Influenza Vaccination in Patients with Diabetes: Exploration of the Healthy User in Pharmacoepidemiology Studies

by

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ABSTRACT

Pharmacoepidemiologic studies of preventive medications or therapies are prone to the healthy user bias, as patients who are prescribed and adhere to preventive medications/therapies are likely different than patients not receiving these medications in multiple aspects of their lives. These differences can be a source of bias in estimating the isolated effect of the medication/therapy under study. The objectives of this research were to explore characteristics and behaviors of patients who receive influenza vaccination, which has previously been shown to be a strong marker of healthy users. Two studies were conducted; the first study was done in a prospective cohort of adults with type 2 diabetes, and involved statistical modeling to identify predictors of influenza vaccine receipt, which included: taking preventive medications (e.g., aspirin, blood pressure medications and cholesterol-lowering medications) and having foot checks done by a healthcare professional. These associated behaviors reinforce the need for observational studies of influenza vaccine effectiveness to control for healthy user attributes in order to reduce associated biases. The second study involved building a healthy user index to be used for adjustment of bias in large administrative databases. The score was developed based on characteristics believed to be associated with the healthy user (identified using influenza vaccination as a prototypical surrogate) from the literature. The index was internally validated and significantly predicted influenza vaccination. Future research should be aimed at evaluating the ability of the index to control for healthy user bias in real-world observational studies of preventive medications/ therapies.

PREFACE

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LIST OF ABBREVIATIONS

AAA- abdominal aortic aneurysm

ADG – aggregated diagnosis groups

aOR - adjusted odds ratio

ABCD - Alberta's Caring for Diabetes Project

CI - confidence interval

CPT – Current Procedural Terminology

HCPC – Healthcare Common Procedure Coding System

ICD-9-CM – International Classification of Diseases- 9th Revision- Clinical Modification

IPPE – initial preventive physical examination

MCS-12 – Mental Component Summary of the Short-Form 12 Version 2 Survey

MPR – medication possession ratio

OR - odds ratio

PCS-12 – Physical Component Summary of the Short-Form 12 Version 2 Survey

RCT – randomized controlled trial

SD - standard deviation

SDSCA - Summary of Diabetes Self Care Activities

VIF – variance inflation factor

CHAPTER 1: INTRODUCTION

1.1 STATEMENT OF THE PROBLEM

1.1.1 The Healthy User in Observational Studies

Evidence derived from observational studies about preventive medications has misled the medical community in the past[1]. One of the most well-known examples involved hormone replacement therapy and cardiovascular outcomes. In the 1980s a number of observational studies, including the Nurses' Health Study, showed an association between hormone replacement therapy and decreased risk of coronary heart disease[2]. A review of the literature published in 1992 recommended use of hormone replacement therapy in post-menopausal women to prevent cardiovascular disease[3]. Best medical practice was based on evidence from observational studies until the results of two large-scale randomized clinical trials, the HERS trial[4] (published in 1998) and the Women's Health Initiative[5] (published in 2002), showed the reverse effect: that hormone replacement therapy was associated with increased risk of coronary heart disease. This same scenario, where an association observed in observational trials of preventive medications/practices is later refuted once a randomized controlled trial (RCT) is done, has been repeated numerous times in recent medical history.

The reason for the discrepancy between observational studies of preventive medication and RCTs is multifactorial, but often the differences have been attributed to a category of biases known in the literature as the "healthy user effect"[1]. The healthy user effect is a form of selection bias, and it is a complex bias to control for as it includes a host of interrelated patient behaviors and physician and health system factors. An editorial responding to an observational study on the

potential benefit of statins in sepsis, depicted a conceptual model to explain the healthy user (Figure 1-1)[6] for the perceived pleotropic statin effects, which have been repeatedly shown to be susceptible to healthy user bias. Collectively, healthy users tend to follow more healthy behaviors including: consuming a better diet, exercising regularly, not smoking, drinking alcohol in moderation, and adhering to their medications[6]. In the observational study of statins' effects on mortality in sepsis, indeed statin users were less likely to be smokers, and were less likely to be prescribed thiamine in hospital (a marker of alcohol abuse)[7]. The observed benefit of statins on sepsis has since been refuted by RCTs[8] highlighting the difficulty of assessing these types of preventive therapies in observational settings.

The healthy user effect goes well beyond just lifestyle behaviors. Indeed, healthy users more often partake in and adhere to preventive services, such as cancer screening, osteoporosis screening, and routine physical exams[6]. One study that was done to explore this showed that patients who adhere to statin therapy are more likely to partake in cancer screening tests (e.g., prostate-specific antigen testing for prostate cancer, mammograms for breast cancer and fecal-occult blood tests for colon cancer), as well as receive vaccinations (e.g., pneumococcal vaccinations and influenza vaccinations)[9]. These associations remained even after adjusting for age, sex and other commonly measured covariates used in observational research. Healthy users also adhere to preventive medications such as aspirin, multivitamins and statins[6]. Interestingly, just the behavior of being adherent has been shown to be associated with better health outcomes. This is most profoundly noted in a meta-analysis that showed that adherence to the placebo arm in trials is associated with lower rates of mortality[10].

Another aspect of the healthy user includes normal functional status and cognition[1,6]. Patients with functional and cognitive limitations may find it more difficult to visit or interact with their physician, partake in preventive services, adhere to their medications and follow healthy behaviors. For example, an observational study looking at disabled patients and their access to preventive services showed that women with higher levels of disability were less likely to receive Pap smears and mammograms[11]. Physicians may also selectively not prescribe preventive medications or therapies to patients who are more frail. Functional status and cognition are often difficult variables to capture, and thus control for, especially when using administrative data.

Overall, the combinations of the above factors make it very difficult to isolate the effects of the preventive medication or therapy under examination in an observational study. Regarding the story of hormone replacement therapy, the healthy user bias likely had a large influence in the results of observational studies, in that women who were prescribed and adhered to hormone replacement therapies were healthier in other ways: they were thinner, exercised more, had fewer risk factors and had higher socioeconomic status[12]. All of these factors led to the observed decrease in coronary heart disease; not the hormone replacement therapy per se.

1.1.2 The Healthy Vaccinee

Likewise, observational studies of influenza vaccine effectiveness are prone to the healthy user bias, or sometimes referred to as the "healthy vaccinee" bias in this setting[13-15]. Influenza vaccination is one of the largest public health campaigns worldwide, and most people are recommended to receive the influenza vaccination annually[16,17]. However, there is still

considerable debate as to the overall benefit of the vaccination programs relative to the cost of implementing the programs on a yearly basis. Much of the evidence behind the effectiveness of influenza vaccination, especially in the elderly, comes from observational studies[18,19], and there is current discussion in the medical community about the actual effectiveness of the influenza vaccine due to the potential for bias in these studies. Patients who choose to be vaccinated may be inherently different than their non-vaccinated counterparts, apart from vaccination status. This can include vaccinated patients being healthier overall, but may also include lower vaccination rates among frail seniors[13,20]. An observational study of influenza vaccine effectiveness in a nursing home setting showed that baseline characteristics of vaccinees and non-vaccinees differed, with non-vaccinees being more likely to be bedridden, have dementia and have lower serum albumin than vaccinees[21]. These factors can all influence the outcomes studied (febrile illness, pneumonia, death) independent of vaccine status and conceptually fit with the theoretical framework of the healthy user.

There are a number of inconsistencies in the influenza vaccination evidence base that have led researchers to question the current effectiveness cited[13,15]. First of all, the mortality benefit associated with influenza vaccination originally reported from observational studies is approximately 50%[18,19]. This value has since been suggested to be implausible by numerous research groups[13,15,22-24]. Influenza may account for approximately 5% of annual winter deaths among the elderly USA population. Therefore, the greatest efficacy we can expect from the vaccine would be to eliminate these 'influenza-attributable' excess deaths[24]. Secondly, ecological trends show that, while influenza vaccination coverage in the United States has been increasing over the past decades, there has not been a corresponding decrease in hospitalizations or all-

cause mortality[13,15,23,24]. Lastly, the effects of influenza vaccination on mortality should be greatest during the period of circulating virus. Multiple studies have used the unique temporality of influenza circulation to show that a substantial amount of the mortality benefit associated with the vaccine during influenza season is likely due to confounding, as a similar benefit exists during the influenza-off season[13-15,24]. Collectively, observational data on the effectiveness of the influenza vaccine has been difficult to isolate, as many of the characteristics associated with healthy users in the literature are also major factors for receipt of vaccine in the first place.

1.1.3 Controlling for Confounding

Due to the lack of randomization in observational studies, researchers often need to control for confounding in the analysis stage of their studies. Unfortunately with the healthy user bias this proves to be a very difficult task, as many of the factors that act as confounders are hard to measure[1] or are not available in existing administrative databases. The healthy user bias is multidimensional, involving health behaviors, adherence, frailty, cognition, prescriber preferences, and health system factors[6], and adjusting for all of these factors is a complex process. For example, in a study on medication adherence, the 'healthy adherer' bias was addressed by controlling for a number of variables thought to be associated with medication adherence, such as marital status, income, education, self-reported health status and health habits, including influenza vaccination[25]. However, as this example illustrates, many other factors may have contributed to healthy user bias as previously discussed, and even after adjustment for the above variables, there still may be residual bias.

There are a number of suggestions for researchers to pursue in order to minimize the healthy user bias in observational studies[1]. First of all, in the design phase, new-user designs are preferred to prevalent user designs[26]. Prevalent user studies include a select group of patients who adhere to and tolerate the medication under study. Another suggestion in the design phase is to use active comparator groups. For example, when studying preventive medication A, if the comparator group is a group of individuals who take preventive medication B, it is more likely that baseline characteristics related to the healthy user will be similar. In the analysis phase of studies, some suggestions for researchers to pursue are to use proxy variables (e.g., vaccination or mammography) or propensity scores as ways to adjust for the healthy user. One group of researchers built a propensity score around hormone therapy use[27]. Nine predictors of hormone therapy were identified and used to build a propensity score which estimates the probability of using hormone therapy for each individual. They hypothesized that with further validation, this score could be used to estimate the propensity of being a healthy user. Whether these techniques truly eliminate healthy user bias in observational studies is still unknown. However, given the numerous examples in the literature, it is clear that better techniques are required, as traditional epidemiological techniques (e.g., matching, regression) are insufficient in most cases to control for healthy user bias.

Unique strategies have also been suggested for controlling bias in observational studies of influenza vaccine effectiveness[13]. Firstly, researchers should explore additional predictors of influenza vaccination, especially the difficult-to-measure predictors such as behaviors and functional status. This can be especially challenging with the use of administrative data, and it may be necessary to include medical chart reviews or patient participation[13]. Additionally,

researchers should avoid using all-cause mortality as an outcome measure for vaccine effectiveness, as attributes of the healthy user are largely associated with all-cause mortality, and the potential for bias is large. A more suitable outcome which has been proposed is influenza-related pneumonia[13]; although it is still likely associated with some bias. Lastly, sensitivity analyses should be included where influenza vaccine effectiveness is assessed outside of the influenza season. If confounding has been appropriately adjusted for, we would anticipate the estimate of relative risk to be close to one[13-15]. This is an example of the use of 'negative controls', which can be a useful tool in epidemiology to identify potential confounding and design flaws in observational studies of medications/therapies[1,28]. Lastly, as has been completed for comorbidity and risk adjustment, there exists the potential to develop a 'summary' score, similar to the Charlson comorbidity index or Framingham risk scores, to capture the multiple characteristics of the healthy vaccinee for adjustment in observational studies.

1.2 SUMMARY

Pharmacoepidemiologic studies of preventive medications are prone to the healthy user bias. Patients who are prescribed and adhere to preventive medications are likely different from their non-healthy user counterparts in multiple ways, including health behaviors and functional status. Observational studies of influenza vaccine effectiveness are prone to healthy user bias, and there is current debate in the medical literature about the actual effectiveness of the influenza vaccine, especially in the elderly. Much of this debate stems from the high potential for healthy user bias in studies assessing effectiveness of preventive medications/therapies, like influenza vaccination. There have been multiple methods suggested to control for healthy user confounding in influenza vaccination studies. This research will expand on this previous work and explore potential

predictors of influenza vaccination, as well as develop a new prediction score for healthy users, which may be used to control confounding in future pharmacoepidemiologic studies of preventive medications/therapies.

1.3 OBJECTIVES

The objectives of this program of research were (1) to identify characteristics and health behaviors of patients who receive the influenza vaccine in comparison to patients who do not and (2) to build and internally validate a prediction score for influenza vaccination, as a proxy for being a healthy user. These objectives were met through two related studies.

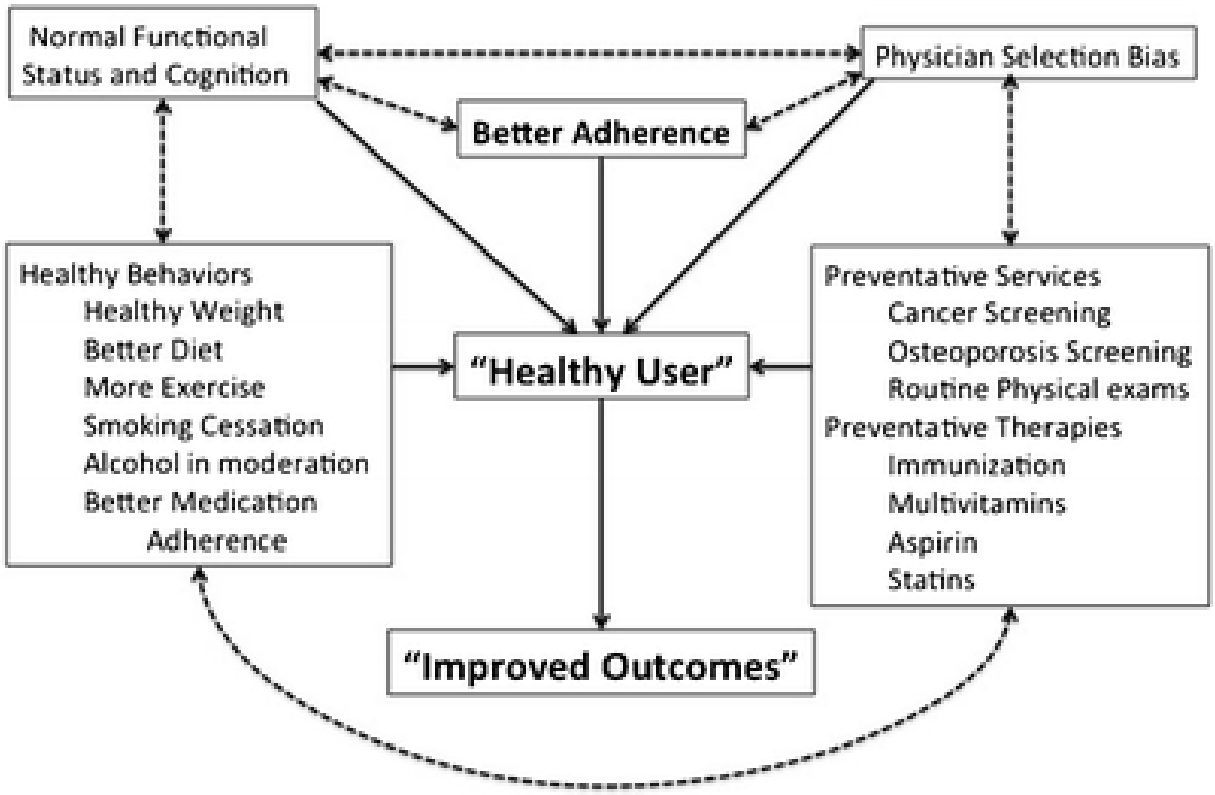
1.4 PROGRAM OF RESEARCH

Two studies were undertaken to achieve the objectives of this research project. The first study (Chapter 2) determined predictors of influenza vaccination in a cohort of patients with type 2 diabetes in Alberta, Canada. This study took advantage of a rich source of data from a ongoing prospective cohort study of 2040 patients, with information including not only sociodemographics and comorbidities, but also difficult-to-capture information such as health behaviors, functional status and health beliefs. Multivariable logistic regression modeling was used to identify variables that predicted vaccine receipt.

The second study (Chapter 3) involved building a prediction score for influenza vaccination and internally validating it. A large administrative database of patients with type 2 diabetes was randomly split in half, yielding derivation and validation cohorts. A prediction score for a healthy user was built in the derivation cohort and included age, sex, and selected healthy user

predictor variables identified in the literature and available within typical administrative databases. This score was then tested in the validation cohort for overall performance and discrimination ability.

Figure 1-1: Conceptual model explaining the healthy-user effect



Springer and J Gen Intern Med 27(3):268-9, Statins and Sepsis- Scientifically Interesting but Clinically Inconsequential, Eurich D, Majumdar S, Figure 1 © Society of General Internal Medicine 2011. With kind permission from Springer Science and Business Media

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CHAPTER 2: CHARACTERISTICS AND HEALTH BEHAVIORS OF DIABETIC PATIENTS RECIEVING INFLUENZA VACCINATION [1]

2.1 INTRODUCTION

Influenza vaccination is undoubtedly one of the largest public health prevention programs around the world. Most guidelines recommend influenza vaccination for all patients aged ≥6 months unless contraindicated; however, certain high-risk groups are prioritized for vaccination, including those with diabetes [1,2]. Clinical practice guidelines for the management of type 2 diabetes recommend that all diabetes patients receive the annual influenza vaccine [3,4].

Although several observational studies have assessed influenza vaccine effectiveness in diabetes patients[5-8], the true effectiveness is still debated due to lack of high quality randomized controlled trials and concerns of bias in observational studies[9]. Of particular concern is a 'healthy user' bias, whereby patients who choose to be vaccinated are postulated to be healthier, presumably through engagement in more preventive and health-seeking behaviors (e.g., getting annual check-ups, following cancer-screening guidelines, adhering to prescribed medications)[10]. Because many observational studies of vaccine effectiveness are based on administrative claims data, such healthy-user attributes are rarely accounted for and can lead to severe bias [11-13]. Healthy user bias is not specific to influenza vaccination and has been used to explain the relationships detected in observational studies between hormonal therapy or vitamins and

[1] A version of this chapter has been accepted for publication by Vaccine. K.A. Achtymichuk, J.A. Johnson, F. Al Sayah, and D.T. Eurich, "Characteristics and Health Behaviors of Diabetic Patients Receiving Influenza Vaccination", *Vaccine* [serial online]. July 9, 2015;33:3549-3555. Available from: ScienceDirect, Ipswich, MA.

cardiovascular outcomes, statins and multiple outcomes including hip fracture, Alzheimer's disease, sepsis, and cancer[14].

To date few studies have specifically explored potential healthy-user attributes. This is due, in part, to reliance on administrative databases, which often lack important patient information characterizing attributes and healthy user behaviors. In the few non-administrative database studies conducted, higher functional status has been shown to be a major determinant of vaccine receipt and associated outcomes [11,13]. Given the importance of influenza vaccination in public health, and the potential impact of the healthy user bias in observational studies of preventive strategies and treatments, we sought to determine the differences in healthy-user attributes between patients who receive the influenza vaccine compared to patients who do not. To do so we used a large clinically-rich population-based cohort of patients with type 2 diabetes.

2.2 METHODS

The Alberta's Caring for Diabetes Project (ABCD) is an ongoing prospective population-based cohort of adults with type 2 diabetes in the province of Alberta, Canada [15,16]. Eligible patients included those over 18 years of age and who are able to communicate in English. Patients with known type 1 diabetes or gestational diabetes were excluded. Patients were recruited between December 2011 to December 2013 through multiple approaches including invitations through primary care networks, diabetes clinics, and community pharmacies as well as radio, print and television advertising. Eligible patients willing to participate received a self-administered survey via the mail. Follow-up reminders were issued approximately 4 weeks following initial contact to non-responders. The representativeness of the ABCD cohort has been previously assessed and

shown to be a representative sample of Albertans and Canadians with diabetes [16]. The data for this analysis were limited to the baseline survey which, depending on the participant, could have been filled out between December 2011 and December 2013. One year of data (one survey) were used per participant. All participants provided written informed consent and the ABCD project was approved by the University of Alberta Research Ethics Board.

Outcomes

Our primary outcome of interest was whether or not the patient reported receipt of the influenza vaccine in the past twelve months. In Alberta, influenza vaccination is free of charge and is available through community vaccination campaign clinics, primary care centers, hospitals, as well as community pharmacies. Self-report of influenza vaccination has been described in previous studies as a valid method with high sensitivity and moderate specificity [17-20].

Measurements

Self-reported data covered a wide range of clinical, behavioral, psychosocial and process of care factors believed to be associated with influenza vaccine use and health outcomes in patients with diabetes. Specific data collected included, but was not limited to: sociodemographic variables consisting of age (greater or equal to 65 years vs less), sex, marital status (married vs not), educational level (high school or more vs less), ethnicity (Caucasian vs other) and annual household income (≥$80,000/year vs less).

Comorbidities included heart disease, cerebrovascular disease, respiratory disease, and cancer, as well as an overall count of other major comorbidities (range 0-10). Preventive medications often

prescribed in diabetes patients and known to be associated with the healthy user were included: aspirin, blood pressure medications (e.g., ACE inhibitors), and cholesterol-lowering medications (e.g., statins). Duration of diabetes and insulin use were included as markers of disease severity. Information on the use of pneumococcal vaccine was collected but not included in our primary model as co-receipt with influenza vaccination was common (correlation coefficient= 0.54, p <0.001); however, we did include it in sensitivity analyses.

Health status was measured by the Short Form "SF-12" version 2, which yields 2 summary scores: the PCS-12 (physical component summary) and MCS-12 (mental component summary). These were analyzed as continuous variables with higher scores indicating better physical and mental health status respectively [21]. Self-care management was measured by the Summary of Diabetes Self Care Activities (SDSCA) [22]. The SDSCA domains of general diet, blood sugar testing, footcare and medication adherence were included as continuous scores from 0 to 7, representing the mean number of days per week that these self-care activities were followed. Other health behaviors assessed include: smoking (current or not), alcohol consumption [23] (yes or no), and meeting guidelines for physical activity (yes or no) which was measured by the Godin and Shephard Leisure-time physical activity questionnaire [24].

Clinical monitoring indicators including checks for A1C, cholesterol, blood pressure, and dilated eye exams, as well as healthcare professional activities including checking feet for lesions, testing urine for protein and measuring weight on a scale were also included.

Lastly, patients were asked to rate their healthcare experience over the past year on a scale from 0 to 10. This was analyzed as a continuous variable with higher scores indicating higher satisfaction with care [25,26].

Analysis

All analyses were done using logistic regression. In building our multivariable model, two different approaches were taken. In our primary analysis, we postulated that all clinical and behavioral factors as noted above should be related to the healthy user and influenza vaccine receipt. Thus, we organized the covariates into 5 major blocks to assess the impact of increasing clinical and behavioral data on predicting influenza vaccine receipt: 1) sociodemographics, 2) comorbidities & medications, 3) health status, 4) self-care behaviors, and 5) clinical monitoring. We then completed a series of multivariable logistic regression models to evaluate the association between available covariates and influenza vaccination. Specifically, we first calculated unadjusted estimates. Second, we conducted simple adjustments for sociodemographic variables. Third, we included comorbidities and medications that can typically be derived from most administrative datasets. Lastly we included more difficult-to-capture health status and measures of self-care behaviors and clinical monitoring. We report unadjusted and adjusted odds ratios (ORs) from our logistic regression models with their respective 95% confidence intervals (95% CI). We report the c-statistic for each block of covariates independently and the cumulative c-statistic for all blocks currently in the model. In our secondary analysis, we built a more parsimonious multivariable model, including only variables based on statistical significance ($p<0.1$) in univariate analyses. In all models, multicollinearity was examined by calculating the variance inflation factor (VIF), where values more than 10 were

interpreted as important multicollinearity; however, none were observed in our multivariable model. Statistical analysis was conducted with Stata version 12.1 (StataCorp LP, College Station, TX).

Sensitivity Analyses

Several sensitivity analyses were conducted to evaluate the robustness of our results. First, receipt of pneumococcal vaccination was added to the multivariable model. As well, analyses were repeated with patients stratified by sex and age (<65 and ≥65 years).

2.3 RESULTS

From our cohort of 2040 patients with type 2 diabetes, nearly two-thirds (1287/2040, 63%) reported receiving the influenza vaccine. Average age of our cohort was 64 years (standard deviation 11) and 55% were male. Overall, patients who received the influenza vaccine tended to be older, have more comorbidities, take more medications, follow more healthy behaviors, have more clinical monitoring examinations completed, and were more satisfied with their healthcare experience. Conversely, high income, high physical health status and being a current smoker were associated with not receiving the vaccine (Table 2-1).

In our blocked multivariable models, the covariates with the largest influence on predicting influenza vaccination included measures of comorbidities and medication use (c-statistic= 0.68), followed by clinical monitoring (c-statistic= 0.62), sociodemographics (c-statistic= 0.60), self-care behaviors (c-statistic= 0.58) and health status (c-statistic= 0.54). Interestingly, beyond sociodemographics and comorbidities and medication use, the addition of difficult to capture

data like health status, self-care behaviors and clinical monitoring only had marginal impact on the discrimination ability of the model. Overall, the final model provided acceptable discrimination ability between vaccine receipt and non-receipt, with an overall c-statistic of 0.72.

Covariates independently associated with receiving influenza vaccination in the final multivariable model were largely related to comorbidities, preventive medications, and preventive screening measures (Table 2-2). Specifically, age over 65 years (53% vs 36%; aOR 1.75, 95% CI 1.39-2.19); having respiratory disease (21% vs 14%; aOR 1.51, 95% CI 1.15-1.99); number of additional comorbidities (mean 3.5 vs 2.8; aOR 1.16, 95% CI 1.08-1.24); taking aspirin (64% vs 44%; aOR 1.65, 95% CI 1.34-2.04); taking blood pressure medications (76% vs 56%; aOR 1.36, 95% CI 1.07-1.71); taking cholesterol-lowering medications (74% vs 53%; aOR 1.50, 95% CI 1.19-1.89); having a healthcare professional check feet for lesions in the last year (47% vs 31%; aOR 1.39, 95% CI 1.12-1.74); and a higher rating of healthcare experience over the last year (mean 8.3 vs 8.0; aOR 1.08, 95% CI 1.02-1.15) were all associated with increased likelihood of receiving the influenza vaccination.

In our secondary analysis, with a more parsimonious model, the same predictors related to comorbidities, medications and preventive screening procedures were observed (Table 2-3).

Results of the sensitivity analyses were similar to our primary analysis. First, as expected, pneumococcal vaccination was highly predictive of influenza vaccine receipt (aOR 11.67, 95% CI 9.13-14.90) and increased the c-statistic from 0.72 to 0.84. Second, sex- and age- specific analyses showed only minor differences (Table 2-4). For example, being married was predictive

of influenza vaccination in males but not in females. Having respiratory disease and taking cholesterol-lowering medications was predictive of influenza vaccination in elderly but not in young patients.

2.4 DISCUSSION

Our study suggests that the patient and healthcare factors associated with influenza vaccination in diabetes patients are very complex. Some identified predictors may be related to encounters with the healthcare system (i.e., patients with more comorbidities encounter the healthcare system more frequently which increases the opportunity for influenza vaccination to occur), while others are important markers of comprehensive diabetes care and are known to improve outcomes in patients with diabetes. For example, patients who receive the influenza vaccine also tend to take preventive medications, such as aspirin, blood-pressure and cholesterol-lowering medications, as well as partake in regular screening (e.g., checking feet for lesions). Thus, influenza vaccination may serve as an overall marker of quality care in people with diabetes, and lack of influenza vaccination in patients with diabetes may inform health professionals that other aspects of their diabetes care may be in need of attention.

The results of our study largely agree with what is available in current literature on influenza vaccination predictors [27-29]. Age, sex and marital status are known predictors of influenza vaccination. Comorbid respiratory disease has been shown to be a predictor of influenza vaccination and is a targeted group for vaccination campaigns [27]. A commonly identified predictor of influenza vaccination has to do with contact with the healthcare system (e.g., having a physician visit recently) [27,30,31]. Indeed systematic reviews have clearly shown that the

organization of care by patients' physicians or other healthcare providers play an important role in determining who does or does not get vaccinated [32]. Predictors identified in our model (e.g., utilization of medications, having feet checked by a healthcare professional) are likely multifactorial in how they predict influenza vaccination: not only are these healthy behaviors, but they also are encounters with the healthcare system where vaccination can occur, or be recommended by the healthcare team. Lastly, while other studies have identified functional status as a predictor of influenza vaccination[11,13], in our analysis the PCS-12 and MCS-12 were not predictive, perhaps due to our population being relatively highly functional.

Evaluating influenza vaccine effectiveness in observational research has proven to be a difficult task, and our study highlights why this may be. Many behavioral factors that are associated with influenza vaccination are also postulated to be associated with the healthy user (e.g., taking preventive medications, getting regular checkups). Healthy user bias is difficult to quantify in most research because it includes many different inter-related factors. Our data supports this premise whereby, although only a few specific independent predictors emerged, as a whole our model for the healthy user had high discriminating ability in predicting who received the vaccine. Given how closely aligned many of these factors are with influenza vaccine receipt, research on influenza vaccination in observational studies must control for the majority of these factors to minimize healthy user bias. Conversely, in observational studies not evaluating influenza vaccination, influenza vaccination itself may serve, at least in part, as a surrogate for many difficult-to-capture-and-control healthy behaviors postulated to be associated with healthy users.

Our analyses also highlight the challenges of vaccine campaigns. Although most clinical practice guidelines for the management of chronic disease, including those for type 2 diabetes, recommend the annual influenza vaccine, many had not received it in our sample [3,4]. Medical practices and facilities that deal with patients with diabetes should incorporate the annual influenza vaccination as part of their routine clinical care pathways. Current evidence for increasing influenza uptake suggest that identifying a specific team member (e.g., nurse, pharmacist, diabetes educator) in the care setting responsible for vaccine administration is an effective method to increase rates. Other avenues including patient outreach programs, clinician reminders, and focusing of public health messaging around the importance of the vaccine in patients with chronic diseases, will also serve to help increase vaccine uptake in this population [32,33].

Our study has some limitations. First, as with any survey, there is the potential for selection bias. Patients who choose to fill out health surveys may be overall healthier individuals to start with. For example, we noted that the overall vaccination rate in our population, 63%, was higher than anticipated, which could indicate a selectively healthier population responding to our survey. Second, our information was based on self-report, which may be prone to recall or social desirability biases. Moreover, we do not have any objective measures of physiologic health (e.g., A1C, blood pressure) or health service use (e.g., physician visits, hospitalizations), so we do not know for certain which patients are healthier. And lastly, although we collected information on a wide range of variables, our final model did not perfectly discriminate between influenza vaccine users and non-users. However, this also highlights the significant complexity in decisions around the use of influenza vaccination. One can speculate on behaviors and variables that we did not

capture that may play a role in explaining influenza vaccination. For example, both the patient's and the physician's beliefs on influenza risk and influenza vaccine effectiveness may play a role, alongside more technical aspects such as vaccine availability and accessibility.

In conclusion, our study suggests that influenza vaccination may serve as a marker of care in people with chronic disease such as diabetes. Lack of influenza vaccination in patients may inform health professionals that other aspects of their care may be in need of attention. Vaccine campaigns, to increase uptake, may consider targeting individuals with less frequent encounters with the healthcare system. In addition, our study suggests that future observational studies of influenza vaccine effectiveness need to account for healthy user bias in order to provide realistic estimates of effect.

Table 2-1: Characteristics of vaccinated and non-vaccinated respondents

	Vaccinated (N=1287; 63%)	Non-Vaccinated (N=753; 37%)	
	N (%) or mean (SD)		P-value
Sociodemographics			
Age, >=65 years old	684 (53.1%)	267 (35.5%)	<0.001
Sex, male	694 (53.9%)	430 (57.1%)	0.163
Marital status, currently married	928 (72.1%)	531 (70.5%)	0.443
Educational level, high school or more	1097 (85.2%)	655 (87.0%)	0.274
Ethnicity, Caucasian	1181 (91.8%)	688 (91.4%)	0.756
Income, >=$80,000/year	278 (21.6%)	207 (27.5%)	0.003
Comorbidities & Medications			
Comorbidity: Heart disease	278 (21.6%)	109 (14.5%)	<0.001
Comorbidity: Cerebrovascular disease	443 (34.4%)	198 (26.3%)	<0.001
Comorbidity: Respiratory disease	268 (20.8%)	107 (14.2%)	<0.001
Comorbidity: Cancer	199 (15.5%)	76 (10.1%)	0.001
Number of additional comorbidities (range 0-10)	3.5 (1.8)	2.8 (1.7)	<0.001
Currently taking aspirin	818 (63.6%)	332 (44.1%)	<0.001
Currently taking BP medications	981 (76.2%)	421 (55.9%)	<0.001
Currently taking cholesterol-lowering medications	956 (74.3%)	401 (53.3%)	<0.001
Currently taking medications to protect kidneys	221 (17.2%)	98 (13.0%)	0.013
Currently using insulin	474 (36.8%)	198 (26.3%)	<0.001
Pneumococcal vaccine	955 (74.2%)	135 (17.9%)	<0.001
Duration of diabetes	13.0 (8.9)	10.8 (8.5)	<0.001
Health Status			
PCS-12	44.0 (10.5)	45.1 (10.1)	0.021
MCS-12	48.2 (9.3)	48.1 (9.9)	0.806
Self-Care Behaviors			
SDSCA general diet	4.8 (1.9)	4.6 (2.0)	0.056
SDSCA blood sugar testing	4.2 (2.5)	3.8 (2.4)	0.001
SDSCA footcare	3.4 (1.6)	3.2 (1.5)	0.002
SDSCA medication adherence	6.3 (1.7)	6.2 (1.7)	0.072
Current smoker	114 (8.9%)	99 (13.1%)	0.002
Drinks alcohol	880 (68.4%)	473 (62.8%)	0.010
Physically active	279 (21.7%)	159 (21.1%)	0.765
Clinical Monitoring			
Last A1C check within one year	1130 (87.8%)	641 (85.1%)	0.085
Last cholesterol check within one year	1212 (94.2%)	686 (91.1%)	0.009
Last eye exam with dilation within one year	906 (70.4%)	497 (66.0%)	0.039

Blood pressure check at most diabetes appointments	1194 (92.8%)	670 (89.0%)	0.003
In the past year has a healthcare professional...			
...Checked feet for lesions	609 (47.3%)	234 (31.1%)	<0.001
...Tested urine for protein	1163 (90.4%)	648 (86.1%)	0.003
...Measured weight on a scale	1040 (80.8%)	586 (77.8%)	0.106
Rate all healthcare over past year (0-10)	8.3 (1.7)	8.0 (1.8)	<0.001

Table 2-2: Blocked model building

	Results: OR (95% CI) p-value									
	Sociodemographic								**Full Model**	
Age, >=65 years old	2.04 (1.68-2.48)	<0.01							1.75 (1.39-2.19)	<0.01
Sex, male	0.85 (0.70-1.02)	0.09							0.82 (0.66-1.01)	0.07
Marital status, currently married	1.20 (0.97-1.48)	0.09							1.22 (0.97-1.53)	0.09
Educational level, high school or more	1.02 (0.78-1.34)	0.88							0.95 (0.71-1.27)	0.72
Ethnicity, Caucasian	1.01 (0.73-1.41)	0.93							1.07 (0.75-1.53)	0.71
Income, >=$80,000/year	0.90 (0.72-1.13)	0.42	**Comorbidities & Medications**						0.93 (0.72-1.19)	0.56
Comorbidity: Heart disease			0.99 (0.76-1.29)	0.93					0.95 (0.72-1.26)	0.73
Comorbidity: Cerebrovascular disease			1.01 (0.81-1.26)	0.93					1.04 (0.82-1.32)	0.74
Comorbidity: Respiratory disease			1.39 (1.07-1.81)	0.013					1.51 (1.15-1.99)	<0.01
Comorbidity: Cancer			1.37 (1.02-1.84)	0.04					1.23 (0.91-1.66)	0.18
Number of additional comorbidities			1.13 (1.06-1.20)	<0.01					1.16 (1.08-1.24)	<0.01
Currently taking ASA			1.66 (1.35-2.03)	<0.01					1.65 (1.34-2.04)	<0.01
Currently taking BP medications			1.47 (1.18-1.84)	0.01					1.36 (1.07-1.71)	0.01
Currently taking cholesterol-lowering medications			1.60 (1.29-1.99)	<0.01					1.50 (1.19-1.89)	<0.01
Currently taking medications to protect kidneys			1.03 (0.78-1.36)	0.83					1.04 (0.78-1.38)	0.79
Currently using insulin			1.19 (0.95-1.47)	0.12					1.23 (0.96-1.57)	0.10
Duration of diabetes			1.02 (1.00-1.03)	0.01	**Health Status**				1.01 (0.99-1.02)	0.25
PCS-12					0.98 (0.97-0.99)	<0.01			1.01 (0.99-1.02)	0.47
MCS-12					1.01 (1.00-1.03)	0.028	**Self-Care Behaviors**		1.00 (0.99-1.02)	0.61
SDSCA general diet							1.02 (0.97-1.07)	0.52	1.01 (0.96-1.07)	0.66
SDSCA blood sugar testing							1.05 (1.01-1.09)	0.02	1.00 (0.96-1.05)	0.83
SDSCA footcare							1.09 (1.02-1.15)	0.01	1.06 (0.99-1.13)	0.09
SDSCA medication adherence							1.03 (0.98-1.09)	0.28	0.98 (0.93-1.04)	0.54
Current smoker							0.66 (0.49-0.88)	0.01	0.78 (0.57-1.08)	0.14
Drinks alcohol							1.34 (1.10-1.62)	<0.01	1.15 (0.93-1.43)	0.19
Physically active (based on MVPA-level)							0.97 (0.77-1.21)	0.77	1.16 (0.90-1.48)	0.26
Last A1C check within one year								**Clinical Monitoring**	1.14 (0.84-1.54)	0.39
Last cholesterol check within one year									1.13 (0.76-1.68)	0.55
Last eye exam with dilation within one year									1.06 (0.86-1.31)	0.59
Blood pressure check at most diabetes appointments									1.25 (0.88-1.78)	0.21

In the past year has a healthcare professional...								
...Checked feet for lesions					1.93 (1.58-2.35)	<0.01	1.39 (1.12-1.74)	<0.01
...Tested urine for protein					1.25 (0.92-1.68)	0.15	1.12 (0.81-1.54)	0.48
...Measured weight on a scale					0.86 (0.67-1.09)	0.21	0.94 (0.73-1.22)	0.65
Rate all healthcare over past year (0-10)					1.10 (1.05-1.16)	<0.01	1.08 (1.02-1.15)	0.01
C-stat	0.60	0.68	0.54	0.58		0.62		
Cumulative C-stat		0.70	0.70	0.71		0.72		

Table 2-3: Multivariate model of variables with initial p<0.1 in univariate analyses

	OR (95% CI)	P-value
Age, >=65 years old	1.76 (1.41-2.19)	<0.001
Income, >=$80,000/year	0.95 (0.74-1.20)	0.651
Comorbidity: Heart disease	0.93 (0.70-1.23)	0.603
Comorbidity: Cerebrovascular disease	1.02 (0.81-1.29)	0.857
Comorbidity: Respiratory disease	1.52 (1.16-2.00)	0.002
Comorbidity: Cancer	1.23 (0.91-1.67)	0.177
Number of additional comorbidities	1.17 (1.09-1.25)	<0.001
Currently taking ASA	1.63 (1.32-2.01)	<0.001
Currently taking BP medications	1.35 (1.07-1.70)	0.012
Currently taking cholesterol-lowering medications	1.51 (1.20-1.90)	<0.001
Currently taking medications to protect kidneys	1.03 (0.78-1.36)	0.853
Currently using insulin	1.20 (0.95-1.53)	0.133
Duration of diabetes	1.01 (1.00-1.02)	0.238
PCS-12	1.01 (1.00-1.02)	0.175
SDSCA general diet	1.02 (0.97-1.08)	0.416
SDSCA blood sugar testing	1.00 (0.96-1.05)	0.833
SDSCA footcare	1.06 (1.00-1.14)	0.068
SDSCA medication adherence	0.98 (0.93-1.04)	0.548
Current smoker	0.76 (0.55-1.04)	0.087
Drinks alcohol	1.14 (0.93-1.41)	0.215
Last A1C check within one year	1.16 (0.86-1.57)	0.327
Last cholesterol check within one year	1.11 (0.75-1.65)	0.598
Last eye exam with dilation within one year	1.07 (0.87-1.32)	0.538
Blood pressure check at most diabetes appointments	1.21 (0.86-1.70)	0.285
In the past year has a healthcare professional...		
...Checked feet for lesions	1.36 (1.10-1.68)	0.005
...Tested urine for protein	1.12 (0.82-1.54)	0.479
Rate all healthcare over past year (0-10)	1.09 (1.02-1.15)	0.005

Table 2-4: Sensitivity Analyses

	Age <65 (n=1089)		Age >=65 (n=951		Male (n=1124)		Female (n=916)		Plus Pneumococcal Vaccine	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	P
Age, >=65 years old	.	.	.	.	1.86 (1.37-2.54)	<0.01	1.67 (1.19-2.36)	<0.01	1.12 (0.86-1.46)	0.38
Sex, male	0.76 (0.58-1.00)	0.05	0.90 (0.63-1.29)	0.57	.	.	.	.	1.02 (0.80-1.31)	0.85
Marital status, currently married	1.33 (0.97-1.82)	0.08	1.09 (0.76-1.55)	0.65	1.43 (1.01-2.02)	0.04	1.02 (0.74-1.40)	0.92	1.06 (0.81-1.38)	0.68
Educational level, high school or more	0.81 (0.51-1.31)	0.39	1.06 (0.72-1.57)	0.77	0.81 (0.54-1.21)	0.29	1.16 (0.74-1.82)	0.51	0.93 (0.66-1.30)	0.66
Ethnicity, Caucasian	1.49 (0.94-2.35)	0.09	0.62 (0.33-1.18)	0.15	1.00 (0.62-1.60)	0.99	1.23 (0.70-2.16)	0.46	1.04 (0.69-1.57)	0.86
Income, >=$80,000/year	0.85 (0.64-1.14)	0.27	1.51 (0.86-2.64)	0.15	0.86 (0.62-1.18)	0.35	1.11 (0.74-1.68)	0.61	1.01 (0.76-1.34)	0.95
Comorbidity: Heart disease	0.73 (0.48-1.10)	0.13	1.22 (0.82-1.82)	0.33	0.97 (0.67-1.40)	0.86	0.95 (0.60-1.51)	0.83	0.92 (0.67-1.27)	0.61
Comorbidity: Cerebrovascular disease	1.17 (0.84-1.63)	0.35	0.92 (0.64-1.31)	0.64	0.98 (0.71-1.35)	0.90	1.05 (0.73-1.51)	0.81	1.01 (0.77-1.33)	0.94
Comorbidity: Respiratory disease	1.42 (0.99-2.05)	0.06	1.70 (1.09-2.63)	0.02	1.40 (0.95-2.08)	0.09	1.62 (1.09-2.40)	0.02	1.36 (1.00-1.86)	0.05
Comorbidity: Cancer	1.12 (0.71-1.76)	0.64	1.32 (0.86-2.01)	0.21	1.27 (0.83-1.93)	0.27	1.27 (0.81-1.98)	0.30	1.06 (0.75-1.51)	0.73
Number of additional comorbidities	1.17 (1.07-1.29)	<0.01	1.13 (1.01-1.26)	0.04	1.25 (1.13-1.39)	<0.01	1.08 (0.98-1.20)	0.12	1.13 (1.04-1.22)	<0.01
Currently taking ASA	1.75 (1.31-2.32)	<0.01	1.59 (1.15-2.22)	0.01	1.77 (1.32-2.38)	<0.01	1.57 (1.14-2.15)	0.01	1.71 (1.34-2.18)	<0.01
Currently taking BP medications	1.38 (1.01-1.88)	0.04	1.33 (0.91-1.94)	0.14	1.29 (0.93-1.80)	0.13	1.42 (1.01-2.01)	0.05	1.13 (0.86-1.48)	0.38
Currently taking cholesterol-lowering medications	1.20 (0.88-1.64)	0.26	2.00 (1.40-2.86)	<0.01	1.49 (1.07-2.06)	0.02	1.61 (1.14-2.26)	0.01	1.57 (1.20-2.05)	<0.01
Currently taking medications to protect kidneys	0.96 (0.67-1.40)	0.85	1.14 (0.72-1.80)	0.58	0.99 (0.68-1.44)	0.95	1.06 (0.68-1.65)	0.80	0.93 (0.68-1.29)	0.68
Currently using insulin	1.22 (0.88-1.68)	0.23	1.11 (0.75-1.64)	0.61	1.21 (0.87-1.69)	0.26	1.28 (0.88-1.86)	0.20	1.07 (0.81-1.42)	0.64
Duration of diabetes	1.02 (1.00-1.05)	0.06	1.00 (0.99-1.02)	0.82	1.00 (0.98-1.02)	0.94	1.02 (1.00-1.04)	0.08	1.00 (0.99-1.01)	0.96
PCS-12	1.00 (0.98-1.02)	0.96	1.01 (0.99-1.04)	0.20	1.00 (0.98-1.02)	0.92	1.01 (0.99-1.03)	0.27	1.01 (0.99-1.03)	0.22
MCS-12	1.01 (0.99-1.03)	0.32	1.00 (0.97-1.02)	0.77	1.01 (0.99-1.03)	0.49	1.00 (0.98-1.02)	0.95	1.00 (0.99-1.02)	0.57
SDSCA general diet	0.97 (0.90-1.04)	0.40	1.07 (0.98-1.16)	0.13	1.01 (0.94-1.08)	0.79	1.03 (0.94-1.13)	0.52	0.99 (0.93-1.05)	0.74
SDSCA blood sugar testing	1.00 (0.94-1.06)	0.95	1.04 (0.97-1.12)	0.25	1.06 (1.00-1.12)	0.06	0.94 (0.88-1.01)	0.08	1.00 (0.95-1.05)	0.87
SDSCA footcare	1.09 (1.00-1.20)	0.05	1.02 (0.92-1.13)	0.73	1.06 (0.97-1.16)	0.21	1.07 (0.97-1.18)	0.19	1.05 (0.98-1.14)	0.18
SDSCA medication adherence	1.00 (0.93-1.08)	0.98	0.95 (0.87-1.05)	0.33	1.02 (0.94-1.11)	0.60	0.95 (0.87-1.04)	0.26	0.96 (0.90-1.03)	0.22
Current smoker	0.79 (0.54-1.17)	0.25	0.68 (0.37-1.25)	0.22	0.76 (0.49-1.17)	0.21	0.89 (0.54-1.46)	0.63	0.83 (0.57-1.20)	0.33
Drinks alcohol	1.09 (0.82-1.46)	0.54	1.20 (0.86-1.67)	0.28	1.13 (0.83-1.54)	0.43	1.11 (0.81-1.51)	0.52	0.99 (0.77-1.27)	0.93
Physically active	1.21 (0.87-1.67)	0.25	1.05 (0.71-1.56)	0.82	1.24 (0.90-1.73)	0.19	1.08 (0.73-1.61)	0.70	1.07 (0.80-1.42)	0.66
Last A1C check within one year	1.51 (0.96-2.39)	0.08	0.88 (0.57-1.36)	0.57	0.91 (0.61-1.36)	0.65	1.38 (0.85-2.25)	0.19	1.10 (0.78-1.54)	0.60
Last cholesterol check within one year	0.87 (0.52-1.47)	0.60	1.67 (0.88-3.18)	0.12	1.60 (0.93-2.76)	0.09	0.79 (0.43-1.45)	0.45	1.41 (0.89-2.22)	0.14
Last eye exam with dilation within one year	1.01 (0.77-1.32)	0.97	1.12 (0.78-1.59)	0.54	1.14 (0.85-1.52)	0.37	1.00 (0.72-1.39)	0.98	1.12 (0.88-1.43)	0.35

Blood pressure check at most diabetes appointments	1.42 (0.89-2.27)	0.14	1.01 (0.57-1.78)	0.98	1.39 (0.84-2.29)	0.21	1.19 (0.71-1.97)	0.51	1.55 (1.04-2.33)	0.03
In the past year has a healthcare professional...										
...Checked feet for lesions	1.35 (1.00-1.81)	0.05	1.47 (1.05-2.06)	0.03	1.60 (1.19-2.16)	<0.01	1.16 (0.84-1.62)	0.37	1.28 (0.99-1.65)	0.06
...Tested urine for protein	1.24 (0.82-1.88)	0.32	0.89 (0.51-1.52)	0.66	1.23 (0.78-1.93)	0.38	1.03 (0.64-1.66)	0.90	1.09 (0.76-1.56)	0.66
...Measured weight on a scale	1.03 (0.73-1.46)	0.85	0.83 (0.56-1.23)	0.35	0.97 (0.67-1.38)	0.85	0.90 (0.62-1.31)	0.58	0.89 (0.66-1.19)	0.43
Rate all healthcare over past year (0-10)	1.07 (1.00-1.16)	0.07	1.08 (0.98-1.19)	0.11	1.09 (1.00-1.18)	<0.01	1.09 (1.00-1.19)	0.06	1.09 (1.02-1.16)	0.01
Pneumococcal vaccine	.	.	.	.	.	.	.	.	11.67 (9.13-14.90)	<0.01

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CHAPTER 3: DEVELOPMENT OF A HEALTHY USER INDEX FOR USE IN OBSERVATIONAL STUDIES OF PREVENTIVE THERAPIES

3.1 INTRODUCTION

Evidence derived from observational studies about preventive therapies have misled the medical community in the past (e.g., hormone replacement therapy)[1]. It has since come to light that many observational studies looking at the effectiveness of preventive therapies are prone to bias, specifically healthy user bias[1-4]. This is a selection/sampling bias that stems from the fact that patients who either seek out or are prescribed preventive therapies are often inherently different than their non-healthy counterparts. Healthy users follow healthy behaviors (diet, exercise, cancer screening, vaccinations, etc.), adhere to their medications and preventive therapies, have higher functional status, and may be prescribed medications and therapies differently than their non-healthy counterparts[2]. The combination of these factors makes it very difficult to isolate the effect of the preventive medication or therapy under examination in observational studies using current techniques, often because the required data is simply not available in most datasets.

Observational studies of influenza vaccine effectiveness are prone to healthy user bias, which is sometimes referred to as "healthy vaccinee" bias in this setting[5-7]. Most people are recommended to receive the annual influenza vaccine in order to reduce their risk of complications from influenza and hospitalization[8,9]. However, much of the evidence behind influenza vaccine effectiveness has been based on observational studies[10-13], and recent literature has brought to question the actual effect of the vaccine, due to concerns of healthy user bias[6]. It has been shown

in many cases that patients who receive the influenza vaccine are less frail and overall healthier than their non-vaccinated counterparts[14,15].

Although studies have been able to identify the bias in some cases[6,7], control for the bias within the analyses has been difficult. It is clear that better methods to control for confounding in these observational studies are needed, which may include using proxy measures (e.g., hormone therapy use has been studied as a marker of healthy users[16]) or predictive scores[1]. Predictive scores are particularly appealing as they combine a large amount of data into an overall score or index which can be used for adjustments in models. In clinical practice, prediction scores are used frequently, such as the Framingham score to predict cardiovascular disease[17] and the Pneumonia Severity Index to predict prognosis of patients with pneumonia[18,19]. In health research, one of the most well-known examples is the Charlson comorbidity index, which is a prediction score for mortality often used for statistical adjustment in observational studies[20].

We hypothesized that the healthy user bias can be captured, at least partially, in a prediction score, which can then be used to lessen the impact of confounding within observational studies of preventive therapies. Therefore, the objective of this study was to develop a healthy user index using influenza vaccination receipt as a 'prototypical' example of a healthy user, and to internally validate it in our population of adult patients with type 2 diabetes.

3.2 METHODS

Data Sources

We analyzed data from a large US claims and integrated laboratory database (Clinformatics Data Mart™, OptumInsight Life Sciences Inc.) which has been used in numerous previous observational studies. This database includes de-identified longitudinal data on patients, such as administrative and demographic information, medical service claims, laboratory data and pharmacy claims data. Clinical diagnoses are recorded as ICD-9-CM (International Classification of Diseases- 9th Revision- Clinical Modification) codes and procedure codes are recorded as ICD-9 and CPT-4 (Current Procedural Terminology- 4) codes. More than 13 million annual lives are included in the database, and information is updated every 90 days.

Study Population

We developed our healthy user index in adults (aged 18 years and older) with type 2 diabetes who were part of the database between January 1, 2003 and Dec 31, 2011. Diabetes patients were chosen as influenza vaccination is universally recommended for this population[21,22]. Moreover, the current evidence base for influenza vaccination is patients with diabetes is based almost solely on observational research, and a recent systematic review has noted that the quality of the studies is low or very low due to major concerns of confounding due to the healthy user[23].

As influenza vaccination occurs on an annual cycle, we divided calendar time into years from July 1st to June 30th, as others have done[6,24]. Then, using US national surveillance data[25], we defined our influenza season as a continuous period with the first to last occurrence of 50 positive isolates per week[26]. One exception was in the year 2009, with the H1N1 outbreak, where the flu season did not terminate according to our above definition. In this scenario we truncated

the flu season on June 30th, 2009 (which is the end of our calendar year) and started the next flu season on July 1st, 2009.

Identification of Healthy Users

Influenza vaccination has been previously shown in the literature to be a strong marker of healthy users[1,3]; therefore, we used influenza vaccine receipt as our proxy for the healthy user, as no gold criterion exists in the literature. Within each influenza year, receipt of the influenza vaccine was identified. Influenza vaccine receipt was determined based on Current Procedural Terminology/ Healthcare Common Procedure Coding System (CPT/HCPC) codes (4037F, 4274F, 90470, 90655-90664, 90666-90670, 90724, 90737, 9952, G0008, G8108, G8423, G9141, G9142, Q0034)[27]. In addition, as pharmacists can dispense and administer influenza vaccinations, pharmacy codes for 'influenza virus vaccines' was also used to identify recipients of influenza vaccination.

Healthy User Predictor Variables

Predictors included variables that are readily available in many observational databases and that have been postulated to be associated with the healthy user[2,3] (Appendix 1). Specifically, variables included those identified within the US Medicare preventive services codes[27]: a) cancer screening (including Pap test, pelvic exam, mammography, colorectal screening and prostate screening), b) cardiovascular disease screening, c) osteoporosis screening and d) other screening (including initial preventive physical examination (IPPE), abdominal aortic aneurysm (AAA) screening, glaucoma screening and HIV screening), and e) medical nutrition therapy, which must be provided by a registered dietician or nutritional professional. In addition, medication

adherence (≥80% was considered "adherent" as per convention[28-30]) was included and assessed by the medication possession ratios (MPR). Other medications that have been shown or postulated to be related to the healthy user, including hormone replacement therapy[31], smoking cessation therapy, obesity medications, statins[3,4] and bone resorption inhibitors[32], were also considered.

Statistical Analysis

To develop our healthy user index, we first randomly divided our sample into 2 approximately equal sized cohorts: a derivation cohort and a validation cohort. The derivation cohort was used to develop the healthy user index. The healthy user index was then internally validated within the validation cohort. Although different methods exist for internally validating prediction scores (e.g., split-sample, cross-validation, bootstrapping), we chose to follow the simplest form, the split-sample, because with large sample sizes (as ours is) the methods provide similar results[33].

To develop the healthy user index, a logistic regression model was used to predict yearly influenza vaccine receipt based on age, sex, and our healthy user predictor variables. Within each influenza season, patients were identified as having received or not received the influenza vaccine. If a patient received the influenza vaccine that year, their index date was the day of vaccination. If a patient did not receive the influenza vaccine that year, their index date was the last day of the influenza season as others have done[6]. Then all potential predictor variables were identified for each patient any time prior to their assigned index date for each season. Thus, all predictors and receipt of the influenza vaccine were updated on a yearly basis within the cohort.

We first built a parsimonious model using multivariable mixed effects logistic regression in the derivation cohort. Logistic regression was chosen because our outcome was binary (influenza vaccination, yes or no) and a mixed-effects model was used as our data were clustered (patients could contribute data for each year they were in the database). To facilitate analyses, certain variables were collapsed together if they measured the same underlying constructs (e.g., bone mineral density screening and bone resorption inhibitor medications). Age and sex were forced into the models and healthy user predictor variables with a $p<0.10$ in univariate analyses were entered into our multivariate model to determine their independent associations with influenza vaccine receipt. Then, we further excluded healthy user predictor variables from the multivariate model with a $p>0.05$ (in sensitivity analyses we included all variables irrespective of p-values). The overall model performance was assessed using a scaled brier score (which incorporates the incidence of the outcome in the population)[34], and model discrimination was assessed with the c-statistic.

Second, a points-based system was then used to construct the index score, which has been extensively described previously[35,36]. These methods are similar to what has been completed in developing the Framingham risk score and mortality risk scores[35,36]. For each predictor retained in the final multivariate model, the estimated regression coefficient was divided by the estimated regression coefficient for age and then rounded to a single integer. Similar to the Framingham risk score and the mortality risk score, we chose age as our constant, which is the variable that determines the number of regression units per point in the scoring system[35,36]. The healthy user index for an individual was then constructed by summing the following: age-18 years (as our

data contained only patients 18 years of age and older), the component for the patient's sex, and the component for each of the predictor variables retained in the final model.

To assess the performance of the healthy user index, we calculated the healthy user index in our validation cohort based on the values obtained for each predictor variable identified in the derivation cohort. We then completed a univariate mixed effects logistic regression model with our healthy user index as the independent variable and receipt of influenza vaccination as the dependent variable. Overall model performance was assessed using a scaled brier score and model discrimination was assessed with the c-statistic. Statistical analysis was conducted with Stata version 12.1 (StataCorp LP, College Station, TX).

Sensitivity Analyses

To assess whether the healthy user index could be improved, we conducted several sensitivity analyses. First, a number of variables that have been mentioned in the literature as being associated with the healthy user were not included in our final model, such as dementia and having lab work (albumin, cholesterol, triglycerides, HDL, LDL, A1C, hemoglobin and creatinine) completed[14]. Thus we repeated our healthy user index development and forced these variables into the final multivariate model and reevaluated our score. Second, as our index score was developed by dividing each regression coefficient by a constant regression coefficient (age), we also developed a point-scoring system that assigned weights to the predictor variables, which did not account for age or sex. A weight was determined for each predictor variable by multiplying each regression coefficient by 10 and rounding to the nearest integer. A score was then computed by multiplying each predictor variable (1=present; 0=absent) by its estimated

weight and summing. This approach is similar to the Charlson Score and the ADG score[20,36]. Last, we changed our 'marker' of the prototypical healthy user from receipt of influenza vaccination to receipt of statin therapies, as statin therapy has also been shown to be a marker of healthy users[4], and repeated the analysis.

3.3 RESULTS

Our study population consisted of 1 827 963 patients aged 18 to 88 years. Mean age of the population was 52.7 years (standard deviation (SD) 10.4) and 47.4% were female. Average length of follow-up was 5.5 years (SD 2.0 years). Average prevalence of influenza vaccination was 12.7%, with year over year receipt of vaccination ranging from 6.1% to 20.6% of patients. As expected, vaccination rates were highest in those >=65 years of age (range 16.8% to 21.4% year over year) and lowest in those <40 years of age (2.5% to 12.0% year over year). Our study sample was randomly divided into two approximately equal groups: a derivation cohort (n=914 732) and a validation cohort (n=913 231). As would be expected with a random split, characteristics between the two groups were similar (Table 3-1).

With respect to healthy user predictors, in the derivation cohort, the utilization of statins (39.7%) and cardiovascular screening (27.4%) were the most common, which is not unexpected given the underlying diagnosis of diabetes. Other predictors of the healthy user were less frequent, with hormone replacement therapy (6.1%) and cancer screening (3.8%) being the next most common. Overall, 37.7% of patients in the derivation cohort had a MPR ≥80% during the follow-up (Table 3-1).

The scoring of the healthy user index is presented in Table 3-2. In the derivation cohort, the mean healthy user index was 41.6 (SD 12.9), and the median score was 43 (interquartile range 33 to 51 and scores ranged from a minimum of 0 to a maximum of 91). The distribution of the healthy user index is shown in Figure 3-1. Points for each component of the healthy user index ranged from a low of 2 (female sex and average MPR ≥80%), to a high of 22 (other screening) indicating that for a given age, female sex and average MPR ≥80% were weakly associated with healthy users while other screening was highly associated with healthy users, as defined by receipt of influenza vaccination. All predictor variables were associated with positive scores as hypothesized. Overall model fit in the derivation cohort was moderate to good with a c-statistic of 0.611 and a scaled brier score of 0.110. The estimated regression model was logit(P) = -5.51 + 0.062X; where P represents the probability of receiving the influenza vaccine during the particular flu season and X denotes the patient specific healthy user index score.

When the healthy user index was scored in the validation cohort, the mean healthy user index was 41.6 (SD 12.9), and the median score was 43 (interquartile range 33 to 51, and scores ranged from a minimum of 0 to a maximum of 96). The distribution of the healthy user index was very similar to that observed in the derivation cohort. When the healthy user index was regressed on receipt of influenza vaccination in the validation cohort, the c-statistic was 0.605 and the scaled brier score was 0.111, suggesting moderate to good model fit, similar to that observed in the derivation cohort.

Sensitivity Analyses

First, inclusion of variables that have been associated with the healthy user in the literature but not included in our main model (e.g., dementia and having any routine lab work completed[14]) had minimal impact on our result. In the derivation cohort, dementia did not independently predict receiving influenza vaccination and was assigned a point of 1 (c-statistic 0.611 and scaled brier score 0.110) and lab work was assigned a point of 8 (c-statistic 0.613 and scaled brier score 0.114). When tested in the validation cohort, the model with dementia had a c-statistic of 0.604 and a scaled brier of 0.110, and the model with lab work had a c-statistic of 0.607 and a scaled brier of 0.107; suggesting minimal influence on the performance or discrimination ability of the healthy user index.

Second, using a point-scoring system that assigned weights to the predictor variables that did not account for age or sex performed similarly. The weighted healthy user index is presented in Table 3-3. In the derivation cohort, the average weighted score was 3.6 (SD 3.3) with a median score of 3 (interquartile range 0 to 6, and scores ranged from a minimum of 0 to a maximum of 25). Points for the weighted score ranged from a low of 1 (obesity medications), to a high of 9 (other screening). Overall model fit in the derivation cohort was moderate to good with a c-statistic of 0.609 and a scaled brier score of 0.104. When this model was applied to the validation cohort, the c-statistic was 0.608 and scaled brier score was 0.113, suggesting similar performance relative to our main model.

Lastly, we altered the logistic regression model with statin therapy as the dependent variable, and influenza vaccination added as a healthy user predictor variable (Table 3-4). In the derivation cohort, the average score was 45.8 (SD 14.1) with a median score of 46 (interquartile range 37 to

56 and scores ranged from a minimum of 0 to a maximum of 102). Points ranged from a low of 1 (cancer screening, medical nutrition therapy and obesity medications), to a high of 11 (male sex, cardiovascular disease screening). Overall model fit in the derivation cohort was moderate to good with a c-statistic of 0.642 and a scaled brier score of 0.035. When this model was applied to the validation cohort the c-statistic was 0.666 and the scaled brier score was 0.058.

3.4 DISCUSSION

Healthy user bias appears in many observational studies of preventive therapies[1-4], including influenza vaccination[6]. We built the healthy user index as a point-scoring prediction summary to assist in the control of healthy user bias in studies evaluating preventive medicines and therapies. The healthy user index combines age, sex and a number of healthy behaviors hypothesized to be associated with healthy users into one summary score. Overall, the healthy user index score was shown to have moderate to good performance and discriminating ability with respect to utilization of influenza vaccination, which we used as a prototypical marker of the healthy user. We anticipate this score could be used as a method of confounding adjustment in future observational studies of preventive therapies.

Although we have developed a summary score for controlling of healthy user bias in observational studies of preventive therapies, other approaches have also been suggested. One option is simply to adjust for the predictor variables we have identified separately. This may not be possible in all applications, as observations or outcomes may be low, which precludes the addition of a large number of variables into models. A second option is to adjust for a single variable that serves as a proxy for the healthy user, for example, use of vaccines, mammography

or colonoscopy[1]. This approach may be too simple, as a single variable may only partially cover the many factors that are associated with healthy users. Lastly, another option is to build a propensity score around a proxy variable believed to represent healthy users. This was done by a group of researchers who built a propensity score around hormone therapy use[31]. A limitation behind this is that the propensity to use hormone therapy may not completely represent the propensity to be a healthy user. As well, using hormone therapy limits the application of this model to only female subjects. Alternatively, our approach to build a healthy user index score, overcomes many of these issues. First of all, by incorporating a large number of variables into a single summary score, we are not limited by low numbers of observations/events. Using one score for adjustments will preserve degrees of freedom in regression models, as others have previously proposed for the ADG mortality risk score[36], and also the Charlson comorbidity index[20,37].

From a research perspective, beyond adjustment for healthy user bias, our healthy user index could be beneficial in characterizing a population, as it provides an overall summary of the patients' health behavior attributes and is not reliant on a single 'marker' of the healthy user. Moreover, the healthy user index could also be used to evaluate the consistency of medication/therapy effects in those with low healthy user index scores (i.e., in those with lower probability of being a healthy user) and in those with high healthy user scores (i.e., those with higher probability of being a healthy user) to assist in the identification of healthy use bias within preventive medication/therapy studies. Thus, even if the healthy user index score is not able to fully control for the bias, evaluation of the consistency of study effects among potential

subgroups of the index would provide value by helping to identify if healthy user bias may be at play in the results observed in a study of preventive medications/therapies.

A strength of this study was the large population and the wealth of information available in the database, including administrative and demographic information, medical service claims, laboratory data and pharmacy claims data. Our study was not without limitations. First, the population we studied was limited to adult patients with type 2 diabetes. The healthy user index will need to be externally validated in the future, including populations with other comorbidities. Moreover, future studies will also need to be completed within administrative databases to evaluate the benefits of the index in controlling for healthy user bias in observational studies. Second, in the index we grouped a number of variables together (i.e., cancer screening was a composite of Pap test, pelvic exam, mammography, colorectal screen and prostate screen; we grouped bone mineral density screening with filling a prescription for a bone-resorption inhibitor medication). This may not be appropriate when applying the score to different populations. Third, we used receipt of influenza vaccination as our prototypical marker of the healthy user. Although a significant amount of literature points to influenza vaccination as a marker of healthy users, this may not be the case. We may have misclassified individuals in the study, although no gold standard to identify healthy users in administrative data exists, and we did do sensitivity analyses with statin use as a marker of healthy users with similar results. Fourth, our index was based on variables typically available within administrative databases. Other databases may have access to other variables that could be incorporated into the index (e.g., smoking status, exercise behaviors, etc.). Furthermore, the healthy predictive variables we used were based on typical

administrative coding and may not be fully validated; although the majority of the codes were based on the Medicare recommended preventive services codes[27].

In conclusion, we developed a summary score that combines age, sex and healthy behaviors to predict healthy users within administrative datasets. Our summary score performed well when internally validated, and in the future it will require refinement and external validation. This index score may allow researchers to better identify and adjust for healthy user bias in health services research.

Table 3-1. Characteristics

Characteristics	Overall n= 1 827 963	Derivation Cohort n= 914 732	Validation Cohort n= 913 231
Mean age (SD), y	52.69 (10.37)	52.70 (10.37)	52.68 (10.37)
Female (%)	866 653 (47.41)	432 515 (47.28)	434 138 (47.54)
Vaccination			
Influenza Vaccination (%)	232 869 (12.74)	117 188 (12.81)	115 681 (12.67)
Screening			
Any Cancer Screening* (%)	69 378 (3.80)	34 608 (3.78)	34 770 (3.81)
Cardiovascular Disease Screening	500 919 (27.40)	250 854 (27.42)	250 065 (27.38)
Other Screening**	252 (0.01)	216 (0.02)	36 (<0.01)
Nutrition			
Medical Nutrition Therapy	2 097 (0.11)	1 036 (0.11)	1 061 (0.12)
Medications			
Average MPR>=80% (%)	688 768 (37.68)	344 550 (37.67)	344 218 (37.69)
Hormone replace therapy (%)	111 183 (6.08)	55 143 (6.03)	56 040 (6.14)
Smoking cessation therapy (%)	63 028 (3.45)	31 419 (3.43)	31 609 (3.46)
Obesity medications (%)	4 678 (0.26)	2 340 (0.26)	2 338 (0.26)
Statins (%)	725 051 (39.66)	362 649 (39.65)	362 402 (39.68)
Screening/Medication			
Osteoporosis screening and/or Bone resorption inhibitors (%)	53 220 (2.91)	26 469 (2.89)	26 751 (2.93)

*Pap test, pelvic exam, mammography, colorectal screen, prostate screen

**IPPE, AAA screen, glaucoma screen, HIV screen

Table 3-2: The Healthy User Index: Point-scoring system

Predictor Variable	Score
Age (for each year above 18 years old)	1
Female Sex	2
Any Cancer Screening*	4
Cardiovascular Disease Screening	6
Other Screening**	22
Medical Nutrition Therapy	8
Average MPR >=80%	2
Hormone Replacement Therapy Prescription	4
Smoking Cessation Therapy Prescription	6
Obesity Medication Prescription	4
Statin Prescription	7
Osteoporosis Screening and/or Bone Resorption Inhibitor Prescription	6

*Pap test, pelvic exam, mammography, colorectal screen, prostate screen

**IPPE, AAA screen, glaucoma screen, HIV screen

Table 3-3: The Weighted Healthy User Index

Predictor Variable	Score
Any Cancer Screening*	2
Cardiovascular Disease Screening	3
Other Screening**	9
Medical Nutrition Therapy	4
Average MPR >=80%	2
Hormone Replacement Therapy Prescription	2
Smoking Cessation Therapy Prescription	3
Obesity Medication Prescription	1
Statin Prescription	4
Osteoporosis Screening and/or Bone Resorption Inhibitor Prescription	5

*Pap test, pelvic exam, mammography, colorectal screen, prostate screen

**IPPE, AAA screen, glaucoma screen, HIV screen

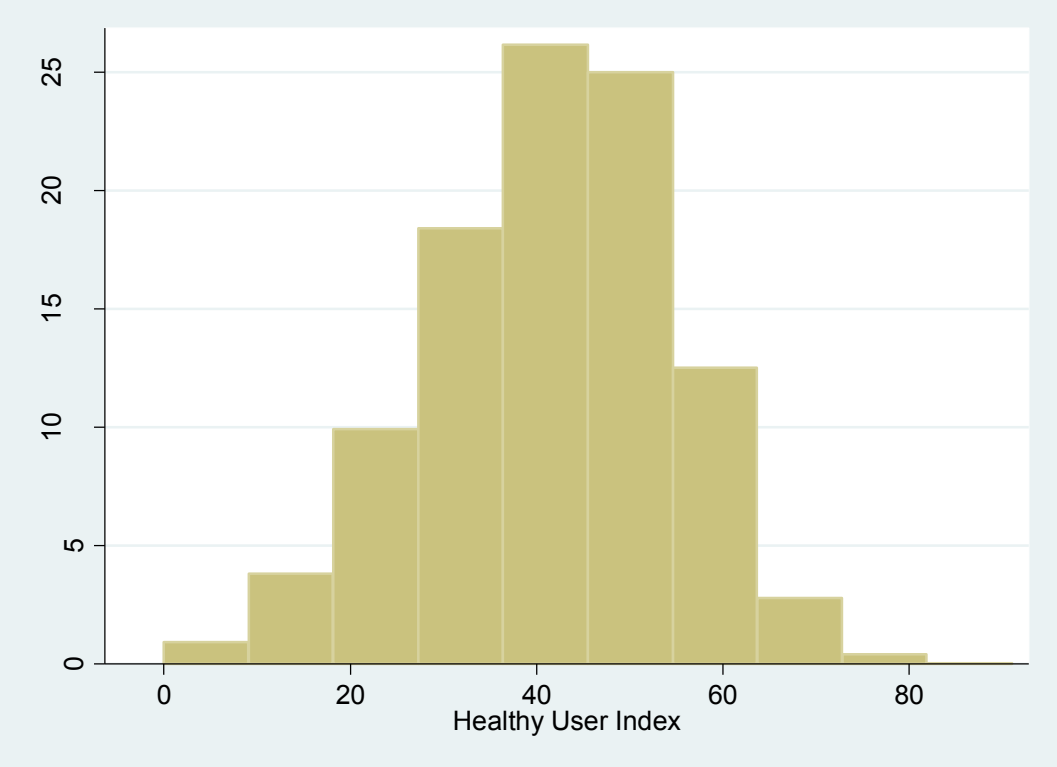
Table 3-4: The Statin Healthy User Index: Point-scoring system

Predictor Variable	Score
Age (for each year above 18 years old)	1
Male Sex	11
Any Cancer Screening*	1
Cardiovascular Disease Screening	11
Other Screening**	6
Medical Nutrition Therapy	1
Average MPR >=80%	4
Hormone Replacement Therapy Prescription	4
Smoking Cessation Therapy Prescription	8
Obesity Medication Prescription	1
Osteoporosis Screening and/or Bone Resorption Inhibitor Prescription	9

*Pap test, pelvic exam, mammography, colorectal screen, prostate screen

**IPPE, AAA screen, glaucoma screen, HIV screen

Figure 3-1: Distribution of the Healthy User Index in the derivation cohort



Appendix 3-1: Codes

Any Cancer Screening

- Pap Test

ICD9= 'V762', 'V7647', 'V7649', 'V1589', 'V7231'
proc_cd= 'G0123' ,'G0124', 'G0141', 'G0143', 'G0144', 'G0145', G0147', 'G0148', 'P3000', 'P3001', 'Q0091'

- Pelvic Exam

ICD9= 'V762', 'V7647', 'V7649', 'V1589', 'V7231'
proc_cd= 'G0101'

- Mammography

ICD9= 'V7611', 'V7612'
proc_cd= '77052', '77057', 'G0202'

- Colorectal Screen

proc_cd= 'G0104', 'G0105', 'G0106', 'G0120', 'G0121', 'G0122', 'G0328', '82270'

- Prostate Screen

ICD9= 'V7644'
proc_cd= 'G0102', 'G0103'

Cardiovascular Screening
ICD9= 'V810', 'V811', 'V812'
proc_cd= '80061', '82465', '83718', '84478'

Other Screening

- Initial Preventive Physical Examination (IPPE)

proc_cd= 'G0402', 'G0403', 'G0404', 'G0405'

- Ultrasound Screening for Abdominal Aortic Aneurysm (AAA Screen)

proc_cd= 'G0389'

- Glaucoma Screen

ICD9= 'V801'
proc_cd= 'G0117', 'G0118'

- HIV Screen

ICD9= 'V7389', 'V220', 'V221', 'V698', 'V239'
proc_cd= 'G0432', 'G0433', 'G0435'

Medical Nutrition Therapy
proc_cd= '97802', '97803', '97804', 'G0270', 'G0271'

Hormone Replacement Therapy Prescription
AHFS= 68:16.04 (Estrogens), 68:16.12 (Estrogen Agonist-Antagonists), 68:32 (Progestins)

Smoking Cessation Therapy Prescription
AHFS= 12:92 (nicotine replacement therapy, varenicline), 28:16.04.92 (bupropion)

Obesity Mediation Prescription
56:92 (orlistat)

Statin Prescription

AHFS='240608' or '24060800'

Osteoporosis Screening and/or Bone Resorption Inhibitor Prescription

- Osteoporosis Screen

  proc_cd= '76977', '77078', '77079', '77080', '77081', '77083', 'G0130'

- Bone Resorption Inhibitor Prescription

  AHFS= 92:24 (alendronate, denosumab, etidronate, gallium nitrate, ibandronate, pamidronate, risedronate, zoledronic acid)

Dementia

EDC= edcNUR11

Labs Completed

If any of the following were completed in the last year:
Albumin, cholesterol, triglycerides, HDL, LDL, A1C, hemoglobin, creatinine

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CHAPTER 4: SUMMARY

4.1 SUMMARY OF RESEARCH

Observational studies of preventive medications or therapies are prone to healthy user bias[1]. The concept of the healthy user incorporates a large number of intertwined characteristics and behaviors, such as medication adherence and high functional status, which can be hard to identify and control for [2,3]. Strategies suggested for addressing healthy user bias in observational studies include controlling for variables that capture the healthy user (e.g., functional status, health behaviors), using a proxy variable as a marker of the healthy user (e.g., vaccination or mammography) or using propensity scores[1]. However, the ability of these methods to completely control for healthy user bias is not fully known.

Observational studies on influenza vaccination are inherently prone to the healthy user bias. Indeed, one of the key attributes of healthy users which has been repeatedly shown in the literature is whether or not the patient has received the influenza vaccine[2,4]. Individuals who seek out the annual influenza vaccine are likely very different than their counterparts who do not get vaccinated. In the literature, well-known predictors of influenza vaccination include age, sex, marital status and respiratory disease[5-7]. Other studies have suggested that higher functional status as well as contact with the healthcare system (e.g., a recent physician visit) also predict influenza vaccination[5,6,8-10].

In our research we aimed to gather further information on a wider range of predictors of influenza vaccination to assist in identifying attributes related to healthy users. Previous literature has often been limited in identifying predictors, as the data that is accessible (e.g., administrative databases) often do not fully capture the behaviors hypothesized to be associated with the healthy user. Moreover, few studies have collected all information simultaneously on patients to evaluate the true independent effects of the behaviors and characteristics. To circumvent these limitations, we used survey data from an ongoing prospective cohort of patients with type 2 diabetes that included information on health status, self-care management, health behaviors, clinical monitoring and satisfaction with healthcare[11,12]. Our first research project (Chapter 2) involved using logistic regression to identify predictors of influenza vaccination in this cohort. In our multivariable analysis, attributes independently associated with influenza vaccination included receiving preventive medications: aspirin, blood pressure medications, and cholesterol-lowering medications, as well as having a healthcare professional check feet for lesions. Additional covariates independently associated with influenza vaccination included: age over 65 years, respiratory disease, the number of additional comorbidities, and higher ratings of healthcare experience. We had originally hypothesized that functional status and self-care would also be highly predictive of influenza vaccination; however, they did not prove to be so, which may be due to the fact that the population studied was overall relatively highly functional and undertook regular self-care activities. Thus, there may have been insufficient variation in our data to detect differences in these characteristics as they related to influenza vaccination.

Many of the predictors (e.g., utilization of preventive medications such as aspirin) are likely multifactorial in how they relate to influenza vaccination. Not only are they a healthy behavior

(seeking and being adherent to a preventive medication), but they are also a sign of contact with the healthcare system (a physician or other healthcare provider likely recommended this therapy to them). The role of the physician and the healthcare system in determining whether or not patients get vaccinated is another dimension of the healthy user effect which has not received as much attention as individual patient attributes. As shown in systematic reviews, the organization of care by patients' physicians or other healthcare providers influences who does and does not get the influenza vaccine[13]. It is highly likely this concept also expands to other preventive medications/therapies as well. However, observational studies trying to capture/adjust for healthy user bias have generally not assessed these organizational variables in analyses, likely owing to the fact that this information is rarely, if ever, captured.

The characteristics and behaviors captured and included in our analyses were predictive of receipt of the influenza vaccination. Indeed, our multivariate model had very good discriminating power, with a c-statistic > 0.7. We feel that collectively the variables in our model represent the complex, interrelating factors that influence the decision to get vaccinated. Some variables were not statistically significant in the final model (e.g., functional status), but we believe that these variables still have a role in identifying the healthy vaccinee effect (and thus, the healthy user), and it may be important to adjust for them in models to reduce healthy user bias. If each variable explains even a small percentage of the bias related to healthy users, as a whole, these variables may collectively explain a significant proportion of the healthy user bias and may sway the statistical or clinical importance of a study's findings.

Overall we feel that our research project demonstrates the complexity of the factors associated with vaccination. From a clinical perspective, influenza vaccination may serve as a marker of care in people with chronic disease such as diabetes. From a research perspective, influenza vaccination may serve as a reasonable surrogate for some, but not all, difficult-to-capture data related to healthy users. Clearly, our study confirms the need for future observational studies of influenza vaccine effectiveness to control for healthy user bias to ensure accurate estimate of effectiveness of the vaccine.

Given that our study, along with previous research in the area, suggest that influenza vaccination may be a reasonable surrogate for characteristics related to the healthy user, we hypothesized that this information could be used to develop a prediction score to help control for healthy user bias in observational studies. Thus, our second research project (Chapter 3) involved building a healthy user prediction score for receipt of influenza vaccination in a large administrative cohort of patients with type 2 diabetes. Our goal was to summarize many of the behaviors and characteristics associated with receipt of the influenza vaccine into one summary score. The ultimate goal of this score would be to incorporate it into analyses of preventive medications/therapies as a proxy measure to predict and adjust for healthy user bias. The use of a summary score would be especially beneficial in studies with a low number of observations and/or outcomes, as it will preserve degrees of freedom in regression models[14].

To facilitate the development of the score, we randomly split our dataset into two cohorts, a derivation cohort to build our model and a validation cohort to test its performance. Predictors of influenza vaccination in our model included attributes which have been previously shown to be

associated with healthy users including: cancer screening (Pap test, pelvic exam, mammography, colorectal screening and prostate screening), cardiovascular disease screening, osteoporosis screening, other screening (initial preventive physical examination (IPPE), abdominal aortic aneurysm (AAA) screening, glaucoma screening and HIV screening), medical nutrition therapy, medication adherence ≥80%, and other medications that have been shown or postulated to be related to the healthy user (hormone replacement therapy[15], smoking cessation therapy, obesity medications, statins[2,16], and bone resorption inhibitors[17]).

In building our index, we used a points-based system which has been described previously with the Framingham risk score and mortality risk scores[14,18]. For each predictor in our multivariable model, the estimated regression coefficient was divided by the estimated regression coefficient for age and then rounded to a single integer. The healthy user index for an individual was then constructed by summing the following: age-18 years, the component for the patient's sex, and the component for each of the predictor variables. When tested in the validation cohort, the healthy user index significantly predicted influenza vaccination with a c-statistic of 0.605 and a scaled brier of 0.111, suggesting moderate to good discrimination and performance ability. Sensitivity analyses were done, including utilizing different combinations of healthy user variables, and using a second "weighted" point-scoring system, and these performed similarly. Variables that we did not have access to include physician- and system-level variables, and therefore, these factors are not captured in the score. These factors likely play a role in the complex, multidimensional healthy user bias, and therefore, this is a limitation of our score. In the future, a score such as ours will need to be externally validated and tested for its ability to control for healthy user bias in observational studies.

4.2 IMPLICATIONS FOR FUTURE RESEARCH

The healthy user bias needs to continue to be researched in order for observational studies of preventive medications/therapies to provide realistic estimates of effect. This is a complex bias as it incorporates multiple intertwined characteristics and behaviors of the patient, the healthcare provider, and the system. In our first study we developed a model with high discriminating ability to predict who does and does not receive the influenza vaccine. Although our model included information on a wide range of variables, it did not provide perfect discrimination, highlighting the complexity in the decisions behind vaccination. One aspect we believe requires special attention is the role of the patient's physician, allied health professionals, and the healthcare system factors in determining whether or not the patient gets vaccinated. If we are able to capture these variables and include them in our models, this will likely improve the discrimination ability.

Our influenza vaccination prediction score was developed and internally validated in a population of patients with type 2 diabetes. In the future, this prediction score will need to be externally validated in groups of patients with other comorbidities. Variables in the score may need to be refined. For example, we may want to include variables such as body mass index, markers of physical activity, and other measures of mental health. In our prediction score we collapsed a number of variables together (e.g., we grouped bone mineral density and filling a prescription for bone-resorption inhibitor medications together). Depending on the population, this may not be ideal. Additionally, a score similar to ours will need to be tested in a setting of known healthy user bias to ensure the score indeed removes healthy user bias in estimates. If

addition of the score to the model is able to reverse a previously biased relationship, this will help to verify and validate the usefulness of the score in observational studies. The healthy user bias needs to be addressed in all observational studies of preventive medications/therapies. We believe that a prediction score, similar to the one we developed, is something that should be rigorously evaluated and if proven to be valid, should be included in all future observational studies of preventive medications/therapies.

4.3 IMPLICATIONS FOR FUTURE POLICY

Patients with diabetes are a targeted group for influenza vaccination, yet our research shows that there are still a large portion of this population who do not receive the vaccine. For future campaigns, public health messages should highlight the importance of vaccination in certain groups of patients, including patients with diabetes. The organization of care around vaccine campaigns is important for reaching the most critical groups of patients, and it is suggested that having one team member (e.g., a nurse or pharmacist) responsible for vaccinations can increase rates[13,19]. As well, influenza vaccination may serve as an overall marker of quality care in patients with diabetes. In patients who are not vaccinated, this may be a flag to health professionals that other aspects of their diabetes care may also be in need of attention.

Most of the evidence behind the influenza vaccine does come from observational data, and as our second research project highlighted, this type of data is often biased from the healthy user effect. Until better techniques are developed to control/adjust for this bias, observational studies of preventive therapies should be thought as hypothesis-generating, and should be confirmed by definite randomized controlled trials if possible, before changing clinical practice guidelines and

policy. It appears that simple regression techniques are not sufficient to adjust for this bias. Whether the solution is the development of a healthy user score as we proposed, or the use of propensity scores, or other more complex statistical modeling (e.g., instrumental variable approach), minimizing the bias from healthy users in observational studies should be a major focus for the research community moving forward.

Lastly, although better techniques to improve estimates from observational studies of vaccine effectiveness are important, the development of high-level statistical methods to account for imperfect study designs should be viewed as a second-tiered solution to the problem. Given the extensive resources that are put into the influenza vaccination campaigns around the world, patients and key players at all levels of research, clinical care, and governments should push for large-scale randomized controlled trials to fully evaluate the true impact of influenza vaccination on health outcomes and to better inform policy. Indeed, a recent systematic review of the use of influenza vaccination highlighted this enormous evidence gap. Although universal vaccination is recommended for diabetes patients, not a single RCT on important health outcomes (e.g., hospitalizations, mortality) was identified in patients with diabetes to inform this policy. Moreover, of the 11 observational studies that have been completed and form the evidence base for the policy in diabetes, all were deemed of low to very low quality due to significant concerns of confounding due to healthy user bias[20]. Thus, despite our best intentions, many of our policies around influenza vaccination are imperfect due to a reliance on imperfect evidence. Although advances in observational research to better control for healthy user bias are important, ideally our policies should be based on best evidence which can be generated from large-scale clinical trials of influenza vaccination.

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