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The Association Between Latent Tuberculosis Infection and Diabetes Mellitus Control in the United States

Whitney L. Remy
University of Kentucky

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Whitney L. Remy, Student

David Mannino, MD, Committee Chair

Corrine Williams, ScD, MS, Director of Graduate Studies

The Association Between Latent Tuberculosis Infection and Diabetes Mellitus Control in the United States

Whitney L. Rémy

University of Kentucky College of Public Health

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Committee Members:

David M. Mannino, MD - chair

April Young, PhD

Wayne T. Sanderson, PhD

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Abbreviations

TB	Tuberculosis
LTBI	Latent Tuberculosis Infection
DM	Diabetes Mellitus
TST	Tuberculin skin test
QFT-G or QFT-GIT	QuantiFERON®-TB Gold In-Tube blood test
HbA_{1c} or A_{1c}	Hemoglobin A1c
CDC	Center for Disease Control
NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
MEC	Mobile Examination Centers
CAPI	Computer-Assisted Personal Interview
Audio - CASI	Audio Computer-Assisted Self Interview
IFN-y	Interferon gamma
ELISA	Enzyme-linked immunosorbent assay
SAS	Statistical Analysis System
BMI	Body Mass Index
SES	Socioeconomic Status
AIC	Akaike information criterion

Abstract

Rationale: Diabetes mellitus (DM) is recognized as a common comorbid condition for tuberculosis (TB). Those with comorbid conditions are more likely to develop active TB, to have trouble with treatment, and to have more severe symptoms.

Objective: To measure the prevalence and distribution of latent tuberculosis infection (LTBI) and DM control in the United State and test their association when measured by tuberculin skin test (TST) or QuantiFERON®-TB Gold In-Tube blood test (QFT-GIT) and by HbA1c, respectively.

Literature Review: One-third of the world population is infected with TB. Ten percent of TB cases worldwide are linked to diabetes mellitus. Studies have found that the risk of TB increases with the presence of DM.

Methods: This is a cross-sectional, secondary analysis study of the 2011-2012 National Health and Nutrition Examination Survey. The study population included 4,222 participants. Frequency and proportions of each variable were calculated. Then calculations of the frequency and conditional distribution of LTBI for the predictors were made. The chi-square test of association was used to test relationship between LTBI and DM control. Finally, unadjusted and adjusted odds of LTBI were calculated using binary and multiple logistic regressions, respectively.

Main Results: The chi-square test of association found that LTBI and DM control are not independent. The unadjusted logistic regression showed significantly increased odds of having LTBI for those with HbA1c levels corresponding prediabetes and diabetes compared to those with normal HbA1c levels, which the adjusted logistic regression did not.

Conclusion: This study found that LTBI and DM control were associated. There was increased likelihood of having LTBI with poorer diabetes mellitus control, however, the increased odds disappeared when accounting for covariates. Word Count: 272

Introduction

Identification and management of comorbid conditions are becoming essential elements for successful tuberculosis (TB) control programs, especially in regions with high incidence of TB. Health organizations around the world are recognizing a rapidly increasing trend of TB cases concomitant with communicable or noncommunicable diseases. These comorbidities are significantly affecting the incidence and prevalence rates of TB (Narasimhan, Wood, MacIntyre and Mathai, 2013). Those with comorbid conditions are more likely to develop active TB from exposure to Mycobacterium tuberculosis, to have reactivation of the disease from latent tuberculosis infection (LTBI), to have an increased likelihood of treatment relapse and to express more severe symptoms when active with TB disease (Narasimhan et al., 2013). Even regions of the world with low prevalence of TB are beginnning to notice the effect of comorbid burdens, especially in their most at- risk populations.

Diabetes mellitus (DM) has become recognized as the most common comorbid condition for TB. Health organizations in regions endemic for TB have deemed it more common than even the more severe and widely known co-infection, HIV/AIDS (Garcia-Elorriaga & Del Rey-Pineda, 2014). The trend of this connection between DM and TB is found in both low and high incidence countries. The United States is a low incidence country. Typically, the TB health burden in low incidence countries rests on the most vulnerable portions of the population. These groups are more likely to be burdened due to recent exposure because of migration from higher incidence countries or because of the effects of health disparities. In any case, transmission is low in non-endemic countries, so most TB cases arise due to reactivation of latent tuberculosis infection (LTBI) from past exposure.

Specific Aims:

The purpose of this study is to assess the relationship between latent tuberculosis infection (LTBI) and diabetes mellitus (DM) control in the United States. This study aims to determine if there is a significant statistical association between the nationwide prevalence trends and also to review the influence of confounders, effect modifiers, and covariates on that relationship. In developed, high-income countries like the United States, LTBI is most prevalent in groups. This study will also highlight some of the most at-risk subpopulations that are more likely to be affected by health disparities or are most likely to have had previous exposure thus, are most vulnerable to developing concomitant DM/TB.

Objectives:

1. To test the association of the DM control measured by hemoglobin A_{1C} levels to LTBI identified by tuberculin skin test measurements and QuantiFERON blood test results.
2. To assess the prevalence and distribution of LTBI and DM control in the US population in the year span of 2011-2012.

Literature Review

The following is a review of the literature outlining important concepts for understanding the nature of the relationship between tuberculosis and diabetes mellitus. The references cited include published scholarly articles, organizational reports, public health organization and governmental fact sheets and websites. Searches for these sources were performed using Google search engine, Google Scholar, Endnote, and PubMed Central databases. The works cited only includes articles and documents published in English. Keywords and phrases used in searches

include: *latent tuberculosis infection, tuberculosis and diabetes mellitus, diabetes mellitus control, glycemic control, bidirectional screening, co-epidemic of communicable and noncommunicable diseases, tuberculosis in the United States, diabetes epidemic, risk factors for diabetes, risk factors for tuberculosis, national and global prevalence, comorbidity, WHO, CDC, developed country, developing country, epidemiology, DR- & MDR-TB, race and ethnicity and tuberculosis, socioeconomic status and tuberculosis, tuberculosis in low incidence country, risk factors, U.S. and global statistics, and etc.* Additional sources were found by subsequent review of the bibliography of previously found works cited. The review begins with a summary of current health burden of tuberculosis and latent tuberculosis infection highlighting key characteristics of the disease in the 21st century. Then it goes on to describe the global epidemic of diabetes mellitus and explores aspects of its convergence with tuberculosis.

Global epidemiology of tuberculosis (TB):

The CDC reports that one-third of the world's population is infected with TB, second only to HIVAIDS as an infectious disease killer worldwide ("Data and Statistics," 2014; "Tuberculosis," 2016). Some 9.6 million persons became sick with TB resulting in 1.5 million TB-related deaths worldwide in 2014 ("Data and Statistics," 2015). At least 58% of these cases were in South-East Asia and Western Pacific regions ("Global Tuberculosis Report," 2015). According to the WHO, 95% of TB-related deaths occur in low- and middle- income countries ("Tuberculosis," 2016). The Millennium Development Goal target of halting and reversing TB has been met throughout the world, and incidence has fallen 1.5% per year since 2000 leading to a current rate 18% lower than the incidence level in 2000 ("Tuberculosis," 2016). The new Sustainable Development Goal is to end the TB epidemic by 2030 ("Tuberculosis," 2016). Currently the WHO also reports that

the death rate due to TB has dropped 47% between 1990 and 2015 with an estimated 43 million lives saved by diagnosis and treatment by 2000 and 2014 ("Tuberculosis," 2016). The WHO established a global reporting system in 1995, which has since reported 78 million TB cases with 66 million of them successfully treated ("Global Tuberculosis Report," 2015).

Active Tuberculosis in the United States:

Reports for 2014 indicated an overall incidence rate of 3.0 cases per 100,000 persons in the United States between 2013 and 2015 (Salinas, Mindra, Haddad, Pratt, Price, & Langer, 2016). According to the CDC, 9,421 TB cases were reported in the United States in 2014 (with a rate of 2.96 cases per 100,000 persons), and other sources indicate a preliminary count of 9,563 TB cases reported for 2015 ("Data and Statistics," 2015; Kanabus, 2016). Similar to the global trend, the rate of tuberculosis in the United States is steadily declining. In 2014, the number of TB cases reported decreased 1.5% and the case rate decreased 2.2% from the number reported in 2013 (Scott, Kirking, Jefferies, & Price, 2015). Though the number of TB-related deaths was 555 in 2013, which was an 8%, increase from the previous year, the annually reported number of fatalities has declined 67% since 1992 (Scott et al., 2015). Despite the stable nature of TB in the United States, the goal of elimination set in 1989 (recommitted in 1999) has not been met, and the decline rate has experienced the smallest decrease in decades (Scott et al., 2015). In fact, most recent reports affirm a leveling or stalling of the decline or reduction of most measures for TB, but experts are striving to develop effective methods of TB detection and treatment (Salinas et al., 2016).

Latent M. tuberculosis infection (LTBI):

LTBI refers to a "state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB" ("Latent Tuberculosis" 2014). The primary differences between latent and active tuberculosis infection is that the former is without symptoms, non-infectious, sputum smear test results are negative, has normal chest X-ray findings and the treatment focus is to prevent progression to active disease (Hartman-Adams, Clark, & Juckett, 2014). LTBI is a major factor hindering complete elimination of tuberculosis, even in low-risk countries like the United States. Most cases of TB arise from reactivation of LTBI instead of new exposures; this is particularly evident in high-risk groups or vulnerable subpopulations (Scott et al., 2015). The WHO estimates that one in three people in the world has an LTBI and are at risk of TB reactivation ("Latent Tuberculosis," 2014) This includes the estimate for the U.S. of 11 million persons with LTBI ("Latent Tuberculosis Infection, 2014; "Tuberculosis & Diabetes," 2015). It is estimated that the lifetime risk of TB reactivation is 5-10% with 50% of this risk being in the first five years of initial infection, and the risk is higher when predisposing risk factors are present ("Latent Tuberculosis," 2014; Hartman-Adams et al., 2014). The CDC equates this reactivation probability to 550,000 to 1,100,000 people developing TB in their lifetime without appropriate treatment for LTBI ("Latent Tuberculosis Infection" 2014).

Progression from TB to LTBI: Screening practices and risk factors:

Risk of progression to disease from infection with *Mycobacterium tuberculosis* is one of the focuses of most TB control strategies in use today. The risk is mitigated by monitoring exposure to exogenous risk factors, screening, and treatment (Narasimhan et al., 2013). Identification and

treatment of LTBI is the key to TB elimination especially in persons with coexisting risk factors ("Targeted Tuberculin Testing," 2000; "Latent Tuberculosis," 2014; "Targeted Tuberculin Testing," 2000). Strong screening practices have significantly helped keep the incidence and prevalence of TB down in all regions of the world because a decision to test for TB is typically a decision to provide follow-up treatment ("Targeted Tuberculin Testing," 2000). There are multiple screening methods available to identify LTBI; the choice is made based on the exposure situation and type of clinical presentation. In most cases, proactive screening is done using tests like the Tuberculin Skin Test or IGRAs (Interferon-Gamma Release Assays) (i.e. QuantiFERON® Gold in Test Tube blood test) ("Latent Tuberculosis," 2014). These tests are widely used in non-endemic regions like the United States. In endemic areas with high incidences of active TB disease these tests are not favorable. They cannot differentiate between immune responses due to viable (and infectious) microorganisms and healed/treated infections, nor do they accurately predict which infected cases will actually progress to active TB ("Latent Tuberculosis," 2014). Also, preventive measures like the BCG vaccine, widely used in these regions, can produce confounding immune response results; this is especially true with tuberculin skin tests (TST) ("Targeted Tuberculin Testing," 2000; Belknap, Wall, & Reves, 2008). Sweeping, routine screening is avoided bases on recommendations made by public health experts. They state that the application of routine testing outside of high-risk groups produces "more false-positive results" and "creates needless anxiety" (Hartman-Adams et al., 2014). Primary care providers are the front line towards elimination of the disease responsible for finding high-risk groups and promoting active screening efforts in endemic and non-endemic regions alike ("Latent Tuberculosis Infection," 2014). Such efforts have worked well in countries like the United States to reduce incidence of active TB to the current low rates ("Targeted

Tuberculin Testing," 2000; Narasimhan et al., 2013). The "central pillar of the TB control in the U.S." is the targeted testing and treatment of high-risk population for LBTI as they serve as a reservoir of LTBI and the greatest challenge for eliminating active TB from the U.S. population (Manuco, Diffenderfer, Ghassemieh, Horn, & Kao, 2016). This practice is called "targeted tuberculin testing" and current recommendations encourage a TB control strategy consisting of a combination of this and "preventive therapy" which is the treatment of LTBI before progression to disease ("Targeted Tuberculin Testing," 2000).

Several risk factors contribute to LTBI and TB disease at both individual and population levels (Narasimhan et al., 2013). One article arranges these risk factors into three categories: factors related to the index case, factors related to the individual, and finally demographic factors (Narasimhan et al., 2013). The first category includes factors that affect risk of infection (e.g. bacillary load at exposure or proximity to an infectious case); the second category relates to the factors characteristic to the at-risk individual; and the final group accounts for population characteristics (Narasimhan et al., 2013). These categories would be considered first by exposure situation then by population characteristics and finally by individual characteristics. Membership of certain subgroups will affect the influence of these categories. For example, in the United States, recent immigrants and foreign-born persons from high incidence countries, individuals living or working in institutional settings, the homeless, or patients and healthcare workers are at special risk (Narasimhan et al., 2013; Cain, Haley, Armstrong, Garman, Wells, Iademarco, Castro, & Laserson, 2006; Hartman-Adams et al., 2014). For a more specific example, there are factors like differences in the rate of active TB by ethnicity in the U.S. For example, the cases per 100,000 persons for is 18.9 Asians, 12.3 for Native Hawaiians/other Pacific Islanders, 6.3 for

American Indians/Alaska Natives, 5.8 for Blacks, 5.3 for Hispanics and 0.8 for Whites (Hartman-Adams et al., 2014). Sources find that the incidence and prevalence of active TB for these ethnic groups in the U.S. corresponds somewhat with the global distribution of those measures in high-incidence areas like most of the countries in African, Asia, Eastern Europe, Central American, and South America (Hartman-Adams et al., 2014). Additional individual level risk factors include "illicit drug use", "age younger than five", being underweight, abuse of alcohol, "immunosuppressive disease (e.g. AIDS, HIV, leukemia, lymphoma, chronic kidney disease requiring dialysis)", immunosuppressive therapy, lung parenchyma abnormalities in smokers and patients with lung cancer, being of a medically underserved or low-income groups, "abnormalities on chest X-rays displaying health fibrotic changes from past M.tuberculosis infection", and diabetes mellitus especially in cases with poor glycemic control (Hartman-Adams et al., 2014). Another source describes the risk of progression as a "two-stage process governed by both exogenous and endogenous risk factors. Exogenous factors play a fundamental role in accentuating the progression from exposure to infection (Garcia-Elorriaga & Del Rey-Pineda, 2014). It also goes on to describe endogenous factors similar to the three previously described plus two more: socioeconomic and behavioral factors and health system issues (Garcia-Elorriaga & Del Rey-Pineda", 2014).

Growing Global Burden of Diabetes Mellitus:

Diabetes mellitus (DM) is a disease where blood glucose levels are above normal because the body is either not making or cannot make use of insulin to prevent build-up of glucose in the blood and to help distribute it to the cells of the body ("Basics About Diabetes," 2015). DM is one of the few chronic diseases listed as a risk factor for TB. It is also a rapidly growing chronic

epidemic worldwide. According to the WHO, the prevalence of diabetes has "quadrupled since 1980 to 422 million (8.5%) in adults today" ("World Health Day," 2016). Currently, 29.1 million people have diabetes (21.0 million diagnosed and 8.1 million undiagnosed) in the U.S.; this accounts for 9.3% of the total population ("National Diabetes Statistics Report," 2014). Diabetes is the seventh leading cause of death in the United States, responsible for serious health complications such as heart disease, blindness, kidney failure, and lower-extremity amputations ("Basics about Diabetes," 2015). DM is typically diagnosed with the start of symptoms (i.e. frequent urination, excessive thirst, unexplained weight loss, extreme hunger, sudden vision changes, tingling or numbness in hands or feet, very dry skin, more infections than usual, and sores that are slow to heal) rather than regular screening ("Basics About Diabetes," 2015). The lifetime risk of progression from LTBI to active TB with DM is 30% compared to the 5-10% estimated previously without it (Hartman-Adams et al., 2014; "Latent Tuberculosis," 2014).

Five percent of diagnosed cases are Type 1 diabetic (insulin-dependent), 90-95% of all diagnosed cases are Type 2 diabetic (non-insulin-dependent), and 1%-5% of all diagnosed cases of diabetes result from other illnesses, genetic syndromes, surgery, drugs, malnutrition, and infections; other cases arise due to gestational diabetes which occurs only in pregnant women ("Basics About Diabetes," 2015). Common risk factors for Type 2 diabetes include a family history of DM, prior history of gestational diabetes, impaired glucose tolerance, older age, obesity, physical inactivity, and race/ethnicity, while the risks for Type 1 are less defined ("Basics About Diabetes," 2015). Type 1 and Type 2 DM are both treated by healthy eating, physical activity, and insulin injections, but Type 2 DM patients also require "oral medication, insulin, or both to control their blood glucose" ("Basics About Diabetes," 2015). Another DM

related classification of growing concern and relevant to this study is called prediabetes. Pre-diabetes is when the blood glucose level is higher than the normal range, but not high enough to be diagnosed with diabetes ("National Diabetes Statistics Report," 2015). Prediabetics are at a high risk of developing Type 2 diabetes, though not all cases progress to diabetes. Even so, experts state that without intervention the progress from prediabetes to diabetes would happen in 10 years or less ("National Diabetes Statistics Report," 2015; "Prediabetes," 2015).

History of the convergence:

The association between diabetes mellitus and tuberculosis has been observed and reported since quite early in medical history. Some sources cite reports made by ancient Greek philosophers like Avicenna around 1000 A.D. and texts written by Indian siddhars (saints) sometime in the 15th century (Restrepo, 2007). These accounts clearly describe conditions and symptoms that are now known to be attributed to concomitant diabetes mellitus and tuberculosis (Niazi & Kalra, 2012). In the early 20th century, European and American physicians conducted observational medical studies observing the serious distress of patients with DM/TB (Restrepo, 2007; Oscarsson, 2009; Root, 1934; Dillon, Boucot, Cooper, Meir, & Richardson, 1952; Banyi, 1931). These studies occurred before the development of modern synthetic insulin or effective mycobacterial drugs meaning these particular associations were observed when either condition was not able to be best controlled (Restrepo, 2007; Oscarsson, 2009, Root, 1934; Dillon et al., 1952; Banyi, 1931). There are even surveys administered before the 1960s, which determined that TB was 2-4 times more common in diabetics than in non-diabetics (Restrepo, 2007; Oscarsson, 1958; Root, 1934; Dillon et al., 1952; Banyi, 1931). It has been reported as far back as the 1930s that patients with DM have a 3 to 4-fold increased risk of developing TB (Garcia-

Elorriaga & Del Rey-Pineda, 2014; Restrepo, 2007). The studies and surveys highlighted the inclusion of juvenile subjects comorbid with insulin dependent (Type 1) diabetes and pulmonary tuberculosis in their results, while more recent studies reveal a sort of "rediscovery" of the relationship between DM and TB where the connection is being noticed more often in cases with Type 2 DM (Jeon & Murray, 2008; Baker et al., 2011). In any case, Type 1 DM still adds a stronger risk of contracting TB when present despite the fact that Type 2 DM is more prevalent (Niazi & Kara, 2012).

DM as a risk factor for TB:

The WHO reports that 10% of TB cases around the world are linked to diabetes, and the rapidly growing health burden of DM has taken the risk associated with TB from an individual level to a population level ("Tuberculosis & Diabetes," 2011; "Garcia-Elorriaga & Del Rey-Pineda", 2014; Restrepo, 2007). The WHO reports 2-3 times higher risk of TB in diabetics compared to people without DM ("Tuberculosis & Diabetes," 2011). DM is becoming a more common risk factor associated with TB ("Garcia-Elorriaga & Del Rey-Pineda", 2014). Now in endemic regions, the WHO recommends rigorous implementation of treatments for people with TB/DM ("Tuberculosis & Diabetes," 2011). The concern is that as the global burden of DM rises the efforts to reduce the incidence of TB will be undermined and all regions of the world – endemic and non-endemic – will witness an increase in TB cases (Baker et al., 2011; Jeon & Murray, 2008).

Efforts for TB control are now focused on preventive strategies prompting a shift in research to explore evolving risk factors influencing the spread of TB (Niazi & Kalra, 2012). Global and

local organizations are proactively collaborating in research and control program development resulting in the publication of guidelines like the *Collaborative Framework for Care and Control of Tuberculosis and Diabetes* ("Collaborative Framework," 2011). The summaries of consultation meetings to determine research gaps, update the knowledge base with recent discoveries, and provide consolidated recommendations to be disseminated ("Tuberculosis & Diabetes," 2011; Ottmani, Murray, Jeon, Baker, Kapur, Lonnroth, and Harries, 2010). The evidence available to support the association between DM and TB is limited according to the latest consultation meeting (Ottmani et al., 2010). The identified limitations are that "1) many of the studies were health facility-based, with a case-control design; 2) most of the studies were carried out in industrialized countries; and 3) none of the studies used the oral glucose tolerance test (OGTT) to diagnose DM" (Ottmani et al., 2010). These points address epidemiologic requirements for generalization of samples and accuracy of measures. Since these observations were made at this particular meeting in 2009, more studies have been performed outside of industrialized countries in developing regions in Sub-Saharan Africa, Asia, and South East Asia where TB is most prevalent in the world using differenct biomarkers for TB (Jeon & Murray, 2008; Baker et al., 2011).

Biological elements of the convergence:

A weak immune system increases the risk of progression from latent infection to active TB disease. Thus chronic illnesses like DM with immunosuppressive effects are understandably predisposing factors ("Tuberculosis & Diabetes," 2011). Actually, without considering connections to TB, DM is an independent risk factor for lower respiratory tract infections, and diabetics suffer more severe complications due to infections than non-diabetics (Niazi & Kalra,

2012). Growing evidence is demonstrating a consistently evolving relationship, and many source describe a bi-directional interaction where each disease exacerbates and increases the likelihood of adverse outcomes for the other (Niazi & Kalra, 2012). For example, DM increases the risk of progression to disease from infection, reactivation of latent infection, death during TB treatment, and of relapse after treatment, while concomitant DM/TB is associated with poor glycemic control in DM patients mostly due to the stress of the infection on the body (Garcia-Elorriaga & Del Rey-Pineda, 2014). It is important to note that it is diabetes, specifically DM control, observed as a predisposing factor to TB rather than TB infection leading to DM (Skowronski, Zozulinska-Ziotkiewicz, & Barinow-Wojewodzki, 2013). Nonetheless, increased screening for both conditions would improve outcomes for patients. Most studies show and experts are urging testing for DM, and subsequent efforts to maintain glycemic control to improve the outcome of TB treatment in endemic or high risk populations ("Tuberculosis & Diabetes," 2011; Garcia-Elorriaga & Del Rey-Pineda, 2014). Public health organizations like the WHO recommend that all persons with TB be screened for DM along with screening for TB in DM patients living in endemic or high-risk populations ("Tuberculosis & Diabetes," 2011). Early detection is crucial to controlling and reducing severity of both, but a significant portion of people with DM and TB are not diagnosed ("Tuberculosis & Diabetes," 2011).

There are many speculations of the pathogenesis of concomitant DM and TB. The complexity of the association lies in determining if DM increases susceptibility to initial TB infection or if it only increases the likelihood of progression from latent infection to active disease (Skowronski et al., 2013). In either case, diabetes studies in animal models and even human plasma cells prove that diabetes "impairs the innate and adaptive immune responses necessary to counter the

proliferation of TB" (Jeon & Murray, 2008). There is evidence of a reduced number of macrophages and a delayed innate immune response to the presence of infected alveolar macrophages in diabetics (Skowronski et al., 2013). Studies also observed that tuberculosis specific IFN-y-producing T cells migrated later to lymph nodes and the lungs (Skowronski et al., 2013). The adaptive immune response begins to express a shift to T helper 2 (Th2) cell bias and their cytokines, which correlates with susceptibility to TB unlike Th1 response (Skowronski et al, 2013). The offset of the ratio of Th2 cells to Th1 cells significantly impairs the adaptive immune response, because of decreased T (Th1) cell-mediated immune signaling essential for control defenses against infections like TB (Jeon & Murray, 2008; Garcia-Elorriaga & Del Rey-Pineda, 2014). Even with these findings, the exact pathophysiological mechanisms of the effect of DM as a predisposing risk factor for TB is unconfirmed, and research continues to explore the extent of physiological complications found in concomitant DM/TB cases (Baghaei, Marjani, Javanmard, Tabarsi, & Masjedi, 2013).

Epidemiology of the convergence:

Systematic reviews of cohort studies reveal that DM presents 3 times the risk of developing TB, and it increases the risk of death to 6.5-6.7 times (Baker et al., 2011; Jeon & Murray 2008; Garcia-Elorriaga & Del Rey-Pineda, 2014). It is evident now that the link between DM and TB is most prominent in developing countries where TB is endemic, and there are high incidences of TB; for example India, has the largest number of TB cases and about 25% of those patients have diabetes (in addition to 24% of patients with prediabetes) (Baghaei et al., 2013; Restrepo et al., 2006; Dobler, Flack & Marks, 2012; Skowronski et al., 2013). Notably, the risk of TB due to DM is smaller at the individual level compared with HIV infection by 113-170 fold, but at the

population level, the number of diabetic patients is likely to have an equal or greater effect (Skowronski et al., 2013). Even a study conducted in Australia which has a low TB burden, demonstrates an association, though a moderate one (RR= 1.48; 95% CI: 1.04-2.10 for Type 2 DM and RR=2.27; 95% CI: 1.41-3.66 for Type 1 DM) (Skowronski et al. 2013). However, the results can vary as seen where a study from the UK demonstrates an overall adjusted DM of 3.8 (95% CI: 2.3-6.1), while in another from Denmark, after controlling for comorbidities the OR was low and not significant (OR= 1.18, 95% CI: 0.96-1.45) (Skowronski et al., 2013).

Almost all of these observational studies show significant interactions in high-risk subgroups in non-endemic regions like Australia, the United Kingdom, and the United States (Restrepo et al., 2006; Dobler et al., 2012; Suwanpimolkul, Grinsdale, Jarisberg, Higashi, Osmond, Hopewell, & Kato-Maeda, 2014; Skowronski et al, 2013). One study on a population on the South Texas-Mexico border found that DM comorbidity with TB is exceeding that of HIV/AIDS (though HIV/AIDS is a more potent risk factor) as is becoming a trend observed in many other studies (Restrepo et al., 2006). Another study performed on the Texas-Mexico border found that self-reported DM is the most common risk factor for TB and DM, and is associated with more severe and contagious TB (Restrepo et al., 2006). Finally, a study performed in San Francisco found a disproportionate association of TB, using LTBI as the measure) and DM among older foreign-born individuals (Suwanpimolkul et al., 2014). These results justify a current trend of focusing on subgroup characteristics in non-endemic regions to keep from missing potential outbreak causing issues. Though there is no doubt of the association between DM and TB, there is a lack of for more etiological evidence (Ottmani et al., 2010). Also, the nature of the association and actual potential impact is ever evolving from a public health perspective.

Methods

Design & Data Collection:

This is a cross-sectional study assessing the association between DM and LTBI in adults in the United States via secondary analysis of the 2-year cycle 2011-2012 National Health and Nutrition Examination Survey. The National Health and Nutrition Examination Survey (NHANES) is part of a program of studies used by the National Center for Health Statistics (NCHS) to assess the health and nutritional status of adults and children in the U.S ("About the National Health," 2014). The NCHS is a division of the Centers for Disease Control and Prevention (CDC) responsible for collecting vital and health statistics ("About the National Health," 2014). The NHANES is a unique program that uses a complex, multistage probability design to sample through a combination of examinations, laboratory tests, and questionnaires performed in mobile examination centers (MECs) ("Survey Overview," 2013; "NHANES 2011-2012 Overview," 2014). This design also involves oversampling of certain subpopulations to allow for more reliable and precise estimates of health status indicators. A survey team consists of a physician, medical and health technicians, and dietary and health interviewers (bilingual interviewers are also available when necessary), which travels to randomly selected sites throughout the country ("Survey Overview," 2013). The MECs provide a standardized environment, equipment, and specimen collection procedures to minimize site-specific errors during examinations and laboratory testing. An interviewer using Computer-Assisted Personal Interview (CAPI) technology administers questionnaires. Questionnaires on special topics of a sensitive nature are completed on Audio Computer-Assisted Self Interview technology (Audio-CASI) to allow for privacy. Each participant is given a brochure and asked to sign participation consent forms collecting and storing their information ("2011-2012 National Health," 2014;

"Survey Overview," 2013). Additional information about the NHANES study design and data collection process can be found on the CDC website[1] ("National Health and Nutrition," 2016).

Study population:

The sample selection process was performed in 4 stages: 1) selection of primary sampling units (PSUs) which were counties or small groups of adjacent counties, 2) selection of segments within PSUs which consisted of a block or group block of a cluster of indeviduals within households ("NHANES 2011-2012 Overview," 2014). In addition to oversampling of Hispanics, non-Hispanic Blacks, older adults and low-income Whites/Other[2], a change in sample design for this survey cycle includes a oversample of Non-Hispanic Asians ("NHANES 2011-2012 Overciew," 2014). The sample sizes for each cycle are fied due to operational constraints, so to accommodate the increase in sample sizes fro Asian sample sizes for Hispaic persons and non-low income White/Other are reduced ("NHANES 2011-2012 Overview," 2014). As a result, the sample size for Mexican American Hispanic persons is noticeably lower than previous years. Suvey materials were made available in various languages to promore participant interaction and facilittate data collection and oversamping. For example, a video shown to participants to explain aspects and benefits of particiapting in the NHANES was made available in Mandarin Chinese, Koren, Vietnamese, Amharic, French, Haitian Creole, Hindi, and Spanish ("NHANES 2011-2012 Overview," 2014). The staff who administered the surveys received cultural competency training and were supported by local interpreters and professional medical interpretation phone services. The original 2011-2012 NHANES dataset targeted the civilian, noninstitutionalized

[1] http://www.cdc.gov/nchs/nhanes/index.htm

[2] Other refers to Non-Hispanic persons reporting races other than black, Asian, or white.

popoulation residing in the 50 states and D.C. The initial sample included 13,431 inidividuals of all ages from 30 different study locations: of those selected 9,756 completed the interview, and 9,338 were examined resulting in unweighted responses rates of 72.6% and 69.5% respectively ("NHANES 2011-2012 Overview," 2014; National Health and Nutrition," 2013").

The selection process from this study began with 9,756 paricipants from the original dataset. Participants weere evaluated to meet the following critereia to confirm inclusion in the study: 1) participant in 20 years[3] or older and 2) participant is not missing measures for TST induration and QFT-G blood test and and HbA1c levels. This resulted in the unweighted study sample sample size of 4,222. Figure 1 provides a breakdown of this selection process.

Measures of Interest:

Outcome Variables

Latent Tuberculosis Infection is the dependent /response variable of interest identified by a positive tuberculin skin test induration measurement (TST) or QuantiFERON®-TB Gold In-Tube blood test (QFT-GIT). A TST is performed by injecting 0.1 mm of purified protein derivative product, acting as a TB antigen, into the inner surface of the forearm ("Tuberculin Skin Testing," 2012). A properly administered injection will produce a skin reaction which is measured to determine if a person is infected with Mycobacterium tuberculosis ("Tuberculin Skin Testing," 2012). The skin reaction appears as an elevation of the skin (a wheal or "palpable, raised, hardened area or swelling") which must be read 48 to 72 hours after the injection by

[3] Age criteria updated to 20+ years due to the nature of how original data was collected. NHANES survey includes data for 18-19 years with children & adolescents for most covariates relevant to this study. This separation resulted in a significant amount of missing data.

measuring the diameter of the indurated area in millimeters ("Tuberculin Skin Testing," 2012). Interpretation of the measurement of induration to determine LTBI status varies by the risk of exposure to *Mycobacterium tuberculosis* and risk of infection once exposed. An induration of ≥10 millimeters is used to indicate a positive TST and LTBI (Mancuso et al., 2016). QuantiFERON®-TB Gold In-Tube test (QFT-GIT) is an FDA-approved blood test for detecting TB infection. It was included in the NHANES 2011-2012 cycle as a secondary screening administered on the MECs on the same day the participants are skin tested. This test detects Cell Mediated Immune (CMI) responses to peptide antigens that simulate mycobacterial proteins ("Interferon-Gamma," 2016). Anyone infected with *M. tuberculosis* will usually have lymphocytes able to recognize mycobacterial antigens; this recognition process generates and secretes a cytokine, IFN-y and the basis of this test is the recognition and quantification of IFN-y ("Interferon-Gamma," 2016). Blood samples were collected via venipuncture into three specialized blood collection tubes – a Nil (negative) control tube, a TB Antigen tube, and a Mitogen or positive control tube ("Interferon-Gamma," 2016). The contents of the tube are mixed then incubated at 37˚C + 1˚C for 16 to 24 hours; then the plasma collected is measured by ELIZA (enzyme-linked immunosorbent assay) for the amount of IFN-y produced in response to the peptide antigens present ("Interferon-Gamma," 2016). International Units (IU) are used to report the results of the test samples relative to a standard curve created by testing dilutions of a recombinant human IFN-y standard; the test is positive when there is an IFN-y response significantly higher than the Nil IFN-y IU/mL value which adjusts for background, non-specific IFN-y in the blood samples, and other special immunological traits ("Interferon-Gamma," 2016). A result will be labeled Indeterminate when the blood sample has a low response to the IFN-y

positive control, the mitogen stimulated plasma sample, paired with a negative response to the TB antigens ("Interferon-Gamma," 2016).

Independent Variable

The independent or explanatory variable of interest is diabetes mellitus (DM) control. The test used to identify level of DM control employed in this study measures blood glycohemoglobin levels. This test reflects plasma glucose for the previous 120 days and results are reported as percentages ("Glycohemoglobin," 2013). The categories are based on clinical recommendations of diagnosis: 6.5% or greater indicates diabetes, 5.7%-6.4% indicates pre-diabetes, and less than 5.7% is normal ("Glycohemoglobin," 2013). Pre-diabetes is where the sugar level is consistently higher than normal yet not as high as what is required to be classified as diabetes ("Prediabetes," 2015). This category is included in this study because these participants are at most risk of developing Type 2 diabetes. This study does not differentiate Type 1 or Type 2 diabetes.

Covariates

There were eight covariates included in this study, which were chosen, based on potential as confounders[4], effect modifiers, and significant cofactors. These included age, race/ethnicity, socioeconomic status, body mass index (BMI), country of origin, gender, time of residence in the US, and smoking status. The variable for age, AGECAT, was coded by SEQN into three groups: 20-39, 40-59, and 60+ years using the original NHANES variable DMDEDUC3. This study excluded18-19 years because they were included with children/youth measures for other covariates in the original NHANES data.

[4] First potential confounders were chosen based on prior literature, then they were confirmed with further analysis.

The original variable for race/ethnicity, RIDRETH3, had six groups: Non- Hispanic White, Mexican American, Other Hispanic, Non-Hispanic Black, Non-Hispanic Asian, and Other race including multi-racial. Three versions of this variable were tested to compare the effect of race with varied stratification: Race2g (White or Other), Race3g (White, Hispanic[5] or Other) and Race4g (White, Hispanic, Black or Other). Race4g was the final version included in statistical analysis. Socioeconomic status was measured in this study using education level. The original educational level variable, DMDEDUC2, categorized participants into groups, and the new variable, SESEDUC, used 5 of those groups ("Less than 9th grade, 9-12 grade without a diploma", "High school graduate or GED equivalent", "Some college education or an Associate degree", and "College graduate or above") as socioeconomic groups. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared rounded to one decimal place ("Body Measures," 2013). Clinically, BMI measures are grouped as Normal (18.5 to 24.9), overweight (25 to 29.9), underweight (less than 18.5), and obese (30 or more). The original NHANES variable, BMXBMI, was continuous, and the variable for this study was coded to an ordinal variable BMICAT2. BMICAT2 only included three categories: Normal, Overweight, and Obese. Underweight measures were combined with the lowest risk group, Normal[6]. The NHANES does not collect specific details about origin. This characteristic can be partially determined with the dataset variable, DMDBORN4, which answers the question "In what country were you born?". The variable, CTRYOB, was created as a dichotomous variable (U.S. born or Foreign born) for this study; any participants missing information were grouped with the lowest risk category, U.S. born. Length of time in the US is measured in the original dataset as DMDYRSUS and was used to code this study's variable for this indicator,

[5] Hispanic combines Mexican American and Other Hispanic categories from original dataset
[6] Underweight produced insignificant values because of extremely small sample size.

TIME3INUS. The new variable collapses the groups of DMDYRSUS into three groups: "Less than five years", "5 to 20 years", and "Greater than 20 years". The variable smoking status was created by combining two NHANES variables, SMQ020 (answer if "Smoked at least 100 cigarettes in life") to establish smoking history and SMQ040 (answering the question "Do you now smoke cigarettes?") to determine current smoking status. These were arranged into three categories smoking status: "Never," "Former" and "Current" for this studies smoking status variable, SMOKE.[7] Finally, the original variable, RIAGENDR, for gender was simply renamed GENDER for this study.

Statistical Analysis:

Statistical analysis software (SAS) Version 9.4 was used for analysis of study population data. All applicable datasets were checked for duplicate records and then merged by respondent sequence number (SEQN) into one sample dataset. This was a combination of datasets for demographics, body measures, examination and laboratory measures from the NHANES database (DEMO_G. sas7bdat; BMX_g. sas7bdat, SMQ_g. sas7bdat; TBX_G. sas7dbat; GHB_G. sas7bdat). Variables from these datasets were renamed, re-coded, or combined as needed for analysis and all irrelevant variables were dropped. For a list of all variables included in the new dataset, refer to Table A. for the dataset codebook. Sampling weights was applied to all subsequent analysis of data from the 4,222 participants included in this study. This dataset was analyzed using Proc Surveyfreq and Proc Surveylogistic SAS procedures to account for the weighting, stratification, and clustering used in the survey study design.[8]

[7] The proportions for these groups match expected national values: 50%, 25% and 25% respectively.
[8] See the codebook, Table B., for more details.

Frequencies and proportions were calculated in univariate analyses to characterize the distribution of the LTBI, DM and potential risk factors in the study population. Bivariate analysis was used to produce frequencies and proportions to assess the association of DM (HbA_{1c}) and covariates (Race, age, gender, etc.) to LTBI (TST and QFT-G). A chi-square goodness of fit test was performed for one-way tables for each variable to assess their univariate distributions and a chi-square test of association/independence was conducted to examine the relationship of DM (HbA1c) and the covariates to LTBI (TST and QFT-G). The relationship between the predictors and the response variables (TST and QFT-G) was further assessed by using binary logistic regressions to produce unadjusted odds ratios and confidence intervals. Adjusted odds ratios and confidence intervals to assess the association between DM and LTBI accounting for significant covariates and confounder and effect modifiers were obtained from multivariate logistic regressions.

The test for confounding was performed by comparing the crude odds ratio of LTBI for DM control with the odds ratio of LTBI for DM stratified by the potential confounder. The test for effect modification was performed using SAS by including an interaction variable in the adjusted model.

Model selection was performed using SAS to perform an automatic stepwise selection process (using a p value= 0.05 for entry and exit) to observe the effect of each covariate on the relationship HbA1c with QFT-G and TST in multiple logistic regression. Stratified analysis was used to test for confounders and identify potential effect modifiers. Variables and their categories were reassessed to best inclusion in model. Additionally, a set of criteria were used to build a

model. Variables were included the model if they 1) had a significant association to QFT-G or TST or 2) were a confounder and an effect modifier. AIC was used to compare final models to determine best option for final analysis. The three candidate models were one chosen based on automatic selection process (adding the primary predictor), another chosen based on the criteria listed above, and finally, one which included all the predictors of the study. Adjusted odds ratios and confidence intervals obtained from the best model were used to assess the association between HbA1c and LTBI accounting for significant covariates, confounders and effect modifiers.

The model selection process resulted in three models shown in Table 8 and Table 9. Model-1 included all of the predictors. Model-2 included only variables deemed significant by stepwise auto-selection process based on p-value = 0.05 for entry and exit of the model using SAS. This method produced different combinations of covariates for TST and QFT-G, and to remain within the scope of this study HbA1c was manually added back into the model. In addition to HbA1c, Model-2 for TST included covariates: race/ethnicity, age, country of birth and smoking status. Model-2 for QFT-G included covariates: race/ethnicity, age, country of birth, smoking status and SES. Model-3 selected variables based on the set of criteria[9] described previously in the methods section. The rules ensure that each of these predictors was chosen for specific reasons. HbA1c was included as the primary predictor. Race/ethnicity and SES were significantly associated with LTBI measures as risk factors, and they are considered risk factors and potential confounders for DM status. Country of birth and length of time of residence in the U.S. were significantly associated with LTBI measures, and they were essential to study of at risk groups. Finally, age,

[9] These are listed in the methods section under the covariates description (pg. 25)

gender, and smoking status were included in the models as controls and as characterizing variables. The Akaike Information Criterion (AIC) was used to measure the quality of the models to choose the "best fit" model. Based on this statistic the "best fit" model was Model-1 for both LTBI measures; followed by Model 3 and the "least fit" Model-2. However, it is important to note that the difference between those values was not substantial.

This protocol was approved as an exempt study by the University of Kentucky Institutional Review Board.

Results

Prevalence and distribution of DM and LTBI in study population:

Table 1a[10] presents the prevalence measures. The prevalence of LTBI in this population, when measured by TST and QFT-G, were 5% (CI: 3.9% to 6.8%) and 5.6% (CI: 4.5% to 6.6%), respectively. In this study sample, 8.5% (CI: 7.3% to 9.7%) were diabetic, 25% (CI: 22.9% to 27.3%) were prediabetic and 66% (CI: 64.1% to 68.8%) had normal levels of HbA1c. Table 2 presents values from the χ^2 Goodness of Fit test for equal proportions; all of the variables included in this study rejected the null hypothesis of equal proportion between the levels (p-value < 0.05).

Description of LTBI based on DM status:

Table 3a presents the conditional probability and distribution of LTBI for DM status and covariates. The primary values of interest are those indicating the relationship between DM

[10] Table 1b presents the corresponding frequency counts

status and LTBI measures. When measured by TST, 6.4% of prediabetics, 8.1% of diabetics and 4.1% of individuals with normal HbA1c levels were indicated LTBI. Table 4a presents the same values when measured by QFT-G: 7.5% of prediabetics, 10% of diabetics and 4.3% of individuals with normal HbA1c levels indicated LTBI. These proportions were reviewed to check for an association between LTBI and the covariates. Gender, socioeconomic status, the length of time of residence in the U.S. and race/ethnicity showed significant association with LTBI when measured by TST, while age, gender, socioeconomic status, race/ethnicity and country of birth showed significant association with LTBI when measured by QFT-G. The corresponding weighted frequency counts are displayed in Table 3b and Table 4b.

Test of Association and Univariate Odds of LTBI for DM status:

Table 5 presents values from the Rao-Scott χ^2 tests of association between LTBI measures, DM status, and covariates. DM status, the primary predictor, indicated a significant association with LTBI when measured by both tests. The results of the test of association with the covariates varied between QFT-G and TST. Race/ethnicity, the length of time of residence in the U.S. and country of birth were significantly associated with LTBI measured by TST, while gender, smoking status and body mass index were not. Race/ethnicity, length of time of residence in the U.S., country of birth, and gender were significantly associated with LTBI measured by QFT-G, while smoking status and body mass index were not.

Table 6 presents the unadjusted odds ratio of LTBI obtained using binary logistic regressions. Diabetics had twice the odds of LTBI than those with normal HbA1c levels (OR=2.1; CI: 1.27 to 3.5), and prediabetics had one and half times the odds of LTBI than those with normal HbA1c

levels when measure by TST (OR=1.6; CI: 1.001 to 2.52). Table 7 presents the unadjusted odds ratios of LTBI for DM status when measured by QFT-G. Diabetics had two and a half times the odds of LTBI than those with normal HbA1c levels (OR=2.5; CI: 1.4 to 4.4), and prediabetics had almost twice the odds of LTBI than those with normal HbA1c levels (OR=1.8; CI: 1.4 to 2.4).

Multivariate Odds of LTBI for study population:

Table 8 and Table 9 also present the adjusted odds ratios of LTBI for DM status and the covariates measured by TST and QFT-G, respectively. Models-1 as the "best fit" model was used in multiple logistic regressions to calculate the odds of LTBI for DM status. The adjusted odds of LTBI, when measured with TST in diabetics, decreased two-fold and was no longer significant after controlling for other covariates (OR=1.12; CI: 0.59 to 2.12). The adjusted odds of LTBI in prediabetics also decreased and was no longer significant (OR=1.22; CI: .71 to 2.08). Also, the odds of LTBI in prediabetics became slightly higher than the odds of LTBI in diabetics. The adjusted odds of LTBI when measured with QTF-G also decreased for prediabetics and diabetics and were no longer significant (OR=1.28; CI: 0.86 to 1.92 and OR=1.34; CI: 0.62 to 2.89, respectively).

Testing for confounding and effect modification identified SES as a positive confounder for diabetics and Race4g as having a slightly significant interaction with DM status. The confounding effect of SES was addressed by including it in the regression analyses DM and

LTBI. Effect modification of Race4g at a few of its levels was addressed by analyzing the association between DM and LTBI for each strata of the variable

Discussion

Evaluation of the study

This study tested for a relationship between LTBI and DM and attempted to determine if DM status influenced the impact of LTBI at the population level. This study provided estimates of the prevalence of LTBI and DM in the United States in the year span of 2011-2012. A test for association confirmed that DM and LTBI were significantly associated and that the probability of having LTBI was likely to be different depending on DM status.

The prevalence of LTBI in the study population was quite low, as would be expected of a sample from a low-incidence country like the United States. Only about 5 - 5.6% of the total population indicated LTBI. This corresponded to 9.2 - 10 million people of a total population of 182.9 million people. Another study which also used 2011-2012 NHANES cycle had similar results; they estimated that 4.4 - 4.8% of their total population indicated LTBI with a corresponding with 12.4 - 13.6 million people (Mancuso et al., 2016). Overall, their study had lower estimates compared to ours. One reason for the different results could be the difference in sample size and selection criteria. This study excluded participants under 20 years of age, while the other previously mentioned study included those six years and older (Mancuso et al., 2016). The prevalence of DM was higher than that of LTBI. Of the total population, 8.5% were diabetic, and 25.1% were prediabetic. These proportions corresponded to 15.5 million and 45.9 million, respectively. The conditional estimates of LTBI by DM status provided insight to the magnitude

of the relationship between the two variables in this study population. Diabetics had the highest prevalence of LTBI. Of the 15.5 million diabetics identified, 8.1 - 10% indicated LTBI that corresponded with 1.3 - 1.5 million people. For prediabetics, 6-7% of 45.9 million indicated LTBI, which corresponded with 2.9 - 3.4 million people.

Based on the test of association for the total study population, DM measured by HbA1c was related to LTBI measured by TST and QFT-G. Before accounting for covariates, the odds of LTBI varied by DM status. Diabetics and prediabetics were significantly more likely to have LTBI than those with normal HbA1c. To account for confounding or effect modification, this relationship was tested by including relevant covariates in the model. The variables of the best fit model were included because they were characteristically relevant to the relationship of DM and LTBI. However, though the odds of LTBI was higher than diabetics and prediabetics it was not a significant result. Meaning that when accounting for race/ethnicity, SES, gender, BMI, age, country of birth, smoking status and length of time in the US the odds of LTBI was no longer different based on DM status.

Limitations

The limitations of this study involved the data collection process, the study design, screening tests and nature of disease of interest. Selection bias was inevitable with the use of survey data because of responder bias. Also, because of the cross-sectional study design used, it was impossible to infer temporality or the direction of the association between DM and LTBI. There was also a chance of misclassification when testing for LTBI or diagnosis of DM. There is no "gold standard" for LTBI detection, and the tests available are not exempt from errors (Diel,

Loddenkemper, Meywald-Walter, Gottschalk, & Nienhaus, 2009). Results identified by TST may have been confounded by factors such as the BCG vaccine or infection with nontuberculous mycobacterium. Typically, when TST and QFT-G have low correspondence levels, it is an indication of potential error and misclassification (Abdel-Samea, Ismail, Fayed, & Mohammad, 2013). Previous studies were performed to explain the discordance in TST and QFT-G results (Diel et al., 2009). Something that was visible in the results for LTBI prevalence amongst diabetics later on in this paper. QFT-G was considered to be more accurate than TST. More specifically, QFT-G has higher sensitivity, specificity, positive predictive value and negative predictive value than TST over all (Diel et al., 2009). However, these distinctions were not categorical when accounting for difference characteristics of subgroups. For example, TST was more likely to overestimate the level of LTBI in foreign-born persons because of the chance of history of the BCG vaccine, while there was evidence of QFT-G producing more false-positives in US-born or when used in low-risk population contrary to it being more specific. Exploring the variability in LTBI detecting methods is popular topic of study in low-risk populations. This study supported previous findings and recommendations to use TST to investigate LTBI in low-risk groups and to use QFT-G to investigate in high-risk groups to reduce inaccuracies. Also, this study uses a TST reaction size ≥10 mm to indicate LTBI, which was not the recommended measure for populations from low-incidence regions. However, it the measure used commonly in in previous studies (Mancuso et al., 2016).

There are also limitations associated with diagnosis of diabetes using HbA1. HbA1c is primarily used as a marker of glycemic control in established diabetes, and there is concern that it may not be sensitive enough for accurate diagnosis (Cohen, Haggerty, & Herman, 2010). Researchers

have also discovered evidence of discordance between HbA1c and the results of other measures of glycemia (Cohen et al., 2010). Fasting plasma glucose (FPG) is a more favorable test for diagnosing diabetes because it is more cost efficient and has less of the chances of misclassification potential than HbA1c in initial diagnosis. HbA1c is typically more appealing because it is a simple, one-time test and is considered more sensitive the FPG (Bonora & Tuomilehto, 2011). Other factors include: the primary symptoms of clinically defined DM is high blood glucose and not glycation of proteins which is the secondary symptoms, HbA1c is likely to miss asymptomatic early cases of diabetes, those with abnormal hemoglobin traits could be misclassified, and finally it is not generally recommended to use the same biomarker for diagnosing and as for monitoring diabetes (Bonora & Tuomilehto, 2011).

Public Health Implications

Low-incidence countries like the United States have special challenges to achieve elimination of TB. Progression from LTBI to TB, cross-border migration and dwindling administrative or political commitment and visibility are a few of these challenges. Studies like ours are helpful because they support the relevancy of studying TB even though it is not a focus of medicine and public health in countries like the U.S. with the development of effective treatment tool significantly reduce the risk of outbreak or death. Standardization of screening, monitoring, and control practices are primary challenge for managing TB in populations with low- incidence. In high-incidence and typically low-income regions, health organizations like the WHO recommend that concomitant DM/TB be addressed as soon as a connection was identified. Now bidirectional screening practices and co-management programs are common. TB is a persistent problem even in both high-income countries and low-incidence countries like the U.S.

Bidirectional screening and co-management procedures could be considered for groups with confirmed risks, but the results of this study do not support the need such efforts in the U.S.

Conclusion

This study identified that DM and LTBI were associated in the U.S. depending on the type of group being studied. More studies should be performed focusing on the presence of comorbidity in known reservoir population like the homeless community, those in high-risk professions, and institutional settings like prisons. This study did not confirm that co-management practices are necessary in the general population. Because of the variable results found for subgroups, it did justify the need for more targeted studies. Performing comparative studies to review of the relationship of DM and TB (LTBI) in low-incidence countries in contrast to the trends in high incidence countries could be a direction for future studies. In this study, however, the association of DM and LTBI was tested and found significant for the total population, but not when accounting for related variables. This study found evidence of noticeable prevalence and distribution of potential concomitant DM/TB in groups identified with LTBI and high glycemic levels. Variables like SES and race/ethnicity were confirmed as a confounder and potential effect modifier, respectively. Further studies exploring the nature of DM and LTBI based on country of birth would be insightful as that was an unconfirmed potential modifier. Finally, using variables based on medical history or stronger screening test would help to truly identify the nature of any existing burden of DM/LTBI in at most risk subpopulations. Overall, the need for further exploration of concomitant DM/TB can be ascertained from this study.

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Biographical Sketch

Whitney L. Rémy received her Bachelor of Arts degree in Biology from Berea College in May of 2012. She earned a Global Health Certificate for University of Kentucky College of Public Health in May of 2015 and is a candidate for a Masters of Public Health concentrating in Epidemiology to be issued August of 2016. She claims both Corbin, Kentucky by birth and residence and Port-au-Prince, Haiti by heritage and upbringing as her home places. During her time at the University of Kentucky, she visited Mutare, Zimbabwe and interned with the Manicaland Provincial Medical Directorate Tuberculosis Control Programme to fulfill her internship and practicum experience requirements. Whitney's research areas of interest include infectious/emerging diseases, health disparities, and global health.

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Appendix:

Tables:

Table 1a. Descriptive statistics of study population from one-way *Proc Surveyfreq* analysis

		Sample Frequency	Weighted Frequency▪
TST	< 10 mm	3816	173.70
	≥ 10 mm	406	9.18
QFT-G	Negative	3813	172.7
	Positive	409	10.1
HbA1c	Normal	2490	121.5
	Prediabetic	1222	45.9
	Diabetic	510	15.5
Race/Ethnicity	White	1619	123.4
	Hispanic	868	26.5
	Black	1100	20.3
	Others	635	12.6
Length of time in the US*	Greater than 20 years	3592	165.9
	5 to 20 years	477	12.9
	Less than 5 years	153	4.1
Gender	Female	2137	95.4
	Male	2085	87.5
Age	20 to 39 years	2490	64.7
	40 to 59 years	1222	71.3
	60+ years	510	46.8
Country of birth*	United States	3002	152.3
	Other	1220	30.6
Body mass index	Normal	1328	55.5
	Overweight	1353	61.8
	Obese	1541	65.6
Smoking status	Never	2389	102.0
	Former	981	45.0
	Current	852	35.8
Socioeconomic status*	College graduate or above	1029	55.3
	Some college or associate degree	1301	59.6
	High school graduate or GED equivalent	903	37.6
	9^{th} – 11^{th} grade	583	19.8
	Less than 9^{th} grade	406	10.6

| *Missing observation combined with lowest risk group | ▪Frequency count is divided by 1 million & rounded to 1 decimal place | Totals: 4,222 (unweighted) and 182.9 million (weighted) |

Table 1b. Descriptive statistics of study population from One-way *Proc Surveyfreq* analysis

		(%)	Standard Error of Percent	95% Confidence Limits of Percent	
TST	< 10 mm	94.98	0.82	93.25	96.71
	≥ 10 mm	5.02	0.82	3.29	6.75
QFT-G	Negative	94.45	0.51	93.38	95.53
	Positive	5.55	0.51	4.47	6.62
HbA1c	Normal	66.42	1.11	64.08	68.75
	Prediabetic	25.10	1.03	22.93	27.28
	Diabetic	8.48	0.57	7.27	9.69
Race/Ethnicity	White	67.50	4.09	58.86	76.15
	Hispanic	14.50	2.70	8.81	20.19
	Black	11.11	2.27	6.32	15.90
	Other	6.88	0.99	4.80	8.96
Length of time in the US*	Greater than 20 years	90.69	1.37	87.79	93.59
	5 to 20 years	7.08	1.03	4.90	9.26
	Less than 5 years	2.23	0.53	1.12	3.34
Gender	Female	52.16	0.77	50.53	53.79
	Male	47.84	0.77	46.21	49.47
Age	20 to 39 years	35.39	2.28	30.59	40.19
	40 to 59 years	39.01	1.42	36.02	42.00
	60+ years	25.60	1.12	23.23	27.97
Country of birth*	United States	83.26	2.01	79.03	87.50
	Other	16.74	2.01	12.50	20.97
Body mass index	Normal	30.34	1.80	26.55	34.14
	Overweight	33.77	1.31	31.01	36.53
	Obese	35.88	1.44	32.83	38.94
Smoking status	Never	55.79	1.44	52.76	58.82
	Former	24.61	1.33	21.80	27.41
	Current	19.60	1.05	17.38	21.82
Socioeconomic status*	College graduate or above	30.25	2.68	24.59	35.91
	Some college or associate degree	32.57	1.66	29.06	36.08
	High school graduate or GED equivalent	20.58	1.57	17.26	23.90
	9^{th} – 11^{th} grade	10.84	1.50	7.67	14.00
	Less than 9^{th} grade	5.77	0.66	4.37	7.16

| *Missing observation combined with lowest risk group |

Table 2. Design adjusted Chi Square‡ Goodness of Fit Test from One-way *Proc Surveyfreq* analysis

	Rao-Scott X^2	DF	Pr > ChiSq
TST	572.71	1	<0.001
QFT-G	1593.26	1	<0.001
HbA1c	1072.68	2	<0.001
Age	23.37	2	<0.001
Body mass index	4.34	2	<0.001
Country of birth	153.08	1	<0.001
Gender	7.84	1	0.0051
Race/Ethnicity	215.92	3	<0.001
Socioeconomic status	151.40	4	<0.001
Length of time in the US	1002.70	2	<0.001
Smoking status	279.03	2	<0.001

| ‡ Rao-Scott Chi-square for survey data analysis | H_0: equal proportions for the levels of the variable |

Table 3a. Conditional distribution of predictors by TST

		Row % (Standard Error)	
		<10 mm	≥10 mm
Race/Ethnicity	White	98.89 (0.33)	1.11 (0.33)
	Hispanic	84.55 (2.65)	15.45 (2.65)
	Black	92.29 (1.16)	7.71 (1.16)
	Other	82.92 (1.93)	17.08 (1.93)
Length of time in the US*	Greater than 20 years	96.70 (0.58)	3.30 (0.58)
	5 to 20 years	77.71 (2.59)	22.29 (5.35)
	Less than 5 years	79.88 (5.35)	20.12 (5.35)
Country of birth*	United States	98.24 (0.46)	1.76 (0.46)
	Other	78.77 (2.79)	21.23 (2.79)
Socioeconomic status*	College graduate or above	96.36 (0.70)	3.64 (0.70)
	Some college or associate degree	96.64 (0.56)	3.36 (0.56)
	High school graduate or GED equivalent	95.30 (1.05)	4.70 (1.05)
	9^{th} – 11^{th} grade	90.98 (2.38)	9.02 (2.38)
	Less than 9^{th} grade	84.72 (2.24)	15.28 (2.24)
HbA1c	Normal	95.89 (0.69)	4.11 (0.69)
	Pre-diabetic	93.62 (1.65)	6.38 (1.65)
	Diabetic	91.88 (1.55)	8.12 (1.55)
Gender	Female	95.36 (0.74)	4.64 (0.74)
	Male	94.57 (0.99)	5.43 (0.99)
Age‡	20 to 39 years	95.35 (0.83)	4.65 (0.83)
	40 to 59 years	94.39 (1.03)	5.61 (1.03)
	60+ years	95.35 (0.91)	4.65 (0.91)
Smoking status‡	Never	95.04 (0.89)	4.96 (0.89)
	Former	95.17 (0.85)	4.83 (0.85)
	Current	94.55 (1.40)	5.45 (1.40)
Body mass index‡	Normal	94.86 (0.94)	5.14 (0.94)
	Overweight	95.17 (0.79)	4.83 (0.79)
	Obese	94.90 (1.08)	5.10 (1.08)

| *Missing observation combined with lowest risk | ‡These variables are not significantly associated with TST |

Table 3b. Characteristics of study population from Two-way *Proc Freq* analysis by TST

		Weighted Frequency▪	
		<10 mm	≥10 mm
Race/Ethnicity	White	122.1	1.4
	Hispanic	51.6	7.8
	Black	18.8	1.6
	Other	10.4	2.2
Length of time in the US*	Greater than 20 years	160.4	5.5
	5 to 20 years	10.1	2.9
	Less than 5 years	3.3	0.8
Country of birth*	United States	145.9	2.7
	Other	24.1	6.5
Socioeconomic status*	College graduate or above	53.3	2.0
	Some college or associate degree	57.6	2.0
	High school graduate or GED equivalent	35.9	1.8
	9^{th} – 11^{th} grade	18.0	1.8
	Less than 9^{th} grade	8.9	1.6
HbA1c	Normal	116.5	5.0
	Pre-diabetic	43.0	2.9
	Diabetic	14.3	1.3
Gender	Female	91.0	4.4
	Male	82.7	4.8
Age‡	20 to 39 years	61.7	3.0
	40 to 59 years	67.3	4.0
	60+ years	44.6	2.2
Smoking status‡	Never	97.0	5.1
	Former	42.8	2.2
	Current	33.9	1.9
Body mass index‡	Normal	52.6	2.9
	Overweight	58.8	3.0
	Obese	62.3	3.3

| *Missing observation combined with lowest risk group | ▪Frequency count are divided by 1 x 10^6 & rounded to 1 decimal place |

Table 4a. Conditional distribution of predictors by QFT-G

		Row % (Standard Error)	
		Negative	Positive
Length of time in the US*	Greater than 20 years	95.59 (0.46)	4.41 (0.46)
	5 to 20 years	81.92 (2.44)	18.08 (2.44)
	Less than 5 years	88.24 (3.15)	11.76 (3.15)
Country of birth*	United States	96.84 (0.53)	3.16 (0.53)
	Other	82.57 (1.53)	17.43 (1.53)
Race/Ethnicity	White	97.17 (0.47)	2.83 (0.47)
	Hispanic	86.84 (1.27)	13.15 (1.27)
	Black	93.11 (0.99)	6.89 (0.99)
	Other	86.00 (1.18)	14.00 (1.18)
Socioeconomic status*	College graduate or above	95.80 (0.76)	4.20 (0.76)
	Some college or associate degree	96.88 (0.51)	3.12 (0.51)
	High school graduate or GED equivalent	92.80 (1.34)	7.20 (1.34)
	9^{th} – 11^{th} grade	92.54 (1.20)	7.46 (1.20)
	Less than 9^{th} grade	83.25 (2.24)	16.75 (2.24)
HbA1c	Normal	95.75 (0.48)	4.25 (0.48)
	Pre-diabetic	92.54 (0.93)	7.46 (0.93)
	Diabetic	89.96 (2.08)	10.04 (2.08)
Age	20 to 39 years	96.00 (0.45)	4.00 (0.45)
	40 to 59 years	94.91 (0.99)	5.09 (0.99)
	60+ years	91.63 (0.98)	8.38 (0.98)
Gender‡	Female	95.41 (0.60)	4.59 (0.60)
	Male	93.41 (0.59)	6.59 (0.59)
Smoking status‡	Never	95.26 (0.42)	4.74 (0.42)
	Former	93.70 (0.97)	6.30 (0.97)
	Current	93.13 (1.33)	6.87 (1.33)
Body Mass Index‡	Normal	93.62 (1.04)	6.38 (1.04)
	Overweight	94.92 (0.65)	5.08 (0.65)
	Obese	94.72 (0.60)	5.28 (0.60)

| *Missing observation combined with lowest risk | ‡These variables are not significantly associated with TST |

Table 4b. Characteristics of study population from Two-way *Proc Freq* analysis by QFT-G

		Weighted Frequency▪	
		Negative	Positive
Length of time in the US*	Greater than 20 years	158.5	7.3
	5 to 20 years	10.6	2.3
	Less than 5 years	3.6	0.5
Country of birth*	United States	147.5	4.8
	Other	25.3	5.3
Race/Ethnicity	White	120.0	3.5
	Hispanic	23.0	3.5
	Black	18.9	1.4
	Other	10.8	1.8
Socioeconomic status*	College graduate or above	52.9	2.3
	Some college or associate degree	57.6	1.9
	High school graduate or GED equivalent	34.9	2.7
	9^{th} – 11^{th} grade	18.3	1.5
	Less than 9^{th} grade	8.8	1.8
HbA1c	Normal	116.3	5.2
	Pre-diabetic	42.5	3.4
	Diabetic	14.0	1.5
Age	20 to 39 years	62.1	2.6
	40 to 59 years	67.7	3.6
	60+ years	42.9	3.9
Gender‡	Female	91.0	4.4
	Male	81.7	5.8
Smoking status	Never	97.2	4.8
	Former	42.2	2.8
	Current	33.4	2.5
Body Mass Index	Normal	51.9	3.5
	Overweight	58.6	3.1
	Obese	62.2	3.5

| *Missing observation combined with lowest risk group | ▪Frequency count are divided by 1 million & rounded to 1 decimal place |

Table 5. Design adjusted Chi Square‡ Test of Association

		TST	QFT-G
Race/Ethnicity	X^2	527.58	209.32
	DF	3	3
	Pr > ChiSq	<.0001	<0.0001
Length of time in the US	X^2	556.48	108.36
	DF	2	2
	Pr > ChiSq	<0.0001	0.0001
Country of birth	X^2	278.58	100.82
	DF	1	1
	Pr > ChiSq	<0.0001	<0.001
Socioeconomic status	X^2	98.21	67.49
	DF	4	4
	Pr > ChiSq	<0.0001	<0.0001
HbA1c	X^2	9.40	24.19
	DF	2	2
	Pr > ChiSq	0.0091	<0.001
Age	X^2	2.28	14.35
	DF	2	2
	Pr > ChiSq	0.3195	0.0008
Gender	X^2	2.22	9.55
	DF	1	1
	Pr > ChiSq	0.1363	0.0020
Smoking status	X^2	0.30	4.95
	DF	2	2
	Pr > ChiSq	0.8612	0.0842
Body mass index	X^2	0.18	1.92
	DF	2	2
	Pr > ChiSq	0.9152	0.3824

| ‡ Rao-Scott Chi-square for survey data analysis | H_0: There is no association between the predictor and response |

Table 6. Unadjusted Odds Ratio from Binary Logistic Regression – TST vs. Predictors

	TST	
Predictor	OR	95% CI
A1C		
Normal	1.00	
Pre-Diabetic	1.588	1.001 – 2.519
Diabetic	2.060	1.268 - 3.345
Race/Ethnicity		
White	1.00	
Hispanic	16.33	6.988 – 38.139
Black	7.46	3.934 – 14.135
Other	18.40	9.546 – 35.399
Length of time in the US		
Greater than 20 years	1.00	
5 to 20 years	8.400	5.754 – 12.265
Less than 5 years	7.380	3.542 – 15.375
Gender		
Female	1.00	
Male	1.181	0.928 – 1.501
Age		
20 to 39 years	1.00	
40 to 59 years	1.219	0.942 – 1.577
60+ years	1.00	0.651 – 1.534
Country of birth		
United States	1.00	
Other	15.020	8.044 – 28.047
Body Mass Index		
Normal	1.00	
Overweight	0.993	0.652 – 1.513
Obese	0.936	0.691 – 1.269
Smoking status		
Never	1.00	
Former	0.973	0.633 – 1.495
Current	1.105	0.688 – 1.775
Socioeconomic status		
College graduate or above	1.00	
Some college or associate degree	0.922	0.598 - 1.422
High school graduate or GED equivalent	1.306	0.781 – 2.184
9^{th} – 11^{th} grade	2.627	1.533 – 4.501
Less than 9^{th} grade	4.775	2.943 - 7.755

Table 7. Unadjusted Odds Ratio from Binary Logistic Regression – QFT-G vs. Predictors

	QFT-G	
Predictor	OR	95% CI
A1C		
Normal	1.00	
Pre-Diabetic	1.818	1.371 – 2.411
Diabetic	2.518	1.427 – 4.441
Race/Ethnicity		
White	1.00	
Hispanic	5.207	3.187 – 8.507
Black	2.542	1.663 – 3.886
Other	5.597	3.582 – 8.746
Length of time in the US		
Greater than 20 years	1.00	
5 to 20 years	4.779	3.269 – 6.988
Less than 5 years	2.887	1.296 – 6.432
Gender		
Female	1.00	
Male	1.466	1.122 – 1.917
Age		
20 to 39 years	1.00	
40 to 59 years	1.289	0.780 – 2.130
60+ years	2.196	1.517 – 3.178
Country of birth		
United States	1.00	
Other	6.447	3.941 – 10.647
Body Mass Index		
Normal	1.00	
Overweight	0.818	0.537 – 1.245
Obese	0.786	0.513 – 1.203
Smoking status		
Never	1.00	
Former	1.482	0.949 – 2.316
Current	1.351	0.943 – 1.937
Socioeconomic status		
College graduate or above	1.00	
Some college or associate degree	0.734	0.415 – 1.300
High school graduate or GED equivalent	1.770	0.927 – 3.377
9^{th} – 11^{th} grade	1.837	1.019 – 3.312
Less than 9^{th} grade	4.587	2.952 – 7.128

Table 8. Adjusted Odds Ratio from Multiple Logistic Regression – TST

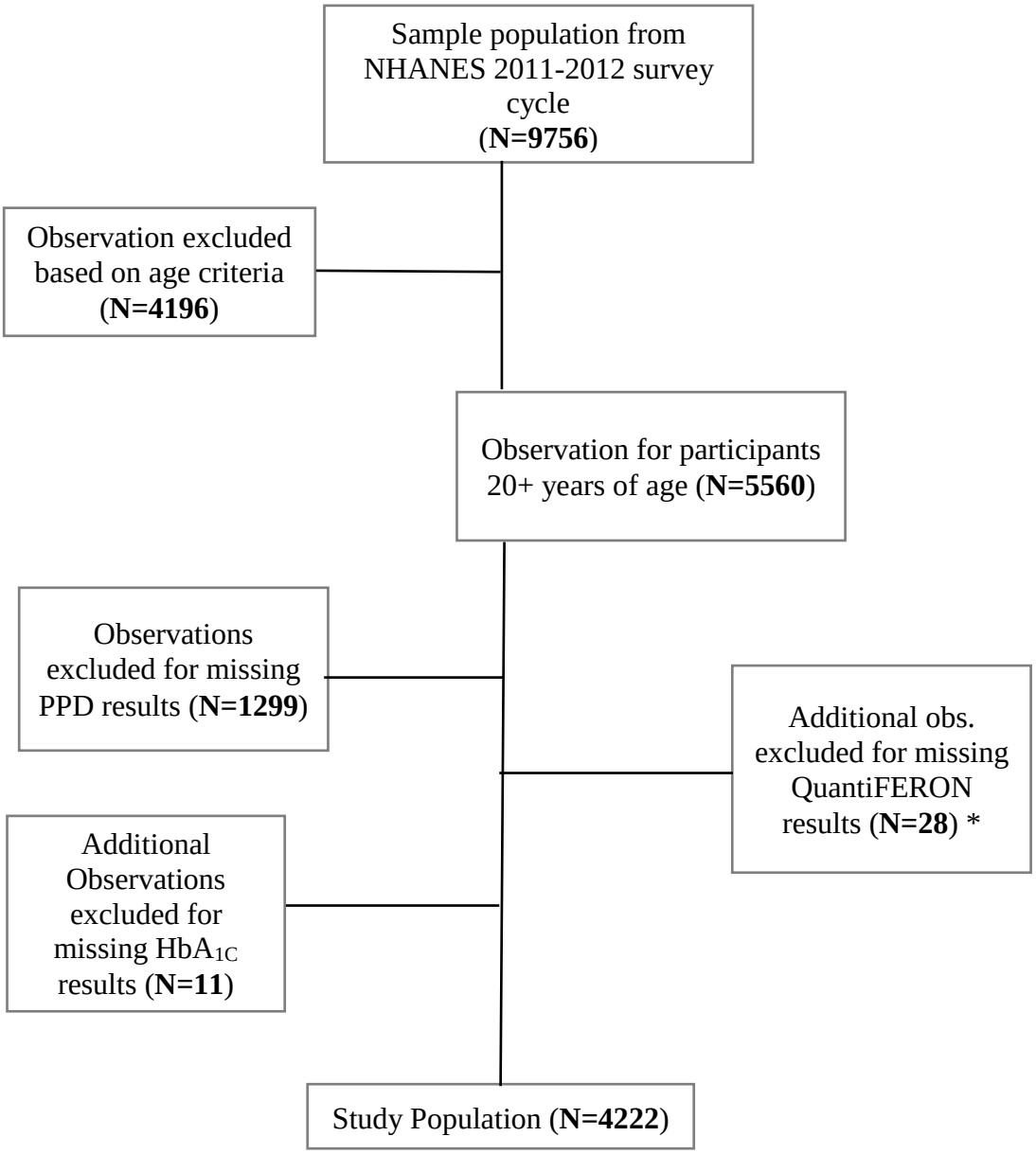
	Model 1	Model 2	Model 3
Predictor	OR (95% CI)		
A1C			
Normal	1.00		
Pre-Diabetic	1.217 (0.711 – 2.086)	1.252 (0.716 – 2.189)	1.249 (0.713 – 2.188)
Diabetic	1.124 (0.593 – 2.120)	1.199 (0.658 – 2.186)	1.192 (0.658 – 2.159)
Race/Ethnicity			
White	1.00		
Hispanic	3.987 (1.595 – 9.963)	4.369 (2.049 – 9.317)	4.093 (1.665 – 10.063)
Black	6.616 (3.827 – 11.436)	6.753 (4.056 – 11.245)	6.703 (3.904 – 11.507)
Other	5.703 (3.079 – 10.564)	5.650 (3.098 – 10.306)	5.606 (3.002 – 10.467)
Length of time in the US			
Greater than 20 years	1.00		
5 to 20 years	1.204 (0.885 – 1.638)	--	1.201 (0.879 – 1.641)
Less than 5 years	1.388 (0.780 – 2.467)	--	1.381 (0.779 – 2.448)
Gender			
Female	1.00		
Male	1.024 (0.730 – 1.437)	--	1.014 (0.726 – 1.416)
Age			
20 to 39 years	1.00		
40 to 59 years	1.430 (1.031 – 1.983)	1.373 (1.017 – 1.854)	1.419 (1.015 – 1.984)
60+ years	1.773 (0.983 – 3.197)	1.682 (1.022 – 2.766)	1.733 (0.965 – 3.113)
Country of birth			
United States	1.00		
Other	7.525 (4.917 – 11.516)	8.327 (5.474 – 12.666)	7.318 (4.741 – 11.297)
Body Mass Index			
Normal	1.00		
Overweight	0.989 (0.717 – 1.363)	--	--
Obese	1.180 (0.742 – 1.876)	--	--
Smoking status			
Never	1.00		
Former	1.455 (0.911 – 2.324)	1.447 (0.952 – 2.291)	1.462 (0.918 – 2.330)
Current	1.779 (1.138 – 2.781)	1.811 (1.149 – 2.855)	
Socioeconomic status			
College graduate or above	1.00		
Some college or associate degree	0.891 (0.591 – 1.342)	--	0.893 (0.593 – 1.345)
High school graduate or GED equivalent	0.940 (0.607 – 1.456)	--	0.943 (0.608 – 1.463)
9^{th} – 11^{th} grade	1.375 (0.765 – 2.471)	--	1.388 (0.781 – 2.465)
Less than 9^{th} grade	1.098 (0.477 – 2.524)	--	1.094 (0.478 – 2.505)

Table 9. Adjusted Odds Ratio from Multiple Logistic Regression – QFTG

	Model 1	Model	Model 3
Predictor	OR (95% CI)		
A1C			
Normal	1.00		
Pre-Diabetic	1.281 (0.856 – 1.917)	1.260 (0.859 – 1.847)	1.251 (0.852 – 1.836)
Diabetic	1.344 (0.623 – 2.899)	1.327 (0.660 – 2.668)	1.312 (0.650 – 2.648)
Race/Ethnicity			
White	1.00		
Hispanic	2.060 (1.295 – 3.275)	2.047 (1.292 – 3.243)	2.024 (1.263 – 3.245)
Black	2.538 (1.717 – 3.753)	2.540 (1.685 – 3.829)	2.541 (1.686 – 3.828)
Other	2.482 (1.649 – 3.734)	2.582 (1.773 – 3.761)	2.601 (1.789 – 3.781)
Length of time in the US			
Greater than 20 years	1.00		
5 to 20 years	1.165 (0.734 – 1.849)	--	1.153 (0.733 – 1.813)
Less than 5 years	0.864 (0.474 – 1.574)	--	0.895 (0.505 – 1.586)
Gender			
Female	1.00		
Male	1.350 (0.972 – 1.874)	--	1.327 (0.966 – 1.822)
Age			
20 to 39 years	1.00		
40 to 59 years	1.380 (0.821 – 2.320)	1.302 (0.784 – 2.162)	1.341 (0.794 – 2.265)
60+ years	3.110 (1.732 – 5.583)	2.936 (1.692 – 5.094)	3.075 (1.732 – 5.462)
Country of birth			
United States	1.00		
Other	4.628 (2.497 – 8.576)	4.919 (2.871 – 8.426)	4.639 (2.587 – 8.320)
Body Mass Index			
Normal	1.00		
Overweight	0.726 (0.447 – 1.179)	--	--
Obese	0.830 (0.472 – 1.459)	--	--
Smoking status			
Never	1.00		
Former	1.397 (1.203 – 3.074)	1.449 (1.069 – 2.103)	1.389 (0.946 – 2.041)
Current	1.923 (1.203 – 3.074)	2.130 (1.375 – 3.299))	1.969 (1.211 – 3.203)
Socioeconomic status			
College graduate or above	1.00		
Some college or associate degree	0.679 (0.364 – 1.267)	0.665 (0.357 – 1.236)	0.675 (0.360 – 1.267)
High school graduate or GED equivalent	1.321 (0.672 – 2.598)	1.299 (0.667 – 2.526)	1.308 (0.662 – 2.584)
9^{th} – 11^{th} grade	1.022 (0.599 – 1.743)	1.005 (0.584 – 1.731)	1.015 (0.586 – 1.759)
Less than 9^{th} grade	1.306 (0.855 – 1.996)	1.313 (0.848 – 2.034)	1.308 (0.851 – 2.011)

Figures:

Figure 1. Selecting Study Population



*Indeterminate results are treated as negative results for parts of this study.

Supporting Documents:

Table A. WLRCap2015.Sas Codebook

SAS Variable	Value	Label	Predictor description
Outcome indicators			
INDURATIONBIN	0	< 10 mm	Tuberculin skin test result
	1	≥ 10 mm	
QFTG	0	Negative	QuantiFERON Gold blood test result
	1	Positive	
Exposure			
A1CCAT	1	< 5.7 (Normal)	Glycohemoglobin (%)
	2	5.7 to 6.4 (Prediabetic)	
	3	≥ 6.5 (Diabetic)	
Covariates			
AGECAT	1	20 to 39 years	Age
	2	40 to 59 years	
	3	60+ years	
BMICAT3	2	18.5 to 24.9 (Normal)	Body Mass Index (kg/m^2)
	3	25 to 29.9 (Overweight)	
	4	≥ 30 (Obese)	
CTRYOB	1	United States	Country of Birth
	2	Other	
GENDER	1	Female	Gender
	2	Male	
RACE4G	1	White	Race with 4 categories
	2	Hispanic	
	3	Black	
	4	Others	
SESEDUC	1	College graduate or above	Socioeconomic Status (education level)
	2	Some college or associate degree	
	3	High school graduate or GED equivalent	
	4	9 - 11^{th} grade	
	5	Less than 9^{th} grade	
SMOKE	1	Never	Smoking Status
	2	Former	
	3	Current	
TIME3INUS	1	Greater than 20 years	Length of time in the US
	2	5 to 20 years	
	3	Less than 5 years	

Table B. NHANES 2011-2012 modeling variables for data analysis

Variable	Value	Label	Description
RIDSTATR	2	Both interviewed, and MEC examined	Interview/Examination status
SDDSRVYR	7	NHANES 2011 – 2012 public release	Data release cycle
SDMVSTRA	90 to 103	Masked variance pseudo-stratum	Masked variance unit pseudo-stratum variable for variance estimation
SDMVPSU	1 to 3	Masked variance pseudo-PSU	Masked variance unit pseudo –PSU variable for variance estimation
WTMEC2YR	0 – 222579.78343	Full sample 2 year MEC exam weight	Both interviewed, and MEC examined participants