OUTPATIENT FOLLOW-UP VISITS AND THE RISK OF ALL-CAUSE 30-DAY HOSPITAL READMISSIONS FOR PATIENTS DISCHARGED FOLLOWING A CARDIOVASCULAR OR COPD RELATED EVENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

OUTPATIENT FOLLOW-UP VISITS AND THE RISK OF ALL-CAUSE 30-DAY HOSPITAL READMISSIONS FOR PATIENTS DISCHARGED FOLLOWING A CARDIOVASCULAR OR COPD RELATED EVENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Hospital readmissions are important as they are costly, are associated with high mortality, morbidity and an increased risk of long-term care, and are important as readmissions are now included in Pay-for-Performance (P4P) programs (1-3). One potential mechanism to reduce readmission is through outpatient follow-up visits with a physician after initial discharge (4). This review seeks to understand the effect outpatient follow-up visits have on all-cause 30-day readmissions for patients with an initial discharge of Acute Myocardial Infarction (AMI), heart failure, Chronic Obstructive Pulmonary Disease (COPD) or an acute stroke event. We conducted a systematic review and meta-analysis of observational studies, searching the PubMed and CINAHL databases. The search consisted of articles published in the United States over a 10 year period 2007 through 2017. We calculated relative risk (RR) and 95% confidence intervals for each outcome and assessed heterogeneity using the I^2 and Q-statistics. From 573 hits, we identified 10 eligible studies. The pooled RR from the six patient-level studies found that outpatient follow-up visits reduced the risk of readmission by 13% (RR= 0.87; 95% CI 0.77-0.97, p= 0.014). However, the I^2 statistic was 65.5% and the Q-statistic p-value was 0.05, indicating that there is a moderate to substantial amount of heterogeneity. Hospital-level studies were not included in the analysis. Although some evidence exists for the benefit of outpatient follow-up visits with a physician, additional evidence is needed in order to quantify the impact of outpatient follow-up visits to reduce 30-day readmissions.

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KEY TO ABBREVIATIONS

ACC	American College of Cardiology
AMI	Acute Myocardial Infarction
BOOST	Better Outcomes for Older Adults through Safe Transitions
CABG	Coronary Artery Bypass Grafting surgery
CAD	Coronary Artery Disease
CCTP	Community Based Care Transitions Program
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
DMPs	Disease Management Programs
ES	Effect Summary
FFS	Medicare Fee-for-Service
FY	Fiscal Year
H2H	Hospital to Home
HR	Hazard Ratios
HRRP	Hospital Readmission Reduction Program
ICPCA	Integrating Care for Populations and Communities Aim
INTERACT	Interventions to Reduce Acute Care Transfers
IPPS	Inpatient Prospective Payment System
IRF	Inpatient Rehab Facility
NOS	Newcastle-Ottawa Scale
NP	Nurse Practitioner

NPP	National Priorities Partnership
NQF	National Quality Forum
OR	Odds Ratios
P4P	Pay-for-Performance
PCP	Primary Care Physician
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PubMed	United States National Library of Medicine
RCT	Randomized Controlled Trial
RR	Relative Risk
RED	Re-Engineered Discharge
SES	Socioeconomic Status
SNF	Skilled Nursing Facility
STAAR	State Action on Avoidable Rehospitalizations
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
VA	Veterans Affairs

CHAPTER 1: INTRODUCTION

Section 1: Hospital Readmissions and Programs Designed to Address Them

Hospital Readmissions and their Importance:

Hospital readmissions are admissions to a hospital within a specific time period after initial hospital discharge. While there are various time periods over which readmissions can be measured, a common measure, used by the Centers for Medicare and Medicaid Services (CMS) is 30 days from discharge (5). Readmissions are important as they are costly, are associated with high mortality, morbidity, and an increase in risk of long-term care (1-3, 6). Furthermore, readmissions are now included in Pay-for-Performance (P4P) programs which provide hospitals with incentive payments to reduce readmissions (1-3, 6). One potential mechanism to reduce readmissions is through an outpatient visit with a physician following initial discharge (4). However, physician outpatient follow-up visits have shown inconsistent results in terms of lowering the rate of all-cause 30-day readmissions (4, 7-16). Therefore, this systematic review and meta-analysis seeks to understand the association between outpatient follow-up visits and all-cause 30-day readmissions for patients with an initial discharge of Acute Myocardial Infarction (AMI), heart failure, Chronic Obstructive Pulmonary Disease (COPD) or an acute stroke event.

History and Explanation for CMS Readmission Reduction Efforts:

CMS is a branch of the U.S. Department of Health and Human Services that provides health insurance to over 100 million individuals through its Medicare, Medicaid, Children's Health Insurance, and Health Insurance Marketplace programs (17). CMS has made reducing hospital readmissions a priority. One important reason CMS began penalizing hospitals is the costs that accrue due to readmissions. In 2009, the average treatment cost for all Medicare

beneficiaries with an all-cause readmission was $11,200 per patient. Costs are similar for the conditions of interest included in this review: $13,200 per AMI patient, $13,000 per heart failure patient, and $10,900 per COPD patient (2). In addition, the treatment cost was $13,000 per pneumonia patient (2). The total cost of 30-day readmissions to Medicare beneficiaries have been estimated around $17 billion/year (3). Potentially $1.9 billion a year would be saved if all hospital readmission rates were lowered to the level of the highest performing hospitals in the United States (3).

In 2009, CMS started publically reporting all-cause 30-day readmission rates for all US hospitals on its Hospital Compare website (1). Furthermore, CMS developed quality improvement initiatives, including P4P programs, with the primary goal of improving patient outcomes and reducing medical costs (8). A major component of the P4P programs has been the Hospital Readmission Reduction Program (HRRP) which was established in 2012 by the Affordable Care Act (1). The HRRP penalizes hospitals that have high readmission rates by reducing the financial payment given to hospitals as part of the Inpatient Prospective Payment System (IPPS) (1). The IPPS is a payment received by hospitals that is based on the diagnosis-related group for each admitted patient which covers inpatient stays, and outpatient diagnostic and nondiagnostic services (1). Penalties are based on an excess readmission ratio comparing individual hospitals to the national average and are calculated based on data from a three year average (18). A hospitals adjustment readmission factor of less than one (*i.e.*, <1.0000) will trigger a penalty (19). The excess readmission ratio is calculated by the total number of predicted readmissions at a hospital, compared to the total number of expected readmissions supposing the patient was treated at an average hospital with a similar patient population (1). The adjustment readmission factor is calculated by using the excess readmission ratio for each condition

multiplied by the sum of the base operating DRG payments for that condition; these two results are then summed (19). The excess readmission ratio is then divided by the aggregate payments for all discharges and subtracted by one (19). The penalty administered by the HRRP was a maximum of 1% in 2013, 2% in 2014, and has remained at 3% since 2015 (1). The first year [Fiscal Year (FY) 2013] of the HRRP (using data from the three year window, June 2008 to July 2011) included Medicare beneficiaries discharged with AMI, heart failure or pneumonia (1, 18), totaling $290 million administered to 2,213 hospitals (1, 18). The second year (FY 2014) the estimated total fines were $227 million but rose significantly to an estimated $428 million in the third year (FY 2015) (5, 18). This significant rise may be explained by the addition of three patient populations: COPD, total hip arthroplasty (THA), and total knee arthroplasty (TKA) to the FY 2015 program (1, 5, 18). The fourth year (FY 2016) fines were an estimated $420 million but rose significantly to an estimated $528 million in the fifth and most recent year (FY 2017) (18). This latter increase may be explained by the addition of patients with additional pneumonia diagnoses (patients with aspiration pneumonia or non-severe sepsis with pneumonia existing upon admission) and coronary artery bypass grafting (CABG) surgery to the FY 2017 program (5, 18). The fines collected from the penalties are placed in the Medicare hospital insurance trust fund that provides support for existing and new benefits for all Medicare beneficiaries (1).

Several studies have examined the early impact of the HRRP on hospital readmissions. The implementation of this program has shown significant reductions in hospital readmissions (19). Data suggests that the HRRP has been associated with lower readmission rates for Medicare beneficiaries (1). McIlvennan *et al.* found the readmission rate for Medicare beneficiaries remained stable from 2007-2011 at 19%, but in 2012 (when the HRRP started) and 2013 the average readmission rate lowered to 18.5% and 17.5%, respectively (1). Lu *et al.* used

publicly available HRRP data files and found that after the first three years of the program, readmissions for Medicare beneficiaries with an initial admission for AMI, heart failure and pneumonia had an adjusted risk ratio reduction of 7.6%, 3.3% and 3.2%, respectively (20). For AMI, heart failure, and pneumonia, the Kaiser foundation found that national Medicare readmission rates changed from 19.7%, 24.7% and 18.5% (data from July 2008-June 2011) to 17.0%, 22.0% and 16.9% (data from July 2011-June 2014), respectively (18). In conclusion, the HRRP has been shown to have reduced readmissions for Medicare beneficiaries with these three targeted medical conditions (1, 18, 20, 21).

CMS Readmission Definition:

The definition of a readmission is important, as a readmission defines what the numerator is and impacts how penalties are administered in the HRRP. The National Quality Forum (NQF) has worked on measure endorsement projects to help CMS accurately measure and define readmissions (3, 22). CMS defines a readmission as an all-cause (any underline medical diagnosis) unplanned admission to a non-federal, short-stay, or acute-care hospital occurring within 30 days after initial discharge to home from a similar setting (5, 23). CMS electing to make polices based on 30-day readmissions is thought to give a more accurate way to measure the quality of care and transition services provided by the hospitals to prevent readmissions (1). According to CMS, the 30-day timeframe was chosen because it represents a critical period when patients are transitioning home, and because hospitals need to identify and understand the environment where patients are discharged in order to reduce readmission and mortality rates (24). Although CMS has made the 30-day timeframe a standard, readmissions have been identified using other timeframes (e.g., 60 days, 90 days, one year, two years, and four years) after hospital discharge (25). For Medicare beneficiaries between 2003 to 2004, 19.6% were

readmitted within 30 days, 28.2% within 60 days, 34.0% within 90 days, 44.8% within six months, and 56.1% were readmitted within one year following hospital discharge (25). For the purposes of this systematic review and meta-analysis, the readmission window is defined as 30 days after initial discharge.

Readmissions can be defined as either planned or unplanned. A planned readmission is part of the process of regular medical care, and an unplanned readmission is an unexpected event. CMS defines a planned readmission as a non-acute readmission which has been scheduled (23). In order to identify if a given readmission was planned, CMS uses an algorithm to search Medicare claims (26). Planned readmissions include readmissions for any non-acute readmission or for any of the following procedures: obstetrical delivery, transplant surgery, maintenance chemotherapy, and rehabilitation (APPENDIX A, Table A1) (3, 23). CMS excludes planned readmissions from the numerator of its definition of readmission (23). In 2008, according to a study conducted by Yale University, there were 181,203 all-cause planned 30-day readmissions for Medicare beneficiaries, accounting for 12% of all readmissions (3). CMS does not distinguish between preventable and unpreventable readmissions, most likely because of the difficulty in defining a preventable readmission accurately. Furthermore, CMS counts only the first readmission within 30 days of hospital discharge and does not count readmissions on the same day of hospital discharge to the same hospital with the same complication (23).

Specific criteria identifying which patients are included in the denominator of the readmission calculation are equally critical to the accurate identification of hospitals with high readmission rates. Therefore, CMS has provided specific eligibility criteria on readmissions for Medicare beneficiaries (3, 23). Eligible patients include Medicare beneficiaries, 65 years of age

or older, hospitalized to a non-federal, short-stay, or acute-care hospital with at least 30 days of post-discharge enrollment in Medicare Fee-for-Service (FFS) (APPENDIX B, Table A2) (3, 23).

Specific exclusion criteria must also be identified to allow an accurate measure of readmissions. Valid denominator exclusions for the CMS 30-day readmission measure include patients discharged against medical advice, in-hospital death, and patients transferred to another acute care hospital (APPENDIX B, Table A2) (3, 23).

Criticism of the CMS Readmission Definition:

As previously described, CMS has created specific criteria that define eligible index admissions (*i.e.*, the denominator) and readmissions (*i.e.*, the numerator). Although P4P programs have forced hospitals to become more aware of the quality of care provided, care coordination, and follow-up planning, there have been controversies associated with CMS criteria. One issue includes the lack of control for socioeconomic status (SES) (1, 27-31). This criticism has gained traction as a large majority of hospitals that have been penalized to date serve a high proportion of poor patients (1). Penalizing hospitals that serve poor communities may come at a cost, as these penalties may unintentionally take away hospital resources (1). It has been argued that SES should be adjusted for, as low-income areas have poor social supports, poverty, and inadequate community resources which hospitals have no control over and may also induce hospital readmissions (28). Low SES was shown to be associated with a greater readmission rate for Medicare beneficiaries for AMI (risk ratio 1.09, 95% CI 1.03-1.15), heart failure (risk ratio 1.07, 95% CI 1.01-1.12), and pneumonia (risk ratio 1.09, 95% CI 1.03-1.15) (28).

The 30-day timeframe CMS chose to measure readmissions has also been under discussion (1, 32, 33). Their timeframe was chosen because readmissions closer to discharge are

more likely to be related to hospital quality of care and the transition from the hospital (1). For this same reason, others have suggested using a weighted average for the timing of readmissions within the 30-day timeframe, as early readmissions (within seven days of discharge) may be more closely related to the hospital quality of care (1). Under the current approach (which does not use a weighted average approach), a readmission on the fourth day is regarded the same as a readmission on the thirtieth day. This may give an inaccurate representation of the quality of care provided by the hospital, as an individual readmitted closer to the end of the 30-day timeframe is less likely to be readmitted as a result of the quality of care that was provided to them (1). Other authors have been even more pointed in their criticism of the CMS readmission criteria. For example, Vaduganathan *et al.* claimed there has not been any evidence (biological, clinical, or therapeutic) supporting the use of a 30-day timeframe to penalize hospitals (32). This comment suggests that a shorter timeframe, closer to the time of discharge, or a weighted average within 30 days of discharge, may be more justifiable.

Another important issue when calculating readmission rates is that CMS does not account for patients who die post-discharge and therefore cannot be re-hospitalized (1). Although this may artificially improve readmission rates because deceased individuals cannot be readmitted, the CMS Hospital Compare program also reports 30-day mortality rates for hospitals (34). Several studies have stated that correcting these readmission issues is important when determining hospital penalties as some hospitals may be unjustly penalized due to flaws in the criteria (1, 27, 32).

Section 2: Risk Factors for Readmissions and Predicting Readmissions

Risk Factors for Readmissions:

Understanding factors on a patient, hospital, or system level that lead to readmissions is important, as it might allow health care workers and hospitals to improve care to avoid readmission. A few systematic reviews have evaluated the risk factors associated with an increase in readmissions (35, 36). For COPD patients these include advanced age, gender, physical inactivity, smoking, low body mass index (BMI), longer hospital length of stay (LOS), previous hospital admission, history of COPD exceeding five years, diabetes, severity of dyspnea, use of oral and inhaled corticosteroids, long-term oxygen therapy, right heart strain, coronary artery disease (CAD), and left ventricular failure (35). For stroke patients these include advanced age, poor physical functioning post-stroke, LOS, high number of prior hospitalizations, stroke type, diabetes, discharge destination, physician seen, insurance type, and hospital certification status (36). Furthermore, several individual studies have evaluated the risk factors associated with an increase in readmissions (37-39). For heart failure patients these include advanced age, gender, race, discharge to a skilled nursing facility or with a home nurse, LOS, admission from another facility, emergent admission, Medicare coverage, and comorbidities (38). For AMI patients these include LOS, diabetes, COPD, anemia, higher Killip class, and reperfusion treatment (37). A study on general Medicare patients found risk factors for readmissions to include race, weight loss, narcotics, corticosteroids, disease states of cancer, renal failure, CHF, and Medicare payer status (39). To summarize, common risk factors for readmissions across disease conditions include age, race, weight loss, LOS, number of index admissions, diabetes, corticosteroids, insurance type, SES, geographical location, comorbidities (e.g., ischemic heart disease, atrial fibrillation, heart failure, COPD, and malignant neoplasm), no

primary care, severity of disease, lack of social support or access to care, and substance abuse (8, 11, 14, 40-45).

Predicting Readmissions:

For hospitals to prevent readmissions it would be helpful to predict patients who are at a higher risk for readmission. The ability to predict preventable readmissions is important because it will allow healthcare workers to target resources to patients who are most at risk for readmission (40). However, determining preventable readmissions has shown to be complex and unreliable (45). Studies have sought to distinguish standard criteria for a preventable readmission (40, 45-47). A prior systematic review has identified various models used to predict preventable readmissions (e.g., the Striving for Quality Level and Analyzing of Patient Expenses model, the Charlson score based model, the HCFA model, and the HOSPITAL score) (45). The most widely used is the HOSPITAL score, which uses a multivariable prediction that includes factors such as hospital LOS and the number of index admissions in the prior year to predict preventable readmissions (40).

Approaches to Preventing Readmissions:

Preventing readmissions is a significant topic for hospitals as high readmission rates may reflect poor patient outcomes and reduce hospital reimbursement (24). A comprehensive report from CMS identified the following programs that have been specifically designed to reduce readmissions including: the Integrating Care for Populations and Communities Aim (ICPCA), the Community Based Care Transitions Program (CCTP), Hospital to Home (H2H), State Action on Avoidable Rehospitalizations (STAAR), the Interventions to Reduce Acute Care Transfers (INTERACT), Better Outcomes for Older Adults through Safe Transitions (BOOST), and RED (Re-Engineered Discharge) (24). In addition to the development of hospital and community

based programs to reduce readmissions, certain organizations have also become involved in reducing readmissions including: the National Priorities Partnership (NPP), the American College of Cardiology (ACC), and the American Hospital Association (24).

The majority of the strategies employed by these programs are targeting actions and interventions already in use by hospitals. Strategies may be introduced during the hospital visit, the transition from hospital to home, and in the post hospital period. These strategies may including having hospitals establish quality improvement teams for reducing readmissions, increased patient education on medications, scheduling outpatient follow-up visits before discharge, having a system in place to send all necessary medical paper work (e.g., electronic medical record) to the patients primary care physician (PCP), and patients and caregivers being well informed about their discharge plan when they leave the hospital. Furthermore, these programs may include strategies to help with the transition from hospital to home such as a transition team led by nurses or case managers to help coordinate with physicians to improve communication between local hospitals, other physicians (e.g., PCP), family members and the community. Finally, these programs may include specific strategies in the post hospital period such as allocating staff to follow-up with test results delivered after a patient has been discharged, physicians being alerted within 48 hours of the patients discharge, follow-up calls from the hospital to schedule appointments or to further educate treatment plans, and outpatient follow-up visits and home visits (2, 48, 49).

These specific programs designed to reduce readmissions have showed varied results. The BOOST program has been shown to reduce readmissions with an absolute reduction of 2% and a relative reduction of 13.6% after the programs implementation in 2008 (50). Some programs have also shown no reduction in readmission rates (49, 51). After the H2H program

was implemented in 2009 by the ACC and the Institute for Healthcare Improvement, a single study of 104 Veterans Affairs (VA) hospitals found no impact on 30-day readmissions (51). Furthermore, after the CCTP was implemented in 2011 by CMS, the final first annual report which included data on 48 hospitals found no impact on 30-day readmissions (49). The overall lowering of readmissions for Medicare beneficiaries across the United States may be due to a combination of methods used in these programs (52). Bradley *et al.* found that hospitals with three or more strategies significantly reduced the risk for readmission compared to hospitals with fewer than three strategies (52).

Section 3: Follow-up Visits, Improvement of Transitional Care, Reduction of Readmissions

There remains great uncertainty over the effectiveness of outpatient follow-up visits. This is partly due to the fact that there is variation in the type of visit, timing of visit, different study populations, and random study to study variation. An outpatient follow-up visit with a physician is one method used to attempt to reduce readmissions. Early outpatient follow-up visits with a physician after discharge (typically defined as within seven days of discharge) are recommended in clinical guidelines as a standard care for heart failure, AMI, COPD and stroke patients (4, 53-56).

Although outpatient follow-up visits are only one component of care, a large retrospective cohort study with 30,136 patients (225 hospitals) consisting of Get With the Guidelines (GWTG) heart failure patients found a 10-14% relative risk reduction when comparing 30-day readmission rates between hospitals frequencies of outpatient follow-up visits (4). One systematic review and meta-analysis by Vedel *et al.* found improved transitional care programs with multicomponent strategies which included a combination of structured periodic

follow-up in an outpatient clinic, home visits, telephone follow-up, telecare, and video visits for heart failure patients had a significant pooled relative risk reduction of 8% for readmission (0.92; 95% CI, 0.87-0.98, based on 41 studies) compared to usual care as a whole, but stated that outpatient follow-up visits alone did not improve all-cause readmissions (7). Another systematic review and meta-analysis found the use of multidisciplinary-heart failure clinic visits was associated with a statistically significant reduction in all-cause readmissions 3-6 months after discharge (pooled relative risk 0.70; 95% CI, 0.55–0.89, based on two studies) (57). Furthermore, they found outpatient follow-up visits to a nurse-led clinic had no effect (pooled relative risk 0.88 95% CI 0.57–1.37 based on two studies), and visits to a primary care clinic were associated with a statistically significant increase in risk for all-cause readmissions 3-6 months after discharge (relative risk 1.27; 95% CI, 1.05–1.54, based on one study) (57). One systematic review concluded there was no consistent benefit for a specific type of disease management programs (DMPs) for reducing heart failure hospitalizations (58). These DMPs included home visits, telemanagement, and outpatient clinic visits (58). Another systematic review concluded that no single intervention but a combination of interventions was associated with reducing the risk for 30-day readmissions (59). The interventions examined in this review included pre-discharge interventions (e.g., patient education, discharge planning, and medication reconciliation), post-discharge interventions (e.g., outpatient follow-up visits, timely PCP communication, and patient hotlines) and interventions active both before and after discharge (e.g., transition coach, patient-centered discharge instructions, and provider continuity) (59). These reviews have provided little evidence to show any effectiveness between outpatient follow-up visits and 30-day readmissions and no review has looked directly at outpatient follow-up visits and since follow-up visits are commonly recommended guidelines, we have chosen to

conduct a meta-analysis solely on the association of outpatient follow-up visits and 30-day readmissions.

Although the association between outpatient follow-up visits and 30-day readmissions is unclear, there have been obstacles preventing a patient's attendance to an outpatient follow-up visit, especially within seven days of discharge. For AMI Medicare patients, about one in every four have an outpatient follow-up visit within seven days of discharge and for heart failure Medicare patients, about one in every three have an outpatient follow-up visit within seven days of discharge (4, 60). Furthermore, about one in every four Medicare patients with AMI, heart failure or COPD do not attend an outpatient follow-up visit within 30 days of discharge. A retrospective study with 20,976 Medicare patients with AMI, from 461 Acute Coronary Treatment and Intervention Outcomes Network Registry–GWTG hospitals in the United States found that 26% of patients attended a follow-up visit within seven days of discharge (60). A study conducted in the United States had 94% of heart failure patients schedule an outpatient follow-up visit with a PCP before discharge but found only 38% attended the visit within seven days after discharge (4), although 82% of these patients attended a follow-up within 30 days of discharge (4). The prevalence of outpatient follow-up visits within 30 days of discharge was 70% for a study of 62,746 hospitalized COPD patients (16). Furthermore, the prevalence of outpatient follow-up visits within 30 days of discharge was 61% for a study of 188,611 AMI patients from 1,088 hospitals across the United States (9).

Understanding why patients do not attend follow-up visits is important. Individuals have looked to identify reasons for patients not attending outpatient follow-up visits in the United States (61, 62). One study used semistructured interviews on adults patients attending a clinic for outpatient care (61). In addition, an article by patient bond looked to identify the top four reasons

patients do not attend a follow-up visit (62). For modifiable factors, the main reason patients did not attend follow-up visits was a patient having a negative opinion or emotional barrier keeping them from a follow-up visit (e.g., receiving bad news, being lectured on behaviors, waiting time or lack of respect from healthcare workers) (61, 62). In addition, other reasons include a patient not understanding the reason for a follow-up visit, lack of time (e.g., child care), lack of transportation, or social support (61, 62). For non-modifiable factors, readmissions or discharges to a facility (e.g., nursing home or long-term care facility) before a follow-up visit will obviously prevent the opportunity for a patient to attend a follow-up visit.

There have been issues with outpatient follow-up visits and their efficacy to reduce readmissions (63). One issue regarding outpatient follow-up visits has been the variable results regarding their effectiveness in reducing readmissions. Individual studies have shown outpatient follow-up visits to have both a relative risk reduction (12, 14-16) and a null association (4, 8, 9, 11) for lowering the risk of readmission for heart failure, COPD and AMI patients. Although some individual studies have shown that outpatient follow-up visits lower the risk of readmissions for certain conditions such as heart failure and COPD (12, 14-16), patients may benefit more if they attend a follow-up visit with a specific physician specialist (4). For example, heart failure patients may have a greater benefit if the outpatient follow-up visit involves a cardiologist where COPD patients may benefit more if treated by a pulmonologist compared to a PCP or a physician seen for the first time (4, 64). Another issue is the lack of a consistent definition for an outpatient follow-up visit and the minimal specific treatment components that should occur during the visits (63). Assessments and interventions that should occur at an outpatient follow-up visit may include medication readjustment, identification of a new

diagnosis, follow-up diagnostic tests (e.g., blood or urine samples), patient education and physical examinations (63).

Outpatient follow-up visits may be a key component of care to reduce readmissions, but recommendations have relied mainly on the opinions of experts and little evidence has been shown to guide the timing of follow-up visits after hospital discharge (65). This topic of outpatient follow-up visits and readmissions has only recently been in the spotlight due to the implementation of programs designed to reduce readmissions (as previously described) within the last decade and in 2012, the implementation of the HRRP (1-3, 6, 24). As previously discussed, individual studies have found inconsistent results when studying the association of outpatient follow-up visits on all-cause 30-day readmissions (4, 7-16). The large variability of strategies, disease conditions, government policies, and readmissions has made this topic difficult for researchers to study in a consistent manner. Therefore, this systematic review and meta-analysis looks to understand these inconsistences and to further shed light on the role of outpatient follow-up visits on changing readmission risk in common disease conditions.

Important Confounders for Outpatient Follow-up Visits and 30-day Readmissions:

The variables discussed below are important to identify as they could create confounding leading to an incorrect association between outpatient follow-up visits and readmissions. For example, patients with a more severe illness at the time of the first admission are more likely to have an outpatient follow-up visit but are also more likely to have a readmission compared to patients with a minor illness (11). Other important potential patient-level confounders include advanced age, gender, race, SES, severity of condition, and major comorbidities (coronary artery disease, atrial fibrillation, renal insufficiency, and diabetes mellitus) (8-16). Important hospital-

level confounders may include hospital size, teaching versus non-teaching status, census region, urban versus rural, and profit versus non-profit hospitals (66).

Confounding factors can operate at the patient-level and hospital-level. Therefore, some studies have looked at the association of outpatient follow-up visits and readmissions at the patient-level and some at the hospital-level (4, 8, 9, 12). Identifying confounders on a patient-level and hospital-level status is important as these levels may contain different variables and reflect different results.

Risk-standardized readmission rates have been used to compare readmission rates across the hospital-level. In order to fairly compare readmission rates between hospitals, the risk adjustment accounts for the case mix of each hospital. The model endorsed by NQF is used by CMS to publicly report all-cause 30-day readmissions rates at the hospital-level using administrative data to risk adjust estimates for age, a large number of comorbid diseases, and indicators of patient frailty (67, 68).

Section 4: Disease Conditions: Systematic Review and Meta-Analysis

This systematic review and meta-analysis of the effect of outpatient follow-up visits on all-cause 30-day readmission will focus on AMI, heart failure, COPD, and acute stroke patients only. Each condition is briefly described below.

Acute Myocardial Infarction:

Acute Myocardial Infarction sometimes called heart attack, occurs when an ischemic event affects the myocardium (69). The most common cause of an AMI is atherosclerosis or CAD (69). The primary risk factors include smoking, high blood pressure, obesity, high cholesterol, unhealthy lifestyle (*i.e.*, poor diet, lack of physical activity), diabetes, advanced age,

and family history (70). In 2011, in the United States, more than 321,000 individuals were hospitalized due to AMI and in 2014, more than 114,000 deaths occurred due to a heart attack (71, 72). Additionally, the American Heart Association estimates that about 790,000 heart attacks will occur in 2017 (71). According to data from the CMS Hospital Compare program (2012-15), 14.1% of Medicare beneficiaries hospitalized with myocardial infarction died, and 16.8% were readmitted within 30 days after hospital discharge (34).

Heart Failure:

Heart failure is an end stage organ disease where the myocardium is unable to maintain appropriate output of blood flow throughout the body (73). The most common causes are CAD and hypertension (74). The primary risk factors for the underlying cause CAD include advanced age, race, smoking, unhealthy lifestyle (*i.e.*, poor diet and lack of physical activity), family history, obesity, high blood pressure, high blood sugar, high cholesterol, metabolic syndrome stress, prior heart attack and diabetes (75). Each year in the United States approximately 550,000 new cases and more than 280,000 deaths occur due to heart failure (76). Furthermore, in 2010, there were 1 million hospitalizations due to CHF (77). According to data from the CMS Hospital Compare program (2012-15), 12.1% of Medicare beneficiaries hospitalized with heart failure died, and 21.9% were readmitted within 30 days after hospital discharge (34).

Chronic obstructive pulmonary disease:

COPD is a chronic disease inhibiting airflow through the bronchioles and is primarily caused by emphysema and chronic bronchitis (78). The primary risk factors include advanced age, smoking, individuals with asthma who are smokers, long term exposure to air pollution, chemicals, dust particles, or fumes from burning fuel, and genetics (78, 79). In 2014, COPD was

the third leading cause of death (more than 140,000 deaths) in the United States (80, 81). Furthermore, each year there are more than 822,000 hospitalizations for COPD in the United States (82). According to data from the CMS Hospital Compare program (2012-15), 8.0% of Medicare beneficiaries hospitalized with COPD died and 20.0% were readmitted within 30 days after hospital discharge (34).

Stroke:

Stroke is an ischemic event inhibiting the flow of blood to the brain tissue and is primarily caused by a blockage (ischemic stroke) or a ruptured blood vessel (hemorrhagic stroke) (71, 83). The primary risk factors include advanced age, smoking, unhealthy lifestyle (*i.e.*, poor diet and lack of physical activity), obesity, high blood pressure, high cholesterol, diabetes, carotid artery disease, peripheral artery disease, atrial fibrillation and sickle cell disease (84). In 2012, stroke was the fifth leading cause of death (with more than 130,000 deaths) in the United States. In 2009, over 970,000 hospitalizations occurred due to stroke and each year approximately 800,000 individuals suffer a new or recurrent stroke (71, 85). Stroke is one of the leading causes of disability and a leading cause of placement of individuals in long-term care (6, 71). Of stroke survivors, up to 70% of those who suffered a severe stroke need long-term care (6). According to data from the CMS Hospital Compare program (2012-15), 14.9% of Medicare beneficiaries hospitalized with stroke died and 12.5% were readmitted within 30 days after hospital discharge (34).

Section 5: The Effect of Survival Bias on Outpatient Follow-up Visits and Readmissions

When studying the association between outpatient follow-up visits and readmissions, one bias in particular may cause errors in the estimation of the magnitude of the association between the exposure and outcome. This bias which is known as survival bias can occur when time-dependent variables which can change in a short period of time in a meaningful way, are used as exposure or outcome variables (86). When time-dependent exposure variables are used, survival bias may occur when an individual has an event (outcome) before the treatment (exposure) occurs (87). In this systematic review and meta-analysis, survival bias is important to control as it can artificially inflate the effect of an outpatient follow-up visit by assigning a participant as unexposed (no outpatient follow-up visit) if the outcome (readmission) occurs before the exposure (outpatient follow-up visit) (16). In this case, a participant with a readmission is marked as being unexposed which increases the number of readmissions for the unexposed group and potentially decreasing the number of readmissions for the exposed group. Under the assumption that outpatient follow-up visits are associated with a reduction in readmissions the net result is an artefactual exaggeration of the association between an outpatient follow-up visit and a reduced risk of readmission.

The time-dependent Cox proportional hazards regression model has been used to control for survival bias (16, 87). This model is used for time to event data which may include covariates, independent variables or predictor variables that change over time (86). When covariates are time-dependent rather than fixed, the time-dependent Cox model can be used by multiplying the hazard function by a function of the explanatory covariates (86).

An example of the potential impact of the survival bias on studies of outpatient follow-up visits is the study by Sharma *et al.* conducted on patients with COPD (16). When the effect of an

outpatient follow-up visit was measured as a fixed variable, the hazard ratio was 0.48 (95% CI 0.47-0.50) implying that an outpatient follow-up visit reduced the risk of readmission by 52% (16). However, this compares to a hazard ratio of only 0.91 (95% CI 0.87-0.96) when the effect of an outpatient follow-up visit was measured using a time-dependent Cox model implying that an outpatient follow-up visit reduced the risk of readmission by only 9% (16). To lower the risk of survival bias, studies should use the time-dependent Cox model in the analysis. In addition, survival bias may be controlled for in the study design by excluding patients who are readmitted before outpatient follow-up visits occur (11). In this review, documentation of if and how survival bias was addressed will be included in the assessment in an overall quality score.

Section 6: Aims and Hypotheses

The purpose of this thesis is to systematically review the literature on the association between outpatient follow-up visits and all-cause 30-day readmissions for cardiovascular and COPD patients. We looked to answer the question: for patients discharged from a short-stay, acute-care hospital in the United States with AMI, heart failure, COPD or stroke, does the occurrence of the first outpatient follow-up visit [with a PCP, nurse practitioner (NP), or physician specialist] within 30 days of discharge reduce the risk for all-cause 30-day readmission to a short-stay, acute-care hospital when compared with patients who have no outpatient follow-up visit? Aims and hypothesis include:

Aim 1: Conduct a systematic review to understand the association between an outpatient follow-up visit with a physician within 30 days after hospital discharge and the risk of any all-cause 30-day readmission for patients discharged with AMI, heart failure, COPD or stroke.

Hypothesis 1: Outpatient follow-up visits with a physician after hospital discharge from a cardiovascular or COPD related event will lower the risk of all-cause 30-day readmissions.

Aim 2: If there is sufficient commonality in the organization, conduct, and analysis of the studies we will conduct a meta-analysis to produce a single pooled estimate of effect.

Hypothesis 2: Data may not undergo pooling if individual studies use substantially different study designs, populations, exposures, analytic methods, or a variety of healthcare professionals seen.

Aim 3: Assess heterogeneity in the effect of outpatient follow-up visits on readmission risk between studies and to understand the sources of between study variability.

Hypothesis 3: Between study variability in effect of outpatient follow-up visits will be high due to variability introduced by condition type (AMI, heart failure, COPD, and stroke), exposure type (timing of outpatient follow-up visit), location of studies, and insurer (Medicare verses commercially insured).

Aim 4: To understand if studies identify and address the potential for survival bias in the timing of the exposure (outpatient follow-up visit) with the outcome (all-cause 30-day readmission).

Hypothesis 4: Studies that do not address survival bias will show a larger (spurious) effect of outpatient follow-up visits on readmission.

CHAPTER 2: METHODS

A protocol template of the Cochrane Library (88) was used to guide the development and organization of the protocol (see APPENDIX C) for this systematic review and meta-analysis. In addition, textbooks by Guyatt G *et al.* (89) and Petitti D *et al.* (90) were used to guide the content in this chapter, as well as the subsequent analysis, and results chapter. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was also used to guide the conduct and reporting of this systematic review and meta-analysis (91).

Section 1: Study Objectives

This systematic review and meta-analysis was structured around the four objectives previously described in Chapter 1 (pages 19 and 20). For the first objective we conducted a systematic review to identify if outpatient follow-up visits after hospital discharge [with a PCP, NP, or physician specialist (e.g. cardiologist or pulmonologist)], were associated with a lower risk of all-cause 30-day readmission for patients discharged with AMI, heart failure, COPD or stroke. For the second objective, we assessed if there was sufficient commonality in the organization between studies to support a meta-analysis that generated summary estimates of effect. For the third objective, we assessed heterogeneity between studies to understand the sources of between study variability. For the final objective, we assessed if studies identified and addressed the potential for survival bias in the timing of the exposure (outpatient follow-up visit) relative to the timing of the outcome (all-cause 30-day readmission).

Section 2: Primary Exposure and Outcome Measures

The primary exposure for this systematic review and meta-analysis was the occurrence and timing (*i.e.*, days since discharge) of the first outpatient follow-up visits (with a PCP, NP, or physician specialists) within 30 days after initial discharge from a short-stay or acute-care hospital in the United States. The primary outcome was the occurrence of the first all-cause readmission to a short-stay or acute-care hospital in the United States within 30 days of initial discharge.

Section 3: Eligibility and Exclusion Criteria

Table 1 was used as a checklist to identify eligible studies. Table 1 includes location, time frame, study population, exposure, outcome, and study type. Eligible studies had to meet all of the inclusion criteria listed in Table 1. These eligibility criteria include studies measuring the association between outpatient follow-up visits and 30-day readmissions. Other eligibility criteria include only studies conducted in the United States, published in English, and consisting of study participants who are 18 years of age or older. Eligible studies also had to define the primary exposure as an outpatient follow-up visit (with a PCP, NP, or physician specialist) within 30 days after initial discharge, and include a primary outcome that was defined as the first all-cause 30-day readmission. Finally, studies must have been original peer reviewed publications published within the last 10 years (starting in January 2007). My rationale for this latter criteria was that the CMS Hospital Compare program began publically reporting readmissions in 2009 and the establishment of the HRRP and other CMS related P4P programs which provide health care providers with incentive payments to reduce readmissions began before 2012 (1, 92).

Studies meeting any of the following four criteria were excluded. First, articles identified as commentaries, conference notes, letters, editorials, opinions, abstracts only, or review articles were excluded. Second, intervention studies that were based on setting up a specific single outpatient clinic (often set up in the hospital where the patient was originally admitted) that the majority (>80%) of patients used for their outpatient follow-up visits were excluded. The rationale for this is that these studies are not generalizable to typical outpatient follow-up visits with physicians who work in ambulatory care settings. Third, studies that included more than 50% of patients with an initial discharge to specific rehabilitation setting [e.g., skilled nursing facility (SNF) or inpatient rehab facility (IRF)] were excluded. Fourth, studies where all or the majority (>80%) of patients included were discharged from an emergency department (*i.e.,* not hospitalized) were also excluded.

Section 4: Study Identification (Search criteria)

A Michigan State University librarian specialized in identifying search terms aided with this literature search. Two databases, the US Nation library of Medicine Medline (PubMed) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were systematically searched to identify eligible articles. PubMed was chosen because it is the most comprehensive US based database that captures a large range of biomedical journals. Although PubMed is a comprehensive database, it was important to expand the search in order to capture a larger range of relevant articles because depending only on the National Library of Medicine databases may fail to include 30% to 80% of relevant studies (93). Thus, CINAHL was searched because it contains nursing and allied health journals that could include studies that were related to outpatient follow-up visits and readmissions.

Search terms were developed to identify potentially eligible studies that met the primary target population of interest which consisted of studies examining the association between our exposure (outpatient follow-up visit) and outcome (all-cause 30-day readmission) for patients discharged from a short-stay, acute-care hospital in the United States with AMI, heart failure, COPD or stroke.

For the PubMed database, potentially eligible studies were identified using a combination of *[All Fields]* and *[MeSH]* terms as shown in APPENDIX D. A separate search with the addition of "*AND Randomized Controlled Trial[ptyp]*" was used to identify potential randomized controlled trials. Filters used included the English language and published date from 2007-2017.

For the CINAHL database, potentially eligible studies were identified using the following combination of search terms: *(patient readmission OR patient discharge OR discharge) AND (office visits OR outpatient OR outpatient follow up OR ambulatory care) AND (heart failure OR myocardial infarction OR (copd or chronic obstructive pulmonary disease) OR stroke).* Filters used included the English language, published date from 2007-2017, and academic journals. CINAHL required a shorter list of search terms because it uses a different search algorithm from PubMed, which does not use MeSH terms.

Section 5: Study Selection

Two individuals [author (GR) and Dr. Mat Reeves (MR)] independently screened titles and abstracts to identify potentially eligible studies that were to undergo full-text review. Search results (*i.e.*, hits) from PubMed and CINHAL were combined. After duplicates were removed, titles were reviewed to determine their potential relevance. The abstracts of potentially relevant

titles were then independently assessed by GR and MR to identify articles for full-text review (based on inclusion and exclusion criteria). GR and MR then independently conducted full-text reviews to determine the final set of eligible studies that would undergo data abstraction. For the studies that underwent full-text review, we documented the primary reason if a study was subsequently excluded. The reference list of articles that underwent full-text review were also reviewed to find additional articles not identified by the search strategy. At each step, discrepancies were resolved by a consensus meeting. A PRISMA flow diagram (see APPENDIX E) was used to show the number of articles identified at each stage (*i.e.*, identification, screening, eligibility, and final inclusion) (91).

Section 6: Data Abstraction from Eligible Studies

Two individuals GR and MR independently abstracted relevant data from each included study. Table 2 describes the definitions used to abstract important data fields from the eligible studies. Data of interest include study design, purpose/objective, disease condition, study population, study setting, sample size, and analytic design or approach (Table 2). In addition, data was abstracted on the exposure including type of study (intervention or observational study, single-component or multicomponent, the multicomponents included), timing of follow-up visit, and type of visit (Table 2).

Finally, data was abstracted on the study findings including the prevalence of outpatient visits, crude readmission rate, unadjusted and adjusted effect estimates for outpatient follow-up visits, variables adjusted for in models, 95% confidence intervals, and p-values (Table 2). If a study did not provide an unadjusted effect measure and if data was available, the unadjusted

effect (odd ratio) was calculated using the readmission rates for patients with and without outpatient follow-up visits. Any disagreements with data abstraction were solved by consensus.

Section 7: Control for Confounders and Survival Bias

Covariates listed below are important to identify as they could bias the association between outpatient follow-up visits and the risk of readmission. For example, patients with a more severe illness are more likely to have a follow-up visit but are also more likely to have a readmission compared to patients with a minor illness (8, 11, 14). Therefore, we identified important confounders and incorporated whether they were adequately controlled into our quality assessment score. Important confounders include demographics (age and gender), SES (as defined by income, education, or occupation), and disease severity of each specific condition. Disease specific severity scales included the Killip classification (range I-IV) (41) for AMI, the New York Heart Association (function capacity range I-IV and objective assessment A-D) (42) for heart failure, Spirometric classification (for adults 70% or greater is normal and less than 70% is abnormal) (94) for COPD, and the NIH Stroke Scale (range 0-42) for stroke (95). In addition, articles were assessed to determine if methods were used to control for survival bias. As described in Chapter 1, survival bias can artificially inflate the effect of an outpatient follow-up visit by classifying a participant as unexposed (no outpatient follow-up visit) if the outcome (readmission) occurs before the exposure (outpatient follow-up visit) (16). Therefore, we identified if studies used methods designed to prevent or control survival bias, either at the design or the analysis phase. Methods used at the design phase may include the exclusion of patients who were readmitted before outpatient follow-up visits occur. Studies can also control for survival bias at the analysis phase by using the time-dependent Cox Proportional Hazards

Regression model, where the presence or absence of an outpatient visit is specified as a time-dependent variable.

Section 8: Quality Assessment Score

The Newcastle-Ottawa Scale (NOS) was originally designed to assess bias in nonrandomized observational studies (96). The original NOS included eight items, and was centralized around three categorizes that address the selection and assessment of the exposed and non-exposed groups, important confounding factors controlled for, and the selection and assessment of the outcome measure. The original scale had a range of scores of 0-8 with an item receiving a star only if considered to meet the threshold of high quality. A study was given a star if the study met the criteria listed in APPENDIX F for each item. The NOS was modified so it was more relevant to the type and design of studies included in this systematic review and meta-analysis. My final modified quality scoring system also included eight items with a possible range of scores of 0-8. For each item a binary scoring scale was used where each study either received or did not receive a star (point), depending on criteria listed below (pages 28-31) for each item. Category 1 (Selection of study population) and Category 3 (Outcome) included two items each while Category 2 [Comparability between exposure groups (*i.e.*, control of confounding)] included four items. Modifications included changing the original item of "representativeness of the exposed cohort" to the "representativeness of the broad United States population". This was done to give greater importance to the origin of the overall study population and because for the particular studies included in this systematic review and meta-analysis, the same data source was used to identify both the exposed and unexposed study populations. This change also involved the removal of the second original NOS item concerning

the "selection of the non-exposed cohort". I also dropped the item described as the "demonstration that outcome of interest was not present at start of study" because this issue of when readmissions do occur before an outpatient follow-up visit is addressed when controlling for survival bias, thus control for survival bias was added as a new criteria in Category 2. Furthermore, I also dropped the item "was follow-up long enough for outcomes to occur" from Category 3 because all eligible studies used the same outcome measure of 30-day readmissions.

The quality assessment score was used to identify high and low quality studies which were defined using a pre-specified threshold of five or greater. This quality assessment score was then used to compare studies on specific characteristics including hospital-level analysis compared to patient-level analysis, across disease conditions, studies controlling for survival bias compared to not controlling for survival bias, and studies controlling for SES compared to not controlling for SES. Furthermore, the assessment score was explored to identify if study quality had an impact on the results. Due to a large amount of clinical variability and methodological variability (further described below in Section 9: Evaluation of the Appropriateness of Meta-analysis) assessment scoring was only compared across studies that used a patient-level analysis (n=5).

Details of the scoring of the eight items are provided below:

Category 1: Selection of study population

1. Representativeness of the broad United States population
    a. Study population broadly representative of the United States in terms of age, gender, racial distributions, and geographically (e.g., Medicare database or CRUSADE registry involving patients from multiple states and hospitals throughout the United States).

i. Star

b. Study population not representative of the United States, or no information provided (e.g., a single hospital based study, a single ethnic group, a single group of individuals such as veterans, or a database or registry that does not represent the whole of the United States population).

i. No star

2. Ascertainment of outpatient follow-up visit (exposure)

a. Exposure retrieved from a reliable source (e.g., Medicare database, electronic medical records, administrative or billing data, or structured patient interviews).

i. Star

b. Unreliable source data including patient self-reported or study failed to mention origin or collection of exposure data.

i. No star

Category 2: Comparability between exposure groups (*i.e.*, control of confounding)

In order for the study to control for important confounders, the following criteria must have been met: availability of data on confounders, and their inclusion in a statistical model that generates adjusted estimates or rationale for why a potential confounder was not included in the model.

3. Demographics

a. Study controlled for at least age and gender. It was not necessary for studies to control for race.

i. Star

b. Study failed to control or mention if demographics were controlled.
    i. No star

4. Socioeconomic status
    a. Study controlled for SES measured by either income, education, or occupation (97).
        i. Star
    b. Study failed to control for or mention socioeconomic status.
        i. No star

5. Severity of disease
    a. Study controlled for severity of disease by using an established scale or severity classification (41-44). Examples of scales used may include: AMI (Killip classification (41)), heart failure scale (New York Heart Association (42)), COPD (Spirometric Classifications (43)) and stroke (NIH Stroke Scale (44)).
        i. Star
    b. Study failed to control for or mention severity of disease.
        i. No star

6. Survival bias
    a. Controlled for survival bias in their study design (e.g., by excluding individuals readmitted before an outpatient follow-up visit occurred) or by using a time-dependent Cox proportional hazard regression model in their analysis (86).
        i. Star

b. Study did not appropriately control for or mention survival bias.

i. No star

Category 3: Outcome

7. Assessment of outcome

a. Outcome retrieved from a reliable source (e.g., Medicare database, structured patient interview or record linked data).

i. Star

b. Outcomes retrieved from unreliable source such as self-report or failed to mention how data was collected.

i. No star

8. Adequacy of follow-up of cohorts

c. ≥80% of patients accounted for after follow-up.

i. Star

d. <80% of patients accounted for after follow-up, or no mention.

i. No Star

Two individuals GR and MR independently assessed quality assessment scoring by the items provided above. Any disagreements with data abstraction were solved by consensus.

Section 9: Evaluation of Meta-analytic Approach

In order to determine if a meta-analysis was suitable to conduct, study populations, designs, exposures, and results were identified and compared between individual studies. A final decision was made depending on the commonality of these criteria between individual studies to determine whether data could be pooled for a meta-analysis. In the protocol (APPENDIX C) we

intended to include the following subgroups in a meta-analysis: disease condition (AMI, HF, COPD, stroke), participation in a readmission prevention program/intervention (QI programs) versus none, insurance type (Medicare versus commercially insured), white versus minority, type of healthcare professional seen at follow-up visit (PCP versus NP versus specialist), survival bias (controlled versus not controlled), and quality assessment score [high scoring (≥5) studies versus low scoring (<5) studies]. However, as indicated in the Results section, many of these pre-specified comparisons were not possible due to a limited number of studies available.

As specified in the protocol, we chose to use a random effects model for our meta-analysis. This model was chosen because there was variation across study characteristics by disease condition (e.g., AMI, heart failure, and COPD), definition of outpatient visits (e.g., physician seen and timing of visit), age, patient populations, location of studies, and insurance type (Medicare verses commercially insured). With random-effects model, between-study variability is accounted for by allowing the true effect size to differ and have its own distribution. This between-study variability is estimated as another parameter in the model and is added to the overall variance of the summary estimate, resulting in wider confidence intervals and more conservative estimates compared with that generated by the fixed effects model (98).

Heterogeneity may occur due to statistical heterogeneity (*i.e.*, random error or by chance) in the observed effects, clinical heterogeneity (*i.e.*, variation of patients, interventions, or outcomes), and/or methodological diversity in the study design (*i.e.*, retrospective cohort versus nested matched case-control study) (93). Forest plots, Q-statistics and I^2 statistics were used as tools to determine the degree of heterogeneity that was present. Heterogeneity was interpreted by a p-value for the Q-statistic and by a percentage for the I^2 statistics. The Q-statistic tests the null hypothesis of homogeneity which states that all studies share a common effect size. If the p-

value is less than 0.05 the null is rejected and you conclude there is significant between study heterogeneity. The Q-statistic determines if there is statistical heterogeneity or not, but does not quantify the magnitude of statistical heterogeneity (93). Furthermore, the Q-statistic is highly dependent on the number of studies in a meta-analysis and generates a low power when few studies are included (93). The I^2 statistic quantifies the degree of heterogeneity and is calculated using between study variation between total variation (93). The I^2 statistic refers to the percent of variation between studies that is associated with heterogeneity (93). An I^2 value of less than 25% equates to low heterogeneity, 25-75% to moderate heterogeneity, and more than 75% to high heterogeneity. The analyses was conducted with STATA 14 statistical software using the metan command (99). The metan procedure produces an effect summary (ES) with a 95% confidence interval as well as the test of whether the ES is statistically significant (using a Z-score and p-value) from the null value of 1.0 (indicating that the ES is a rates measure).

Analyses were performed on both unadjusted and adjusted data (when available) and were pooled across all types of effect measures [*i.e.,* hazard ratios (HR), odds ratios (OR), and relative risk (RR)]. For the purpose of this study I labeled the ES as the RR regardless of its original origin as OR, HR, or RR. The rare disease assumption was used to justify combining these different ES's. Therefore, for this study the ES was defined as the relative risk in 30-day readmissions between individuals with an outpatient follow-up visit compared to individuals with no outpatient follow-up visit. The ES was a weighted average of the combined study specific ES's. A relative risk below one indicates that the risk of 30-day readmissions was lower for individuals with an outpatient follow-up visit compared to individuals without an outpatient follow-up visit. A 95 percent confidence interval and a p-value of the pooled ES were used to determine statistical significance. If the 95% confidence interval did not include the null value of

1.0, there was a statistically significant reduction or a statistically significant increase in the risk of readmission with an outpatient follow-up visit.

Table 1: Study Eligibility and Selection: Location, Time Frame, Study Population, Exposure, Outcome, and Study Type

	Eligibility Criteria
1	Study conducted in the United States
2	Published from 2007-2017
3	Study population AMI, HF, COPD, stroke
4	Study participants ≥18 years of age
5	Original research
6	Outpatient follow-up visit within 30 days of discharge
7	Outcome includes 30-day readmission
8	Study measures the association between outpatient follow-up visits and 30-day readmissions
9	Initial admission was to an acute care hospital

Note: Included studies had to meet all nine of the eligibility criteria

Table 2: Data Abstraction: Study Characteristics, Exposure, and Study Findings/Results

Criteria	Description
Study design	Type of observational or experimental design as described by authors; if not provided by authors, we generated our own description
Purpose/objective	As described by authors
Disease condition	AMI, heart failure, COPD or stroke
Study population	Origin of the underline study population (e.g., VA hospitals, Medicare population, location discharged, program type, or regional hospital network)
Study setting	Time frame and location
Sample size	The number of patients and/or number of hospitals
Analytic design or approach	The unit of analysis defined as either patient-level (where the exposure-outcome relationship was examined at the individual patient-level) versus the hospital-level (where the exposure-outcome relationship was examined after aggregating patient level data within each hospital)
Intervention or Observational Study	Intervention studies that were not based on a randomized allocation such as a quality improvement project to promote outpatient follow-up visits to reduce readmissions. Observational studies simply observed the association of outpatient follow-up visits and hospital readmissions
Single-component or multicomponent	Single component: where the intent is to increase the use of outpatient follow-up visits only. Multicomponent: where the intervention to increase the use of outpatient follow-up visits is combined with one or more concomitant intervention strategies
What multicomponents were included	Multicomponents included as described by authors (e.g., discharge planning, home health nursing, or making discharge summaries available to follow-up health care providers)
Timing of visit	Time point of primary exposure as defined by author (ex within 7 days)
Type of visit	Was visit by a PCP, pulmonologist, cardiologist, or any physician
Prevalence of outpatient visits	At a given primary time point
Crude readmission rate	For the total study population, the exposed group (outpatient follow-up) and unexposed (no outpatient follow-up)
Unadjusted and adjusted effect estimates	Effect estimate of an outpatient follow-up visit on readmission defined as a hazard ratio, odds ratio, and relative risk. In addition, 95% confidence intervals
Variables Adjusted for	Variables included in the model

Abbreviations: VA, veteran affaire; PCP, primary care physician

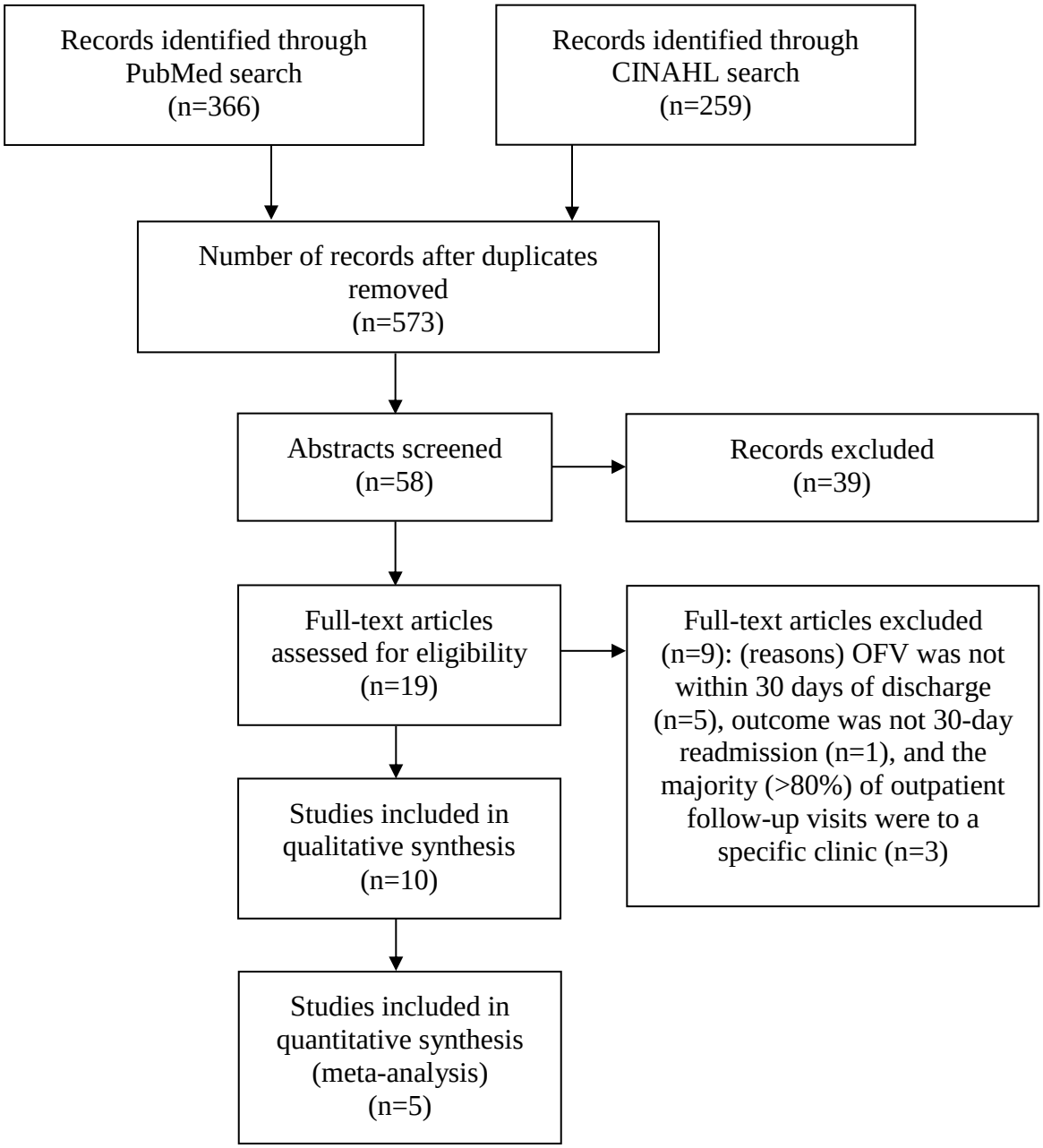
CHAPTER 3: RESULTS

Section 1: Description of Search Results and Selected Studies

A PRISMA flow diagram (Figure 1) describes the initial search results of the two databases, which identified 573 unique and potentially relevant articles. Titles were reviewed and 58 articles were deemed potentially relevant. Screening the abstracts of these 58 articles resulted in the elimination of 39 that did not meet eligibility. After full-text review of the remaining 19 articles, nine were excluded for the following reasons: outpatient follow-up did not occur within 30 days of discharge (n=6), study outcome did not include 30-day readmissions (n=3), initial admission was not to an acute care hospital (n=2), the majority (>80%) of outpatient follow-up visits were to a specific clinic (n=3). Because studies could be excluded for multiple reasons the number of reasons (n=14) exceeds the number of studies excluded.

An additional 25 potentially relevant articles were identified by title from the references of the 19 articles that underwent full-text review. Of these references, four articles underwent full-text review but none met our eligibility criteria. These four studies were excluded because the study was conducted outside the United States (n =1), and the study condition did not include AMI, heart failure, COPD or stroke patients (n=3). Therefore, in total, out of 598 potentially relevant references, 10 met our eligibility criteria for this systematic review (Figure 1).

Figure 1: PRISMA Flow Diagram



Abbreviations: OFV, outpatient follow-up visit

Table 3 describes important study characteristics of the 10 studies including study design, purpose/objective, disease condition, study population, study setting, sample size, and the analytic design or approach. Of these 10 studies, eight were retrospective cohorts (4, 8, 9, 11, 13-16), one was a prospective cohort (10), and one was a nested matched case-control study (12) (Table 3). All studies included patients with a single condition: five studies included only heart failure patients (4, 10, 12-14), three included only COPD patients (8, 15, 16), and two only AMI patients (9, 11) (Table 3). Although stroke patients were included in the search, no study that included a stroke population fulfilled eligibility criteria. For the study population, six studies used Medicare patients (4, 9-11, 13, 16), one used commercially insured patients (15), one used patients from the Kaiser Permanente Northern California health system (San Francisco bay area) (12), one used patients from a Mayo Clinic hospital in Rochester, Minnesota (8), and one used patients from the VA database (14) (Table 3). The sample sizes of patients for the 10 studies ranged from 839 to 188,611 and the number of hospitals ranged from one to 1,088 (Table 3). Six studies (8, 12-16) used a patient-level analysis while four (4, 9-11) used a hospital-level analysis. It was important to separate studies that were based on patient-level analyses from those that conducted hospital-level analyses because they measured the association between outpatient follow-up visits and readmissions differently. Patient-level studies compared patients with an outpatient follow-up visit to patients with no outpatient follow-up visit for all-cause 30-day readmissions. However, hospital-level studies calculated the average frequency of outpatient follow-up visits that occurred among each hospital's patient population and then compared the effect of outpatient follow-up visits by aggregating hospitals into four quartiles based on the frequency of outpatient follow-up visits. These studies then compared the 30-day readmission rates (calculated at the hospital-level) between hospitals with the highest frequency of outpatient

follow-up visits (*i.e.*, quartile 4) to hospitals with the lowest frequency of outpatient follow-up visits (*i.e.*, quartile 1).

Table 3: Characteristics of Included Studies: Design, Objective, Study Population and Time Frame (n=10)

First Author (year)	Study Design	Disease Condition	Study Population	Study Setting	Sample Size	Analytic Design or Approach
Fidahussein SS (2014)	Retrospective cohort	COPD	Discharged from a Mayo Clinic medical center to home or to a skilled nursing facility	Rochester, MN, January 2004 to November 2011	1,422 discharges with 839 patients	Patient level cohort analysis
Lee KK (2016)	Nested matched case-control	Heart Failure	Discharged from Kaiser Permanente hospitals to home without hospice care	Northern CA, January 2006 to June 2013	Case (1,587) Control (7,935)	Patient level matched CCS design
Murtaugh CM (2016)	Retrospective cohort	Heart Failure	Medicare beneficiaries discharged to home health care	United States, July 2009 to June 2010	98,730	Patient level instrumental variables (IV) analysis
Muus KJ (2010)	Retrospective cohort	Heart Failure	US veterans identified by VA administrative data	United States, October 2005 to September 2007	32,998	Patient level cohort analysis
Sharif R (2014)	Retrospective cohort	COPD	Commercially ensured patients, ages 40 to 64 identified by the Clinformatics Data Mart	United States, January 2009 and November 2011	8,263	Patient level cohort analysis (patient, provider and system factors)
Sharma G (2010)	Retrospective cohort	COPD	Medicare FFS beneficiaries discharged to home	United States, 1996 and 2006	62,746	Patient level cohort analysis

Abbreviations: VA, veterans affairs; FFS, fee-for-service; CCS, case-control study

Table 3 (cont'd)

First Author (year)	Study Design	Disease Condition	Study Population	Study Setting	Sample Size	Analytic Design or Approach
Baker H (2015)	Prospective cohort	Heart Failure	Medicare patients discharged to home from 10 hospitals in Southeast Michigan	Southeast MI, May 2011 to April 2013	CH (24,849); NPH (92,321) (11 hospitals)	Hospital level pre-post design, with control (non participating hospitals)
Brown JR (2014)	Retrospective cohort	AMI	Medicare FFS beneficiaries with Part A and Part B coverage	United States, 2008 and 2009	188,611 patients (1,088 hospitals)	Hospital level cohort analysis (quality, capacity and intensity measures)
Hernandez AF (2010)	Retrospective cohort	Heart Failure	Medicare FFS beneficiaries discharged home, in OPTIMIZE-HF and the GWTG-HF program	United States, January 2003 to December 2006	30,136 patients (225 hospitals)	Hospital level cohort analysis
Hess CN (2013)	Retrospective cohort	AMI	Medicare FFS beneficiaries discharged to home	United States, 2003 to 2006	25,872 patients (228 sites)	Hospital level cohort analysis

Abbreviations: FFS, fee-for-service; OPTIMIZE-HF, program to initiate lifesaving treatment in hospitalized patients with heart failure; GWTG-HF, get with the guidelines heart failure; CH, collaborating hospitals; NPH, non-participating hospitals

With respect to our primary exposure of interest (presence and timing of outpatient follow-up visits), Table 4 describes important exposure characteristics of the 10 studies including the type of study (*i.e.*, intervention study vs. observational study, and single vs. multicomponent), timing of follow-up visit (as defined by author), and type of physician. Only two studies (4, 10) used an intervention (Table 4). Six studies (4, 8, 11, 14-16) used a single-component exposure containing only outpatient follow-up visits, while the remaining four studies (9, 10, 12, 13) evaluated a multicomponent exposure containing additional strategies to lower readmissions along with an outpatient follow-up visit (Table 4). The timing of outpatient follow-up visits varied between studies from within seven days, within 14 days, or within 30 days after initial discharge (Table 4). All studies defined an outpatient follow-up visit as a visit with either a PCP, cardiologist, pulmonologist or any type of physician (Table 4).

Table 4: Exposure Related Study Characteristics: Intervention Study, Single or Multicomponent, Timing and Type of Follow-up (n=10)

First Author (year)	Interventional or Observational Study	Single or Multicomponent	Multicomponents Included	Timing of Follow-up Visit (primary)	Type of Visit
Fidahussein SS (2014) (8)	Observational	Single	NA	Within 30 days	PCP or Pulmonologist
Lee KK (2016) (12)	Observational	Multicomponent	Phone or clinic visit	Within 30 days (clinic)	Internal medicine, family medicine, or cardiology providers
Murtaugh CM (2016) (13)	Observational	Multicomponent	Intensive home health nursing and physician follow-up	Within seven days	Physician
Muus KJ (2010) (14)	Observational	Single	NA	Within 30 days	Physician or Physician Extender
Sharif R (2014) (15)	Observational	Single	NA	Within 30 days	Any Physician
Sharma G (2010) (16)	Observational	Single	NA	Within 30 days	Established PCP or Pulmonologist
Baker H (2015) (10)	Interventional	Multicomponent	Seven care processes (Footnote)	Within seven days	Any Physician
Brown JR (2014) (9)	Observational	Multicomponent	Discharge planning and PCP visit within 14 days	Within 14 days	PCP
Hernandez AF (2010) (4)	Interventional	Single	NA	Within seven days	Physician or Cardiologist
Hess CN (2013) (11)	Observational	Single	NA	Within seven days	Any Physician

Footnote: Seven care processes = Identify HF patients prior to discharge, Schedule and document a follow-up visit with cardiologist or PCP that takes place within seven days of discharge, Provide all patients with documentation of the scheduled follow-up appt, Identify and address barriers to keeping appointment, Ensure all HF patients arrive at scheduled appointment within seven days of discharge, Make discharge summary available to follow-up health care providers for all HF patients, and Collaborative hospitals shared best practices and Quarterly Progress Reports.

Abbreviations: NA, not applicable; QI, quality improvement; PCP, primary care physician

Section 2: Individual Study Findings/Results

The primary findings and results of the six studies that used a patient-level analysis (8, 12-16) is shown in Table 5, while the results for the four studies that used a hospital-level analysis (4, 9, 11) are shown in Table 6. For each study, we include data on the prevalence of outpatient follow-up visits in the study population, the crude readmission rate, unadjusted and adjusted effect estimates for outpatient follow-up visits on readmission, and the list of variables included in the adjusted model. For the six studies (8, 12-16) using a patient-level analysis, the prevalence of outpatient follow-up visits during the 30-day period ranged from 24.3% to 68.4% (Table 5). For the four studies (4, 9-11) using a hospital-level analysis, the prevalence of outpatient follow-up visits during the 30-day period ranged from 23.3% to 81.5% (Table 6). For the five patient-level studies (8, 12-15) that provided data on the observed (crude) readmission rate, the range of study specific estimates was 8.9% to 20.8% (Table 5). For the three hospital-level studies (4, 9, 11) that provided data on the observed (crude) readmission rate, the range of study specific estimates was 18.5% to 21.3% (Table 6).

Although six studies used a patient-level analysis (8, 12-16), one study (13) was not included in our meta-analysis due to incomplete information on study findings that consisted of percentage point change of readmissions (Table 5). For these five patient-level studies, three (8, 12, 16) provided unadjusted effect estimates while the author [GR], was able to calculate an unadjusted relative risk for the other two studies (14, 15). Three studies (14-16) found a statistically significant relative risk reduction between 12% and 63%, one (12) found a non-significant reduction of 10%, and one (8) found a no association between outpatient follow-up visits and readmissions (Table 5). Four of the patient-level studies (8, 12, 15, 16) provided adjusted results. Of these, three studies (12, 15, 16) found a statistically significant relative risk reduction between 9% and 30%, and one study (8) again found no association (Table 5).

Common variables controlled for between these studies include age and sex (Table 5). Less common variables controlled for include length of stay (LOS), medical history, and SES (Table 5). There was little change after adjustment between unadjusted and adjusted effect estimates for three of the four individual patient-level studies and the adjustment resulted in only a 3% to 6% relative change between the unadjusted and adjusted (8, 12, 15, 16). The relative change was calculated by taking the absolute value of the unadjusted subtracted by the adjusted over the unadjusted. This study adjusted for age, sex, LOS, Charlson Comorbidity Index, and number of admission cycles (Table 5).

Although four studies used a hospital-level analysis (4, 9-11), one study (10) had incomplete information on study findings that was limited to percent of readmission (Table 6). The other three studies used quartiles (as previously described in this Chapter) to describe the association between the frequency of outpatient follow-up visits and readmission. For this review, data was only abstracted on the result of the fourth verses the first quartile. Two (4, 9) provided unadjusted results while the author [GR], calculated the other one (11). For the unadjusted results, one study (4) found a statistically significant relative risk reduction of 13%, one (9) found a statistically significant increase of 7%, and one (11) found no association for hospital studies with patients at the highest frequency of outpatient follow-up visits for readmission compared to hospitals with the lowest frequency of outpatient follow-up visits (Table 6). For the adjusted results, all three hospital studies found a non-statistically significant relative risk reduction of between 2% and 9% for readmission in quartile four compared to quartile one hospitals (Table 6). There was little change after adjustment between unadjusted and adjusted effect estimates for each of the individual hospital-level studies. The relative percent change in the effect estimate after adjustment ranged from 5% to 9% for the three studies (4, 9,

11). Common variables controlled for in these studies include advanced age, sex, race, medical history, and LOS (Table 6).

Table 5: Patient-level Study Findings/Results: Prevalence of Visits, Crude Readmission Rate (Total Study, Exposed, and Unexposed), Unadjusted and Adjusted Effect (n=6)

First Author (year)	Prevalence of Outpatient Visits	Crude Readmission Rate (Total)	Crude Readmission Rate (Exp)	Crude Readmission Rate (Unexp)	Unadjusted Effect	Adjusted Effect	Variables in the Adjusted Model
Fidahussein SS (2014) (8)	68.4%	19.0%	19.0%	18.0%	HR= 1.07 (95 % CI 0.83-1.37)	HR= 1.02 (95% CI 0.80-1.32)	Age, sex, LOS, Charlson Comorbidity Index, and number of admission cycles
Lee KK (2016) (12)	Cases=59.4%; Control=60.6%	13.2%	NA	NA	OR= 0.90 (95% CI 0.79-1.02)	OR= 0.85 (95% CI 0.73-0.98)	Age, sex, race, annual household income, high school graduation, medical history, number of laboratory checks and heart failure medication changes
Murtaugh CM (2016) (13) *	24.3%	20.8%	NA	NA	NA	NA	NA
Muus KJ (2010) (14)	63.5%	17.3%	NA	NA	Calculated OR= 0.37 (95% CI 0.35-0.39)	NA	NA
Sharif R (2014) (15)	57.3%	8.9%	7.6%	10.9%	Calculated OR= 0.67 (95% CI 0.58-0.78)	OR= 0.7 (95% CI 0.6-0.9)	Age, sex, medical history, alcohol abuse, obesity, prescriptions within 12 months before index hospitalization, type of provider and number of hospitalization within the year before index hospitalization, prescriptions, LOS, discharge follow-up, and type of provider in the discharge follow-up
Sharma G (2010) (16)	66.9%	NA	18.9%	21.4%	HR= 0.88 (95% CI 0.84-0.92)	HR= 0.91 (95% CI 0.87-0.96)	Age, sex, race, SES, region, comorbidity, admission day, year of admission, history of COPD, LOS, source of admission, hospital teaching status, metropolitan size, type of hospital, size of hospital

Abbreviations: Exp, exposed; Unexp, unexposed; NA, not available; HR, hazard ratio; OR, odds ratio; LOS, length of stay; SES, socioeconomic status; COPD, chronic obstructive pulmonary disease.

Note: * refers to study with an absence of usable information

Table 6: Hospital-level Study Findings/Results: Prevalence of Visits, Crude Readmission Rate (Total Study, Exposed, and Unexposed), Unadjusted and Adjusted Effect (n=4)

First Author (year)	Prevalence of Outpatient Visits	Crude Readmission Rate (Total)	Crude Readmission Rate (Exp)	Crude Readmission Rate (Unexp)	Unadjusted Effect	Adjusted Effect	Variables in the Adjusted Model
Baker H (2015) (10) *	32.0% (estimated)	NA	29.0 to 27.3% (pre-post in CH)	29.8 to 28.9% (pre-psot in matched NPH)	NA	NA	CMS risk-standardized readmission rates
Brown JR (2014) (9)	60.7%	20.3%	NA	NA	Q4 RR= 1.07 (95% CI 1.04-1.11)	Q4 RR= 0.98 (95% CI 0.94-1.02)	CMS readmission model factors
Hernandez AF (2010) (4)	81.5%	21.3%	NA	NA	Q4 HR= 0.87 (95% CI 0.79-0.95)	Q4 HR= 0.91 (95% CI 0.83-1.00)	Age, sex, race, medical history, results of admission laboratory tests, completion of discharge instructions, referral to a heart failure disease management program, LOS for the hospitalization more than seven days, year of the index hospitalization
Hess CN (2013) (11)	Median 23.3% (IQR 17.7%-29.1%)	18.5%	NA	NA	Calculated OR= 1.05 (95% CI 0.97-1.15)	Q4 OR= 0.96 (95% CI 0.84-1.10)	Age, sex, race, weight, medical history, transfer status, heart rate, blood pressure, and EKG findings, signs of CHF, baseline hematocrit, troponin, and creatinine, LOS, hospital region, teaching status, bed size, cardiac catheterization, PCI, CABG, discharge medications, smoking, cardiac rehabilitation referral, diet

Abbreviations: Exp, exposed; Unexp, unexposed; IQR, interquartile range; NA, not available; CH, collaborating hospitals; NPH, non-participating hospitals; Q4, quartile four; RR, relative risk; HR, hazard ratio; OR, odds ratio; CMS, center for Medicare and Medicaid services; LOS, length of stay; EKG, electrocardiogram; CHF, congestive heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Note: * refers to study with an absence of usable information

Section 3: Meta-Analysis

A meta-analysis was conducted to generate a pooled estimate and assess its heterogeneity for the association between outpatient follow-up visits and all-cause 30-day readmission. Due to high study variability and lack of commonality, the primary meta-analysis was conducted only on studies that used a patient-level analysis (n=5). Only one subgroup analysis consisting of studies with a COPD study population (n=3) was conducted. These subgroups were considered common because they examined the same question of the effect of patients with an outpatient follow-up visit compared to patients without an outpatient follow-up visit for readmissions, and they used the same (or similar) patient-level data.

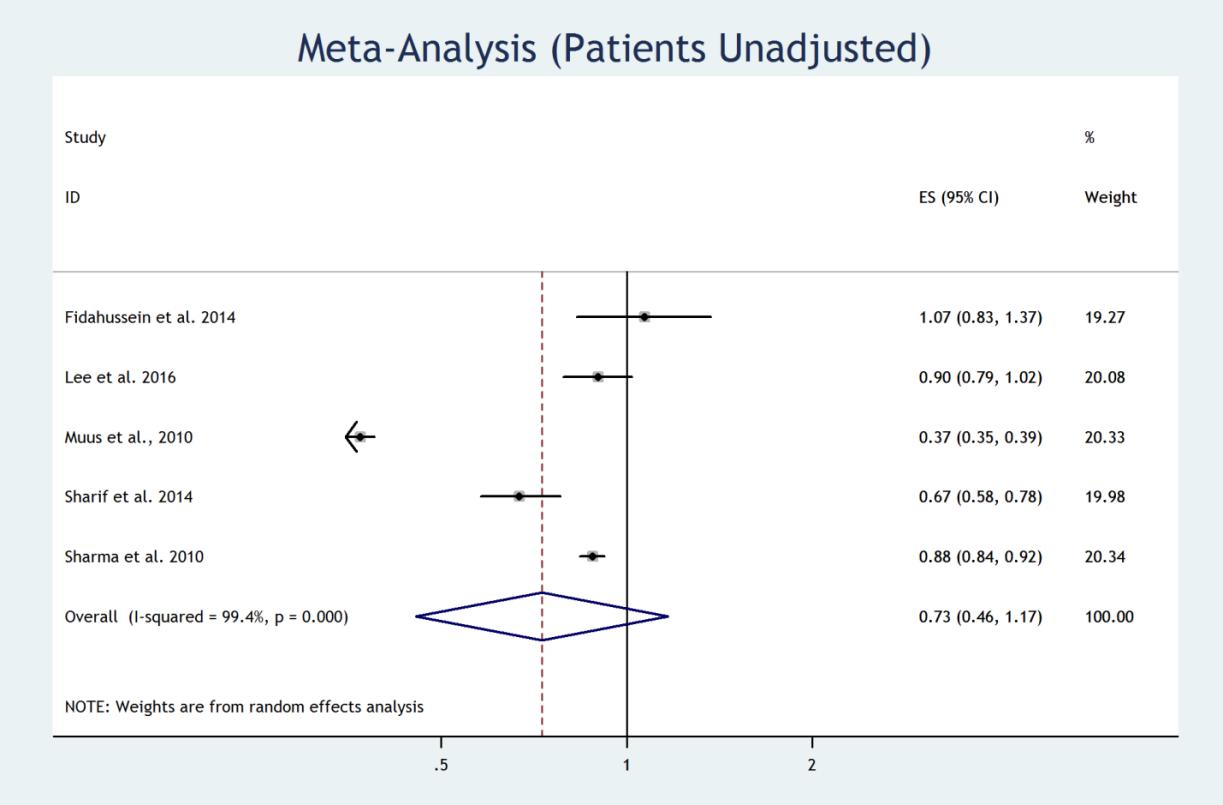
We did not conduct analyses for all of our original pre-specified subgroups that included disease conditions (AMI, heart failure, and stroke populations), quality improvement program versus none, insurance type (Medicare versus commercially insured), white versus minority, healthcare professional seen upon follow-up visit, survival bias (controlled versus not controlled), and quality assessment score (studies with high scores versus studies with low scores) (APPENDIX C). The primary reason for not conducting these subgroup analyses was the inadequate number (<3) of studies. Furthermore, studies had variable exposures (*i.e.*, timing of visit and type of physician seen), and variations in how the effect estimates was structured (*i.e.*, percentage point change for readmissions, or percent of readmissions).

Meta-analysis of studies using patient-level data (n=6):

For studies based on a patient-level analysis (as previously described in this Chapter), unadjusted results were available for five studies (8, 12, 14-16). The summary pooled result for the unadjusted effect estimates of these five studies was 0.73 (95% CI 0.46, 1.17, p= 0.188) (Figure 2, Table A3). The full results table for each analysis generated by STATA is shown in

APPENDIX G. For the unadjusted result, the I^2 statistic was 99.4% and the Q-statistic p-value was less than 0.001, indicating that there is a high amount of heterogeneity that was highly statistically significant. Adjusted results were provided by four studies (8, 12, 15, 16); the summary pooled estimate was 0.87 (95% CI 0.77, 0.97, p= 0.014) (Figure 3, Table A4). For the adjusted result, the I^2 statistic was 65.5% and the Q-statistic p-value was attenuated but remained statistically significant at 0.055, indicating that there is a moderate amount of heterogeneity that was marginally statistically significant. However, due to the small amount of studies in the adjusted analysis the Q-statistic will have low power and so the results should be interpreted as showing heterogeneity.

Figure 2: Meta-Analysis of Patient-Level Studies (Unadjusted): Outpatient Follow-up Visits and Association with All-cause 30-day Readmissions (n=5)

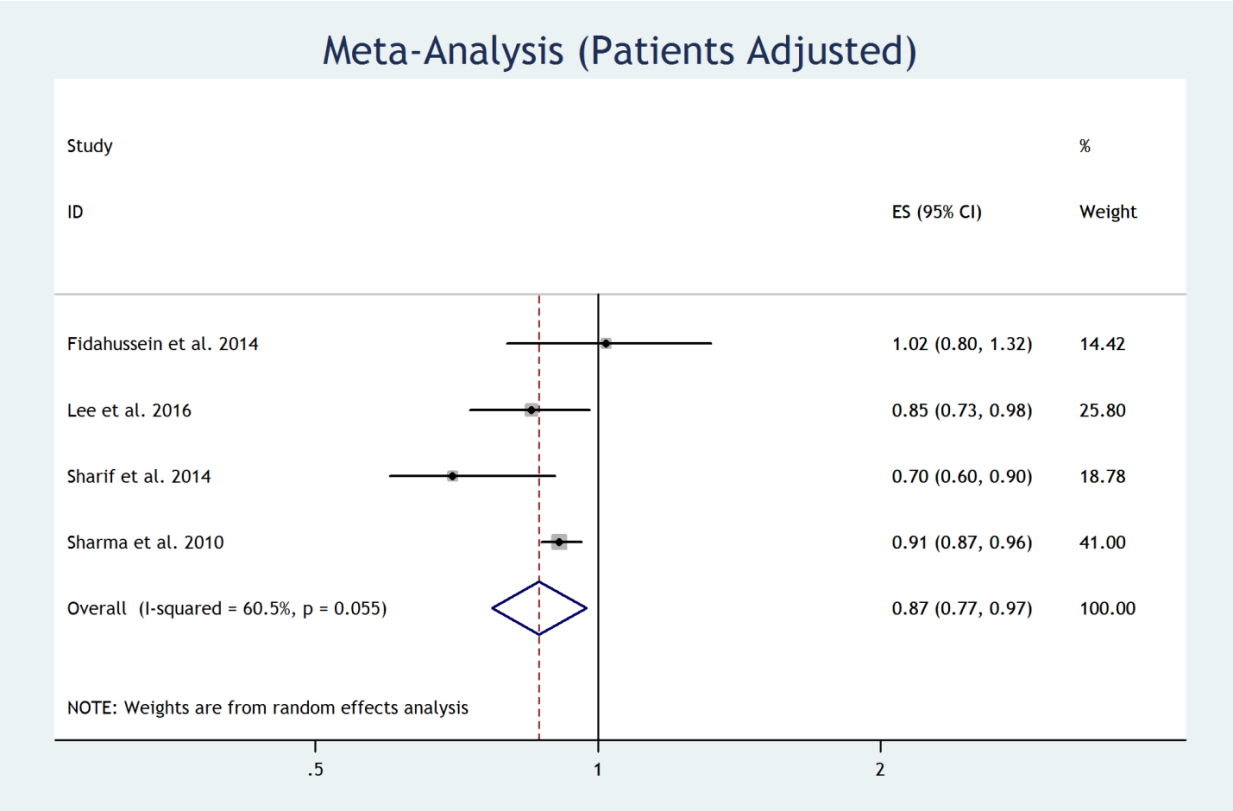


Note: Weights are from a random effects analysis

Test of ES=1; z= 1.32; p = 0.188

Heterogeneity chi-squared = 626.16; (d.f. = 4)

Figure 3: Meta-Analysis of Patient-Level Studies (Adjusted): Outpatient Follow-up Visits and Association with All-cause 30-day Readmissions (n=4)



Note: Weights are from a random effects analysis

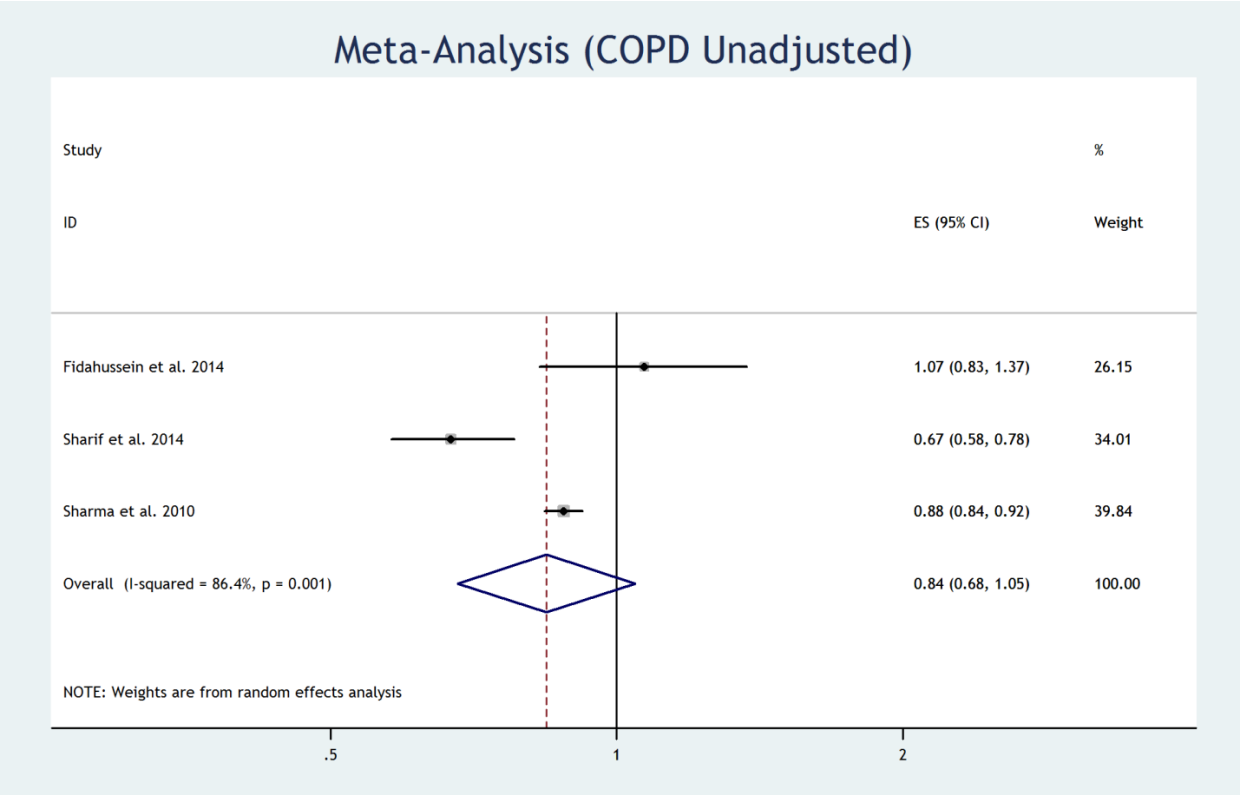
Test of ES=1; z= 2.45; p = 0.014

Heterogeneity chi-squared = 7.60; (d.f. = 3)

COPD subgroup of studies using patient-level analyses (n=3):

Among the six studies that conducted patient-level analyses, three studies (8, 15, 16) used only COPD study populations and all provided unadjusted and adjusted effect estimates of the effect of patients with an outpatient follow-up visit compared to patients without an outpatient follow-up visit on all-cause 30-day readmission. In addition, these three studies all evaluated the single-component exposure of only outpatient follow-up visits as a strategy to reduce readmissions. The summary result for the unadjusted effect estimate of these three studies was 0.84 (95% CI 0.68, 1.05) (Figure 4, Table A5). For the unadjusted result, the I^2 statistic was 86.4% and the Q-statistic p-value was 0.001, indicating that there is a large amount of between study heterogeneity that was highly statistically significant. The adjusted results included a similar effect estimate of 0.87 (95% CI 0.72, 1.04) (Figure 5, Table A6). For the adjusted result the I^2 statistic was 71.7% and the Q-statistic p-value was 0.029, indicating that there is a moderate amount of heterogeneity that was statistically significant.

Figure 4: Meta-Analysis of COPD Study Population (Unadjusted): Outpatient Follow-up Visits and Association with All-cause 30-day Readmissions (n=3)

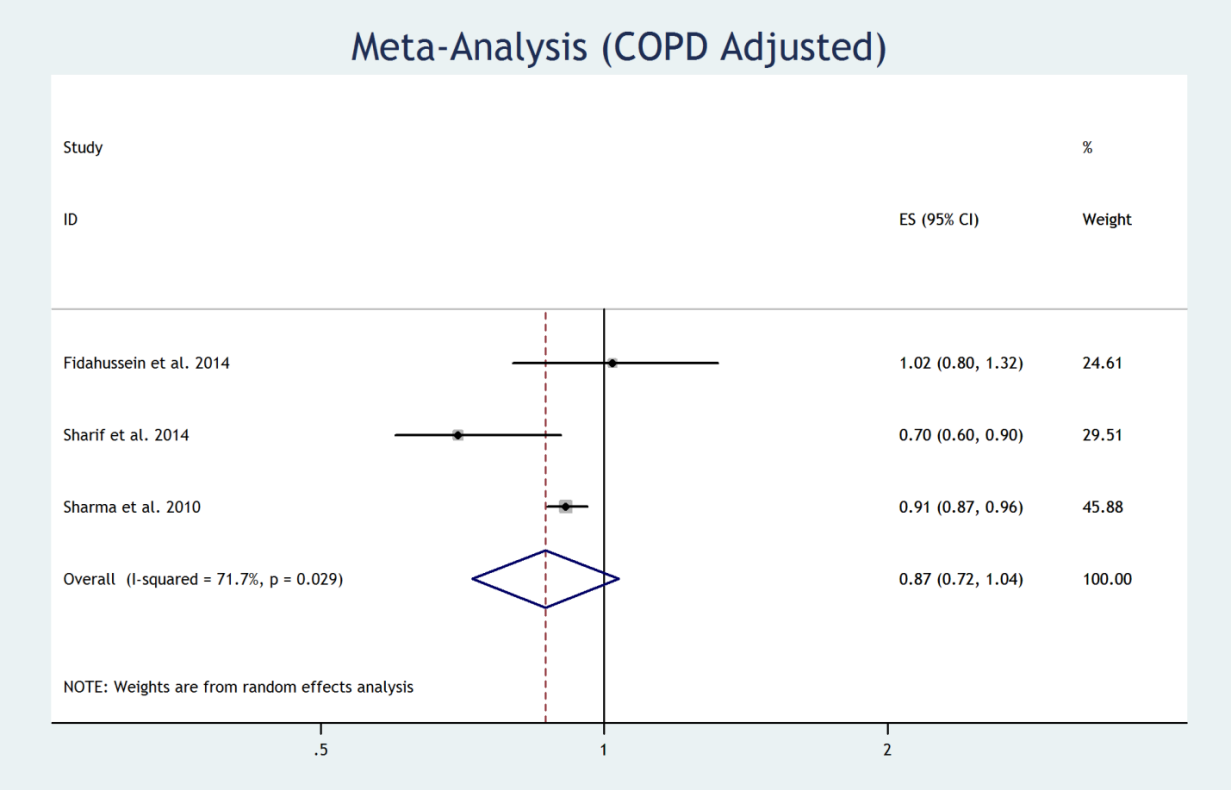


Note: Weights are from a random effects analysis

Test of ES=1; z= 1.54; p = 0.122

Heterogeneity chi-squared = 14.74; (d.f. = 2)

Figure 5: Meta-Analysis of COPD Study Population (Adjusted): Outpatient Follow-up Visits and Association with All-cause 30-day Readmissions (n=3)



Note: Weights are from a random effects analysis

Test of ES=1; z= 1.57; p = 0.115

Heterogeneity chi-squared = 7.05; (d.f. = 2)

Section 4: Quality Assessment Score

The quality assessment score was based on a binary scale of receiving a star (point) if the study was considered adequate for meeting a particular criterion. If a study did not meet the particular assessment criteria, the study did not receive a star. Each study was assessed on eight items, categorized into three groups as described in the Methods section.

I. *Category 1: Selection of study population and ascertainment of outpatient follow-up visit:*

Two criteria were included in this category. Assessment of representativeness was defined according to how well the study population represented the broad US population. Five studies (4, 9, 11, 13, 16) received a star (Table 7) because they included a target population that was broadly representative of the US population in terms of age, gender, racial distributions, and geography. The five studies that failed to receive a star included one study that included only 11 hospitals in southeast, Michigan (10), one that included only the Mayo Clinic hospital in Rochester, Minnesota (8), one that included the Kaiser Permanente database of over 3.7 million patients from Northern California (12), one study did not provide information on how the study population was dispersed in the United States (15), and one study that included only VA patients (14).

The ascertainment of outpatient follow-up visits (*i.e.*, the exposure) was based on if the exposure was retrieved from a reliable source. All 10 studies received a star because data on the exposure came from reliable databases including a Medicare database, Mayo Clinic administrative database, Kaiser Permanente hospitalization files, VA patient treatment files, and the Clinformatics Data Mart (Table 7).

II. *Category 2: Comparability between exposure groups (i.e., control of confounding):*

There were four criteria included in the assessment of comparability; demographics, socioeconomic status, severity of disease, and survival bias. For the comparability of study demographics, all studies received a star indicating each study controlled for at least age and gender (Table 7). Four studies received a star for controlling for SES (12-14, 16), whereas six studies did not receive a star. The approach used to obtain information on SES varied substantially between studies. One study used census-based estimates from a health plan databases to estimate annual household income (less than or equal to $35,000) and for percent graduating from high school (12). One study linked Medicare beneficiaries ZIP codes to census data in order to obtain data on the mean family annual income mean in the patient's area of residence (13). One study used patient treatment file discharge records, VA enrollment files, and outpatient care files to determine annual income (14). Finally, one study used a Medicare indicator (state buy-in) in the enrollment files as a proxy for low SES (16) (Table 7).

For severity of disease, only one study received a star because they adequately controlled for disease severity using the laboratory-based acute physiology score (12). Most studies did not receive a star because they used administrative or billing data which does not provide information on severity of disease. Four studies received a star for controlling for survival bias, one used a time-dependent Cox proportional hazards model (16), two excluded patients who were readmitted before receiving a follow-up visit (11, 13), and one used individual-level matching on duration of available follow-up time between cases and controls (12) (Table 7).

III. *Category 3: Assessment of Outcome:*

All studies received a star for the assessment of outcome and the adequacy of follow-up of cohorts. All studies received a star because it is highly likely that readmission data is reliably recorded in billing based datasets and electronic medical records that were used, for example, Medicare billing data, Mayo Clinic administrative data, and the Kaiser Permanente hospitalization files (Table 7). These databases were considered reliable because they are well-established administrative data sources that include admission and discharge dates, diagnoses, procedures, and source of care. All studies received a star for the adequacy of follow-up of cohorts because they accounted for more than 80% of patients after follow-up (Table 7).

Sensitivity Analysis of the Quality Assessment Score (High Quality Studies) (n=3):

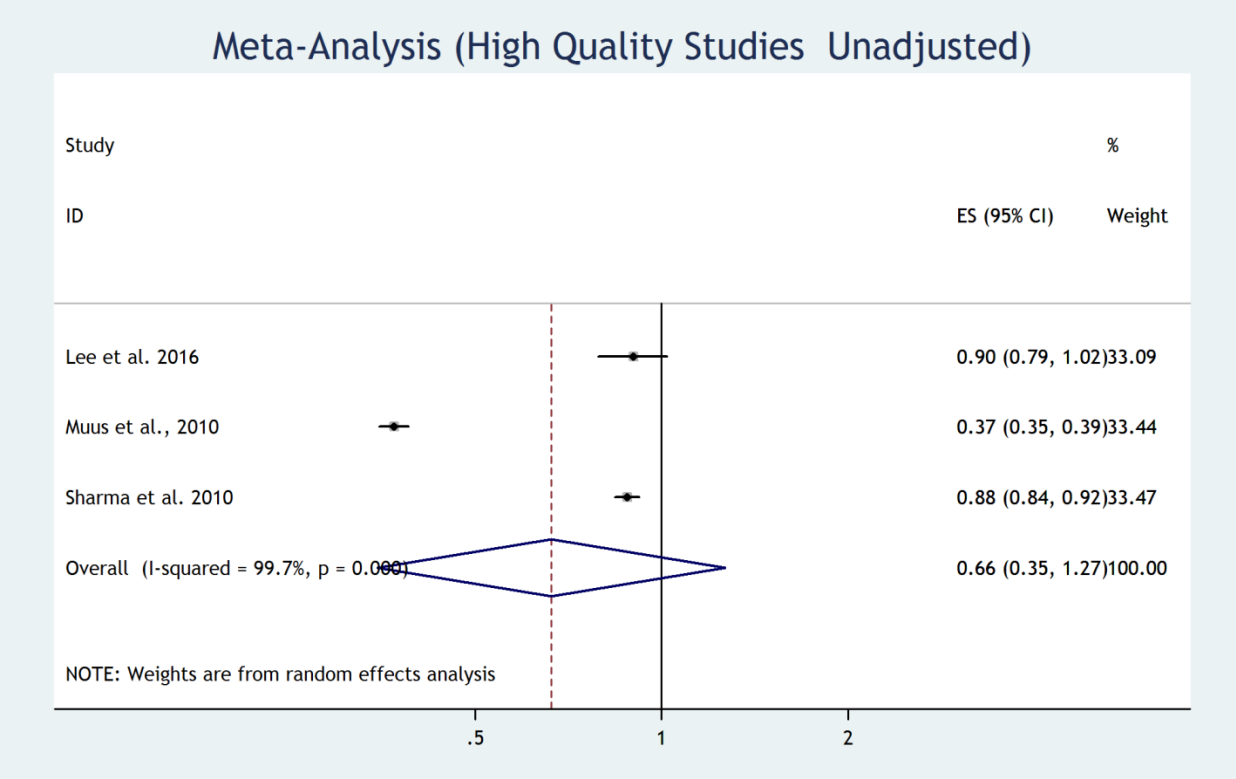
We initially planned to do a subgroup analysis comparing high quality studies to low quality studies but due an insufficient number of low quality studies, we resorted to doing a sensitivity analysis by dropping the two low quality studies (8, 15) from the primary patient-level analysis. The summary result for the unadjusted effect estimates was therefore based on only three studies and was 0.66 (95% CI 0.35, 1.27) (Figure 6, Table A7) compared to our primary analysis 0.73 (95% CI 0.46, 1.17, p= 0.188) (Figure 2, Table A3). For the unadjusted result, the I^2 statistic was 99.7% and the Q-statistic p-value was less than 0.001, indicating that there is a large amount of between study heterogeneity that was highly statistically significant. Adjusted results were available from only two studies with a summary estimate of 0.90 (95% CI 0.86, 0.95) (Figure 7, Table A8) compared to our primary analysis 0.87 (95% CI 0.77, 0.97, p= 0.014) (Figure 3, Table A4). For the adjusted result, the I^2 statistic was 0.0% and the Q-statistic p-value was 0.389, indicating that the studies in this analysis were homogeneous. This variation in these

results was due to Muus *et al.* (14) because I dropped the study and the heterogeneity decreased. These findings are not reliable because heterogeneity cannot be assessed when using only two studies.

Table 7: Quality Assessment Score (n=10)

	Selection of study population		Comparability between exposure groups (*i.e.*, control of confounding)				Outcome		Total
First Author (year)	**Representativeness of the broad US population**	**Ascertainment of exposure**	**Demographics**	**Socioeconomic status**	**Severity of disease**	**Survival bias**	**Assessment of outcome**	**Adequacy of follow-up of groups**	
Fidahussein SS (2014)		*	*				*	*	4
Lee KK (2016)		*	*	*	*	*	*	*	7
Murtaugh CM (2016)	*	*	*			*	*	*	6
Muus KJ (2010)		*	*	*			*	*	5
Sharif R (2014)		*	*				*	*	4
Sharma G (2010)	*	*	*	*		*	*	*	7
Baker H (2015)		*	*				*	*	4
Brown JR (2014)	*	*	*				*	*	5
Hernandez AF (2010)	*	*	*				*	*	5
Hess CN (2013)	*	*	*			*	*	*	6

Figure 6: Meta-Analysis of High Quality Studies (Unadjusted): Outpatient Follow-up Visits and Association with All-cause 30-day Readmissions (n=3)

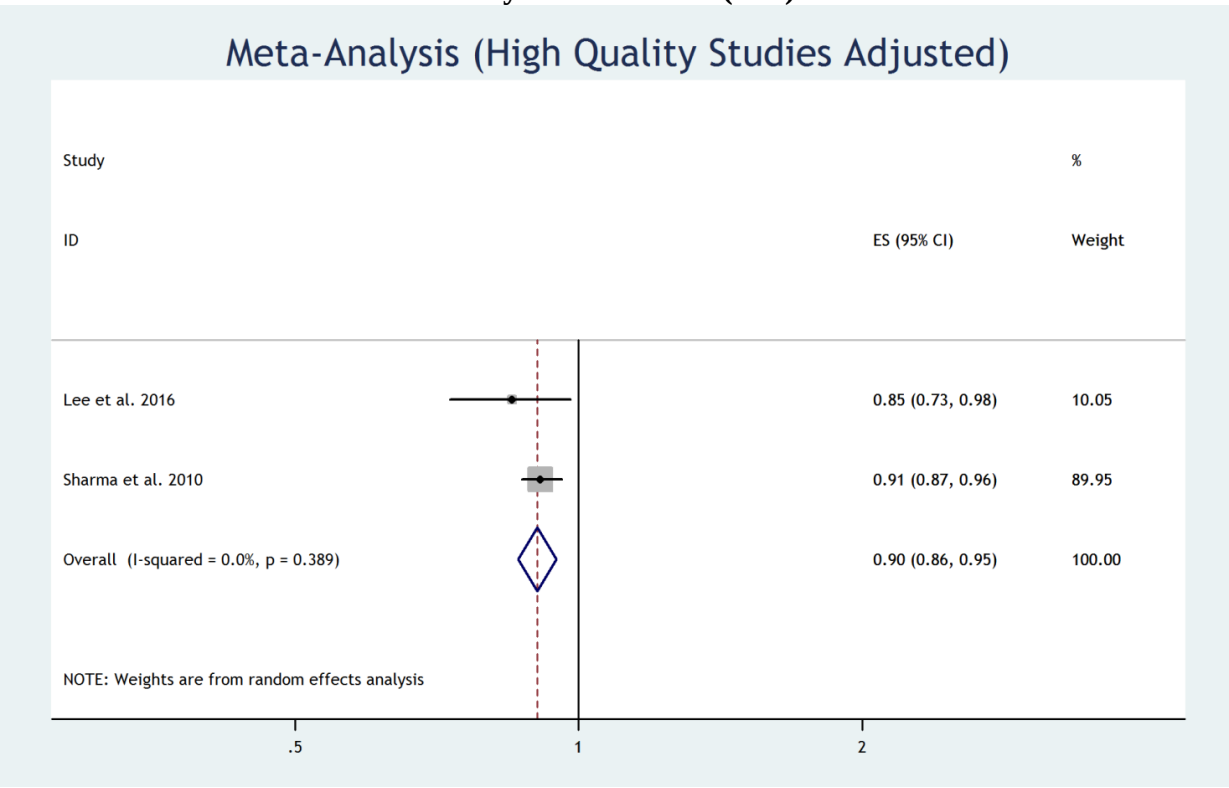


Note: Weights are from a random effects analysis

Test of ES=1; z= 1.24; p = 0.214

Heterogeneity chi-squared = 608.99; (d.f. = 2)

Figure 7: Meta-Analysis of High Quality Studies (Adjusted): Outpatient Follow-up Visits and Association with All-cause 30-day Readmissions (n=2)



Note: Weights are from a random effects analysis

Test of ES=1; z= 4.25; p = 0.000

Heterogeneity chi-squared = 0.74; (d.f. = 1)

CHAPTER 4: DISCUSSION

Section 1: Summary of Primary Findings

Studies included in this systematic review and meta-analysis represent data from 10 observational studies that reported on the association between outpatient follow-up visits with a physician and risk of all-cause 30-day readmissions. Most studies included only COPD or heart failure patients and no eligible studies with stroke patients were identified. Six studies provided data at the patient-level while four studies conducted analyses at the hospital-level. Most studies were classified as 'natural history' studies meaning that they did not assess a specific intervention or program to promote outpatient follow-up visits to prevent readmissions. Furthermore, the majority of studies were classified as 'single component' studies meaning that they assessed the association between only outpatient follow-up visits in isolation and readmissions. No eligible randomized studies were identified. For this systematic review, based on multivariable adjusted results, three (12, 15, 16) out of seven studies (4, 8, 9, 11, 12, 15, 16) found outpatient follow-up visits to have a statistically significant reduction in risk for all-cause 30-day readmissions. Among the four patient-level studies that provided adjusted data we found that outpatient follow-up visits lowered the relative risk of 30-day readmission by 13%, but we found large and statistically significant levels of heterogeneity between study results and so our results should be interpreted with caution. Finally, although we had several pre-specified sub-groups analyses we were unable to conduct most of them because of a limited number of studies. Of note, we were unable to compare studies that controlled for survival bias to those studies that did not control for survival bias. Overall, our results suggest additional research is needed to clarify whether outpatient follow-up visits are associated with reduced readmissions, and what contributes to the variation in their effectiveness across studies and populations.

The first objective of this systematic review was to understand the association between an outpatient follow-up visit with a physician within 30 days after hospital discharge and the risk of all-cause 30-day readmission for patients discharged with AMI, heart failure, COPD or stroke. Despite a well-developed protocol and a comprehensive search, only 10 studies were included in this systematic review. Among these few studies that did address the topic of outpatient follow-up visits and all-cause 30-day readmission they varied significantly in terms of their design and approach. The variation in this literature made it extremely difficult to summarize due to the variation in exposures, single versus multicomponent interventions, different disease conditions, study design (particular patient-level versus hospital-level analysis) and study populations.

The second and third objective of this thesis was to conduct a quantitative meta-analysis and assess between-study heterogeneity. When looking at all 10 articles jointly, we were unable to conduct a meta-analysis due to lack of commonality of approach between the individual studies, specifically, six studies used a patient-level analysis while four studies used a hospital-level analysis. Hospital-level analyses aggregate data at the hospital-level to compare the rate of the exposure (% of patients with an outpatient visit) with the outcome (% of patients who have a 30-day readmission). Analyses that compare hospitals are important because policies related to CMS readmission penalties operate at the hospital-level. In addition, researchers use hospital-level analyses because of the concerns about confounding that may occur at the patient-level. Because it was impossible to provide a quantitative analysis of the four hospital-level studies we were limited to conducting a meta-analysis of the six patient-level studies. Also, we had originally pre-specified seven sub-group analyses (see protocol APPENDIX C) but there was an insufficient number of studies available to do more than the single subgroup of three COPD

studies. This prevented us from understanding more about the sources of between study heterogeneity.

The final objective was to understand if studies identify and address the potential for survival bias in the timing of the exposure (outpatient follow-up visit) with the outcome (all-cause 30-day readmission). Although survival bias is important to control, survival bias was hardly mentioned specifically and only four of the 10 studies [by design (n=3) versus statistical methods (n=1)] adequately controlled for it. Furthermore, we were unable to quantify the effect of when studies control for survival bias as they did not provide effect estimates prior to control for survival bias. It would be helpful if future studies that control for survival bias provide effect estimates before and after control for survival bias to truly understand the effect of bias. The lack of control and mention of survival bias is important as survival bias has the potential to significantly inflate the effect of an outpatient follow-up visit on readmission (16). Therefore, future studies need to mention and control for survival bias by using either a design or statistical approach.

Section 2: Comparison of Results to Prior Literature

During our comprehensive literature search, only two previously published relevant meta-analyses (7, 57) and two systematic reviews (58, 59) were identified. The key features of these reviews are summarized in Table 8. These four reviews are used to compare findings to our systematic review and meta-analysis because they include similar objectives in terms of identifying the role of transitional care strategies (one of which includes outpatient follow-up visits) to reduce readmissions. However, it is important to note that no review looked at outpatient follow-up visits in isolation, and that most of the studies in these reviews used

randomized designs. The findings of our systematic review and meta-analysis were of small (in terms of total number of studies) but highly variable effects which is broadly concordant with the four prior reviews (7, 57, 58, 59). Of the four reviews, two studies (7, 57) were a systematic review and meta-analysis (Table 8). The study by Vedel and colleagues (7) that included 41 RCT studies found an overall 8% relative risk reduction (0.92; 95% CI, 0.87-0.98) but with substantial and significant heterogeneity (Q-statistic p= <0.0001; I^2 = 50%) in readmission risk associated with transitional care interventions (TCIs) (Table 8). The definition of TCIs in this review could include a combination of clinic visits, home visits, structured telephone follow-up, telecare, or periodic follow-up in a clinic (7). The author stated that outpatient follow-up visits alone did not improve all-cause readmissions but they did not provide a summary estimate (7). Of the 41 Randomized Controlled Trials (RCT) in this review, two studies consisted of only outpatient follow-up visits and 15 studies with a combination of outpatient follow-up visits, telephone follow-up, and structured home visits (7). Of the 17 RCTs in this review, no study was included in our systematic review and meta-analysis because patients only attended a single outpatient follow-up clinic, rather than a typical community based physician office that we used in our review. The other systematic review and meta-analysis by Feltner (57) that included a total of 47 RCTs found the use of multidisciplinary-heart failure clinic visits was associated with a statistically significant reduction in all-cause readmissions 3-6 months after discharge (pooled relative risk 0.70; 95% CI, 0.55–0.89), however, of the 47 RCTs, only two studies we based on multidisciplinary-heart failure clinic visits (57). Furthermore, they found outpatient follow-up visits to a nurse-led clinic had no effect (pooled relative risk 0.88, 95% CI=0.57–1.37 but this was also based on only two studies) (57). The review found only one study that examined the effect of visits to a primary care clinic on readmission which were associated with a statistically

significant increase in risk for all-cause readmissions 3-6 months after discharge (relative risk 1.27; 95% CI, 1.05–1.54) (57). This particular study was not included in our review because the outcome was not defined as 30-day readmission. Another systematic review by Gorthi and colleagues of the 46 RCTs (which did not conduct a meta-analysis) concluded there was no consistent benefit for a specific type of DMPs for reducing heart failure hospitalizations (58). These DMPs included multiple components consisting of outpatient clinic visits, home visits, and telemanagement (58). Finally, another systematic review of 43 (16 RCTs, 20 Quasi-experimental and cohort studies, and seven non-controlled before–after studies) which included interventions evaluated in studies aimed at reducing readmissions concluded that no single intervention but a combination of interventions (most notably, a combination including patient-centered discharge instructions and post discharge telephone calls) was associated with reducing the risk for 30-day readmissions (59). The interventions examined in this review included pre-discharge interventions (e.g., patient education, discharge planning, and medication reconciliation), post-discharge interventions (e.g., outpatient follow-up visit, timely PCP communication, and patient hotlines) and interventions active both before and after discharge (e.g., transition coach, patient-centered discharge instructions, and provider continuity) (59). Again, contrary to our systematic review and meta-analysis, no prior review was conducted with the goal of examining the effect of outpatient follow-up visits in isolation (7, 57, 58, 59).

Table 8: Comparison of Current Review Results with Prior Systematic Reviews and Meta-analyses of Readmission Reduction Strategies (n=4)

First Author (year)	Study Design	Purpose/Objective	Disease Condition	Study Setting	Sample Size	Exposure	Outcome
Reichle (2017)	SR-MA	Examine the effect of an outpatient follow-up visit with a physician on all-cause 30-day readmissions	AMI, Heart Failure, COPD	United States, 2007 to 2017	10 observational studies	Outpatient follow-up visit with a physician	All-cause 30-day readmission
Vedel I (2015) (7)	SR-MA	To determine the impact of TCIs and to identify the most effective TCIs and their optimal duration	Heart Failure	All countries, 1995 to 2014	41 RCT studies	TCIs	All-cause hospital readmissions and ED visits (time period not specified)
Feltner C (2014) (57)	SR-MA	To assess the efficacy, comparative effectiveness, and harms of transitional care interventions to reduce readmission and mortality rates	Heart Failure	All countries, 1990 to 2013	47 RCT studies	TCIs	Readmission and mortality 30d to 6months
Gorthi J (2014) (58)	SR	To define the efficacy of DMPs in reducing hospitalizations and/or mortality	Heart Failure	1975 to 2013	46 RCT studies	DMPs	All-cause mortality and all-cause hospitalization (time period not specified)
Hansen LO (2011) (59)	SR	To describe interventions evaluated in studies aimed at reducing rehospitalization within 30 days of discharge	All conditions	All countries, 1975 to 2011	43 RCTs and observational studies	Interventions to reduce readmission	All-cause 30-day readmission

Abbreviations: SR-MA, systematic review and meta-analysis; SR, systematic review; RCT, randomized controlled trial; TCIs, transitional care interventions; DMPs, disease management programs; ED, emergency department

Section 3: Strengths and Limitations

This systematic review and meta-analysis has several strengths. First, this review identified studies of three disease conditions (AMI, heart failure, and COPD) with high readmission rates. No other study has compared all three disease conditions in the same systematic review. Second, a comprehensive search was conducted of two well established databases (PubMed and CINAHL) relevant to US based studies. Third, we found no other prior review that looked exclusively at the effect of outpatient follow-up visits with a physician within 30 days of discharge on all-cause 30-day readmissions. Instead, the prior systematic reviews included a mix of interventions and exposures including home visits, clinic interventions, telephone support interventions, and some individual studies consisting of the reviews measured disease specific readmissions rather than all-cause readmissions (7, 57-59). Although the reviews included studies with outpatient follow-up visits, they only consisted of a small part of those reviews (7, 57-59). Fourth, this systematic review and meta-analysis was able to fill an important gap in literature as we exclusively identified a 30-day timeframe for readmissions to match current policy approaches, where as other reviews looked at different timeframes. Finally, a rigorous protocol was developed following the well-recognized Cochrane Library approach (88).

However, this systematic review has several limitations. First, we were only able to identify a small number (10) of eligible studies. Furthermore, the eligible studies lacked commonality in their study designs, exposure definition and effect estimates making them challenging to summarize, and combine for meta-analysis. We were therefore, unable to conduct a meta-analysis across all studies and identify meaningful results for specific a priori subgroups. Second, grey literature (material not published or material published in non-indexed journals or proceedings) was not searched (101). Therefore, our data may be subject to publication bias, as

positive results are more likely to be published than negative studies (102). Third, we were unable to identify studies that included acute stroke populations aiming to understand the association between outpatient follow-up visits and all-cause 30-day readmission. Fourth, although we used the well-established Newcastle-Ottawa scale, to suit the contents of our study we had to change the definitions and scoring of items. Furthermore, we were unable to conduct any comparison of high quality studies to low quality studies due to a low number of studies in each group. Fifth, we limited our search to studies published in the United States and in the last 10 years, because of our interest in readmission reduction policies and strategies, like the HRRP, which began in 2012. Six, we were unable to include hospital-level studies in our meta-analysis due to differences of how outpatient follow-up visits were measured between hospital-level studies and patient-level studies. Furthermore, patient specific data on potential confounders (such as SES and severity of disease) was often unavailable, especially in billing data.

Section 4: Further Research

We found significant limitations in the current literature base in terms of the number and quality of studies. Furthermore, there were no RCTs identified in our literature search. For observational studies we suggest that future studies provide a more consistent study population (in terms of age, gender, race, and geographical location), exposure definition (in terms of the physician seen, and the timing of outpatient follow-up visits), and better control for confounders (SES and severity of disease) in order to quantify an unbiased association between outpatient follow-up visits with a physician and all-cause 30-day readmissions. The lack of control for SES and severity of disease is primarily due to unavailable data provided through Medicare claims data. Although hospitals are only penalized on Medicare beneficiaries through the CMS HRRP, limited research has been done on non-Medicare populations. The lack of control for survival

bias was important as survival bias has the potential to significantly inflate the effect of an outpatient follow-up visit on readmission. Future research should focus on controlling and quantifying the effect of survival bias by providing effect estimates prior to control. This systematic review and meta-analysis also found that the majority of studies looked at heart failure patients, and that limited research has been done on AMI, COPD and stroke populations. Although studies identified specific time periods of follow-up visits, articles did not compare early follow-up (e.g., <7 days) to late follow-up (e.g., >21 days) within the 30-day window. Although outpatient follow-up visits are almost universally recommended, current evidence gives little clarity over their effect on readmissions. However, the recommendation of an outpatient follow-up visit is a strategy that will likely always be recommended regardless of the evidence for its effectiveness in lowering readmissions. Researchers may want to focus on different aspects of an outpatient follow-up visit. For example, although studies in this systematic review and meta-analysis evaluated a single component exposure (outpatient follow-up visits), they did not identify if patients were receiving other components which have been integrated into many hospitals care process to prevent readmissions, or to evaluate the community in which each patient resides (available social and community support). Therefore, a shift in focus may be to look at outpatient follow-up visits as a process measure. Exploring the content and process of a follow-up visit is another important focus for research as physicians are more likely to concentrate on symptoms and treatment rather than the patient's ability to appropriately afford, take medications other and treatments, as well as to provide patient education.

Section 5: Conclusions

This systematic review and meta-analysis summarizes current research findings on the association of outpatient follow-up visits with a physician and all-cause 30-day readmissions for AMI, heart failure and COPD patients in US based studies published in the last 10 years. We conclude that outpatient follow-up visits have a small but inconsistent effect on reducing the risk of all-cause 30-day readmission. Outpatient follow-up visits are only one strategy used to lower the risk for readmission and are obviously not capable of completely preventing all readmissions. Outpatient follow-up visits normally occur seven or more days after hospital discharge and so cannot influence readmissions that occur before a typical seven day follow-up (103). For this systematic review and meta-analysis, based on four studies that provided adjusted patient-level estimates, we found that patients who had an outpatient follow-up visit with a physician had a statistically significant 13% reduction in relative risk for all-cause 30-day readmission compared to patients without an outpatient follow-up visit with a physician. A relative risk reduction of 13% was also shown for our subgroup analysis of three studies that included only COPD patients but this was not statistically significant. However, although a significant relative risk reduction was shown for outpatient follow-up visits with a physician to lower the risk for all-cause 30-day readmissions, due to high amounts of statistically significant between study heterogeneity, more consistent evidence is needed in order to clearly understand the value of an outpatient follow-up visit.

APPENDICES

APPENDIX A: Planned Procedures (3, 23)

Table A1: Planned Readmission Procedures

Planned Procedures	
1) Percutaneous transluminal coronary angioplasty	17) Aortic resection; replacement or anastomosis
2) Cholecystectomy and common duct exploration	18) Nephrectomy; partial or complete
3)Amputation of lower extremity	19) Embolectomy and endarterectomy of lower limbs
4) Endarterectomy; vessel of head and neck	20) Inguinal and femoral hernia repair
5) Colorectal resection	21) Hysterectomy; abdominal and vaginal
6) Coronary artery bypass graft (CABG)	22) Mastectomy
7) Arthroplasty knee	23) Arthroplasty other than hip or knee
8) Transurethral resection of prostate (TURP)	24) Gastrectomy; partial and total
9) Hip replacement; total and partial	25) Open prostatectomy
10) Therapeutic radiology for cancer treatment	26) Oophorectomy; unilateral and bilateral
11) Spinal fusion	27) Thyroidectomy; partial or complete
12) Insertion; revision; replacement; removal of cardiac pacemaker or cardioverter/defibrillator	28) Bone marrow transplant
13) Laminectomy; excision intervertebral disc	29) Lumpectomy; quadrantectomy of breast
14) Lobectomy or pneumonectomy	30) Kidney transplant
15) Peripheral vascular bypass	31) Other organ transplantation
16) Heart valve procedures	32) Electroshock therapy

APPENDIX B: CMS Readmission Criteria (3, 23, 24)

Table A2: CMS Readmission Eligibility Criteria

Eligibility Measures on Readmissions
1) Alive upon discharge
2) Age 65 or older
3) Admitted to a non-federal, short-stay, or acute-care hospital
4) Fee-for-Service Medicare beneficiaries
5) At least 30 days of post-discharge enrollment in Medicare Fee-for-Service or died within the 30-day post-discharge period
6) Admission is not to a Prospective Payment System-exempt cancer hospital
Excluded Patients
1) Patients not enrolled in FFS Medicare for the 12 months prior to the index admission
2) Patients discharged against medical advice
3) Enrolled in Medicare Part A only or Medicare Part B only during the performance period
4) Enrolled in Medicare managed care (for example, a Medicare Advantage plan) for any month during the performance period
5) Patient resided outside of the United States, its territories, and its possessions for any month during the performance period
6) Patient died during the admission
7) Not continuously enrolled in Medicare Part A FFS for at least 30 days
8) Patient lacked complete Medicare Part A FFS enrollment history for prior 12 months
9) Transferred from the admission to another acute care hospital
10) Hospitalized in a prospective payment system-exempt cancer hospital
11) Hospitalized for medical treatment of cancer
12) Hospitalized for a primary psychiatric disease
13) Rehabilitation centers, psychiatric hospitals, hospice facilities, long-term care or long-term acute care hospitals, and skilled nursing facilities

APPENDIX C: Protocol

OUTPATIENT FOLLOW-UP VISITS AND THE RISK OF 30 DAY ALL-CAUSE HOSPITAL READMISSIONS FOR PATIENTS DISCHARGED FOLLOWING A CARDIOVASCULAR OR COPD RELATED EVENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

I. Background Rationale:

Cardiovascular disease (CVD) is a significant burden in the United States. According to data from July 1, 2012 to June 30, 2015 from the Centers for Medicare and Medicaid Services (CMS) Hospital Compare program, 16.8% of myocardial infarction, 21.9% of heart failure, 20.0% chronic obstructive pulmonary disease (COPD), and 12.5% of stroke Medicare beneficiaries were readmitted within 30 days after discharge (34). The overall cost to Medicare of readmissions is approximately $26 billion per year, $17 billion of which is estimated to be potentially avoidable (3).

Hospital readmissions are defined as an admission to a hospital within a specific time period after initial hospital discharge. There are various time periods over which readmissions can be measured, but a common measure as used by CMS to define this time period is a hospitalization within 30 days from initial hospital discharge (104). In 2012, due to high readmission rates and associated costs, the Hospital Readmission Reduction Program (HRRP) was developed by CMS which include a system to penalize hospitals with high readmission rates (1). The implementation of the HRRP has prompted others to develop approaches to prevent readmissions. Initiatives are many and varied and include: a care team to help with the transition from hospital to home, having nurses re-educate patients on medications, schedule outpatient follow-up visits before patients are discharged, patients and caregivers being well informed with a discharge plan when they leave the hospital, and outpatient follow-up visits and home visits (105).

One method used to prevent readmissions is an outpatient follow-up visit with a physician shortly after discharge (*i.e.*, within 7 days) (4). This systematic review will seek to quantify the effect of outpatient follow-up visits on readmission risk. The effectiveness of outpatient follow-up visits on all-cause 30 day readmissions has been studied using a variety of conditions (Acute Myocardial Infarction (AMI), heart failure, COPD or stroke) and study designs. Due to the variability between studies, this systematic review looks to provide an overview of current evidence, identify methodology previously used, and provide combined effects across conditions in order to understand the effect outpatient follow-up visits have on all-cause unplanned 30 day readmissions for patients with an initial discharge. This systematic review may have potential implications for improving public health policy and to our knowledge; no review has been previously published on this specific topic.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines will be used to guide the conduct and reporting of this systematic review (91). Standard text and the Cochrane protocol covering meta-analysis will be used as a guide for determining the organization and conduct of this protocol (88-90).

II. Objectives:

1. Conduct a systematic review to identify if outpatient follow-up visits after hospital discharge [PCP, NP, or physician specialist (e.g. cardiologist or pulmonologist)], are associated with a lower risk of all-cause unplanned 30 day readmission for patients discharged with AMI, heart failure, COPD or stroke.
2. Assess if there is sufficient commonality in the organization between studies to conduct a meta-analysis and obtain summary estimates of effect.
3. Assess heterogeneity between studies and to understand the sources of between study variability.
4. To understand if studies identify and address the potential for survivor bias in the timing of the exposure (outpatient follow-up visit) relative to the timing of the outcome (all-cause unplanned 30 day readmission).

III. Answerable Question:

For patients discharged from a short-stay, acute-care hospital in the United States with AMI, heart failure, COPD or stroke, does the occurrence of the first outpatient follow-up visit (with a PCP, NP, or physician specialist) within 30 days of discharge reduce the risk for all-cause unplanned 30 day readmission to a short-stay, acute-care hospital when compared with patients who have no outpatient follow-up visit?

PECO:

Patient/population: Patients discharged with AMI, heart failure, COPD, and stroke from a short-stay, acute-care hospital in the United States.

Exposure: The occurrence and timing of the first outpatient follow-up visit (with a PCP, NP, or physician specialist) within 30 days of initial discharge from a short-stay, acute-care hospital in the United States.

Control: Either lack of or delayed outpatient follow-up visit (with a PCP, NP, or physician specialists) within 30 days of initial hospital discharge from a short-stay, acute-care hospital in the United States.

Outcome: The risk of all-cause unplanned 30 day readmission to a short-stay, acute-care hospital in the United States after initial discharge from a short-stay, acute-care hospital in the United States.

IV. Definitions of Primary Exposure and Outcome Measures:

Primary Exposure: The occurrence and timing (*i.e.*, days since discharge) of the first outpatient follow-up visits (with a PCP, NP, or physician specialists) within 30-days after initial discharge from a short-stay, acute-care hospital in the United States.

Primary Outcomes: The occurrence of the first all-cause unplanned 30 day readmission to a short-stay, acute-care hospital in the United States after initial discharge.

V. Eligibility Criteria:

Eligible studies must meet ALL the following inclusion criteria:

1. Non-intervention (referred to as natural history studies) that do not include any specific intervention to promote outpatient follow-up visits, OR Intervention studies that include either a single or multiple component intervention to increase the use of outpatient follow-up visits (with a PCP, NP, or physician specialist).
2. Primary exposure defined as an outpatient follow-up visit (with a PCP, NP, or physician specialist) within 30 days after initial discharge.
3. Primary outcome defined as all-cause unplanned 30 day readmission.
4. Studies that include either patients who are discharged from hospital to home or studies that include a mix of patients discharged either to home or to a rehab facility (*i.e.*, IRF or SNF).
5. Study participants ≥18 years of age.
6. Literature published in English.
7. Published within the last 10 years (starting in January 2007).
    a. (rationale) The CMS Hospital Compare program began publically reporting readmission in 2009 (1). Furthermore, the establishment of the hospital readmission reduction program and other CMS related P4P programs centered on readmission began in 2012 (92).
8. Studies only conducted in the United States.
9. Original peer reviewed research studies.

Exclusion Criteria:

Studies meeting ANY of the following criteria will be excluded:

1. Articles identified as commentaries, conference notes, letters, editorials, opinions, abstracts only, or review article.

2. Intervention studies that are based on setting up a specific single outpatient clinic that the majority (>80%) of patients use for outpatient follow-up visits.

a. (rationale) Not generalizable to a usual outpatient follow-up visit with a physician and provides different care than a usual outpatient follow-up visit.

3. Studies that include patients with an initial discharge ONLY to specific rehab settings (e.g. SNF or IRF).

4. All or the majority (>80%) of patients initially discharge from an emergency department.

VI. Information Retrieval:

Databases:

PubMed and CINAHL were systematically searched to identify eligible articles.

PubMed:

Potentially eligible studies were identified using the following combination of search terms:

("Patient Readmission"[Mesh] OR (30[All Fields] AND day[All Fields] AND readmission[All Fields]) OR readmission[All Fields] OR ("patient readmission"[MeSH Terms] OR ("patient"[All Fields] AND "readmission"[All Fields]) OR "patient readmission"[All Fields]) OR "Patient Discharge"[Mesh]) AND ((7[All Fields] AND day[All Fields] AND visits[All Fields]) OR (("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields]) AND visit[All Fields]) OR "Outpatients"[Mesh] OR (follow-up[All Fields] AND visit[All Fields]) OR ("office visits"[MeSH Terms] OR ("office"[All Fields] AND "visits"[All Fields]) OR "office visits"[All Fields] OR ("office"[All Fields] AND "visit"[All Fields]) OR "office visit"[All Fields]) OR "Office Visits"[Mesh] OR (("physicians"[MeSH Terms] OR "physicians"[All Fields] OR "physician"[All Fields]) AND follow-up[All Fields]) OR "Physicians"[Mesh] OR (("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields]) AND follow-up[All Fields]) OR "Ambulatory Care"[Mesh] OR "Outpatient Clinics, Hospital"[Mesh] OR "early patient discharge"[All Fields]) AND ("Heart Failure"[Mesh] OR "Myocardial Infarction"[Mesh] OR "heart attack"[All Fields] OR "Acute myocardial infarction"[All Fields] OR "heart failure"[All Fields] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields]) OR "Stroke"[Mesh] OR ("stroke"[MeSH Terms] OR "stroke"[All Fields]))

Filters used:

("2007/05/12"[PDat]: "2017/05/08"[PDat] AND English[lang])

CINAHL:

Potentially eligible studies were identified using the following combination of search terms:

(patient readmission OR patient discharge OR discharge) AND (office visits OR outpatient OR outpatient follow up OR ambulatory care) AND (heart failure OR myocardial infarction OR (copd or chronic obstructive pulmonary disease) OR stroke)

Filters used:

English Language, Published Date from 2007-2017, and Academic Journals.

VII. Study Eligibility Assessment:

Two individuals will independently screen titles and abstract to assess eligibility of studies and identify studies for full text review.

Process for identifying eligible studies:

Search results (*i.e.,* hits) from PubMed and CINHAL will be combined. After duplicates are removed, titles will be screened to determine potential relevance. Abstracts of relevant titles will be independently assessed by the GR and MR to determine relevant articles for full text review (based on inclusion and exclusion criteria). The grading system includes articles being assigned a "yes", "maybe" or "no" upon evaluation of exclusion criteria for full text review. If articles receive a "yes" and a "maybe" from both assessors, the articles will be included for full text review. Questionable articles [articles including a combination of a ("yes" and "no") or a ("maybe" and "no")] will be discussed by GR and MR at a consensus meeting and a final decision will be made regarding need for full text review. GR and MR will then independently conduct a full text review to determine the final set of eligible studies to undergo data abstraction. Primary reasons for study exclusion will be documented. Finally, references of articles included for quantitative synthesis will be reviewed to find additional articles.

A PRISMA flow diagram (APPENDIX E) will be used to show how the final numbers of eligible articles were determined (91).

VIII. Data Abstraction of eligible studies:

Two individuals will independently abstract data. Disagreements will be solved by discussion. If disagreements cannot be solved a third party will be consulted. The following data will be abstracted

1. Study Description [study design (observational or experimental), purpose/objective, study population, disease condition, time frame, location]
2. Data Source [database, sample size, unit of analysis (*i.e.*, patient –level or hospital-level)]
3. Exposure and Outcome [exposure definition, outcome definition, unplanned readmission (*i.e.*, unplanned vs planned readmission)]
4. Results [prevalence of outpatient follow-up visits, crude readmission rate (total study population), crude readmission rate (exposed and unexposed), unadjusted effect,

adjusted effect, variables adjusted for in models, and variables identified but not adjusted for in models].

IX. Covariates:

Covariates listed below are important to identify as they could bias the association between outpatient follow-up visits and the risk of readmission. For example, patients with a more severe illness are more likely to have a follow-up visit but are also more likely to have a readmission compared to patients with a minor illness (8, 11, 14). Therefore, it is important to identify covariates before data abstraction in order to indicate if a study has properly controlled for potential confounders. We will look to identify if studies have included important confounders in their descriptive tables, and will identify which variables were controlled for (or assessed) in any multivariable analysis. We will identify which of the following covariates were reported at baseline and at endpoint.

Potential covariates include:

1. Demographics [age, gender, race, socioeconomic status (SES) (as described by author), and geographic location (as described by author)]
2. Severity of condition (AMI, HF, COPD, or stroke) (as described by author)
3. Major comorbidities (coronary artery disease, atrial fibrillation, osteoporosis, renal insufficiency, diabetes mellitus)
4. Insurance status (Medicare vs Medicaid vs private vs none)

X. Controlling for Survival Bias:

Articles will be assessed to determine if methods were used to control for time dependent bias. This will be included in our quality assessment scoring. The time dependent bias that applies to our exposure (outpatient follow-up visits) and outcome (all-cause unplanned 30 day readmissions) is survival bias. Survival bias artificially inflates the effect of an outpatient follow-up visit by assigning a readmission that occurs before an outpatient follow-up visit has had the chance to occur to the unexposed group (no outpatient follow-up visit) (16). We will identify if the study methods (as described by author) were designed to prevent survival bias or if the time-dependent Cox Proportional Hazards Regression model was used to control for survival bias in the analysis.

XI. Quality Assessment Score:

The Newcastle-Ottawa Scale (NOS) (APPENDIX F) will be used as a guide to determine study quality (96). The NOS was specifically designed to assess bias in nonrandomized studies (96). The NOS will be modified to develop a quality assessment scale relevant to these studies. For each number listed below, a study will receive a star if the quality of the study is considered adequate. Category 1 (Selection of study population) and Category 3 (Outcome) included two items each while Category 2

(Comparability between exposure groups (*i.e.*, control of confounding)) included four items. Hence the range is 0-8. This quality assessment score will be used descriptively to describe studies with high quality (score greater than 5) to studies with low quality (score less than or equal to 5). This quality assessment score will then be used to compare studies on specific characteristics including hospital-level analysis compared to patient-level analysis, across disease conditions, studies controlling for survival bias compared to not controlling for survival bias, and studies controlling for SES compared to not controlling for SES. Furthermore, the assessment score will be explored to identify if study quality had an impact on the results.

Assessment Categories:

Category 1: Selection of study population

9. Representativeness of the broad United States population
    a. Study population broadly representative of the United States in terms of age, gender, racial distributions, and geographically (e.g. Medicare database or CRUSADE registry involving patients from multiple states and hospitals throughout the United States).
        i. Star
    b. Study population not representative of the United States, or no information provided (e.g. a single hospital based study, a single ethnic group, a single group of individuals such as veterans, or a database or registry that does not represent the whole of the United States population).
        i. No star
10. Ascertainment of outpatient follow-up visit (exposure)
    a. Exposure retrieved from a reliable source (e.g. Medicare database, electronic medical records, administrative or billing data, or structured patient interviews).
        i. Star
    b. Patient self-reported or study failed to mention origin or collection of exposure data.
        i. No star

Category 2: Comparability between exposure groups (*i.e.*, control of confounding)

In order for the study to control for important confounders, the following criteria must have been met: availability of data on confounders, and their inclusion in a statistical model that generates adjusted estimates or rationale for why a potential confounder was not included in the model.

11. Demographics
    a. Study controlled for at least age and gender. It was not necessary for studies to control for race.
        i. Star
    b. Study failed to control or mention if demographics were controlled.
        i. No star
12. Socioeconomic status
    a. Study controlled for socioeconomic status measured by either income, education, or occupation (97).
        i. Star
    b. Study failed to control for or mention socioeconomic status.
        i. No star
13. Severity of disease
    a. Study controlled for severity of disease by using an established scale or severity classification (41-44). Examples of scales used may include: AMI (Killip classification (41)), heart failure scale (New York Heart Association (42)), COPD (Spirometric Classifications (43)) and stroke (NIH Stroke Scale (44)).
        i. Star
    b. Study failed to control for or mention severity of disease.
        i. No star
14. Survival bias
    a. Controlled for survival bias in their study design (e.g. by excluding individuals readmitted before an outpatient follow-up visit occurred) or by using a time-dependent Cox proportional hazard regression model in their analysis (86).
        i. Star
    b. Study did not appropriately control for or mention survival bias.
        i. No star

Category 3: Outcome

15. Assessment of outcome
    e. Outcome retrieved from a reliable source (e.g. Medicare database, structured patient interview or record linked data).
        i. Star
    f. Outcomes retrieved from self-report or failed to mention how data was collected.
        i. No star
16. Adequacy of follow-up of cohorts
    g. ≥80% of patients accounted for after follow-up.
        i. Star
    h. <80% of patients accounted for after follow-up, or no mention.
        i. No Star

XII. The Following Results will be Collated when Available:

1. Prevalence of outpatient follow-up visits (*i.e.*, % of patients with any outpatient follow-up visit within 30 days after initial hospital discharge)
2. Crude readmission rate (overall study population and by outpatient follow-up visit status)
3. Unadjusted HR, OR, and RR
    a. These measures identify the association between outpatient follow-up visit and risk of all-cause unplanned 30 day readmission. Odds ratio will be regarded as a proxy of the relative risk (using the rare disease assumption). For this reason, HR, OR, and RR will be considered equivalent and abstracted as a single measure.
4. Adjusted HR, OR, and RR
    a. If available, adjusted estimates will be collated. Furthermore, we will identify what variables studies adjust for, what variables studies included and dropped from their final models, and if the studies identified variables but did not adjust for.

Also, 95% confidence intervals, standard error, and p-values will be abstracted if available. If not provided in the paper, unadjusted measures will be calculated using the readmissions rates for patients with and without outpatient follow-up visit.

XIII. Dealing with Missing Data:

We will not reach out to authors with missing data. Therefore, studies with missing data will be reported as a study limitation.

XIV. Appropriateness of Data Pooling:

Articles will be read to determine consistency of study population, outcome, exposure, and variability of results. This will help to determine if the study design, conduct and data reported are similar enough to pool results together in the form of a meta-analysis. If studies are adequate to pool, a meta-analysis will be conducted.

XV. Heterogeneity:

Heterogeneity will be assessed to understand the variability between studies. Methodological heterogeneity will assess similarity between included study populations, outcomes, exposures and interventions. Statistical heterogeneity will assess the effect estimates of included studies and if point estimates are close or if confidence intervals overlap. Methods used to assess heterogeneity include:

1. Forest plots (Non-Statistical method)
2. Q-statistic and I^2 statistic (Statistical methods)

a. For the Q-statistic, if the p-value is less than 0.05 the null is rejected and you conclude there is significant heterogeneity

b. The I^2 statistic is considered satisfactory if less than 25%, moderate if 25-75%, and high heterogeneity if more than 75%.

If there is significant variation between studies determined by forest plots, the Q-statistic, and I^2 statistic, studies will be considered as having too much variability to generate a single summary effect estimate from a meta-analysis may be inappropriate to conduct. The statistical analysis will be conducted using STATA 14 statistical software.

XVI. Analysis:

If a meta-analysis is performed a random effects model will be used because the study design, study populations, and exposures will differ across studies. A random effects model takes into account both within-study and between-study variability where a fixed effect model only takes into account within-study variability (89).

XVII. Sub-group Analysis:

Potential subgroups of interest will include:

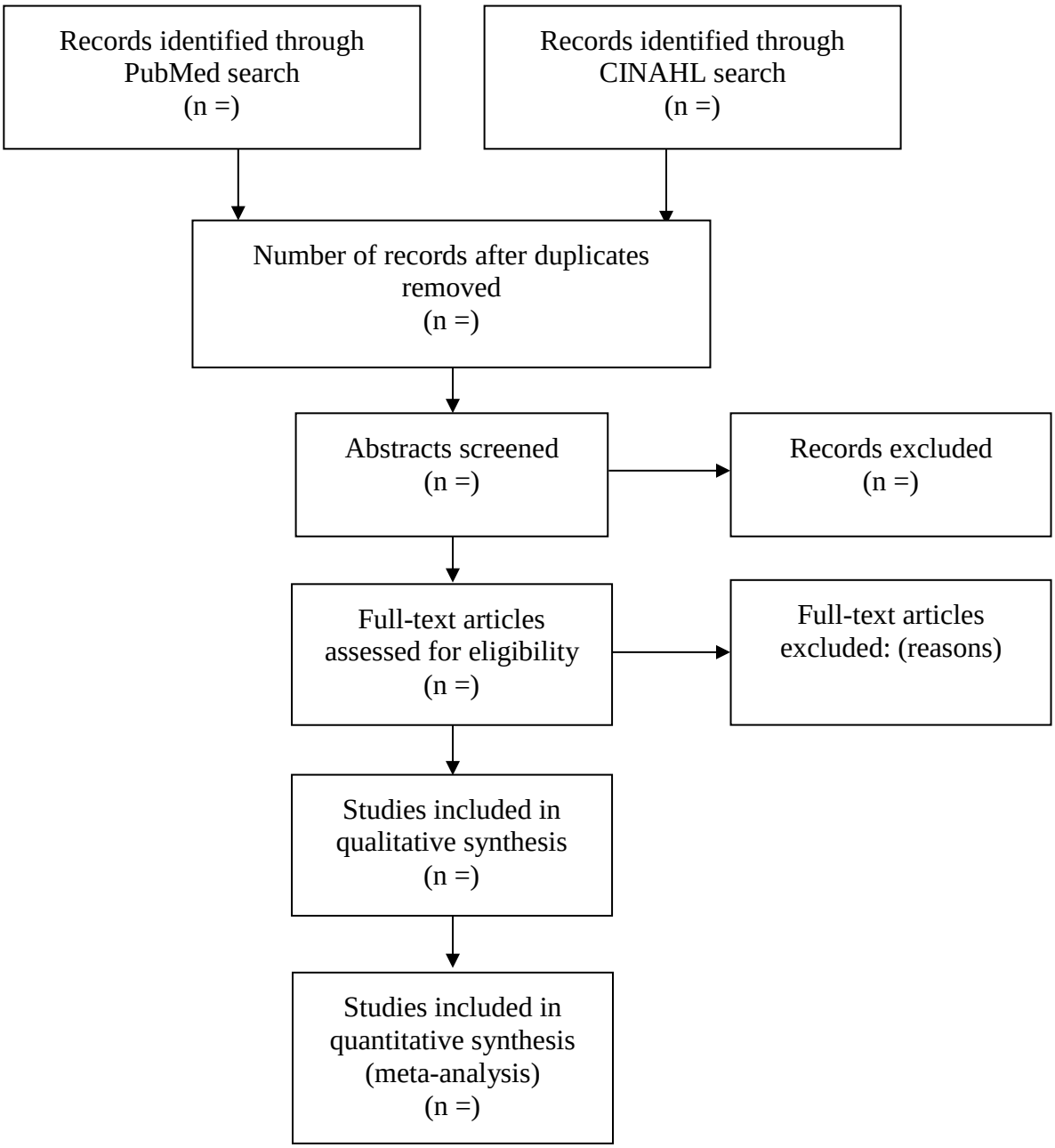
1. Disease condition
    a. AMI, HF, COPD, stroke
2. Participation in readmission program/intervention (quality improvement programs) versus none
3. Insurance type
    a. Medicare versus commercially insured
4. White versus minority
5. Healthcare professional seen upon follow-up visit
    a. PCP versus NP versus specialist
6. Survival bias
    a. Controlled versus not controlled
7. Quality assessment score
    a. Studies with high scores (≥5) versus studies with low scores (<5)

APPENDIX D: PubMED Search Terms

("Patient Readmission"[Mesh] OR (30[All Fields] AND day[All Fields] AND readmission[All Fields]) OR readmission[All Fields] OR ("patient readmission"[MeSH Terms] OR ("patient"[All Fields] AND "readmission"[All Fields]) OR "patient readmission"[All Fields]) OR "Patient Discharge"[Mesh]) AND ((7[All Fields] AND day[All Fields] AND visits[All Fields]) OR (("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields]) AND visit[All Fields]) OR "Outpatients"[Mesh] OR (follow-up[All Fields] AND visit[All Fields]) OR ("office visits"[MeSH Terms] OR ("office"[All Fields] AND "visits"[All Fields]) OR "office visits"[All Fields] OR ("office"[All Fields] AND "visit"[All Fields]) OR "office visit"[All Fields]) OR "Office Visits"[Mesh] OR (("physicians"[MeSH Terms] OR "physicians"[All Fields] OR "physician"[All Fields]) AND follow-up[All Fields]) OR "Physicians"[Mesh] OR (("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields]) AND follow-up[All Fields]) OR "Ambulatory Care"[Mesh] OR "Outpatient Clinics, Hospital"[Mesh] OR "early patient discharge"[All Fields]) AND ("Heart Failure"[Mesh] OR "Myocardial Infarction"[Mesh] OR "heart attack"[All Fields] OR "Acute myocardial infarction"[All Fields] OR "heart failure"[All Fields] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields]) OR "Stroke"[Mesh] OR ("stroke"[MeSH Terms] OR O("2007/05/12"[PDat]: "2017/05/08"[PDat] AND English[lang]).

APPENDIX E: PRISMA Flow Diagram (91)

Figure 8: Example PRISMA Flow Diagram



APPENDIX F: Newcastle Ottawa Quality Assessment Scale (96)

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community □

b) somewhat representative of the average _____ in the community □

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort □

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) □

b) structured interview □

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes □

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) □

b) study controls for any additional factor □ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment □

b) record linkage □

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) □

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for □

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) □

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

APPENDIX G: STATA Output (Meta-Analyses)

Table A3: Meta-Analysis of Five Patient-Level Studies (Unadjusted)

```
Study |              ES        [95% CI]       % Weight
----------------------+-----------------------------------------
---------
Fidahussein et al.| 1.070     0.830 1.370       19.27
Lee et al.        | 0.900     0.790 1.020       20.08
Muus et al.       | 0.370     0.350 0.390       20.33
Sharif et al.     | 0.670     0.580 0.780       19.98
Sharma et al.     | 0.880     0.840 0.920       20.34
----------------------+-----------------------------------------
---------
D+L pooled ES     | 0.729     0.455 1.167      100.00
----------------------+-----------------------------------------
---------
Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 626.16 (d.f. = 4) p = 0.000
I-squared (variation in ES attributable to heterogeneity) =
99.4%

Estimate of between-study variance Tau-squared = 0.2833
Test of ES=1 : z= 1.32 p = 0.188
```

Table A4: Meta-Analysis of Four Patient-Level Studies (Adjusted)

Study	ES	[95% CI]		% Weight
Fidahussein et al.	1.020	0.800	1.320	14.42
Lee et al.	0.850	0.730	0.980	25.80
Sharif et al.	0.700	0.600	0.900	18.78
Sharma et al.	0.910	0.870	0.960	41.00
D+L pooled ES	0.865	0.771	0.971	100.00

Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 7.60 (d.f. = 3) p = 0.055
I-squared (variation in ES attributable to heterogeneity) = 60.5%
Estimate of between-study variance Tau-squared = 0.0079

Test of ES=1 : z= 2.45 p = 0.014

Table A5: Meta-Analysis of Three COPD Population Studies (Unadjusted)

Study	ES	[95% CI]	% Weight
Fidahussein et al.	1.070	0.830 1.370	26.15
Sharif et al.	0.670	0.580 0.780	34.01
Sharma et al.	0.880	0.840 0.920	39.84
D+L pooled ES	0.844	0.681 1.047	100.00

Heterogeneity calculated by formula
Q = SIGMA_i(8)
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 14.74 (d.f. = 2) p = 0.001
I-squared (variation in ES attributable to heterogeneity) = 86.4%
Estimate of between-study variance Tau-squared = 0.0297

Test of ES=1 : z= 1.54 p = 0.122

Table A6: Meta-Analysis of Three COPD Population Studies (Adjusted)

Study	ES	[95% CI]	% Weight
Fidahussein et al.	1.020	0.800 1.320	24.61
Sharif et al.	0.700	0.600 0.900	29.51
Sharma et al.	0.910	0.870 0.960	45.88
D+L pooled ES	0.866	0.724 1.036	100.00

Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 7.05 (d.f. = 2) p = 0.029
I-squared (variation in ES attributable to heterogeneity) = 71.7%
Estimate of between-study variance Tau-squared = 0.0175

Test of ES=1 : z= 1.57 p = 0.115

Table A7: Meta-Analysis of Three High Quality Studies (Unadjusted)

Study	ES	[95% CI]	% Weight
Lee et al.	0.900	0.790 1.020	33.09
Muus et al.	0.370	0.350 0.390	33.44
Sharma et al.	0.880	0.840 0.920	33.47
D+L pooled ES	0.664	0.348 1.267	100.00

Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 608.99 (d.f. = 2) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 99.7%
Estimate of between-study variance Tau-squared = 0.3247

Test of ES=1 : z= 1.24 p = 0.214

Table A8: Meta-Analysis of Two High Quality Studies (Adjusted)

```
Study |               ES        [95% CI]       % Weight
----------------------+-----------------------------------------
---------
Lee et al.          | 0.850     0.730 0.980       10.05
Sharma et al.       | 0.910     0.870 0.960       89.95
----------------------+-----------------------------------------
---------
D+L pooled ES       | 0.904     0.863 0.947      100.00
----------------------+-----------------------------------------
---------
Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 0.74 (d.f. = 1) p = 0.389
I-squared (variation in ES attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000


Test of ES=1 : z= 4.25 p = 0.000
```

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