at 12-months in the ISLAND RCT.

- ***Ethnicity:*** **Ethnicity data was captured via** patient self-reported response to question 8 of the ISLAND 12-month outcome assessment: "People living in Canada come from many different cultural and racial backgrounds. How would you define your ethnicity?". Patient self-reported responses will be collected across 12 ethnic identifiers defined in the ISLAND protocol.[53] We expect the magnitude and direction of exposure effects to approximate the following outcomes observed in the literature:
    - Aboriginal: No population-appropriate effect data of reasonable quality was found in the literature.
    - Korean: Persistence rates of 86.03% at 12-months among patients prescribed statins indicated for acute coronary syndrome.[65] Based

on the available evidence, we were unable to hypothesize an exposure effect direction.

- Japanese: The odds of statin adherence at 12-months from an index AMI were 15% higher (OR 1.15; 95% CI 0.95-.40) in Asian men and 5% lower (OR 0.95; 95% CI 0.80-1.13) in Asian women compared to whites after adjustment for length of hospitalization, morbidity, AMI risk, sociodemographic factors.[66] Based on the available evidence, we hypothesize the exposure effect to favour statin adherence in the Japanese compared to white participants.
- West Asian: No population-appropriate effect data of reasonable quality was found in the literature.
- Arab: No population-appropriate effect data of reasonable quality was found in the literature.
- Southeast Asian: The odds of statin adherence at 12-months from the first statin prescription fill indicated for AMI was 17% lower (OR 0.83; 95% CI 0.52-1.35) compared to non-Asian patients after adjusting for sociodemographic exposures, hospital re-admissions, and morbidity. [67] Based on the available evidence, we hypothesize that there will be no exposure effect when comparing Southeast Asians to white participants.
- Latin American: Lauffenburger *et al.* reported odds ratios for statin adherence comparing hispanic men (OR 0.77; 95% CI 0.66-0.89)

and women (OR 0.71; 95% CI 0.61-0.83) to white men in a retrospective cohort study of Medicare service claims in the United States at 12 months after AMI discharge.[66] Based on the available evidence, we predict hypothesize that there will be an exposure effect when comparing Latin American to white participants.

- Filipino: The odds of statin adherence at 12-months from an index AMI were 15% higher (OR 1.15; 95% CI 0.95-.40) in Asian men and 5% lower (OR 0.95; 95% CI 0.80-1.13) in Asian women compared to whites after adjustment for length of hospitalization, morbidity, AMI risk, sociodemographic factors.[67] Based on the available evidence, we hypothesize that there will be no exposure effect when comparing the Filipino to white participants.
- Black: Odds ratios were reported for statin adherence in black men (OR 0.73; 95% CI 0.67-0.79) and women (OR 0.72; 95% CI 0.65-0.81) compared to white men 12-months after AMI discharge.[66] Based on the available evidence, we hypothesize there will be an exposure effect when comparing black to white participants.
- South Asian: The odds of statin adherence at 12-months from the first statin prescription fill indicated for AMI was 26% greater (OR 1.26; 95% CI 0.88-1.79) compared to non-Asian patients after ajustin for sociodemographic exposures, hospital re-admissions, and morbidity.[67] Based on the available evidence, we hypothesize

that no exposure effect will be found when comparing South Asian to white participants.

- Chinese: The odds of statin adherence at 12-months from the first statin prescription fill indicated for AMI was 17% lower (OR 0.83; 95% CI 0.52-1.35) compared to non-Asian patients after adjusting for sociodemographic exposures, hospital re-admissions, and morbidity. [67] Based on the available evidence, we hypothesize that there will be no exposure effect when comparing the Chinese to white participants.
- White: Odds ratio for statin adherence among white women (OR 1.05; 95% CI 1.01-1.09) compared to white men were reported at 12-months from AMI discharge in an American setting.[66]

- ***Age:*** Collected at baseline through the CHR. We expect to observe a diminishing treatment effect with increasing age.[68,69] A dichotomous age variable of participants <65 and ≥65 years will be assessed. The threshold of 65 years was selected to agree with the age where most patients become eligible for prescription drug coverage through the Ontario Drug Benefit program.
- **Duration of Canadian Residency:** Collected through patient self-report and expressed as the number of years of residence in Canada since immigration. The literature demonstrates that the number of years lived in the host country is a surrogate measure for acculturation exposure[27,28,31].

Acculturation is the process where immigrants integrate to adopt the sociocultural norms and behaviours of the local population. The variable will be expressed as categorical data. Participants' data will be grouped into the following categories: <10 year residency, >10 year residency. We expect that adherence to secondary therapies will decrease as the proportion of time lived in Canada increases.

- **Diabetes:** Diabetic participants were determined reference to CorHealth registry information by the ISLAND RCT.[53] Diabetes may modify behaviours associated with drug adherence. A systematic review and meta-analysis of adherence to secondary cardiovascular therapies reported an odds ratio of 0.92 (95% CI 0.88-0.95) for statin non-adherence comparing patients with a history of diabetes to patients without a history of diabetes.[22] Based on the literature, we expect patient with a history of diabetes to experience a moderate exposure effect when compared to patients without a history of diabetes.
- **Smoking Status:** Smoking status will be self-reported. Smoking may modify drug adherence. We expect that participants who do not smoke to experience a moderately larger treatment effect. Patients who smoke may hold attitudes or beliefs that limit patient intentions to carry out planned behaviour, such as adhere to treatment recommendations.[70] A systematic review on smoking status and cardiac rehabilitation participation

concluded that smoking was a strong predictor for participant dropout and nonattendance.[71]

- **Average Income by Postal Code:** Participants will be categorized into income quintiles based on the average household income of the postal code associated with the participant's home address. Income quintiles will be determined by linking home addresses to the most recent Canadian census data on average household income. The postal code conversion file (PCCF) will be used to link census data to postal codes. We hypothesize that the odds of cardiac rehabilitation attendance among patients who reside in postal codes in the lower two quintiles of average household income (OR 1.58, 1.39-1.71) will be less than participants who reside in postal codes in the upper three quintiles of average household income.[72,73] Participants with lower incomes are more likely to experience interruption in therapy due to medication cost and financial barriers.[66] In contrast, we expect to see a relatively larger treatment effect in patients due to the effects of education and actively linking patients to continued care.
- **Rurality:** Patient household postal codes will be used to asses urban versus rural home addresses. Rurality will be evaluated by Statistics Canada's Postal Code Conversion File (PCCF). The PCCF categorizes urban and rural regions based the population size of the municipality and whether the municipality is a population centre.[74] Accessibility of care is

plays a key role in adherence to therapy. Cardiac rehabilitation programs and primary care tend to be clustered around urban centres. Patients living in population centres have an accessibility advantage over patients who live in rural areas.[16] We expect that patients who reside in rural areas will experience a reduced attendance to cardiac rehabilitation and medication adherence compared to patients who reside in population centres.

- **Education Level:** Education level is captured by patient self-report. Patients with low levels of educational attainment will experience a relatively larger treatment effect compared to individuals with who completed a post-secondary program. Lower education levels have a negative effect on adherence to secondary cardiovascular therapies.[72,75]
- **Drug Coverage:** Patient access to drug insurance coverage will be assessed in patients <65 years. Patients will self-report their method of payment for prescription medications (ex. out of pocket expense), and whether they have forgone prescription medication in the past year due to financial costs. We expect that patients aged <65 years who pay a lower proportion of their prescription costs out of pocket will experience moderately higher medication adherence. A systematic review of predictors for statin adherence found evidence of a robust dose-response in the cost of medication and rate of adherence.[22]
- **Marital Status:** Assessed by patient self-report. We expect that patients who are either married or in a common-law relationship will have improved

medication adherence compared to single patients. Atzema *et al* reported that marriage was associated with a 54% decrease in the odds (OR 0.46, 95% CI 0.30-0.71) of delay in seeking care for Myocardial infarction compared to unmarried patients.[76] We surmise that the social support from a patient's social network may reinforce behaviours that favour adherence to secondary therapies.

- **Study Site:** Assessed by the location of cardiac rehab. Variance in outcomes may be related to site specific variances. We expect that there will be no significant differences in medication adherence and attendance to cardiac rehabilitation.

Outcomes

The outcomes were 30-day and 7-day adherence to statins and completion of cardiac rehabilitation. The outcomes were selected in order to assess whether the "healthy immigrant effect", detailed in Chapter 1, is observed in patient adherence to secondary preventative therapies. Statin adherence was defined by the ISLAND study protocol as a dichotomous outcome. 7-day statin adherence was determined to be no missed days of medication in the 7 days prior to the outcome assessment date. 30-day statin adherence was defined as <6 missed days in the 30 days prior to the outcome assessment date. Completion of cardiac rehabilitation was defined in the ISLAND protocol as at least the partial attendance of a cardiac rehabilitation with a formal reassessment at the program's end.[53]

The outcomes were collected by patient self-report 12-months post-myocardial infarction. Centralized outcome adjudication was conducted for all outcomes by an independent committee from the Population Health Research Institute.

Statistical analysis

This study has three co-primary outcomes: adherence to guideline-recommended statin therapy, assessed at 30 and 7 days prior to the ISLAND outcome assessment, and cardiac rehabilitation completion. Statin adherence was defined as no days of missed medication in the week prior to the assessment dates of 7-days and 30-days prior to outcome assessment. Patients who reported completing cardiac rehabilitation with 100% attendance were denoted as completing their rehabilitation. We analyzed all co-primary outcomes using multivariable logistic regression.

Main effect analysis of the first study question included immigration status as a covariate in regression models. Analysis of the second study question included duration of Canadian residency as the covariate, while the third study question included ethnicity. Co-primary outcomes were analyzed in separate models.

For the fourth study question, four regression models were generated. Two models included the interaction term between Canadian residency (<10 years vs. >10 years) and ISLAND RCT intervention in assessing co-primary

outcomes. The remaining models used the interaction term between immigration status and ISLAND RCT intervention as the covariate. We will report main effect models without the interaction term as well.

In total, we used eight different regression models, four per primary outcome. The four models per outcome differed with respect to the additional covariate adjusted for in each, i.e. immigration status or Canadian residency duration.

All models were adjusted for age, sex, diabetes, and smoking status due to their association with both outcomes in the literature.

A step-down approach will be used for model selection. The advantage of the step-down approach over forward-selection is that all *a priori* explanatory variables will be assessed.[77] Age, diabetes, and sex will be analyzed using fixed-effect models to improve statistical efficiency.[3]

The alpha level will be set at 0.05. Multiple testing and multiple primary objectives raise issues of multiplicity. The Sidak correction will be used to reduce alpha level inflation from multiple comparisons.[78] The Sidak correction is marginally more powerful compared to the Bonferonni correction.[79] The analysis will be conducted as per protocol.

Missing data biases outcomes and weakens inferences made from analyses. To mitigate bias from missing data, the ISLAND RCT implemented a series of robust measures to reduce the extent of missing data, including updating contact information and applying intention-to-treat methods.[53] Missing

value patterns were evaluated with missing data contingency tables. No data imputation methods were used to infer missing values.

Sensitivity analysis will be conducted for both the best-case and worst-case scenarios. Best-case scenario will assume that patients who have missing outcomes were adherent, while the worst-case scenario will assume those with missing outcomes were nonadherent. These assumptions will favour an assessment of no association in our sensitivity analysis with increasing missing outcomes.

Ethical considerations and conflict of interests

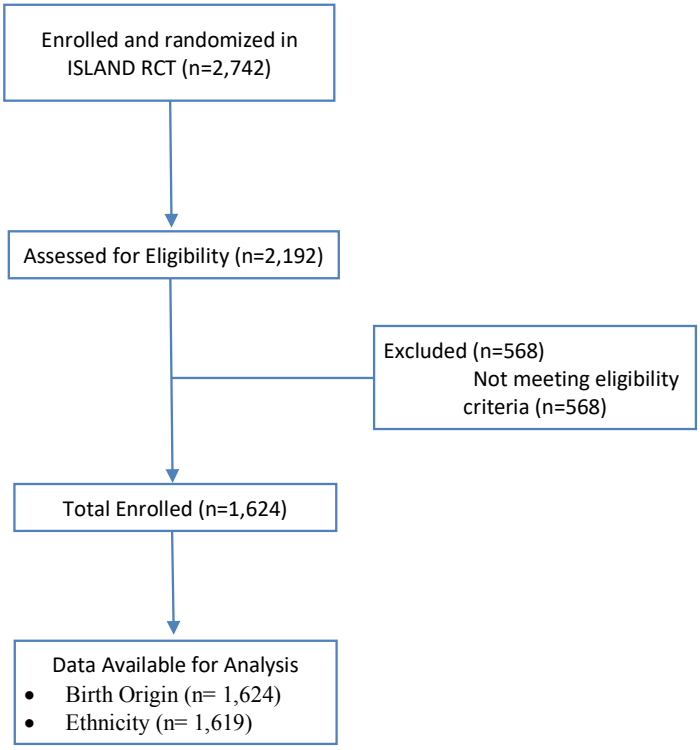
Permission for database access was granted by the principal investigators of ISLAND trial. As part of the ISLAND trial, each site participants signed consented to the sharing their data for the ISLAND study. A waiver of consent was obtained by the Research Ethics Board. The data set used for analysis was scrubbed of personal identifiers prior to analysis by a statistician with access to the secured ISLAND database. The author has no conflict of interests to report related to conduct of this study or the preparation of this thesis manuscript.

CHAPTER 4: RETROSPECTIVE COHORT ANALYSIS RESULTS

Study participants

A total of 2,192 ISLAND clinical trial participants completed the 12-month outcome assessment. Of the 2,192 eligible participants, 1,624 were enrolled in the study and included in the analysis (**Figure 3**). 568 participants who completed outcome assessments were excluded from the study for not reporting a dichotomous foreign-immigration status. Comparison of the effect of missing data was conducted and a table of frequencies was reported.[ii]

Figure 3 - *Participant Flow Diagram*



[ii] **Appendix 4.0** Baseline characteristics and outcomes of the actual and evaluable sample size

Baseline characteristics

Baseline Exposure by Immigration Status

A summary of all statistics reported in this section is included in **table 4.1a**. The average age was 65.4 years (95% CI, 64.9-65.9) across all enrolled participants. The mean age of immigrants was 64.9 (95% CI, 63.9-66.0) years and 65.3 (95% CI, 64.6-66.0) years for participants in born in Canada. The proportion of participants ≥65 years was 51.1% in Canadian-born and 52.3% in immigrants (p=0.640). A Pearson's chi-square test found a statistically significant difference (p=0.001) in the distribution of participant's sex when grouped by immigration status.

The frequency of participants living in urban and rural neighborhoods was statistically different across income quintiles for immigrants and Canadian-born participants (p<0.001). 89.5% of immigrants residing in urban-settings compared to 76.2% of Canadian-born participants.

There was a smaller proportion of post-secondary graduate among Canadian-born participants (32.3%) than immigrant participants (43.9%). A similar but reverse trend was found when comparing immigrants and Canadian-born individuals who did not graduate high school. 259 (25%) of Canadian-born participants did not complete high school compared to 105 (18.2%) of immigrant participants. A chi-square analysis of education exposure by immigration status reported a statistically significant difference (p<0.001).

Table 2a - Summary statistics by birth origin: means with 95% confidence intervals (95% CI) for continuous data; column percentages and frequencies for categorical data

VARIABLE	CANADIAN-BORN (N=1,041)	IMMIGRANT (N= 583)	TOTAL (N= 1,624)
AGE (Year)			
mean (95% CI)	65.29 (64.58, 66.00)	64.93 (63.91, 65.95)	65.38 (64.86, 65.89)
≥65, % (n)	51.10% (532)	52.32 % (305)	51.54 % (837)
		Pearson chi^2 = 0.22	Pr = 0.640
SEX			
Female, % (n)	30.16 % (314)	22.64 % (132)	27.46 % (446)
Male, % (n)	69.84 % (727)	77.36 % (451)	72.54 % (1,178)
		Pearson chi^2 = 10.61	Pr = 0.001
RURALITY			
Urban , % (n)	76.18 % (793)	89.54 % (522)	80.97 % (1,315)
Rural, % (n)	23.82 % (248)	10.46 % (61)	19.03 % (309)
		Pearson chi^2 = 43.30	Pr < 0.001
INCOME QUINTILE			
1-20%, % (n)	19.92 % (206)	18.04 % (105)	19.25 % (311)
21-40%, % (n)	20.79 % (215)	20.62 % (120)	20.73 % (335)
41-60%, % (n)	18.47 % (191)	20.62 % (120)	19.25 % (311)
61-80%, % (n)	20.70 % (214)	22.34 % (130)	21.29 % (21.29 344)
81-100%, % (n)	20.12 % (208)	18.38 % (107)	19.49 % (315)
		Pearson chi^2 = 2.63	Pr = 0.622
EDUCATION LEVEL			
Less than high school (less than high school graduation), % % (n)	24.95 % (259)	18.23 % (105)	22.55 % (364)
High school graduate (no Post-Secondary education), % (n)	24.57 % (255)	23.09 % (133)	24.04 % (388)
Some Post-Secondary (received some college or university education), n (%)	18.21 % (189)	14.76 % (85)	16.98 % (274)
Post-Secondary graduate (received degree/diploma), % (n)	32.27 % (335)	43.92 % (253)	36.43 % (588)
		Pearson chi^2 = 24.16	Pr < 0.001

MARITAL STATUS			
Married, % (n)	60.50% (628)	72.33% (413)	64.70% (1,041)
Living common-law, % (n)	6.55% (68)	2.45% (14)	5.10% (82)
Widowed, % (n)	11.56% (120)	9.46% (54)	10.81% (174)
Separated, % (n)	3.08% (32)	2.98% (17)	3.05% (49)
Divorced, % (n)	9.15% (95)	7.88% (45)	8.70% (140)
Single, never married, % (n)	9.15% (95)	4.90% (28)	7.64% (123)
		chi^2 = 31.01	Pr < 0.001
PRESCRIPTION PAYMENT			
Yes, majority or all of costs, % (n)	9.57% (99)	16.17% (93)	11.93% (192)
Yes, but only co-pay, % (n)	32.59% (337)	32.17% (185)	32.44% (524)
Yes, for some meds but not for other meds, % (n)	7.74% (80)	6.96% (40)	7.46 %(120)
No, none, % (n)	50.10% (518)	44.70% (257)	48.17% (775)
		chi^2 = 16.05	Pr = 0.001
HISTORY OF DIABETES			
Yes, % (n)	27.15% (278)	30.92% (179)	28.51% (457)
No, % (n)	72.85% (746)	69.08% (400)	71.49% (1,146)
		chi2 = 2.58	Pr = 0.109
HISTORY OF SMOKING			
Never, % (n)	30.63% (313)	47.75% (276)	36.81% (589)
Current, % (n)	26.52% (271)	16.78% (97)	23.00% (368)
Former, % (n)	32.58% (333)	24.05% (139)	29.50% (472)
Unknown, % (n)	10.27% (105)	11.42% (66)	10.69% (171)
		chi^2= 54.19	Pr < 0.001
Group Allocation			
Arm 1 - Usual Care	36.31% (378)	35.33% (206)	35.96% (584)
Arm 2 - Postal reminders	33.53% (349)	36.19% (211)	34.48% (560)
Arm 3 - Postal reminders + interactive voice response phone calls	30.16% (314)	28.47% (166)	29.56% (480)
		chi^2 = 1.23	Pr = 0.540

A statistically significant difference was reported between marriage status exposure when grouped by immigration status ($p<0.001$). There was a greater proportion of Canadian-born participants who reported living common law (6.6%), and single but never married (9.2%). The proportion of immigrants who were married was larger (72.3%) than that of Canadian-born participants (60.5%).

The majority of immigrant (n=257, 44.7%) and Canadian-born (n=518, 50.1%) participants reported that they did not pay for prescription medication. Across all participants, the majority of patients who paid for their prescriptions reported that they only pay for the co-pay amount (32.4%, n=524). There was a statistical difference ($p=0.001$) in the proportion of participants who reported medication payment exposure by immigrant status.

28.5% of all evaluable participants reported that they had been diagnosed with diabetes mellitus. The proportion of participants with a previous diabetes diagnosis was 30.9% and 27.2% among immigrants and Canadian-born cases, respectively.

Proportions for reported smoking status were 30.6% (never smoked), 26.5% (currently smoke), and 32.6% (former smokers) for Canadian-born cases. Immigrants reported proportions of 47.8% (never smoked), 16.8% (currently smoke), and 24.1% (former smoker) per smoking status category. A chi-square tests for homogeneous proportions reported a statistically significant difference ($p<0.001$) in the distribution of smoking exposure when grouped by immigration status.

Baseline Exposure by Ethnicity

Small sample sizes among the planned *a priori* ethnic categories made analysis by the planned ethnic categories infeasible. A table of the distribution of immigration status by planned ethnic category is reported.[iii] An analysis of ethnicity was conducted by pooling all non-white ethnic categories to form a *visual minority* ethnic category.

A summary of the following statistics reported in this section is included in **table 2b**. A chi-square test reported a statistical difference in the distribution of participants aged ≥ 65 when grouped by dichotomous ethnicity ($p<0.001$). Participants aged ≥ 65 represented 43.8% of all white participants and 7.72% of visual minorities. On average, white participants were older (mean age 66.5, 95% CI 65.8-67.1) compared to visual minorities (mean age 60.3, 95% CI 59.0-61.6).

There was a statistically significant difference in the distribution of sex when grouped by dichotomous ethnicity ($p=0.003$). A greater proportion of white, female participants (23.0%) was reported compared to visual minority female participants (4.5%).

The distribution of participants by rurality was statistically significant ($p<0.001$). The proportion of whites (77.7%, n=991) and visual minorities (93.0%, n=319) living in an urban setting was greater compared to rural settings.

[iii] **Appendix 4.1** Frequencies and column proportions of included subjects categorized by *a priori* ethnic categories

Table 2b - Summary statistics by ethnicity (white vs. visual minorities): means with 95% confidence intervals (95% CI) for continuous data; cell proportions and frequencies for categorical data

VARIABLE	White (n=1,276)	Visual Minority (n=343)	Total (n= 1,619)
AGE (Year)			
Mean [95% CI]	66.46 [65.83-67.09]	60.28 [58.95-61.58]	65.14 [64.56-65.73]
≥65 years , % (n)	43.79 (709)	7.72 (125)	51.51 (834)
		chi2 = 39.57	Pr <0.001
SEX			
Female, % (n)	23.04 (373)	4.51 (73)	27.55 (446)
Male, % (n)	70.77 (903)	78.72 (270)	72.45 (1,173)
		chi2 = 8.56	Pr = 0.003
RURALITY			
Urban, % (n)	77.66 (991)	93.00 (319)	80.91 (1,310)
Rural, % (n)	22.34 (285)	7.00 (24)	19.09 (309)
		chi2 = 41.18	Pr < 0.001
INCOME QUINTILE			
1-20%, % (n)	18.93 (241)	21.01 (71)	19.37 (312)
21-40%, % (n)	20.19 (257)	22.49 (76)	20.67 (333)
41-60%, % (n)	18.62 (237)	21.60 (73)	19.24 (310)
61-80%, % (n)	21.45 (273)	20.41 (69)	21.23 (342)
81-100%, % (n)	20.82 (265)	14.50 (49)	19.49 (314)
		chi2 = 8.11	Pr = 0.087
EDUCATION LEVEL			
Less than high school (less than high school graduation), % (n)	24.09 (306)	17.11 (58)	22.62 (364)
High school graduate (no Post-Secondary education), % (n)	24.72 (314)	20.94 (71)	23.93 (385)
Some Post-Secondary (received some college or university education), n (%)	18.03 (229)	13.27 (45)	17.03 (274)
Post-Secondary graduate (received degree/diploma), % (n)	33.15 (421)	48.67 (165)	36.42 (586)
		chi2 = 28.63	Pr < 0.001

MARITAL STATUS			
Married, % (n)	62.40 (795)	73.35 (245)	64.68 (1,040)
Living common-law, % (n)	5.65 (72)	2.99 (10)	5.10 (82)
Widowed, % (n)	12.09 (154)	5.99 (20)	10.82 (174)
Separated, % (n)	2.75 (35)	4.19 (14)	3.05 (49)
Divorced, % (n)	9.18 (117)	6.89 (23)	8.71 (140)
Single, never married, % (n)	7.93 (101)	6.59 (22)	7.65 (123)
		chi2 = 21.71	Pr = 0.001
PRESCRIPTION PAYMENT			
Yes, majority or all of costs, % (n)	9.96 (126)	18.88 (64)	11.85 (190)
Yes, but only co-pay, % (n)	31.86 (403)	34.51 (117)	32.42 (520)
Yes, for some meds but not for other meds, % (n)	7.75 (98)	6.78 (23)	7.54 (121)
No, none, % (n)	50.43 (638)	39.82 (135)	48.19 (773)
		chi2 = 25.11	Pr < 0.001
HISTORY OF DIABETES			
Yes, % (n)	26.63 (335)	36.18 (123)	28.66 (458)
No, % (n)	73.37 (923)	63.82 (217)	71.34 (1,140)
		chi2 = 11.93	Pr = 0.001
HISTORY OF SMOKING			
Never, % (n)	32.91 (413)	51.76 (176)	36.93 (589)
Current, % (n)	24.62 (309)	17.35 (59)	23.07 (368)
Former, % (n)	32.19 (404)	19.41 (66)	29.47 (470)
Unknown, % (n)	10.28 (129)	11.47 (39)	10.53 (168)
		chi2 = 47.07	Pr < 0.001
Group Allocation			
Arm 1 - Usual Care	29.15% (472)	6.73% (109)	35.89% (581)
Arm 2 - Postal reminders	26.68% (432)	7.91% (128)	34.59% (560)
Arm 3 - Postal reminders + interactive voice response phone calls	22.98% (372)	6.55% (106)	29.52% (478)
		chi^2 = 3.26	Pr = 0.196

There was no reported statistically significant difference (p=0.087) in the distribution of income quintile responses by dichotomous ethnicity. There was no observable trend in the distribution of income quintile responses.

Most white (n=421) and visual minority (n=165) participants had completed a post-secondary graduate program. The distribution of ethnicity by education levels (p<0.001), prescription payment (p<0.001), and marital status (p=0.001), separate chi-square tests reported significant outcomes.

7.7% (n=123) of all participants with a recorded ethnicity response were reported as visual minorities with diabetes and 21% (n=335) were reported as whites with diabetes. >50% of all participants reported they were 'white and never smoked' (25.9%) and 'white and a former smoker' (25.3%). A chi-square test reported statistically significant differences in the distribution of ethnicity by diabetes (p=0.001) and smoking status (p<0.001).

Duration of Residency and Immigration Status

The mean time spent living in Canada since immigration was 40.9 years, (95% CI 39.4 - 42.3) (**Table 3**). The frequency of immigrants with <10 years of Canadian residency exposure (n=29) was too low to produce a summary table significantly different from Table 2a.

Table 3 - Frequency of duration of Canadian residency among immigrants

Years of Canadian Residency	Immigrant (n=570)
Mean, (95% CI)	40.86 (39.39-42.34)
≤ 10 years, % (n)	5.09 (29)
11-20 years, % (n)	94.91 (541)

Study Outcomes

The Association of Immigration Exposure to Statin Adherence & Cardiac Rehabilitation Completion

Table 4a - *Frequency, row proportion, and chi-square test values for participants adherent to statins at seven (7) days stratified by immigration status*

Immigration Status	Not Adherent	Adherent	Total
Canadian-born, % (n)	22.38 (190)	77.62 (659)	100 (849)
Immigrant, % (n)	16.73 (73)	83.63 (373)	100 (446)
Total, % (n)	20.31 (263)	79.69 (1032)	100 (1295)
	chi^2= 6.53	p-value = 0.011	

Table 4b - Frequency, row proportion, and chi-square test values for participants adherent to statins at thirty (30) days stratified by immigration status

Immigration Status	Not Adherent	Adherent	Total
Canadian-born, % (n)	16.37 (139)	83.63 (710)	100 (849)
Immigrant, % (n)	12.11 (54)	87.89 (392)	100 (446)
Total, % (n)	14.90 (193)	85.10 (1102)	100 (1295)
	chi^2= 4.19	p-value = 0.041	

Table 4c - Frequency, column proportion, and chi-square test values for participants who completed cardiac rehabilitation stratified by immigration status

Immigration Status	Not Adherent	Adherent	Total
Canadian-born, % (n)	66.31 (689)	33.69 (350)	100 (1,039)
Immigrant, % (n)	64.09 (373)	35.91 (209)	100 (582)
Total, % (n)	65.52 (1,062)	34.48 (559)	100 (1,621)
	chi^2= 0.82	p-value = 0.366	

Table 5 *-Univariable logistic regression analysis of immigration status exposure on 7-day statin adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for 7-day statin adherence after stepwise model selection (adjusted)*

	Unadjusted (n=1,295)			Adjusted* (n=1,277)		
Covariate	**OR**	**P-value**	**[95% CI]**	**OR**	**P-value**	**[95% CI]**
Canadian-Born	1.00	–	–	1.00	–	–
Immigrant	1.47	0.01	1.09- 1.99	1.36	0.05	1.00 – 1.85
*Adjusted for age, smoking behaviour, sex, and diabetes.						

Two-way contingency tables of study outcomes (statin adherence at 7- & 30-days, and cardiac rehabilitation completion) by binary immigration category are reported (**Tables 4.3a, 4.3b, 4.3c**). Chi-square test of contingency tables of 7-day and 30-day statin adherence were statistically significant (p=0.011 and p=0.041, respectively). A greater proportion of Canadian-born participants were adherent to statins at 30-days (83.6%) compared to 7-days (77.6%) (**Tables 4a, 4b**). A greater proportion of immigrants reported adherence to statins (7-day: 83.63%; 30-day: 87.89%) compared to Canadian-born participants. Row and column percentages for the cardiac rehabilitation completion by immigration status were similar (p=0.366) (**Table 4c**).

Table 6 *- Univariable logistic regression analysis of immigration status exposure on 30-day statin adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for 30-day statin adherence after stepwise model selection (adjusted)*

	Unadjusted (n= 1,295)			Adjusted* (n=1,277)		
Covariate	**OR**	**P-value**	**[95% CI]**	**OR**	**P-value**	**[95% CI]**
Canadian-Born	1.00	–	–	1.00	–	–
Immigrant	1.42	0.04	1.01– 1.99	1.36	0.84	0.96 – 1.94
*Adjusted for age, smoking behaviour, sex, and diabetes.						

Odds ratios for unadjusted and adjusted models are reported (**Table 5, 6, & 4.6**). For all of the adjusted models for 7-day and 30-day statin adherence reported in this chapter, the model covariates included a dichotomous age, dichotomous diabetes, and nominal smoking status as covariates. All other *a priori* covariates were dropped from the model for statistical non-significance after stepwise Sidak adjustment. In the adjusted models, age was significantly correlated with smoking (Pearson's correlation: 0.063; $p<0.050$), diabetes (Pearson's correlation: 0.11; $p<0.050$), and sex (Pearson's correlation: 0.158; $p<0.050$).

Table 7 - Univariable logistic regression analysis of immigration status exposure on cardiac rehab completion outcomes (unadjusted); multivariable logistic regression of the risk factors for cardiac rehab completion after stepwise model selection (adjusted)

	Unadjusted (n= 1,621)			Adjusted* (n=1,388)		
Covariate	**OR**	**P-value**	**[95% CI]**	**OR**	**P-value**	**[95% CI]**
Canadian-Born	1.00	–	–	1.00	–	–
Immigrant	1.35	0.05	1.00 – 1.85	0.91	0.414	0.72 – 1.14
*Adjusted for age, smoking behaviour, sex, diabetes, marital status, education and income quintile.						

For 7-day statin adherence, the odds ratio decreased by 9% after multivariable adjustment in favour of no statistically significant effect in the adjusted model with sex (OR 1.36; 95% CI 1.00-1.85). Although the effect is not statistically significant, a large confidence interval was found favouring 7-day statin adherence in immigrants compared to Canadian-born participants.

Compared to the unadjusted model, the adjusted odds ratio for 30-day statin adherence (OR 1.36; 95% CI 0.96-1.94) decreased by 44% in favour of no statistically significant effect. Confidence intervals in the adjusted 30-day statin adherence models favour statin adherence among immigrants compared to Canadian-born participants based on the length and direction of the confidence intervals.

Odds ratios for all covariates in the adjusted model for statin adherence outcomes are reported (**Figure 4**). Participants ≥65 years had a 31% reduction in the odds of 30-day statin adherence compared to participants <65 years when controlling for immigration, age, smoking status, diabetes and sex. This observation was statistically significant. A similar trend in age was not observed in 7-day statin adherence.

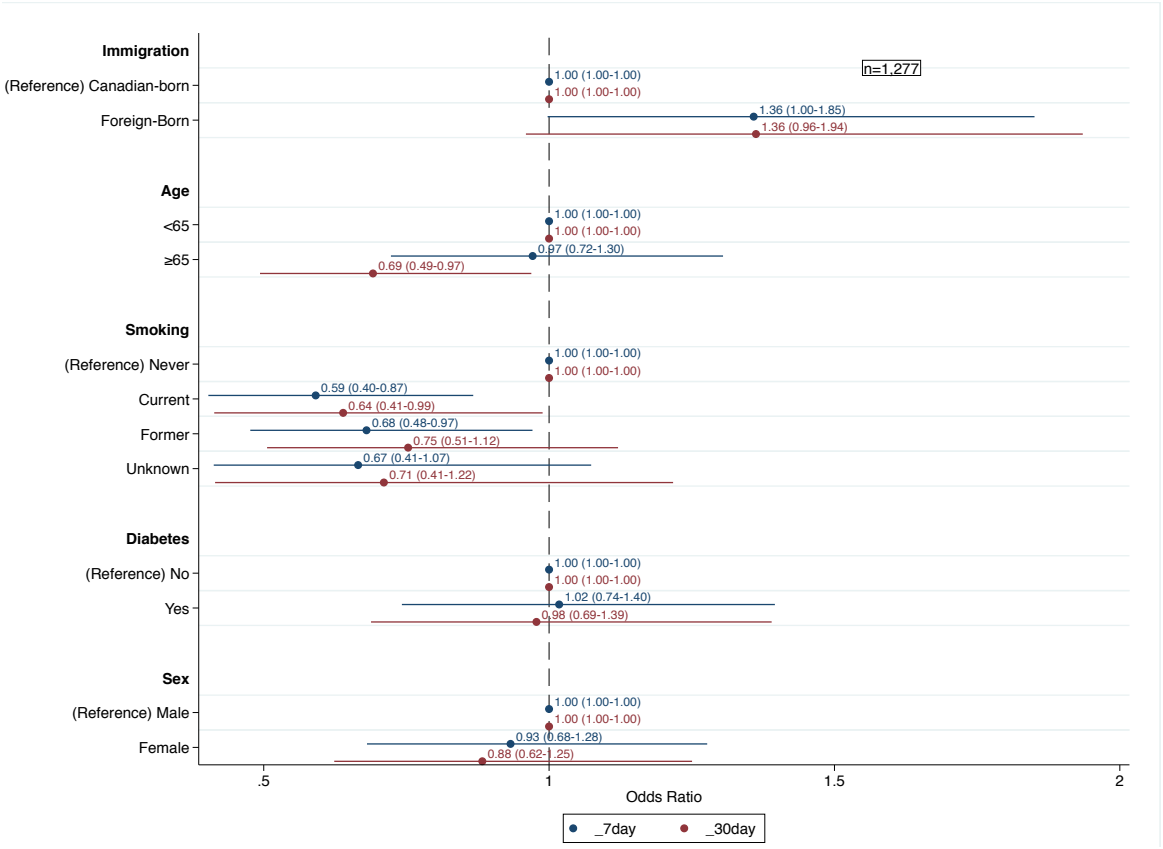


Figure 4 - multivariable logistic regression of the risk factors for 7- & 30-day statin adherence controlling for immigration exposure after stepwise model selection

The magnitude and direction of the effect size was similar across smoking categories. Current or former smokers were at a reduced odds of statin adherence at 7- and 30-days compared to participants who never smoked. A similar trend was observed in participants whose smoking history was unknown. No exposure effect was observed in Females, who were on average at a reduced odds of statin adherence at 7- days (OR 0.88; 95%CI 0.62-1.25)) and 30-days (odds ratio 0.93; 95%CI 0.68-1.28)).

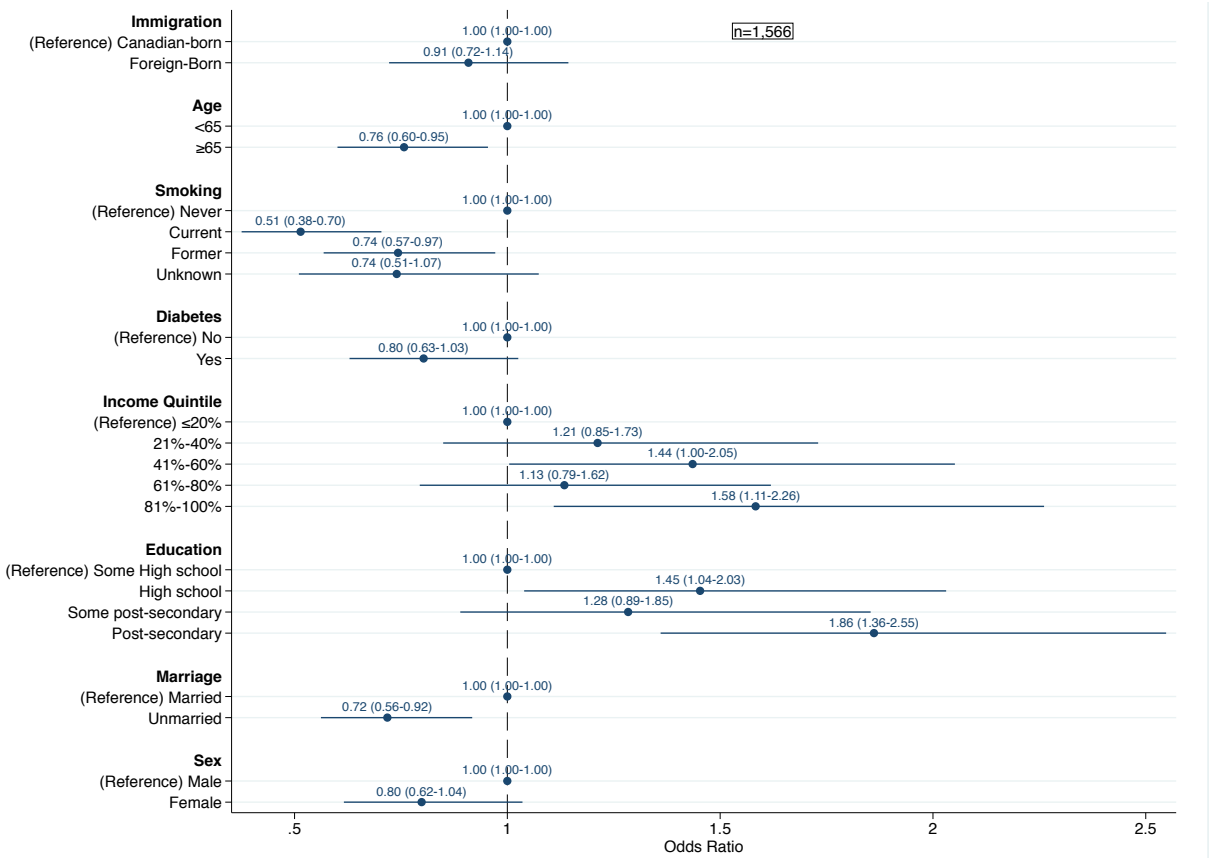


Figure 5 - Multivariable logistic regression of the risk factors for completion of cardiac rehabilitation controlling for immigration exposure after stepwise model selection

The odds ratios for all covariates included in the final adjusted model for cardiac rehabilitation completion outcomes is reported (**Figure 5**). A statistically significant odds ratio was found in participants ≥65 (OR 0.76; 95% CI 0.66-0.95)) compared to participants <65 years. The categorical covariate for smoking history demonstrated an overall trend similar to that observed in statin adherence outcomes. Participants who smoked, or with an unknown smoking history, where less likely to complete cardiac rehabilitation. Across levels of smoking history,

current smokers were the least likely to complete cardiac rehabilitation (OR 0.51; 95% CI: 0.38-0.70)).

Patients with diabetes were less likely to complete cardiac rehabilitation, however this effect was not statistically significant (OR 0.80; 95% CI: 0.63-1.03). A graduated effect size was observed when participants were grouped by neighbourhood income quintile. Participants in the highest income quintile were at the highest odds of cardiac rehabilitation completion. The trend was not observed in participants with in the 4th neighborhood income quintile. The odds ratios in these participants were similar to participants with an average neighborhood income in the in 2nd quintile. The magnitude and direction of the effect size were similar for both unmarried participants and women, with a 28% and 20% decrease in odds of cardiac completion compared to their respective references.

Forest plots for the complete model for statin outcomes[iv] and cardiac rehabilitation outcomes[v] were completed.

[iv] **Appendix 4.2** Forest plot of the complete model for statin outcomes (7 day and 30 day) by immigration exposure

[v] **Appendix 4.3** Forest plot of the complete model for cardiac rehabilitation attendance outcomes by immigration exposure

Ethnicity Exposure and the Association to Statin Adherence and Cardiac Rehabilitation Completion

Table 8a - Frequency, row proportion and chi-square test values for participants adherent to statins at seven (7) days stratified by ethnicity

Ethnicity	Not Adherent	Adherent	Total
White, % (n)	21.49 (222)	78.51 (811)	100 (1,033)
Visual Minority, % (n)	15.77 (41)	84.23 (219)	100 (260)
Total, % (n)	20.34 (263)	79.66 (1,030)	100 (1,293)
	chi^2= 4.20	p-value = 0.041	

Table 8b - Frequency, row proportion and chi-square test values for participants adherent to statins at thirty (30) days stratified by ethnicity

Ethnicity	Not Adherent	Adherent	Total
White, % (n)	15.97 (165)	84.03 (868)	100 (1,033)
Visual Minority, % (n)	10.77 (28)	89.23 (232)	100 (260)
Total, % (n)	14.93 (263)	85.07 (1,030)	100 (1,293)
	chi^2= 4.43	p-value = 0.035	

Table 8c - Frequency, row proportion and chi-square test values for participants who completed cardiac rehabilitation stratified by ethnicity

Ethnicity	Not Adherent	Adherent	Total
White, % (n)	66.35 (846)	33.65 (429)	100 (1,275)
Visual Minority, % (n)	62.17 (212)	37.83 (129)	100 (341)
Total, % (n)	65.47 (1,058)	34.53 (558)	100 (1,616)
	chi^2= 2.08	p-value = 0.149	

Two-way contingency tables of study outcomes (statin adherence at 7- and 30-days, and cardiac rehabilitation completion) by ethnicity exposure are reported (**Tables 4.7a, 4.7b, 4.7c**). The null hypothesis of no relationship was rejected in the contingency tables for 7-day statin adherence (p=0.041) and cardiac rehabilitation completion (p=0.035) as assessed by the chi-square test. When grouped by binary adherence, a larger proportion of visual minorities were adherent to statins at 7-days (84.2%) and 30-days (89.2%) than Canadian-born participants (7-day: 78.5%; 30-day: 84.0%). A similar trend was observed where cardiac rehabilitation was completed by 37.8% of all visual minority participants and 33.7% of all Canadian-born participants (**Table 8c**).

Unadjusted and adjusted logistic models for 7-day statin adherence outcomes by ethnicity exposure are reported (**Table 9**). There was a 13% decrease in the average effect size in the adjusted models compared to the unadjusted model. In all models, the direction of the effect favoured cardiac rehab completion in visual minority participants. This effect direction was accompanied by wide and statistically insignificant confidence intervals in the final adjusted model (95% CI: 0.96-2.04).

The odds ratios for 30-day statin adherence in the unadjusted and adjusted models are reported (**Table 10**). Adjustment resulted in an absolute reduction of 0.16 compared to the unadjusted odds ratio.

Table 9 *- Univariable logistic regression analysis of dichotomous ethnicity exposure on 7-day statin adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for 7-day statin adherence after stepwise model selection (adjusted)*

	Unadjusted (n= 1,293)			Adjusted* (n=1,275)		
Covariate	**OR**	**P-value**	**[95% CI]**	**OR**	**P-value**	**[95% CI]**
White	1.00	–	–	1.00	–	–
Visual Minority	1.46	0.04	1.01– 2.11	1.33	0.14	0.91– 1.95
*Adjusted for age, smoking behaviour, sex, and diabetes.						

Table 10 *Univariable logistic regression analysis of dichotomous ethnicity on 30-day statin adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for 30-day statin adherence after stepwise model selection (adjusted)*

	Unadjusted (n=1,293)			Adjusted (n=1,275)		
Covariate	**OR**	**P-value**	**[95% CI]**	**OR**	**P-value**	**[95% CI]**
White	1.00	–	–	1.00	–	–
Visual Minority	1.58	0.04	1.03–2.41	1.39	0.15	0.89– 2.18
*Adjusted for age, smoking behaviour, sex, and diabetes.						

Table 11 *- Univariable logistic regression analysis of dichotomous ethnicity on cardiac rehab completion adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for cardiac rehab completion after stepwise model selection (adjusted)*

	Unadjusted (n=1,616)			Adjusted (n=1,565)		
Covariate	**OR**	**P-value**	**[95% CI]**	**OR**	**P-value**	**[95% CI]**
White	1.00	–	–	1.00	–	–
Visual Minority	1.45	0.15	0.93– 1.54	1.04	0.31	0.80–1.37
*Adjusted for age, smoking behaviour, sex, diabetes, income quintile, education, marriage status						

Odds ratios for cardiac rehabilitation outcomes by ethnicity exposure are reported (**Table 11**)**.** The average effect size of the final adjusted model favoured a 4% increase in odds of the outcome compared to whites (OR 1.04). However, the 95% confidence interval was not a strong indicator of the direction of the effect (95% CI: 0.80-1.37). The adjusted model included the following covariates: categorical education, neighborhood income quintile, dichotomous marriage, diabetes, dichotomous age, and smoking history. Adjustment decreased the average effect size by 39% relative to the unadjusted model. These changes in effect size and direction after adjustment were consistent in all three models. Odds ratios and 95% confidence intervals were similar in both the per-protocol adjusted model and the adjusted model with sex as a covariate.

Main effects for the final adjusted models are reported (**Figure 6, Figure 7**). The direction and effect size of main effects observed in smoking status, dichotomous age, diabetes and sex were similar to trends reported in the final model of statin adherence and immigration exposure for all outcomes. A cross-tabulation of ethnicity and immigration exposure found that approximately 84% of visual minorities were immigrants. A chi-square test determined with 94% confidence that the observed distribution of ethnic exposure by immigration exposure was non-random ($p<0.001$) (**Table 12**)

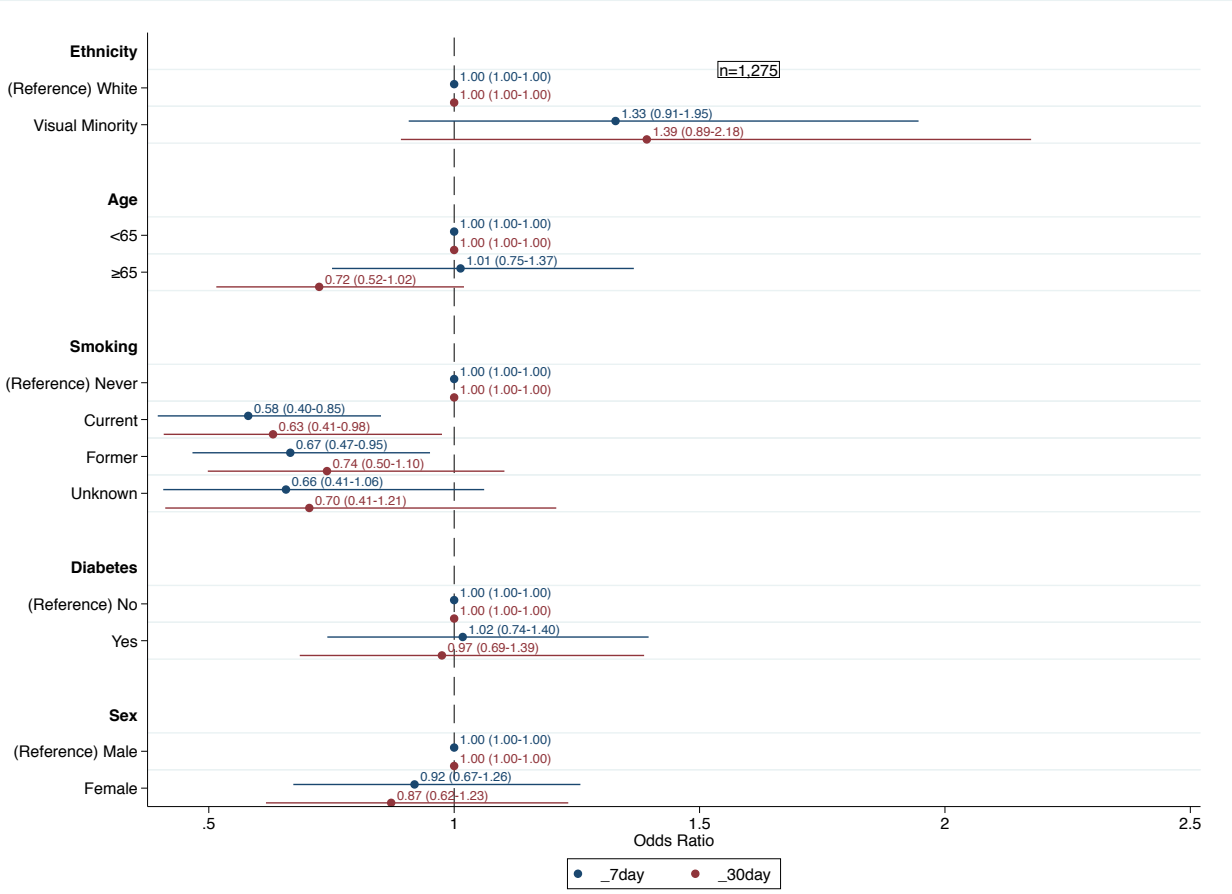


Figure 6 - Multivariable logistic regression of risk factors for 7- & 30-day statin adherence after stepwise model selection controlling for ethnicity exposure

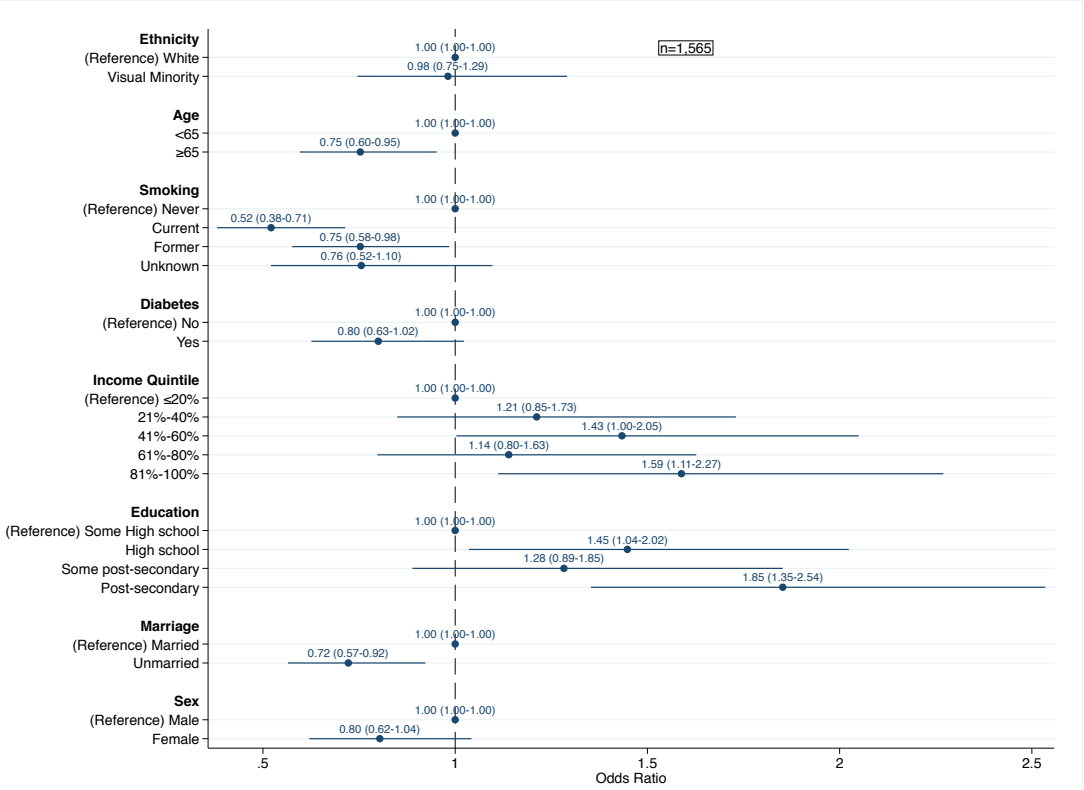


Figure 7 - Multivariable logistic regression of the risk factors for cardiac rehab completion after stepwise model selection

Table 12 - Frequency, row proportion and chi-square test values for participant ethnicity exposure by immigration exposure

Duration	Canadian-Born	Immigrant	Total
White	77.19 (985)	22.81 (291)	100 (1,276)
Visual Minority	16.37 (56)	83.63 (286)	100 (342)
Total, % (n)	64.34 (1,041)	35.66 (577)	100 (1,618)
	chi^2= 434.83		p-value = <0.001

Duration of Canadian Residency Exposure and the Association to Statin Adherence and Cardiac Rehabilitation Completion

Table 13a - Frequency, row proportion and Fisher's Exact Test for participants adherent to statins at seven (7) days stratified by duration of Canadian residency

Duration	Not Adherent %(n)	Adherent %(n)	Total %(n)
Canadian-Born	22.38 (190)	77.62 (659)	100 (849)
<10 years Immigrant	14.29 (3)	85.71 (18)	100 (21)
>10 years Immigrant	16.03 (67)	83.97 (351)	100 (418)
Total	67 (260)	351 (1,028)	100 (1,288)

Fisher's Exact = 0.023

Table 13b - Frequency, row proportion and Fisher's Exact Test for participants adherent to statins at thirty (30) days stratified by duration of Canadian residency

Duration	Not Adherent %(n)	Adherent %(n)	Total %(n)
Canadian-Born	16.37 (139)	83.63 (710)	100 (849)
≤10 years Immigrant	0 (0)	100 (21)	100 (21)
>10 years Immigrant	12.20 (51)	87.80 (367)	100 (418)
Total	14.75 (190)	85.25 (1,098)	100 (1,288)

Fisher's Exact = 0.018

Table 13c - Frequency, row proportion and chi-square test values for participants who complete cardiac rehabilitation stratified by duration of Canadian residency

Duration	Not Adherent %(n)	Adherent %(n)	Total %(n)
Canadian-Born	66.31 (689)	33.69 (350)	100 (1,039)
<10 years Immigrant	68.97 (20)	31.03 (9)	100 (1.80)
>10 years Immigrant	63.70 (344)	36.30 (196)	100 (540)
Total, % (n)	65.49 (1,053)	34.51 (555)	100 (1,608)

chi^2= 1.23 p-value = 0.541

Two-way contingency tables of study outcomes (statin adherence at 7- & 30-days, and cardiac rehabilitation completion) by duration of Canadian residency are reported (**Tables 13, 13, 13**). The chi-square reported statistically significant distributions in contingency tables for 7-day (p=0.023) and 30-day (p=0.018) statin adherence. However, the frequency of immigrants with <10 years of Canadian residency exposure (n=29) was insufficient to infer valid results from the planned analysis. Tables for the logistic regression outcomes for 7-day[vi], 30-day[vii], and cardiac rehabilitation completion[viii] outcomes were completed. Forest plots for statin adherence[ix] and cardiac rehabilitation completion[x] outcomes are reported in the appendix.

Forest plots for the complete model for statin outcomes[xi] and cardiac rehabilitation outcomes[xii] were completed.

[vi] **Appendix 4.4** Univariable logistic regression analysis of duration of Canadian residency exposure on 7-day statin adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for 7-day statin adherence after stepwise model selection (adjusted)

[vii] **Appendix 4.5** Univariable logistic regression analysis of duration of Canadian residency exposure on 30-day statin adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for 30-day statin adherence after stepwise model selection (adjusted)

[viii] **Appendix 4.6** Univariable logistic regression analysis of duration of Canadian residency exposure on cardiac rehab completion outcomes (unadjusted); multivariable logistic regression of the risk factors for cardiac rehab completion after stepwise model selection (adjusted)

[ix] **Appendix 4.7** Multivariable logistic regression of risk factors for 7- & 30-day statin adherence after stepwise model selection controlling for duration of Canadian residency with the addition of sex as a risk factor

[x] **Appendix 4.8** Multivariable logistic regression of the risk factors for cardiac rehab completion after stepwise model selection controlling for duration of Canadian residency with the addition of sex as a risk factor.

[xi] **Appendix 4.9** Forest plot of the complete model for statin outcomes (7 day and 30 day) by ethnicity exposure

[xii] **Appendix 4.10** Forest plot of the complete model for statin outcomes (7 day and 30 day) by ethnicity exposure

Modification of the ISLAND Group Effects by Immigration Exposure

Contingency tables for distribution of participants with 7-day statin adherence (**Table 14a**), 30-days statin adherence (**Tables 14b**), and cardiac rehabilitation completion (**Table 14c**) outcomes by immigration exposure within each ISLAND allocation arm. Chi-square tests for all outcomes reported no statistically significant in the distribution of immigrants across ISLAND allocation arms. This result is aligned with our expectations due to the randomization and sequence generation methods of the ISLAND trial.

Table 14a - Frequency, column proportion and chi-square test values for participants adherent to statins at seven (7) days within ISLAND allocation arms stratified by immigration status

Duration	Not Adherent*			Adherent**		
	Arm 1 % (n)	Arm 2 % (n)	Arm 3 % (n)	Arm 1 % (n)	Arm 2 % (n)	Arm 3 % (n)
Canadian-Born	76.29 (74)	65.75 (48)	73.12 (68)	62.81 (228)	63.82 (224)	65.09 (207)
Immigrant	23.71 (23)	34.25 (25)	26.88 (25)	37.19 (135)	36.18 (127)	34.91 (111)
Total	100 (97)	100 (73)	100 (93)	100 (363)	100 (351)	100 (318)
	*chi^2= 2.36	p-value = 0.31		**chi^2= 0.38	p-value = 0.83	

Table 14b - Frequency, column proportion and chi-square test values for participants adherent to statins at thirty (30) days within ISLAND allocation arms stratified by immigration status

Duration	Not Adherent*			Adherent**		
	Arm 1 % (n)	Arm 2 % (n)	Arm 3 % (n)	Arm 1 % (n)	Arm 2 % (n)	Arm 3 % (n)
Canadian-Born	76.06 (54)	67.86 (38)	71.21 (47)	63.75 (248)	63.59 (234)	66.09 (228)

Immigrant	23.94 (17)	32.14 (18)	28.79 (19)	36.25 (141)	36.41 (134)	33.91 (117)
Total	100 (71)	100 (56)	100 (66)	100 (389)	100 (368)	100 (345)
	*chi^2=1.08	p-value = 0.58		**chi^2= 0.61	p-value = 0.74	

Table 14c - Frequency, column proportion and chi-square test values for participants complete cardiac rehab within ISLAND allocation arms stratified by immigration status

	No Completion*			Completion**		
Duration	**Arm 1 % (n)**	**Arm 2 % (n)**	**Arm 3 % (n)**	**Arm 1 % (n)**	**Arm 2 % (n)**	**Arm 3 % (n)**
Canadian-Born	66.42 (273)	62.53 (227)	65.62 (189)	60.69 (105)	62.24 (122)	64.74 (123)
Immigrant	33.58 (138)	37.47 (136)	34.38 (99)	39.31 (68)	37.76 (74)	35.26 (67)
Total	100 (411)	100 (363)	100 (288)	100 (173)	100 (196)	100 (190)
	*chi^2=1.38	p-value = 0.50		**chi^2=0.65	p-value = 0.72	

Main Effect Models

Unadjusted and adjusted main effect models for 7-day statin adherence are reported (**Table 15**). The final adjusted model with sex added as a covariate was similar to the model adjusted as per the planned *a priori* statistical analysis. Adjustment did not change the direction or magnitude of the observed effect. Participants who initiated statin in ISLAND arms 2 and 3 were at a 34% increase

and 9% decrease in the odds of adherence compared to participants who received usual care controlling for diabetes, dichotomous age, smoking exposure and sex.

Table 15 - Main effect models controlling for the effect of immigration exposure and ISLAND allocation on 7-day statin adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for 7-day statin adherence after stepwise model selection (adjusted)

	Unadjusted (n= 1,295)			Adjusted✂ (n= 1,277)			
	OR	**P-value**	**[95% CI]**	**OR**	**P-value**	**P-value Adjusted**	**[95% CI]**
Arm 1	1.00	–	–	1.00	–	–	–
Arm 2	1.28	0.153	0.91 1.79	1.34	0.097	0.335	0.95 1.90
Arm 3	0.92	0.601	0 .66 1.27	0.91	0.565	0.811	0.65 1.26

✂Adjusted for age, smoking, diabetes, and sex

Table 16 - Main effect models controlling for the effect of immigration exposure and ISLAND allocation on 30-day statin adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for 30-day statin adherence after stepwise model selection (adjusted)

	Unadjusted (n= 1,295)			Adjusted✂ (n=1,277)			
	OR	**P-value**	**[95% CI]**	**OR**	**P-value**	**P-value Adjusted**	**[95% CI]**
Arm 1	1.00	–	–	1.00	–	–	–
Arm 2	1.19	0.359	0.82 1.74	1.29	0.201	0.490	0.87 1.90
Arm 3	0.96	0.818	0.66 1.38	0.96	0.814	0.814	0.66 1.38

✂Adjusted for age, smoking, diabetes, and sex

Unadjusted and adjusted main effect models for 30-day statin adherence are reported (**Table 16**). 95% confidence intervals for odds ratios were not statistically significant. The unadjusted and adjusted models for 30-day statin adherence were similar to their equivalent models for 7-day statin adherence outcomes in regards to the average effect size, magnitude and direction. The odds of statin adherence at 30-days increased by 30% decreased by 4% in study arms 2 and 3, respectively, compared to usual care.

Unadjusted and adjusted main effect models for cardiac rehabilitation completion outcomes are reported (**Table 17**). Adjustment with dichotomous age, smoking exposure, sex, diabetes, neighborhood income quintile, education and sex, resulted in similar odds ratios and 95% confidence intervals as the unadjusted model. The final adjusted main effect model reported a 30% and 60% increase in the odds of cardiac rehabilitation completion in participants allocated to arm 2 and 3 when compared to usual care. The treatment effect in arm 3 was statistically significant (95% CI 1.22-2.09).

Table 17 - Main effect models controlling for the effect of immigration exposure and ISLAND allocation on cardiac rehab completion (unadjusted); multivariable logistic regression of the risk factors for cardiac rehab completion after stepwise model selection (adjusted)

Unadjusted (n= 1,621)	Adjusted✂ (n= 1,597)

	OR	P-value	[95% CI]	OR	P-value	P-value Adjusted	[95% CI]
Arm 1	1.00	–	–	1.00	–	–	–
Arm 2	1.28	0.052	1.00 1.64	1.30	0.049	0.222	1.00 1.69
Arm 3	1.57	0.001	1.22 2.02	1.60	0.001	.006	1.22 2.09
✂Adjusted for age, diabetes, smoking, income, marital status, education, and sex							

Odds ratios for all covariates in the final adjusted main effect models for statin adherence outcomes are reported (**Figure 8**). When controlling for ISLAND allocation group, dichotomous age, diabetes, smoking exposure and sex, immigrants experienced an approximately 36% greater odds of statin adherence at 7 (OR 1.35, 95% 0.99-1.84) and 30-days (OR1.36, 95% CI 0.96-1.93). Odds ratio confidence intervals for ISLAND arm 2 provide moderate evidence for a treatment effect in favour of improved odds of statin adherence compared to usual care. Age is a statistically significant covariate in the final adjusted model for 30-day statin adherence. Patients aged ≥65 years experienced a 32% decrease in the odds of statin adherence at 30-days, when controlling for

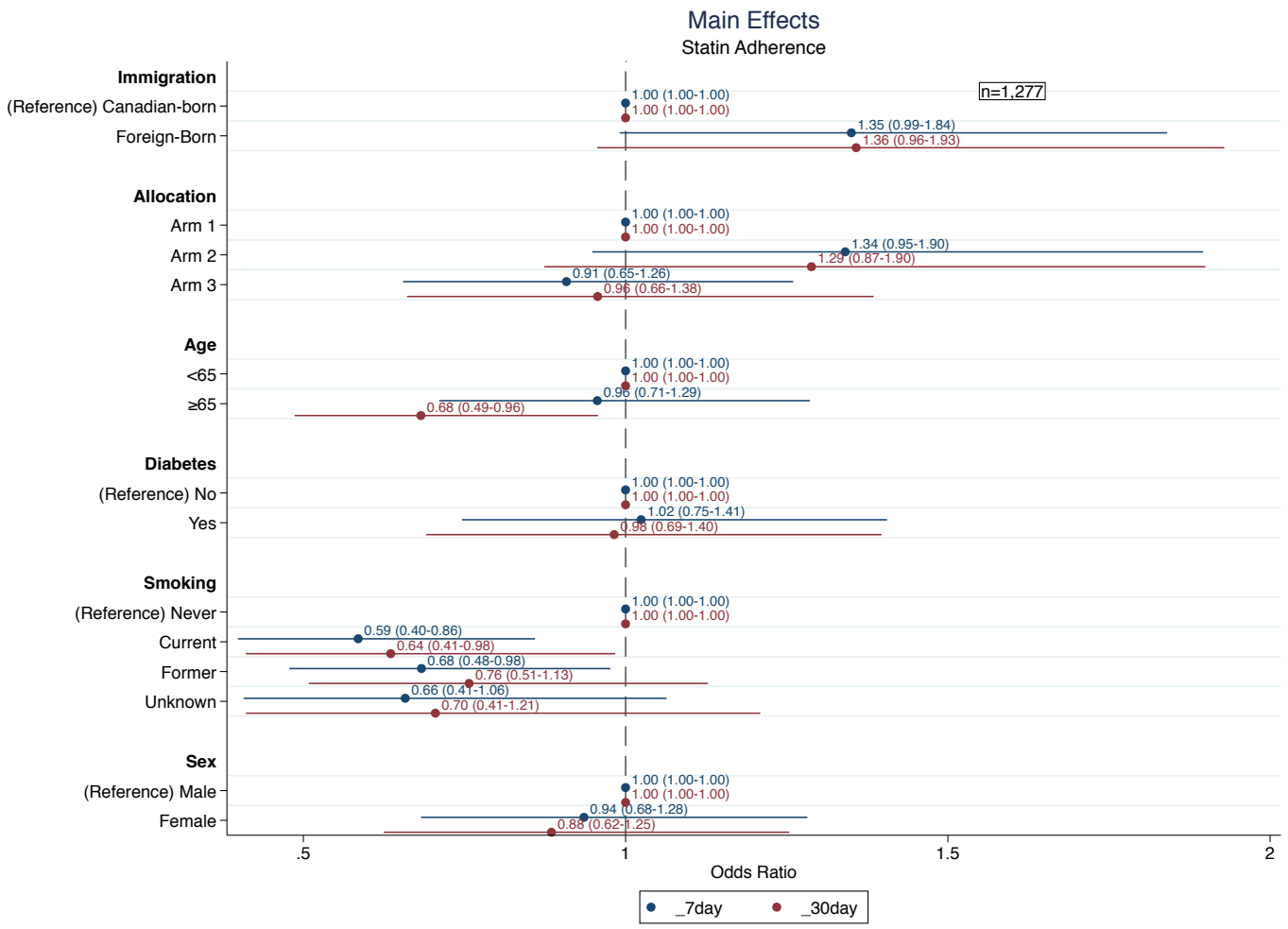


Figure 8 *- Main effects of multivariable logistic regression of risk factors for 7- & 30-day statin adherence after stepwise model selection controlling for immigration exposure and ISLAND allocation ISLAND allocation, immigration exposure, dichotomous age, diabetes, smoking, and sex.*

A past or current history of smoking reduced the odds of cardiac rehabilitation in the final adjusted main effect model. There was strong evidence that current smokers experienced reduced odds of cardiac rehabilitation completion (OR 0.64; 95% CI 0.41-1.21), 7-day (OR 0.59; 95% CI 0.40-0.86)

and 30-day (OR 0.64; 95% CI 0.41-0.98) statin adherence. Sex was not a statistically significant covariate in the adjusted main effect model.

Odds ratios for all covariates in the final adjusted main effect models for cardiac rehabilitation completion are reported (**Figure 9**). The average treatment effect in immigrants was a reduction in the odds of rehabilitation completion, however the odds ratio is moderate evidence for no treatment effect (OR 0.91; 95% CI 0.73-1.15). Participants in ISLAND arm 3 experienced a greater improvement in the odds of cardiac rehabilitation completion (OR 1.60 1.22-2.09) those in ISLAND arm 2 (OR 1.30; 95% CI 1.00-1.69).

Age was a statistically significant covariate in the adjusted model. Participants aged ≤65 years experienced a 24% reduction in their odds of cardiac rehabilitation completion (OR 0.76; 95% CI 0.60-0.96) compared to participants >65 years.

Diabetes exposure was moderately associated with a 20% reduction in cardiac rehabilitation completion (OR 0.80; 95% CI 0.63-1.02). Smoking was negatively associated with cardiac rehabilitation completion with the greatest reduction in odds experienced by current smokers (OR 0.52; 95% CI 0.38-0.72). Average neighborhood income was positively associated with cardiac rehabilitation completion.

Participants in the fourth income quintile (OR 1.13; 95% CI 0.79-1.61) experienced a similar odd of cardiac rehabilitation completion as those in the second quintile (OR 1.22; 95% CI 0.85-1.74).

Unmarried participants experienced a 28% decrease in the odds of cardiac rehabilitation completion (OR 0.72; 95% CI 0.56-0.91) compared to the reference, unmarried participants.

Education was positively associated with improved cardiac completion. Participants who completed a high school (OR 1.44, 95% OR 1.03-2.02) or post-secondary program (OR 1.86, 95% CI 1.36-2.55) experienced a 44% and 86% increase in the odds of cardiac rehabilitation completion. There was moderate evidence that women were at a 20% decreased odds of cardiac rehabilitation completion (OR 0.80, 0.62-1.04) compared to men.

Interaction

The complete Stata output for interaction effects for 7 and 30-day statin adherence and cardiac rehabilitation is reported.[xiii,xiv] Interaction terms between birth origin and ISLAND group allocation were not statistically significant in 7- and 30-day statin adherence outcomes (immigrant x arm 2: p=0.173; immigrant x arm 3: p=.467).

Sensitivity analysis

[xiii] **Appendix 4.11** Stata logistic regression output for interaction effect between ISLAND allocation and immigration exposure on 7 and 30-day statin adherence
[xiv] **Appendix 4.12** Stata logistic regression output for interaction effect between ISLAND allocation and immigration exposure on cardiac rehabilitation completion

Sensitivity analysis was conducted for the primary study question as outlined in the planned statistical analysis (**Figure 12**). A total of 1,624 participants had recorded values for immigration exposure. Among participants with a known immigration exposure: 329 participants were missing 7 and 30-day statin adherence outcomes, and 3 participants were missing cardiac rehabilitation completion outcomes.[xv]

Best-case analyses of statin adherence outcomes were nearly similar in the effect direction and magnitude to the observed outcomes. The worst case shifted the direction of the effect in favour of reduced odds of statin adherence, however this shift in the effect direction was not statistically significant. The confidence interval of the worst-case scenario was reduced by ~50% for 7-day statin adherence and ~42% for 30-day statin adherence. Sensitivity analysis resulted in no change in the effect size or direction for cardiac rehabilitation completion.

[xv] **Appendix 4.13** Stata version 13.1 output of missing outcomes by immigration exposure

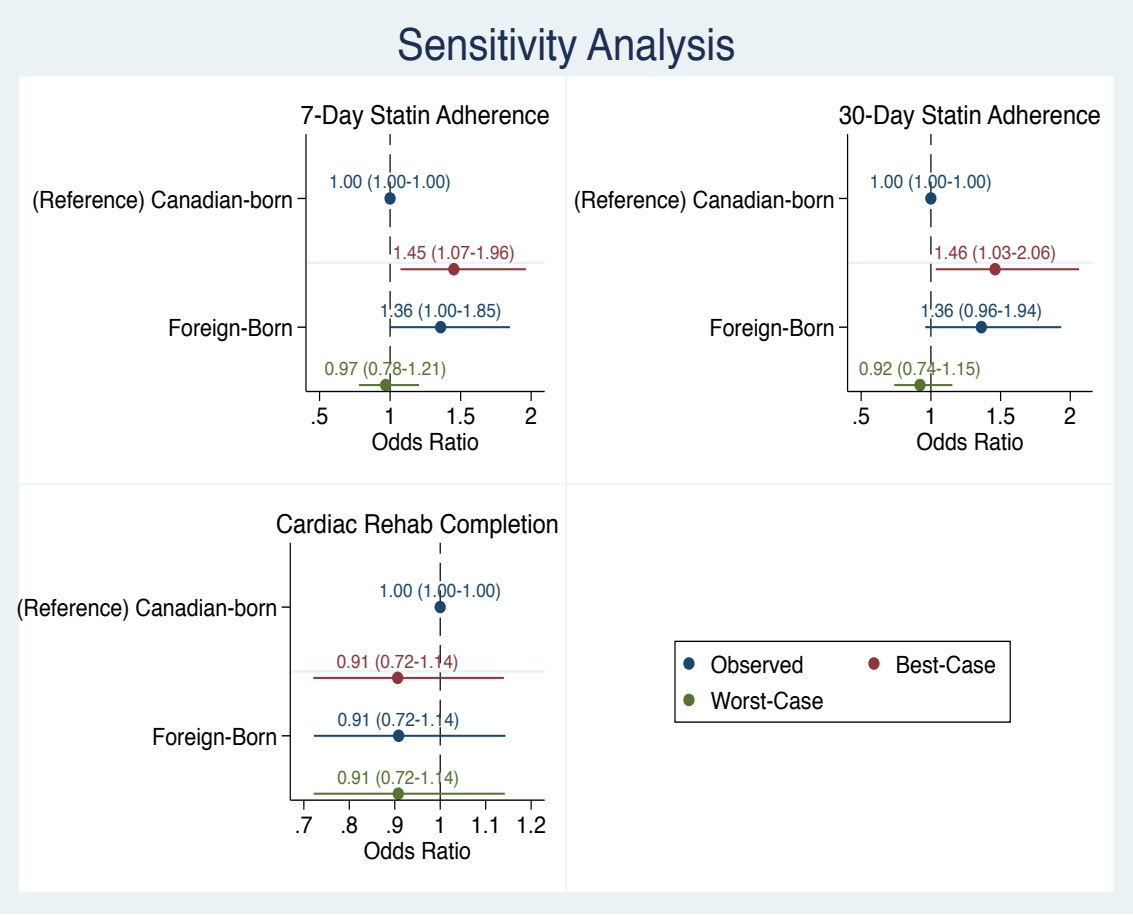


Figure 8 - Sensitivity analysis by best-case and *worst-case* scenario for each 7-day and 30-day statin adherence and cardiac rehabilitation completion

CHAPTER 5: DISCUSSION

Chapter Introduction

This thesis presents the results of the quantitative analysis of adherence to statins and completion of cardiac rehabilitation among subgroups of the ISLAND RCT. The focus of this thesis is to assess health inequity in guideline-

recommended secondary preventative cardiac care by immigration status and ethnicity. The research program was directed by the following questions:

1. *In adult, post-MI participants with evidence of coronary disease, is immigration associated with medication adherence to statins and completion of cardiac rehabilitation at one-year post-MI?*
2. *Is ethnicity associated with statin adherence or completion of cardiac rehabilitation at one-year post myocardial infarction?*
3. *Is the duration of Canadian residency associated with statin adherence or completion of cardiac rehabilitation at one-year post myocardial infarction?*
4. *Does immigration status modify the effects of the ISLAND educational reminder interventions (i. standard care, ii. educational reminders via post, iii. educational reminders via post plus interactive voice response educational reminders)?*

Results from the the planned analysis of this study are reported in Chapter 3. This final chapter provides an overview the study's major findings, limitations, contributions, public heatlh implications and future research suggestions.

Summary of Major Findings

Association of immigration and secondary cardiac preventative therapy

We report moderate evidence for an association between immigrants and secondary preventative care as evidenced by the 95% confidence intervals skewed towards statin adherence in immigrants. Immigrants experienced non-significant greater odds of statin adherence at 7-days (OR 1.36, 95% CI 1.00-1.85) and 30 days (OR 1.36, 95% CI 0.96-1.94) after adjusting for age, diabetes, sex, and smoking status. We found no evidence of an association between immigration and cardiac rehabilitation completion (OR 0.91; 0.72-1.14) as the confidence interval did not markedly skew in any direction.

Association of ethnicity and secondary cardiac preventative therapy

There is moderate evidence that the odds of statin adherence at 7-days (OR 1.33, 95% CI 0.89-2.18) and 30-days (OR 1.39, 95% CI 0.89-2.18) is greater in visual minorities than white patients. Although the evidence is not statistically significant, the 95% confidence intervals strongly favour adherence in immigrants. We found no evidence of an association between ethnicity and cardiac rehabilitation completion (OR 0.98, 95% CI 0.75-1.29).

Association of duration of Canadian residency and secondary cardiac preventative therapy

Our analysis was unable to infer any valid conclusions due to a low evaluable sample size (n=29) among immigrants with <10 years Canadian residency exposure. As a result, our study was unable to make inferences with respect to the *healthy immigrant effect* reported in chapter 1.

Modification of ISLAND educational reminder interventions by immigration

A description of the ISLAND RCT study arms are reported in Chapter 2. We found no evidence of modification of statin outcomes or cardiac rehabilitation completion outcomes in each ISLAND study arm by immigration status. Immigrants experienced a nonstatistically significant greater effect size within each study arm, with the greatest effect size achieved in study arm 3 for both Canadian-born and immigrant participants for all outcomes.

Findings in the context of the literature

Our results are consistent with previous studies that have reported statin adherence and cardiac rehabilitation participation outcomes in ethnic and immigrant populations. For example, *Chiu et al*. reported that major cardiovascular risk factors, including smoking status and diabetes, were more prevalent among long-term Ontario residents compared to recent immigrants[31].

Our findings on the association of ethnicity and statin adherence contrast those of a systematic review of predictors of nonadherence to statins.[22] The systematic review found three studies that investigated associations between ethnicity and statin adherence. The review concluded that visual minorities were less likely to adhere to statin compared to whites. The systematic reviews results were similar to the results of a meta-analysis of racial disparities in statin

adherence which included 11 studies conducted in the United States.[5] The discrepancy is possibly attributed to differences in sample size. Ontario's universal public-payer system may improve and promote access and maintenance to therapy for immigrants compared to the hybrid private-public health care systems of the United States.

Modification of outcomes among educational interventions by immigration status was suggested by several narrative reviews and qualitative publications.[80-82] The literature suggests that cultural factors, such as attitudes towards healthcare, would alter behaviour associated with medication adherence and attendance to cardiac rehabilitation dependent on the educational reminder intervention. Our findings are in contrast to the literature. One plausible reason for this observation is that our findings largely reflect immigrants who have resided in Canada for >10 years and who are largely acculturated to respond to interventions similarly to Canadian-born participants.

Limitations and threats to validity

This study has the following limitations. First, missing data may have influenced statin adherence outcomes in favour of statin adherence in immigrants. Compared to the evaluable sample size, there was a 20.32% and 24.93% increase in the frequency of the evaluable participants adherent at 7- and 30-days, respectively. This difference in adherence is attributed to patients with

missing immigration exposure being more likely to not self-report their immigration exposure at the 12-month outcome assessment. Effectively, poor statin adherence resulted in poor completion of the outcome assessment.

The generalizability of outcomes is limited due to the effects of language bias. Participant inclusion was limited to individuals who could communicate in English as highlighted in Chapter 2. Language bias may result in an overestimation of the effect size in favour of greater adherence to therapy. However, the effect of language bias on this study may be minimal. Canada's immigration system favours immigrants proficient in either English or French.[54] 2016 Canadian census data report that 86% of Ontario residents can conduct a conversation in English.[55]

Responder bias may also limit the generalizability of outcomes. Participants who completed outcome assessments at 12-months may share similar characteristics such that they are prognostically different from patients who failed to complete the outcome assessment. Responder bias may also be introduced in the methods we used to manage missing outcomes. We opted to include incomplete cases in our outcome analysis to maximize the use of the available dataset. There is a moderate risk that responder bias may influence our outcomes. Responder bias may be attributed to the limited inclusion of immigrants with <10 years of Canadian residency exposure in our study.

The study may be limited by self-reporting bias. Self-reporting methods are used to assess adherence outcomes. Self-reported outcomes are known to

overestimate adherence.[56] However, the primary measure of adherence, an adapted version of the Brief Medication Questionnaire, was found to have 80%-90% and 90% sensitivity for assessing major dosage errors and minor dosage errors, respectively. The Brief Medication Questionnaire was verified in a population prescribed the angiotensin-converting enzyme inhibitors, enalpril and captopril.[57]

The measurement methods of many of our exposures and outcomes were dependent on patient recall increasing the likelihood our outcomes were influenced by recall bias. For example, asking patients their year of immigration may not be accurate among individuals who immigrated at a young age or who are not recent immigrants.

Outcomes may be negatively influenced by participants modifying their behaviour in response to perceived health provider expectations. [83] Known as the Hawthorne Effect, a potential source of bias is in the administration of the 12-month outcome assessment and during the collection of statin adherence outcomes. Trained ISLAND research staff were responsible for the collection of the 12-month outcome assessment, where patients may have overstated their adherence and cardiac rehabilitation attendance. The Hawthorne effect would bias our outcomes in favour of adherence to secondary therapies for all patients.

In order to improve statistical efficiency of our analysis marital status and prescription coverage were pooled to form binary categories. Pooling results in a loss of information as we transform the dataset. Consideration was taken to

balance the goal to make accurate inferences from the data while reducing the risk of data loss from pooling. For our exposures, we pooled on categories that were mutually similar in regards to the concepts they measured.

Study contributions and suggestions for further research

The primary goal of this study was to evaluate health disparity in patient adherence to guideline-recommended secondary cardiac prevention by immigration status. By highlighting factors that facilitate and hinder outcomes among immigrants, and by understanding how educational reminders can improve adherence, future interventions can be tailored to maintain the health advantage experienced by immigrants over a lifetime. In particular, interventions that address income, educational status, and marital status to improve completion of cardiac rehabilitation may be insightful.

This study contributes to the literature on preventative cardiac health among immigrants and ethnicities in a Canadian context. Our study addresses a gap in the literature with respect to medication adherence and cardiac rehabilitation completion among immigrants in Ontario. This study will be of interest to health policy decision-makers and guideline developers interested in the generalizability of non-tailored reminder interventions.

Further research is required on the effect of Canadian residency time on adherence outcomes. Larger sample sized studies are required to assess the

influence of the *healthy immigrant effect* on patient adherence to secondary cardiac therapy post-myocardial infarction.

Furthermore, a greater emphasis on including recent immigrants, visual minorities and women in high-quality prospective studies of patient adherence to secondary cardiac therapy post-MI is needed. On a review the literature, these patient populations are underrepresented in study samples, making our knowledge of health inequity among these populations grounded in a number of qualitative studies. Robust prospective studies inclusive of these populations would improve our knowledge on the factors attributed to improved therapeutic adherence.

Conclusion

In conclusion, immigrants who have lived in Canada for >10 years and visual minorities are associated with greater, but non-significant, statin adherence at 12-months post-myocardial infarction compared to Canadian-born patients and white patients, respectively. There was no difference in cardiac rehabilitation completion rates when patient's immigration and ethnicity were considered. These findings can be used to develop further population-level knowledge translation interventions for secondary cardiovascular care. Our study has reported outcomes that are aligned with outcomes reported in the literature.

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Supplementary appendix

Appendix 3.1 Statistical code for the calculation of Canadian residency duration using Stata version 13.1

```
label variable qavdt_yr "Date of Outcome Assessment Completion"
destring qavdt_yr, generate (qavdt_yr1)
gen imyear = .
replace imyear = qavdt_yr1 - qacandy if qacandy<. & qavdt_yr1<.
label variable imyear "Canadian Residency Duration"
 gen dur_cat = .
 replace dur_cat=0 if qacadct==2
 replace dur_cat=1 if (imyear <= 5 & imyear >= 0)
 replace dur_cat=2  if (imyear > 5 & imyear <= 10)
 replace dur_cat=3  if (imyear > 10 & imyear <= 15)
 replace dur_cat=4  if (imyear > 15 & imyear <= 20)
 replace dur_cat=5  if (imyear > 20 & imyear <= 25)
 replace dur_cat=6  if (imyear > 25 & imyear <= 30)
 replace dur_cat=7  if (imyear > 30 & imyear <= 35)
 replace dur_cat=8  if (imyear > 35 & imyear < .)
 label variable dur_cat "Years of Canadian Residency"
 label define dur_cat_label ///
 0 "Canadian-Origin, Lifetime" ///
 1 "Foreign-Origin, 5 years or less" ///
 2 "Foreign-Origin, 6-10 years" ///
 3 "Foreign-Origin, 11-15 years" ///
 4 "Foreign-Origin, 16-20 years" ///
 5 "Foreign-Origin, 21-25 years" ///
 6 "Foreign-Origin, 26-30 years" ///
 7 "Foreign-Origin, 31-35 years" ///
 8 "Foreign-Origin, >35 years"
 label values dur_cat dur_cat_label
```

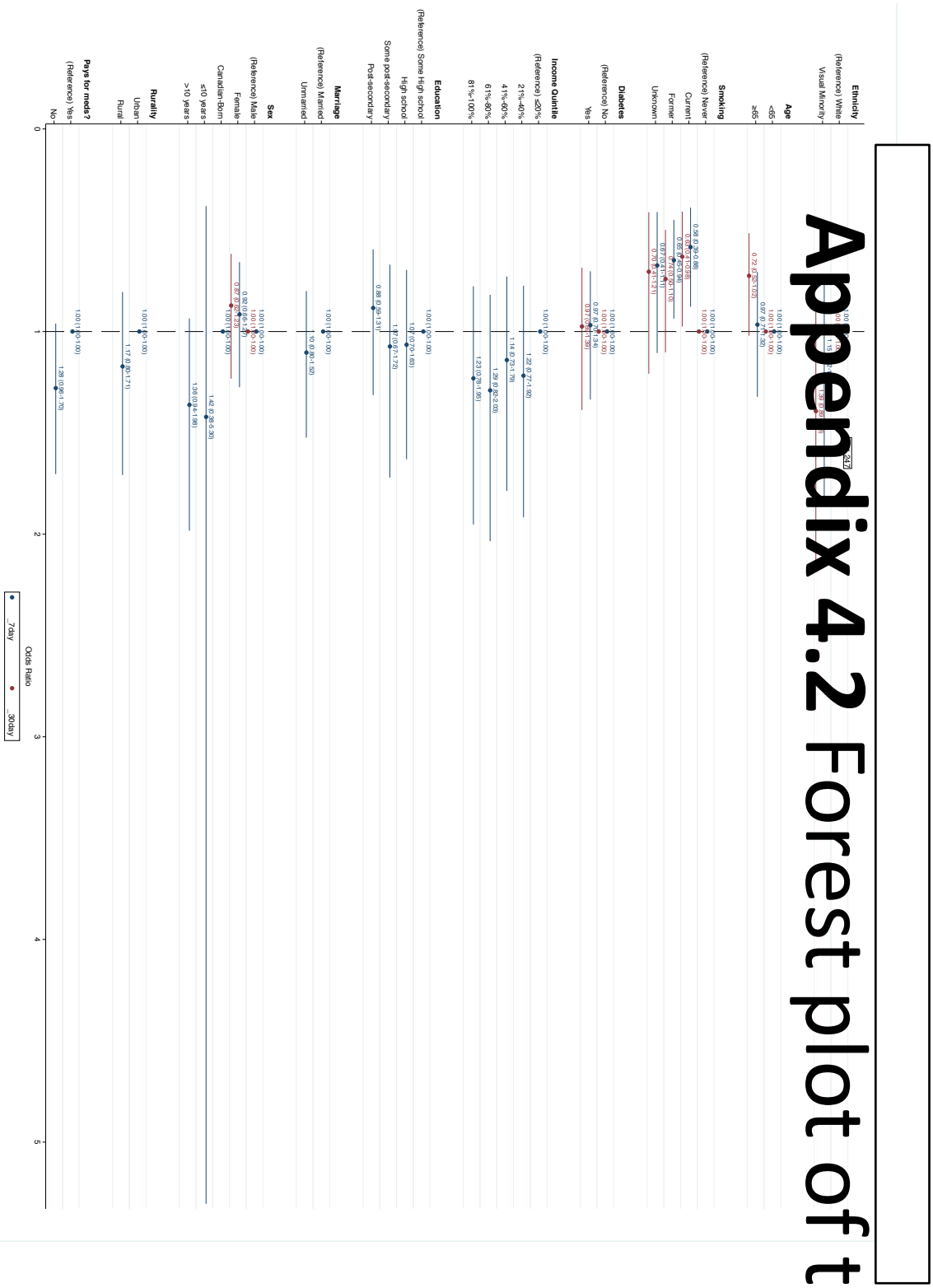
Appendix 4.0 Baseline characteristics and outcomes of the actual and evaluable sample size

	Actual Sample (n=2,192)	Evaluable Sample (n=1,624)
7-day Statin Adherence, n(%)	56.37 (1,036)	79.69 (1,032)
30-day Statin Adherence, n(%)	60.17 (1,106)	85.10 (1,102)
Cardiac Rehabilitation, n(%)	31.86 (568)	34.48 (559)
AGE (Year)		
mean (95% CI)	65.37 (64.87-65.89)	65.16 (64.58-65-74)
≥65, % (n)	51.60 (1,131)	51.54 (837)
SEX		
Female, % (n)	27.74 (608)	27.46 (446)
RURALITY		
Urban , % (n)	82.57 (1,810)	80.97 (1,315)
Rural, % (n)	17.43 (382)	19.03 (309)
INCOME QUINTILE		
1-20%, % (n)	20.58 (448)	19.25 (311)
21-40%, % (n)	21.04 (458)	20.73 (335)
41-60%, % (n)	19.02 (414)	19.25 (311)
61-80%, % (n)	20.40 (444)	21.29 (344)
81-100%, % (n)	18.97 (413)	19.49 (315)
EDUCATION LEVEL		
Less than high school (less than high school graduation), % % (n)	22.55 (364)	22.55 (364)
High school graduate (no Post-Secondary education), % (n)	24.02 (388)	24.04 (388)

Some Post-Secondary (received some college or university education), n (%)	16.98 (274)	16.98 (274)
Post-Secondary graduate (received degree/diploma), % (n)	36.43 (588)	36.43 (588)
MARITAL STATUS		
Married, % (n)	64.70 (1,041)	64.70 (1,041)
Living common-law, % (n)	5.10 (82)	5.10 (82)
Widowed, % (n)	10.81 (174)	10.81 (174)
Separated, % (n)	3.05 (49)	3.05 (49)
Divorced, % (n)	8.70 (140)	8.70 (140)
Single, never married, % (n)	7.64 (123)	7.64 (123)
PRESCRIPTION PAYMENT		
Yes, majority or all of costs, % (n)	11.95 (193)	11.93 (192)
Yes, but only co-pay, % (n)	32.38 (523)	32.44 (522)
Yes, for some meds but not for other meds, % (n)	7.49 (121)	7.46 (120)
No, none, % (n)	48.17 (778)	48.17 (775)
HISTORY OF DIABETES		
Yes, % (n)	30.38 (658)	28.51 (457)
HISTORY OF SMOKING		
Never, % (n)	36.34 (786)	36.81 (589)
Current, % (n)	24.64 (533)	23.00 (368)
Former, % (n)	28.43 (615)	29.50 (472)
Unknown, % (n)	10.59 (229)	10.69 (171)
Group Allocation		
Arm 1 - Usual Care	36.09 (791)	35.96 (584)
Arm 2 - Postal reminders	35.36 (775)	34.48 (560)
Arm 3 - Postal reminders + interactive voice response phone calls	28.56 (626)	29.56 (480)

Appendix 4.1 Frequencies and column proportions of included subjects categorized by *a priori* ethnic categories

VARIABLE	FOREIGN-ORIGIN IMMIGRANT (n= 583)	CANADIAN-ORIGIN (n=1,041)	SUBJECTS WITH RECORDED ORIGIN RESPONSE (n= 1,624)
ETHNICITY			
White, n (%)	291 (50.43)	985 (94.62)	1,276 (78.86)
Chinese, n (%)	5 (0.87)	1 (0.10)	6 (0.37)
South Asian (e.g. East Indian, Pakistani, Sri Lankan), n (%)	137 (23.74)	1 (0.10)	138 (8.53)
Black, n (%)	41 (7.11)	3 (0.29)	44 (2.72)
Filipino, n (%)	12 (2.08)	2 (0.19)	14 (0.87)
Latin American, n (%)	11 (1.91)	–	11 (0.68)
Southeast Asian (e.g. Cambodian, Indonesian, Laotian, Vietnamese), n (%)	9 (1.56)	–	9 (0.56)
Arab, n (%)	7 (1.21)	_	7 (0.43)
West Asian (e.g. Afghan, Iranian), n (%)	15 (2.60)	1 (0.10)	16 (0.99)
Japanese, n (%)	–	–	–
Korean, n (%)]	2 (0.35)	–	2 (0.12)
Aboriginal (e.g. North American Indian, Métis or Inuit), n (%)	–	23 (2.21)	23 (1.42)
Other, n (%)	34 (5.89)	11 (1.06)	45 (2.78)
Don't know, refuse, n (%)	13 (2.25)	14 (1.34)	27 (1.67)



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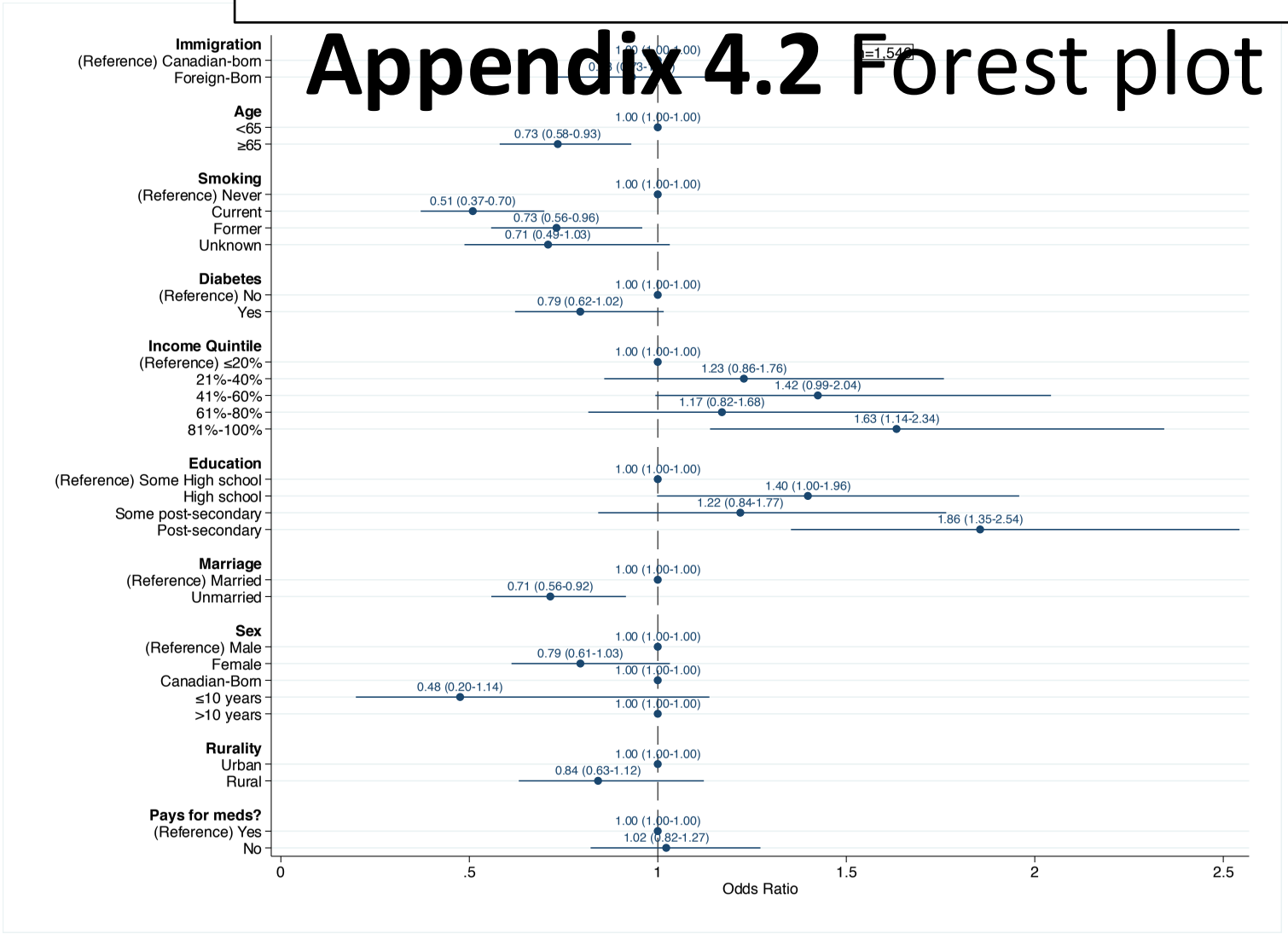


Appendix 4.4 Univariable logistic regression analysis of duration of Canadian residency exposure on 7-day statin adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for 7-day statin adherence after stepwise model selection (adjusted)

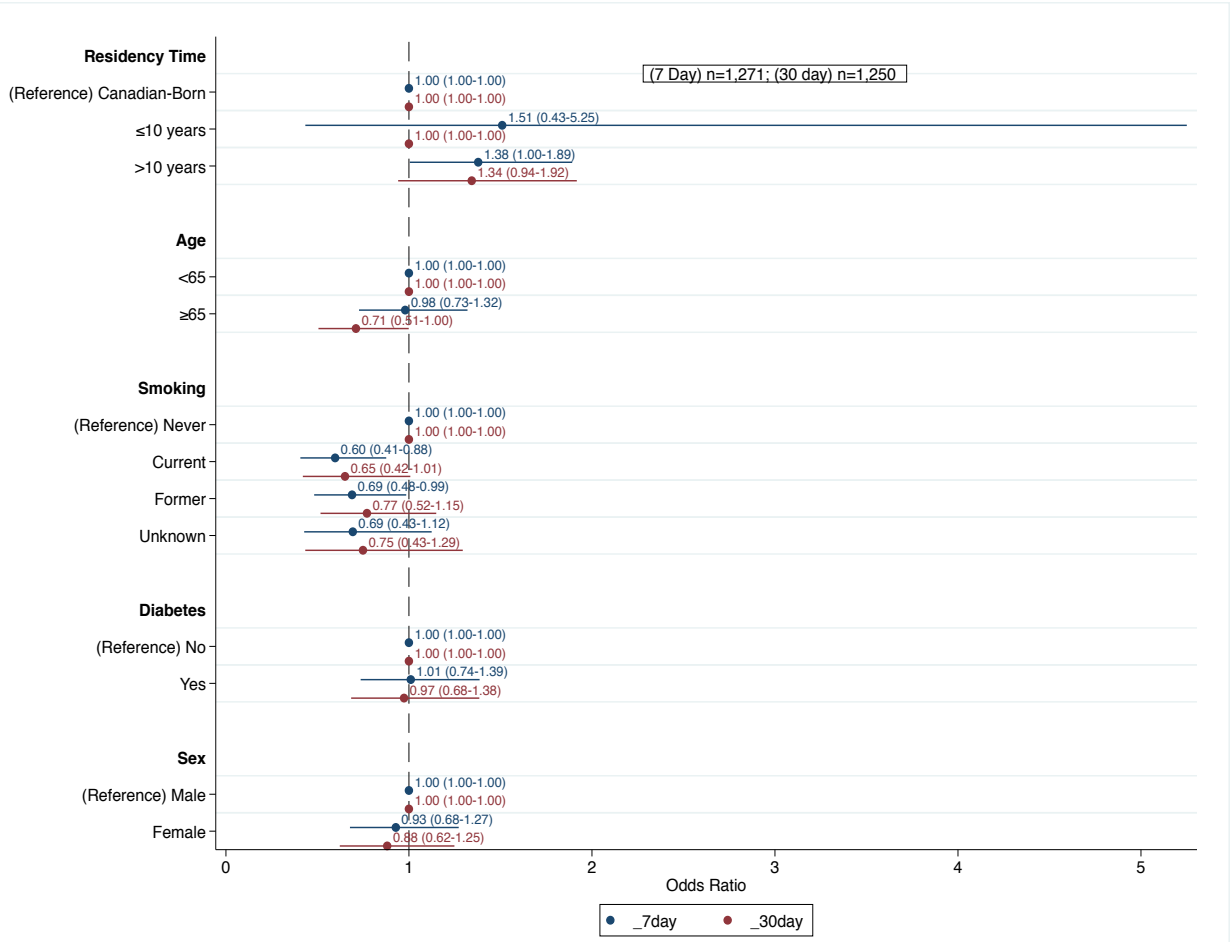
	Unadjusted (n= 1,288)			Adjusted (n= 1,271)		
Covariate	**OR**	**P-value**	**[95% Conf. Interval]**	**OR**	**P-value**	**[95% Conf. Interval]**
Canadian-Born	1.00	–	–	1.00	–	–
<10 years	1.73	0.87	0.50–5.94	1.65	0.43	0.48–5.73
≥10 years	1.51	0.01	1.11–2.05	1.44	0.02	1.05–1.97

Appendix 4.5 Univariable logistic regression analysis of duration of Canadian residency exposure on 30-day statin adherence outcomes (unadjusted); multivariable logistic regression of the risk factors for 30-day statin adherence after stepwise model selection (adjusted)

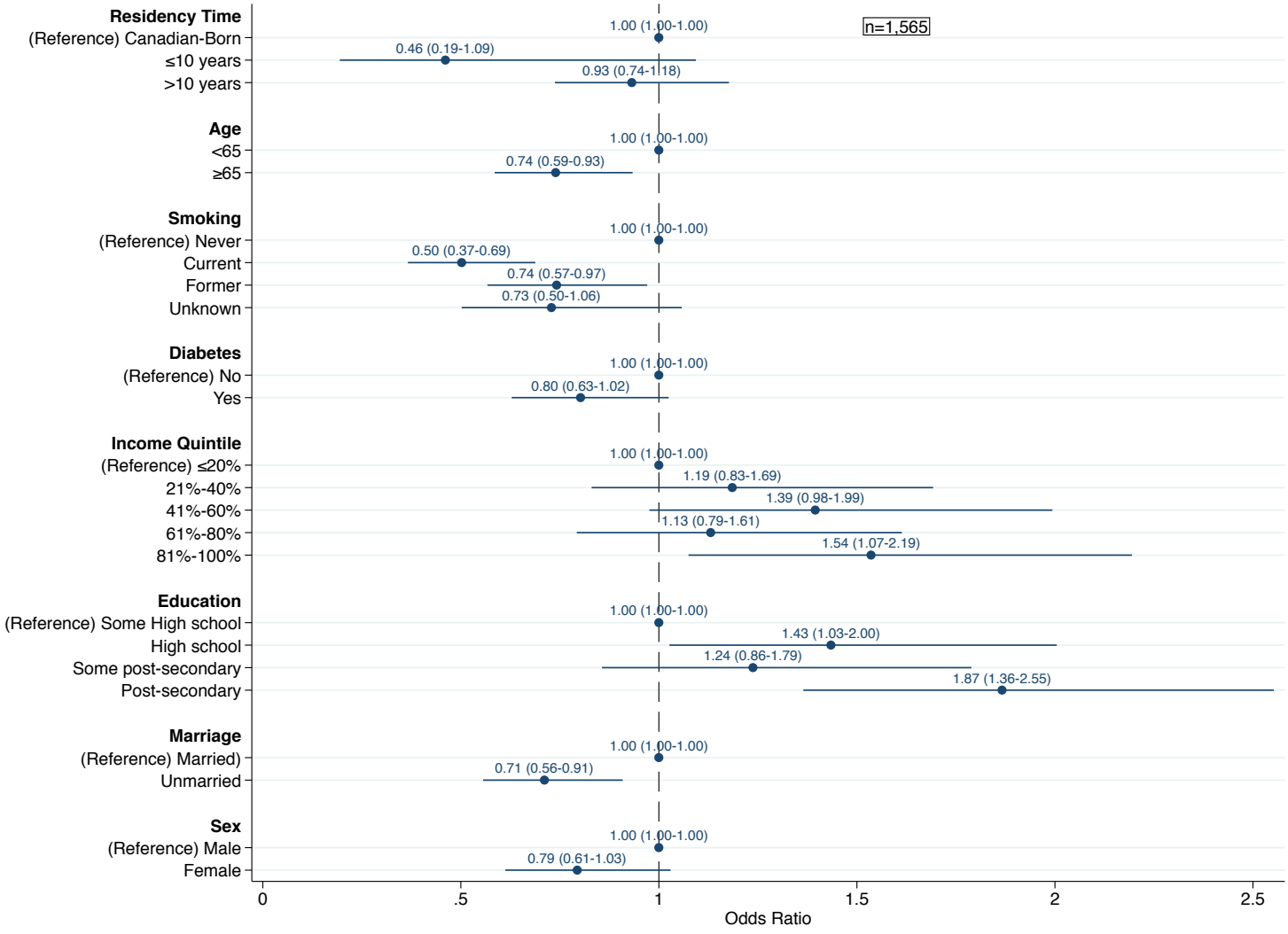
	Unadjusted (n= 1,267)			Adjusted + Sex (n=1,250)		
Covariate	**OR**	**P-value**	**[95% Conf. Interval]**	**OR**	**P-value**	**[95% Conf. Interval]**
Canadian-Born	1.00	–	–	1.00	–	–
<10 years	1.00	–	–	1.00	–	–
≥10 years	1.41	0.05	1.00-1.99	1.39	0.07	0.98–1.98

Appendix 4.6 Univariable logistic regression analysis of duration of Canadian residency exposure on cardiac rehab completion outcomes (unadjusted); multivariable logistic regression of the risk factors for cardiac rehab completion after stepwise model selection (adjusted)

	Unadjusted (n= 1,608)			Adjusted + Sex (n=1,559)		
Covariate	**OR**	**P-value**	**[95% Conf. Interval]**	**OR**	**P-value**	**[95% Conf. Interval]**
<10 years	0.89	0.77	0.40–1.97	0.46	0.08	0.20–1.10
≥10 years	1.12	0.301	0.90–1.39	0.93	0.57	0.74–1.18

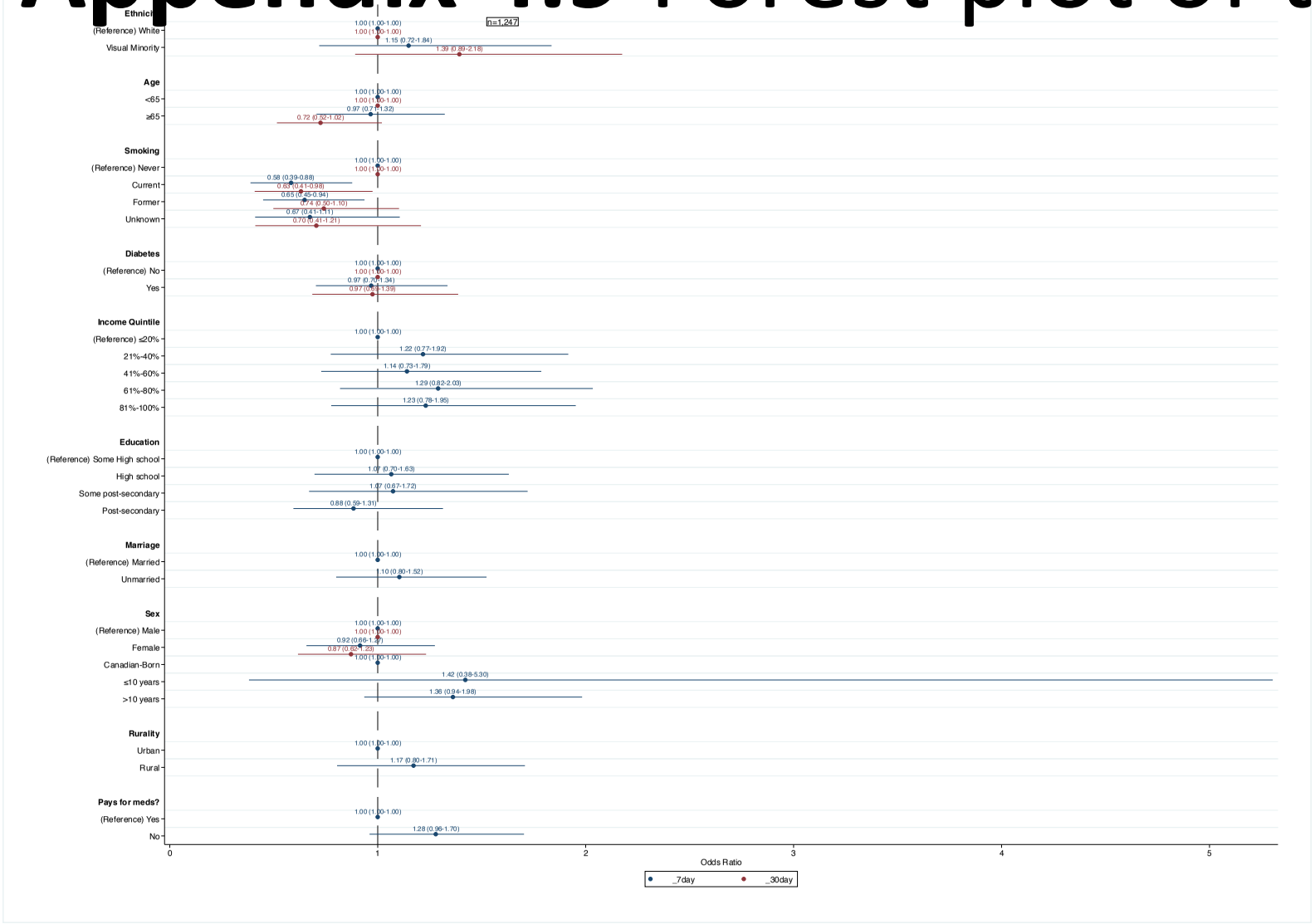


Appendix 4.7 Multivariable logistic regression of risk factors for 7- & 30-day statin adherence after stepwise model selection controlling for duration of Canadian residency with the addition of sex as a risk factor

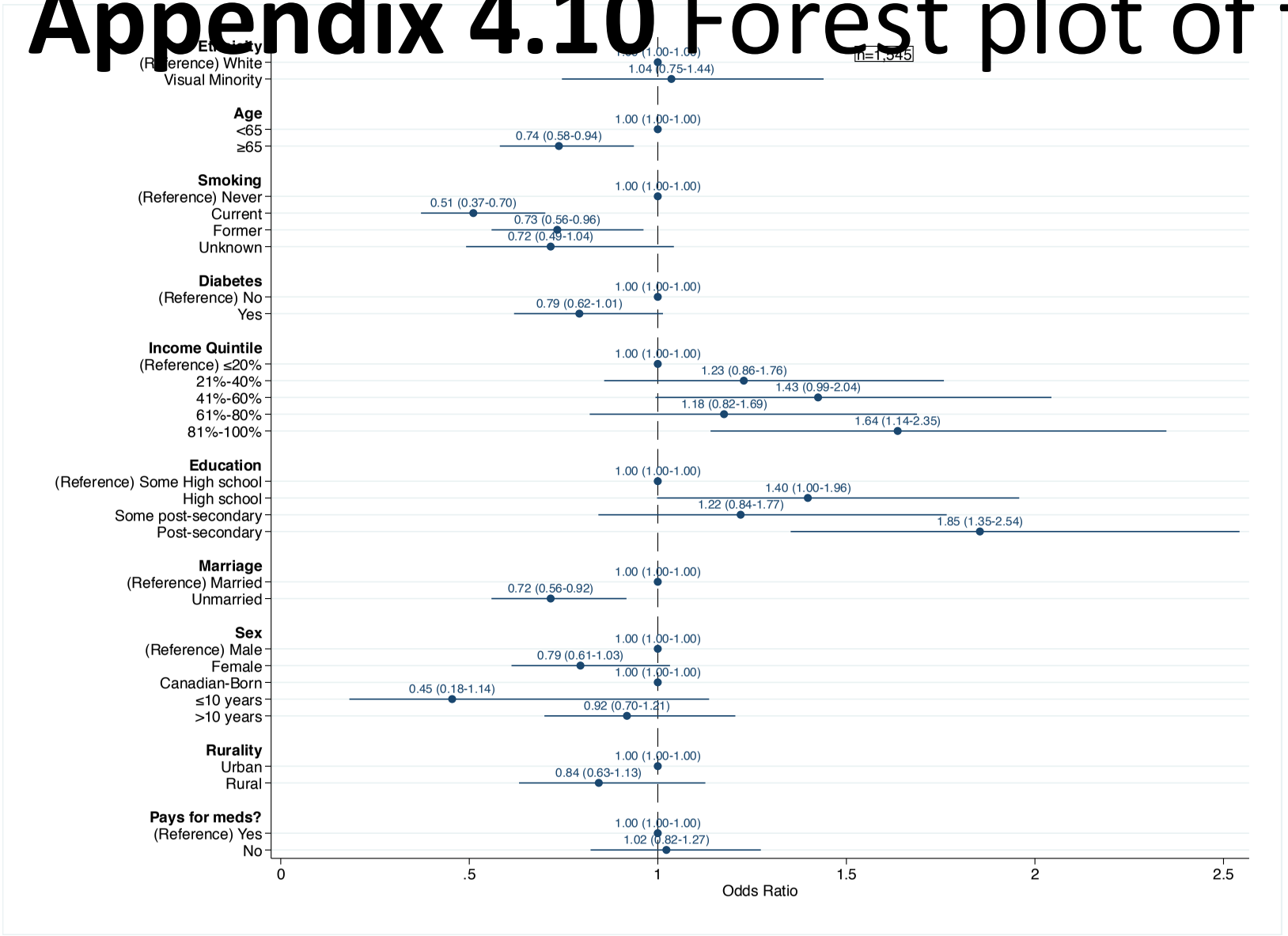


Appendix 4.8 Multivariable logistic regression of the risk factors for cardiac rehab completion after stepwise model selection controlling for duration of Canadian residency with the addition of sex as a risk factor.

Appendix 4.9 Forest plot of the co



Appendix 4.10 Forest plot of the



Appendix 4.11 Stata logistic regression output for interaction effect between ISLAND allocation and immigration exposure on 7 and 30-day statin adherence

```
. *7-day statin adherence outcome
.         logistic stad_7d  i.birth_origin##i.a2alloc i.age_cat i.indiab i.insmk i.insex

Logistic regression                               Number of obs   =       1277
                                                  LR chi2(11)     =      22.48
                                                  Prob > chi2     =     0.0209
Log likelihood =  -627.2184                       Pseudo R2       =     0.0176
```

stad_7d	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
birth_origin						
Foreign-Born	1.731204	.4596971	2.07	0.039	1.028782	2.913217
a2alloc						
Arm 2	1.570033	.3340173	2.12	0.034	1.034712	2.382309
Arm 3	.9790806	.1925634	-0.11	0.914	.6658954	1.439564
birth_origin#a2alloc						
Foreign-Born#Arm 2	.5908489	.2280453	-1.36	0.173	.2772968	1.258948
Foreign-Born#Arm 3	.7622863	.2847498	-0.73	0.467	.3665678	1.585192
age_cat						
≥65	.9552554	.1447388	-0.30	0.763	.7098177	1.28556
indiab						
Yes	1.018809	.1647713	0.12	0.908	.7420425	1.398805
insmk						
Current	.5809133	.1141297	-2.76	0.006	.3952566	.8537751
Former	.6835065	.1246222	-2.09	0.037	.4781289	.9771028
Unknown	.6688372	.1639532	-1.64	0.101	.4136795	1.081377
insex						
Female	.9365304	.1507621	-0.41	0.684	.6831183	1.283949
_cons	4.478186	.9223274	7.28	0.000	2.990809	6.705261

```
.
. *30-day statin adherence outcome
.         logistic stad_30d  i.birth_origin##i.a2alloc i.age_cat i.indiab i.insmk i.insex

Logistic regression                               Number of obs   =       1277
                                                  LR chi2(11)     =      17.50
                                                  Prob > chi2     =     0.0939
Log likelihood = -524.85277                       Pseudo R2       =     0.0164
```

stad_30d	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
birth_origin						
Foreign-Born	1.677576	.5046133	1.72	0.085	.9303394	3.024982
a2alloc						
Arm 2	1.416985	.3330973	1.48	0.138	.8938596	2.246266
Arm 3	1.046938	.2328847	0.21	0.837	.6769815	1.619069
birth_origin#a2alloc						
Foreign-Born#Arm 2	.7137143	.3134361	-0.77	0.442	.3017929	1.687873
Foreign-Born#Arm 3	.7223953	.3046188	-0.77	0.441	.3161122	1.650854
age_cat						
≥65	.6844277	.1183577	-2.19	0.028	.4876742	.960562
indiab						
Yes	.9783621	.1759857	-0.12	0.903	.6876814	1.391913
insmk						
Current	.6344891	.1416044	-2.04	0.042	.4096889	.9826394
Former	.7557252	.1537955	-1.38	0.169	.5071522	1.126133
Unknown	.7112064	.1959695	-1.24	0.216	.41443	1.220506
insex						
Female	.8867867	.1577348	-0.68	0.499	.6257689	1.256679
_cons	7.560296	1.777065	8.61	0.000	4.76938	11.98438

```
.
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```

Appendix 4.12 Stata logistic regression output for interaction effect between ISLAND allocation and immigration exposure on cardiac rehabilitation completion

```
. logistic cr_comp i.birth_origin##i.a2alloc i.age_cat i.indiab i.insmk i.qaippe i.qamarts_bi i.qaedc i.insex

Logistic regression                             Number of obs   =       1566
                                                LR chi2(19)     =     103.56
                                                Prob > chi2     =     0.0000
Log likelihood = -957.65646                     Pseudo R2       =     0.0513
```

cr_comp	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
birth_origin						
Foreign-Born	1.108865	.2212232	0.52	0.604	.7499987	1.639445
a2alloc						
Arm 2	1.45598	.2451343	2.23	0.026	1.046752	2.025196
Arm 3	1.757966	.3007269	3.30	0.001	1.257185	2.458224
birth_origin#a2alloc						
Foreign-Born#Arm 2	.7352479	.2022349	-1.12	0.264	.4288497	1.260557
Foreign-Born#Arm 3	.762914	.219086	-0.94	0.346	.4345463	1.339415
age_cat						
≥65	.7603733	.0902505	-2.31	0.021	.6025537	.9595287
indiab						
Yes	.796682	.0998619	-1.81	0.070	.6231452	1.018546
insmk						
Current	.5260056	.0847252	-3.99	0.000	.3836056	.7212666
Former	.7520442	.1034608	-2.07	0.038	.5743032	.9847942
Unknown	.7415727	.1414488	-1.57	0.117	.510263	1.077738
qaippe						
21%-40%	1.224745	.2236493	1.11	0.267	.8562665	1.751793
41%-60%	1.469544	.2695478	2.10	0.036	1.025777	2.105292
61%-80%	1.136702	.2072973	0.70	0.482	.7950881	1.625092
81%-100%	1.618369	.2953683	2.64	0.008	1.131683	2.314357
1.qamarts_bi	.7126386	.0895734	-2.70	0.007	.5570313	.9117148
qaedc						
High school graduate (no Post-Secondary educat..)	1.437826	.2470133	2.11	0.035	1.02677	2.013445
Some Post-Secondary (received some college or ..)	1.307206	.2468436	1.42	0.156	.9028364	1.892688
Post-Secondary graduate (received degree/diploma)	1.84805	.2972923	3.82	0.000	1.348288	2.533056
insex						
Female	.8044569	.1069328	-1.64	0.102	.6199496	1.043877
_cons	.4075296	.100927	-3.62	0.000	.2508154	.6621616

Appendix 4.13 Stata version 13.1 output of missing outcomes by immigration exposure

```
. tab stad_7d birth_origin, missing column
```

Key
frequency *column percentage*

Statins adherence in the Past 7 days	birth_origin Canadian-	Foreign-B	.	Total
No	190 18.25	73 12.52	539 94.89	802 36.59
Yes	659 63.30	373 63.98	4 0.70	1,036 47.26
.	192 18.44	137 23.50	25 4.40	354 16.15
Total	1,041 100.00	583 100.00	568 100.00	2,192 100.00

```
. tab stad_30d birth_origin, missing column
```

Key
frequency *column percentage*

Statins adherence in the past 30 Days	birth_origin Canadian-	Foreign-B	.	Total
No	139 13.35	54 9.26	539 94.89	732 33.39
Yes	710 68.20	392 67.24	4 0.70	1,106 50.46
.	192 18.44	137 23.50	25 4.40	354 16.15
Total	1,041 100.00	583 100.00	568 100.00	2,192 100.00

```
. tab cr_comp birth_origin, missing column
```

Key
frequency *column percentage*

Cardiac Rehab Completion	birth_origin Canadian-	Foreign-B	.	Total
No	689 66.19	373 63.98	153 26.94	1,215 55.43
Yes	350 33.62	209 35.85	9 1.58	568 25.91
.	2 0.19	1 0.17	406 71.48	409 18.66
Total	1,041 100.00	583 100.00	568 100.00	2,192 100.00