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Diabetes Mellitus in California: Complications, Modifiers and Spatial Determinants

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By

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Abstract

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Diabetes mellitus (DM) is a metabolic disease whose prevalence has steadily risen in the United States and globally over the last three decades. In addition to its direct effects on hyperglycemia, DM has a variety of associated complications, ranging from an increased risk of cardiovascular disease to an increased risk for multiple infectious diseases. Because of these complications, DM remains a major source of disease burden in the United States and globally. Even as the prevalence of DM has risen, so too have awareness of the disease and the armamentarium of medications available for its treatment. These changes in both awareness and the ability to treat the disease have ostensibly had an impact. Rates of some of the most important complications of DM, including cerebrovascular accident (CVA) and myocardial infarction (MI) have declined in the United States while at the same time, the prevalence of DM has leveled off.

In this dissertation, I focus on three separate, but linked issues about DM. All of the work I present here was done either at the state level in California or at the level of the city of San Francisco. In chapter 1, I examine whether the decreases that have been observed for non-infectious complications of DM are also true for its infectious complications in California overall. In chapter 2, in a cohort of patients in San Francisco, I examine the potential role of medications that are frequently used to treat other conditions in persons with DM in driving the increased risk of infection in persons with DM as well as the findings I describe in chapter 1. Finally, in chapter 3, working with the same cohort studied in chapter 2, I examine the role of distance to the primary care clinic, a potentially modifiable factor, in determining diabetes control.

In chapter 1 of this dissertation, I show that in California, rates of hospitalization for infectious diseases among persons with DM have steadily increased. This result contrasts both with what has been reported for non-infectious disease complications of DM nationally as well as with my own findings for two important non-infectious disease complications of DM, CVA and MI. My results suggest that other factors beyond the level of control of DM could drive the risk of infection among persons with DM. In

chapter 2, I show that while one such potential factor, collateral effects of medications used to treat other conditions (e.g. hyperlipidemia,hypertension) in persons with DM, does not appear to drive the increase risk of infection in persons with DM, two medication classes, angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) could actually reduce the risk of developing in infection. Finally, in chapter 3, I show that minimizing the distance between patients and their primary care clinics has the potential to result in a significant improvement in control of DM, as measured by the glycated hemoglobin level. Together, the three chapters of this dissertation provide a comprehensive view of DM in California as a whole and in San Francisco in particular. My findings shed new light on one of DM's most important complications, infectious diseases, while at the same suggesting two potential methods to limit the development of these and potentially other DM-related complications.

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BACKGROUND

The burden of diabetes mellitus

Diabetes Mellitus (DM) is a metabolic disease whose global prevalence has steadily risen over the last three decades. The most recent Global Burden of Diseases Survey, ranked it as the eighth highest cause of both Years of Life Lost (YLL) and Years Lived with Disability (YLD) [1]. In the most recent United States Burden of Diseases survey, DM was ranked as the seventh highest cause of YLL and the eighth highest cause of YLD [2]. It is important to note, however, that because of DM's ability to affect multiple organ systems, examining DM burden alone may underestimate its actual impact on morbidity.

Pathophysiology of DM

DM has classically been divided into two forms: type I (juvenile) and type II (adult-onset). The pathophysiologies of type I and type II DM are distinct. Type I DM is thought to be an autoimmune disease, with destruction of the islet cells of the pancreas resulting in the loss of glucose homeostasis [3]. Prior viral infection, particularly by enteroviruses, is thought to be a potential trigger for the autoimmune destruction of the islet cells [4]. The pathophysiology of type II DM is different than that of type I DM, with insulin resistance occurring in the setting of obesity recognized as the primary underlying disease mechanism. It is now known that this insulin resistance is caused by obesity-induced activation of the NLRP3 inflammasome, making type II DM a disease of inflammation [5-12].

Diagnosis and management of DM

The primary clinical manifestation of DM is dysglycemia, which remains the cornerstone of diagnosis. In the past, fasting hyperglycemia was used to diagnose DM but has now largely been replaced by the measurement of the glycated hemoglobin level (HbA1c) [13]. The development of point of care HbA1c testing has facilitated this transition [14]. One of the collateral effects of using the HbA1c level as a diagnostic test for DM is that it has led to the recognition of a large number of persons with pre-diabetes/glucose intolerance, all of whom are at increased risk of progression to DM [15].

Clinical management of DM necessarily focuses on glycemic control. Extreme dysglycemia can cause severe complications, including diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS), both of which are considered medical emergencies [16]. Although both of these complications continue to occur, morbidity and mortality related to both conditions has steadily decreased presumably because of the wide availability of effective treatment [17].

DM and its complications

DM produces other complications/sequelae in addition to the direct effects of dysglycemia. One of its most important complications is an increased risk of infectious diseases, including tuberculosis, urinary tract infections (UTI), skin and soft tissue infections (SSTI), fungal infections, pneumonia and sepsis [5, 7, 18-25]. The biological basis of this increased risk of infection is unknown, but is thought to be due to defects in both the innate and adaptive immune responses [5, 7]. DM is also associated with coronary artery disease (CAD), ocular disease (diabetic retinopathy), renal disease (diabetic nephropathy), and dyslipidemia [26-30]. CAD, retinopathy and nephropathy are all thought to be caused by microvascular damage and are thus a direct consequence of DM-associated inflammation. Infections, CAD, retinopathy and nephropathy together cause the majority of DM-related morbidity.

As demonstrated by a large, national study from the CDC in 2014, however, the incidence of non-infectious DM-related complications steadily decreased in the United States between 1990 and 2010 [31]. A related study provided a potential explanation for this decrease, showing that the prevalence of diabetes, which had been steadily rising in the United States, has now plateaued and may be declining [32]. An important question that remains unanswered, however, is whether the trends that have been reported for DM's non-infectious complications are also true for its infectious complications.

Medication use in persons with DM and collateral effects

Treatment for DM has been available for decades, starting with the the recognition of the central role of insulin in glycemic control. In addition to insulin, a variety of other classes of medication, including sulfonylureas, biguanides, thiazolidinediones, and GLP-1 inhibitors are available for the treatment of DM. Each of these medications targets the dysglycemia which is the defining characteristic of DM.

Because of its multiple complications, however, pharmacotherapy targeting risk factor modification is common in persons with DM. The increased risk of cardiovascular disease in persons with DM leads to treatment with aspirin, statins and beta-blockers. Similarly, the risk of renal disease in persons with DM leads to treatment with either angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). While each of these medications acts on a specific system or even cell-type, some may have collateral effects, with effects on the immune system being of particular importance.

Statins have been shown to be directly immunomodulatory and glyburide has been shown to be associated with a decreased risk of gram negative sepsis in a cohort of hospitalized patients in Thailand [33, 34]. Whether these two examples are isolated phenomena or are indicative of a broader phenomenon is unknown. Little is also known about the effects of medication combinations on the risk of infection and whether some combinations might be synergistic or antagonistic. Determining the effect of individual medications and medication combinations on infectious risk in persons with DM is important because it has immediate implications for clinical management of DM.

The effect of location on DM and its complications

Rates of both infectious and non-infectious complications of DM vary by race, income, and neighborhood [35-38]. In the case of race, minority groups have higher rates of both types of complications compared to persons of white race. In the case of income, lower income persons have higher rates of both types of complications compared to higher income persons. Because neighborhoods are often a proxy for race and/or income, it is unsurprising that different neighborhoods, with different demographic and socioeconomic characteristics also can have different rates of DM-related complications.

A variety of factors likely drive these differences in rates of DM complications, but one particularly important one is access to care. The risk of all DM-associated complications increases with worsening DM control. Consistent access to care is a pre-requisite for optimal DM control because it facilitates the tight monitoring and medication dose adjustment needed to achieve this goal. One measure of access in a city is the distance to the primary care clinic. If an individual requires frequent visits to adjust medication dosing, for example, being closer to the site of primary care is likely to increase the chance that such visits will happen. Surprisingly, few studies have formally examined and measured the impact of distance on DM control and, by extension, on DM complications. Distance to the clinic, like medications, is something that can be modified (e.g. by ensuring that patients are seen in clinics that are physically close to them), therefore quantifying its impact on DM control is an actionable item that, like modification of medications, could have an impact on DM-related complications.

A multi-level of view of DM and its complications

This dissertation has three primary aims: 1) to determine and compare the rates of infectious and non-infectious diseases complications among hospitalized adults with and without DM in California, 2) to quantify the association between commonly used medication classes and infections, 3) to understand and quantify spatial variation in DM control. While aim 1 is at the state level, aims 2 and 3 focus on a cohort of patients in San Francisco, CA.

Chapter 1 of this dissertation addresses aim 1, examining statewide hospital discharge data from California spanning a 25-year period (1986-2011). It lays the foundation for the work described in chapters 2 and 3 by identifying a trend in DM-related infectious complications, one with multiple potential causes. In chapter 2, I address aim 2 and, in doing so, address one potential cause of the trends observed in chapter 1: collateral effects of medications on infectious risk in persons with DM. Unlike chapter 1, chapter 2 is done at the city and not at the state level, a necessary compromise in order to obtain the kind of highly detailed, individual-level data used here. I elected to focus on medications as a potential driver of the trends in infections because they are a potentially modifiable risk factor. In chapter 3, I address aim 3. In this chapter, instead of focusing directly on a specific outcome (infections) as I do in in chapters 1 and 2, I

examine DM control and how it is affected by distance to the site of primary care. As has already been noted, the level of DM control is an important determinant of an individual's risk for DM-related complications, including infections. Like medications, DM control is thus also a potential cause of the trends that are described in chapter 1, particularly if trends in DM control over time match the trends in infections among persons with DM over time as described in chapter 1. The latter question is not specifically addressed in this dissertation as the necessary data (longitudinal individual-level measurements of glycemic control) are not available at a state-wide level. I elected to focus on the impact of clinic distance on DM control because clinic distance, like medications, is a potentially modifiable factor.

Together the three aims of this dissertation provide a global view of the interaction between DM and infectious disease in the state of California (aim 1), as well as a local-level view in a single city within the state focusing on potentially modifiable drivers of this interaction. While the results presented here are specific to a single state and a single city within that state, both the state and the city have large, diverse populations. Therefore, the findings that I report here could apply in many other settings in the United States.

Chapter 1: Rising Rates of Hospitalization for Infection Among Persons with Diabetes Mellitus in California from 1986-2011

Introduction

The prevalence of diabetes mellitus (DM) has risen over the last several decades in the United States [39]. In California, DM has been linked to up to one third of all hospitalizations and is thought to be a driver of increasing healthcare costs [40]. These rises parallel global increases in DM burden, with the most recent Global Burden of Diseases survey reporting that DM is the eighth highest cause of both years of life lost (YLL) and years lost to disability (YLD) [41]. Because DM is an underlying cause of cardiovascular disease, this ranking may underestimate its contribution to morbidity and mortality.

DM is a multisystem disease. In addition to associated cardiovascular complications, DM is associated with an increased risk of infection, peripheral arterial disease, and neuropathy, the last of which can lead to lower extremity infections, as well as with bladder dysfunction, which can lead to urinary tract infections (UTI) [18-22, 42, 43]. Fungal infections, skin and soft tissue infections (SSTI), osteomyelitis and tuberculosis are all more common in persons with DM when compared to those without DM [23-25, 44, 45]. Immune dysregulation is thought to play a role in DM-mediated susceptibility to infections, although the precise mechanisms remain unknown [46, 47].

In 2014, a large study by the Centers for Disease Control and Prevention (CDC) examining trends in non-infectious disease complications of DM showed that despite the increasing prevalence of DM, rates of hospitalization for such complications dramatically declined in the United States between 1990 and 2010 [31]. This decline may reflect more effective treatment of the non-ID complications, as well as earlier and better treatment of DM. Whether a similar decline in rates of hospitalization for the infectious disease complications of DM has occurred, however, is unknown. Here, I examine trends in the rate of acute-care hospitalization for infections in adults with and without DM in California from 1986 to 2011.

Methods

Study Design

In this study, I employed a time trend study design. I obtained hospital discharge data for the state of California for the years 1986, 1991, 1996, 2001, 2006 and 2011 and calculated the annual rate of hospitalization by primary discharge diagnosis. For each year studied, rates for persons with and without DM were calculated separately but in both cases were calculated relative to the entire adult population of Californa. California adult population estimates were obtained from the United States Census Bureau (http://www.census.gov/data.html; Appendix B Table 1).

Data Source

The California Office of Statewide Health Planning and Development (OSHPD) releases individual-level, de-identified data on all hospital discharges in the state annually. These data include discharge diagnosis coding information which, for the data used in this studt, follow the ninth International Classification of Diseases Clinical Modification (ICD-9-CM).

Study Population

The study population consisted of persons aged 18 years or older hospitalized in an acute care setting in California. I excluded non-acute hospitalizations to skilled nursing facilities or inpatient hospice. I also excluded pregnant patients because they are a distinct population with a different spectrum of infections than other hospitalized adults. In addition, it was not possible using the available data to distinguish between gestational and non-gestational diabetes mellitus, the former being a distinct clinical entity [48]. Finally, institutionalized adults were excluded. Their numbers were low (<1% of all hospitalizations per year) and their exclusion did not affect my rate calculations (data not shown).

Data analysis

Each observation (hospitalization) in the data used had a maximum of twenty-five diagnosis codes, one of which was the primary discharge diagnosis (reason for hospitalization). For each observation, all diagnosis codes were scanned for the presence of DM or a DM-associated complication ICD-9-CM code (250, V58.67) and all observations were classified as having DM or not (type 1 or type 2). Next, I prepared a master list of ICD-9-CM codes for infectious diseases based on the 2011 edition of the ICD-9-CM (Appendix B, Table 2). This master code list was cross checked against ICD-9-CM code definitions for all years of data examined here (obtained from the CDC http://www.cdc.gov/nchs/icd/icd9.htm) and modified to ensure that discharge diagnosis codes for each year were correctly classified and comparable. I used this master code list to classify each observation as having an infectious disease primary discharge diagnosis or not, focusing on the following known DM-associated infectious and non-infectious diagnoses: pneumonia (480-486, 487.0), SSTI (680-686, 695.3, 614.3, 728.86, 608.84), UTI (590.0, 595.0, 595.3, 595.4, 595.8, 597.0, 599.0, 601.0, 601.2, 601.3, 601.4), sepsis (038, 995.91, 995.92), myocardial infarction (MI; 410), and cerebrovascular accident (CVA; 430-434, 436).

My primary disease burden measure was the number of hospitalizations/100,000 adult population in each year for each specific diagnosis. Because the data used here were de-identified, all hospitalizations were treated as independent events. For 1986-2011, I calculated both age adjusted as well as age and age-group specific DM prevalence adjusted hospitalization rates in order to account for, respectively, changes in both the adult population age distribution and the prevalence of DM. Age adjustment was done by calculating age-group specific rates for the following age groups: 18-34 years, 35-64 years and 65 and older. These age group categories were selected because they were

available for all observations for all years of data. Age-group specific rates for each year were subsequently weighted by the 2011 population age distribution and summed to generate the population rate for a given year.

To calculate rates adjusted for both age and age-group specific DM-prevalence, it was necessary to use different age-group categories in order to match those used in data on DM prevalence in California obtained from the CDC (http://gis.cdc.gov/grasp/diabetes/DiabetesAtlas.html). The CDC's DM prevalence estimates were divided into the following four age categories: 18-44 years, 45-64 years, 65-74 years, and 75 and older. These age-group specific DM prevalence estimates were available from the CDC for California starting with 1994. Therefore, it was only possible to calculate rates that accounted for changes in the prevalence of DM for the years 1996-2011. In addition, because of data masking by OSHPD, for 1996-2011, 10-15% of observations from each of these years were not classifiable into the CDC's age categories. These unclassifiable observations were excluded from rate calculations. After age-group specific DM prevalence adjusted rates were calculated, they were subsequently weighted by the overall adult population age distribution for 2011 and summed to give the final age and age-group specific DM prevalence adjusted annual rate of hospitalizations per 100,000 adults in California for 1996-2011.

After rates were calculated for all years studied, I fit linear regression models with the R *glm* function to examine rate trends. Trends were determined for age adjusted rates spanning 1986-2011 as well as for age and age-group DM prevalence adjusted rates for 1996-2011. In each of these models, the rate of hospitalization was the dependent variable and time in years was the independent variable. I examined data fit/linearity with the R *cor* function, calculating the correlation coefficient based on the method of Spearman. I also assessed the impact of data exclusion on rate trends for the age and age-group specific DM prevalence adjusted rates for 1996-2011. To do so, I determined age adjusted rates for all disease categories for this subset of patients using both the complete data as well as the incomplete data excluding the 10-15% of observations with missing data as described previously. I fit linear models to both the complete and incomplete datasets to determine the effect of data exclusion on rate trends. All data analysis was conducted with R version 3.1.1 (www.r-project.org) with R Studio version 0.98.507 (www.rstudio.org). All figures were made using the R *ggplot2* package.

Results

Between 1986 and 2011, there were a total 9.72 million adult hospitalizations in California, of which 2.05 million (21%) were identified as having a diagnosis of DM (Appendix B, Table 3). The proportion of adult hospitalizations with DM increased steadily from 10% in 1986 to 31.3% in 2011.

Age-adjusted annual rates of hospitalization for pneumonia, SSTI, UTI, sepsis, MI and CVA increased among hospitalized adults with DM in California between 1986 and 2011 (Appendix B, Table 4 gray rows; Appendix B, Figure 1 top). The rate of hospitalizations for pneumonia increased by 2.08 hospitalizations/100,000 adults per year ($p = 0.03$), for

SSTI by 1.52 hospitalizations/100,000 adults per year (p=0.001), for UTI by 1.3 hospitalizations/100,000 adults per year (p=0.001), for sepsis by 5.4 hospitalizations/100,000 adults per year (p=0.02), for MI by 1.08 hospitalizations/100,000 adults per year (p=0.03) and for CVA by 0.83 hospitalizations/100,000 adults per year(p=0.006).

I observed the opposite trend for age-adjusted population rates of most infectious and all non-infectious diagnoses in hospitalized adults without DM (Appendix B, Table 4 white rows; Appendix A, Figure 1 bottom). The rate of hospitalization for pneumonia decreased by 5.96 hospitalizations/100,000 adults per year (p=0.02), for UTI by 0.61 hospitalizations/100,000 adults per year (p=0.25), for MI by 3.62 hospitalizations/100,000 adults per year (p=0.002) and for CVA by 3.14 hospitalizations/100,000 adults (p=0.001). The rate of hospitalization for SSTI increased by 0.32 hospitalizations/100,000 adults per year (p=0.55) and that of sepsis by 6.6 hospitalizations/100,000 adults per year (p=0.05).

CDC estimates of age group specific DM prevalence were available for 1994-2011. Therefore, for 1996-2011 I was able to adjust rates of hospitalization for both age and background prevalence of DM. As noted earlier, it was not possible to classify all observations into CDC age categories, resulting in an incomplete dataset. To assess the potential impact of these missing data, I performed a sensitivity analysis by calculating age adjusted rates for 1996-2011 on both the whole dataset as well as the incomplete dataset. I found that the missing observations had minimal impact on both hospitalization rates for each year as well as on the rate change trends for each disease category examined (Appendix B, Table 5).

When adjusted for the prevalence of DM, I found that from 1996-2011 the trends in the rates of hospitalization for pneumonia, UTI, MI and CVA among adults with DM reversed (Appendix B, Table 6; Appendix A, Figure 2 top). Instead of increasing, from 1996-2011, the rate of hospitalization for pneumonia decreased by 23.3 hospitalizations/100,000 adults with DM per year (p=0.04), for UTI by 5.9 hospitalizations/100,000 adults with DM per year, for MI by 24.2 hospitalizations/100,000 adults with DM per year (p=0.06) and for CVA by 26 hospitalizations/100,000 adults with DM per year (p=0.11). Rates of hospitalization for SSTI increased by 5.0 hospitalizations/100,000 adults with DM per year (p=0.11) and for sepsis by 34.9 hospitalizations/100,000 adults with DM per year (p=0.26). No change was observed in the trends of rates of hospitalization for the 6 conditions examined among hospitalized adults without DM (Appendix B, Table 5; Appendix A, Figure 2 bottom). The rate of hospitalization for pneumonia decreased by 6.4 hospitalizations/100,000 adults without DM per year (p=0.147), for MI by 3.6 hospitalizations/100,000 adults without DM per year (p=0.137), and for CVA by 2.6 hospitalizations/100,000 adults without DM per year (p=0.081). Rates of hospitalization for SSTI increased by 1.3 hospitalizations/100,000 adults without DM per year (p=0.190), for UTI by 1.2 hospitalizations/100,000 adults without DM per year, and for sepsis by 13.1 hospitalizations/100,000 adults without DM per year (p=0.121).

Discussion

A 2014 CDC survey reported a steady decrease between 1990 and 2010 in the rate of hospitalizations due to non-ID complications of DM in the United States [31]. Here, I show the opposite trend in the rates of hospitalization for pneumonia, sepsis, SSTI and UTI in adults with DM in California between 1986 and 2011. I found that age-adjusted rates of hospitalization for pneumonia, sepsis, SSTI and UTI all increased significantly in adults with DM while they decreased or remained unchanged in adults without DM. Rates of hospitalization for MI and CVA also increased among adults with DM, but at a slower rate. When adjusted for age-group specific DM prevalence as well as age, however, rates of hospitalization for pneumonia, UTI, MI and CVA decreased. In contrast, the rates of hospitalization for both SSTI and sepsis continued to increase even after adjustment for age-group specific DM prevalence.

My results have important implications. They suggest that at a population level, infections may be increasing as a cause of hospitalization among persons with DM even as they are decreasing or remain stable as a cause of hospitalization among persons without DM. With both an aging population and a continuing increase in the prevalence of obesity, both drivers of DM, there is some reason to believe that this trend will continue. A second implication of my results is that the profile of infections seen among hospitalized adults with DM is changing, with rates of hospitalization for certain types of infections (sepsis, SSTI) increasing, while rates for other types of infections (pneumonia, UTI) decrease.

Our primary finding of an increase in the rate of hospitalizations for known DM-associated infections among persons with DM in California is surprising. While the simplest explanation would be to attribute it to an overall rise in hospitalizations of persons with DM, the fact that the two non-infectious complications of DM I examined, MI and CVA, decreased over the same time period argues against this possibility. There may be a simple explanation for this discrepancy: risk factor modification. Both MI and CVA are cardiovascular diseases with proven risk factor modification strategies, including smoking cessation, treatment with aspirin and treatment with statins [49]. No such strategies, other than improving DM control, exist for infectious diseases in persons with DM. In addition, because of both risk factor modification and the development of more effective treatment, mortality as a result of cardiovascular disease has steadily declined in all persons [50]. Therefore, where in the past persons with DM who developed cardiovascular disease may have had higher mortality, they now live longer, increasing the effective number of persons with DM who could go on to develop an infectious complication.

There are several potential ways to explain the shift in the profile of infections I observed after adjusting for DM prevalence. The decrease in rates of hospitalization for pneumonia may in part be explained by increased rates of pneumococcal vaccination among adults over the 25 year study period [51-53]. Supporting this possibility is the fact that the rate of hospitalization for pneumonia declined in persons without DM as well, indicating that this decline is independent of DM status. In contrast to pneumonia,

rates of SSTI and sepsis increased. Unlike pneumonia, neither of these conditions is a vaccine preventable illness, which could in part explain the discrepancy in the observed rate trends. In addition, the rise in the rates of hospitalizations for sepsis may be due to more aggressive diagnosis, since much of the increase occurred between 2001 and 2011, coinciding with prominent national anti-sepsis campaigns [54]. Unlike both SSTI and sepsis, rates of UTI decreased after adjustment for DM prevalence. Like both SSTI and sepsis, however, UTI is not a vaccine preventable illness. As such, my results suggest that the increase in UTI hospitalizations seen in unadjusted rates may simply reflect an increase in the number of persons with DM. Further work is required to determine other potential causes for the non-significant decline in the rate of hospitalization for UTI after adjustment for DM prevalence.

As is true of any study based on hospital discharge data, my results rely on accurate diagnosis coding. A systematic bias in discharge diagnosis coding, including under- or over- reporting of both DM and/or specific infections, could result in under- or over-estimation of the rates of infections in persons with DM. If this bias increased or decreased over time, it alone could explain the trends I observed. A second limitation of my work is the absence of any clinical information about the degree of DM control in individuals, such as a glycosylated hemoglobin level. Because the risk of infection in DM is thought to correlate with glycemic control, there may be considerable variability in rate trends among patients with DM stratified by severity of disease. A final limitation of my results is that they represent a single state, thereby limiting their generalizability. Although California is the largest state in the United States in terms of population, I cannot say with certainty that the findings I report here will hold in other stayes or countries.

Over a time period when both awareness and treatment of DM improved in the United States, as indicated by declining rates of non-infectious complications of DM, I found that rates of hospitalization for sepsis, pneumonia, UTI and SSTI in adults with DM rose in California [31]. As Americans with DM live longer because of continued improvements in the management of DM, my results suggest that hospitalizations of persons with DM for infectious complications may continue to rise. In addition to its implications for individual health, this rise has public health ramifications in part because of the economic impact of infections in adults with DM [24]. There is an urgent need to improve efforts at prevention of DM while simultaneously improving early treatment/detection of DM and redoubling efforts to understand the biological basis of the risk of infectious diseases in adults with DM. Such understanding could lead to the development of novel diagnostic and therapeutic strategies that, along with a robust prevention effort, could blunt a potential syndemic of infectious disease and DM.

Chapter 2: Angiotensin Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Use is Associated with a Lower Risk of Infectious Disease in a Cohort of Adults with Diabetes Mellitus in San Francisco, California

Introduction

As noted in chapter 1 of this dissertation, persons with diabetes mellitus (DM) are known to be at increased risk for several different types of infections, including pneumonia, skin and soft tissue infections (SSTI), urinary tract infections (UTI), and sepsis [19-22, 24]. The biological basis of this increased risk of infection among persons with DM remains unknown, but is thought to be related to alterations in both the innate and adaptive immune responses [5-7, 55].

A defining feature of persons with DM is treatment with multiple medications [56-58]. This treatment is often for DM-associated complications, including hyperlipidemia, hypertension, and chronic kidney disease. Some of the medications that are used to treat these conditions are thought to have immunomodulatory properties, with statins, which are used to treat hyperlipidemia, being a leading example [33, 59, 60]. Medications that are used to treat DM itself and not its complications have also been shown to affect specific components of the immune system. One good example of such a medication is glyburide, an oral sulfonylurea that promotes increased insulin secretion in persons with DM. Glyburide has been shown to inhibit the NLRP3 inflammasome *in vitro* and is associated with a decreased risk of death from gram negative sepsis due to *Burkholderia pseudomallei* (the pathogen that causes melioidosis) in a cohort of hospitalized patients in Southeast Asia [34, 61]. Whether the effects of statins and glyburide are isolated examples or suggest that many other classes of medications that are used to treat persons with DM is unknown.

In chapter one of this dissertation, I show that the rate of hospitalizations for several known DM-associated infectious diseases rose steadily between 1986 and 2011 among adults with DM in California. This rise could not be explained by an increase in the prevalence of DM alone and was surprising, as it occurred during a time period of both rising DM awareness and wide availability of medications to treat DM complications. I hypothesized that one potential explanation for this observation might be modulation of the immune response by single medications or by groups of medications that are used to treat DM complications. While for some medications, this modulation could be beneficial, for others or in combination, it could potentially further raise the risk of infectious disease. In this chapter, I address this possibility by systematically examining the associations between several medication classes that are commonly used among persons with DM and their combinations with acute infections in a cohort of persons with DM in San Francisco, California.

Methods

Study Population

The study population consisted of persons aged 18 years and older with DM. All cohort members received care between January 2008 and March 2009 in a San Francisco Health Network (SFHN) clinic. Persons who were not assigned to a primary care clinic within the SFHN and thus did not receive primary care within the system were excluded.

Cohort identification and data extraction

I obtained a list of all prescriptions between January 1, 2008 and December 31, 2008 from the San Francisco General Hospital (SFGH) outpatient pharmacy for the following four medications: glyburide, glipizide, metformin and insulin. No SFHN clinic has its own pharmacy and while some prescriptions are filled at outside pharmacies, a record of all prescriptions is maintained by the SFGH outpatient pharmacy. We identified a list of unique medical record numbers (MRN) from the list of prescriptions and extracted all outpatient, inpatient and emergency visit data between January 1, 2008 and March 31, 2009 for each MRN. Extracted clinical data included: age, race/ethnicity, gender, visit-associated ICD-9-CM diagnosis codes, and all hemoglobin A1c measurements made for each individual between January 1, 2008 and March 31, 2009. The data extraction was performed by the University of California, San Francisco Health Records Data Extraction Service (THREDS). In addition to medications used to treat DM, prescriptions for the following medication classes, frequently used in persons with DM were obtained for all cohort members from the SFGH outpatient pharmacy: β-blockers (including metoprolol, atenolol and carvedilol), Angiotensin Converting Enzyme Inhibitors (including enalapril, captopril, lisinopril and benazepril), statins (including lovastatin, simvastatin, pravastatin and atorvastatin), and aspirin. For all medications, both the prescription date and the duration of the prescription were available. Only prescriptions that were documented as having been filled were included int his study.

Data analysis

For each visit for each individual in the cohort, I reconstructed visit-specific medication histories by examining the date of a visit (in the case of inpatient admissions, this was considered the date of admission) and reconciling this with all medication prescriptions for each individual. I classified an individual as being ‘on’ a medication for a given visit if the visit date fell between the start date and end date (determined by the number of days for which the prescription was written) for at least one prescription of the medication being considered.

I scanned all visit-associated ICD-9-CM diagnosis codes for each individual in the cohort. The following ICD-9-CM codes were used to classify individuals as having had an acute infection: 038, 995.9, 790.7, 451 (sepsis); 680-686, 695.3, 614.3, 728.86, 608.4 (skin and soft tissue infections); 590.1-590.9, 595.0, 595.3, 595.4, 595.8, 599.0, 601.0-601.4 (urinary tract infection); 465, 462, 382, 461, 466, 380.1 (upper respiratory infection); 110 (dermatophyte infection); 079, 004, 112, 421 (other acute infection).

For each visit, I determined whether the individual had a hemoglobin A1c measurement within one month (before or after) of the visit. If only one of the two hemoglobin A1c

measurements was present, this value was assigned as the visit-specific A1c measurement. If both measurements were present, the mean of the two measurements was assigned as the visit-specific A1c measurement.

All statistical models to examine the association between medication use and acute infections were done using a general effects estimation approach (GEE) as implemented by the R *gee* package. Observations (visits) were clustered by MRN. The dependent variable in all models was a binary indicator of whether a visit was for an acute infection or not with a logistic link function. Odds ratios (OR) were calculated by exponentiating linear model coefficients. Robust error estimates for each coefficient were used to calculate 95% confidence intervals.

All models were built step-wise. I began with the simplest model predicting whether a visit was for an infection or not as a function of each of the eight medications studied here. The second step was to adjust these models for age (continuous scale); the third step was to adjust for race (coded as a set of binary 'dummy' variables, with the largest group serving as the reference category); the fourth step was to adjust for hemoglobin A1c level (continuous scale); and the fifth step was to adjust for all three factors simultaneously. Of the four medications used to treat DM complications, only those for which the odds ratio (OR) estimate did not cross null (1.0) in the model adjusted for age, race and hemoglobin A1c were retained for the next stage.

Because treatment of DM often involves the use of multiple medications and because I observed this to be the case in our cohort, I incorporated this fact into our final models. As before, the final set of models was constructed step-wise. The dependent variable remained the same, i.e. a binary indicator of whether a specific clinical visit was for an acute infection or not. All models included binary indicators for treatment with glyburide, glipizide, insulin and metformin and binary interaction terms of each of the first three medications with metformin. Indicators for three of the medications used to treat DM complications, ACE inhibitors/Angiotensin Receptor Blockers, β-blockers, and statins were added stepwise, along with all pair-wise interaction terms for each. In total, for each DM treatment regimen, 15 different regression models, incorporating all of the medication interaction permutations were run to assess the stability of the generated predictions (Appendix B, Table 6).

Results

Our cohort of persons with DM was composed of 743 unique individuals (Appendix B, Table 7). The cohort was evenly divided between men and women, had a mean age of 53.7 years +/- 9.9 and a mean Hemoglobin A1c of 8.3 mg/dl +/- 2.1. Persons of Hispanic ethnicity comprised the single largest group (41.6%) in the cohort, followed by Asians (29.4%) and African Americans (13.9%). Together, these three groups represented 84.9% of persons in the cohort. The cohort accounted for a total of 4776 visits, the majority of which were outpatient (88.4%). Of the 4776 visits, 236 (4.9%) were for an acute infection. Skin and soft tissue infections (28.8%), dermatophyte infections (21.1%) and upper respiratory infections (20.3%) accounted for 70.2% of all infections.

Several medications were significantly associated with acute infection, even after adjustment for age, race and hemoglobin A1c level (Appendix B, Table 8). Persons on insulin, were 1.75 (95% confidence interval: 1.18, 2.56) times more likely to present with an acute infection than persons not taking insulin. Persons on an Angiotensin Converting Enzyme Inhibitor (ACEI) or an Angiotensin Receptor Blocker (ARB) were 1.92 (1.39, 2.70) times more likely to present with an acute infection than those not on an ACEI or an ARB. Persons on a β-blocker were 1.64 (1.08, 2.50) times more likely to present with an acute infection than persons not taking a β-blocker. Finally, persons taking a statin were 1.72 (1.23, 2.44) times more likely to present with an acute infection than persons not taking a statin.

Because many persons with DM are on multiple medications, both for the treatment of DM and for the treatment of DM-associated complications, and because of the potential for synergistic and/or antagonistic interactions between these medications, I next examined the impact of these interactions on our results (Appendix B, Table 9). In models adjusting for age, race, hemoglobin A1c level, interaction between DM medications and interactions between pairs of medications used to treat DM complications, I found that only treatment with either an ACEI or ARB had a significant association with presentation for an acute infection. This association was consistent regardless of the DM treatment regimen persons were on. Persons on Glipizide/Metformin, Glyburide/Metformin and Insulin/Metformin who were also treated with an ACEI or ARB were respectively 1.64 (1.05, 2.56), 1.82 (1.16, 2.86) and 1.61 (1.04, 2.44) times less likely to present with an acute infection as compared to persons on the same DM treatment regimen who were not on an ACEI or ARB.

Discussion

Treatment of persons with DM is directed towards management/prevention of its complications, as well as treatment of DM itself. One potential ramification of the treatment of the complications of DM is the secondary effects of the medications used. I hypothesized that some of these medications and/or their combinations could increase the risk of infection in persons with DM and thus in part explain my observations in chapter 1 of this dissertation. Instead, in a cohort of adults with DM cared for in an urban safety-net, I show that treatment with an ACEI or ARB is associated with a reduced risk of presenting with an acute infection in the outpatient, inpatient or emergency setting. This protective effect of an ACEI/ARB did not vary with different DM treatment regimens and persisted even after adjustment for age, race, hemoglobin A1c level and other medications. Of these other medications, I initially observed a protective effect for both β-blockers and statins as well, although this effect was not robust to adjustment for age, race, hemoglobin A1c level and other medications. No other medications examined, including glipizide, glyburide, metformin or aspirin, had had a significant positive or negative association with presentation for an acute infection.

There are two plausible explanations for our results. The first possible explanation is that both ACEI and ARB are immunomodulatory. Consistent with this possibility is prior

work showing decreases in circulating levels of inflammatory cytokines (IL-6, TNF-α, IL-18), levels of anti-inflammatory cytokines (IL-10, IL-1Ra) and levels of non-specific markers of inflammation (CRP) in response to ACEI and ARB treatment [62-72]. Additional support for an immunomodulatory role for ACEI and/or ARB comes from other work showing a decreased risk of pneumonia in persons treated with these medications [73-75]. The second potential explanation for our findings is that an unmeasured factor that is highly correlated (negatively or positively) with ACEI or ARB treatment is responsible for our observation that treatment with these medications is associated with a lower risk of infection in persons with DM. Such factors could include administration of other immunomodulatory medications (e.g. glucocorticoids), variation in exposure to infectious pathogens in persons who are treated with an ACEI or ARB compared those not treated with either, or a higher prevalence of conditions that increase the risk of infection in persons who are not treated with an ACEI or ARB. For instance, if persons who are not treated with an ACEI or ARB are more likely to have HIV or to have had an organ transplant compared to persons treated with an ACEI or ARB, all other factors being equal, they would be expected to have a higher risk of infection.

When I examined each of the eight medications I studied here individually, I found that both β-blockers and statins, even after adjustment for age, race/ethnicity and hemoglobin A1c level, were associated with a reduced risk of infection. In my final models accounting for multiple medication classes and interactions, these associations did not remain significant. These results are unsurprising. Prior studies of the relationship between β-blockers and the risk of infection have produced mixed results [76-78]. This fact, coupled with my results, suggests that any potential effect of β-blockers on the risk of infection is likely to be small. Studies reporting larger effects may not have accounted for the effects of other medications and medication interactions as rigorously as I did in this study. In contrast to the data on β-blockers, evidence from observational studies suggesting that statin treatment globally reduced the risk of infection is strong. It led to several randomized controlled trials (RCT) for different infections, including each of the infectious syndromes I examined here [79]. The results of RCTs examining whether statins could reduce infections show that statin therapy does not do so, consistent my results. Finally, similar to my results for both β-blockers and statins, I did not find that treatment with glyburide reduced the risk of infection. Again, as was true for both β-blockers and statins, the two prior studies that specifically address this question are inconsistent, with one reporting glyburide treatment in patients with DM was associated with a lower risk of sepsis due to *Burkholderia pseudomallei,* and another reporting the opposite result [34, 80]. For all three classes of medication, β-blockers, statins and glyburide, the heterogeneity of prior study results may be due to differences in the study populations and design. Regardless, they all suggest that at a population level, none of the three medication classes is likely to modify the risk of infection in persons with DM, consistent with my findings.

Although the consistency of my primary observation that ACEI/ARB treatment suggests that my finding is robust, it is important to recognize the limitations of my work. First, as was true of the results presented in chapter 1, the diagnosis of an infection in the

patients in the cohort was based on discharge diagnosis codes and not on objective clinical criteria such as laboratory, microbiologic or radiographic data. This lack of clinical information could result in misclassification of the outcome, identifying persons as having or as not having an infectious disease such as UTI or SSTI. If biased, such misclassification could lead to lead to either an erroneous association or non-association. This limitation can be addressed in future work by using objective clinical data such as cultures (urine, wound), urinalysis and radiography (chest x-ray or CT-scan) instead of diagnosis codes to identify persons with infections. A second limitation of my work is that I treated prescriptions as a proxy for medication use, leading to potential misclassification of the exposure. Unlike misclassification of the outcome, misclassification of the exposure wen the exposure is medication use is not easily addressed in a study involving outpatients without either directly observing therapy or measuring drug levels. One potential solution to this problem is to focus a follow-up study exclusively on inpatients, since medication administration records are available and medication use can be confirmed. Alternatively, an outpatient study of the risk of infection could incorporate directly observed therapy, although the logistics of doing such a study would be challenging.

A central feature of the care of persons with DM is the treatment with multiple medications. These medications are directed at both the primary disease process as well as at secondary complications. Although I had hypothesized that some of these medications could increase the risk of infection and might in part explain the increasing rates of hospitalization for infections in persons with DM I describe in chapter 1, my results do not support this possibility. Instead, I found that the use of two commonly used classes of medications, ACEI and ARB are associated with a reduced risk of acute infections, that this protection occurs is independent of the level of DM control, and that it is not affected by treatment with other medications. Future work is required to confirm these findings and to determine the biological basis of my observation, its specificity by type of infection and whether the effect of ACEI/ARB is specific to persons with DM or is present in a general population.

Chapter 3: Where You Live Matters: The Effect of Residence on Control of Diabetes Mellitus in an Urban, Underserved Population in San Francisco, California

Introduction

The risk of diabetes mellitus (DM) related complications, including infections, coronary artery disease, diabetic nephropathy and retinopathy, is directly related to the degree of control of the DM [26, 81-89]. In clinical practice, this control is typically measured by tracking capillary blood glucose as an indicator of short-term control and the glycosylated hemoglobin level (HbA1c) as a measure of long-term control. In response to these measurements, medication doses and regimens are adjusted. Optimal management therefore requires steady contact with healthcare providers and personalized care planning [90].

One potential barrier to regular contact with healthcare providers for persons with DM is the physical distance between them and the clinics where they receive care. Although this barrier presumably exists for all persons with DM, it can be particularly problematic for persons served by safety-net institutions [91]. Specific examples of the potential barriers faced by persons who receive their care in safety-net institutions include not having a car, limitations in mobility and limited access to public transportation. Few studies have specifically examined the relationship between distance to the site where one receives primary care and DM control.

In chapter one of this dissertation I showed that the rate of hospitalizations for infections has risen among adults with DM in California. This rise was consistent across all types of institutions, public, private and safety net (data not shown). In chapter two, I examined the hypothesis that collateral effects of medications commonly used in persons with DM, which have increased in use over time, could in part account for these trends. In this chapter, I complement the analysis presented in chapter two by examining the relationship between DM control and the spatial distribution of patients in a cohort of patients served by an urban safety-net healthcare system in San Francisco, CA. I focus on this relationship because another potential explanation for the trends described in chapter one could be that even as the number of persons with DM has increased over time, mean DM control in these persons has not improved. A potential driver of worsening control of DM might be access to care, as measured by distance. Therefore, in this chapter, I determine both how DM control varies by location in the cohort studied here and how this variation may be a function of the distance of patients' homes to their primary care clinics. My findings provide insights that could have implications for the management of DM and other chronic illnesses, particularly in patient populations served by urban safety net systems.

Methods

Study Population

I identified a cohort of patients with DM by searching San Francisco General Hospital (SFGH) outpatient pharmacy records from 1/1/2008 to 12/31/2008 for the following four medications: insulin (all types), glyburide, glipizide and metformin. Only non-homeless adults, aged 18 years and older who received outpatient care at a San Francisco Health Network (SFHN) clinic were included. Patients whose residence was not located in San Francisco county were excluded.

Extraction and processing of clinical data

I used unique medical record numbers (MRN) for each patient in the cohort to extract the following information from the electronic medical record (EMR): home address, age, gender, race/ethnicity, and hemoglobin A1c. Hemoglobin A1c measurements for all patients in the cohort were obtained for calendar years 2008, 2009 and 2010. EMR data extraction was done by the UCSF Clinical and Translational Science Institute's The Health Records Data Service (THREDS). Patients' primary care clinics were determined by examining visit frequencies.

Mapping of patients and clinics

I geocoded all patient addresses using Google's mapping application programming interface (API) with the R *geocode* function from the *ggmap* package. I used the same method to geocode the locations of all SFHN outpatient clinics.

Data analysis

All data analysis was done using a combination of Matlab R2016a (Mathworks, Inc.), the Matlab mapping toolbox, R version 3.2.3 and R Studio version 0.99.486. For spatial analysis, I obtained a shapefile for San Francisco county at www.diva-gis.org and approximated San Francisco county by a raster-grid of 0.001'x0.001' polygons.

I determined the number of patients in 5.6 square miles polygons (0.02' x 0.02') overlapping windows centered at each pixel in the raster grid covering San Francisco county. To isolate the effect of ones residence on HbA1c level, I used the same approach, but instead of summing the number of patients, I fit two regression models in each window. Both models featured Hemoglobin A1c level as the outcome and varied only by the set of predictors used. The first model used age alone as a predictor ($A1c = \beta_0 + \beta_1 * age$), while the second model used age and distance to the assigned primary care clinic as predictors ($A1c = \beta_0 + \beta_1 * age + \beta_2 * distance$). Straight-line distances in miles from patients' residences to their assigned primary care clinics were calculated in Matlab using the *distance* function. Race/ethnicity was not included as a covariate because of the small number of observations in many of these models. For all models, we interpreted the intercept term (β_0) as a measure of the effect of a specific location on HbA1c level. I visualized the results of all moving window analyses as a scaled color image with the Matlab *imagesc* function.

I quantified the impact of the distance to an individual's primary care clinic on HbA1c level cross-sectionally by modelling HbA1c as a function of age and distance to the assigned primary care clinic (HbA1c = $\beta_0 + \beta_1$*age + β_2*distance + β_3*race indicator). I modeled hemoglobin A1c with the R *SuperLearner* package, training the model using a library of machine learning algorithms and using 20-fold cross validation to assess model performance. The library of algorithms included: generalized linear model (glm), random forest, step-wise glm, step-wise glm with interaction terms, generalized additive model (gam), neural networks (nnet), ridge regression, and support vector machines.

I next determined the closest SFHN primary care clinic for each patient in the cohort. I used the Matlab *plot* function to visualize the observed network of patients and clinics as well as the distance-optimized network of patients and clinics. Next, for each patient, I generated a predicted HbA1c based on reassignment to his or her closest SFHN primary care clinic using the trained ensemble model. I calculated the observed mean HbA1c for each individual in the cohort and used the Matlab *histogram* function to visualize the distribution of both the observed mean HbA1c and the predicted mean HbA1c in individuals with poorly controlled DM (mean HbA1c > 8.0, N=356). I next determined the effect of clinic reassignment on the mean HbA1c in the subpopulation of persons with poorly controlled DM. I used the non-parametric bootstrap to determine a 95% confidence interval for the weighted mean difference in the observed HbA1c and the predicted HbA1c. Specifically, for each bootstrap iteration, I sampled individuals in the cohort with replacement. I calculated the weighted mean observed HbA1c (weighting each cluster equally) as well as the weighted mean predicted HbA1c. From these two values, I determined the weighted mean difference in the observed and predicted HbA1c. A total of 10,000 bootstrap iterations were run.

Results

I identified a cohort of 735 unique patients with presumed DM who received a prescription for glyburide, glipizide, metformin or insulin from the San Francisco General Hospital outpatient pharmacy between January 1, 2008 and December 31, 2008. From January 1, 2008 until December 31,2010, these patients had a total of 4174 outpatient visits at a San Francisco Health Network primary care clinic for which a HbA1c measurement could be associated within a one month window of the visit. The mean age of persons in this cohort was 54.3 years, 51.7% were female and 48.3% were male. The racial/ethnic distribution of the cohort was 41.8% Hispanic, 31.3% Asian, 12.2% Black, and 9.5% White. The weighted mean HbA1c in the full cohort of patients was 8.30 mg/dl.

Residences of patients in the cohort were concentrated in downtown San Francisco and in the immediate vicinity of San Francisco General Hospital (Appendix A, Figure 3). Most of the sectors of the city were represented. The strongest age-adjusted, location-related effects on DM control occurred in downtown San Francisco (upper right corner of the city polygon) and in the city's periphery (Appendix A, Figure 4). These regions were 'hot spots' (colored yellow-green to red) of poor DM control.

A majority (78.1%) of patients lived more than one mile from their primary care clinic. The weighted mean HbA1c among patients living more than one mile from their primary care clinic was 8.30 and 8.30 in persons who lived within one mile of their clinic. Visually, however, the first group appeared to account for the majority of persons living in or near DM hot spots (Appendix A, Figure 5), with the only exception being the hot-spot located in downtown San Francisco (Appendix A, Figure 6). The locations of DM hot spots in the two groups of patients remained unchanged even after adjustment for distance to a patient's assigned primary care clinic was included in the prediction model (Appendix A, Figures 7-9).

When I visualized the network of patients and their assigned clinics, I noted a highly centralized structure (Appendix A, Figure 10). This observation indicated that the majority of the patients in this cohort of persons with DM received their care at one of three hospital-based primary care clinics. Assignment of patients to their closest clinic resulted in a more dispersed network structure (Appendix A, Figure 11).

Focusing on the the subset of patients with poorly controlled DM (mean HbA1c > 8.0 over the study period), I determined the potential effect of reassigning these patients to their closest clinic by predicting the effect of doing so using an ensemble model of HbA1c as a function of distance and age trained on the full set of data (see Appendix for cross validation results and model weights). I found that reassignment could have a significant effect on HbA1c control, shifting the distribution of mean HbA1c to the left (Appendix A, Figure 12). The observed weighted HbA1c in persons with poorly controlled DM was 9.43 mg/dl (95% confidence interval: 9.29, 9.59). After reassignment to the closest clinic, the weighted HbA1c in persons with poorly controlled DM was 8.39 mg/dl (8.29, 8.48). The difference between the two means was 1.14 mg/dl (0.90, 1.20). Few of the patients with poorly controlled DM were assigned to a clinic within one mile of their respective residences (Appendix A, Figure 13), with the majority having been assigned to a clinic more than one mile away (Appendix A, Figure 14), resulting in a highly centralized patient-primary care clinic network. As was true for the entire cohort, re-assigning patients to their nearest clinic resulted in a more dispersed network structure (Appendix A, Figure 15).

Discussion

DM can result in a variety of different complications, including infections, coronary artery disease, and chronic kidney disease. The risk of each of these complications is thought to increase with worsening DM control. In a cohort of patients served by an urban safety-net institution in San Francisco, CA, I show that how far patients live from their primary care clinic can have a major impact on long-term DM control, as measured by HbA1c level. I found that reassigning persons with poorly controlled DM (HbA1c > 8.0 mg/dl) to the closest primary care clinic would have a major impact, resulting in a full unit (1.0 mg/dl) improvement in the HbA1c level in this group of patients. One of the main effects of such a reassignment would be the transformation of the existing patient-primary care clinic network in the cohort of patients examined from a centralized to a more decentralized structure.

As noted earlier, few studies have formally examined the relationship between distance to the primary care clinic and DM control and none have done so in an urban healthcare safety net setting as I do here. Prior studies that have addressed the relationship between distance to the site of care and DM control have all been done in rural underserved populations [91-96]. These studies show that increasing distance between a patient and his or her primary care clinic is associated with both poorer disease control and adherence to care, consistent with my results. One important difference between urban and rural populations, however, is the magnitude of the distances involved in the two settings. In the cited studies, mean travel distances in rural populations often spanned tens of miles, as opposed to less than five miles in my study population. This difference in the distance travelled might suggest that distance is in practice a proxy for travel time. While in a rural setting, travel time would primarily be a function of distance, in urban settings such as San Francisco, it may reflect a combination of factors, including congestion and the relative efficiency of the local public transit system.

The mechanism(s) by which increasing distance to the clinic results in poorer control of DM are unclear. One potential mechanism is that it directly leads to fewer visits with a healthcare provider and that this reduced contact in turn leads to poorer control of DM. Even if correct, it remains to be determined whether this mechanism is driven by lack of access to transportation (public or car), concerns about time or other factors. A second potential mechanism by which increasing distance to the clinic directly could lead to poorer control of DM is that it may influence the management choices made by providers. For example, a provider could elect to treat a patient with very poor DM control who clearly needs insulin therapy with oral agents because the patient in question has a consistent history of poor follow-up. Further work is required to distinguish between these possibilities as well as to identify other potential mechanisms for how increasing distance to the clinic results in poorer control of DM.

Although I believe that my observations about the impact of distance on DM control are correct, my work does have some limitations. First, because I used medication prescriptions to identify patients with DM, it is possible that some of the patients in the cohort did not have DM. Metformin, for example, is used to treat other conditions, including non-alcoholic fatty liver disease [97]. Very few patients (<5%) in the cohort, however, were on metformin alone and the effect of excluding these patients was negligible (data not shown). A second limitation of my study is the way in which I calculated distances. I used Euclidean distances, which may not accurately represent the actual distances people travel over city streets. A third limitation of my study is analytical: the moving window regression models I used to determine the effect of residence on DM control included a limited set of covariates. Not adjusting for confounders such as comorbidities and medications could result in over-estimation of the strength of the association between the location of an individual's residence and DM. This same criticism could apply to my predictive models of A1c as a function of distance to the primary care clinic, which were equally parsimonious. Finally, all of the regression modeling in this study did not account for correlation between multiple

measurements on the same individual. Not accounting for this correlation could lead to incorrect error estimates and therefore to incorrect statistical inference. Each of these limitations will be addressed in future work, in part by making a concerted effort to improve both the quality (e.g. identifying patient's with DM by HbA1c level and not by medications) and quantity (a requirement in order to fit more complex regression models) of the data.

Management of chronic diseases such as DM is challenging, especially so in an urban, underserved patient population. I show here that distance to the primary care clinic can be a major barrier to achieving optimal DM control. In populations such as the one studied here, where the patient-primary care clinic network is highly centralized, one potential solution is enforced decentralization of services. The simplest way to create a decentralized patient-primary care clinic network is to limit choice by assigning patients to the clinic closest to their residences. I show here that the potential effect of doing so on control of DM, as measured by the HbA1c level, could be substantial. In practice, however, this approach might be ineffective, as limiting choice, even when justified, would likely be unpopular. An alternative means to achieve the same end is to push services out of the clinic and into the community through home nurse visits and/or telemedicine visits. Telemedicine in particular has already been shown to be a potentially effective strategy for management of DM [98]. While such approaches would not directly affect the distance between patients and their clinics, they would increase contact with providers and the healthcare system, thereby addressing one potential direct effect of the distance between patients and their primary care clinics. Whether the findings I report here are generalizable to other settings or not remains to be seen. Regardless, my work highlights the need for a more holistic view of chronic disease management among the urban underserved that takes into account potentially modifiable factors that are often not taken into account, such as the distance between patients and their clinics.

Discussion and future steps

Together, the three chapters of this dissertation make an important contribution to our understanding of DM and its complications. In chapter 1, I describe the evolving landscape of DM-related complications in California. I show that in adults with DM, rates of hospitalization for infectious diseases have increased even as those for non-infectious complications complications of DM have decreased. Although a number of different factors have presumably driven this rise, in chapter 2 I examine one potential cause in a cohort of patients in San Francisco, CA: modulation of the immune response because of collateral effects of medications that are commonly prescribed for the treatment of associated conditions in persons with DM. I chose to focus on medications for two primary reasons: 1) they can be modified and thus intervened upon, 2) the biology of their effects is amenable to laboratory investigation. Although my results did not support a major role for collateral effects of medications in driving the rising rates of hospitalizations for infections among persons with DM in California, I did find that both angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) were strongly associated with a decreased risk of infection. As I discuss below, this information is potentially actionable and has important implications. Finally, while understanding the biology of why infections appear to be more common in persons with DM is important, improving control of DM is the key to preventing any DM-association complication, including infections. Therefore, to complement chapter 2, I examined the interaction between residence and distance to the primary care clinic in chapter 3. Like chapter 2, chapter 3 focuses on a factor that can be intervened upon. Unlike chapter 2, the implications of the results of chapter 3 are much broader, since all complications of DM, not just infections, are directly related to the severity of disease [26, 81-89]. I show that minimizing the distance between patients and their primary care clinics can result in substantial improvements in the control of DM as measured by the HbA1c level.

Strengths. The work presented in this dissertation has a number of strengths. First, although the association between DM and infectious disease is well established, no prior studies have examined long-term trends in infectious diseases among persons with DM. This fact stands in contrast to the non-infectious complications of DM, for which such trends have been examined [31]. While further work is required to confirm the findings described in chapter 1, I believe that they are unlikely to change, in part because of the large data set used. The findings I report in chapter 1 are based on <u>all</u> adult hospitalizations in the state of California. They thus represent the entire universe of hospitalizations for each year examined, thereby reducing the likelihood of bias.

A second major strength of this dissertation is that in chapter 2 I move beyond the epidemiological observations of chapter 1 (increasing rates of hospitalization for infections in persons with DM) to examine one plausible biological factor (modulation of the immune response by medications) that could explain what I observed. The design of the analysis presented in chapter 2 is its greatest strength. By reconciling the date and duration of medication prescriptions with the dates of patient visits, I establish temporality, strengthening the case for a potential causal link for any associations observed. Unfortunately, my results did not support my hypothesis that medications

used to treat other conditions in persons with DM might increase the risk of infection. In fact, I found the opposite result for two medication classes, since both ACEI and ARB were associated with a significant reduction in the risk of infection. It should be noted, however, that two medications, glyburide and aspirin, were associated with an increased risk of infection. Neither of these associations was significant, although this lack of significance may mainly be a result of insufficient statistical power. Whatever the case, the results I present in chapter 2 provide a basis to justify further examination of the medications used to treat other conditions in persons with DM. Such investigation could lead to novel therapeutic uses (e.g. using an ACEI or ARB in women with DM with recurrent UTI) and, can be used as a tool to better characterize the defects in immunity that underlie the increased risk of infection in persons with DM.

A third major strength of this dissertation is that the spatial analysis I present in chapter 3 represents a novel contribution to the body of work on DM. As described earlier, while some prior studies have examined the association between distance and the control of DM, most of this prior work is descriptive and does not go beyond reporting an association. In formally quantifying the effect of distance on control of DM by combining causal inference methods, machine learning and spatial analysis, my work represents a novel synthesis and makes a substantial new contribution to our understanding of DM. More importantly, in quantifying the impact of reducing the distance between patients and their clinics, it demonstrates the potential benefit of intervening on this factor.

Limitations. Although I believe that the results I report here are robust and represent a valuable contribution to the existing literature on DM and its complications, my work does have some important limitations. The work I present in chapter 1 suffers from the limitation of all work that is based on claims/discharge data: the absence of clinical information. The identification of persons with DM and the determination of the infections that they have in chapter 1 is dependent on accurate diagnostic coding but without clinical information to corroborate diagnoses (e.g. a urine culture to confirm that a patient has a UTI) it is impossible to confirm this accuracy. Because of this inability to confirm diagnoses, it is not possible to determine if there is any systematic bias in discharge diagnosis coding that could lead to a spurious association. For example, it is possible that for a patient presenting with a cough and fever but a negative chest x-ray, that providers may be more inclined to classify him or her as having pneumonia if he or she has DM because providers know that persons with DM have a higher risk of infection. Such a bias could easily be in the other direction as well. While my expectation is that the scale of the data used, consisting of all adult hospitalizations in all hospitals in California, may nullify all such biases, future work is required to assess whether this is true or not.

Like the work I present in chapter 1, the work I present in chapter 2 also has some important limitations. The first limitation of the work presented in chapter 2 relates to exposure assessment, in this case medication use. I make the assumption that having a prescription for a medication is equivalent to taking it. Even though the study design of the work ensures that the criterion of temporality is met, no causal inference can be made without making this assumption. Fortunately, this limitation is addressable through

small changes in study design, either by incorporating the measurement of drug levels or by directly observing therapy, although the logistics of doing either are not trivial. A second limitation of the work I present in chapter 2 is that the models I used do not account for all possible medication interactions. This limitation is also addressable and in the case of the analysis I present, the lack of accounting for all possible medication interactions was deliberate. More complex models, accounting for all pairwise medication interactions could easily be implemented, but also require a much larger data set to fit. As before, this limitation will be addressed in future work.

Like the work presented in chapters 1 and 2, the work I present in chapter 3 also has some limitations. The first of these limitations is that the spatial regression analyses adjusted for a small set of potential confounders. Other, unaccounted-for factors, including medications, could have played an important role in determining the relationship between location and control of DM. For example, prescribing patterns could vary by location within the city and, unaccounted for, this variability could result in overestimation of the effect of residence on control of DM. A second limitation of the spatial analysis I present in chapter 3 is that I did not account for correlation between repeated measures on the same individual. It is important to note, however, that not doing so would not affect the estimate of the effect of residence on control of DM, only the error estimate. Because my analysis of the effect of residence on control of DM was intended to be qualitative/descriptive and does not attempt to make any kind of statistical inference, however, inaccuracy in the error estimate did not affect my results. Nevertheless, future work could incorporate analytical techniques designed for repeated-measures data, such as the general effects estimation (GEE) approach used in chapter 2 applied to the spatial analysis presented in chapter 3. To do so, however, will again require increasing the size of the data set used in order to be able to fit such a model.

Finally, all three chapters of this thesis share two limitations. The first of these common limitations is generalizability. In the case of chapter 1, whether trends on hospitalization for infections in persons with DM in California apply in other states of the United States with a different demographic make-up is unclear. Similarly, in the case of chapters 2 and 3, whether the findings from a cohort of patients served at an urban safety-net institution in a single city will apply in other cities and hospitals in California and/or the United States is unclear. The second common limitation shared by all three chapters in this dissertation is that each makes use of secondary data sources. The lack of control over the data collection process that is a defining characteristic of all secondary data sources thus remains a major concern. As was true of the other limitations identified, however, each of the limitations I identify here are addressable. In this case, a new study with a prospective, multi-center design could directly address both the generalizability of the work presented here while generating high-quality, primary data.

Future steps. The work I present in this dissertation provides a solid foundation for future investigation. One starting point for such work is to confirm the results I report in chapter 1. One potential approach is to use national hospital discharge data (such as the HCUPS dataset), while an alternative approach is to leverage the growing

availability of electronic medical record (EMR) data. While the second of these two approaches might initially need to be limited to a single health system or hospital, it offers one significant benefit: it would allow for accurate assessment of the outcomes because of the availability of diagnostic test results (e.g. cultures and imaging).

EMR data have further advantages that would strengthen the work presented here. One of the biggest advantages opf EMR data is that they are linked to medication administration records. This fact would address one of the primary limitations of the analysis in chapter 2, since it would be possible to know for certain if a patient had taken a specific medication or not. This confirmation would strengthen the case for a causal interpretation of any observed association between a medication and an infection, thus justifying laboratory-based experimentation to determine the mechanisms of how a specific medification might modify the risk of infection. Finally, EMR data include residence information, are longitudinal and, in some cases, are available at a national scale in the United States. In short, future studies based on the use of EMR data have the potential to address all of the limitations of the analyses presented in the three chapters of this dissertation.

A final, and possibly the most important, future direction based on the results reported here is the development of interventions to improve the control of DM. At least two strategies result directly from the work presented in chapters 2 and 3: 1) use of either ACEI or ARB to reduce infection risk in persons with DM who develop recurrent infections, 2) the development of geographically targeted interventions and/or health-system re-design to de-centralize care, particularly in urban safety-net institutions. The effectiveness of each of these interventions could be assessed by a clinical trial and, if proven to be effective, become part of routine management. In short, the work I present in this dissertation opens up multiple avenues for future inquiry on the interaction between DM and infectious diseases, the development of novel interventions to reduce the risk of infectious diseases in persons with DM, and the development of interventions to improve control of DM.

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Appendix A: Figures

Figure 1. Age adjusted rates of hospitalization for complications of diabetes mellitus in California, 1986-2011. The upper panel shows rate trends for cerebrovascular accident (CVA), myocardial infarction (MI), pneumonia, sepsis, skin and soft tissue infections (SSTI), and urinary tract infections (UTI) in adults with diabetes. The lower panel shows rate trends for the same conditions in adults without diabetes. All rates are relative to the entire adult population of California. The light gray areas around each trend line show the 95% confidence intervals of the rate estimates.

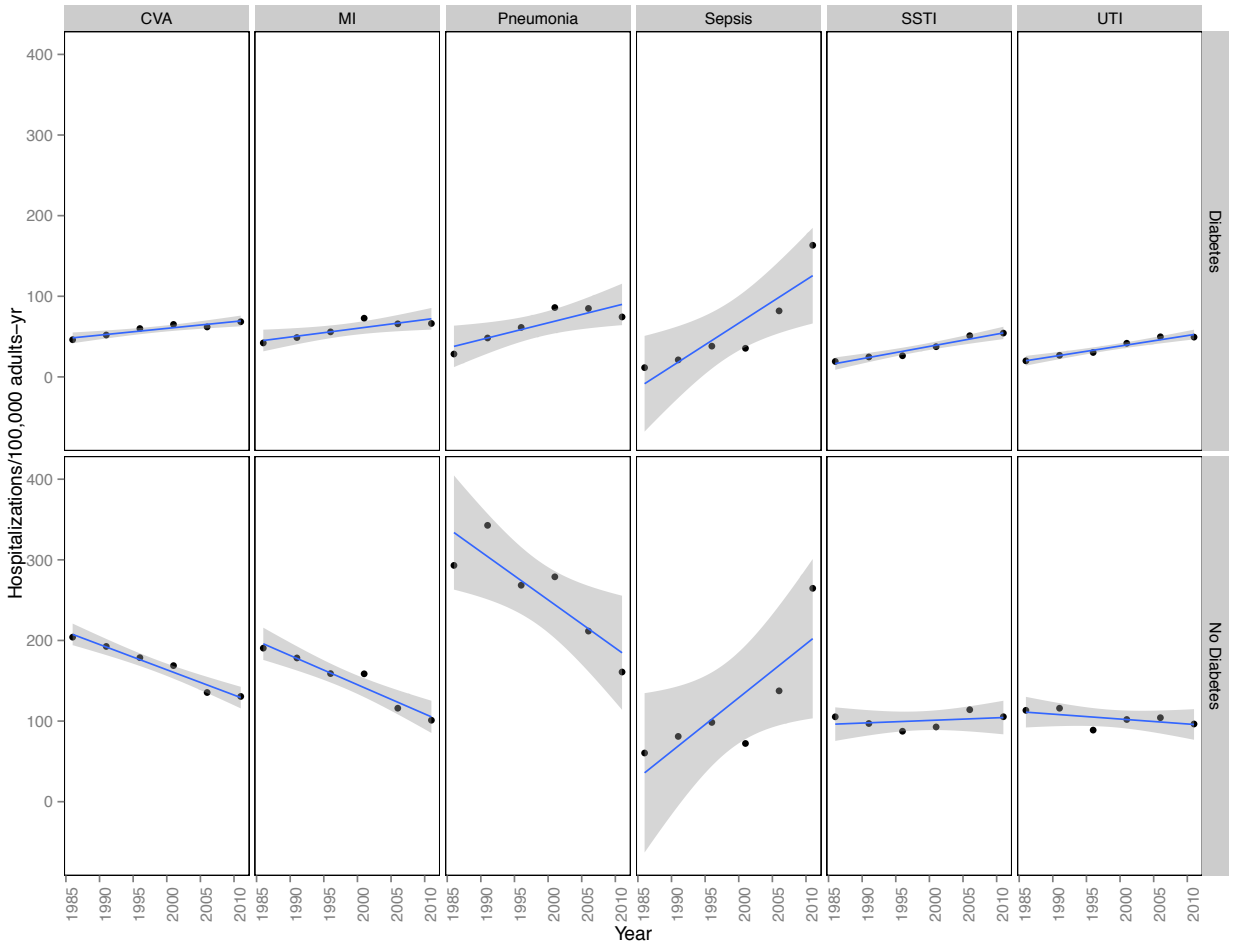


Figure 2. Age and diabetes prevalence adjusted rates of hospitalization for complications of diabetes mellitus in California, 1996-2011. The upper panel shows rate trends for cerebrovascular accident (CVA), myocardial infarction (MI), pneumonia, sepsis, skin and soft tissue infections (SSTI), and urinary tract infections (UTI) in adults with diabetes mellitus. Rates are for the estimated adult population with diabetes mellitus. The lower panel shows rate trends for the same conditions in adults without diabetes mellitus. Rates are for the estimated adult population without diabetes mellitus. The light gray areas display 95% confidence intervals.

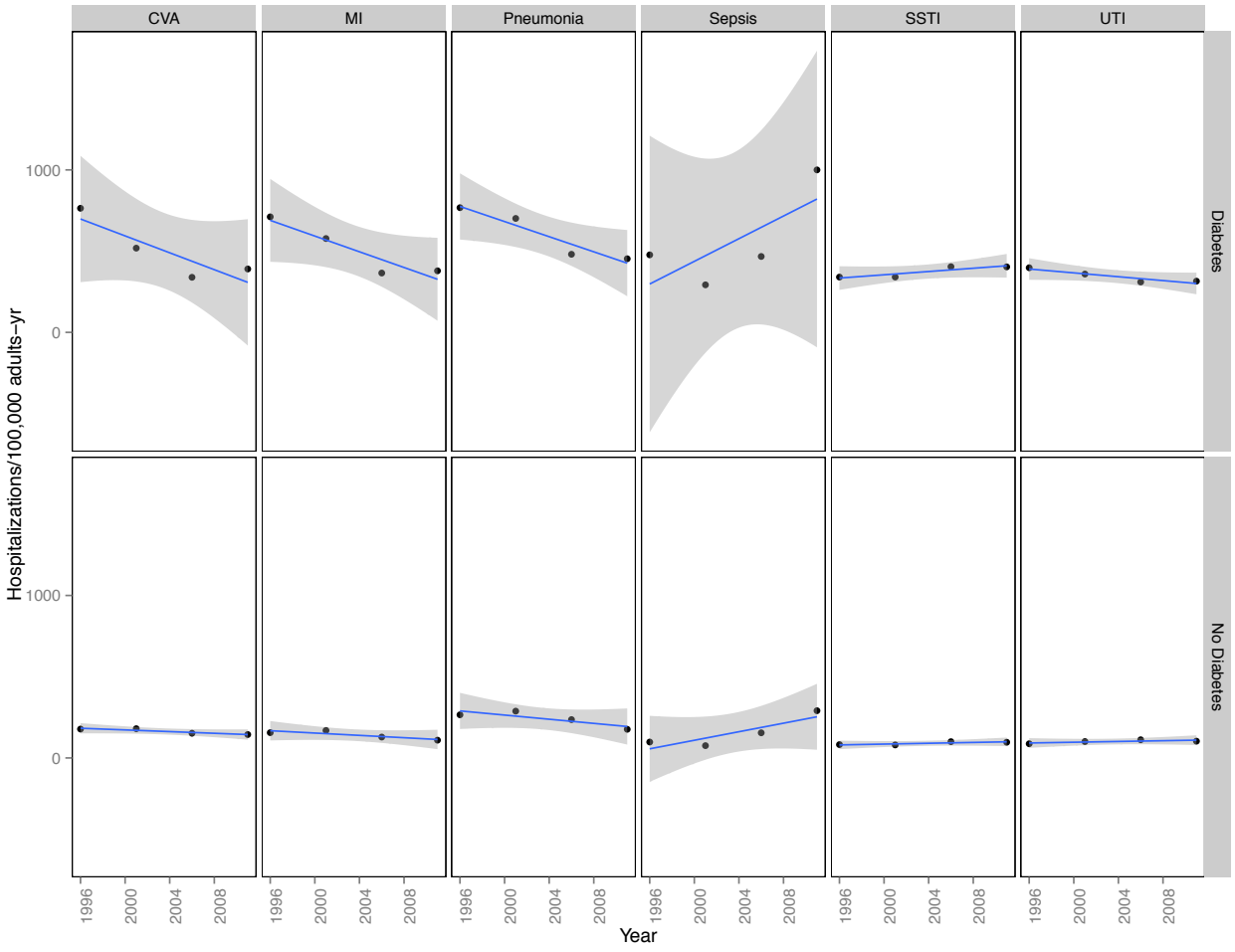


Figure 3. Density within San Francisco County of patients from the cohort of patients with diabetes mellitus. Patient density was estimated using moving window averages over the area of San Francisco County. The size of each window was approximately 5.6 miles^2, with warmer colors indicating a higher density.

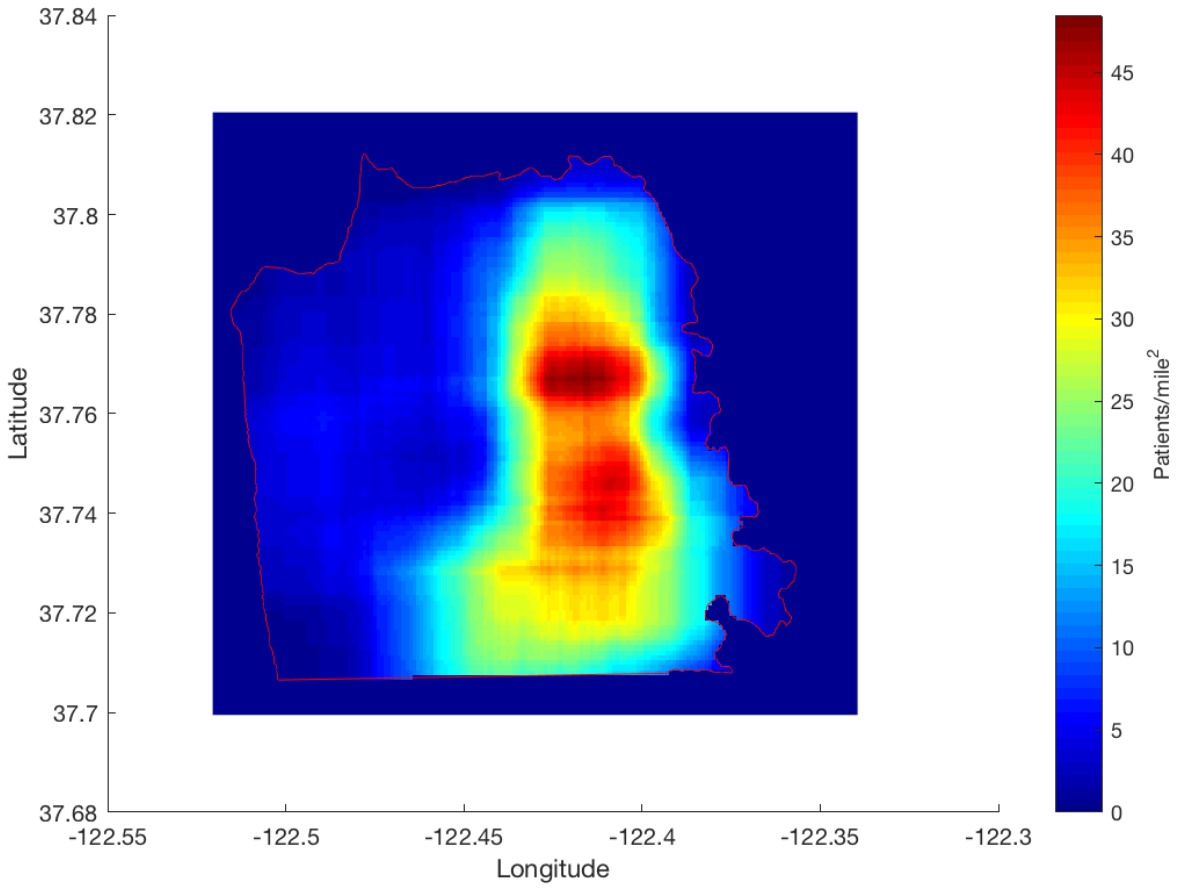


Figure 4. Unadjusted effect of residence on mean hemoglobin A1c level in San Francisco. Hemoglobin A1c level was modeled as a function of patient age and smoothed over San Francisco County city limits using a series a moving window regression models. Warmer colors indicate a stronger effect.

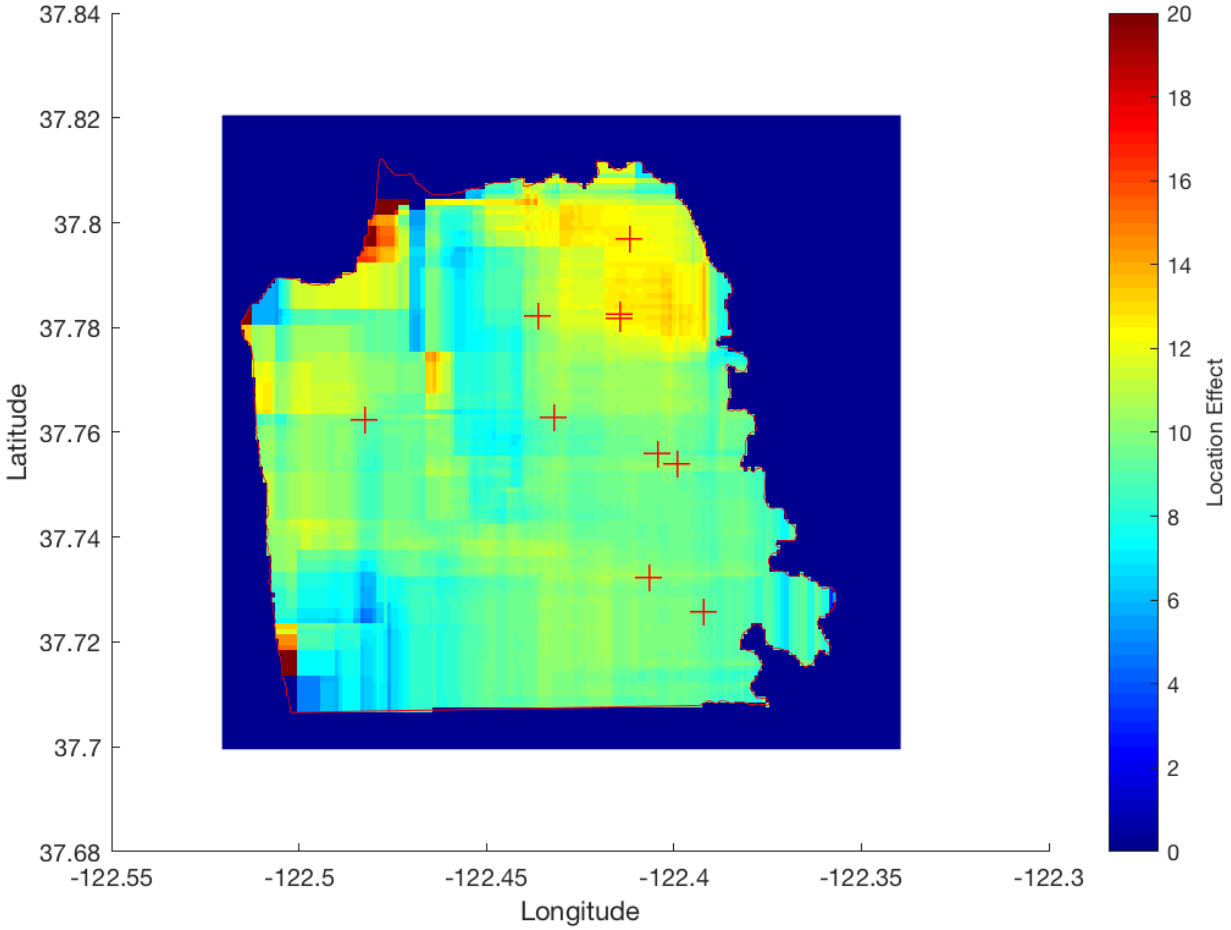


Figure 5. Unadjusted effect of residence on mean hemoglobin A1c level in San Francisco and network of patients who live within one mile of their primary care clinic. Hemoglobin A1c level was modeled as a function of patient age and smoothed over San Francisco County city limits using a series a moving window regression models. Warmer colors indicate a stronger effect. Individual patients are represented by black open circles and straight lines connect patients to their respective primary care clinics.

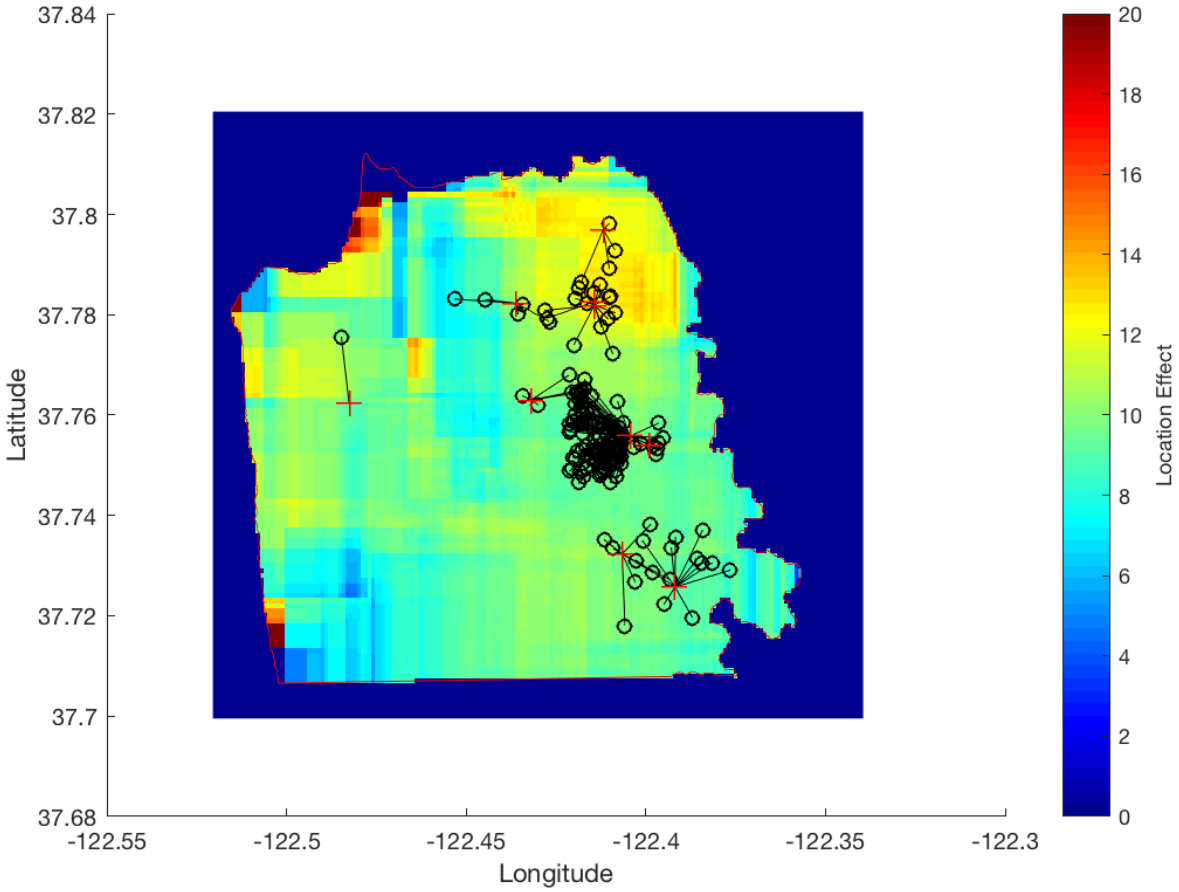


Figure 6. Unadjusted effect of residence on mean hemoglobin A1c level in San Francisco and network of patients who live more one mile of their primary care clinic. Hemoglobin A1c level was modeled as a function of patient age and smoothed over San Francisco County city limits using a series a moving window regression models. Warmer colors indicate a stronger effect. Individual patients are represented by black open circles and straight lines connect patients to their respective primary care clinics.

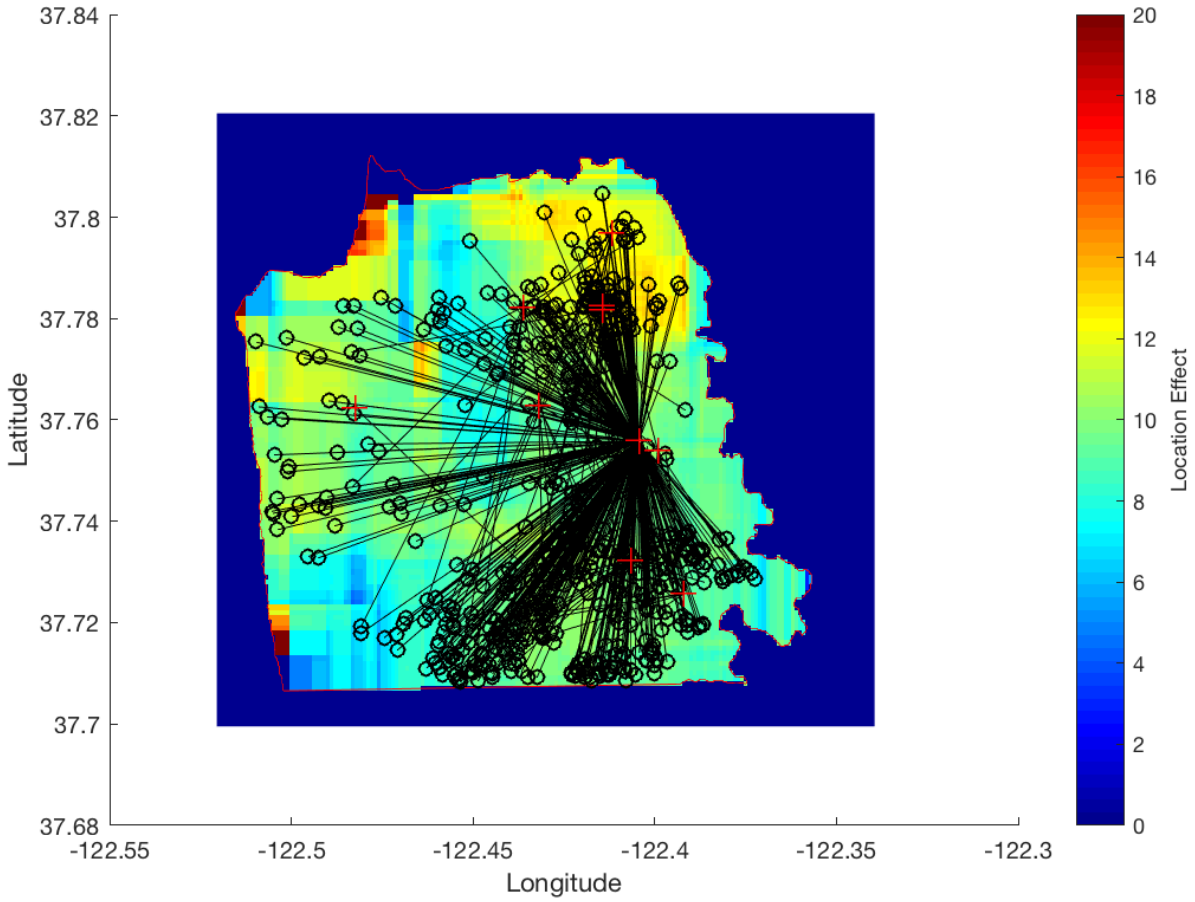


Figure 7. Distance-adjusted effect of residence on mean hemoglobin A1c level in San Francisco. Hemoglobin A1c level was modeled as a function of patient age and distance to the primary care clinic and smoothed over San Francisco County city limits using a series a moving window regression models. Warmer colors indicate a stronger effect.

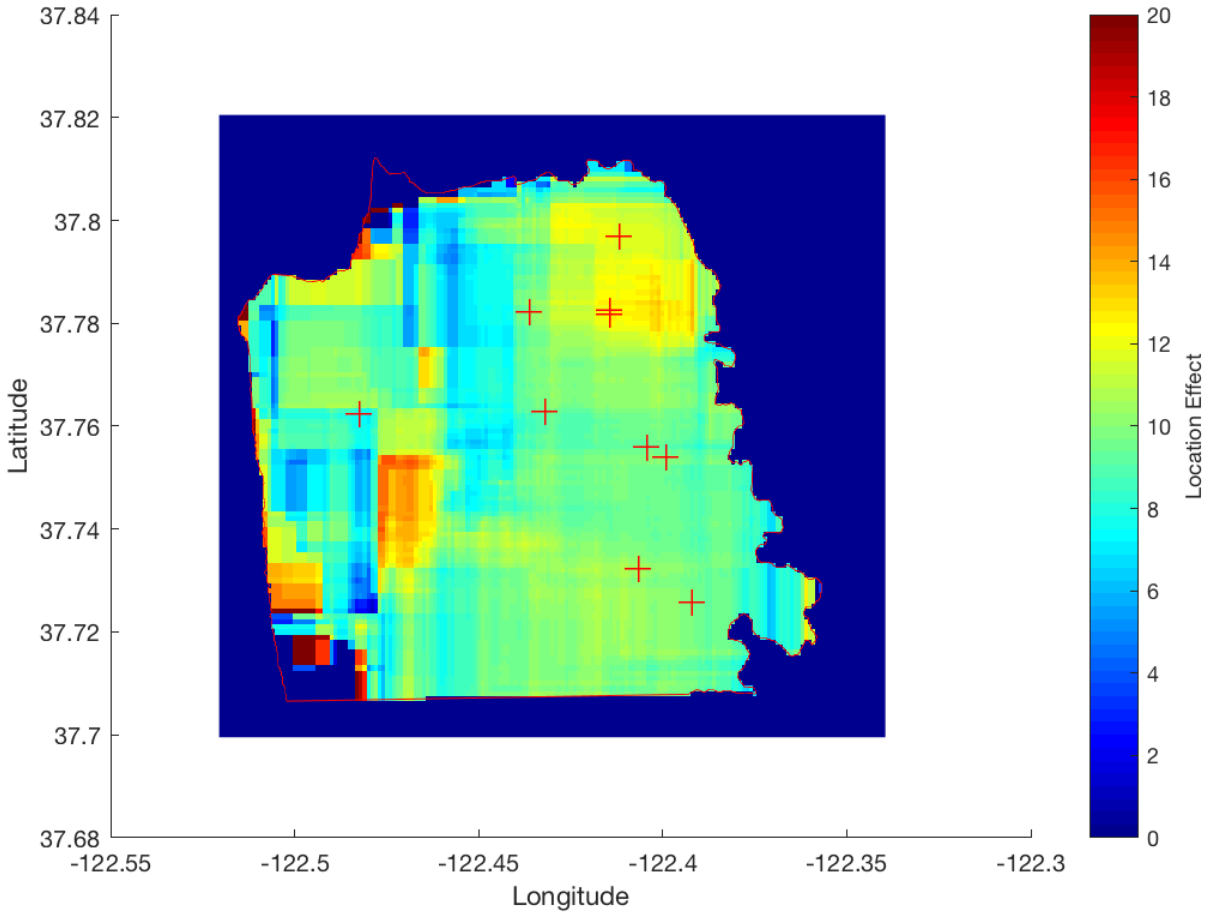


Figure 8. Distance-adjusted effect of residence on mean hemoglobin A1c level in San Francisco and network of patients who live within one mile of their primary care clinic. Hemoglobin A1c level was modeled as a function of patient age and distance to the primary care clinic and smoothed over San Francisco County city limits using a series a moving window regression models. Warmer colors indicate a stronger effect. Individual patients are represented by black open circles and straight lines connect patients to their respective primary care clinics.

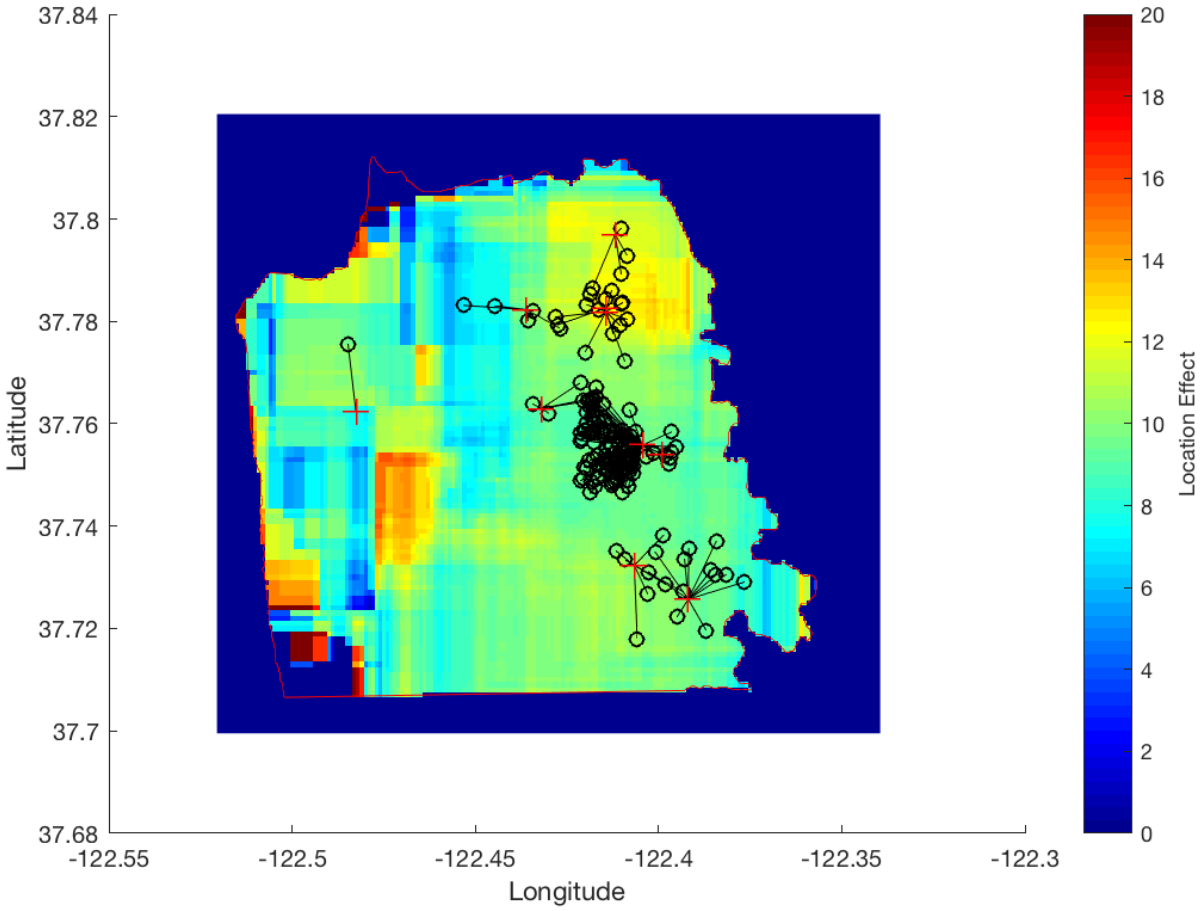


Figure 9. Distance-adjusted effect of residence on mean hemoglobin A1c level in San Francisco and network of patients who live greater than one mile from their primary care clinic. Hemoglobin A1c level was modeled as a function of patient age and distance to the primary care clinic and smoothed over San Francisco County city limits using a series a moving window regression models. Warmer colors indicate a stronger effect. Individual patients are represented by black open circles and straight lines connect patients to their respective primary care clinics.

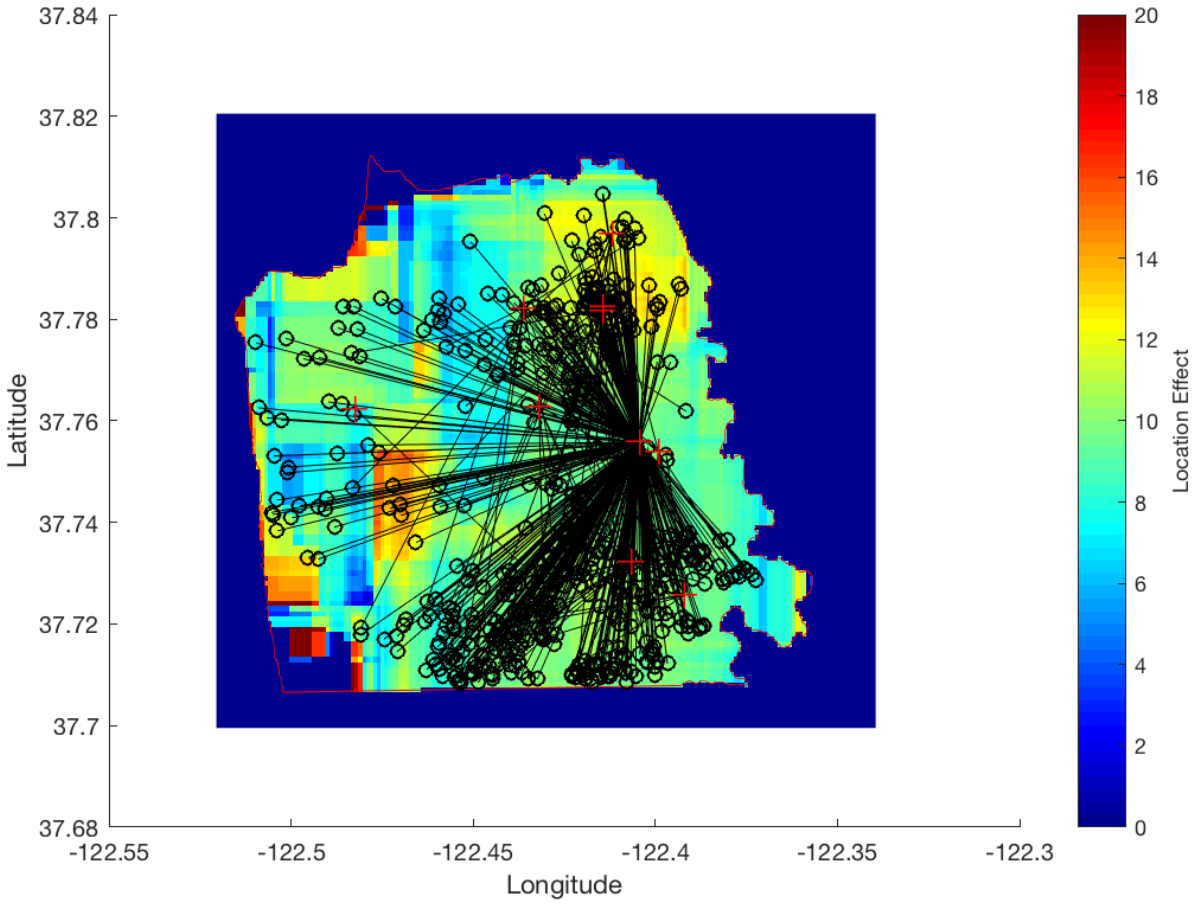


Figure 10. Existing patient and primary care network. Each individual patient in the cohort (black circles) and each of the primary care clinics (red crosses) in the San Francisco Health Network (SFHN) were mapped. Lines in the figure connect each patient to his or her primary care clinic.

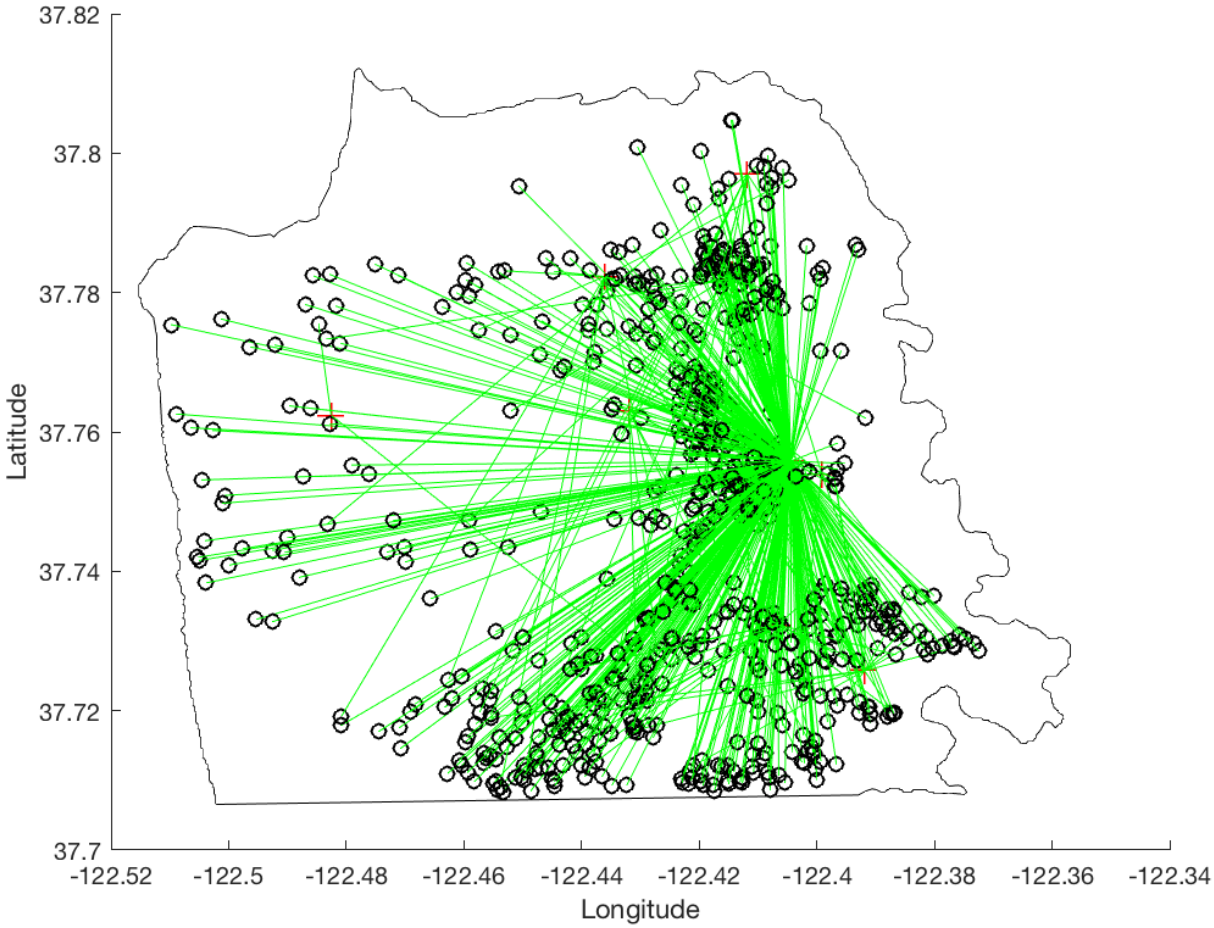


Figure 11. Distance optimized patient and primary care network. The closest primary care clinic was determined for each individual patient in the cohort (black circles). As before, a line connecting a patient to their nearest (distance-optimized) clinic in the San Francisco Health Network (SFHN) was drawn.

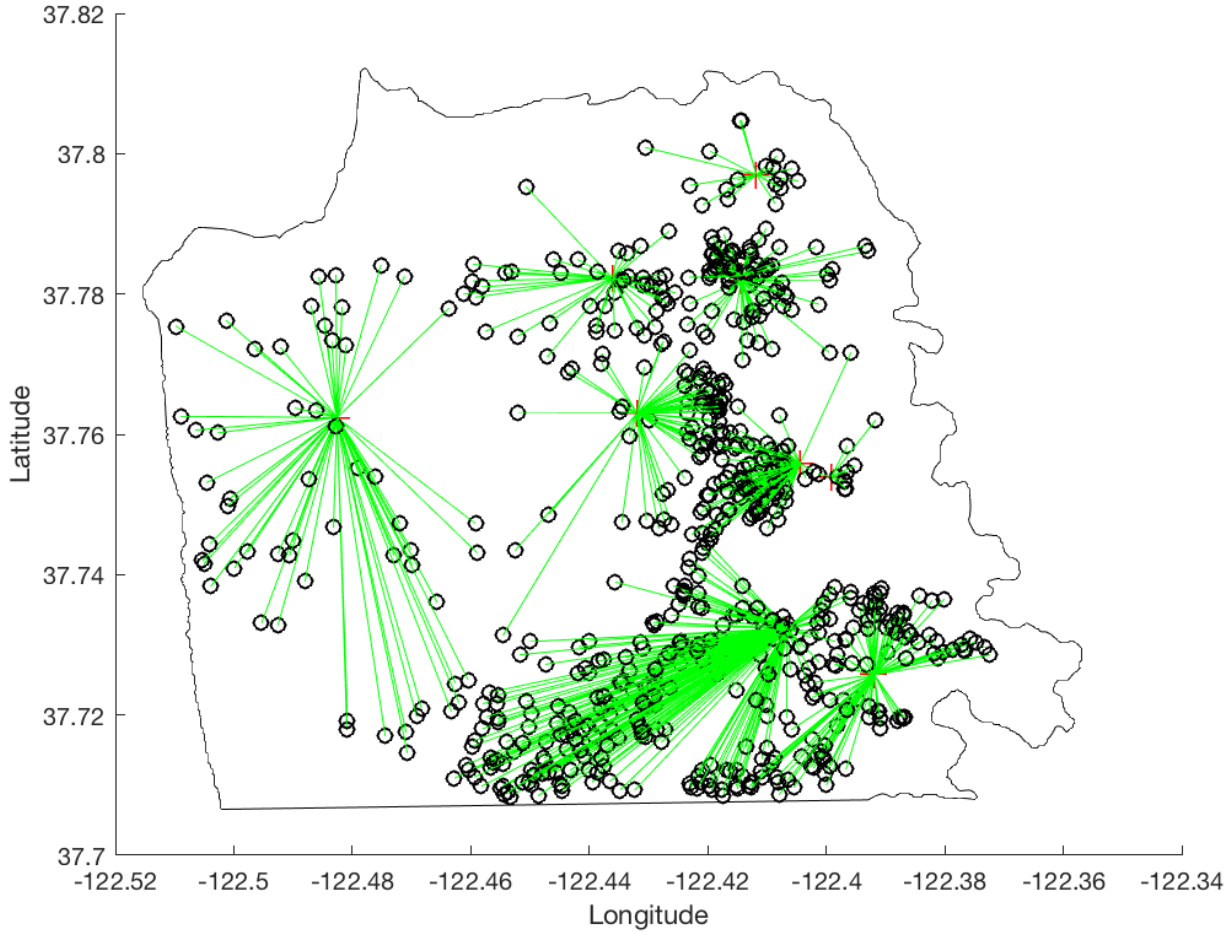


Figure 12. Distribution of observed Hemoglobin A1c and predicted Hemoglobin A1c after reassignment to nearest clinic in persons with poorly controlled diabetes mellitus. The blue histogram shows the observed distribution of hemoglobin A1c (HbA1c) values in persons with poorly controlled diabetes mellitus in the cohort, defined as a mean HbA1c > 8.0. The red histogram shows the predicted effect of reassigning all persons in the cohort to their nearest clinic on the distribution of HbA1c values.

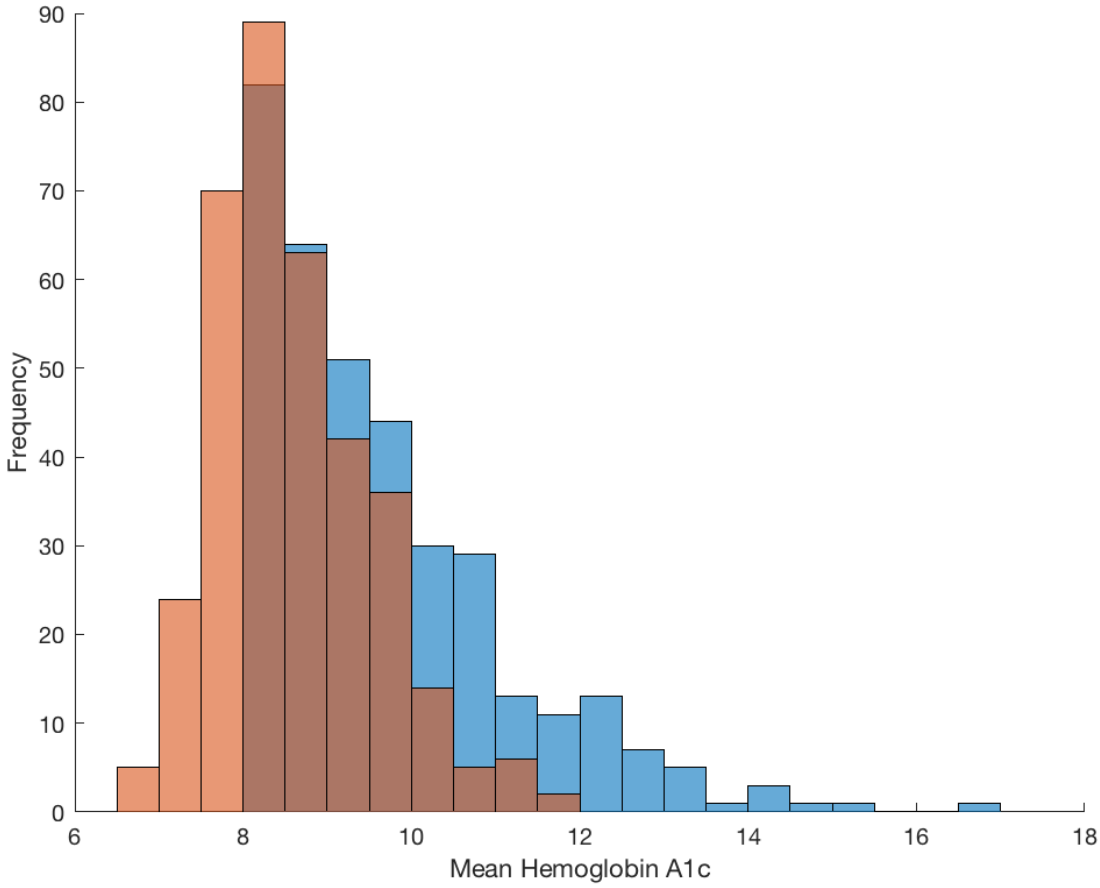


Figure 13. Patients with poorly controlled DM living within one mile of their primary care clinic. Patients in the cohort with poorly controlled DM (defined as a hemoglobin A1c >= 8.0 mg/dl) who live within one mile of their primary care clinic were selected and mapped. Each patient is connected to his or her primary care clinic (red crosses) by a straight line.

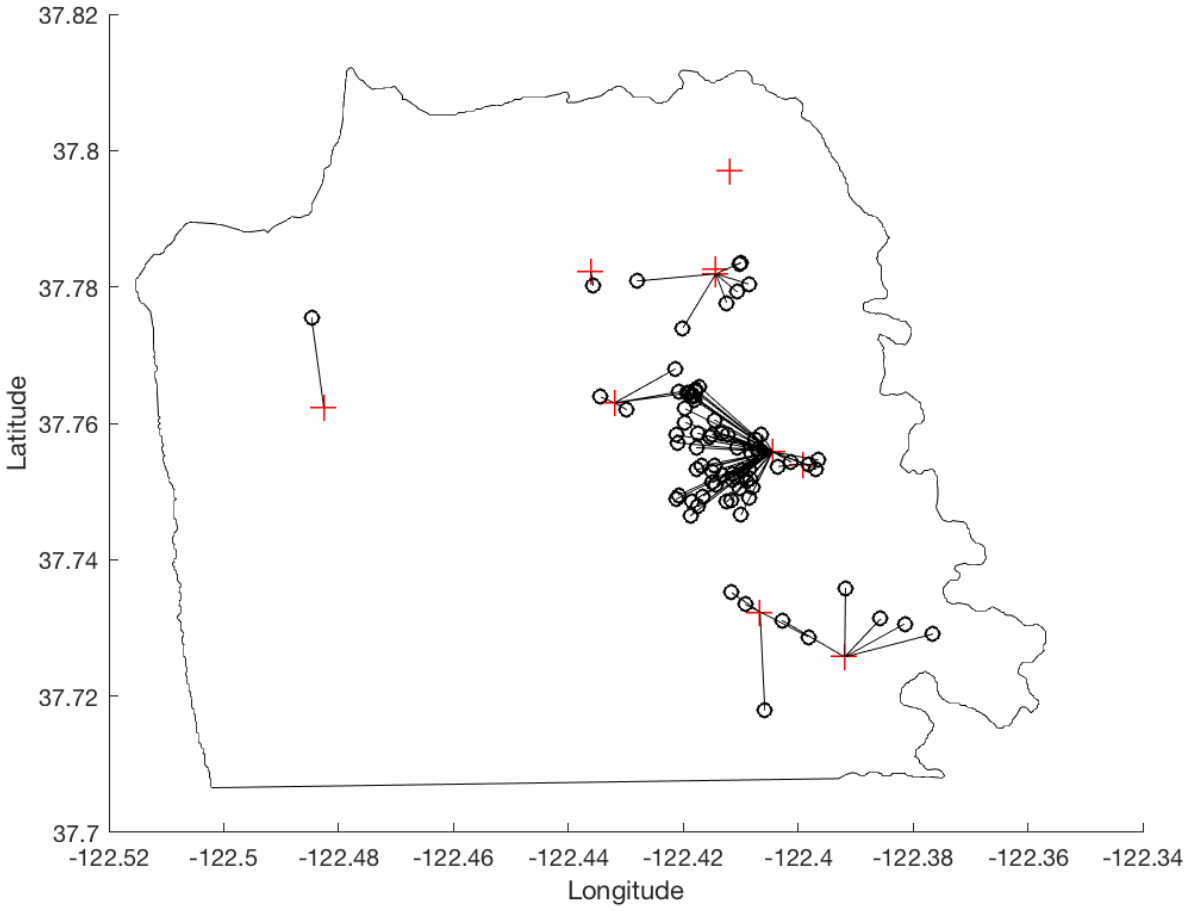


Figure 14. Patients with poorly controlled DM living greater than one mile from their primary care clinic. Patients in the cohort with poorly controlled DM (defined as a hemoglobin A1c >= 8.0 mg/dl) who live more than one mile from their primary care clinic were selected and mapped. Each patient is connected to his or her primary care clinic (red crosses) by a straight line.

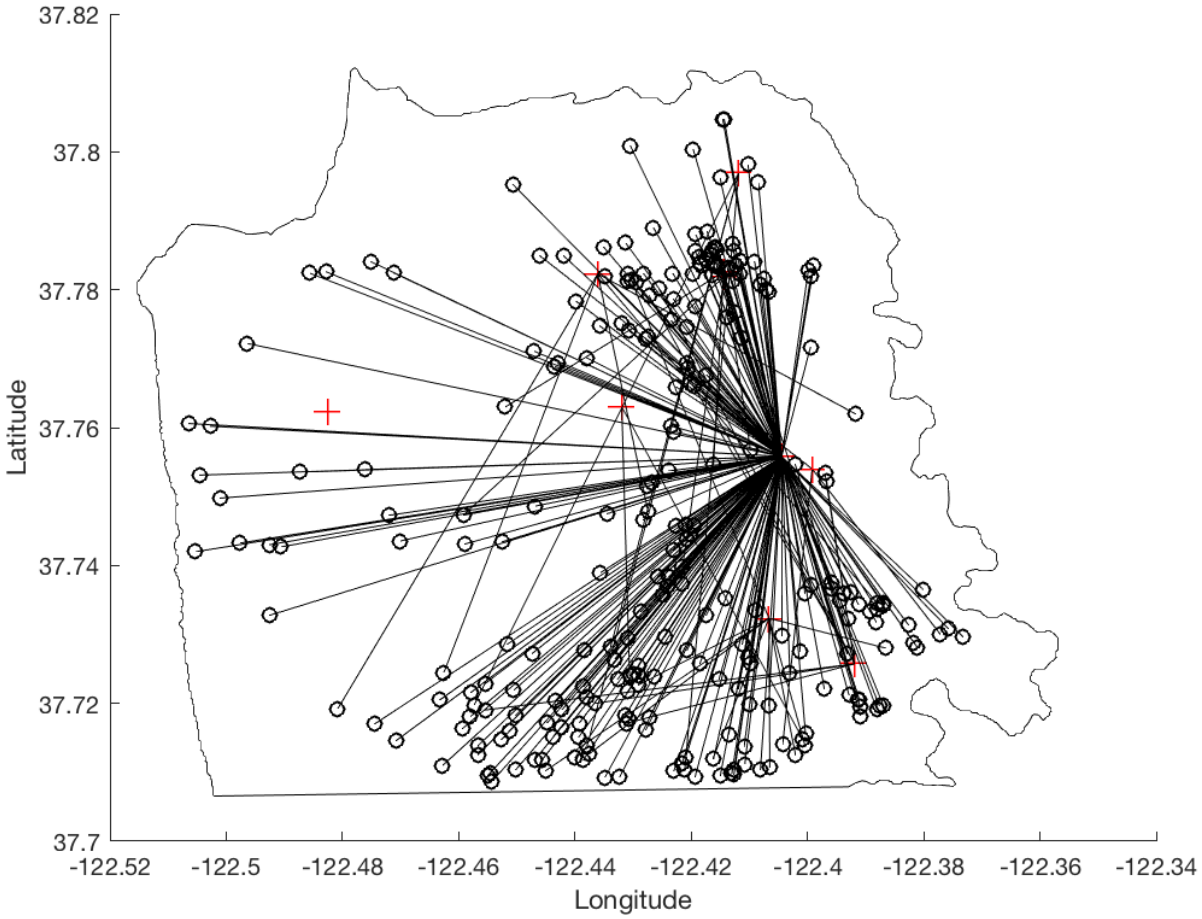
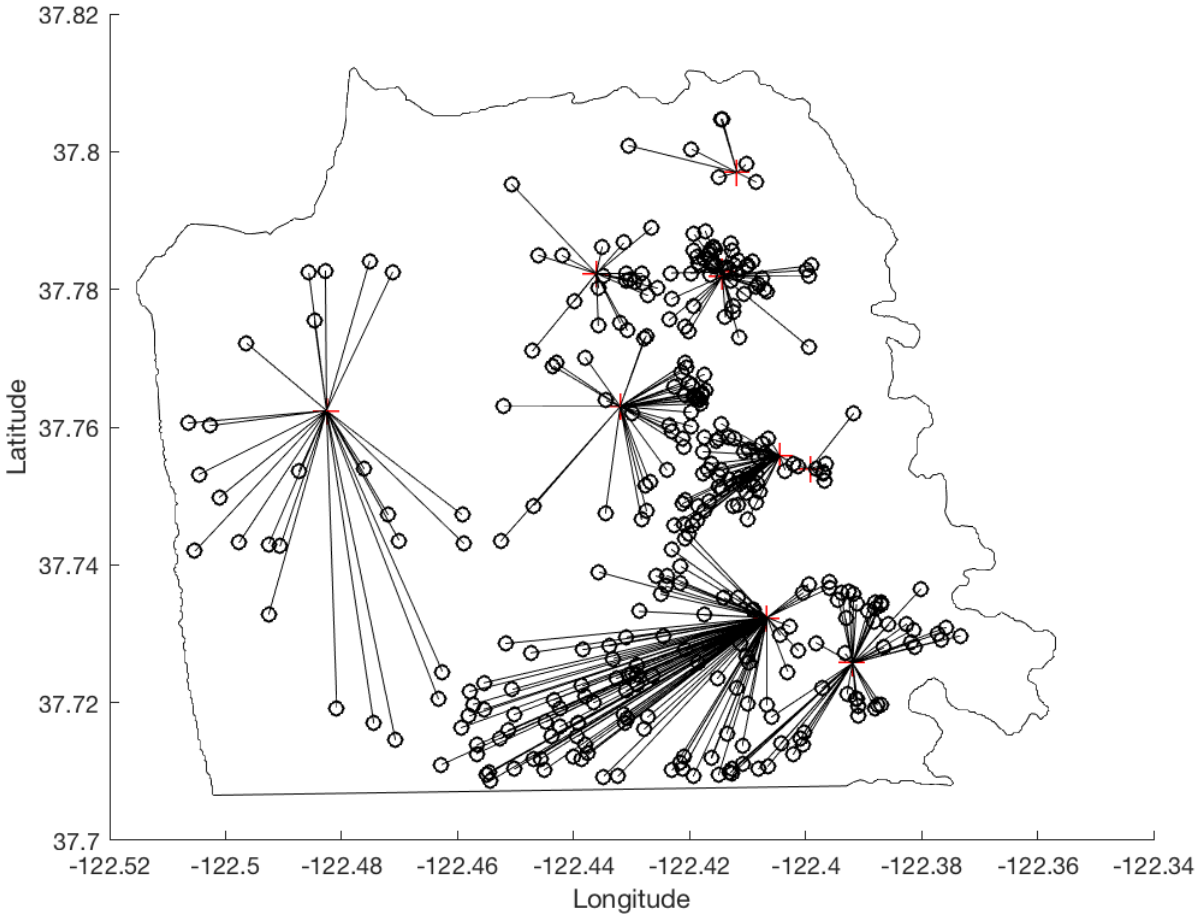


Figure 15. Distance optimized patient-primary care clinic network. The nearest clinic was determined for all patients in the cohort with poorly controlled DM (defined as a hemoglobin A1c >= 8.0 mg/dl). Each patient was mapped (black circles) and connected to their closest primary care clinic (red crosses) by a straight line.



Appendix B: Tables

Table 1. Population estimates for the state of California, by age group. All data were obtained from the United States Census Bureau, with links provided in the last column of the table. Age categories were selected to correspond to the age categories available for each year of hospital discharge data

	18-34 (%)	35-64 (%)	65+ (%)	Total	Source
1986	8608655 (42.9)	8593345 (42.8)	2855000 (14.2)	20057000	https://www.census.gov/popest/data/historical/1980s/state.html, https://www.census.gov/popest/data/state/asrh/1980s/tables/s5yr8090.txt, https://www.census.gov/popest/data/state/asrh/1980s/tables/estage80.txt
1991	9034477 (40.7)	9962939 (44.8)	3203956 (14.4)	22201372	https://www.census.gov/popest/data/historical/1990s/state.html, https://www.census.gov/popest/data/state/asrh/1990s/tables/ST-99-09.txt, https://www.census.gov/popest/data/state/asrh/1990s/tables/ST-99-08.txt
1996	8330389 (36.4)	11034261 (48.2)	3519180 (15.4)	22883830	https://www.census.gov/popest/data/historical/1990s/state.html, https://www.census.gov/popest/data/state/asrh/1990s/tables/ST-99-09.txt, https://www.census.gov/popest/data/state/asrh/1990s/tables/ST-99-08.txt
2001	8723334 (34.7)	12779012 (50.8)	3651646 (14.5)	25153992	https://www.census.gov/popest/data/intercensal/state/tables/ST-EST00INT-02/ST-EST00INT-02-06.csv
2006	9025589 (33.5)	13973084 (51.8)	3927830 (14.6)	26926503	http://factfinder.census.gov/bkmk/table/1.0/en/ACS/06_EST/DP5/0400000US06
2011	9153059 (33.1)	14344790 (51.8)	4167833 (15.1)	27665682	http://factfinder.census.gov/bkmk/table/1.0/en/ACS/11_5YR/DP05/0400000US06

Table 2. ICD-9-CM diagnosis codes. All codes come from the ICD-9-CM (clinical modification). They represent the conditions that were scanned for in the primary diagnosis code field for all hospital admissions. These were: all infections, pneumonia, sepsis, urinary tract infection, skin and soft tissue infection, myocardial infarction and cerebrovascular accident

All infections: 001-139, 320, 321, 323, 324, 325, 326, 360.00, 360.01. 360.02, 360.03, 360.04, 360.13, 370.05, 370.55, 372.00. 372.15, 372.2, 373.0, 373.1, 373.4, 373.5, 373.6, 376.01, 376.02, 376.03, 376.12, 376.13, 379.09, 380.0, 380.1, , 382, 383.0, 383.1, 383.2, 386.33, 386.35, 390, 391, 415.12, 420, 421, 422, 424.9, 451, 460, 461, 462, 463, 464, 465, 466, 473, 475, 480-488, 490-491, 510, 511.1, 513, 521.0, 522.0, 522.1, 522.4, 522.5, 522.6, 522.7, 523.0, 523.1, 523.3, 523.4, 527.3, 528.3, 528.5, 529.0, 530.19, 540-542, 562.01,562.11, 562.03, 562.13, 566, 567.0, 567.1, 567.2, 567.3, 569.5, 569.71, 572.0, 572.1, 573.1, 573.2, 574.0, 574.3, 574.6, 574.8, 575.0, 575.1, 576.1, 590, 595.0-4], 595.89, 595.9, 597.0, 599.0, 601.0, 601.1, 601.2, 601.3, 601.4, 601.9, 604, 608.0, 608.4, 611.0, 614.0-5, 614.7-9, 615, 616.0-1, 616.3-4, 680-686, 695.3, 696.3, 696.4, 696.5, 711.0, 711.4, 711.5, 711.6, 711.7, 711.8, 711.9, 728.0, 728.86, 730.0, 730.1, 730.2, 730.3, 730.8, 790.7, 790.8, 958.3, 996.6, 997.31, 997.62, 998.5, 999.0, 999.3, V02, V08, V09

Sepsis: 038, 995.91, 995.92

Pneumonia: 480-486, 487.0

Skin and soft tissue infection (SSTI): 680-686, 695.3, 614.3, 728.86, 608.4

Urinary tract infection (UTI): 590 (except 590.0), 595.0, 595.3, 595.4, 595.8, 597.0, 599.0, 601.0, 601.2-4

Myocardial infarction (MI): 410

Cerebrovascular accident (CVA): 430-434, 436

Table 3. Demographic characteristics of adult hospitalizations in California, 1986-2011. All demographic characteristics were available hospitalizations, although beginning in 1996, gender was randomly masked for twenty percent of all observation in the publically available data used here. In the bottom row, the number of hospitalizations for which a diagnosis of diabetes was present is listed.

	1986 N (%)	1991 N (%)	1996 N (%)	2001 N (%)	2006 N (%)	2011 N (%)
Total	1613983 (100)	1668539 (100)	1407614 (100)	1581543 (100)	1669897 (100)	1783145 (100)
Male	801294 (0.5)	823372 (0.49)	566721 (0.40)	640924 (0.41)	686558 (0.41)	742833 (0.42)
Female	812626 (0.5)	845138 (0.51)	658347 (0.47)	755189 (0.47)	790303 (0.47)	846160 (0.47)
Unknown	63 (< 0.01)	29 (< 0.01)	182546 (0.13)	185430 (0.12)	193036 (0.12)	194152 (0.11)
White	1160161 (0.72)	1156210 (0.69)	814302 (0.58)	890060 (0.56)	876063 (0.52)	865693 (0.48)
Black	160691 (0.10)	163548 (0.10)	99275 (0.07)	104152 (0.06)	110386 (0.07)	126714 (0.07)
Latino	209391 (0.13)	248998 (0.15)	148992 (0.11)	194002 (0.12)	235378 (0.14)	303554 (0.17)
Asian	55415 (0.03)	78994 (0.05)	43539 (0.03)	62253 (0.04)	76389 (0.04)	90878 (0.05)
Native	3109 (< 0.01)	3977 (< 0.01)	1139 (< 0.01)	1343 (< 0.01)	1365 (<0.01)	1808 (<0.01)
Other	14673 (< 0.01)	9025 (< 0.01)	8557 (< 0.01)	15103 (<0.01)	23426 (0.01)	32218 (0.02)
Unknown	10543 (< 0.01)	7787 (< 0.01)	291810 (0.21)	314630 (0.20)	346890 (0.21)	362280 (0.20)
18-34 yrs	281657 (0.17)	257645 (0.15)	165555 (0.12)	139697 (0.09)	149155 (0.09)	165211 (0.09)
35-64 yrs	527601 (0.33)	565749 (0.34)	529402 (0.38)	604262 (0.38)	673988 (0.40)	733250 (0.41)
65yrs+	804725 (0.50)	845145 (0.51)	712657 (0.50)	837584 (0.53)	846754 (0.51)	884684 (0.50)
Diabetes	161824 (0.10)	216804 (0.13)	266736 (0.19)	375224 (0.24)	474092 (0.28)	559018 (0.31)

Table 4. Age adjusted rates of hospitalization for diabetes mellitus-associated infectious and non-infectious syndromes among hospitalized adults in California, 1986-2011. The rates for each year, along with the overall trend (mean change in the rate) are presented. The following abbreviations are used: myocardial infarction (MI), cerebrovascular accident (CA), pneumonia (PNA), skin and soft tissue infection (SSTI), urinary tract infection (UTI).

	DM	Rate (Hospitalizations/100,000 persons)						Rate Trend (change in hosp/year)	p	Correlation (Spearman)
		1986	1991	1996	2001	2006	2011			
MI	+	42.1	48.8	55.8	72.8	65.8	66.2	1.08	**.03**	0.83
	-	190.4	178.3	158.9	158.6	115.9	101.0	-3.62	**.002**	-1.0
CVA	+	46.1	51.9	59.9	65.1	61.9	68.4	0.83	**.006**	0.94
	-	204.1	192.6	178.6	168.8	135.4	130.5	-3.14	**.001**	-1.0
PNA	+	28.4	48.2	61.4	86.0	84.9	74.3	2.08	**.03**	0.77
	-	293.1	342.8	268.5	278.9	211.6	160.8	-5.96	**.02**	-0.88
SSTI	+	19.1	24.7	26.2	37.4	51.1	54.3	1.52	**.001**	1.0
	-	105.3	97.0	87.4	92.7	114.1	105.4	0.32	.55	0.43
UTI	+	19.9	26.7	30.3	41.7	49.7	49.4	1.30	**.001**	0.94
	-	113.3	115.9	88.8	101.9	104.2	96.4	-0.61	.25	-0.54
Sepsis	+	11.5	21.1	38.1	35.5	81.9	163.2	5.4	**.02**	0.94
	-	60.4	81.0	98.3	72.2	137.5	264.7	6.6	**.05**	0.83

Table 5. Comparison of rates for all conditions in adults with DM. Rates were calculated using all data (gray columns) as well as a subset (white columns) of the data for which it was possible to classify observations into CDC age categories (age categories not masked). All rates reported are per 100,000 adults with DM. Trends for the full and subset data (rate change/year) are provided in the final two columns.

	1996		2001		2006		2011			
	Full data	**Subset**	**Full data**	**Subset**	**Full data**	**Subset**	**Full data**	**Subset**	**Trend (Full)**	**Trend (Subset)**
Sepsis	38.1	33.7	35.5	34.2	81.9	76.5	163.2	152.3	8.4	8.0
UTI	30.3	26.5	41.7	39.0	49.7	46.0	49.4	45.6	1.3	1.3
Sepsis	61.4	54.2	86.0	82.2	84.9	79.7	74.3	69.8	0.76	0.89
UTI	26.2	22.2	37.4	32.8	51.1	43.2	54.3	45.8	1.96	1.62
Sepsis	55.8	49.4	72.8	70.4	65.8	61.7	66.2	60.9	0.48	0.51
UTI	59.9	53.1	65.1	63.4	61.9	58.5	68.4	63.4	0.44	0.52

Table 6. Rates of hospitalization for DM-associated infectious and non-infectious complications adjusted for DM prevalence among adults. All rates in the table are adjusted for DM prevalence in the specified year. Unlike the prior tables, the rates reported here are not relative to the entire adult population of California but, rather, to the adult populations of California with and without DM. Rates for persons with DM are shown in the rows shaded gray, while those for adults without DM are in unshaded rows.

	DM Status	Rate (Hospitalizations/100,000 persons)				Rate Trend (change in hosp/year)	p	Correlation (Spearman)
		1996	2001	2006	2011			
MI	+	711.0	577.5	365.2	378.8	-24.2	**.06**	-0.8
	-	155.6	169.1	128.5	109	-3.6	0.137	-1
CVA	+	763.8	518.4	339.0	390.2	-26.0	0.11	-0.8
	-	177.7	180.0	151.9	144	-2.6	0.081	-1
PNA	+	767.4	701.3	480.6	453.1	-23.3	**0.04**	-1.0
	-	265.5	288.0	236.0	176	-6.4	0.147	-1
SSTI	+	340.2	340.6	404.2	403.1	5.0	0.11	0.8
	-	82.0	80.0	100.1	96	1.3	0.190	1
UTI	+	397.7	358.9	310.1	315.1	-5.9	**.07**	-0.8
	-	87.2	100.8	111.7	103	1.2	0.255	1
Sepsis	+	477.0	292.5	467.2	1000	34.9	0.26	0.4
	-	97.9	75.6	154.7	291	13.1	0.121	1

Table 6. Effect of medication interaction terms on odds ratio estimates for the associations of three classes of medications with presentation for an infection at an outpatient, inpatient or emergency room visit. Columns represent the different medication classes (ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; STAT, statin; BB, beta-blocker. Binary interaction terms are represented by an '*' between two medication classes. Rows marked as 'included' (in black), indicate the variables included in the model for which the odds ratio estimates for a specific class of medication are given. Ninety-five percent confidence intervals are given in parentheses.

				Medications and Interaction terms			
		ACEI/ARB	**BB**	**STAT**	**ACEI/ARB * BB**	**ACEI/ARB * STAT**	**BB * STAT**
Glipizide + Metformin	Included						
	OR	0.55 (0.40, 0.75)					
	Included						
	OR		0.66 (0.43, 1.00)				
	Included						
	OR			0.62 (0.44, 0.88)			
	Included						
	OR	0.58 (0.42, 0.81)	0.81 (0.52, 1.25)				
	Included						
	OR	0.56 (0.38, 0.81)	0.72 (0.35, 1.45)				
	Included						
	OR	0.60 (0.43, 0.84)		0.73 (0.50, 1.05)			
	Included						
	OR	0.61 (0.40, 0.91)		0.74 (0.44, 1.24)			
	Included						
	OR		0.74 (0.48, 1.16)	0.66 (0.46, 0.95)			
	Included						
	OR		0.71 (0.39, 1.27)	0.64 (0.42, 0.98)			
	Included						
	OR	0.62 (0.44, 0.87)	0.86 (0.55, 1.35)	0.74 (0.51, 1.09)			
	Included						
	OR	0.60 (0.41, 0.87)	0.76 (0.38, 1.53)	0.75 (0.51, 1.09)			
	Included						
	OR	0.62 (0.42, 0.94)	0.86 (0.55, 1.35)	0.76 (0.45, 1.27)			
	Included						
	OR	0.62 (0.44, 0.87)	0.84 (0.47, 1.51)	0.74 (0.48, 1.14)			
	Included						
	OR	0.61 (0.40, 0.93)	0.76 (0.38, 1.52)	0.77 (0.46, 1.29)			
	Included						

	OR	0.60 (0.41, 0.88)	0.76 (0.37, 1.58)	0.75 (0.48, 1.16)			
	Included						
	OR	0.63 (0.42, 0.94)	0.84 (0.47, 1.50)	0.75 (0.44, 1.27)			
	Included						
	OR	0.61 (0.39, 0.95)	0.75 (0.36, 1.56)	0.77 (0.46, 1.30)			
Glyburide+ Metformin	Included						
	OR	0.51 (0.37, 0.70)					
	Included						
	OR		0.64 (0.42, 0.97)				
	Included						
	OR			0.61 (0.43, 0.86)			
	Included						
	OR	0.56 (0.38, 0.81)	0.72 (0.35, 1.45)				
	Included						
	OR	0.51 (0.35, 0.75)	0.70 (0.35, 1.40)				
	Included						
	OR	0.56 (0.40, 0.77)		0.73 (0.51, 1.06)			
	Included						
	OR	0.55 (0.36, 0.83)		0.72 (0.43, 1.18)			
	Included						
	OR		0.72 (0.47, 1.12)	0.65 (0.46, 0.93)			
	Included						
	OR		0.66 (0.37, 1.17)	0.62 (0.40, 0.94)			
	Included						
	OR	0.57 (0.41, 0.81)	0.86 (0.55, 1.34)	0.75 (0.52, 1.09)			
	Included						
	OR	0.55 (0.37, 0.80)	0.74 (0.37, 1.48)	0.75 (0.52, 1.09)			
	Included						
	OR	0.56 (0.37, 0.85)	0.86 (0.55, 1.34)	0.73 (0.44, 1.21)			
	Included						
	OR	0.57 (0.41, 0.81)	0.81 (0.46, 1.43)	0.72 (0.47, 1.43)			
	Included						
	OR	0.55 (0.35, 0.84)	0.74 (0.38, 1.47)	0.75 (0.46, 1.22)			
	Included						
	OR	0.55 (0.37, 0.81)	0.72 (0.35, 1.48)	0.73 (0.47, 1.13)			
	Included						
	OR	0.57 (0.38, 0.86)	0.81 (0.46, 1.43)	0.72 (0.43, 1.20)			
	Included						

	OR	0.55 (0.35, 0.86)	0.72 (0.35, 1.48)	0.74 (0.44, 1.22)			
Insulin+ Metformin	Included						
	OR	0.57 (0.42, 0.78)					
	Included						
	OR		0.69 (0.45, 1.05)				
	Included						
	OR			0.66 (0.46, 0.94)			
	Included						
	OR	0.51 (0.35, 0.75)	0.70 (0.35, 1.40)				
	Included						
	OR	0.58 (0.40, 0.83)	0.75 (0.37, 1.51)				
	Included						
	OR	0.61 (0.44, 0.85)		0.76 (0.52, 1.10)			
	Included						
	OR	0.62 (0.42, 0.92)		0.77 (0.46, 1.28)			
	Included						
	OR		0.76 (0.49, 1.18)	0.70 (0.48, 1.01)			
	Included						
	OR		0.73 (0.41, 1.30)	0.68 (0.44, 1.04)			
	Included						
	OR	0.63 (0.45, 0.88)	0.87 (0.55, 1.37)	0.77 (0.53, 1.14)			
	Included						
	OR	0.61 (0.42, 0.88)	0.78 (0.39, 1.58)	0.77 (0.52, 1.14)			
	Included						
	OR	0.64 (0.43, 0.95)	0.87 (0.55, 1.37)	0.78 (0.47, 1.31)			
	Included						
	OR	0.63 (0.45, 0.88)	0.86 (0.48, 1.53)	0.76 (0.49, 1.19)			
	Included						
	OR	0.62 (0.41, 0.94)	0.78 (0.39, 1.56)	0.80 (0.48, 1.32)			
	Included						
	OR	0.61 (0.42, 0.89)	0.78 (0.38, 1.62)	0.77 (0.49, 1.20)			
	Included						
	OR	0.64 (0.43, 0.95)	0.85 (0.48, 1.52)	0.78 (0.46, 1.31)			
	Included						
	OR	0.62 (0.41, 0.96)	0.77 (0.37, 1.60)	0.80 (0.48, 1.33)			

Table 7. Demographic and clinical characteristics of cohort of persons with diabetes. All patients in the cohort were identified from pharmacy records to identify patients with diabetes by querying for prescriptions for one of four medications: glyburide, glipizide, metformin and insulin. All visits between 1/1/2008 and 1/31/2009 were extracted for all of the patients thus identified.

	N (%)	Mean +/- Standard Deviation
Total Persons in cohort	743 (100)	--
Gender		
Male	368 (49.5)	--
Female	375 (50.5)	--
Age	--	53.7 +/- 9.9
Race		
Asian	219 (29.4)	--
Black	103 (13.9)	--
Hispanic	309 (41.6)	--
Native American/Pacific Islander	17 (2.2)	--
White	81 (9.4)	--
Other/Unknown	27 (3.3)	--
Clinical characteristics		
A1c	--	8.3 +/- 2.1
Total visits for persons in cohort	4776	--
Inpatient	283 (5.9)	--
Outpatient	4226 (88.4)	--
Emergency/Urgent care	267 (5.6)	--
Visits for an infection	236	--
Dermatophyte	50 (21.1)	--
Pneumonia	23 (9.7)	--
Sepsis/Bacteremia	2 (0.8)	--
Skin and soft tissue infection	68 (28.8)	--
Upper respiratory infection	48 (20.3)	--
Urinary tract infection	32 (13.6)	--

Table 8. Association of commonly used classes of medications in persons with diabetes with hospital, clinic or emergency visit for an infection. All odds ratio estimates are from longitudinal multiple regression models. Ninety-five percent confidence intervals for all estimates are shown in parentheses. The first column shows the unadjusted odds ratio estimates, while subsequent columns show the effect of adjusting for age, race, hemoglobin A1c level and all three simultaneously.

	Odds Ratios (95% Confidence Interval)				
	Adjustment				
Medication	Unadjusted	Age	Race	A1c	Age, Race, A1c
Glipizide	0.56 (0.34, 0.92)	0.59 (0.36, 0.98)	0.57 (0.35, 0.95)	0.58 (0.35, 0.94)	0.63 (0.38, 1.03)
Glyburide	1.33 (0.89, 1.98)	1.39 (0.93, 2.08)	1.43 (0.96, 2.13)	1.30 (0.87, 1.94)	1.44 (0.95, 2.18)
Insulin	0.66 (0.44, 1.00)	0.64 (0.42, 0.96)	0.62 (0.42, 0.92)	0.63 (0.42, 0.94)	**0.57 (0.39, 0.85)**
Metformin	0.69 (0.50, 0.96)	0.68 (0.49, 0.95)	0.75 (0.53, 1.05)	0.71 (0.51, 0.98)	0.76 (0.54, 1.06)
ACEI/ARB	0.50 (0.36, 0.70)	0.53 (0.37, 0.74)	0.49 (0.36, 0.68)	0.51 (0.36, 0.72)	**0.52 (0.37, 0.72)**
ASA	1.34 (0.79, 2.28)	1.41 (0.83, 2.40)	1.24 (0.77, 2.02)	1.35 (0.80, 2.28)	1.30 (0.80, 2.12)
Beta Blocker	0.62 (0.39, 1.00)	0.66 (0.41, 1.08)	0.57 (0.37, 0.87)	0.64 (0.40, 1.02)	**0.61 (0.40, 0.93)**
Statin	0.55 (0.39, 0.78)	0.57 (0.40, 0.81)	0.56 (0.40, 0.78)	0.56 (0.40, 0.79)	**0.58 (0.41, 0.81)**

Table 9. Adjusted associations of adjunctive medications commonly used in persons with diabetes by diabetes treatment regimen. All odds ratio estimates are from longitudinal multiple regression models that account for medication interactions and are adjusted for age, race, and hemoglobin A1c.

Diabetes Treatment Regimen	Medication	Odds Ratio (95% Confidence Interval)
Glipizide/Metformin	ACEI/ARB	**0.61 (0.39, 0.95)**
	Beta Blocker	0.75 (0.36, 1.56)
	Statin	0.77 (0.46, 1.30)
Glyburide/Metformin	ACEI/ARB	**0.55 (0.35, 0.86)**
	Beta Blocker	0.72 (0.35, 1.48)
	Statin	0.74 (0.44, 1.22)
Insulin/Metformin	ACEI/ARB	**0.62 (0.41, 0.96)**
	Beta Blocker	0.77 (0.37, 1.60)
	Statin	0.80 (0.48, 1.33)