RECEIPT OF CARDIAC CARE FOLLOWING HOSPITALIZATION FOR AN ACUTE MYOCARDIAL INFARCTION FOR INDIVIDUALS WITH A HISTORY OF DEPRESSION OR SCHIZOPHRENIA

by

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Abstract

Background: The goal of this study was to improve upon methodological limitations of previous studies to determine the existence and source of differences in the cardiac care of individuals with a history of depression or schizophrenia. The selected outcomes were three cardiac procedures: catheterization, percutaneous transluminal coronary angiography (PTCA), and coronary artery bypass graft (CABG); and three cardiac pharmaceuticals: beta-blockers, angiotensin converting enzyme (ACE) inhibitors and statins.

Methods: This population-based retrospective cohort study consisted of 309, 790 individuals diagnosed with an AMI and admitted to an acute care hospital in Ontario between April 1, 1995 and March 31, 2009. The time-to-intervention for the depression and schizophrenia was estimated and compared to those without a mental disorder using Cox Proportional Hazards regression. Subgroup analyses were performed to evaluate the interaction between well-established confounders and the receipt of a cardiac intervention.

Results: Persons with a history of depression were found to be more likely to receive a catheterization (HR=1.42, 95% CI=1.34-1.50) or PTCA (HR=1.48, 95% CI=1.40-1.57) if they had no previous CVD history, but were less likely to receive a catheterization (HR=0.71, 95% CI=0.51-0.99) or PTCA (HR=0.64, 95% CI=0.39-1.06) if they had a CVD history. In addition individuals with depression were less likely to receive a CABG, especially if they had a history of CVD (HR=0.38, 95% CI=0.24-0.60). Persons with a history of schizophrenia were found to be just as likely to receive a catheterization (HR=0.90, 95% CI=0.70-1.15) or a PTCA (HR=0.83, 95% CI=0.62-1.11). The likelihood of receiving a beta-blocker or statin was comparable or higher for persons with a history of depression (HR=1.07, 95% CI=1.03-1.11; 1.27, 95%

CI=1.22-1.32, respectively) and comparable for persons with a history of schizophrenia (HR=0.90, 95% CI=0.79-1.02; HR=0.97, 95% CI=0.83-1.14, respectively), with a small but significant prior drug use effect modification.

Interpretation: Persons with depression or schizophrenia with no CVD history are just as likely to receive most recommended cardiac care interventions compared to those without a mental disorder. The source of the differences in care for individuals with a CVD history with depression and schizophrenia needs to be further explored.

Co-Authorship

This thesis is the work of Rachael Morkem in collaboration with her supervisors Dr. Linda Lévesque and Dr. Heather Stuart and with help from statistician Lindsey Colley and Ph.D. candidate Michelle Koller.

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List of Abbreviations

Acronym	Name
ACE	Angiotensin Converting Enzyme
ACC	American College of Cardiology
AHA	American Heart Association
AMI	Acute Myocardial Infarction
CABG	Coronary Artery Bypass Graft
CAPE	Client Agency Program Enrolment Data
CCAC	Community Care Access Center
CCI	Canadian Classification of Health Interventions
CCP	Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures
CI	Confidence Interval
CVD	Cardiovascular Disease
DAD	Discharge Abstract Database
DSM-IV	Diagnostic Statistical Manual
ED	Emergency Department
HCD	Home Care Database
HPA	Hypothalamic Pituitary Adrenal Axis
ICD	International Classification of Diseases
ICES	Institute for Clinical Evaluative Sciences
IHD	Ischemic Heart Disease
IKN	ICES Key Number
LVEF	Left Ventricular Ejection Fraction
MHD	Mental Health Disorder
NACRS	National Ambulatory Care Reporting System
OBD	Ontario Drug Benefit Claims Database
OHIP	Ontario Health Insurance Plan
OMHRS	Ontario Mental Health Reporting System
OR	Odds Ratio
PTCA	Percutaneous Transluminal Coronary Angioplasty
RPDB	Registered Persons Database
RR	Rate Ratio
SDS	Same Day Surgery
SES	Socioeconomic Status
WHO	World Health Organization

Chapter 1: Introduction

> *My contacts with my GP and my psychiatrist have not been very useful. Both of these doctors focus too much on medication and keep on relating my worries about my physical health to my mental illness. They only focus on my physical health when I make a fuss or when I am really, really sick* (1).

Coping with the effects of depression or schizophrenia can be a difficult, lifelong struggle. Yet individuals with a mental disorder also have to deal with the stigma that accompanies their diagnosis. Stigma is the occurrence of labeling, stereotyping, separating or status loss that elicits negative attitudes towards its bearer and leads to negative discrimination and, by extension, unfair or inequitable treatment (2). One place that a person with a mental disorder should reasonably expect to escape discrimination is in the office of a healthcare provider. However, some evidence suggests that the quality of care that a patient receives for their physical ailments, including cardiovascular disease (CVD), may be inadequate if they also have a mental disorder (3, 4).

CVD is the leading cause of morbidity and mortality in Canada accounting for 72, 743 deaths, 447, 218 hospitalizations and 3.9M inpatient days each year (5). In addition, individuals with mental disorders have an even greater risk of dying from CVD than those without a mental disorder (6). Although the mechanism behind this increased mortality and medical morbidity is unclear, research indicates that the pathways are complex and bidirectional (7).

This increased morbidity from CVD in persons with a mental disorder has a substantial public health impact given that 20% of Canadians will be diagnosed with a mental disorder during their lifetime (8). Depression is one of the most common mental disorders, especially among the elderly, with prevalences of 19-30% (9, 10). The World Health Organization (WHO) reports that the leading cause of years lived with disability is major depression, and by the year

2020, major depression and ischemic heart disease will be the foremost contributors to the global burden of disease (11). This mental and medical comorbidity also has significant impact on healthcare spending as individuals with a mental disorder and heart disease have higher health care utilization and worse health outcomes than individuals with heart disease and no mental disorder (12). It is important that there is judicious use of preventive and therapeutic interventions for CVD in this population as individuals with a mental disorder are at an increased risk of developing and dying from CVD.

Health disparities exist when membership in a group is associated with interventions that are unjustified by a person's underlying need (13). Empirical evidence suggests that treatment disparities may account for the excess cardiovascular morbidity and mortality among persons with a mental disorder (14). The primary goal of this thesis is to determine whether treatment disparities exist in the cardiac care of persons with depression or schizophrenia and comorbid CVD.

Chapter 2: Literature Review

2.1 Mental Disorders and Cardiac Treatment Disparities

Studies that have examined the association between mental disorders and treatment disparities among persons receiving care for CVD have produced mixed results (**Appendix II**). Of the thirteen studies published to date, one was cross sectional (15) and lacked temporality, thus it will not be discussed in further detail. The remaining twelve were cohort studies with four being population-based (16-18) and three restricting the study population to persons older than 65 years (3, 19, 20). One of the three cohort studies of a general adult population described their results in a brief *Letter to the Editor* and will not be further considered because of insufficient details on methods (18). The remaining eleven studies were retrospective record linkage cohort studies that used administrative health databases, and most were published in the United States (3, 19-24).

The seven American studies were published between 2000 and 2008 and were well powered having used large Medicaid or Veterans Affairs administrative databases (3, 19-24). An important limitation was their use of cumulative risks (i.e., proportions) to compare cardiac care across exposure groups (i.e., with and without a mental disorder) as opposed to a more sensitive 'time to receipt of treatment' analysis as, in some cases, it is the timing of the cardiac intervention that may reflect a disparity. For example, the timing of a revascularization procedure could be delayed while a person with a mental disorder waits for a psychiatric assessment to determine whether their symptoms are psychosomatic or physical. Three studies (3, 23, 25) examined the use of invasive surgical procedures as the only outcome of interest. Such 'hard' endpoints do not necessitate as much physician judgment as 'soft' endpoints such as pharmaceutical interventions because the latter involve more physician discretion. This may explain why, for example, Jones

and Carney found that individuals with any mental disorder were as likely to undergo Percutaneous Transluminal Coronary Angioplasty (PTCA) (OR=1.10; 95% confidence interval (CI)=0.95-1.29) or Coronary Artery Bypass Graft (CABG) (OR=0.89, 95% CI=0.71-1.11) (23). Finally, because all of these studies were carried out within the American healthcare system, with numerous financial barriers to care for people with mental disorders, results may not be generalizable to Canada.

Using administrative data from the state of Western Australia, Lawrence et al (16) compared the cardiac care of individuals with and without a mental disorder and found a small difference in the admission rate for ischemic heart disease (IHD) (RR=1.10, 95% CI=1.06-1.15). They also reported that individuals with a history of psychosis had significantly lower rates of revascularization procedures than the general population in both males and females (RR=0.3, 95% CI=0.21-0.45; RR=0.34, 95% CI=0.18-0.64, respectively), but individuals with depressive disorders had equitable rates of this procedure in males and females (RR=0.86, 95% CI=0.64-1.15; RR=0.85, 95% CI=0.65-1.2, respectively). These findings illustrate that the magnitude of treatment disparities may be specific to the mental disorder studied, so studies that combine all mental disorders into a single exposure category may be limited by misclassification bias. Research has demonstrated that negative public opinions (prejudice) vary depending on the mental disorder (26). As such, studies that compare disparities across high and low stigma disorders, such as schizophrenia or depression (respectively), may be less susceptible to misclassification bias and yield different results.

Three Canadian studies have examined treatment disparities in the cardiac care of persons with mental disorders (17, 27, 28). Firstly, one study published in 2007 by Kisely et al (17) examined the prevalence of five cardiac interventions among persons with and without a mental disorder using direct standardization. Given the high prevalence of mental disorders in the general

population (20% each year) (8) direct standardization could have introduced exposure misclassification because the comparison group, the standard population, would include exposed and unexposed individuals (13, 16, 17). Similar to other studies, Kisely et al. used a dichotomous outcome (cardiac intervention received or not) rather than a time to intervention approach and only used 'hard' endpoints (cardiac surgical interventions), thereby decreasing the study's ability to detect differences in care. Contrary to their results showing comparable care (PTCA: RR=0.97, 95% CI=0.86-1.09; CABG: RR=0.92, 95% CI=0.83-1.02) Kisely et al. concluded that treatment disparities did exist. Their rationale was that individuals with a mental disorder should have had higher rates of cardiac interventions given the higher incidence of cardiac mortality and morbidity in this population. In addition, as this study did not restrict the cohort to individuals who experienced a cardiovascular event, for which the intervention was indicated, it cannot be used to draw conclusions about cardiac treatment disparities. Due to some of the limitations listed above Kisely et al. conducted a second study published in 2009(27). In this second study Kisely et al. compared the quality of care of persons with and without a psychotic disorder after admission to hospital for IHD or stroke. The authors further improved upon their 2007 study by using 'hard' endpoints, such as PTCA and CABG, as well as 'soft' endpoints, medications like beta-blockers and statins, which are seen in Canada as indicators of the quality of vascular care. Kisely et al. found that individuals with psychosis were significantly less likely to undergo cardiac catheterization (OR=0.47, 95% CI=0.38-0.58), PTCA (OR=0.41, 95% CI=0.29-0.59) and CABG (OR=0.28, 95% CI=0.20-0.39). In terms of the 'soft' endpoints, Kisely et al. found that individuals with psychosis were slightly less likely to receive beta-blockers (OR=0.82, 95% CI=0.71-0.95) and statins (OR=0.51, 95% CI=0.41-0.63). Kisely et al. reveal that small changes in the methods can have a significant impact on a study's findings, as the 2009 results are significantly different than the results reported in 2007.

The third Canadian study, recently published in the *Canadian Medical Association Journal* (CMAJ) by Atzema et al. (28), calculated the odds of low-priority triage for patients with acute myocardial infarction (AMI) who had a charted history of depression compared to the odds for patients having a charted history of asthma or chronic obstructive pulmonary disorder (COPD). Atzema et al. found that patients with a charted history of depression were more likely to receive a low-priority ED triage score than those with other comorbidities (Patients with depression: Odds=1.26, p =0.01; Patients with COPD: Odds=1.12, p=0.01; Patients with asthma: Odds=0.88, p=0.01). In addition, in a secondary analysis the authors found that the adjusted odds of missing the benchmark time for individuals with a charted history of depression were 1.39 ($p<0.001$) for door-to-electocardiogram time, 1.62 (p=0.047) for door-to-needle time and 9.12 (p=0.019) for door-to-balloon time.

As illustrated, previous studies evaluating this issue have been mixed with results dependent on the mental disorder studied and the nature of the endpoints.

2.2 Determinants of treatment disparities

Research has shown that provider factors, patient factors such as gender, age, race/ethnicity, and socioeconomic status, as well as fundamental aspects of healthcare systems such as its organization, financing, and delivery have been associated with various healthcare disparities in Canada (29) as shown in **Figure 2.1**.

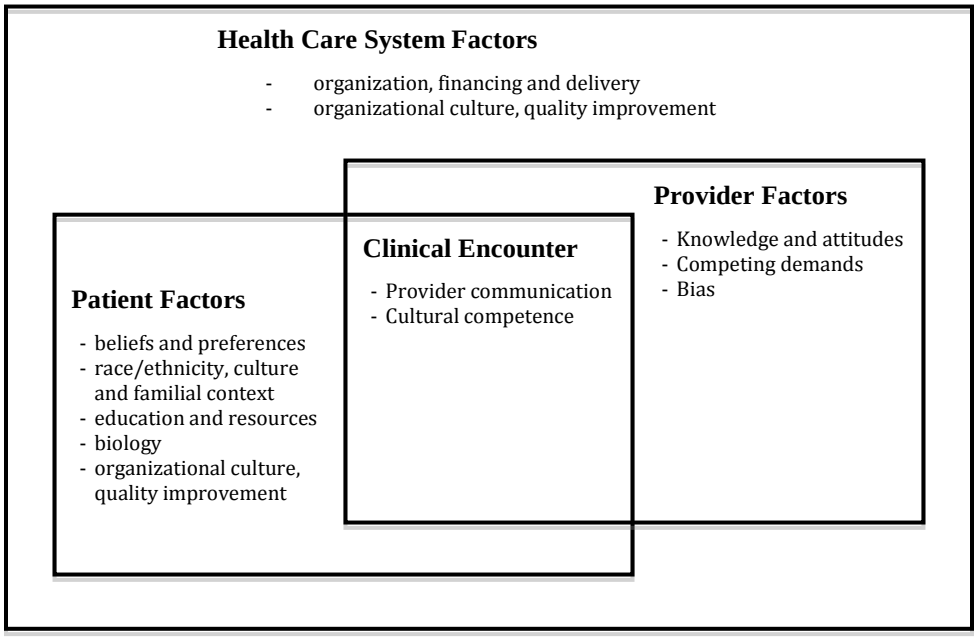

Figure 2.1. Understanding the Origins of Health Disparities

[Adapted from Kilbourne et al (30)]

2.2.1 Patient Factors

There is evidence that gender, age, race and socioeconomic status, socio-cultural beliefs, clinical knowledge, healthcare literacy, and limited English proficiency may all contribute to disparities in health care. However results have been mixed, with some well-designed studies reporting that these factors do not fully explain inequities in care (31).

2.2.1.1. Gender

Although the last decade has seen groundbreaking medical developments in cardiac care and a corresponding decline in overall cardiovascular mortality, the death rate for women has continued to rise (32, 33). There have been a number of studies that have examined whether this difference in gender mortality is due to disparities in cardiac care (34-38). For example, a study by Anand et al (37) found that women were less likely to undergo invasive coronary procedures.

In addition, one of the largest studies investigating this issue found that even accepted pharmaceutical interventions, such as beta-blockers and heparin, were used less frequently in women (33). There are several explanations for these differences including variations in symptom presentation and treatment responses, as well as patient or physician preferences (38). However, it is possible that treatment bias may also play a role. For example, although women have higher risk profiles at presentation and higher mortality rates, men are treated more aggressively than women (39).

2.2.1.2 Age

When treating the elderly a physician must discern how the patient's age will affect their diagnosis and treatment (40). This clinical judgment plays an important part in the decision-making process as age can affect treatment response and risks associated with the treatment. However, if age, in the absence of clinical indicators, is the only characteristic on which treatment, or lack of treatment is based, then a treatment disparity may exist. Naylor et al (41) found that age was a significant consideration for placing patients in a queue for coronary surgery (42). A Norwegian study found that age <75 was a strong predictor of fibrinolytic therapy following an AMI, despite clinical trial evidence that this therapy is more cost effective and saves more lives among patients >75 years (43). However, not all view this as a problem, and as such, age bias is a controversial issue.

2.2.1.3 Race/Ethnicity

The race or ethnicity of an individual has long been associated with treatment discrimination. Consequently treatment inequalities remain widespread despite an abundance of healthcare policies aimed at reducing such occurrences (44). Although there are fewer racial/ethnic healthcare disparities in Canada (45) than in the United States, Canadian racial/ethnic minorities are still at risk for worse chronic disease outcomes than their nonminority

peers (46). This was shown by a study conducted in the United Kingdom, a country with a universal health care system, which found that black and south Asian groups were significantly less likely to meet diabetes treatment targets than the nonminority group (47).

2.2.1.4 Socioeconomic Status

Most developed countries use policies and organizational approaches to minimize the barriers that individuals with lower socioeconomic status (SES) face (48). However, these initiatives have not eliminated the well-documented SES health gradient that exists, even in countries with universal healthcare insurance (48). For example, one Canadian study found that individuals from lower SES neighbourhoods were less likely to have access to hospitals with neurologists and diagnostic imaging technology than those of higher SES, and were more likely to wait longer for invasive cardiac interventions (48).

2.2.2 Provider Factors

Provider factors may play an important role in treatment disparities, especially when the intervention requires active physician participation and complex decision-making. For example, among patients with similar presentation of cardiac disease, there was significant variation in the decision to refer for cardiac catheterization based on the patient's sex and race (49). Another study reported that interventions that required a high degree of discretion were associated with lower utilization for African American patients compared with interventions that required a lower degree of discretion (50). There are many ways that a provider can consciously or unconsciously contribute to disparities including 'diagnostic overshadowing', patient stereotyping, competing demands, and cognitive overload (31).

'Diagnostic overshadowing' occurs when physical symptoms are misattributed to a mental illness (4). Several studies have found that physicians and nurses respond differently to individuals with a mental health history and are less likely to think that a person with a

psychiatric history has a serious physical illness (51, 52). 'Diagnostic overshadowing' may result from factors (1) related to the mental disorder; (2) related to the patient; or (3) related to the clinician (4). As it is too simplistic to suggest that 'diagnostic overshadowing' is only due to bias or discriminatory attitudes, many researchers are closely examining the clinical encounter between doctor and patients to uncover the complexity behind this phenomenon. It has also been suggested that the risk of 'diagnostic overshadowing' may be more problematic in certain medical settings, specifically emergency departments.

Provider behaviour can also influence patient preferences, which can further compound treatment disparities (53). In a study that taped conversations between providers and patients, providers were more likely to communicate in a verbally dominant manner with African American patients compared with Caucasian patients (54). This behaviour may lead to patient mistrust and subsequent refusal of treatment. Finally, cultural competence is another aspect of patient-provider interactions that could contribute to treatment inequalities (55). A provider shows cultural competence when they consider the patient's culture within the clinical encounter and subsequently tailor messages about health promotion and disease prevention (30).

2.2.3 Healthcare System Factors

There are many aspects of a healthcare system that may lead to treatment disparities including the coordination, continuity, and comprehensiveness of services delivered (30), how the healthcare system is accessed, language barriers between patient and provider, referral patterns, and access to specialty care; as well as fragmentation of the healthcare system (56). For example, Canadian seniors have experienced increased hospitalizations, transfers to institutional care, and mortality, which may be due to healthcare system factors (57). Health Canada has stated that there is limited coverage for non-insured health programs, including the withdrawal of some home care for chronically ill or disabled seniors, which has resulted in a decline in health of seniors living in

Canada. Although many components of healthcare delivery can contribute to treatment disparities, many studies have demonstrated disparities within single healthcare centers, indicating that system-level elements do not explain all inequities (58).

2.3 Characteristics of schizophrenia and depression exposure groups

Stigma has been identified as a possible cause of treatment disparities experienced by individuals with mental disorders. Even though there are effective treatments for depression and schizophrenia, stigma may interfere with an individual's willingness to seek help (label avoidance behaviour) and it may contribute to physician bias in the provision of care (diagnostic overshadowing)(4). Public attitudes towards people with a mental disorder vary by diagnostic group. For example, people with depression are among the least stigmatized, whereas people with schizophrenia are among the most stigmatized groups (26). Therefore, comparing the care provided to a person with depression with that of a person with schizophrenia may help elucidate whether treatment disparities are associated with stigma and studies that combine all mental disorders into a single category would be susceptible to misclassification bias.

The stigma associated with a mental disorder persists long after the symptoms resolve. For example, people who have a mental disorder describe the effects of stigma as more long lasting and life limiting than the disorder itself (59). Although depression and schizophrenia are time-dependent exposures, the stigma associated with them is not.

Cohort studies are susceptible to calendar time bias because the accrual of the cohort can take place over a significant period of time. As such, the relationship between the exposure and the outcome may change over time and this needs to be considered in the design or analysis of a study. However, there is no clear evidence that stigma because of a mental disorder has changed over time. For example, a recent study-comparing stigma in 1997 to stigma in 2007 revealed that negative encounters due to stigma still exist (60).

2.3.1 Depression

The average age of onset for major depressive disorder is in the mid to late twenties. Major depression is considered episodic as symptoms can reappear following periodic stressors (61). Although dysthymia has similar symptoms, they are generally more chronic and less severe (41). There are a number of potential confounders that were considered when using depression as an exposure (**Figure 2.2**): (a) depression is twice as prevalent in females (62); (b) a family history of depression is a strong determinant of early onset (i.e., before age 40 to 50) (63); (c) a physical illness, particularly chronic cardiac illnesses or a disability; (d) psychological factors, such as negative coping strategies and certain personality traits are also predictive of depression (64-66); (e) social factors, such as an individual's social network (e.g., marital status, level of social support, and loneliness), and; (f) the occurrence of a stressful event can also precipitate a depressive episode (65, 66). Although there are some inconsistencies in the literature, several studies indicate that a lower level of education and lower income may be risk factors for depression (66).

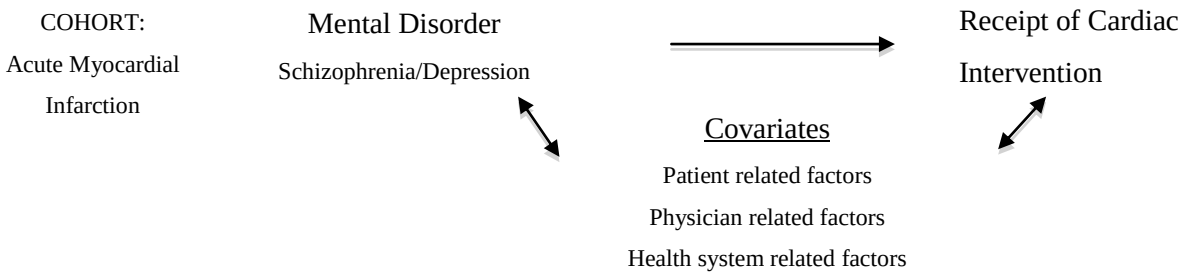

Figure 2.2: Exposure – Cohort Epidemiological Triangle

2.3.2 Schizophrenia

With respect to potential confounders relating to schizophrenia, the following were considered: (a) schizophrenia is most likely to develop in adolescence and early adulthood in males, and slightly later in females (67); (b) men may have a higher risk of developing schizophrenia in their lifetime (68); (c) individuals who have a family member with schizophrenia have a substantially increased risk of developing this disorder (68).

Antipsychotic medications have well documented cardiac side effects that may influence a physician's cardiac treatment decisions. For example, a physician treating a cardiac condition in an individual with schizophrenia on an antipsychotic medication may hesitate to prescribe cardiac medications or undertake a major cardiovascular intervention such as CABG. However, the literature indicates that most cardiac-antipsychotic drug interactions are not contraindicated but do require increased monitoring and alteration of doses or administration schedules (69).

2.4 AMI Treatment

Over the past 30 years there have been considerable advances in cardiovascular care which has significantly reduced the morbidity and mortality associated with an AMI. There are guidelines for the treatment of an acute myocardial infarction set out by the American College of Cardiology (ACC) and the American Heart Association (AHA). These are suggested diagnostic or therapeutic interventions for patients in most circumstances, although significant clinical judgment is still required to adapt these guidelines to the care of individual patients (70-72).

Specifically the ACC/AHA recommendations outline several Class I guidelines: Class I guidelines are procedures or treatments where the benefit is much greater than the risk and should be performed or administered. These Class I guidelines include: (i) aspirin at arrival and prescribed at discharge; (ii) beta-blocker at arrival and prescribed at discharge; (iii) lipid profile and lipid lowering agents prescribed at discharge; (iv) ACE inhibiters administered orally within

24hrs of admission and prescribed upon discharge; (v) rapid evaluation for reperfusion therapy the implementation of a reperfusion strategy promptly after contact with the medical system; and (vi) smoking cessation advice/counseling (70-72).

2.5 Conclusion

Previous studies on treatment disparities among patients with comorbid mental disorders and cardiac conditions have produced mixed results, in part due to methodological shortcomings previously discussed. Furthermore, the majority of these studies may not be generalizable to the Canadian population as most were conducted in the United States and elsewhere. Given that CVD is the major cause of death in persons with mental disorders, treatment disparities add to this burden. It is therefore important to determine whether the presence of mental disorders is associated with treatment disparities. This study assessed whether health care providers are treating patients with depression or schizophrenia differently than those without these mental conditions.

Chapter 3: Methods

3.1 Objectives

The primary objective of this thesis was to evaluate whether disparities exist in the treatment of adults with a mental disorder hospitalized for an AMI compared with the treatment of adults without a mental disorder. Specifically, the association between the time to receipt of cardiac reperfusion or CABG surgery ('hard' endpoint) and cardiac pharmaceutical interventions ('soft' endpoint) was evaluated for individuals with and without a history of depression and schizophrenia.

3.2 Study overview

This study used a retrospective cohort study design and Ontario's administrative health databases. Cohort members were followed from the date of their AMI hospitalization until the earliest of: a study outcome, date of death, end of follow up (discharge date or 30 days post-admission for cardiac procedures, 30 days post-discharge for cardiac pharmaceutical interventions), or end of study (March 31, 2010). The study outcomes selected *a priori* were time to: (i) receipt of cardiac reperfusion (catheterization and PTCA) or CABG surgery) and (ii) receipt of cardiac pharmaceutical interventions (beta-blocker, ACE inhibitor or statins). The analysis of each of these cardiac interventions was carried out using Cox proportional hazard regression comparing adults with a history of depression and schizophrenia prior to AMI hospitalization with persons with no history of a mental disorder.

3.3 Cohort Formation

The study population was drawn from all persons registered with OHIP between April 1, 1995 and March 31, 2009 who had a discharge diagnosis for an AMI (International Classification of Diseases version 9 [ICD-9] code 410 and version 10 [ICD-10] code I21). Individuals were

excluded if they were under the age of 18, of missing a discharge date and date of death. Cohort members were followed from their admission date (cohort entry or t_0) until the earliest of: a study outcome, date of death, end of follow up (discharge date or 30 days post-admission for cardiac procedures, and 30 days from discharge for cardiac pharmaceutical interventions) or end of study (March 31, 2010).

A hospitalization for an AMI was chosen as the cohort defining event because of the high prevalence of this cardiovascular event and its important clinical, quality of life, and socioeconomic implications. An all-diseased cohort was chosen to ensure that all cohort members had an indication for the interventions of interest, thereby minimizing the potential for confounding by indication. The study period (1995–2009) was chosen to maximize both the number of individuals with depression and schizophrenia (exposures) and the number of outcomes observed.

3.4 Data Sources and Quality

The data source for this study was Ontario's computerized health databases, access to which was made available through the Institute for Clinical Evaluative Sciences (ICES). The databases used included the: (1) Registered Persons Database (RPDP) for information on socio-demographics, (2) Ontario Health Insurance Plan Database (OHIP) for physician services claims, (3) Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and Same Day Surgery (CIHI-SDS) for information on hospitalizations including diagnostic and surgical procedural codes, and dates of admission and discharge, and the (4) National Ambulatory Care Reporting System (NACRS) for detailed information on emergency department visits (**Appendix III**).

ICES has evaluated the quality of these data sources in re-abstraction studies. Firstly, the DAD database re-abstraction study found that demographic data and most procedures were coded

with high sensitivity (>80%) and high specificity (>95%), but comorbidities were generally poorly documented (73). A similar study for the NACRS database found high agreement (85.5%) in the selection of the patients' main problem (74). However, the diagnostic code describing the main problem only matched between the original coder and the re-abstractor for 68.8% of the visits. Although the ODB database has not been validated in Ontario, similar prescription databases in Quebec have been validated and used with exemplary results (75). The OHIP database contains information on physician service claims that come from several different sources including office consultation, emergency department visits, hospital care, and laboratory and diagnostic procedures. Unfortunately, the diagnostic codes in the OHIP database have not yet been validated, although the diagnostic codes normally refer to major disease categories rather than specific diseases. Another limitation for the OHIP database is that physicians do not always remember to bill for their services leading to records that are incomplete (76). Lastly, the socio-demographic information obtained from the RPDB has been previously validated and found to be reasonably accurate, although some address information is out-of-date or incorrect (77). For example, Iron et al. (77) found that the percent difference of death counts between ICES-linked RPDB data compare to Ontario health planning (Database maintained by MOHLTC containing death counts from the Ontario Register General (ORG) adjusted by Statistics Canada for deaths occurring outside Ontario) was less than 0.4%.

A detailed description of the data contained within these databases and their use is provided in **Appendix III**.

3.5 Data Access, Linkages and Management

A copy of Ontario's administrative health databases are housed at ICES in Toronto but local access to these data was available at Queen's ICES satellite unit located in Abramsky Hall.

The research data remained on the ICES-Toronto server at all times; however, statistical programs were submitted to this server through a secure high encryption line.

Ontario residents eligible for the province's health insurance programs are assigned a unique health insurance number (OHIP number) that ensures positive identification during clinical encounters. This unique personal identifier is encrypted by ICES to create the ICES key number (IKN), which is contained in each database. The IKN allows complete record linkage at the level of the individual (i.e., deterministic matching) across databases and across time (longitudinally) while preserving confidentiality and ensuring data security.

3.5 Ascertainment and Classification of Exposure

The exposures of interest were a diagnosis of schizophrenia and depression (major depressive disorder or dysthymia), considered separately, and recorded in the health care databases anytime before cohort entry (i.e., the date of the AMI admission). An individual's exposure status was ascertained using the physicians' services claims (OHIP), emergency department (ED) visits (NACRS), and hospitalizations (CIHI-DAD) databases using the diagnostic codes described in **Appendix IV**. The exposure was identified prior to cohort entry primarily because the follow-up is such a short period of time but also because it established a clear temporal relationship between exposure and outcome, which is one of Hill's main criteria of causation (78). In addition, this study is evaluating the association between the label associated with a person with a mental disorder and the receipt of a cardiac intervention. By establishing the exposure prior to cohort entry there is time for the negative construct or label associated with a mental diagnosis to form, which is derived from specific social psychological processes (79).

There are several types of mood disorder diagnoses recognized by the Diagnostic Statistical Manual (DSM-IV) including major depressive disorder, bipolar disorder, cyclothymic disorder, and dysthymic disorder (67). Only major depressive disorder and dysthymic disorder

were considered as they are, by far, the most common depression diagnoses and are not used as a diagnosis when there is any history of psychoses, a medical cause for the symptoms, or if symptoms are of short duration (< 2 months) (67, 80). An individual's exposure status was determined using the following validated algorithm: cohort members were classified as having a history of either depression or schizophrenia (i.e., 'exposed') if they were assigned the corresponding diagnostic code on two separate visits to a physician or ED within a one-year period, or had at least one hospitalization with a discharge diagnosis of depression or schizophrenia (81, 82). The use of two diagnostic codes within a one-year period for claims arising from physician or ED visits reduced the potential for misclassification as the first code could represent a provisional diagnosis that is not subsequently confirmed (81, 82); thus, individuals were considered "exposed" on the date of the second diagnostic code. Those who had only one diagnostic code for depression or schizophrenia, or at least one diagnostic code for any other mental disorder prior to cohort entry were classified as exposed to "other mental disorders". Cohort members who did not fulfill any of these exposure definitions were classified as having "no history of a mental disorder" (i.e., unexposed) prior to cohort entry.

3.6 Ascertainment of Outcomes

The outcomes of interest were the receipt of cardiac reperfusion or CABG surgery during the AMI hospitalization ('hard' endpoint), and in separate analyses, the dispensing of cardiac pharmaceutical interventions ('soft' endpoint) within 30 days of discharge.

The 'hard' endpoints studied included three quality of cardiac care procedures: catheterization, PCTA, and CABG (17). These procedures were identified using the CIHI-DAD database and standardized procedural codes corresponding with the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP; prior to 2000) and the Canadian Classification of Health Interventions (CCI; after 2000) (**Appendix IV**).

The ‘soft’ endpoints included the receipt of an outpatient prescription for a beta-blocker, statin and/or angiotensin-converting enzyme (ACE) inhibitor within 30 days of discharge. These endpoints were identified using Ontario’s Drug Benefit Plan claims database (ODB). This analysis was restricted to cohort members 66 years of age and older at the time of their MI admission, given the age restriction of 65 years for the universal drug insurance program in Ontario, and discharged alive.

The choice of the study outcomes was based on clinical practice guidelines for the management of AMI and endpoints used in previous studies (17).

3.7 Covariates

There are several factors that are associated with the time to receipt of a cardiac intervention that could also be associated with a history of depression or schizophrenia (exposure) and therefore could have confounded the relationships under study. These include age, gender, rurality, SES, comorbidities, pharmaceutical contraindications and previous contact with the medical system. All of these factors were measured using data in Ontario’s health administrative databases. However, some of these measures were approximations, such as using neighborhood income level obtained from linking an individual’s postal code to census data to estimate SES.

Some variables, including some patient and provider behaviors and race/ethnicity could not be adjusted for because information on these potentially confounding factors was not captured by the health care databases.

Age was modeled as a continuous variable after testing the linearity assumption. This was done by dividing age into ten-year age categories, recording the mean age in each category and treating age as a categorical predictor in Cox regression (used dummy codes for each category). Next, the betas from each age category were plotted against the mean age of each age category. If the plot was linear the linearity assumption was met and was kept in the model as a continuous

variable. Both the healthcare utilization variable and Charlson's Index were categorized into clinically relevant categories to simplify the interpretation of the models.

3.7.1 Modeling Strategy

The modeling strategy used in this analysis was the 'change in estimate' method, proposed by Greenland (83), which uses the data to decide whether to adjust for a variable. This method involved starting with a fully adjusted model and following a cycle of removing variables for which its deletion from the model resulted in the smallest change in the estimates exposure effect; if this change is less than 10% and had a minimal effect on the width of the confidence limits the variable was deleted from the model. Variables established as strong risk factors *a priori* were the first to be considered for removal: age, sex, SES, cardiovascular comorbidities, prior healthcare utilization and indicators of overall health (e.g. Charlson's Index). Next, the size of the variable coefficient determined the order of removal, with coefficients closest to 1.0 being removed first and larger magnitude coefficients being removed last. If a variable was established as a strong risk factor it was forced into the model as it can introduce bias even if not determined to be a confounder. In addition, a parsimonious model didn't give any increased power due to the large size of the cohort. Thus, the final model was adjusted for age, sex, SES, as well as an individual's CVD history, several common chronic comorbidities, indicators of overall health (e.g. Charlson index) and measures of health care utilization, without concern of a reduction in power.

3.8 Statistical Analysis

All data manipulation, variable formation and statistical analyses were executed using Statistical Analytical Software (SAS), version 9.2 (84).

3.8.1 Descriptive Analysis

The distribution of socio-demographic factors, medical history, and health care utilization profiles of cohort members with depression, schizophrenia, other mental disorders, and no history of mental disorders (i.e., unexposed) were examined. This descriptive analysis of the cohort was used to identify unexpected sources of potential confounding (i.e., not identified *a priori*).

3.8.2 Primary Analysis

Cox Proportional Hazards regression models were employed to estimate hazard ratios and 95% CIs for the associations between depression and schizophrenia and the receipt of an indicated cardiac intervention, adjusted for the effect of potential confounders (85). The exposure, depression and schizophrenia, were modeled as time-fixed, even though they are time-independent, for several reasons. First, while administrative databases can detect a mental health diagnosis, they cannot detect disease resolution. Secondly, mental health literature indicates that the label and stigma associated with a mental disorder diagnosis does not change over time (26). As we examined whether individuals with a mental disorder could be receiving inadequate care because of the stigma associated with a mental disorder, the exposure, a diagnosis or depression or schizophrenia, can be treated as a time-independent variable.

3.8.2.1 Proportionality Assumption

An important consideration in the time-to-event analysis was assessing if the proportionality assumption of the Cox Proportional Hazards Regression Model was violated. While no assumptions were made about the shape of the underlying hazard function, the Cox models assume that the survival curves for the groups being compared have hazard functions that are proportional over time (i.e. constant relative hazard or hazard ratio). The primary test used to evaluate proportionality was visual inspection of two survival curves: (1) survival function versus survival time; and (2) log(-log(survival)) versus log of survival time. If the predictors satisfy the

proportional hazards assumption then both graphs should result in a graph with parallel curves. To further support the findings from the survival curves a secondary test of proportionality was utilized that involved generating time dependent covariates by creating interactions of the exposures and a function of survival time and including them in the model. If any of the time dependent covariates were significant than those predictors are not proportional. When proportionality was violated the follow-up time was stratified according to where the strata curves crossed in the survival function versus survival time graph.

3.9 Ethics

The data required for this study was available from Ontario's administrative health databases housed at the Institute for Clinical Evaluative Sciences (ICES). Permission to access these databases was granted by the president and CEO of ICES and by the privacy officer and director of ICES@Queen's. All data provided by ICES was rendered anonymous at source using a unique encrypted identifier for each individual personal identifier. Consequently, access to any potentially identifying information was not possible. In addition, no patients were contacted for this study and all study results, whether in public presentation or written format, are reported in aggregate form only. Ethics review and approval was obtained from the Health Sciences Research Ethics Board at Queen's University (**Appendix I**).

Chapter 4: Receipt of cardiac procedures following hospitalization for an acute myocardial infarction for individuals with a history of depression or schizophrenia

4.1 Abstract:

Background and purpose: The time to receipt of three cardiac procedures following admission for an AMI: catheterization, PTCA and CABG, was evaluated for individuals with history of depression and schizophrenia, and those with no history of a mental disorder.

Methods: Our cohort consisted of 309,790 individuals admitted for an AMI between April 1, 1995 and March 31, 2009. Ontario's health administrative databases were used to assess each individual's mental health history and outcomes. The association between depression and schizophrenia and the three cardiac procedures were analyzed using regression techniques.

Results: Compared to people with no history of a mental disorder, people with a history of depression had an increased likelihood of receiving catheterization (HR=1.36, 95% CI=1.29-1.43; HR=1.45, 95% CI=1.37-1.54, respectively) and a decreased likelihood of receiving a CABG (HR=0.73, 95% CI=0.61-0.86). People with a history of schizophrenia were as likely to receive catheterization (HR=0.89, 95% CI=0.69-1.14); or PTCA (HR=0.81, 95% CI=0.61-1.08). People with schizophrenia had less likelihood of receiving a CABG (HR=0.41, 95% CI=0.17-0.99), compared to those without a mental disorder, though the small number of events makes it impossible to draw a firm conclusion. However, the above associations were not independent of CVD history for depression or gender for schizophrenia.

Conclusions: Our results suggest that individuals with depression or males with schizophrenia are receiving comparable cardiac care in terms of receiving catheterizations or a PCTA following an AMI for individuals without a CVD history. However, the evidence suggests that there are differences in care for those with a history of CVD.

4.2 Introduction

Canadians pride themselves on having a universal health care system with equal access to medically necessary services, free of discrimination or disparities in care. In recent years the physical care of individuals with mental disorders has become an important quality of care issue. Because of the high prevalence of cardiovascular disease among people with a mental disorder, identifying disparities in access to cardiac care for this vulnerable population is of particular importance.

Canadian research has shown that patient factors such as age, gender, race/ethnicity, and socioeconomic status, as well as fundamental aspects of healthcare systems, such as its organization, financing, and delivery have been associated with various healthcare disparities (29). Provider factors may also play an important role in treatment disparities, especially when the intervention requires active physician participation and complex decision-making. There are many ways that a provider can consciously or unconsciously contribute to disparities including 'diagnostic overshadowing', patient stereotyping, competing demands, and cognitive overload (31). 'Diagnostic overshadowing' is of particular importance and occurs when physical symptoms are misattributed to a mental illness. (4). Several studies have found that physicians and nurses respond differently to individuals with a mental health history and are less likely to think that a person with a psychiatric history has a serious physical illness (51, 52). People with mental disorders experience diagnostic overshadowing as profoundly stigmatizing (59). Mental health researchers have identified diagnostic overshadowing as an important quality of care issue and considered that it may be a determinant of the higher than average morbidity and mortality noted for people with a mental disorder (86). Therefore, it is important to know whether people who have a history of a mental disorder receive cardiac care that is comparable to those without a mental disorder or whether treatment disparities exist.

Only three studies examining treatment differences in the cardiac care of individuals with a mental disorder have been conducted in Canada (17, 27, 28), with only one conducted using an Ontario cohort (28). In their first study, Kisely et al (17) found no evidence of a difference in the amount of cardiac care provided to people with any mental disorder, compared to those without, but still concluded that disparities existed, reasoning that individuals with a mental disorder should have received higher levels of care compared to individuals with no mental disorder, given their greater risk of cardiac events. In a subsequent study, Kisely et al. (27) improved their methods and found individuals with psychosis were significantly less likely to receive a catheterization (OR=0.47, 95% CI=0.38-0.58), PTCA (OR=0.41, 95% CI=0.29-0.59) and CABG (OR=0.28, 95% CI=0.20-0.39) and less likely to receive beta-blockers (OR=0.82, 95% CI=0.71-0.95) and statins (OR=0.51, 95% CI=0.41-0.63), suggesting that significant disparities may exist in the cardiac care of people with a serious mental disorder. The most recent study conducted in Canada by Atzema et al. (28) found that individuals with depression were more likely to receive a low-priority emergency department triage score than those with other comorbidities (Odds=0.88, p=0.01). These results combined with the mixed results from studies conducted in the United States generates considerable uncertainty about the quality of cardiac care received by individuals with a mental disorder.

We conducted a population-based, retrospective cohort study to compare the cardiac care of persons with and without a history of depression or schizophrenia who were admitted to hospital because of an acute myocardial infarction (AMI).

4.3 Methods

4.3.1 Study Population and Data Sources

The study population was drawn from all persons registered with Ontario's Health Insurance Plan (OHIP) between April 1, 1995 and March 31, 2009 who had a discharge diagnosis of AMI (International Classification of Diseases version 9 [ICD-9] code 410 and version 10 [ICD-10] code I21) Individuals were excluded if they were younger than 18 years of age, were missing their discharge date and had no corresponding death date from which to derive a discharge date, or were admitted to hospital for an AMI after their death date. Cohort members were followed from their admission date (cohort entry or t_0) until the earliest of: a study outcome, date of death, or end of follow up (discharge date or 30 days from t_0).

We used four of Ontario's computerized health databases including (1) the Registered Persons Database (RPDP) for information on socio-demographics, (2) Ontario's Health Insurance Plan (OHIP) database for information on physician service claims, (3) the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and Same Day Surgery (CIHI-SDS) for detailed information on hospitalizations including diagnostic and surgical procedural codes, and the (4) the National Ambulatory Care Reporting System (NACRS) for information on emergency department visits.

4.3.2 Identification and Classification of Mental Disorders

An individual's history of mental disorder (exposure status) was ascertained using the physicians' claims (OHIP), emergency department (ED) visits (NACRS), and hospitalizations (CIHI-DAD) databases and the following diagnostic codes: 296 (ICD 9), F32-34 (ICD 10) for depression; and 295 (ICD 9), F20 (ICD 10) for schizophrenia. We defined the exposure status using the following validated algorithm: cohort members were classified as having a history of

depression and/or schizophrenia if they were assigned the corresponding diagnostic code on two separate visits to a physician or ED within a one-year period, or had at least one hospitalization with a discharge diagnosis for the mental disorder of interest (81, 82). The use of two diagnostic codes within a one-year period has been shown to reduce the potential for misclassification as the first code could represent a provisional diagnosis that was not subsequently confirmed (81, 82). Thus, individuals were considered "exposed" on the date of the second diagnostic code. Cohort members who had only one diagnostic code for depression or schizophrenia, or at least one diagnostic code for any other mental disorder were classified as having a history of "other mental disorders". Cohort members who did not fulfill these exposure definitions were classified as having "no history of a mental disorder" (i.e., unexposed) and constituted the reference group.

Depression was chosen as a mental disorder of interest because it is a wide spread disorder (prevalence of 8%) with effective treatment options and a good prognosis. In addition, depression is now a well-recognized determinant of cardiovascular morbidity and mortality (7). On the other hand, schizophrenia is a disorder with a low prevalence (1%) that can be extremely debilitating and has fewer effective treatments and thus, has a more profound effect on an individual's ability to function (8). It is therefore not surprising that people with depression are among the least stigmatized, whereas people with schizophrenia are among the most stigmatized groups (26). Therefore, juxtaposing these two disorders allowed us to evaluate whether a 'dose-response' effect for treatment disparities existed across mental disorders.

4.3.3 Study End Points

The outcomes of interest were the receipt of three cardiac procedures: (1) catheterization; (2) PTCA; and (3) CABG. In cardiology, revascularization procedures are referred to as 'hard' clinical outcomes, which are end points that are well defined, measureable, and objective (87). The 'hard' end points used in this study were chosen because they are an integral part of post-

AMI care. In addition, the chosen procedures have been used as end points in previous studies of treatment disparities, thereby increasing the comparability of our results (17). The end points were identified using the CIHI-DAD database and standardized procedural codes corresponding with the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP; prior to 2000) and the Canadian Classification of Health Interventions (CCI; after 2000).

4.3.4 Statistical Analysis

We evaluated the effect of a having a history of depression or schizophrenia, considered separately, on the time-to-receipt of the cardiac procedure of interest using Cox Proportional Hazards (PH) regression models. In these analyses, the follow-up for cohort members who did not receive the procedure was censored at the date of death, end of follow-up (hospital discharge date or 30 days post-cohort entry), or end of study (March 31, 2010). Each cardiac procedure was analyzed separately while adjusting for a number of potential confounders including age, sex, neighbourhood income, history of cardiovascular diseases, common comorbidities, an indicator of overall health (e.g. Charlson index), and measures of health care utilization. In all analyses, an individual's history of mental disorders was evaluated as a time independent exposure ('intention-to-treat') because we hypothesized that the stigma associated with schizophrenia or depression would persist even after the resolution of symptoms of the disorder. Moreover, we were unable to determine the resolution of a mental disorder using administrative health databases.

Owing to restrictions on the procedure time variable in the hospitalization database, the unit of analysis used for the Cox regression was 'days' rather than hours. By using 'days' we were unable to differentiate individuals who received an intervention hours apart but on the same day. This likely resulted in some misclassification because the Cox model grouped everyone who had a procedure on one calendar date as having experienced an event at the same time, even though some individuals may have received the intervention as much as 23 hours, and 59 minutes

apart. However, this misclassification affected both the exposed and the unexposed (non-differential) and would have biased the results towards the null. It is important to recognize that although catheterization and the PTCA are procedures that should be undertaken within hours of being admitted for an AMI, the CABG is a more invasive surgery, not usually completed within hours of admission. Thus, this end point was less likely to have been negatively influenced by the use of 'days' as a unit of analysis rather than 'hours'.

An important consideration in the survival analysis was assessing if the proportionality assumption of the Cox Proportional Hazards Regression Model was violated. While no assumptions were made about the shape of the underlying hazard function, it was assumed that the survival curves for the mental disorders of interest had hazard functions that were proportional over time (i.e. constant relative hazard). We evaluated the proportionality assumption by first including a time-dependent interaction term in each Cox model, then by plotting the survival function against survival time, and finally by plotting the log(-log(St)) against survival time (St) looking for parallel lines. When proportionality was violated the analysis was time-stratified according to when during follow-up the survival curves crossed.

Subgroup analyses were undertaken to determine if age, sex, demographics or cardiovascular history modified the association between depression or schizophrenia and receipt of a cardiac intervention by including interaction terms, one at a time, in our Cox regression models.

All analyses were undertaken using Statistical Analytical Software (SAS)® version 9.2(137) (84).

4.4 Results

The study cohort consisted of 309, 790 (**Figure 4.1**) adults admitted for an AMI between 1995 and 2009 with a mean age (±SD) of 68.5 (± 13.9) years at cohort entry, 62% of whom were males. During follow-up, 22,358 (7.21%) individuals received a catheterization, 19,385 (6.25%)

received a PTCA, and 2,832 (0.91%) underwent CABG surgery (**Figure 4.2**). Cohort members were followed for a median of 8.5 days (Inter-Quartile Range [IQR] = 6 days) for the catheterization, 8.6 days (IQR = 6 days) for PTCA, and 8.7 days (IQR = 6 days) for CABG surgery end points.

Table 4.1 describes the baseline characteristics of cohort members according to their history of a mental disorder. Adults with a history of depression or schizophrenia were more likely to reside in poor neighbourhoods and in an urban setting compared with those with no history of a mental disorder. Although there were no important differences in the cardiovascular risk profiles of adults with and without a history of depression or schizophrenia, individuals with a history of depression or schizophrenia appeared to have been hospitalized more often than those with no such history. On the other hand, adults with a history of a mental disorder were less likely to see a physician on an outpatient basis. In addition, those with a history of depression were somewhat more likely to have a history of hypertension, ischemic heart disease, and concomitant macrovascular disease than adults with a history of schizophrenia or with no prior mental disorder.

After adjusting for the influence of multiple risk factors, individuals with a history of depression were significantly more likely to be catheterized or undergo a PTCA following admission for an AMI than those with no history of a mental disorder (HR, 1.39 [95% CI, 1.32 to 1.47] and 1.46 [95% CI, 1.38-1.55], respectively) (**Table 2**). Individuals with a history of schizophrenia were just as likely to be catheterized or undergo a PTCA post-AMI than persons with no history of a mental disorder (HR, 0.90 [95% CI, 0.70-1.15]; HR, 0.83 [95% CI, 0.62-1.11]), respectively). On the other hand, persons with a history of depression or schizophrenia were less likely to undergo CABG surgery post-AMI than persons with no history of a mental disorder (HR, 0.74 [95% CI, 0.62-0.87]; HR, 0.42 [95% CI, 0.17-1.01], respectively).

The association between depression and receipt of a cardiac intervention post-MI was independent of age, SES, urban or rural status or gender but was dependent on CVD history (**Figure 4.3**). A history of congestive heart failure reduced the likelihood of being catheterized or receiving a PTCA or CABG in those with depression ($p<0.001$, $p=0.0011$ and $p=0.0378$, respectively). Similarly, a history of MI or IHD reduced the likelihood of being catheterized or receiving a PTCA or CABG in those with depression ($p=0.0020$, $p=0.0021$, $p=00.10$). On the other hand, the association between schizophrenia and the receipt of a cardiac intervention was only modified by sex. Females with schizophrenia were less likely to receive a catheterization or PTCA (catheterization: HR=0.59, 95% CI=0.35-0.98; PTCA: HR=0.22, 95% CI=0.08-0.59); where as males were just as likely to receive a catheterization or PTCA (catheterization: HR=1.08, 95% CI=0.81-1.43; PTCA: HR=1.12, 95% CI=0.83-1.51) (**Figure 4.4)**.

4.5 Discussion

We used a retrospective, population based cohort study using Ontario's administrative health databases to examine treatment disparities in the cardiac care of adults admitted to hospital for an AMI with a history of depression or schizophrenia. We found that individuals with a history of depression were significantly more likely to be catheterized and undergo a PTCA than those with no history of depression, and that individuals with a history of schizophrenia had comparable rates of catheterization and PTCA. On the other hand, we also found that individuals with a history of depression or schizophrenia were less likely to undergo more invasive procedure such as CABG surgery. However, we found consistent evidence that the association between depression and schizophrenia and the likelihood of receiving any of the three procedures was modified by an individual's CVD history.

These results provide some evidence against the presence of treatment disparities for commonly provided cardiac procedures for adults with a history of depression or schizophrenia.

Indeed, in our study adults with depression appeared to be more aggressively managed than those without depression, which reflects good clinical practice given that depression is now a recognized determinant of cardiovascular morbidity and mortality (7, 10, 64, 88). The lower use of CABG surgery for those with depression and possibly schizophrenia may be explained by a number of factors other than stigma. First, CAGB is a much more invasive procedure than catheterization or PTCA and it is contraindicated in the presence of depression (88). Second, there is some evidence to suggest that individuals with depression have lower health benefits following major cardiac surgery than persons without depression (89), and individuals with schizophrenia have a higher relative odds of having adverse events following medical and surgical hospitalizations (90). Third, these findings may also reflect the influence of patient-based behaviours including refusal to provide consent. Finally, some provider-driven treatment disparities such as concerns with post-operative care can actually represent good clinical care rather than stigma. Unfortunately, administrative health databases cannot discern between provider and patient-induced treatment disparities, nor the clinical appropriateness of such differences.

The subgroup analysis revealed that the comparable care received by adults with a history of depression is not independent of CHF, MI or IHD history. When an individual with depression has a CVD history they are less likely to receive a catheterization, PTCA or CABG. The finding that those with a history of CHF, MI or IHD are less likely to receive one of these procedures is consistent with previous studies evaluating trends in acute reperfusion therapy for AMI patients (91-94). However, the fact that those with depression and CVD history are even less likely to receive a catheterization, PTCA or CABG may be due to the risk paradox that exists in cardiac surgery: the superiority of surgical over medical treatment is most notable in high-risk patients (100). By the same token, the CVD history effect may be a reflection of the fact that individuals

with a history of IHD, MI or CHF with depression were perceived as having an even higher risk profile than their counterparts without a mental disorder.

The subgroup analysis for individuals with schizophrenia revealed the probability of receiving a catheterization or PTCA was independent of age, SES, CVD history but was dependent on sex. This interaction effect, which was only significant for the association between schizophrenia and receipt of a catheterization or PTCA, could be the result of differences in MI presentation or different cardiovascular profiles between males and females.

Most of the previous studies examining disparities in the medical or surgical treatment for cardiovascular disease management of people with a mental disorder have had a number of methodological limitations and results have been mixed (3, 15-20, 22-24, 27, 28). An important limitation of previously published studies has been the use of a dichotomous outcome (cardiac intervention received or not) rather than a time to intervention approach as we used. A recent population-based cohort analysis involving patients with an AMI admitted to acute care hospitals in Ontario was the first to compare the door-to-electrocardiogram, door-to-needle, and door-to-balloon times for individuals with and without a charted history of depression (28). This study found that the adjusted odds of missing the benchmark time for individuals with a charted history of depression were 1.39 ($p<0.001$) for door-to-electocardiogram time, 1.62 ($p=0.047$) for door-to-needle time and 9.12 ($p=0.019$) for door-to-balloon time. Our study, with its larger sample size, allowed a more precise comparison of time-to-cardiac care outcomes, and suggests that individuals with a history of depression with no history of CVD receive the same or better performance on three potentially life-saving cardiac interventions. Our study results are consistent with the findings of a 2007 study by Kisely et al. (17) that indicates that individuals with a mental disorder are receiving comparable cardiac care. On the other hand, our results suggest that females with schizophrenia are receiving decreased levels of vascular care which is somewhat

consistent with the results from a 2009 study by Kisely et al.(27) which looked at ischemic heart disease and psychosis (27), e.g. catheterization (OR, 0.47 [95% CI, 0.38-0.58]), PTCA (OR, 0.41 [95% CI, 0.29-0.59]), and CABG (OR, 0.35 [95% CI, 0.25-0.48]). However, in this 2009 study Kisely et al. found a difference in care for both males and females with schizophrenia. However, we speculate that our results are a more accurate measure of the differences in care received by those with depression or schizophrenia due several limitations in the studies conducted by Kisely et al. For instance, Kisely et al. evaluated rates of procedures for up to 1 year after the index cardiological or stroke admission, rather than the more sensitive time-to-intervention approach we used. Considering that at least two of the three of cardiac procedures studies are interventions that should be administered within hours of the cardiac event, it is likely that some of the recorded outcomes captured by Kisely et al. were not due to the index event and were misclassified. If this misclassification was differential it would bias the results away from the null, inflating the differences in vascular care received by those with psychosis compared to those without.

A strength of our study is that we used a population-based, hospitalized cohort, which would have prevented many sources of selection bias. We used administrative health databases, which ensured follow-up of all cohort members thereby restricting the potential for losses to follow-up. However, administrative health records are vulnerable to recording errors, which might introduce both exposure (mental disorders) and outcome (receipt of cardiac intervention) misclassification. While the use of diagnostic codes to identify persons with depression and schizophrenia has not been validated in Ontario, it has been validated in the United States (82, 95). In addition, depression and schizophrenia are disorders that can be both episodic and chronic. While administrative health databases can detect a diagnosis of either condition, they cannot detect illness resolution. As such, the exposure was analyzed as a time-fixed variable although it may actually be time-dependent in some individuals. As the resulting misclassification of

exposure was independent of an individual's outcome status (receipt of cardiac treatment) it was non-differential and any bias would be towards the null. Lastly, there is a possibility for misclassification because persons with a mental disorder may not appear in the databases as being diagnosed with a mental disorder and will be classified as unexposed. The potential for outcome misclassification is likely to be small in our study by virtue of their invasive nature and high physician remuneration associated with these expensive cardiac interventions.

Unmeasured and uncontrolled factors that could have contributed to residual confounding include patient behaviours, race, and smoking. In addition, in our study SES was measured using postal codes and may not accurately reflect an individual's true SES. However, it is unlikely that these factors contributed to confounding because of the homogeneity of the study population as is evident in **Table 1**. Finally, our results may not be generalizable to cardiac care provided in other settings, or to patients with other types of mental illnesses.

In conclusion, our results provide evidence that individuals with depression and schizophrenia without a CVD history are receiving comparable cardiac care following an AMI in an acute care setting for the more prevalent, lower risk interventions, such as catheterization and PTCA. However, the evidence suggests that there are some differences in the cardiac care for individuals with depression or schizophrenia and a history of CVD.

Table 4.1 Baseline characteristics according to history of mental disorders for adults admitted for an acute myocardial infarction

Characteristics [† ‡]	History of mental disorders				
	None (n=177066)	Schizophrenia (n= 1201)	Depression (n=24044)	Schizophrenia and depression (n=1392)	Other mental disorder (n=106087)
Age, years	69.2±13.9	68.1±13.8	67.3±14.6	63.7±14.6	67.7±13.6
Male	59.5	54.6	52.1	50.3	69.1
Income Quintile					
1 (lowest)	23.0	33.6	24.5	35.7	23.0
2	21.9	24.5	21.9	22.2	21.5
3	19.9	17.6	19.6	17.4	20.4
4	18.2	13.5	17.3	13.0	19.1
5 (highest)	17.0	10.8	16.6	11.7	18.2
Missing	0.4	0.4	0.3	1.1	0.4
Residence					
Rural	18.4	11.4	14.7	10.2	16.0
Urban	81.5	88.5	85.2	89.4	83.9
Missing	0.1	0.1	0.1	0.4	0.1
Comorbid conditions					
Previous AMI	3.3	3.2	3.3	3.1	2.9
Previous stroke	1.3	1.7	1.5	1.1	0.7
Previous angioplasty	1.8	0.9	1.4	0.4	1.8
Hypertension	9.1	8.8	10.3	8.3	6.1
Cerebrovascular disease	2.1	2.0	2.4	1.8	1.2
Chronic heart failure	6.4	6.3	6.5	5.6	4.4
Ischemic heart disease	10.7	7.9	11.1	7.9	8.5
Peripheral vascular disease	1.8	1.2	1.9	1.0	1.4

Characteristics [†] [‡]	History of mental disorders				
	None (n=177066)	Schizophrenia (n= 1201)	Depression (n=24044)	Schizophrenia and depression (n=1392)	Other mental disorder (n=106087)
≥ 2 macrovascular disease	3.1	2.8	3.6	2.7	1.8
Health care services utilization					
Number of hospitalizations					
None	72.1	64.5	57.7	56.0	62.5
1	17.6	23.1	23.3	20.9	21.7
≥ 2	10.3	12.5	18.9	23.1	15.8
Outpatient physician visits					
0-1	16.5	4.5	3.5	2.9	5.6
2-12	50.6	32.1	30.5	24.6	40.0
13+	16.5	63.4	64.9	72.4	54.3
Health indices					
Charlson index [¶]					
0	84.4	72.6	71.7	67.4	75.6
1+	15.6	27.4	28.3	32.6	24.4

Abbreviations: AMI- Acute Myocardial Infarction
[†] Plus-minus values are means ±SD; all others are percentages (%).
[‡] Timeframe: 1 year before t0 (admission for AMI)
[§] Percentages may not add up to 100 due to rounding.
[¶] Higher scores indicative of poorer health.
Exposure definitions :
None – no mental disorder diagnosis prior to index event
Schizophrenia – two diagnoses for schizophrenia within one-year time period prior to index event
Depression – two diagnoses for depression within one-year time period prior to index event
Schizophrenia and Depression – fulfilled both Schizophrenia and Depression definitions
Other mental disorder – had any mental disorder diagnosis prior to index event

Table 4.2 Unadjusted and Adjusted Hazard Ratio for the Receipt of Specific Cardiac Procedures according to History of a Mental Disorder[†]

	Events (n)	Total person-days	Unadjusted HR (95% CI)	Adjusted * HR (95% CI)
Catheterization				
No history of mental disorder	7492	890,412	1.00 (reference)	1.00 (reference)
History of depression	1915	203,096	1.15 (1.10-1.21)	1.39 (1.32-1.47)
History of schizophrenia	64	10,767	0.76 (0.60-0.98)	0.90 (0.70-1.15)
PTCA				
No history of mental disorder	6395	899,145	1.00 (reference)	1.00 (reference)
History of depression	1615	205,883	1.14 (1.08-1.20)	1.46 (1.38-1.55)
History of schizophrenia	47	10,971	0.66 (0.49-0.88)	0.83 (0.62-1.11)
CABG surgery				
No history of mental disorder	1214	917,754	1.00 (reference)	1.00 (reference)
History of depression	163	210,944	0.59 (0.51-0.70)	0.74 (0.62-0.87)
History of schizophrenia	5	11,223	0.35 (0.15-0.84)	0.42 (0.17-1.01)

95% CI = 95% confidence interval; PTCA=percutaneous transluminal coronary angioplasty; CABG= coronary artery bypass graft; AMI=Acute Myocardial Infarction

* Adjusted for age at t_0, sex, number of hospitalizations in past year, number of out patient visits in past year, hospitalizations in past year for: AMI, coronary artery disease, atrial fibrillation, hypertension, congestive heart failure, ischemic stroke; vascular procedures in past year, cardiac procedures in past year, cardiovascular diagnostic tests in past year, cardiovascular imaging in past year and Charlson comorbidity score category.

[†] The exposure group that included individuals with schizophrenia and depression as well as the exposure group that included the individuals with other mental disorders were excluded from the analysis because they did not fulfill Cox's Proportionality Assumption.

Figure 4.1 Flow of Study Cohort

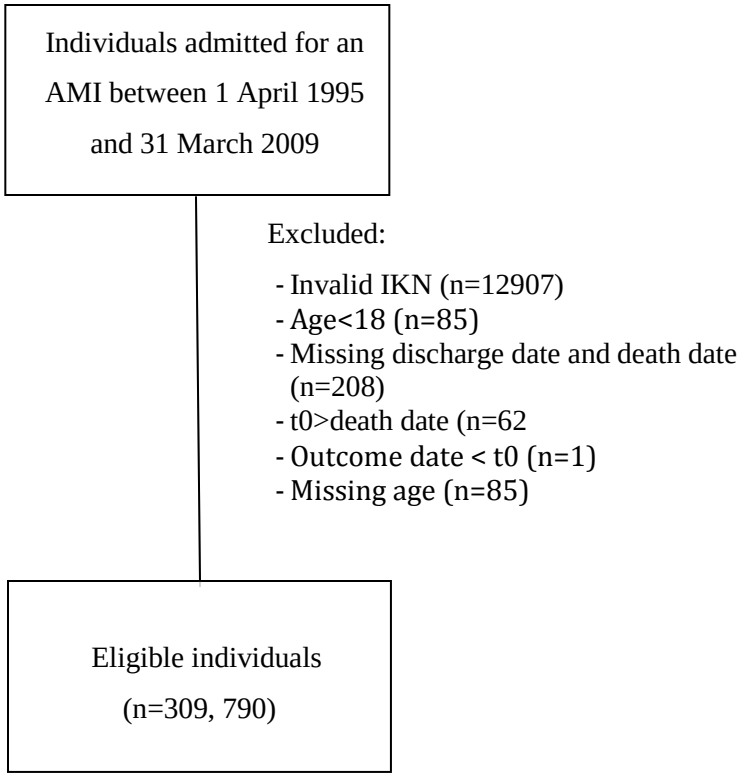

Figure 4.2 Distribution of Cardiac Procedures

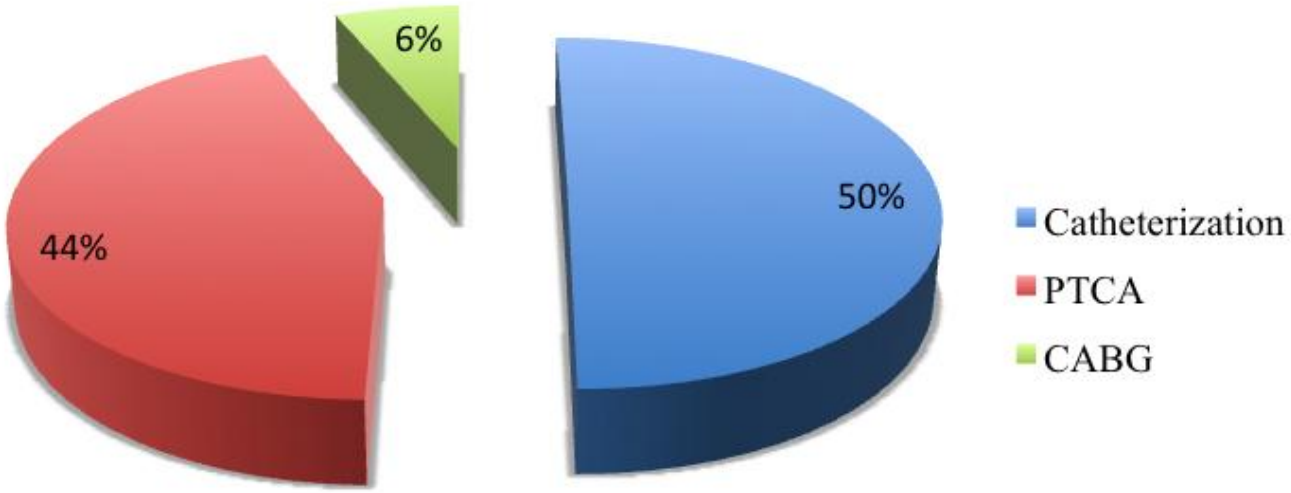

Figure 4.3 (a-c) Subgroup Analyses: fully adjusted risk ratios are plotted for the end points of catheterization, PTCA and CABG for individuals with depression according to various baseline characteristics

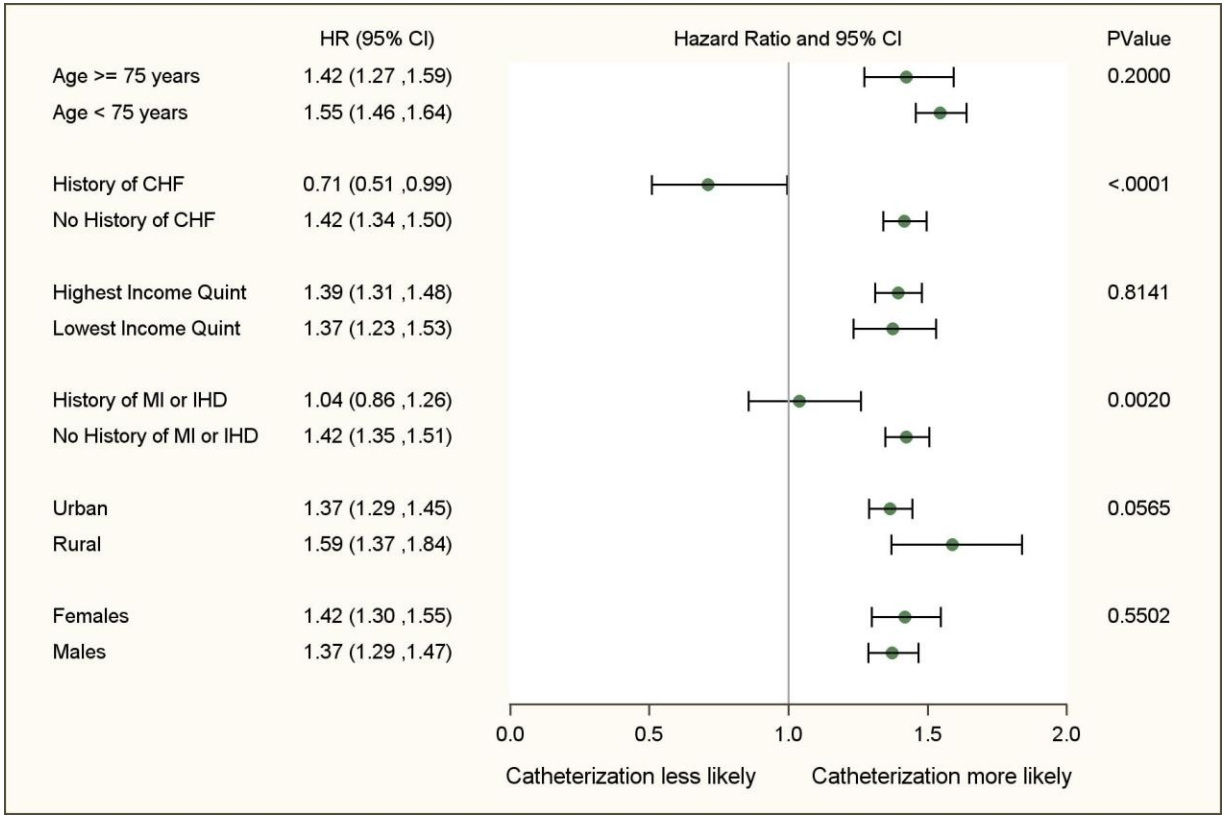

Figure 4.3a Catheterization

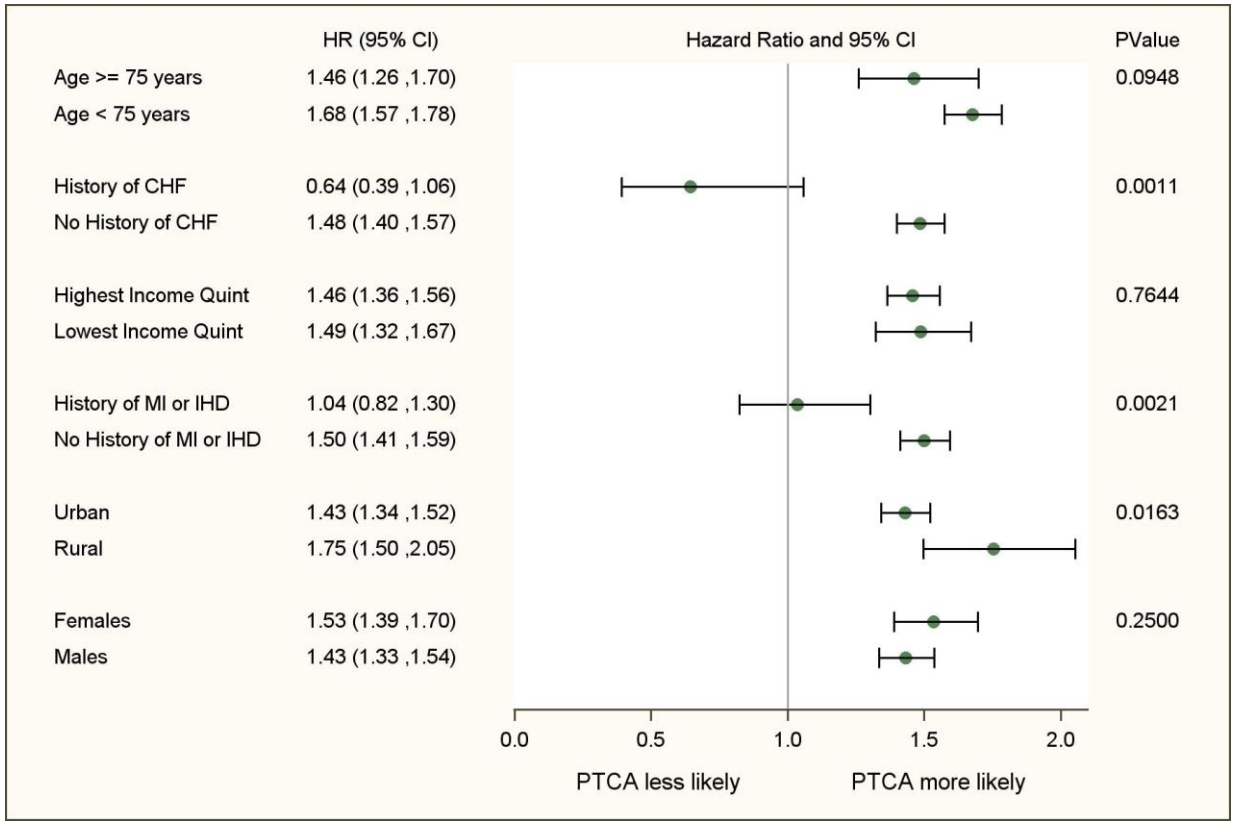

Figure 4.3b PTCA

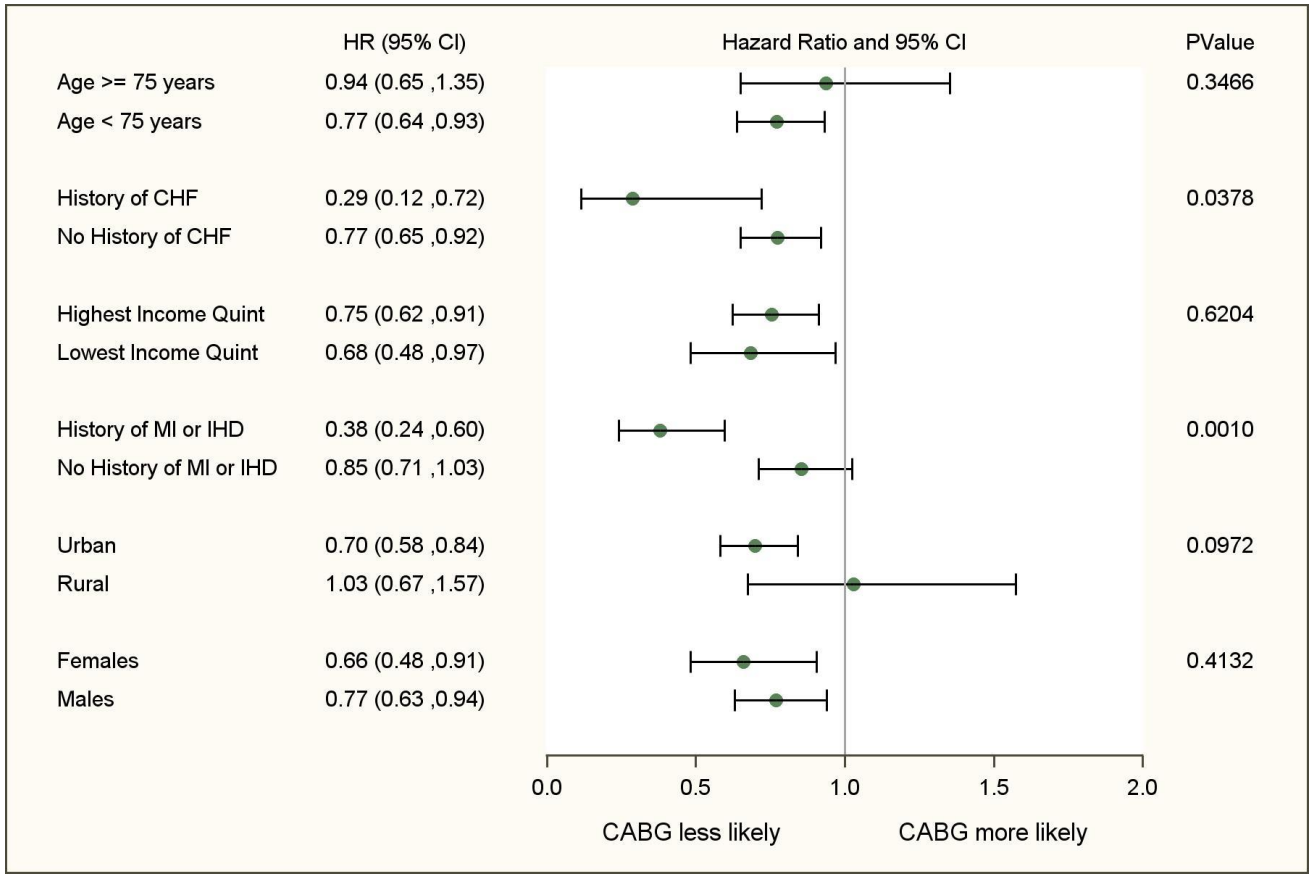

Figure 4.3c CABG

Figure 4.4 (a-c) Subgroup Analyses: full adjusted risk ratios are plotted for the end points of catheterization, PTCA and CABG for individuals with schizophrenia according to various baseline characteristics

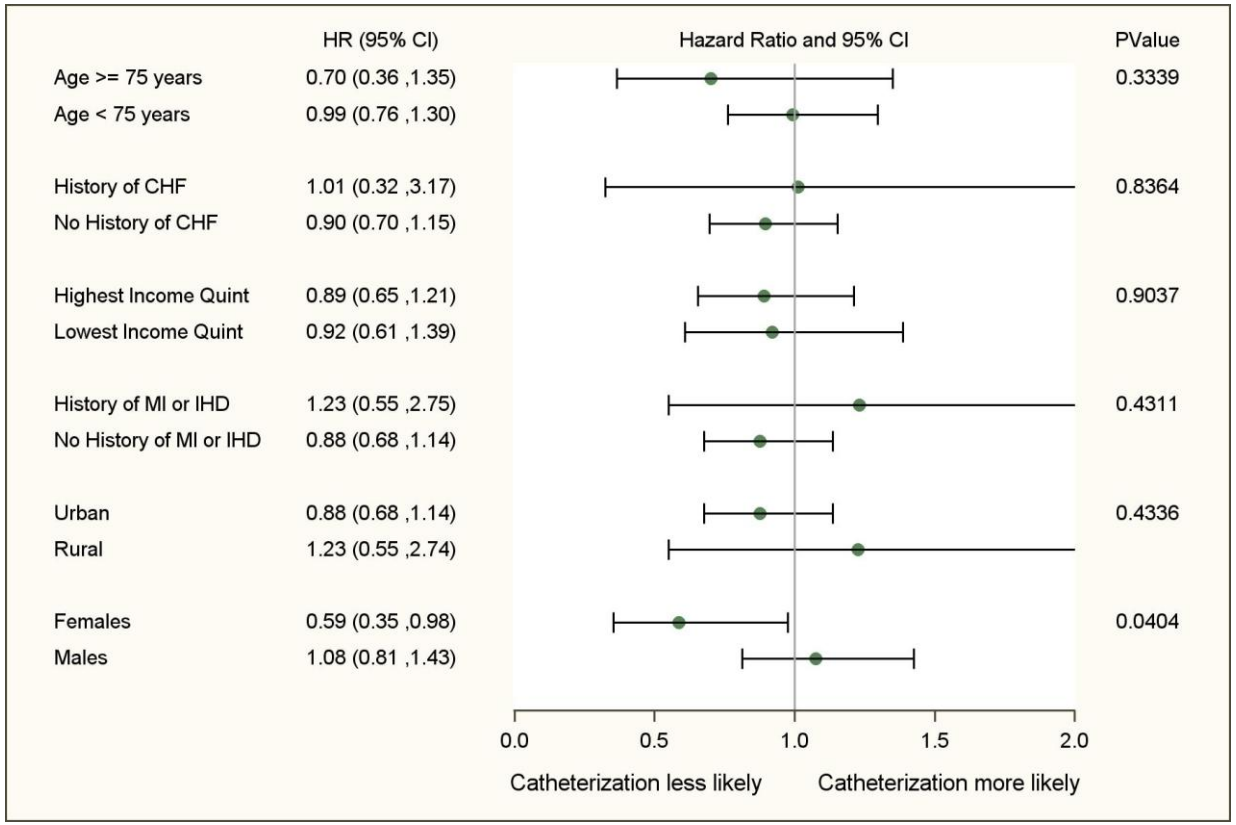

Figure 4.4a Catheterization

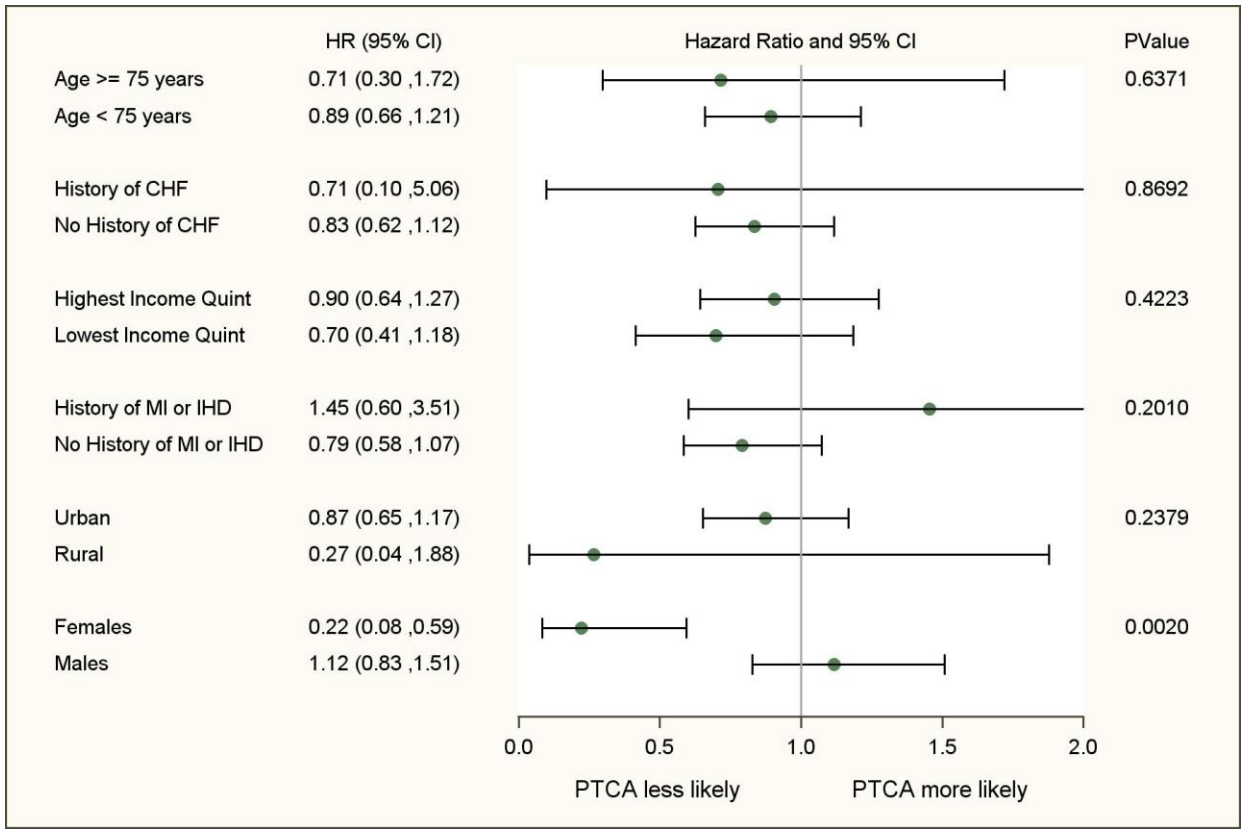

Figure 4.4b PTCA

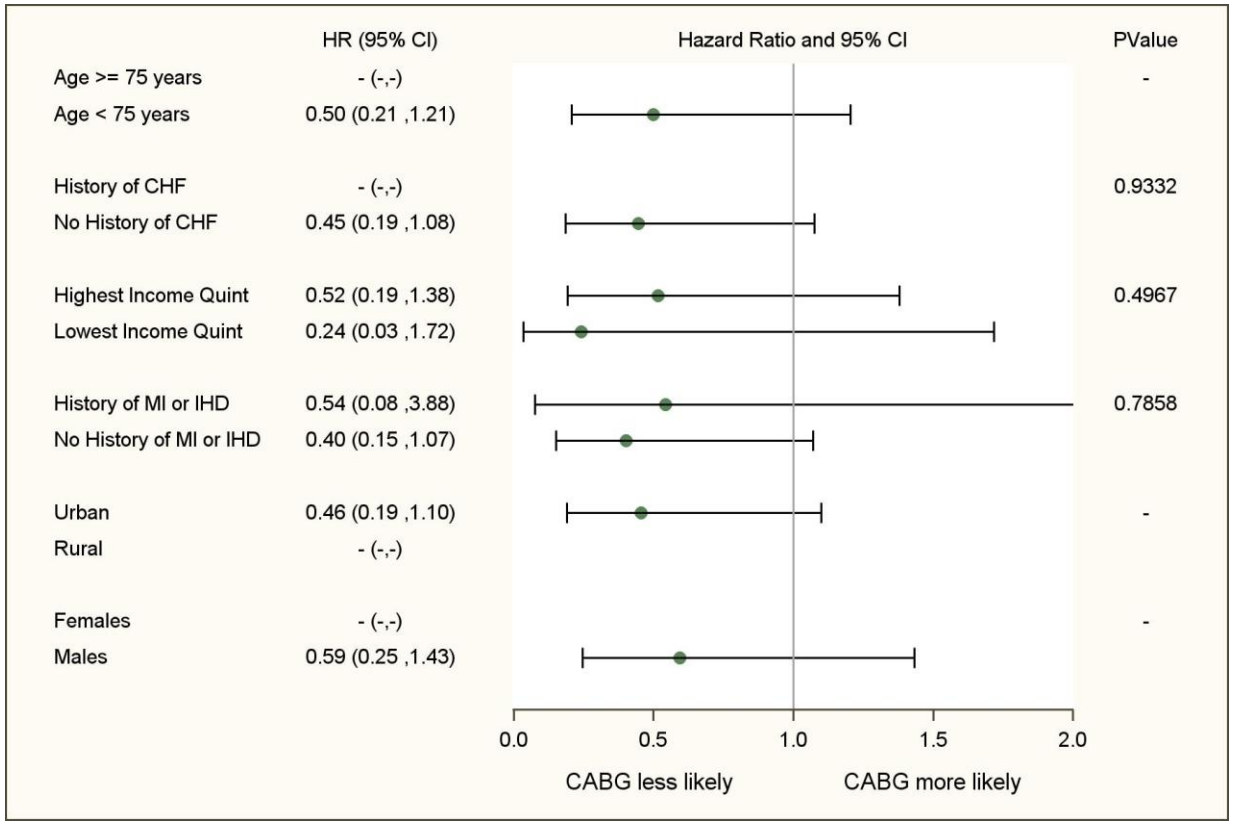

Figure 4.4c CABG

Chapter 5: Receipt of cardiac pharmaceuticals following hospitalization for an AMI for individuals with a history of depression or schizophrenia

5.1 Abstract:

Background: We undertook a large, population-based retrospective cohort study to evaluate the post-MI discharge care of adults with and without a history of depression or schizophrenia.

Methods: We identified a cohort of 188,097 older adults aged 66 years and over hospitalized for an AMI between April 1, 1995 and March 31, 2009. Ontario's administrative health databases were used to assess each individual's mental health history, baseline characteristics and drug use. The association between a history of depression and schizophrenia and receipt of a beta-blocker, ACE inhibitor, or statin post-discharge was assessed using Cox proportional hazards models adjusted for potential confounders.

Results: Older adults with depression or schizophrenia were as likely as individuals without a mental disorder to receive an ACE inhibitor (HR=0.98, 95% CI=0.94-1.02; HR=0.90, 95% CI=0.78-1.03, respectively); follow-up: > 2 days (HR=1.12, 95% CI=1.05-1.19; HR=1.04, 95% CI=0.81-1.34, respectively)). Individuals with depression or schizophrenia were as likely, or more likely to receive a beta-blocker or a statin (beta-blockers: HR=1.07, 95% CI=1.03-1.10; HR=0.90, 95% CI=0.79-1.02, respectively; statins: HR=1.27, 95% CI=1.22-1.32; HR=0.97, 95% CI=0.83-1.14, respectively). However, there was a significant prior drug use effect modification.

Conclusions: This analysis indicates that individuals with a history of depression or schizophrenia are not disadvantaged in the amount of non-acute cardiac care received following hospitalization for an AMI and argues against the presence of treatment disparities in the cardiac pharmaceutical care of individuals with depression or schizophrenia.

5.2 Introduction

In the past several decades there has been vast improvement in the survival of patients admitted for an acute myocardial infarction (AMI). One reason for this decreased mortality is due to the effectiveness of several cardiac medications, including angiotensin converting enzyme (ACE) inhibitors, aspirin, β-blockers and lipid lowering agents, particularly statins (96). Administering these drugs has become a part of clinical practice guidelines for the treatment of an AMI (38). Evaluating the use of these drugs provides an avenue to compare the quality of care received by vulnerable populations, such as those with a history of a mental disorder. Specifically, comparing the time to receipt of an outpatient cardiac pharmaceutical can help uncover if disparities exist in the treatment of individuals with depression or schizophrenia.

There may be many contributing components to healthcare disparities, if they exist, including patient factors such as age, gender, race/ethnicity, and socioeconomic status, as well as fundamental aspects of healthcare systems, such as its organization, financing, and delivery (29). Because cardiac pharmaceuticals are interventions that require active physician participation and complex decision-making, provider factors may be an important determinant of disparities in the receipt of these interventions. There are many ways that a provider can consciously or unconsciously contribute to disparities including 'diagnostic overshadowing', patient stereotyping, competing demands, and cognitive overload (31). 'Diagnostic overshadowing' is of particular importance and occurs when physical symptoms are misattributed to a mental illness (4). Not only do people with mental disorders experience diagnostic overshadowing as profoundly stigmatizing (59), mental health researchers have identified diagnostic overshadowing as an important quality of care issue that may be a determinant of the higher than average morbidity and mortality seen in this vulnerable population (86). Evaluating interventions that

require more physician judgment and discretion can help to isolate the contributing factors to any treatment disparities.

Over the last decade there have been many studies aimed at determining if the medical or surgical treatment for cardiovascular disease management is comparable between people with and without a mental disorder disorder (3, 15-20, 22-24, 27, 28). However, not only have many of these studies had a number of methodological limitations, but the results have been mixed. Furthermore, only two studies evaluating the receipt of cardiac pharmaceuticals have been conducted in Canada (17, 27) In their first study, Kisely et al (17) found no evidence of differences in the amount of cardiac care provided to people with any mental disorder compared to those without. However, Kisely et al still concluded that disparities existed, reasoning that because individuals with a mental disorder have a greater risk of cardiac events they should have received higher levels of care compared to individuals with no mental disorder. In a subsequent study, Kisely et al. (27) improved upon the methodological limitations of their 2007 study and found that individuals with psychosis were significantly less likely to receive a catheterization (OR=0.47(0.38-0.58)), PTCA (OR=0.41(0.29-0.59)) and CABG (OR=0.28(0.20-0.39)) and less likely to receive beta-blockers (OR=0.82(0.71-0.95)) and statins (OR=0.51(0.41-0.63)). The most recent study conducted in Canada by Atzema et al. (28) found that individuals with depression were more likely to receive a low-priority emergency department triage score than those with other comorbidities (Odds=0.88, p=0.01). These results combined with the mixed results from studies conducted in the United States generates considerable uncertainty about the differences in cardiac care received by individuals with a mental disorder.

In our previous study we examined hard endpoints—catheterization, PTCA, and CABG—which may be less susceptible clinical judgment and diagnostic overshadowing and found comparable or better care for adults with depression or schizophrenia for catheterization

and PTCA but possibly not for CABG surgery in individuals less than 75 years old (97). If, as some literature suggests, people with serious mental disorders, such as depression or schizophrenia, receive poorer quality care, then this may be more obvious with soft endpoints such as pharmaceutical interventions that may require greater physician discretion.

We undertook a population-based, retrospective cohort study to compare the time to receipt of three ACC/AHA recommended cardiac pharmaceuticals: beta-blockers, ACE inhibitors, and statins, for individuals with and without a history of depression or schizophrenia who were admitted to hospital with a diagnosis of AMI.

5.3 Methods

The methods for this study were prescribed previously in detail (97).

5.3.1 Study Sample and Data Sources

The study population was drawn from all persons registered with OHIP between April 1, 1995 and March 31, 2009 who had a discharge diagnosis of AMI (International Classification of Diseases version 9 [ICD-9] code 410 and version 10 [ICD-10] code I21). Individuals were excluded if they were missing their discharge date and had no corresponding death date; or had an entry date (t_0) after their death date. Individuals were also excluded if they were less than 66 years old at t_0 given that universal drug coverage is limited to persons 65 years of age and those on social assistance or disability coverage. Cohort members were followed from their date of admission (cohort entry or t_0) until the earliest of: study outcome, date of death, end of follow up (30 days post discharge) or end of study (March 31, 2010).

We used five of Ontario's computerized health databases including: (1) the Registered Persons Database (RPDP) for information on sociodemographics, (2) the Ontario Health Insurance Plan Database (OHIP) for physician services claims, (3) the Canadian Institute for

Health Information Discharge Abstract Database (CIHI-DAD) and Same Day Surgery (CIHI-SDS) for detailed information on hospitalizations and procedures, (4) the National Ambulatory Care Reporting System (NACRS) for Emergency Department visits, and (5) the Ontario Drug Database (ODB) for detailed information on outpatient prescriptions claims.

5.3.2 Identification and Classification of Mental Disorders

An individual's history of mental disorder (exposure status) was ascertained using the physicians' claims (OHIP), emergency department (ED) visits (NACRS), and hospitalizations (CIHI-DAD) databases using the following diagnostic codes: 296 (ICD 9), F32-34 (ICD 10) to define the depression exposure group; and 295 (ICD 9), F20 (ICD 10) to define the schizophrenia exposure group. Cohort members were classified as having a history of either depression or schizophrenia if they were assigned the corresponding diagnostic code on two separate visits to a physician or ED within a one-year period, or had at least one hospitalization with a discharge diagnosis for the mental disorder of interest (81, 82). The use of two diagnostic codes within a one-year period reduced the potential for misclassification as the first code could represent a provisional diagnosis that was not subsequently confirmed (81, 82). Thus, individuals were considered "exposed" on the date of the second diagnostic code. Individuals with only one diagnostic code for depression or schizophrenia, or at least one diagnostic code for any other mental disorder were classified as having a history of "other mental disorders". Cohort members who did not fulfill any of these exposure definitions were classified as having "no history of a mental disorder" (unexposed) and constituted the reference group.

As in our previous paper, focusing on mental disorders that engender different levels of public stigma helped us understand whether observed disparities were due to stigma or to other factors (26). To be consistent with a stigma model, we expected a dose response pattern with the highest disparities occurring among those with a history of schizophrenia.

5.3.3 Study End Points

The outcomes of interest were the filling of a prescription for a beta-blocker, ACE inhibitor, or statin occurring within 30 days of the hospital discharge date. All outcomes were identified using the ODB database and analyzed separately using a time-to-event analysis. The endpoint was defined as the time (in days) from t_0 (AMI admission date) until the earliest of: study outcome, date of death, or end of follow up (30 days post discharge).

In cardiology, pharmaceuticals are referred to as 'soft' clinical outcomes, which are end points that may be affected by an individuals views or interpretations (87). The 'soft' end points used in this study were chosen because these pharmaceuticals are an integral part of post AMI care and have frequently been used as end points in previous studies, increasing the comparability of our results (17).

5.3.4 Statistical Analysis

We evaluated the effect of a having a history of depression or schizophrenia, considered separately, on the time to filling an outpatient prescription for one of the cardiac drugs of interest using a Cox Proportional Hazards (PH) Regression models. In these analyses, the follow-up for cohort members who did not receive a pharmaceutical was censored at the date of death, end of follow-up (30 days post-discharge), or end of study (March 31, 2010). Each cardiac pharmaceutical was analyzed separately while adjusting for a number of potential confounders including age, sex, neighbourhood income, history of cardiovascular diseases, common comorbidities, an indicator of overall health (e.g. Charlson index), measures of health care utilization, and prior pharmaceutical use. In all analyses, an individual's history of mental disorders was evaluated as a time independent exposure ('intention-to-treat') because we hypothesized that the stigma associated with schizophrenia or depression would persist even after

the resolution of symptoms or the disorder. Moreover, we were unable to determine the resolution of a mental disorder using administrative health databases.

An important consideration in the survival analysis was assessing if the proportionality assumption of the Cox Proportional Hazards Regression Model was violated. While no assumptions were made about the shape of the underlying hazard function, it was assumed that the survival curves for the mental disorders of interest had hazard functions that were proportional over time (i.e. constant relative hazard). We evaluated the proportionality assumption by first including a time-dependent interaction term in each Cox model, then by plotting the survival function against survival time, and finally by plotting the log(-log(St)) against survival time (St) looking for parallel lines. When proportionality was violated the analysis was time-stratified according to when during follow-up the survival curves crossed.

Subgroup analyses were undertaken to determine if age, sex, demographics, cardiovascular history or prior drug use modified the association between depression or schizophrenia and receipt of a cardiac pharmaceutical by including interaction terms, one at a time, in our Cox regression models.

All data analyses were undertaken using Statistical Analytical Software (SAS)® version 9.2(137) (84).

5.4 Results

The study cohort consisted of 188, 097 persons adults over 66 years old admitted for an AMI between fiscal year 1995 to 2009 with a mean age (±SD) of 77.9 ± 7.4 years at cohort entry, 53% of whom were male (**Figure 5.1**). During follow-up, 92585 (49.2%) individuals received a beta-blocker, 83237 (44.2%) received an ACE inhibitor, and 65246 (34.7%) received a statin (**Figure 5.2**). This cohort was followed for a median of 8.5 days (IQ Range=6 days) for the beta-

blocker endpoint, a median of 8.6 days (IQ Range=6 days) for the ACE inhibitor endpoint and a median of 8.7 days (IQ Range=6 days) for the statins endpoint. An invalid IKN was the primary source of exclusions.

Table 5.1 describes the characteristics of each group according to their history of a mental disorder. Older adults with a history of depression or schizophrenia were more likely to reside in low-income neighborhood and urban setting compared with persons without a history of mental disorders. Although there were no visible differences between those with and without a mental disorder with regards to the presence of cardiovascular risk factors and comorbidities, the number of outpatient physician visits appeared to be higher for individuals with either mental disorder.

The proportionality assumption was met for the association between depression and schizophrenia and the receipt of beta-blocker and statins but not for the dispensing of ACE inhibitors. Consequently, the ACE inhibitor analysis was stratified as 0-2 days post-discharge and greater than 2 days post-discharge to satisfy the proportionality assumption.

The association between depression or schizophrenia and the receipt of a beta-blocker was independent of age, an individual's rural or urban status, socioeconomic status and gender, but was modified by CVD history, and whether an individual had a prescription for a beta-blocker prior to the index event. On the other hand, the association between depression or schizophrenia and the receipt of a statin was only modified by statin use prior to the index event **(Figures 5.3 and 5.4, Tables 5.3 and 5.4)**.

The stratified analysis for the ACE inhibitor endpoint revealed that during the first two days post-discharge the association between depression and schizophrenia and the receipt of an ACE inhibitor was only modified by prior cardiovascular drug use. Similarly, more than 2 days post-discharge the association was modified by prior use of an ACE inhibitor. Indeed, individuals with

with depression or schizophrenia had a much higher likelihood of receiving this drug if they a previous prescription for an ACE inhibitor. In individuals with no prior prescription for an ACE inhibitor, individuals were just as likely to receive an ACE inhibitor as those without a mental disorder **(Figures 5.5 and 5.6, Tables 5.3 and 5.4)**.

5.5 Discussion

This retrospective, population based cohort study examined treatment disparities in the cardiac care of older adults admitted to hospital with an AMI with a history of depression or schizophrenia. Results from this study indicate that, compared with those with no history of a mental disorder, individuals with a history of depression or schizophrenia are just as likely to receive a beta-blocker, ACE inhibitor or statin. These results provide some evidence against the existence of treatment disparities for the most commonly prescribed cardiac drugs post-MI for older adults with a history of depression or schizophrenia.

A comparison of the results of depression with schizophrenia suggests a small 'dose-response' effect. Indeed, for each of the cardiac drugs tested, individuals with depression are more likely to receive the drug, whereas individuals with schizophrenia are just as likely to receive the drug compared with individuals without a mental disorder. These results are consistent with evidence that depression is a strong determinant of cardiovascular morbidity and mortality (64). On the other hand, the association between schizophrenia and comorbid heart disease is not established, and although this population is known to have a higher prevalence of important risk factors for cardiovascular disease such as smoking, increased body mass index and type 2 diabetes, the cardiovascular history of those with a history of schizophrenia in our study was similar to that of older adults with no history of a mental disorder. Consequently, it is likely that a physician treats individuals with schizophrenia who have had an AMI similarly to individuals without a mental disorder; where as individuals with depression are perceived to be at

higher risk of cardiovascular disease and thus may be appropriately treated more aggressively post-MI. Another factor that could contribute to the difference in the strength of the associations between those with depression and schizophrenia is the increased non-compliance seen in individuals with schizophrenia (98). It is possible that individuals who appear not to have received a cardiac drug of interest were given a prescription but failed to fill it.

The *a priori* selected subgroup analyses indicate that the comparable care received by adults with a history of depression might not be independent of prior drug use (**Figures 5.3, 5.4 and 5.5**, **Tables 5.3 and 5.4**). This drug effect modification: prior use of a beta-blocker, ACE inhibitor or statin, indicates that a person with a history of depression or schizophrenia has an increased likelihood of receiving a cardiac pharmaceutical compared to those without a mental disorder if they were prescribed that pharmaceutical prior to their AMI admission (**Tables 5.3 and 5.4**). This interaction was consistent for all three endpoints, although the interaction was dependent on the length of time since discharge for the ACE inhibitor endpoint. Specifically, individuals with depression who were not on the drug previously are as likely to receive that drug after their AMI but individuals with depression who are on the drug previously are much more likely to receive a prescription for that drug within 30 days of discharge. So in the depression group this effect is indicating that there are no treatment disparities in any of the subgroups. However, this effect modification is indicating that individuals with schizophrenia that were not on the drug prior to their AMI are less likely to receive that drug within 30 days of discharge. It is possible that this effect is due to the fact that these individuals are already being prescribed the cardiac medication and do not need to refill their prescription within the 30-day follow-up of this study. Yet, contrasting the depression and schizophrenia effect modification by prior use of the drug suggests that individuals with schizophrenia may be receiving the prescription but are failing to fill it post-discharge because research has shown that individuals with schizophrenia have

higher ‘failure-to-fill’ rates than the general population (98, 99). As previously mentioned, analog studies would greatly enhance our understanding of the underlying processes of this effect modification.

These results support our previous study which evaluated the time to intervention for three cardiac procedures for individuals with a history of depression or schizophrenia compared to those without a mental disorder (97). This first study indicated that individuals with depression or schizophrenia with no previous CVD history are receiving comparable care to individuals with no mental disorder. In contrast to the first study, our second study used pharmaceutical endpoints, which require more physician judgment than the ‘hard’ endpoints such as a catheterization, PTCA or CABG used in the first study. It is important to note that our second study also indicates comparable care for individuals with a history of depression or schizophrenia. The combined results of our two studies may indicate that provider discrimination is an unlikely source of any treatment differences. This is because contrasting the ‘hard’ and ‘soft’ endpoints allows us to evaluate the level of treatment differences between interventions that are more straight forward and require less physician judgment (cardiac procedures) with interventions that are more susceptible to interpretation and require more physician judgment (cardiac pharmaceuticals). This comparison reveals that even when more physician discernment is required an individual with depression or schizophrenia is as likely to receive an intervention as those without a history of a mental disorder.

An advantage of our study is that we used a population-based, hospitalized cohort, which prevented many sources of selection bias. Also, using administrative health databases ensured follow-up of all cohort members thereby restricting the potential for losses to follow-up. Although the use of diagnostic codes to identify persons with depression and schizophrenia has not been validated in Ontario, it has been validated in the United States (82, 95). On the other

hand, administrative health records are susceptible to recording errors, which could lead to both exposure (depression and schizophrenia) and outcome (receipt of cardiac intervention) misclassification. In addition, depression and schizophrenia are disorders that can be both episodic and chronic. While administrative health databases can detect a diagnosis of either condition, they cannot detect illness resolution. As such, the exposure was analyzed as a time-fixed variable although it may actually be time-dependent in some individuals. As the resulting misclassification of exposure was independent of an individual's outcome status (receipt of cardiac treatment) it was non-differential and any bias would be towards the null. Lastly, there is a possibility for misclassification because persons with a mental disorder may not appear in the databases as being diagnosed with a mental disorder and will be classified as unexposed.

One of the most significant limitations of this study was the potential for outcome misclassification. Because Ontario's Drug Database (ODB) only allows the identification of prescriptions that have been filled; individuals that are given a prescription that they never fill will be misclassified as not having received the indicated cardiac intervention (study outcome). In addition, failure-to-fill rates have been shown to be higher among individuals with psychiatric conditions (8.0%, chi-square=37.4, $p<0.001$) (98, 99). Ultimately this could lead to differential misclassification and under estimation of the true association. Taking this into consideration only strengthens our findings.

Several factors that were not measured or controlled, such as patient behaviors, race, and smoking could have contributed to residual confounding. Also, SES is measured using postal codes and may not accurately assess an individual's true SES. However, it is unlikely that these factors contributed to confounding because of the homogeneity of the study population as is evident in **Table 5.1**. Finally, our study may not be generalizable to cardiac care provided in other settings to patients with other types of mental illnesses.

In conclusion, our results provide evidence that individuals with depression and schizophrenia are receiving comparable cardiac care following an AMI in an outpatient setting. Combined with previous results, this study suggests that physician discrimination is an unlikely source of treatment differences.

Table 5.1 Baseline characteristics according to history of mental disorders for adults ≥ 66 years old admitted for an acute myocardial infarction

Characteristics [†] [‡]	History of mental disorders				
	None (n=62856)	Schizophrenia (n= 720)	Depression (n=13292)	Schizophrenia and depression (n=662)	Other mental disorder (n=110567)
Age	77.1±7.2	77.4±7.6	78.5±7.4	76.3±7.2	78.3±7.5
Male	50.3	43.3	42.0	35.1	50.9
Income Quintile					
1 (lowest)	21.7	30.7	23.3	31.2	23.4
2	22.2	22.7	22.0	21.9	22.4
3	20.1	19.5	19.7	20.1	19.7
4	18.2	14.5	17.6	12.3	17.5
5 (highest)	17.8	12.7	17.3	14.5	17.0
Missing	0.39	0.14	0.35	0.8	0.34
Residence					
Rural	18.4	12.5	14.2	9.8	15.5
Urban	81.5	87.5	85.7	89.6	84.4
Missing	0.1	0	0.1	0.6	0.1
Comorbid conditions					
Previous MI	3.8	3.8	3.9	4.1	4.0
Previous stroke	1.1	2.6	2.1	1.2	1.7
Previous angioplasty	2.0	<0.1	1.3	<0.1	1.8
Hypertension	8.1	10.6	13.0	10.3	11.5
Cerebrovascular disease	1.8	2.9	3.3	2.6	2.8
Chronic heart failure	6.5	7.2	9.3	8.2	8.8
Ischemic heart disease	10.5	9.0	13.1	7.3	12.5
Peripheral vascular disease	1.9	1.5	2.4	1.2	2.3
≥ 2 macrovascular disease	2.4	2.5	4.5	2.7	3.9

Characteristics [† ‡]	History of mental disorders				
	None (n=62856)	Schizophrenia (n= 720)	Depression (n=13292)	Schizophrenia and depression (n=662)	Other mental disorder (n=110567)
Medications					
Beta blockers (BB)	28.7	20.1	31.5	22.2	32.4
Antihypertensives (AHT)	36.1	38.2	42.1	38.1	42.2
Angiotensin receptor blocker	5.8	5.4	9.6	5.6	8.8
Calcium channel blockers	35.5	25.8	37.7	27.7	38.6
Nitrates	29.5	21.4	32.6	22.2	32.6
Thiazide diuretics	22.3	19.2	25.5	17.4	25.5
Loop diuretics	21.1	25.8	30.8	29.9	27.9
Antiplatelets	3.1	2.5	7.2	3.5	5.6
Aspirin	21.4	14.3	19.8	13.6	21.7
Anticoagulants	7.9	8.2	10.9	8.2	10.8
Statins and fibrates (Anti-lip)	30.6	19.0	31.0	22.7	24.2
NSAIDs (missing=2926)	11.8	9.0	11.3	9.8	11.9
Health care services utilization					
Number of outpatient visits					
0-12	55.9	30.6	23.7	20.8	34.4
13-25	30.5	27.4	35.2	29.8	37.1
≥ 26	13.6	42.1	41.1	49.4	28.5
Number of hospitalizations					
0	65.1	60.3	51.2	53.8	55.9
1	21.0	25.8	26.0	23.0	24.6
≥ 2	13.9	13.9	22.8	23.2	19.4

Characteristics [†] [‡]	History of mental disorders				
	None (n=62856)	Schizophrenia (n= 720)	Depression (n=13292)	Schizophrenia and depression (n=662)	Other mental disorder (n=110567)
Health indices					
Charlson index [¶]					
0	78.2	67.1	62.8	58.8	68.4
≥ 1	21.8	32.9	37.2	41.2	31.6
Number of distinct drugs					
0-5	40.9	22.8	14.4	13.7	23.5
6-12	42.2	46.7	40.0	41.2	44.0
≥ 13	16.8	30.6	45.6	45.0	32.5

MI: Myocardial Infarction; NSAIDs: nonsteroidal antiinflammatory drugs.

[†] Plus-minus values are means ±SD; all others are percentages (%).

[‡] In the year preceding cohort entry.

[§] Percentages may not add up to 100 due to rounding.

[¶] Higher scores indicative of poorer health.

Exposure definitions:

None – no mental disorder diagnosis prior to index event

Schizophrenia – two diagnoses for schizophrenia within one-year time period prior to index event

Depression – two diagnoses for depression within one-year time period prior to index event

Schizophrenia and Depression – fulfilled both Schizophrenia and Depression definitions

Other mental disorder – had any mental disorder diagnosis prior to index event

Table 5.2(a) Unadjusted and Adjusted Hazard Ratio for Receipt of Beta-Blockers and Statins according to History of a Mental Disorder†

	Events (n)	Total person-days	Unadjusted H.R.	Adjusted H.R.
Beta Blockers				
No History of mental disorder	32113	946, 556, 853	1.00 (reference)	1.00 (reference)
History of Depression	6160	210, 078, 022	0.91 (0.89-0.94)	1.07 (1.03-1.11)
History of Schizophrenia	270	11, 248, 807	0.76 (0.67-0.85)	0.90 (0.79-1.02)
Statins				
No History of mental disorder	20726	946, 894, 059	1.00 (reference)	1.00 (reference)
History of Depression	4649	210, 121, 992	1.12 (1.09-1.16)	1.27 (1.22-1.32)
History of Schizophrenia	173	11, 2 51,674	0.78 (0.67-0.90)	0.97 (0.83-1.14)

Table 5.2(b) Unadjusted and Adjusted Hazard Ratio for Receipt of an ACE Inhibitor according to History of a Mental Disorder†

	Events (n)	Total person-days	Follow up ≤ 2dys Unadjusted H.R.	Follow up > 2dys Unadjusted H.R.	Follow up ≤ 2dys Adjusted H.R.	Follow up > 2dys Adjusted H.R.
ACE Inhibitors						
No history of mental disorder	28832	946, 665, 097	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
History of depression	5610	210, 096, 760	0.84 (0.81-0.87)	1.02 (0.97-1.08)	0.98 (0.94-1.02)	1.12 (1.05-1.19)
History of Schizophrenia	286	11, 248, 727	0.74 (0.65-0.84)	0.80 (0.61-1.04)	0.90 (0.78-1.03)	1.04 (0.81-1.34)

95% CI = 95% confidence interval; ACE =angiotensin-converting enzyme

* Adjusted for age at t_0, sex, number of hospitalizations in past year, number of out patient visits in past year, hospitalizations in past year for: AMI, coronary artery disease, atrial fibrillation, hypertension, congestive heart failure, ischemic stroke; vascular procedures in past year, cardiac procedures in past year, cardiovascular diagnostic tests in past year, cardiovascular imaging in past year, Charlson comorbidity score category, number of unique drugs, prior use of cardiac pharmaceuticals.

† The exposure group that included individuals with schizophrenia and depression as well as the exposure group that included the individuals with other mental disorders were excluded from the analysis because they did not fulfill Cox's Proportionality Assumption.

Figure 5.1 Flow of Study Cohort

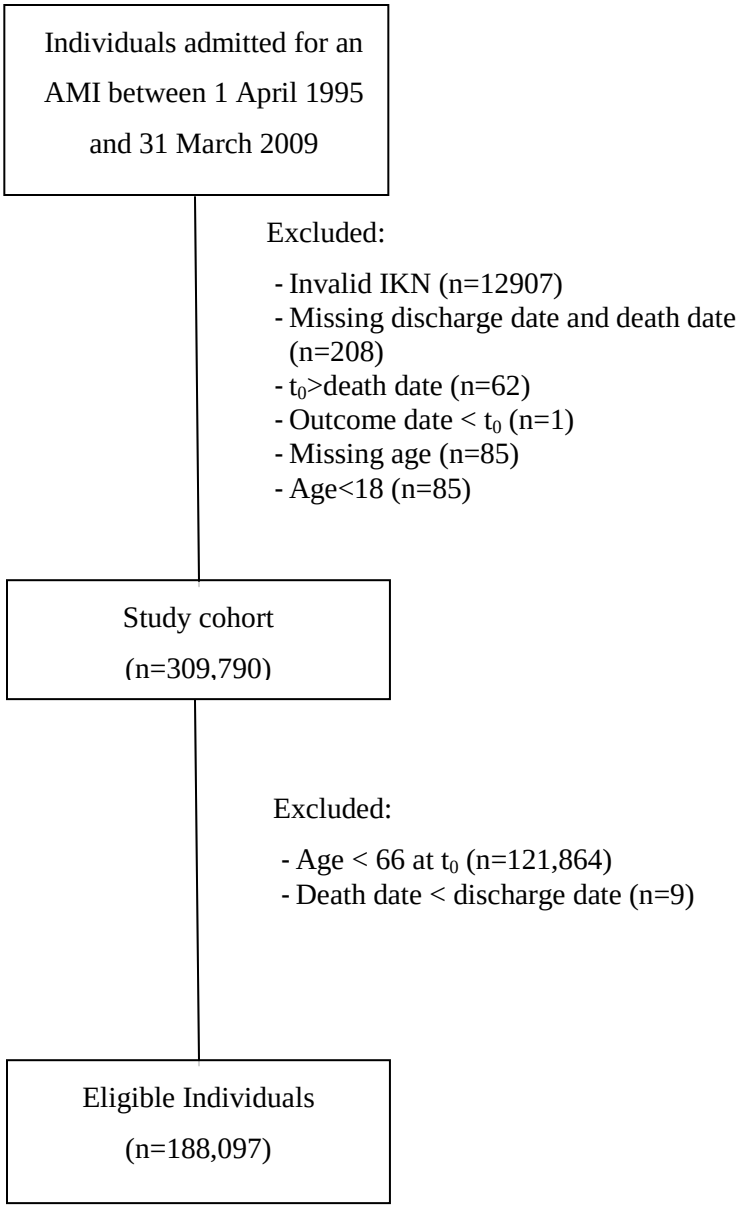

Figure 5.2 Distribution of Cardiac Pharmaceuticals

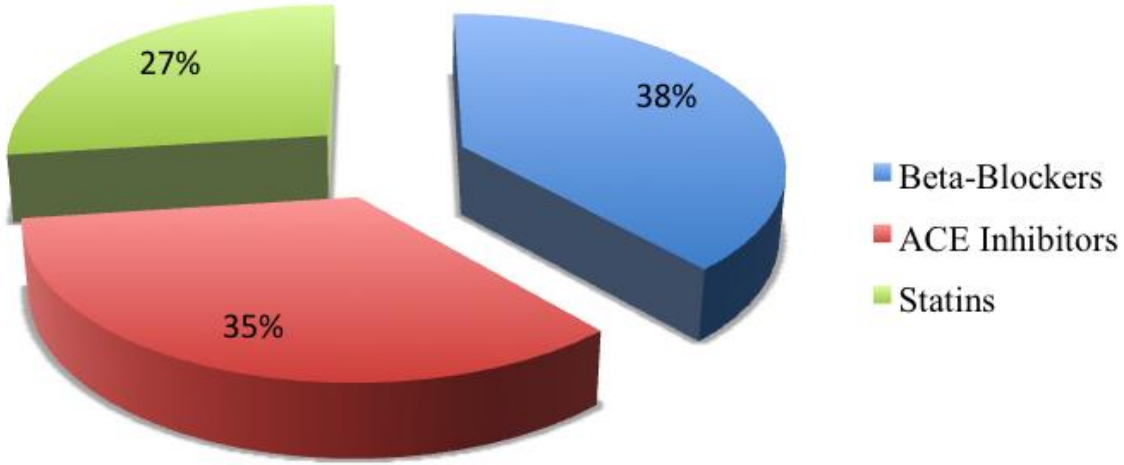

Figure 5.3 (a,b) Subgroup Analysis: fully adjusted risk ratios are plotted for the end points of beta-blockers and statins for individuals with depression according to various baseline characteristics

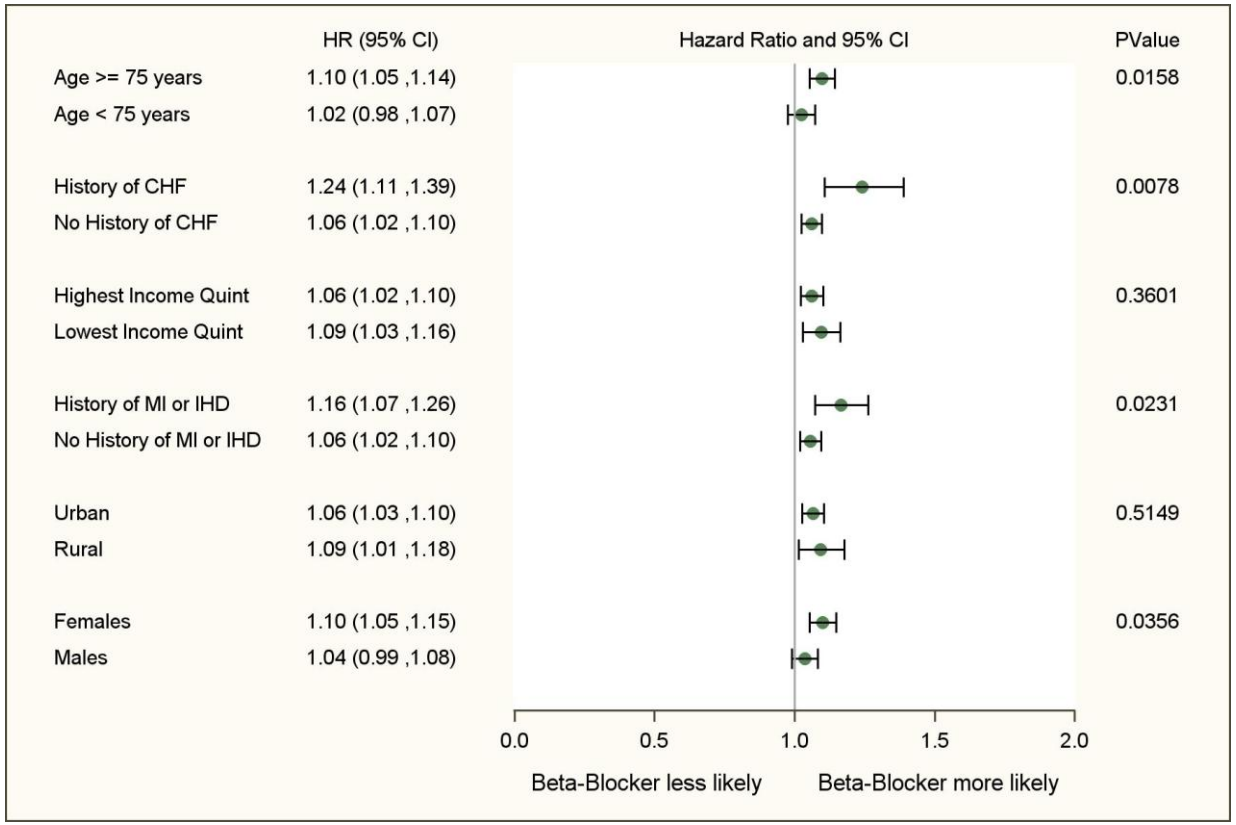

Figure 5.3a beta-blockers

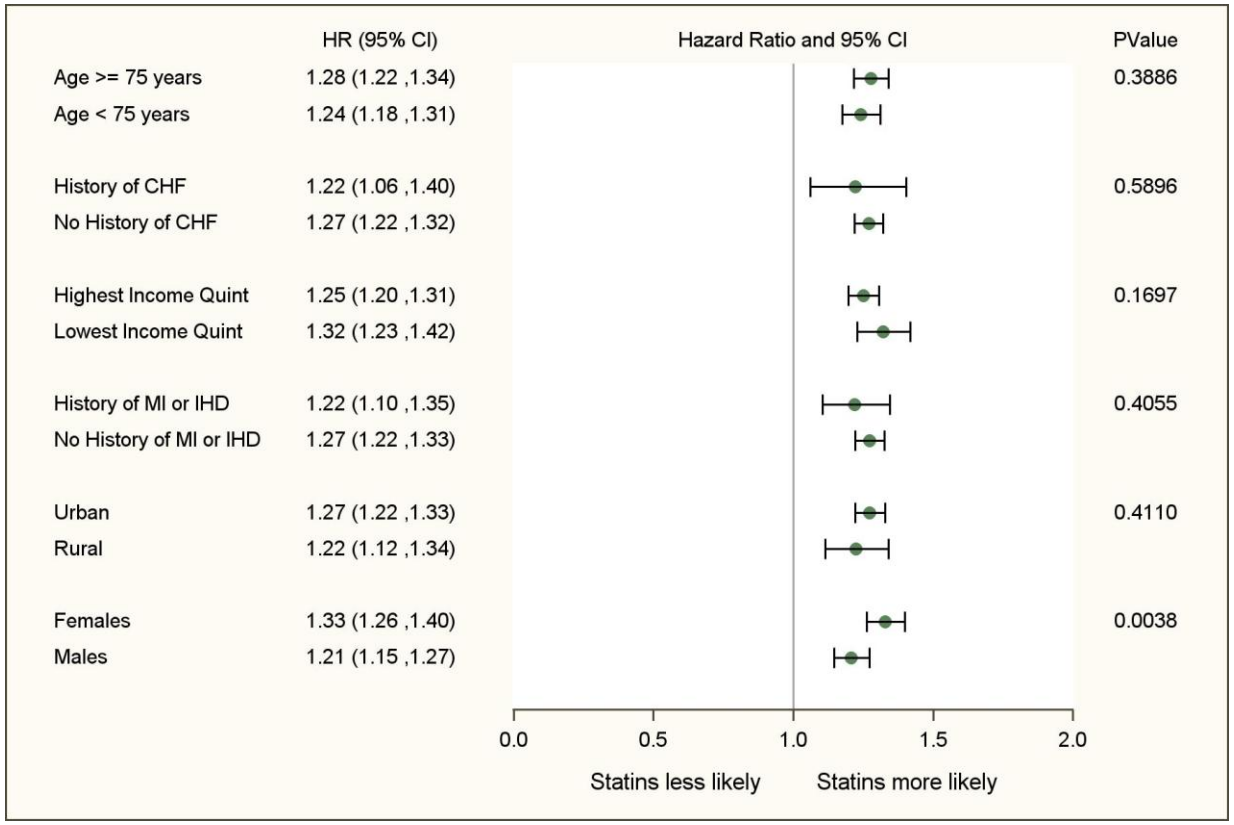

Figure 5.3b statins

Figure 5.4 (a,b) Subgroup Analyses: fully adjusted risk ratios are plotted for the end points of beta-blockers and statins for individuals with schizophrenia according to various baseline characteristics

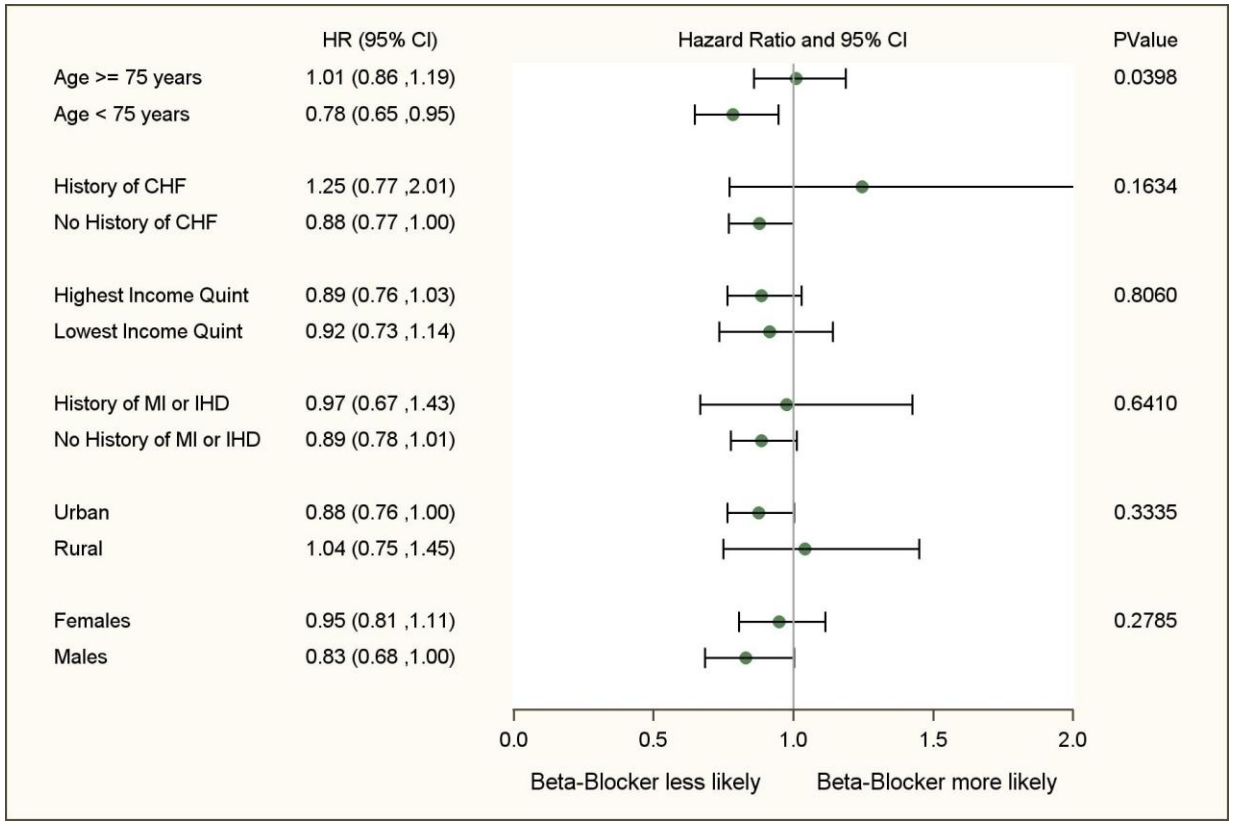

Figure 5.4a beta-blockers

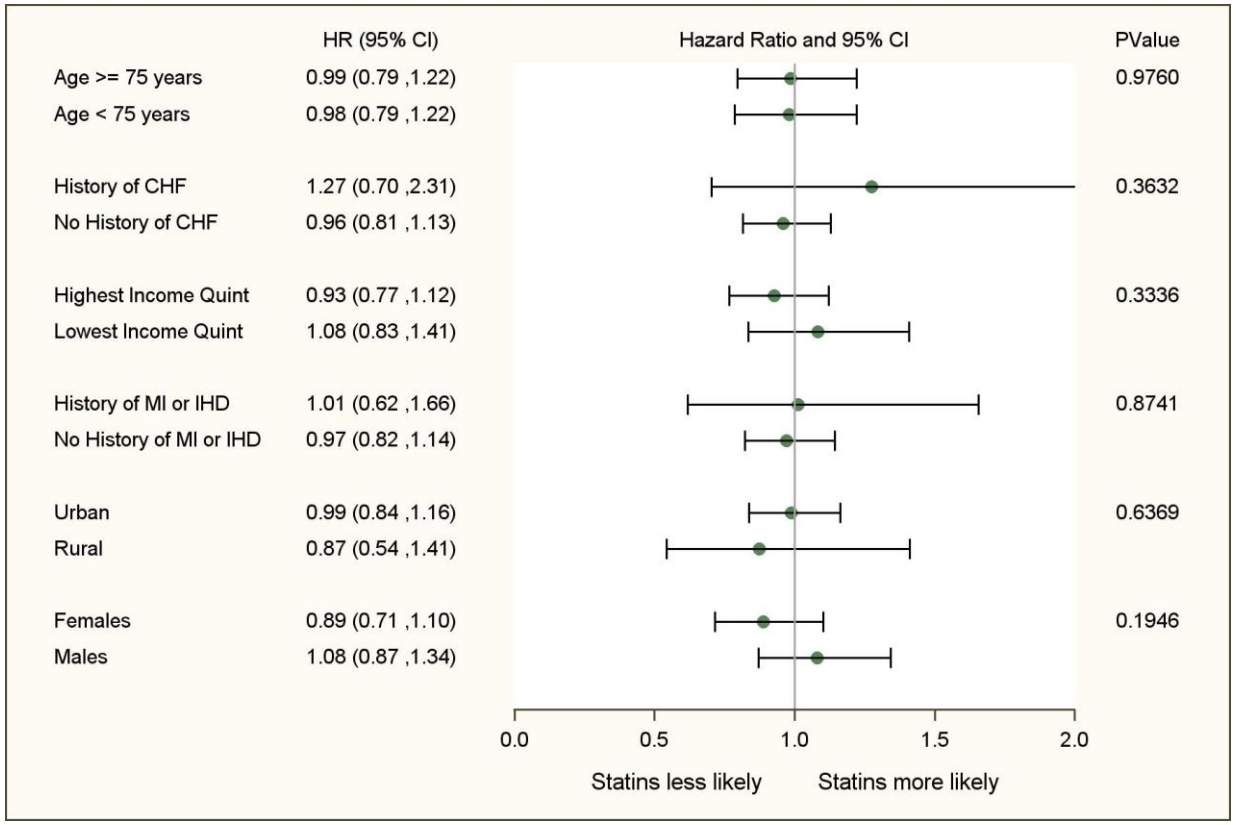

Figure 5.4b statins

Figure 5.5 (a, b) Subgroup Analyses: fully adjusted risk ratios are plotted for ACE inhibitor end point, stratified by follow-up time, for individuals with depression according to various baseline characteristics

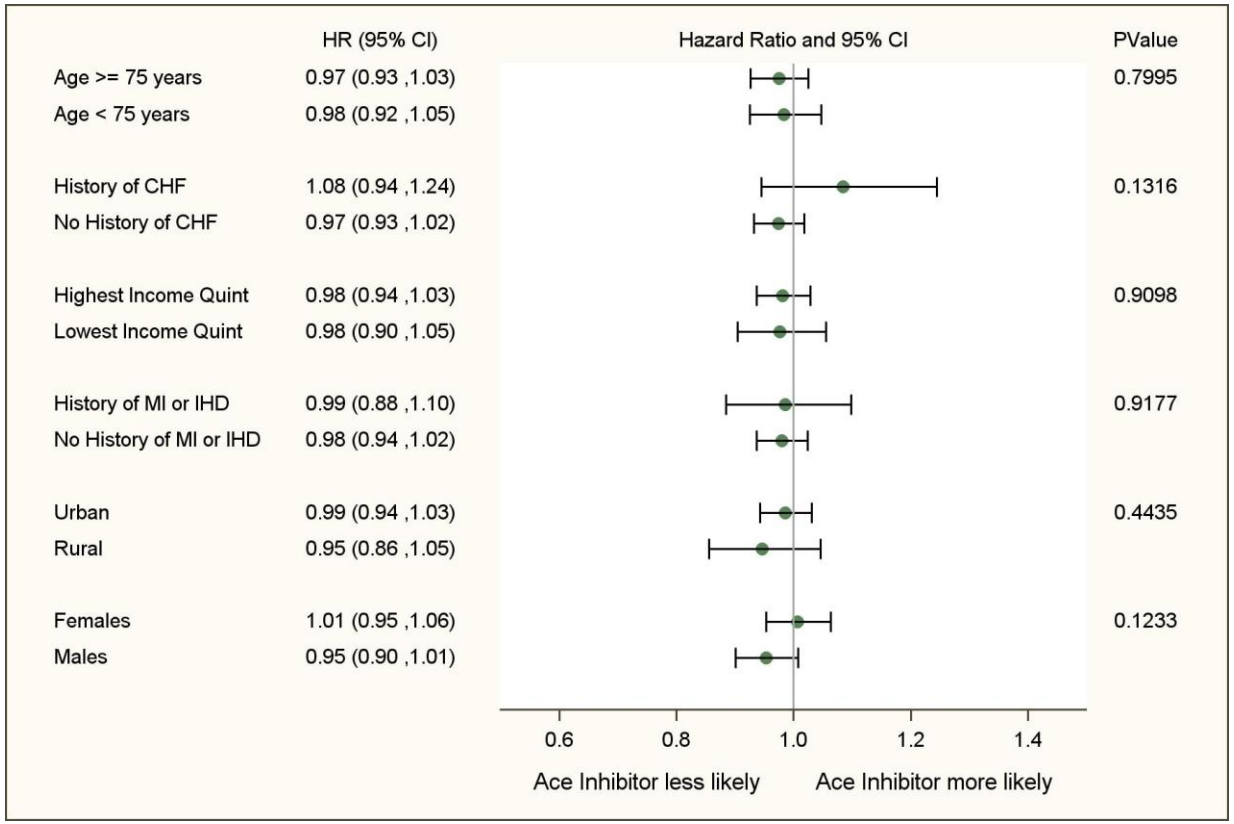

Figure 5.5a Follow-Up: ≤ 2 days post-discharge

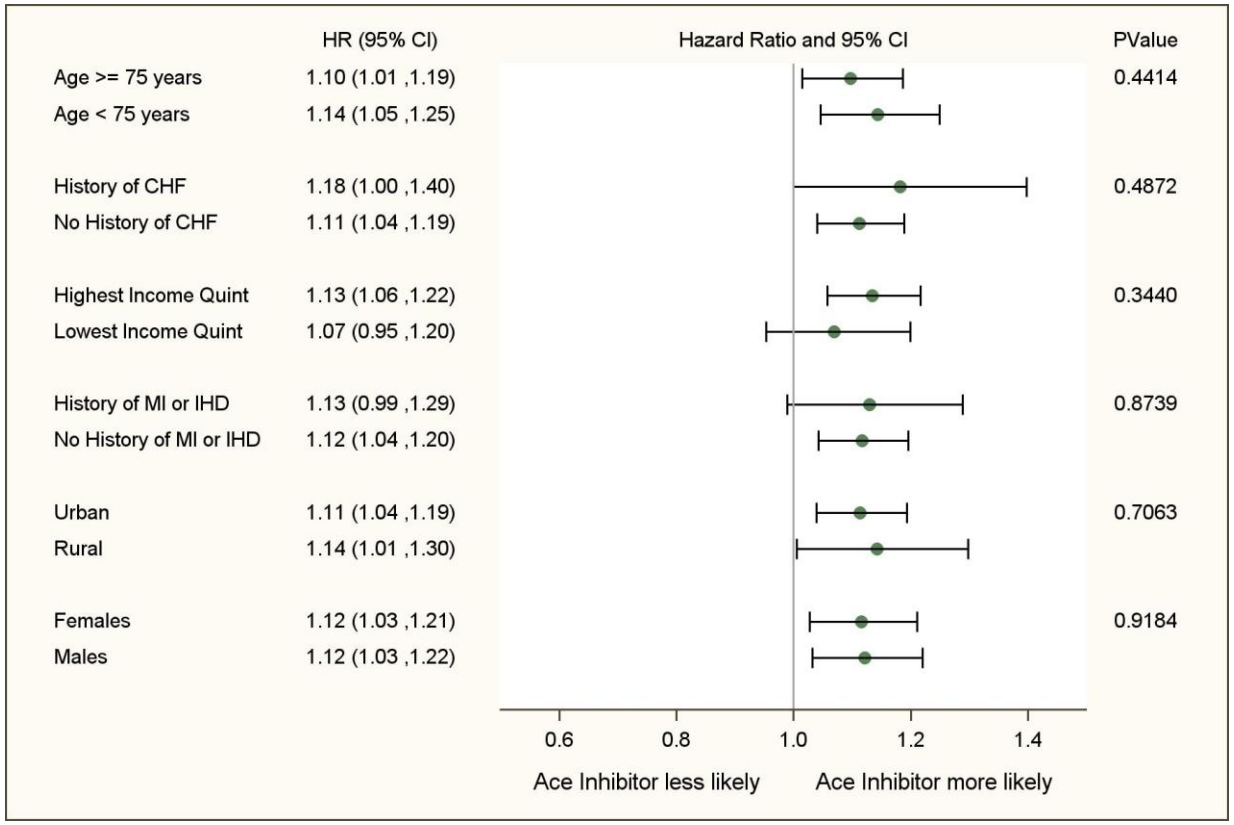

Figure 5.5b Follow-Up: > 2 days post-discharge

Figure 5.6 (a, b) Subgroup Analyses: fully adjusted risk ratios are plotted for the ACE inhibitor end point, stratified by follow-up time, for individuals with schizophrenia according to various baseline characteristics

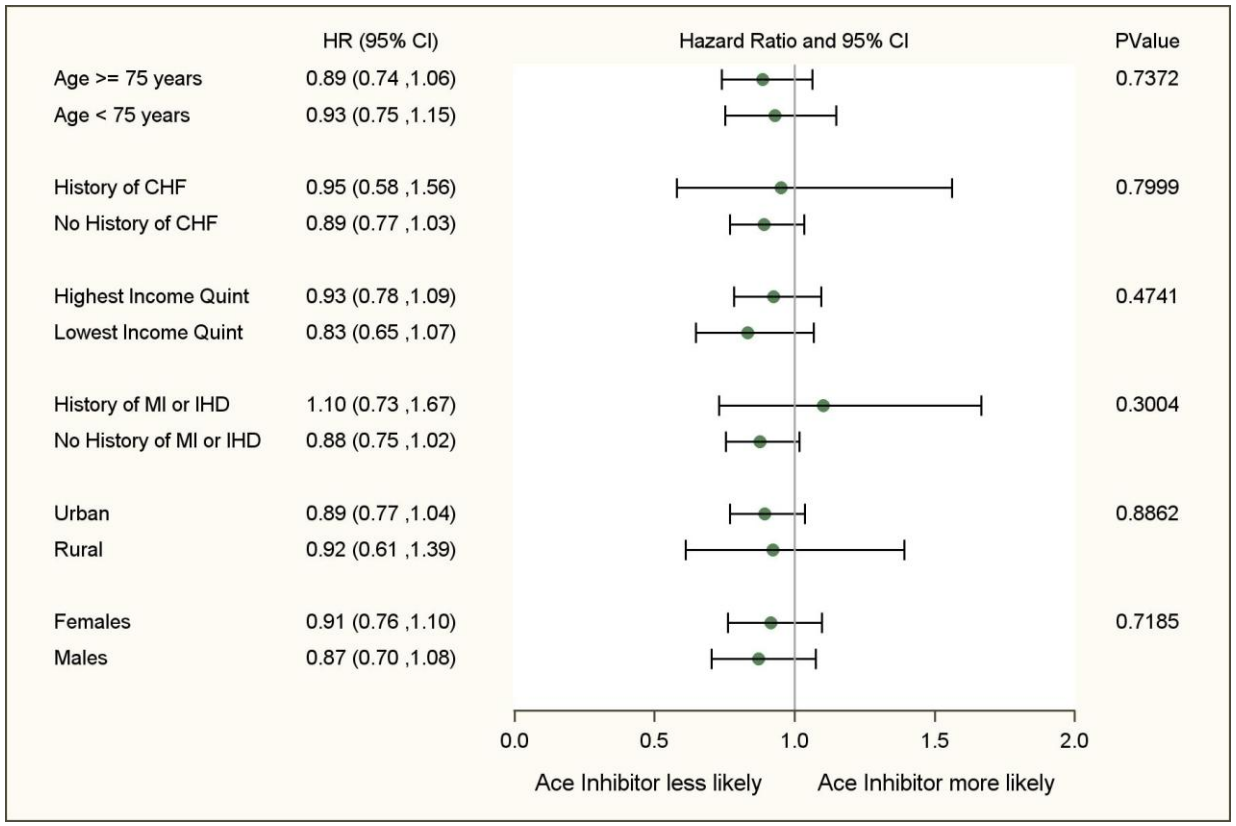

Figure 5.6a Follow-Up: ≤ 2 days post-discharge

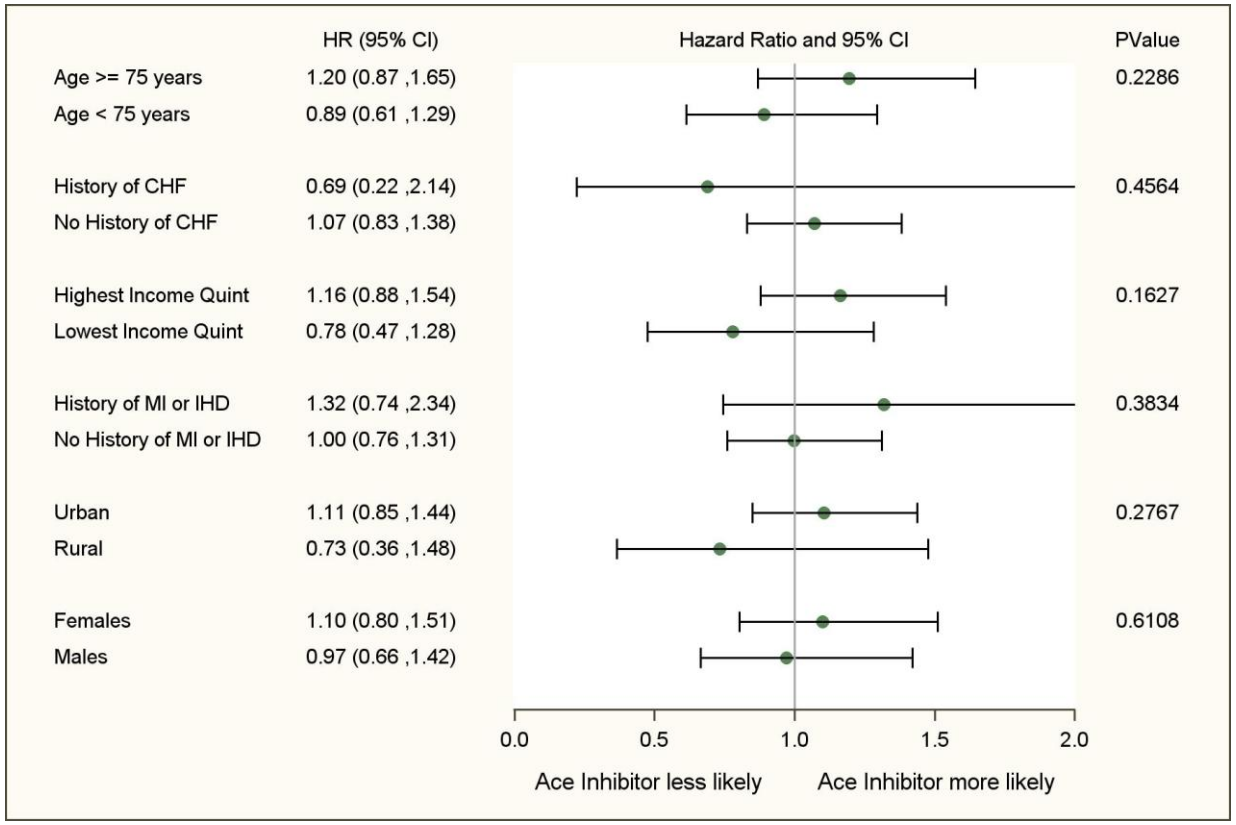

Figure 5.6b Follow-Up: > 2 days post-discharge

Table 5.3 Adjusted Hazard Ratio for Receipt of Beta-Blocker, Statins and ACE Inhibitors according to Prior Drug Use for those with Depression

Outcome	Previous Rx Use	HR (95% CI)	p-value
Beta-Blockers	Prior beta-blocker use	1.19 (1.14-1.26)	<0.0001
	No prior beta-blocker use	1.01 (0.97-1.05)	
	Prior statin use	1.09 (1.03-1.15)	<0.0001
	No prior statin use	1.06 (1.02-1.10)	
	Prior ACE use	1.11 (1.06-1.17)	0.0164
	No prior ACE use	1.04 (0.99-1.08)	

Outcome	Previous Rx Use	HR (95% CI)	p-value
Statins	Prior beta-blocker use	1.25 (1.17-1.32)	0.5202
	No prior beta-blocker use	1.27 (1.22-1.34)	
	Prior statin use	1.18 (1.12-1.24)	<0.0001
	No prior statin use	1.35 (1.28-1.41)	
	Prior ACE use	1.24 (1.17-1.31)	0.2606
	No prior ACE use	1.29 (1.23-1.35)	

Outcome	Previous Rx Use	Follow-Up Time ≤ 2 days		Follow up Time > 2 days	
		HR (95% CI)	p-value	HR (95% CI)	p-value
ACE Inhibitors	Prior beta-blocker use	0.99 (0.93-1.07)	0.4934	1.15 (1.05-1.27)	0.3707
	No prior beta-blocker	0.97 (0.93-1.02)		1.10 (1.02-1.18)	
	Prior statin use	1.03 (0.96-1.11)	0.0600	1.12 (1.02-1.23)	0.9396
	No prior statin use	0.96 (0.91-1.01)		1.12 (1.03-1.20)	
	Prior ACE use	0.98 (0.93-1.05)	0.8058	1.19 (1.11-1.29)	0.0025
	No prior ACE use	0.98 (0.93-1.03)		1.01 (0.92-1.11)	

Table 5.4 Adjusted Hazard Ratio for Receipt of Beta-Blockers, Statins and ACE Inhibitors according to Prior Drug Use for those with Schizophrenia

Outcome	Previous Rx Use	HR (95% CI)	p-value
Beta-Blockers	Prior beta-blocker Use	1.38 (1.11-1.72)	<0.0001
	No prior beta-blocker use	0.77 (0.67-0.90)	
	Prior statin use	1.05 (0.82-1.35)	0.1385
	No prior statin use	0.85 (0.74-0.98)	
	Prior ACE use	1.15 (0.95-1.38)	0.0010
	No prior ACE use	0.76 (0.65-0.90)	

Outcome	Previous Rx Use	HR (95% CI)	p-value
Statins	Prior beta-blocker Use	1.31 (0.98-1.75)	0.0226
	No prior beta-blocker use	0.89 (0.74-1.06)	
	Prior statin use	1.28 (1.01-1.63)	0.0057
	No prior statin use	0.84 (0.68-1.02)	
	Prior ACE use	1.22 (0.97-1.52)	0.01148131
	No prior ACE use	0.83 (0.67-102)	

Outcome	Previous Rx Use	Follow-Up Time ≤ 2 days		Follow up Time > 2 days	
		HR (95% CI)	p-value	HR (95% CI)	p-value
ACE Inhibitors	Prior beta-blocker use	1.14 (0.89-1.47)	0.0254	0.88 (0.48-1.59)	0.5247
	No prior beta-blocker	0.81 (0.69-0.97)		1.08 (0.83-1.42)	
	Prior statin use	0.97 (0.72-1.30)	0.5381	0.94 (0.57-1.54)	0.6119
	No prior statin use	0.88 (0.75-1.03)		1.08 (0.92-1.44)	
	Prior ACE use	1.02 (0.83-1.24)	0.0891	1.21 (0.87-1.67)	0.2054
	No prior ACE use	0.81 (0.67-0.98)		0.89 (0.61-1.28)	

Chapter 6: Discussion

6.1 Main Findings

A retrospective, population-based cohort study was performed to evaluate the association between depression and schizophrenia and the quality of cardiac care following a hospitalization for an acute myocardial infarction.

Individuals with a history of depression or schizophrenia without a CVD history were more likely, or as likely (respectively) to receive cardiac catheterization or PTCA as individuals without a mental disorder. Conversely, CABG was less likely to be provided to individuals with depression and possibly also with schizophrenia. There were too few observations in those with a history of schizophrenia to make a firm conclusion, although the point estimate was also lower. With respect to guideline recommended pharmaceutical interventions, individuals with a history of schizophrenia were as likely to receive beta-blockers or statins and individuals with a history of depression were more likely to receive beta-blockers and statins as persons with no history of depression. For ACE inhibitors, the association was dependent on time since hospital discharge and was therefore time-stratified. In the first two days following discharge individuals with a history of depression or schizophrenia were as likely as someone without a mental disorder to receive an ACE inhibitor. After two days following discharge individuals with a history of depression or schizophrenia were more likely to receive an ACE inhibitor. The sub-analysis revealed that the association between depression and schizophrenia and the receipt of a cardiac pharmaceutical was modified by prior use of that cardiac pharmaceutical.

6.2 Discussion

These results suggest that Ontarians with a history of depression or schizophrenia with no CVD history are receiving comparable cardiac care following hospitalization for an AMI. The

fact that our findings were consistent across 'hard' (surgical) and 'soft' (pharmaceutical) interventions helps to support the conclusion that there are no disparities in the acute cardiac care of adults without prior CVD with a history of depression or schizophrenia hospitalized for an AMI. However, the CVD history effect modification indicates that there are significant differences in cardiac care for individuals who have CHF, IHF or a previous AMI.

In each of the analyses the association was stronger for individuals with depression than that for those with schizophrenia compared with persons with no history of a mental disorder. There are several reasons why the pattern of care between depression and schizophrenia was clinically predictable. Firstly, the increased likelihood of undergoing a catheterization or PTCA, and receiving a cardiac drug intervention for individuals with a history of depression can be explained clinically because depression is well established independent predictor of both the onset and progression of CVD (88). Thus, it is expected that individuals with a history of depression would receive more aggressive cardiac care than persons with no history of a mental disorder. In contrast, while individuals with schizophrenia often present with several cardiovascular risk factors (100), schizophrenia has not been clearly established as a determinant of CVD disease and mortality. Comparable results for the use of catheterization, PTCA and receipt of cardiac drugs, is consistent with this logic.

The lower use of CABG in persons with a history of depression can be explained, in part, by the fact that depression is considered a contraindication to open-heart surgery (89, 90). Indeed, of the three cardiac procedure endpoints, only CABG had a decreased likelihood of being received by individuals with depression, suggesting that the observed pattern of cardiac care is aligned with sound clinical practice.

It may be argued that because individuals with schizophrenia often present with numerous cardiovascular risk factors (101) than individuals without a mental disorder physicians should recognize that they have an increased need for cardiac interventions. However, the soft-endpoint analysis indicates that this vulnerable population may in fact be receiving higher levels of cardiac care than those without a mental disorder despite having a baseline cardiovascular risk profile similar to that of adults with no history of a mental disorder. Research has shown that individuals with schizophrenia have higher 'failure-to-fill' rates than the general population (98, 99). This suggests that there may be significant differential outcome misclassification since the use of administrative databases limits the ability to detect prescribed but unfilled prescriptions. Although this study was only able to find that individuals with schizophrenia are receiving comparable care it is likely that this represents an underestimation of the true association and in reality physicians are considering the cardiovascular risk profile of this population and treating accordingly.

Another patient factor that could contribute to the difference in results for depression versus schizophrenia is refusal to give consent. Research on schizophrenia has found that the level of an individuals' decisional capacity impairment is directly related to the degree of cognitive deficits and whether a patient is in an acute psychotic phase (102). Thus, incapacity to make an informed decision may be a factor that would reduce receipt of invasive surgical interventions such as CAGB.

Treatment decisions for an AMI is a complex process with many contributing factors. The sub-analysis helped to identify some of the components that may have contributed to this process. For example, the association between depression or schizophrenia and the receipt of a cardiac intervention was dependent on diagnoses of CHF, IHD or AMI or cardiac drug prescriptions prior to the index event. The most significant, the CVD history effect modification,

occurred for the receipt of the surgical endpoints. Individuals with depression or schizophrenia were more likely to receive a cardiac procedure if they had no previous CVD diagnoses, but as likely or less likely to receive a cardiac procedure if they had previous CVD diagnoses. This finding may reflect the risk paradox that exists in cardiac surgery: the superiority of surgical over medical treatment is most pronounced in high-risk patients (103). By the same token, the CVD history effect may be a reflection of the fact that individuals with a CVD history with depression or schizophrenia were perceived as being 'sicker' and of having a higher risk profile than their counterparts without a mental disorder. It is not surprising individuals with depression or schizophrenia with CHF, IHD or previous AMI were less likely to receive a cardiac procedure in view of the fact that individuals with a high-risk profile have been associated with cardiac surgical mortality (104-106).

In terms of the effect modification seen in the analysis of the pharmaceutical endpoints there was a marked increase in the likelihood of an individual with depression or schizophrenia receiving a cardiac drug post-discharge if that individual had already been on this medication prior to their AMI admission. It is possible that this effect is due to the fact that these individuals are already being prescribed the cardiac medication and do not need to refill their prescription within the 30-day follow-up of this study. Yet, contrasting the depression and schizophrenia effect modification by prior use of the drug suggests that individuals with schizophrenia may be receiving the prescription but are failing to fill it post-discharge because research has shown that individuals with schizophrenia have higher 'failure-to-fill' rates than the general population (98, 99). As previously mentioned, analog studies would greatly enhance our understanding of the underlying processes of this effect modification. In addition, future studies that defined a longer follow-up period and evaluated primary cardiac care as well as inpatient cardiac care may be able to shed some light on this effect modification.

6.3 Study Strengths and Limitations

A primary strength of this study is that it has addressed several key methodological shortcomings of previous studies of treatment disparities in the care of individuals with cardiovascular disease and a comorbid mental disorder. Firstly, this study restricted the study population to individuals with an indication for the cardiac procedure or intervention of interest; those admitted to hospital with a cardiac event. Secondly, by focusing on two individual mental disorders that are known to be associated with differing levels of stigma (rather than combining all mental disorders into a single group), this reduced the potential for non-differential misclassification of exposure and bias towards finding no differences in treatment. It also helped to differentiate between treatment differences that may be due to stigma from those that may be due to good medical care. Thirdly, this study used 'time to treatment' as a more sensitive measure of treatment disparities. Finally, the use of both cardiac procedures and pharmaceutical intervention endpoints took into account the varying levels of physician judgment and discretion that different cardiac interventions require and as such, helped to differentiate treatment disparities due to stigma from those due to good medical care.

This is one of only a few studies to investigate this issue in the context of the Canadian healthcare system. This is important because the majority of studies published to date have been conducted in the United States, the results of which are unlikely to be generalizable to the Canadian population given the lack of universal healthcare in that country. Furthermore, the study that evaluated the surgical procedures is more generalizable because the cohort was defined as all persons hospitalized for an AMI rather than adults ≥65 years old as most other studies have done.

An important limitation of this study was the inability to conclusively determine if the treatment differences found were due to provider behavior or were masked by patient behaviors.

It is very difficult for a population-based record-linkage study to uncover the underlying cause of treatment differences between individuals with and without a mental disorder.

The possibility of selection bias is minimized by the use of a population-based cohort of all persons admitted for an AMI. Moreover, the use of administrative health databases ensured follow-up of all cohort members thereby restricting the potential for losses to follow-up. The possibility of Berkson's bias needs to be considered when both the exposure and outcome are diseases, as hospitalized individuals have a higher likelihood of having the outcome than non-hospitalized individuals.[92] However, the use of an all hospitalized cohort prevented this source of selection bias.

Administrative health records are vulnerable to recording errors, which might result in both exposure (mental disorders) and outcome (receipt of cardiac intervention) misclassification. The use of diagnostic codes to identify persons with depression and schizophrenia has not been validated in Ontario. However, the use of a two-diagnosis algorithm has been validated in United States (82, 95). In addition, depression and schizophrenia are disorders that can be both episodic and chronic. While administrative health databases can detect a diagnosis of either condition, they cannot detect disease resolution. As such, exposure was analyzed as a time-fixed variable although it may actually be time-dependent in some individuals. Since the resulting misclassification of exposure is independent of an individual's outcome status (receipt of cardiac treatment) it is non-differential and biased the results towards the null. Lastly, there is a possibility for misclassification because persons with a mental disorder may not appear in the databases as being diagnosed with a mental disorder and were classified as unexposed.

It is likely that the potential for outcome misclassification was minimal for the surgical outcomes by virtue of their invasive nature and high physician remuneration for these expensive interventions (thus, encouraging more complete reporting of these procedures in the

administrative data). However, there is an increased likelihood of outcome misclassification for the pharmacological outcomes because the ODB database only allows the identification of prescriptions that have been filled. As such, individuals that are given a prescription by their physician who never filled them were misclassified as not having received the indicated cardiac intervention (study outcome). In addition, failure-to-fill rates have been shown to be higher among individuals with psychiatric conditions (8.0%, chi-square=37.4, $p<0.001$) (98, 107). This could have led to differential misclassification and under estimation of the true association.

All observational studies are susceptible to residual confounding. Unmeasured and uncontrolled factors that could have contributed to residual confounding include patient behaviors, race, and smoking. In addition, SES is measured using postal codes and may not accurately assess an individual's true SES. However, it is unlikely that these factors contributed to confounding because of the homogeneity of the study population.

The analysis of pharmacological interventions was not limited by some of the restrictions that were unavoidable with the analysis of cardiac surgeries. For example, using 'days' as the unit of analysis is ideal when examining pharmaceutical endpoints because an individual would fill their prescription post-discharge, which is likely one to two days following their index event. In contrast, an individual would likely receive a surgical procedure within hours of their index event, making 'hours' a more suitable unit of analysis for these interventions.

6.4 Future Research and Recommendations

There are many directions that future research can take to help give insight into the physical treatment of individuals with a mental disorder. Further analysis using this study population may shed more light on the underlying processes of cardiac care treatment decisions for individuals with depression or schizophrenia. Future analyses that could be undertaken include: (1) undertaking a sensitivity analysis that evaluates the validity of the exposure

definition; (2) defining more than two mental disorder exposure groups; (3) using 'hours' as a unit of analysis rather than 'days' to analyze the surgical endpoints; (4) evaluating an 'episode of care' rather than an admission; (5) extending the follow-up time for the pharmaceutical endpoints to reduce outcome misclassification; and (6) expand the scope of the analysis to interventions provided in primary care.

Individuals with a mental disorder are a heterogeneous group so should not be evaluated as a single entity. As such we recommend that future research evaluate each mental disorder classification as a separate subgroup as each disorder has different characteristics and are associated with different patient profiles, such as age and comorbidity. Although research on the physical care of individuals with a mental disorder has made significant strides in the last decade there is a long way to go before we can safely conclude individuals with a mental disorder are receiving appropriate physical healthcare. However, this study is an important step in establishing the factors that contribute to treatment decisions in the cardiac care of individuals with depression or schizophrenia.

References

1. McCabe MP, Leas L. A qualitative study of primary health care access, barriers and satisfaction among people with mental illness. Psychology, Health & Medicine. 2008;13(3):303.

2. Link BG, Phelan JC. Conceptualizing stigma. Annu Rev Sociol. 2001;27:363.

3. Rathore S, Wagn Y, Druss B, Masoudi F, Krumholz H. Mental disorders, quality of care, and outcomes among older patients hospitalized with heart failure. Arch Gen Psychiatry. 2005;65(12):1402.

4. Jones S, Howard L, Thornicroft G. 'Diagnostic overshadowing': Worse physical health care for people with mental illness. Acta Psychiatric Scand. 2008;118:169.

5. Boyd R, Genuis S. The environmental burden of disease in canada: Respiratory disease, cardiovascular disease, cancer, and congenital affliction. Environmental Research. 2008;106:240.

6. Felker B, Yazel J, Short D. Mortality and medical comorbidity among psychiatric patients: A review. Psychiatric Serv. 1996;47:1356.

7. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity A review of potential mechanisms. Journal of Psychosomatic Research. 2002;53:897.

8. Stewart P. A report on mental illnesses in Canada. 2002.

9. Unutzer J, Patrick DL, Simon G, Grembowski D, Walker E, Rutter C, et al. Depressive symptoms and the cost of health services in HMO patients aged 65 years and older. A 4-year prospective study. JAMA. 1997 May 28;277(20):1618-23.

10. Ariyo AA, Haan M, Tangen CM, Rutledge JC, Cushman M, Dobs A, et al. Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Cardiovascular health study collaborative research group. Circulation. 2000 Oct 10;102(15):1773-9.

11. Murray CJ, Lopez AD. Alternativeprojections of mortality and disability by cause 1990-2020: Global burden of disease study. Lancet. 1997;349(9064):1497.

12. Kurdyak PA, Gnam WH, Goering P, Chong A, Altern DA. The relationship between depressive symptoms, health service consumption, and prognosis after acute myocardial infarction: A prospective cohort study. BMC Health Services Research. 2008;8:200.

13. Balsa AI, McGuire TJ. Prejudice, clinical uncertainty and stereotyping as sources of health disparities. Journal of Economic Health. 2010;24:89.

14. Lawrence D, Kisely S. Review: Inequalities in healthcare provision for people with severe mental illness. J Psychopharmacol. 2010;24:61.

15. Hippisley-Cox J, Parker C, Coupland C. Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: A cross sectional study. Heart. 2007;93:1256.

16. Lawrence DM, Holman CD, Jablensky AV, Hobbs MS. Death rate from ischaemic heart disease in western Australian psychiatric patients 1980-1998. Br J Psychiatry. 2003 Jan;182:31-6.

17. Kisely S, Smith M, Lawrence D, Cox M, Campbell L, Maaten S. Inequitable access for mentally ill patients to some medically necessary procedures. CMAJ. 2007;176(6):779.

18. Young JK, Foster DA. Cardiovascular procedures in patients with mental disorders (letter to the editor). JAMA : the journal of the American Medical Association. 2000;283:3198.

19. Druss B, Bradford D, Rosenheck RA. Mental disorders and use of cardiovascular procedures after myocardial infarction. JAMA: the journal of the American Medical Association. 2000;283(4):506.

20. Druss B, Bradford D, Rosenheck RA, Radford MJ, Krumholz HM. Quality of medical care and excess mortality in older patients with mental disorders. Archives of General Psychiatry. 2001;58:562.

21. Dolder CR, Furtek K, Lacro JP, Jeste DV. Antihypertensive medication adherence and blood pressure control in patients with psychotic disorders compared to persons without psychiatric illness. Psychosomatics. 2005;46:135.

22. Desai M, Rosenheck RA, Druss B, Perlin J. Mental disorders and quality of care among post acute myocardial infarction patients. The Journal of Nervous and Mental Disease. 1999;89:1328.

23. Jones L, Carney C. Mental disorders and revascularization procedures in a commercially insured sample. Psychosomatic Medicine. 2005;67:568.

24. Petersen LA, Normand S, Druss BG, Rosenheck RA. Process of care and outcome after acute myocardial infarction for patients with mental illness in the VA health care system: Are there disparities? Health Services Research. 2003;38(1):41.

25. Kisely S, Smith M, Lawrence D, Cox M, Campbell L, Maaten S. Inequitable access for mentally ill patients to some medically necessary procedures. 2007. CMAJ;176(6):779.

26. Pescosolito B, Link CL, Phelan JC, Bresnahan M, Stueve A. Public conceptions of mental illness: Labels, causes, dangerousness, and social distance. AM J Public Health. 2002;89:1328.

27. Kisely S, Campbell LA, Wang Y. Treatment of ischaemic heart disease and stroke in individuals with psychosis under universal healthcare. The British Journal of Psychiatry. 2009;195:545.

28. Atzema CL, Schull MJ, Tu JV. The effect of a charted history of depression on emergency department triage and outcomes in patients with acute myocardial infarction. CMAJ. 2011;183(6).

29. Montague TJ. Patients first: Closing the healthcare gap in canada. Mississauga, Ontario, Canada: John Wiley and Sons; 2004.

30. Kilbourne AM, Switzer G, Hyman K, Crowley-Matoka M, Fine MJ. Advancing health disparities research within the health care system: A conceptual framework. AM J Public Health. 2006;96:2113.

31. Fiscella K. Eliminating disparities in healthcare through quality improvement. Totowa, NJ, USA: Humana Press Inc; 2007.

32. Wielgosz A. The growing burden of heart disease and stroke in canada. Ottawa, CA: 2003.

33. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, et al. Gender disparities in the diagnosis and treatment of non-st-segment elevation acute coronary syndromes. Journal of American College of Cardiology. 2005;45(6):832.

34. Lagerqvist B, Safstrom K, Stahle E, Wallentin L, Swahn E. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men. JACC. 2001;38(1):41.

35. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TRD, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction-the british health foundation RITA 3 randomized trial. The Lancet. 2002;360:743.

36. Glaser R, Hermann HC, Murphy SA, Demopoulos LA, Cannon CP, Braunwald E. Benefit of an early invasive strategy in women with acute coronary syndromes. JAMA : the journal of the American Medical Association. 2002;288(24):3124.

37. Anand SS, Xie CC, Mehta S, Franzosi MG, Joyner C, Chrolavicius S, et al. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. JACC. 2005;46(10):1845.

38. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA 2002 guideline update for the management of patients with unstable

angina and non-ST-segment elevation myocardial infarction – summary article. JACC. 2002;40(7):1366.

39. Abramov D, Tamariz M, Sever JY, Christakis GT, Bhatanger G, Heenan AL, et al. The influence of gender on the outcome of coronary artery bypass surgery. Ann Thorac Surg. 2000;70:800.

40. Siegler M. Should age be a criterion in health care. The Hastings Center Report. 1984;14(5):24.

41. Nahlor G, editor. Dictionary of pharmaceutical medicine. Germany: Springer-Verlag/Wien.; 2009.

42. Naylor CD, Levinton CM, Baigrie RS, Goldman BS. Placing patients in the queue for coronary surgery: Do age and work status alter canadian specialists' decisions. J Gen Intern Med. 1992;7(5):492.

43. Pettersen KL. Age discrimination in the use of fibrinolytic therapy in acute myocardial infarction in norway. Age and Ageing. 1995;24:198.

44. van Ryan M, Burgess D, Malat J, Griffith J. Physician's perceptions of patients' social and behavioral characteristics and race disparities in treatment recommendations for men with coronary artery disease. American Journal of Public Health. 2006;96(2):351.

45. Siddiqi A, Nguyen QC. Cross-national comparative perspective on racial inequities in health: The USA versus canada. J Epidemiol Community Health. 2010;64:29.

46. Wong MD, Shapiro MF, Boscardin WJ, Ettner SL. Contribution of major diseases to disparities in mortality. N Engl J Med. 2002;347(20):1585.

47. Taylor SL, Lurie N. The role of culturally competent communication in reducing ethnic and racial healthcare disparities. AM J Manag Care. 2004;10:SP1.

48. Kapral MK, Wang H, Mamdani M, Tu JV. Effect of socioeconomic status on treatment and mortality after stroke. Stroke. 2002;33:268.

49. Schuman KA, Berlin JA, Harless W, Kemer JF, Sistrunk S, Gersh BJ, et al. The effect of race and sex on physicians' recommendations for cardiac catheterization. The New England Journal of Medicine. 1999;340(8):618.

50. Mort EA, Weissman JS, Epstein AM. Physician discretion and racial variation in the use of surgical procedures. Arch Intern Med. 1994;154:761.

51. Graber M, Bergus G, Dawson J, Wood GB, Levy BT, Levin I. Effect of a patient's psychiatric history on physicians' estimation of probability of disease. JGIM. 2000;15:204.

52. McDonald D, Frakes M, Apostolidis B, Armstrong B, Goldblatt S, Bernardo D. Effect of a psychiatric diagnosis on nursing care for nonpsychiatric problems. Res Nurs Health. 2003;26:225.

53. Buckley PF, Fenley G, Mabe A, Peeples S. Recovery and schizophrenia. Clinical Schizophrenia & Related Psychoses. 2007;1(1):96.

54. Johnson RL, Roter D, Powe NR, Cooper LA. Patient race/ethnicity and quality of patient-physician communication during medical visits. AM J Public Health. 2004;94:2084.

55. Anderson LM, Scrimshaw SC, Fullilove MT, Fielding JE, Normand J. Culturally competent healthcare systems: A systematic review. AM J Prev Med. 2003;24(3S):68.

56. Smedley BD, Stith AY, Nelson AR. Unequal treatment: Confronting racial and ethnic disparities in health care. Washington, DC: National Academy of Sciences: Institute of Medicine; 2002.

57. Plouffe L. Addressing social and gender inequalities in health among seniors in canada. Cad Saude Publica. 2003;19(3).

58. Saha S, Freeman M, Toure J, Tippens KM, Weeks C, Ibrahim S. Racial and ethnic disparities in the VA health care system: A systematic review. J Gen Intern Med. 2008;23(5):654.

59. Schulze B, Angermeyer MC. Subjective experiences of stigma. A focus group study of schizophrenic patients, their relatives and mental health professionals. Social Science & Medicine. 2008;56:299.

60. Lyons C, Hopley P, Horrocks J. A decade of stigma and discrimination in mental health: Plus ça change, plus c'est la meme chose (the more things change, the more they stay the same). Journal of Psychiatric and Mental Health Nursing. 2009;16:501.

61. Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwalk S, Hwu H, et al. Cross national epidemiology of major depression and bipolar disorder. JAMA : the journal of the American Medical Association. 1996;276(4):293.

62. Altemus M. Sex differences in depression and anxiety disorders: Potential biological determinants. Hormones and Behavior. 2006;50:534.

63. Ranga K, Krishnan R. Biological risk factors in late life depression. Biol Psychiatry. 2002;52:185.

64. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: A review of the epidemiology, risk and treatment evidence. MJA. 2009;190(7):S54.

65. Kendler KS, Gatz M, Gardner CO, Pedersen NL. Personality and major depression. Arch Gen Psychiatry. 2006;63:1113.

66. Vink D, Aartsen MJ, Schoevers RA. Risk factors for anxiety and depression in the elderly: A review. Journal of Affective Disorders. 2008;106:29.

67. American Psychiatric Association, editor. Diagnostic and statistical manual of mental disorders, fourth edition, text revision (DSM-IV-TR). 4th ed. Washington, D.C.: American Psychiatric Association; 1994.

68. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "Just the facts" what we know in 2008. 2. Epidemiology and etiology. Schizophrenia Research. 2008;102:1.

69. Strain JJ, Caliendo G, Alexis JD, Lowe RS, Karim A, Loigman M. PART II: Cardiac drug and psychotropic drug interactions: Significance and recommendations. 1999.

70. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hochman JS, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial Infarction—Executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). Circulation. 2004;110:588.

71. Krumholz HM, Anderson JL, Brooks NH, Fesmire FM, Lambrew CT, Landrum MB, et al. ACC/AHA clinical performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association task force on performance measures (writing committee to develop performance measures on ST-elevation and non-ST-elevation myocardial infarction). Circulation. 2006.

72. Kushner FG, Hand M, Smith SC, King SB, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update). Journal of the American College of Cardiology. 2009;54:2205.

73. Juurlink D, Preyra D, Croxford R, Chong A, Austin P, Tu J, et al. Canadian institute for health information discharge abstract database: A validation study. Toronto, Ontario: Institute for Clinical Evaluative Sciences; 2006.

74. Gibson D, Richards H, Chapman A. The national ambulatory care reporting system: Factors that affect the quality of its emergency data. International Journal of Information Quality. 2008;2(2):97.

75. Levesque L, Brophy JA, Zhang B. The risk of myocardial infarction with cyclooxygenase-2 inhibitors: A population study of elderly adults. Annals of Internal Medicine. 2005;142:481.

76. ICES data holdings: OHIP (ontario's health insurance plan) [Internet].; 2010 [updated August 09, 2011. Available from: https://outside.ices.on.ca/Data%20Holdings/Health%20Services/ohip/index.htm.

77. Iron K, Zagorski BM, Sykora K, Manual DG. Living and dying in Ontario: An opportunity for improved health information. Toronto, Ontario: Institute for Clinical Evaluative Sciences; 2008.

78. Hill AB. The environment and disease: Association or causation? Proceedings of the Royal Society of Medicine. 1965;58:295.

79. Kroska A, Harkness SK. Exploring the role of diagnosis in the modified labeling theory of mental illness. Social Psychology Quarterly. 2008;71(2):193.

80. Dunner DL, Fatemi SH, Clayton PJ. Major depressive disorders - *the medical basis of psychiatry*. In: 4th ed. Totowa, NJ, USA: Humana Press; 2008. p. 73.

81. Asghari S, Courteau J, Carpentier AC, Vanasse A. Optimal strategy to identify incidence of diagnostic of diabetes using administrative data. BMC Medical Research Methodology. 2009;9(62).

82. Lurie N, Popkin M, Dysken M, Moscovice I, Finch M. Accuracy of diagnosis of schizophrenia in medicaid claims. Hospital and Community Psychiatry. 1992;43:69.

83. Greenland S. Modeling and variable selection in epidemiologic analysis. AJPH. 1989;79(3).

84. SAS Institute. SAS (Statistical Analytical Software). 2010.

85. Cox DR. Regression models and life-tables (with discussion). Journal. 1972;34:187.

86. Stuart H, Arboleda-Florez J, Sartorius N. Pardigms lost. Lessons learned in fighting the stigma of mental illness and its consequences. Oxford University Press; 2012 (in press).

87. Kern MJ. Statistics and guidelines. In: Laskey WJ, editor. SCAI Interventional Cardiology Board Review Book. Philadelphia, PA: Lippincott Williams & Wilkins; 2007. p. 271.

88. Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, et al. Depression as a risk factor for coronary artery disease: Evidence, mechanisms, and treatment. Psychosomatic Medicine. 2004;66(3).

89. Mallik S, Krumholz HM, Lin ZQ, Kasl SV, Mattera JA, Roumains SA. Patients with depressive symptoms have lower health status benefits after coronary artery bypass surgery. Circulation. 2005;111:271.

90. Daumit GL, Pronovost PJ, Anthony CB, Guallar E, Steinwachs DM, Ford DE. Adverse events during medical and surgical hospitalizations for persons with schizophrenia. Archives of General Psychiatry. 2006;63:267.

91. Eagle KA, Nallamothu BK, Mehta RH, Granger CB, Steg PG, Van de Werf F, et al. Trends in acute reperfusion therapy for ST-segment elevation myocardial infarction from 1999 to 2006: We are getting better but we have a long way to go. European Heart Journal. 2008;29:609.

92. Masoudi FA, Bonow RO, Brindis RG, Cannon CP, DeBuhr J, Fitzgerald S, et al. ACC/AHA 2008 statement on performance meaures and reperfusion thearpy: A report of the ACC/AHA task force on performance measures (work group to address the challenges of performance measurement and reperfusion therapy). Journal of the American College of Cardiology. 2008;52(24).

93. Bang A, Grip L, Herlitz J, Kihlgren S, Karlsson T, Carldahi K, et al. Lower mortality after prehospital recognition and treatment followed by fast tracking to coronary care

compared with admittance via emergency department in patients with ST-elevation myocardial infarction. International Journal of Cardiology. 2008;129(3):325.

94. Barron HV, Bowlby LJ, Breen T, Rogers WJ, Canto JG, Zhang Y, et al. Use of reperfusion therapy for acute myocardial infarction in the United States. Circulation. 1998;97:1150.

95. Frayne SM, Miller DR, Sharkansky EJ, Jackson VW, Wang F, Halanych JH. Using administrative data to identify mental illness: What approach is best. American Journal of Medical Quality. 2010;25(1):42.

96. Fornasini M, Yarzebski J, Chiriboga D, Lessard D, Spencer FA, Aurigemma P, et al. Contemporary trends in evidence-based treatement for acute myocardial infarction. American Journal of Medicine. 2010;123(3):166.

97. Morkem R, Levesque L, Stuart H, Koller M, Colley L. Receipt of cardiac procedures following hospitalization for an AMI for individuals with a history of depression or schizophrenia compared to those without a mental disorder. 2011.

98. Gianfrancesco FD, Rajagopalan K, Sajatovic M, Wang R. Treatment adherence among patients with schizophrenia treated with atypical antipsychotics. Psychiatry Research. 2006;144:177.

99. Kennedy J, Tuleu I, Mackay K. Unfilled prescriptions of medicare beneficiaries: Prevalence, reasons, and types of medicines prescribed. J Manag Care Pharm. 2008;14(6):553.

100. De Hert M, Schreurs V, Vancampfort D, Van Winkel R. Metabolic syndrome in people with schizophrenia: A review. World Psychiatry. 2009;8:15.

101. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. American Heart Journal. 2005;150(6):1115.

102. Palmer BW, Dunn LB, Appelbaum PS, Jeste DV. Correlates of treatment-related decision-making capacity among middle-aged and older patients with schizophrenia. Archives of General Psychiatry. 2004;61:230.

103. Roques F, Nashef SAM, Michel P, Gauducheau E, de Vincentiis C, Baudet E, et al. Risk factors and outcome in european cardiac surgery: Analsis of EuroSCORE multinational database of 19030 patients. European Journal of Cardio-Thoracic Surgery. 1999;15:816.

104. Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Paranandi L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass surgery patients. Journal of the American Medical Association. 1992;267:2344.

105. Tremblay NA, Hardy JF, Perrault J, Carrier M. A simple classification of the risk in cardiac surgery: The first decade. Canadian Journal of Anesthesia. 1993;40:103.

106. Tuman KJ, McCarthy RJ, March RJ, Najafi H, Ivankovich AD. Morbidity and duration of ICU stay after cardiac surgery: A model for preoperative risk assessment. Chest. 1992;102:36.

107. Kennedy J, Tuleu I, Mackay K. Unfilled prescriptions of Medicare beneficiaries: Prevalence, reasons, and types of medicines prescribed. Journal of Management Care Pharm. 2008;14(6):553.

Appendix I: Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

November 23, 2010

This Ethics Application was subject to:

☐ Full Board Review
Meeting Date:
☒ Expedited Review

Dr. Linda Lévesque
Department of Community Health & Epidemiology
c/o KFL&A Public Health
221 Portsmouth Avenue
Kingston, ON K7M 1V5

Dear Dr. Lévesque,

Study Title: **Comparing cardiac care in persons with and without a mental disorder: a population-based cohort study**
Co-Investigators: **Ms. R. Morkem, Dr. H. Stuart**

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following list of ethics requirements you must fulfill over the course of your study:

- **Reporting of Amendments**: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. (see http://www.queensu.ca/vpr/reb.htm).
- **Reporting of Serious Adverse Events**: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.
- **Reporting of Complaints**: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.
- **Annual Renewal**: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

Albert Clark
Chair, Research Ethics Board

Nov 23, 2010
Date

Appendix II: Studies of treatment disparities associated with individuals with a mental health disorder (MHD)

Study	Design	Exposure	Primary Outcome/Analysis	Comparator Group	Results	Comments
Rathore et al. (2008)(3)	Retrospective Cohort United States Medicare beneficiaries Sample Size = 53314	Definition: Presence of an administrative secondary diagnosis code of any mental disorder recorded at admission during index hospitalization or at any encounter in previous year. Source = Medicaid Services	Quality of care measures, including LVEF assessment, ACE inhibitor, 1year readmission and 1year mortality Analysis: Odds Ratio	Individuals admitted for AMI with no secondary mental disorder diagnosis or any mental disorder diagnosis in previous year	Eligible patients with mental disorder had lower rates of LVEF evaluation (53% vs. 47.3%; P<0.001) but comparable rates of ACE inhib. (71.3% vs. 69.7%; P=0.40).	1. Exposure Misclassification 2. Measured outcome as dichotomous variable 3. Hard endpoints – less sensitivity to capture differences in care due to provider factors
Hippisley-Cox et al. (2007)(15)	Cross Sectional Study Sample Size = 127932	Definition: A recorded diagnosis of schizophrenia or bipolar disorder Source=485 UK general practice anonymized records	Relative risks of receiving statin medication and each of the CHD care indicators defined in UK General Med Services contract	Patients with CHD with neither schizophrenia or bipolar disorder	Patients with schizophrenia were 15% less likely to have a recent prescription for a statin (CI 8%-20%) and 7% less likely to have a recent record of cholesterol level (CI 3%-11%).	1. Measured outcome as dichotomous variable 2. Didn't exclude individuals with any mental disorder from comparator group

Kisely et al. (2007)(17)	Retrospecitve Cohort, NS, Canada Sample Size = 215 889	Definition: Anyone in contact with health services in 1995-2001, in NS for psychiatric problems, specifically ICD-9 diagnoses coded 290-319 as well as nonspecific mental disorders covered in chapter 5 of ICD-9 Source: Canadian medical services insurance database	Rate ratio for death, receipt of specialized or revascularization procedures	Average population distribution in NS from 1995-2001	Rate ratio of death of psychiatric patients was significantly increased (1.34, 95% CI 1.29-1.40); Procedures rates between mental disorder group was comparable to non mental disorder group (PTCA: 0.97, 95% CI 0.86-1.09; CABG: 0.92 95% CI 0.83-1.02)	1. Hard endpoints – less sensitivity to capture differences in care due to provider factors 2. Exposure misclassification due to intention to treat analysis 3. Measured outcome as dichotomous variable
Jones and Carney (2005) (23)	Retrospective Cohort, Iowa Blue Cross/Blue Shield administrative claims data Sample Size = 3368	Definition: Subjects were classified as having an MHD if ICD 9 codes for MHD were identified in the claims data before or within the 30 day period after discharge Source: Iowa Blue Cross/Blue Shield Administrative claims	Receipt of PTCA during hospitalization or within 30 days of discharge Analysis: adjusted odds ratios	Individuals admitted for AMI with no MHD diagnosis before or within the 30 day period after discharge	Subjects with MHD were similarly likely as subjects without mental disorders to have received PTCA (OR, 1.10, 95% CI 0.95-1.29) and CABG (OR, 0.89, 95% CI 0.71-1.11). Revasc rates did not differ by mental disorder type, with few exceptions.	1. Hard endpoints – less sensitivity to capture differences in care due to provider factors 2. Exposure misclassification due to intention to treat analysis
Dolder et al. (2005)(21)	Retrospective Cohort United States, Veterans Affairs Sample Size = 178	Definition: Patients diagnosed with a psychotic disorder Source: Veterans inpatient and outpatient administrative records	Antihypertensive medication adherence and blood pressure control Analysis: mean gap ratio as well as refill records	89 Veterans without a psychotic disorder diagnosis	Similar antihypertensive medication adherence, patients with psychotic disorder significantly less likely to have had controlled BP during 1 year study period (no data given; only a bar table)	1. Comparison: didn't exclude individuals with any mental disorder from comparator group 2. Veterans Affairs: not generalizeable 3. Measured outcome as dichotomous variable

Lawrence et al. (2003)(14)	Population based record linkage study Sample Size = 210 129	Definition: Patients who have made contact with mental health services Source: Mental Health Information System (MHIS), a core component of the WA Linked Database	IHD Mortality rates, hospital admission rates and rates of revascularization procedure	General Population	Little difference in hospital admission rates for IHD between psychiatric population and general population (1.10, 95% CI 1.06-1.15), but much lower rates of revascularization procedures with psychiatric patients, particularly in people with psychoses (males, 0.31, 95% CI 0.21-0.45; females, 0.34, 95% CI 0.18-0.64)	1. Comparison: didn't exclude individuals with any mental disorder from comparator group 2. Measured outcome as dichotomous variable 3. Hard endpoints – less sensitivity to capture differences in care due to provider factors
Petersen et al. (2003)(24)	Retrospective Cohort United States, Veterans Affairs Sample Size= 4340	Definition: Individuals with an admission to an inpatient psychiatric unit or substance abuse unit in 365 days prior to AMI, or had a secondary psychiatric diagnosis on index admission for AMI, or had received psychiatric outpatient services. Source: VA inpatient and outpatient administrative records	RR (age adjusted) for inpatient cardiac procedure use and use of five different QOC indicators; risk adjusted 30 day and one year mortality	Veterans diagnosed with AMI without mental disorder diagnosis	Patients with mental illness marginally less likely to undergo angiography (RR=0.90, 95% CI 0.83, 0.98); no difference in CABG or medication receipt	1. Exposure Misclassification 2. Veterans Affairs: not generalizable 3. Measured outcome as dichotomous variable

Desai et al. (2002)(22)	Retrospective Cohort United States, Veterans Affairs Sample Size= 5869	Definition: Individuals with a diagnosed mental disorder: substance use disorder, schizophrenia or other psychotic disorder, PTSD, Major Affective Disorder, Other Source: VA inpatient and outpatient administrative records	Quality of care after AMI, dichotomous Analysis: Compared proportions	Veterans diagnosed with AMI without mental disorder diagnosis	Use of beta blockers in individuals with substance use disorder compared with those without PR=0.95, 95% CI 0.89, 0.99; schizophrenia 90.5% versus 93.1% (ratio not given)	1. Veterans Affairs: not generalizable 2. Measured outcome as dichotomous variable
Druss et al. (2001)(20)	Retrospective Cohort United States, Veterans Affairs Sample Size= 88241	Definition: Individuals with any secondary admission diagnosis between codes 295 to 319.99, other than dementia and delirium: also compared between different diagnostic groups Source: Medicaid Records	Five established quality of care indicators: referfusion, aspirin, B blockers, ACE inhibitors, smoking cessation counselling Analysis: Proportional hazard models	Individuals hospitalized for confirmed AMI without a secondary mental disorder diagnosis	Presence of any mental disorder was associated with a 19% increase in 1 year risk of mortality (HR=1.19, 95% CI 1.04-1.36); After adding 5 QOC measures association was no longer significant (HR= 1.1, 95% CI 0.96-1.26).	1. Measured outcome as dichotomous variable
Druss et al. (2000)(19)	Retrospective Cohort United States, Medicaid recipients Sample Size=113653	Definition: Diagnosis of schizophrenia, major affective disorder, substance abuse or other mental disorder Source: Medicaid Records	Likelihood of cardiac catheterization, PTCA, CABG during index hospitalization	Individuals hospitalized for confirmed AMI without mental disorder diagnosis	Patients with any comorbid mental disorder were significantly less likely to undergo PTCA (11.8% vs. 16.8%; P<0.001) or CABG (8.2% vs. 12.6%; P<0.001)	1. Exposure Misclassification 2. Measured outcome as dichotomous variable 3. Hard endpoints – less sensitivity to capture differences in care due to provider factors

Young and Foster (2000)(18) *Letter to the Editor*	Retrospective Cohort United States Sample Size=354195	Definition: "similar to Druss et al." Source: Healthcare Investment Analysts (HCIA) – Sachs 1998 projected inpatient database	LIklihood of undergoing cardiac catheterization, PTCA, CABG as a function of mental illness for 2 age groups: >65 years and <65 years	Individuals hospitalized for AMI with no mental disorder	Significantly reduced likelihood of undergoing catheterization and revascularization procedures for those with mental illness in both age groups (>65yo: 0.77, 95% CI 0.75-0.80) (<65yo: 0.88, 95% CI 0.86-0.90)	Unable to comment due to limited methodology given
Kisely et al. (2009)(27)	Retrospective Cohort NS, Canada Sample Size=65039	Definition: Contact with psychiatric services within 12 months from index: diagnosed with schizophrenia or non-affective psychoses	Rates of cardiac catheterization, PTCA and CABG, Beta-blockers, ACE inhibitors, Statins, Angiotensin receptor blockers and clopidogrel; within one year of index event.	Individuals hospitalized for ischemic heart disease or stroke without psychoses	Significantly reduced likelihood of undergoing any of the procedures (or of receiving beta-blockers or statins	1. Measured outcome as dichotomous variable 2. Extremely long follow-up period for acute care procedures 3. Comparison: didn't exclude individuals with any mental disorder dx
Atzema et al. (2011) (28)	Retrospective Cohort ON, Canada Sample Size=6784	Definition: Charted history of depression	Odds of low-priority triage, meeting benchmark door-to-electrocardiogram; door-to-needle and door-to-balloon times	Individuals admitted for an AMI with a charted history of asthma or COPD	Depressed - more likely to receive low triage score (OR=1.26 versus OR=0.88 for asthma and OR=1.12 for COPD); - More likely to miss benchmark times (OR=1.39, 1.62 and 9.12)	1. Measured outcome as dichotomous variable 2. Comparison: didn't exclude individuals with any mental disorder dx 3. Hard endpoints – less sensitivity to capture differences in care due to provider factors

Appendix III: Data Sources

Database	Description	Original Data Source	Main Data Elements	Information Obtained	Use of data	Diagnostic record
DAD (CIHI) Discharge Abstract Database	Record of information on inpatient hospital activity	CIHI	• patient demographics (e.g. sex, date of birth) • clinical data (e.g. diagnoses, procedures) • administrative data (e.g. hospital, length of stay)	• ICES Key Number (IKN; unique identifier) • Sex, birth date • Admission date • Length of stay • Diagnosis code, diagnosis type	• Identification of dates of diagnoses related to hospitalizations	• 1-25 diagnoses per admission • 7-character ICD-10-CA/ICD-9-CA codes • 1-character 'type of diagnoses' codes
NACRS National Ambulatory Care Reporting System	Record of information on patient visits to hospital emergency departments, same day surgery, and selected outpatient services	CIHI	• patient demographics • clinical data • administrative data • financial data • service-specific data elements for day surgery and emergency	• IKN • Arrival date • Problem 1-10 (ICD-10-CA/ICD-9-CA codes) • Problems prefix 1-10	• Identification of date and diagnoses related to emergency consultants	• 1-10 diagnoses per consultation • 7-character ICD-10-CA/ICD-9-CA codes • 1-character 'type of diagnosis' codes

OHIP Ontario Health Insurance Plan	Record of services from health care providers that claim under OHIP	MOHLTC	• patient and physician identifiers (encrypted) • code of service provided, date of service, and associated diagnosis • fee paid	• IKN • Date of admission • OHIP fee code and suffix OR diagnosis code and explanatory code	• Identification of dates and diagnoses related to physician consultations	• Usually 1 diagnosis per visit • 3-digit diagnosis code (variant of ICD-9) • 1-character 'type of diagnosis' code • 1-digit diagnosis code suffix
RPDB Registered Persons Database	Record of basic demographic information about anyone who has ever received an Ontario health card number	MOH	• demographics • geographic data • administrative data	• IKN • Sex, birth date, death date • Postal code • Date of last contact (DOLC)	• Identification of socio-demographic information	N/A
ODB Ontario Drug Benefit Claims	Record of drug claims (i.e. a dispensed prescription) paid for by the MOH for individuals 65 and older	MOH	• Drug identifier • patient and physician identifiers (encrypted) • date prescription was dispensed • fee paid	• DIN (drug identifier) • Quantity, # days supplied • Cost • Patient, Pharmacy and Physician identifiers • Date prescription was dispensed • Long Term Car indicator	• Identification of dates and prescriptions dispensed	N/A

Appendix IV: Exposure and Outcome Classification

Classification of Exposure

Disorder	ICD Version 9	ICD Version 10
Depression		
Major Depressive Disorder	296	F32-33
Dysthymia		F34
Schizophrenia	295	F20

Classification of Outcome

Procedure	CCP	CCI
Cardiac Catheterization	49.95 49.96 49.97	2.HZ.24 3.IP.10
Percutaneous Transluminal Angiography (PTCA)	48.02 48.03	2.HZ.71 1.IJ.50
Coronary Artery Bypass Graft (CABG)	48.1	1.IJ.76