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ABSTRACT

DIABETES MELLITUS IS ASSOCIATED WITH INCREASED PREVALENCE OF LATENT TUBERCULOSIS INFECTION: FINDINGS FROM THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY, 2011-2012

By

MARISSA MARGARET BARRON

APRIL 14, 2017

Background: Type 2 diabetes mellitus is associated with threefold higher risks of active tuberculosis (TB) and an estimated 15% of the 10.4 million annual incident TB cases are attributable to diabetes. While the relationship between diabetes and TB disease is well-established, little is known about the association between diabetes and latent TB infection (LTBI).

Methods: We performed a cross-sectional analysis of data from the 2011-2012 cycle of the National Health and Nutrition Examination Survey. Participants aged ≥ 20 years were eligible for this analysis. Diabetes status was defined by glycated hemoglobin (HbA1c) as no diabetes ($\leq 5.6\%$), prediabetes (5.7-6.4%), and diabetes ($\geq 6.5\%$); participants were defined as having diabetes if they self-reported a diagnosis, regardless of HbA1c. LTBI was defined by interferon gamma release assay (IGRA) as positive, negative, or indeterminate. We used logistic regression to estimate the adjusted odds ratio and 95% confidence interval of LTBI comparing participants with diabetes and prediabetes to those with no diabetes.

Results: Overall the prevalence of diabetes was 11.4% (95%CI 9.8-13.0%) and 22.1% (95%CI 20.5-23.8%) had prediabetes. The prevalence of LTBI was 5.9% (95%CI 4.9-7.0%). After adjusting for confounding factors, the odds of prevalent LTBI was greater among adults with diabetes (aOR 1.91, 95%CI 1.16-3.16) compared to those without diabetes.

Conclusion: Diabetes is associated with LTBI among adults in the US, even after adjusting for confounding factors. Given diabetes increases the risk of active TB, patients with co-prevalent diabetes and LTBI may be targeted for LTBI treatment.

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by

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APPROVAL PAGE

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Author's Statement Page

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Marissa M. Barron

Signature of Author

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CHAPTER I

INTRODUCTION

1.1 Background

Tuberculosis (TB) is an infectious disease that is spread by the causative agent *Mycobacterium tuberculosis* (MTB). TB generally affects the lungs (known as pulmonary TB), but may also spread to other areas of the human host (known as extrapulmonary TB)[1]. The majority of individuals who become infected with MTB do not develop infectious, symptomatic TB (also known as active TB); instead, their immune systems are able to contain the MTB infection, which leads to the development of latent tuberculosis (LTBI)[2, 3] Individuals with LTBI are not symptomatic or infectious so long as their immune system contains the MTB infection.

In 2015, an estimated 10.4 million new cases of TB occurred worldwide, and there were 1.4 million deaths attributed to TB[1]. In addition, an estimated one-third of the world population has LTBI[2, 4]. In the general population, the proportion of persons with LTBI that develop TB is low, but the risk of reactivation of LTBI to TB is increased by comorbidities that affect immune responses[2, 5]. Reactivation of LTBI to TB only occurs in about 10% of all infected individuals[2], but the risk of progression to TB among patients with diabetes mellitus (DM) is approximately 3 times the risk of the general population[6-10]. Although individuals with LTBI are not infectious, they are a reservoir for TB in their communities. According to a review article by Getahun et al., modeling has shown that if a mere 8% of individuals with LTBI were “permanently protected” annually, the incidence of TB worldwide in 2050 would be 14 times as low as in 2013

The association between TB and DM has been known about for centuries[11]. Studies involving TB patients have shown that previously diagnosed DM is one of the most commonly occurring co-morbidities[6]. Of concern, the global prevalence of DM is increasing rapidly, and the largest increases in DM prevalence will occur in settings where TB burdens are greatest[11-13]. An estimated 95% of TB cases occur in low- and middle-income countries, and approximately 70% of individuals with DM reside in these same countries[12]. In 2014, an estimated 415 million adults had type 2 DM and by 2040 the prevalence is expected to reach 642 million adults worldwide[14]. Given the rapid rise in global DM prevalence and the increased risk of TB in this population, an estimated 15% of all TB cases are currently attributed to DM[7, 15].

Observational studies have shown that DM increases the risk of TB. A 2012 cohort study conducted by Baker et al. found that individuals with type 2 DM (whether treated or not) had a significantly higher risk of TB than individuals without type 2 DM (adjusted hazard ratio, 2.09 [95% confidence interval, 1.10-3.95])[4]. Baker et al. also found the risk of TB to be correlated with the amount of type 2 DM-associated complications, with individuals with ≥ 2 type 2 DM complications having more than 3 times the risk of TB than individuals without type 2 DM (odds ratio, 3.45 [95% confidence interval, 1.59-7.50])[4]. A meta-analysis conducted by Jeon et al. of 13 observational studies found a pooled risk ratio of 3.1 (95% confidence interval, 2.3-4.3) for active TB comparing individuals with type 2 DM to individuals without type 2 DM[16].

Our study involved the use of data from the 2011-2012 cycle of the National Health and Nutrition Examination Survey (NHANES) to estimate the prevalence of DM

and LTBI among the civilian, non-institutionalized United States population. NHANES has been conducted in the United States since the early 1960s and focuses on various health issues and populations each cycle. Each year, NHANES retrieves data on approximately 5,000 individuals meant to be a nationally representative sample. Questionnaires, physical examinations, and laboratory measurements are used together to obtain information on risk factors for various diseases and the prevalence of certain diseases in the United States[17].

1.2 Gap and Purpose of Study

Results from recent studies using data from NHANES suggest an association between LTBI and DM[18]. A 2016 cross-sectional study conducted by Hensel et al. also found an association between LTBI and DM, with 43.4% and 39.1% of QFT-positive (QuantiFERON-TB test) individuals having DM and pre-DM, respectively, compared to 25.9% of QFT-positive individuals not having DM or pre-DM[19]. Although studies have shown an association between LTBI and DM, the association has not been further investigated using NHANES data. Using data from the 2011-2012 cycle of NHANES, we hypothesized that DM and pre-DM are associated with LTBI.

The objectives of this study are to:

1. Investigate participant characteristics associated with DM and LTBI
2. Determine the association of DM and pre-DM with LTBI

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Latent Tuberculosis Infection

Approximately one-third of the global population is estimated to have latent tuberculosis infection (LTBI)[2, 3]. There were an estimated 10.4 million new cases of TB globally and 1.4 million deaths attributed to TB in 2015[1]. Though the majority of individuals infected with *Mycobacterium tuberculosis* (MTB) never progress to symptomatic, infectious active tuberculosis (TB), these individuals with LTBI serve as a reservoir for TB in their communities[3].

For individuals who become infected with MTB, progression to active TB only occurs in approximately 5-10% of those infected[9]. MTB will be contained by the immune system for the majority of those infected, and these individuals will develop asymptomatic, non-infectious LTBI[2, 3]. The immune response to MTB begins when the bacteria come into contact with alveolar macrophages of the lungs. In response, these macrophages upregulate production of pro-inflammatory cytokines to signal the presence of an infection[2]. As a result, cells such as T lymphocytes, B cells, fibroblasts, and dendritic cells are recruited to the site of infection, which in the case of LTBI leads to the formation of a granuloma containing the bacteria. Bacteria that survive granuloma formation become a reservoir of latent infection[2].

Studies have shown that the levels of certain cellular immune signals may function in the maintenance of the dormancy of LTBI. Pro-inflammatory cytokines TNF- α and IFN- γ are known to be vital in maintaining the dormancy of LTBI by keeping MTB

contained in granulomas[2, 20, 21]. In a 2015 cross-sectional study in India involving 39 recently diagnosed active TB patients and 35 household contacts with LTBI as confirmed by positive QuantiFERON®-TB Gold In-Tube Test (QFT-GIT) and negative chest X-ray and smear microscopy, Pathakumari et al. reported that, following stimulation with two MTB antigens, Rv2204c and Rv0753c, higher levels of IFN- γ were seen in whole blood samples of those with LTBI compared to those with active TB[22]. Other studies have also reported increased levels of TNF- α and IFN- γ in patients with LTBI compared to patients with active TB[21, 23, 24]. Elevated levels of antimicrobial peptides (AMPs), such as human β -defensin-2 (HBD-2), have been observed in patients infected with LTBI[25-27]. β -defensins may play an important role in maintaining the dormancy of LTBI, as they are able to inactivate one of the crucial proteins involved in the proliferation of bacteria, ftsZ factor[25].

In a cross-sectional analysis of data from the 2011-2012 cycle of the National Health and Nutrition Examination Survey (NHANES), Mancuso et al. determined the prevalence of LTBI among the civilian, non-institutionalized population to be approximately 4.4% by positive tuberculin skin test (TST) results and approximately 4.8% by positive QFT-GIT[28]. Mancuso et al. reported that QFT-GIT test results had a higher specificity, especially among individuals who had received the Bacillus Calmette-Guérin (BCG) vaccine[28]. QFT-GIT may be a more reliable test for LTBI, as false positives using the TST may occur due to cross-reactive antigens in the purified protein derivative (PPD) also being present in non-pathogenic mycobacteria[29].

2.2 Diabetes Mellitus

Approximately 415 million adults were living with type 2 diabetes mellitus in 2014, and the prevalence of type 2 diabetes is projected to increase to 642 million adults worldwide by 2040[14]. Although type 1 diabetes is also a major issue, type 2 diabetes currently comprises approximately 90% of the cases of diabetes worldwide[8]. Among the many known risk factors for developing diabetes, obesity is known to predispose an individual to diabetes[30-32]. The main mechanism by which obesity predisposes an individual to developing diabetes is the elevated levels of pro-inflammatory cytokines, such as TNF- α , seen in adipose tissue of obese individuals[30-32]. The elevated levels of pro-inflammatory cytokines such as IL-1 β , C-reactive protein (CRP), IL-6, IL-8, and MCP-1 have been shown to precede the development of diabetes[30, 31, 33]. Elevated levels of pro-inflammatory cytokines such as TNF- α increase the risk of developing insulin resistance and beta cell dysfunction, key features of diabetes[30, 33].

Diabetes is associated with a chronic, low-grade inflammation that is marked by increased levels of pro-inflammatory cytokines that reflect activation of innate immunity[33]. In a 2015 study involving 14,876 men and women from the Gutenberg Health Study cohort, researchers found elevated plasma levels of CRP in patients with diabetes and pre-diabetes compared to patients without diabetes[31]. CRP is known to be a marker of inflammation that increases in response to increased inflammation and may be associated with insulin resistance syndrome[34]. Other studies have also demonstrated diabetes to be associated with elevated levels of several key pro-inflammatory cytokines, such as CRP, IFN- γ , TNF- α , IL-1 β , IL-6, and IL-17[31, 34-44].

2.3 Co-Occurring Diabetes and Tuberculosis

Despite reactivation of LTBI to active TB only occurring in approximately 10% of individuals infected with MTB[2], certain comorbidities, such as human immunodeficiency virus (HIV)[3, 5, 9] and diabetes[3, 6, 8], have been shown to significantly increase the risk of LTBI reactivation to active TB. The risk of reactivation to active TB for patients with co-occurring HIV and LTBI may exceed 10% per year, while the average risk of reactivation to active TB for those with LTBI only is between 10% and 20% for their entire lifetime[5]. In a review article by Restrepo et al., the risk of developing active TB in those with co-occurring LTBI and HIV is estimated to be more than 50 times the risk in those without co-occurring HIV[9]. Among adults with HIV in under-developed countries, the most common cause of death is TB[5]. In addition to HIV and diabetes, there are many other factors that may impact an individual's risk of reactivation LTBI to active TB, including being homeless, being from a country with a high burden of TB, and being of very young or very old age[3].

Risk of reactivation of LTBI to active TB among individuals with co-occurring diabetes has been found to be approximately three-times the risk of reactivation among individuals without diabetes[6-8]. With diabetes causing such a significant impact on the risk of reactivation to active TB, an estimated 15% of all TB cases are currently attributable to diabetes[7, 15]. The proportion of TB cases attributable to diabetes may increase in the future[45], as the prevalence of diabetes is projected to increase to 552 million individuals worldwide by 2030, and the majority of this increase will likely occur in low- and middle-income countries with high TB burdens[11, 12]. Currently, approximately 95% of patients with TB live in developing, low- and middle-income

countries, such as in Southeast Asia, and approximately 70% of patients with diabetes reside in those same countries[12].

Co-occurring diabetes and LTBI has been shown to have an impact on both the innate and adaptive immune system. It is due to these immunologic effects that having diabetes increases the risk of developing active TB[6, 19]. While not as much is known regarding immunologic dysfunction during co-occurring diabetes and LTBI, there are a few notable studies that have analyzed biomarkers present in individuals with both illnesses. In a 2014 case-control study of 90 patients with LTBI (30 with co-occurring diabetes, 30 with co-occurring pre-diabetes, 30 without diabetes), as determined by positive QFT-GIT and normal chest radiograph, and 60 uninfected controls (30 with co-occurring diabetes and 30 without diabetes), Kumar et al. measured the circulating levels of several cytokines. The study found decreased circulating levels of the pro-inflammatory cytokines IFN- γ , TNF- α , IL-1 β , IL-2, IL-17, and IL-18 in subjects with co-occurring LTBI and diabetes compared to subjects with LTBI only[46]. Pro-inflammatory cytokines are known to be vital in the immune response against mycobacterial infections, so decreased levels of these pro-inflammatory cytokines in individuals with co-occurring diabetes and LTBI may increase the risk of reactivation to active TB[46].

AMPs may also be related to immune dysfunction seen in co-occurring diabetes and LTBI. In a 2011 cross-sectional study of 30 subjects with diabetes (10 uninfected, 10 with co-occurring LTBI, 10 with co-occurring active TB) and 30 subjects without diabetes (10 uninfected, 10 with co-occurring LTBI, 10 with co-occurring active TB), Gonzalez-Curiel et al. measured the gene expression of AMPs in peripheral blood

samples of all subjects. The study found decreased levels of gene expression for AMPs in subjects with co-occurring diabetes and LTBI compared to subjects with LTBI only[47]. Since AMPs are known to function in the killing of engulfed or invasive bacteria[47], a decreased level of AMPs may put individuals with co-occurring diabetes and LTBI at a higher risk of reactivation to active TB.

Interestingly, some studies have suggested that the severity of diabetes, either by amount of complications or by poor glycemic control, increases the risk of TB. Studies have shown a relationship between HbA1c and blood glucose levels and the immune response to TB[9]. In a 2012 prospective cohort study conducted by Baker et al., a patient's risk of TB was found to increase as the number of diabetes-related complications increased, with a three-fold risk of TB being seen among patients with two or more complications (OR 3.45; 95%CI 1.59-7.50)[4]. In a cohort study of 123,546 individuals who participated in a community-based health screening service in northern Taiwan from 2005 to 2008, Lee et al. measured glycemic control using fasting plasma glucose (FPG) and determined occurrence of TB during a follow-up period up until December 2012. Researchers found that patients with diabetes who had poor glycemic control (categorized by a $FPG > 130 \text{ mg/dL}$) had a significantly higher hazard of TB (aHR 2.21; 95%CI 1.63-2.99) compared to patients without diabetes; however, the hazard of TB among patients with diabetes with good glycemic control (categorized by a $FPG \leq 130 \text{ mg/dL}$) was similar to the hazard of TB among patients without diabetes (aHR 0.69; 95%CI 0.35-1.36). Lee et al. also conducted a linear-dose response analysis to determine if the hazard of TB increased with an increase in FPG and found the hazard of TB to slightly increase with increased FPG (aHR 1.06 per 10mg/dL increase in FPG;

95%CI 1.03-1.08)[48]. Other studies have also found higher HbA1c levels to be associated with a higher risk of developing TB[13, 49, 50].

In addition to increasing the risk of reactivation of LTBI to active TB, co-occurring diabetes also increases the likeliness of poor TB treatment outcomes, including treatment failure, relapse, and even death[6, 10, 11]. Patients with both diabetes and active TB generally present with symptoms consistent with more severe clinical manifestations, including higher smear grade and more lung cavities[51]. In a retrospective cohort study conducted among TB cases in Georgia, Magee et al. found patients with co-occurring diabetes and TB to be more likely to have cavitary lung disease at the time of TB diagnosis (51%) compared to both patients with co-occurring HIV and TB and patients with only TB – 19.9% and 34.7%, respectively. However, contradictory to other studies that have reported an increased risk of mortality among patients with co-occurring diabetes and TB[52], Magee et al. found that diabetes was not associated with increased mortality (aOR 1.05; 95%CI 0.60-1.84)[53].

The association between diabetes and TB has been known about for centuries and was even suggested during Roman times[11]. Studies have demonstrated a significant association between LTBI and active TB and diabetes. In a 2011 cross-sectional study conducted by Hensel et al., newly arrived refugees at a health clinic in Atlanta, Georgia were screened for diabetes, pre-diabetes and LTBI. Researchers determined diabetes and pre-diabetes by measuring HbA1c (glycated hemoglobin) levels and screened for LTBI using QFT-GIT. The prevalence of LTBI among patients with diabetes (43.4%) and pre-diabetes (39.1%) was found to be significantly higher ($p < 0.01$) than among patients without diabetes (25.9%). Hensel et al. hypothesized that the reason for a higher

prevalence of LTBI among patients with diabetes may be due to dysglycemia causing immunologic dysfunction[19].

In a cohort study conducted in the country of Georgia during 2011-2014, Magee et al. evaluated 318 new TB patients (with no previous history of TB) for diabetes and pre-diabetes using HbA1c measurements. Researchers found the prevalence of diabetes and pre-diabetes to be fairly high among the new TB patients – 11.6% and 16.4%, respectively. The total combined prevalence of new TB patients with diabetes or pre-diabetes was determined to be 28%[54].

In a systematic review of 13 observational studies of the association between diabetes and active TB, Jeon et al. reported that all 13 studies found diabetes to be associated with an increased risk of TB. A meta-analysis of the results of the three cohort studies found the relative risk of TB among patients with diabetes to be 3.11 (95%CI 2.27-4.26) times the relative risk among patients without diabetes[16]. Contradicting results were seen in a 2011 case-control study conducted in Denmark by Leegard et al. Researchers found the odds of active TB among patients with diabetes to only be 1.18 (95%CI 0.96-1.45) times the odds of active TB among patients without diabetes. This finding of only a “modestly increased” risk of TB in patients with diabetes may be due to the study being conducted in Denmark, a country with a low burden of TB[13]. Though many studies have shown an association between active TB and diabetes, there is an extreme lack of studies on the association between LTBI and diabetes.

2.4 Summary of Literature Review

Highlights from the literature review of previous studies include:

- Immune dysfunction associated with co-occurring diabetes and LTBI increases the risk of progression to active TB
- Poor glycemic control (higher HbA1c levels) may be associated with an increased risk of TB
- It has been well-established that active TB is associated with diabetes, but there are is a lack of studies investigating the association between LTBI and diabetes

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CHAPTER III

MANUSCRIPT

Introduction

There were an estimated 10.4 million incident cases of active tuberculosis (TB) globally in 2015, and 1.4 million deaths attributable to TB[1]. In addition, about one-fourth of the global population has prevalent latent tuberculosis infection (LTBI)[55]. Although the lifetime risk of reactivation of LTBI to TB disease only occurs in approximately 10% of infected individuals [2], the risk of progression to TB is higher in individuals with comorbidities, such as HIV[5] and diabetes mellitus[6-9, 11, 19, 45]. Individuals with diabetes have approximately three times the risk of active TB compared to the general population[6, 7, 9, 10]. As a consequence of this increased risk of active TB, an estimated 15% of TB cases are attributed to diabetes[7, 15].

Of public health concern, the global diabetes epidemic is steadily increasing[6, 11, 12]. In 2014, an estimated 415 million adults were living with diabetes, and the prevalence of diabetes is projected to reach 642 million adults globally by 2040[14]. Additionally, an estimated 95% of TB patients reside in low- and middle-income countries, and the largest projected increases in diabetes will occur in these same countries[11, 12].

Although existing evidence has demonstrated a relationship between diabetes and active TB, it is unclear whether diabetes also increases the risk of LTBI. The limited studies that examined the relationship between diabetes and LTBI have reported substantial heterogeneity across studies[56] and have not accounted for confounding by other clinical comorbidities such as kidney disease or hepatitis[18, 57]. Previous studies that reported a significant association between diabetes and LTBI were not widely generalizable and mostly have not used reliable measures of diabetes and LTBI[56]. Knowledge on the direction of the association between

diabetes and LTBI is also lacking. An increased risk of LTBI in patients with diabetes would have major clinical implications for TB and diabetes, especially with the expected increase in global diabetes prevalence. To address the gap in knowledge related to diabetes and LTBI, we aimed to determine the association between prediabetes and diabetes and LTBI using the National Health and Nutrition Examination Survey (NHANES), a study with data that are representative of the US population.

Methods

We conducted a cross-sectional study using data collected as part of the NHANES 2011-2012 cycle, which is the most recent cycle that includes the QuantiFERON®-TB Gold In Tube (QFT-GIT) test as a measure of LTBI status. Briefly, NHANES is a nationally representative survey of US non-institutionalized civilians that includes an in-person home interview followed by a health examination. Details of NHANES methodology have been published previously[58]. In the 2011-2012 survey cycle, a total of 13,431 individuals were selected for participation from 30 different locations in the United States. Of those individuals, 9,756 completed the in-person home interview and 9,338 completed the in-person home interview and received the health examination[59].

Study Design and Participants

Eligible participants for our study were adults aged 20 years and older who completed the home questionnaire and the health examination. Eligible participants were also required to have both a valid TB test result and a valid diabetes status. A positive or negative result for the QFT-GIT test was considered a valid result. Participants who were missing a result for the QFT-GIT test or who had an indeterminate result for the test were excluded from the study. Participants

who had a glycated hemoglobin (HbA1c) measurement and/or information regarding self-reported diabetes status were considered to have a valid diabetes status. Participants who were missing both an HbA1c measurement and information regarding self-reported diabetes status were excluded from the study.

Biological specimen collection was performed in specially equipped mobile examination centers (MECs)[58]. Blood samples were drawn by a phlebotomist and refrigerated or frozen before being shipped and urine samples were also collected from participants. Samples were transported to laboratories across the United States for processing[60], except samples for QFT-GIT testing, which were sent to only one Clinical Laboratory Improvement Act-certified laboratory for processing[18].

Study Measures and Definitions

Diabetes status of participants was defined by self-reported diabetes status and HbA1c levels. Participants who indicated that they had previously been diagnosed by a healthcare professional to have diabetes were classified as having diabetes regardless of HbA1c measurement. If participants did not indicate a previous history of diabetes diagnosis, diabetes status was then classified by HbA1c as no diabetes ($\leq 5.6\%$), prediabetes (5.7-6.4%), or diabetes ($\geq 6.5\%$) according to the American Diabetes Association guidelines[61]. Participants with diabetes were further classified as having diagnosed or undiagnosed diabetes. Diagnosed diabetes was classified as self-reporting diabetes, and undiagnosed diabetes was classified as self-reporting not having diabetes but having an HbA1c level in the range for diabetes ($\geq 6.5\%$). Among participants with self-reported diabetes, length of time since initial diabetes diagnosis and information regarding diabetes medication were also assessed via questionnaire. Use of

diabetes medications was determined by responses to self-reported questions on the use of insulin and oral agents[62].

Latent TB infection was defined by QFT-GIT according to manufacturer instructions. Results were interpreted according to guidelines from the Centers for Disease Control and Prevention (CDC) for using interferon-gamma release assays (IGRAs)[63]. Participants with a positive QFT-GIT result were classified as LTBI positive, participants with a negative QFT-GIT result were classified as LTBI negative, and participants with an indeterminate QFT-GIT result were classified as missing.

Participants who self-reported they had ever been told by a health care professional to have active TB were defined as having a history of active TB. Body mass index (BMI) ranges were categorized as underweight (<18.5), normal weight (18.5 - 24.9 kg/m²), overweight (25.0 - 29.9 kg/m²), or obese (≥ 30 kg/m²) according to CDC guidelines[64]. Age ranges were categorized as young adult (20-34 years), middle-aged (35-64 years), or elderly (65 years and older). Current smokers were defined as participants who self-reported use of 100 cigarettes in their lifetime and self-reported currently smoking. Former smokers were defined as those who reported smoking 100 cigarettes in their lifetime but did not currently smoke cigarettes. Participants who had not smoked 100 cigarettes in their lifetime were defined as never smokers [65, 66].

Urine samples were analyzed for albumin creatinine ratio (ACR), and ACR levels were categorized as normal to mildly increased (<30 mg/g), moderately increased (30 - 300 mg/g), or severely increased (>300 mg/g) according to National Kidney Foundation guidelines for albuminuria categories in chronic kidney disease[67]. Hepatitis B virus (HBV) core antibody (anti-HBc) and surface antigen (HBsAg) response were determined using the VITROS Anti-HBc

assay and HBsAg assay, respectively; results were defined as positive or negative. The HBsAg assay was only performed for participants that tested positive for anti-HBc; participants with a negative result for anti-HBc were defined as negative for HBsAg. Hepatitis C antibody (anti-HCV) response was determined using the VITROS Anti-HCV assay; results were defined as positive or negative. Non-fasting blood samples were analyzed for total cholesterol and high-density lipoprotein (HDL) cholesterol[68]. Our study categorized total cholesterol levels as desirable ($<200\text{mg/dL}$), borderline high ($200\text{-}239\text{mg/dL}$), or high ($\geq 240\text{mg/dL}$) according to National Institutes of Health guidelines[69]. Our study categorized HDL cholesterol levels as major risk factor for heart disease ($<40\text{mg/dL}$), borderline ($40\text{-}59\text{mg/dL}$), or protective against heart disease ($\geq 60\text{mg/dL}$) according to Medline Plus guidelines[70]. Responses of “don’t know” or “refused” were recoded as missing for all variables.

Statistical Analyses

To examine the association between diabetes and LTBI we used bivariate analyses and multivariable logistic regression. The Rao-Scott chi-square test was used to analyze all bivariate associations between participant characteristics and LTBI and diabetes. To examine the prevalence of diabetes and LTBI in the United States population, we reported weighted prevalence estimates and 95% confidence intervals (CI). Taylor series method was used to estimate variance for all prevalence estimates[71]. Multivariable logistic regression models were used to estimate the adjusted odds ratio (aOR) and 95% CI between diabetes and LTBI and were adjusted for potential confounders. Covariates included in multivariable models as confounders were chosen from observed bivariate associations with diabetes and LTBI, previous study findings, and causal model theory (directed acyclic graphs) [72]. In multivariable models, multiplicative statistical interaction was assessed to determine if the association between diabetes

and LTBI was modified by obesity or HDL cholesterol. In a subgroup analysis, we also examined the bivariate association between participant characteristics and LTBI only among individuals with diabetes. All analyses were performed using SAS version 9.4 and accounted for the weighted stratified probability sample design of NHANES using SAS survey procedures[73]. Because medical examination data were used during the analyses, we used the weight variable WTMEC2YR to obtain accurate prevalence estimates and measures of association. A two-sided p-value <0.05 was considered statistically significant for all tests.

Sensitivity Analysis

We performed sensitivity analyses to assess potential error due to 1) misclassification of diabetes status and 2) covariate misspecification in multivariable models. To assess diabetes misclassification, we re-examined the diabetes-LTBI association after adding fasting blood glucose (prediabetes 100-125mg/dL, or diabetes ≥ 126 mg/dL) to our primary diabetes definition which used self-report and HbA1c only[61]. In the second sensitivity analysis we specified several subsets of adjusted multivariable models to provide a range of plausible aORs and 95%CI for the association between diabetes and LTBI.

Results

Study Participants

Of 9,756 NHANES 2011-2012 participants, 5,560 (57.0%) were aged 20 years or older and thus eligible for our study. A total of 4,958 (89.2%) participants had both valid QFT-GIT results and information on self-reported diabetes status and/or HbA1c results and were included in these analyses (Figure 1). Before accounting for selection weights, 793 eligible participants had diabetes, 513 had LTBI, and 127 had both diabetes and LTBI.

Prevalence of Diabetes and Latent TB Infection

The estimated prevalence of diabetes among adults in the United States population was 11.4% (95%CI 9.8-13.0%) and the prevalence of prediabetes was 22.1% (95%CI 20.5-23.8%) (Table 1). The prevalence of diabetes was highest among the elderly (22.9%; 95%CI 19.8-25.9%), people with obesity (20.4%; 95%CI 17.3-23.5%), those with less than a 9th grade education (25.2%; 95%CI 18.2-32.2%), severely increased ACRs (46.9%; 95%CI 33.7-60.1%), hepatitis C (19.8%; 95%CI 7.1-32.5%), and hypertension (23.3%; 95%CI 20.8-25.9%).

Our results estimated that the prevalence of LTBI among adults in the United States was 5.9% (95%CI 4.9-7.0%) (Table 2). Prevalence of LTBI was highest among the elderly (8.8%; 95%CI 6.6-10.9%), the foreign-born (17.2%; 95%CI 14.3-20.0%), those with less than a 9th grade education (17.9%; 95%CI 13.2-22.7%), Hispanics (12.9%; 95%CI 10.4-15.4%), non-Hispanic Asians (20.3%; 95%CI 16.8-23.8%), and those who reported a previous history of active TB (42.7%; 95%CI 24.1-61.2). LTBI prevalence was also high among those with high (>300mg/g) ACR (12.9%; 95%CI 6.7-19.2%), those who tested positive for anti-HBc (18.0%; 95%CI 11.6-24.4%), and those who tested positive for HBsAg (23.0%; 95%CI 8.2-37.7%).

The prevalence of LTBI was significantly higher among adults with diabetes (11.6%; 95%CI 7.9-15.3%) compared to those without diabetes (4.6%; 95%CI 3.7-5.6%). LTBI prevalence was also higher among those with prediabetes (7.0%; 95%CI 5.2-8.7%) compared to those without diabetes, though the difference was not statistically significant. Adults with diabetes and prediabetes had significantly higher crude odds of LTBI (diabetes: crude OR 2.70; 95%CI 1.76-4.14; prediabetes: crude OR 1.54; 95%CI 1.24-1.91) compared to those without diabetes (Table 3). Reported inversely, among those with LTBI the prevalence of diabetes was 22.2% (95%CI 16.6-27.8%) and the prevalence of prediabetes was 25.9% (95%CI 22.1-29.7%).

Among those without LTBI the prevalence of diabetes was 10.7% (95%CI 9.0-12.4%) and the prevalence of prediabetes was 21.9% (95%CI 20.3-23.6%).

Multivariable Models Results

Multivariable logistic models were examined adjusting for age, sex, smoking status, history of active TB, and foreign born status. Adults with diabetes had significantly higher odds of LTBI (aOR 1.90; 95%CI 1.15-3.14) compared to adults without diabetes (Table 3). Those previously diagnosed with diabetes had significantly higher odds of LTBI (aOR 1.75; 95%CI 1.09-2.80) compared to adults without diabetes, as did adults with previously undiagnosed diabetes (aOR 1.96; 95%CI 1.05-3.68). The odds of LTBI among adults with prediabetes (aOR 1.15; 95%CI 0.90-1.47) was not significantly higher than among adults without diabetes.

We found no indication of significant multiplicative interaction. Although not significantly different from each other, the association between diabetes and LTBI tended to be greater among those with obesity (aOR 2.22; 95%CI 1.08-4.54) compared to those without obesity (aOR 1.48; 95%CI 0.85-2.58) (data not shown). Similarly, the association between diabetes and LTBI was non-significantly greater among those with higher HDL (≥ 60 mg/dL) levels (aOR 2.77; 95%CI 1.13-6.84) compared to those with lower HDL (< 60 mg/dL) levels (aOR 1.80; 95%CI 0.99-3.29).

Subgroup Analysis of Adults with Diabetes

Among adults with diabetes, an estimated 19.9% (95%CI 15.3-24.4%) were previously undiagnosed (Table 4). Prevalence of LTBI was non-significantly (p-value=0.24) different among adults with previously undiagnosed diabetes (14.4%; 95%CI 6.7-22.2%) compared to adults who had been previously diagnosed (10.9%; 95%CI 7.4-14.4%). LTBI prevalence was

significantly higher (p-value=0.03) among adults who reported not using insulin (12.9%; 95%CI 8.5-17.3%) compared to adults who reported using insulin (7.3%; 95%CI 3.1-11.4). Among those with diabetes, LTBI prevalence was found to be highest among Hispanics (24.3%; 95%CI 12.4-36.2%), non-Hispanic Asians (27.5%; 95%CI 19.0-35.9%), those born outside of the United States (30.2; 95%CI 18.8-41.6%), and those with a positive test result for anti-HBc (20.8%; 95%CI 8.9-32.7%).

Sensitivity Analyses

In our sensitivity analysis to assess potential misclassification of diabetes using FBG in addition to self-report and HbA1c, adults with diabetes had significantly higher crude odds of LTBI (crude OR 2.43; 95%CI 1.32-4.49) compared to those without diabetes (data not shown). Adults with prediabetes had non-significantly higher crude odds of LTBI (crude OR 1.21; 95%CI 0.74-2.00) compared to those without diabetes. After adjusting for age, sex, smoking status, history of active TB, and foreign born status, adults with diabetes had a non-significant higher odds of LTBI (aOR 1.36; 95%CI 0.70-2.65) compared to those without diabetes.

In our sensitivity analysis to assess covariate misspecification of adjusted models, we found adjusted odds ratios that ranged from 1.49 (95%CI 0.83-2.68) to 2.20 (95%CI 1.22-3.96) for the odds of LTBI in adults with diabetes compared to those without diabetes (Supplemental Table 1). We found adjusted odds ratios that ranged from 0.95 (95%CI 0.75-1.21) to 1.25 (95%CI 0.93-1.68) for the odds of LTBI in adults with prediabetes compared to those without diabetes; however, none were statistically significant.

Discussion

We used data nationally representative of the US population to examine the association between LTBI and diabetes and found a robust relationship between the two diseases. We reported that the prevalence of LTBI among adults with diabetes was more than twice the prevalence of those without diabetes. Similarly, we found that more than one-fifth of adults with LTBI had diabetes. We did not find significant differences in LTBI prevalence among those who were previously diagnosed compared to those who were previously undiagnosed. We also did not find significant differences in LTBI prevalence among those with prediabetes compared to those without diabetes. To our knowledge, this study is the largest and most generalizable analysis to compare the prevalence of LTBI among adults with and without diabetes and prediabetes.

Our results are consistent with the findings of previous studies. In a systematic review conducted by Lee et al., the meta-analysis included findings from one cohort study and 12 cross-sectional studies investigating the association between diabetes and LTBI. From the 12 cross-sectional studies, researchers calculated a pooled odds ratio of 1.18 (95%CI 1.06-1.30), indicating a slight yet significant increased odds of LTBI among patients with diabetes compared to patients without diabetes[56]. A limitation of several studies reviewed in Lee et al.'s systematic review and meta-analysis was the potential misclassification of LTBI due to measurement error associated with the TST (tuberculin skin test). Unlike many previous studies, our study relied upon the use of QFT-GIT which is not affected by the Bacillus Calmette-Guérin (BCG) vaccine. Our national estimates of LTBI prevalence were similar to previously reported estimates[18, 28]

Our results were similar to a study conducted by Hensel et al. in the metropolitan area of Atlanta, Georgia[19]. This study also utilized both HbA1c and QFT-GIT to determine diabetes status and LTBI status, respectively. Hensel et al. found a nearly doubled prevalence of LTBI among patients with diabetes compared to those without diabetes[19]. Unlike our study, however, the Atlanta study was not generalizable to the US adult population, as it only included recently arrived refugees to the United States[19]. As with the Atlanta study, we found no significant difference in the prevalence of LTBI among patients with previously undiagnosed diabetes compared to those with previously diagnosed diabetes[19].

Although the causal mechanisms that result in increased co-occurrence of LTBI and diabetes remain to be definitively established, there are relevant biologic hypotheses that may explain how LTBI may increase the risk of diabetes and vice-versa. Some LTBI granulomas on the spectrum of high MTB activity include bacterial replication and likely result in proximal immune signaling, a phenomena which may persist in adipose tissue[74]. Secretion of pro-inflammatory adipokines and cytokines within adipocytes could interfere with insulin regulation and contribute to diabetes risk[30, 75]. If LTBI contributes to immune activation within visceral adipose tissue, it would likely increase the risk of diabetes or prediabetes. Alternatively, chronic low-grade inflammation and immunopathology associated with diabetes and prediabetes [31, 33] may contribute to susceptibility to TB infection[8, 9].

Our study was subject to several limitations. First, there may have been misclassification of participant characteristics. For example, self-reported information on smoking status was determined via participant responses to a questionnaire, so smokers may have reported not smoking due to social stigma. While diabetes and LTBI status may also be subject to misclassification, we defined these primary study variables using currently recommended

clinical measures (HbA1c and QFT-GIT)[76, 77]. By using the QFT-GITs instead of the TST to measure LTBI, we avoided potential cross-reaction with antigens found in the BCG vaccine, commonly used outside the United States [29, 77]. However, we did not account for discordance between QFT-GIT and TST, and therefore some misclassification of LTBI may have occurred. Second, in this study we were unable to adjust for the probability being exposed to someone with active TB. Although previous history of active TB was assessed via questionnaire and found to be associated with LTBI but not diabetes status, the inability to adjust for probability of exposure to TB may have distorted our estimated association between LTBI and diabetes. Nonetheless, we did adjust for several other key confounding factors such as smoking, age, and foreign born status. We also were able to assess the distribution of other underlying infections, such as hepatitis B and C and kidney disease, and found no evidence of confounding. Third, our study was a cross-sectional design, and as such we were unable to determine the temporal relationship between LTBI and diabetes. For example, our results are unable to differentiate whether the observed association was due to an increased risk of LTBI from diabetes or if LTBI may increase the risk of diabetes. Longitudinal studies are needed to investigate the temporal association between LTBI and diabetes.

Conclusion

This study reported that diabetes was significantly associated with an increased odds of LTBI prevalence in US adults, even after adjusting for key confounding factors. Overall, more than one-fifth of all adults with LTBI had diabetes. Information from this study greatly improves our understanding of the intersection of the TB and diabetes epidemics. With the increasing prevalence of diabetes in areas with the highest burden of TB, targeted efforts may be needed to address the co-infection of diabetes and LTBI to prevent an increase in TB incidence worldwide.

Table 1: Weighted prevalence of diabetes and prediabetes among the civilian, non-institutionalized

United States population, adults 20 years and older, 2011-2012

Participant Characteristics	Totals for Population N=4,958 % (95% CI)	Diabetes¹ % (95% CI) 11.4 (9.8-13.0)	Prediabetes² % (95% CI) 22.1 (20.5-23.8)	No Diabetes % (95% CI) 66.5 (64.2-68.8)	p-value³
Age (years)					
20 – 34	27.5 (23.1-31.9)	2.0 (1.2-2.8)	9.0 (7.3-10.7)	89.0 (87.0-91.0)	<0.01
35 – 64	54.9 (51.8-57.9)	12.4 (10.2-14.6)	24.0 (20.6-27.3)	63.6 (60.0-67.1)	
≥65	17.6 (15.3-19.9)	22.9 (19.8-25.9)	36.9 (32.8-41.0)	40.3 (34.8-45.7)	
BMI ⁴					
<18.5	1.8 (1.3-2.2)	4.2 (0-8.8)	8.0 (2.1-13.9)	87.8 (81.0-94.5)	<0.01
18.5 – 24.9	29.4 (26.1-32.6)	5.1 (3.4-6.9)	17.6 (14.0-21.2)	77.3 (72.9-81.7)	
25.0-29.9	33.5 (30.7-36.3)	7.7 (6.7-8.6)	22.8 (19.2-26.3)	69.6 (66.1-73.0)	
≥30.0	35.4 (32.3-38.5)	20.4 (17.3-23.5)	26.1 (23.1-29.1)	53.5 (49.3-57.6)	
Foreign Born ⁵					
No	82.1 (77.9-86.3)	11.0 (9.2-12.8)	22.0 (20.0-23.9)	67.0 (64.4-69.6)	0.12
Yes	17.9 (13.7-22.1)	13.2 (11.3-15.0)	22.7 (19.8-25.6)	64.1 (61.1-67.1)	
LTBI ⁶					
Positive	5.9 (4.9-7.0)	22.2 (16.6-27.8)	25.9 (22.1-29.7)	51.9 (45.8-58.0)	<0.01
Negative	94.1 (93.0-95.1)	10.7 (9.0-12.4)	21.9 (20.3-23.6)	67.4 (65.0-69.8)	
TST ⁷					
Positive	4.7 (3.0-6.4)	15.5 (9.4-21.6)	29.2 (18.5-39.9)	55.3 (46.6-63.9)	0.11
Negative	95.3 (93.6-97.0)	11.3 (9.7-13.0)	22.2 (20.2-24.2)	66.5 (64.0-69.9)	
HbA1c (%) ⁸					
<5.7	67.1 (64.9-69.3)	0.91 (0.50-1.3)	0 (0-0)	99.1 (98.7-99.5)	
5.7-6.4	24.8 (22.7-26.9)	10.8 (7.8-13.8)	89.2 (86.2-92.2)	0 (0-0)	
≥6.5	8.1 (6.9-9.3)	100 (100-100)	0 (0-0)	0 (0-0)	
Education					
<9 th Grade	5.7 (4.5-7.0)	25.2 (18.2-32.2)	29.2 (24.0-34.4)	45.6 (39.3-52.0)	<0.01
9 th – 12 th	10.5 (7.6-13.5)	15.0 (13.5-16.5)	26.6 (21.9-31.2)	58.4 (53.7-63.1)	
HS Grad/GED	20.2 (17.2-23.2)	14.7 (11.1-18.2)	27.2 (21.1-33.2)	58.2 (52.1-64.2)	
Some College	32.2 (29.0-35.3)	10.0 (8.3-11.7)	20.7 (17.0-24.5)	69.3 (66.1-72.5)	
≥College Grad	31.4 (26.1-36.7)	7.0 (4.2-9.8)	17.5 (14.2-20.8)	75.5 (70.9-80.1)	
Race/Ethnicity					
Hispanic	14.7 (9.2-20.2)	13.1 (10.5-15.6)	21.8 (19.2-24.3)	65.1 (62.1-68.2)	<0.01
NH White	68.8 (60.2-77.3)	9.4 (7.6-11.2)	20.9 (18.4-23.5)	69.6 (66.2-73.1)	
NH Black	11.3 (6.5-16.1)	17.9 (14.2-21.6)	30.0 (27.1-32.9)	52.1 (48.7-55.6)	
NH Asian	5.2 (3.2-7.1)	12.9 (9.8-16.0)	22.9 (18.3-27.5)	64.2 (57.4-71.0)	
Sex					
Female	52.2 (50.5-53.9)	11.1 (9.3-12.8)	22.2 (19.7-24.8)	66.7 (63.5-69.9)	0.82
Male	47.8 (46.1-49.5)	11.8 (9.7-13.8)	22.0 (20.0-24.0)	66.3 (63.3-69.2)	
Smoking Status ⁹					
Current	19.5 (17.2-21.7)	10.5 (8.8-12.3)	27.1 (21.4-32.8)	62.4 (57.0-67.7)	<0.01
Former	24.3 (21.6-26.9)	15.2 (11.7-18.8)	23.6 (20.2-26.9)	61.2 (56.3-66.1)	
Never	56.2 (53.3-59.1)	10.2 (8.2-12.2)	20.0 (17.4-22.7)	69.8 (66.6-73.0)	

Previous TB ¹⁰ Yes No	0.40 (0.22-0.58) 99.6 (99.4-99.8)	7.3 (0-16.3) 11.4 (9.8-13.0)	30.8 (14.2-47.4) 22.1 (20.4-23.8)	61.9 (45.0-78.8) 66.5 (64.1-68.8)	0.59
TB Meds ¹¹ Yes No	0.24 (0.12-0.36) 99.8 (99.6-99.9)	4.7 (0-12.2) 11.4 (9.8-13.0)	32.8 (4.4-61.2) 22.1 (20.4-23.8)	62.5 (32.5-92.5) 66.5 (64.1-68.8)	0.63
Ratio of Family Income to Poverty ¹² 0-0.99 1-1.99 2-2.99 3-3.99 4-4.99 ≥5	17.2 (13.8-20.6) 21.1 (18.1-24.2) 14.3 (12.1-16.4) 12.1 (9.1-15.1) 10.7 (8.5-12.9) 24.6 (19.6-29.6)	14.9 (11.6-18.1) 14.9 (12.3-17.5) 11.9 (7.9-15.8) 9.4 (7.2-11.6) 13.6 (5.6-21.5) 5.4 (3.0-7.8)	20.5 (15.6-25.3) 24.6 (20.4-28.8) 24.0 (19.1-28.9) 18.5 (14.6-22.4) 17.8 (13.3-22.2) 21.5 (17.2-25.9)	64.7 (57.9-71.5) 60.5 (55.3-65.7) 64.1 (57.8-70.5) 72.1 (67.7-76.6) 68.7 (60.0-77.3) 73.1 (67.1-79.0)	<0.01
Albumin/Creatinine Ratio (mg/g) ¹³ <30 30 – 300 >300	90.4 (89.2-91.6) 8.3 (7.4-9.2) 1.3 (0.94-1.7)	9.2 (7.9-10.5) 28.7 (23.5-33.9) 46.9 (33.7-60.1)	21.9 (20.1-23.8) 24.8 (22.4-27.1) 21.0 (8.6-33.3)	68.9 (66.6-71.2) 46.5 (40.5-52.5) 32.1 (16.2-48.1)	<0.01
HepB Core Ab ¹⁴ Positive Negative	4.6 (3.6-5.5) 95.4 (94.5-96.4)	19.1 (13.1-25.1) 10.8 (9.3-12.3)	28.0 (20.3-35.7) 21.7 (19.9-23.6)	52.9 (46.2-59.6) 67.5 (65.2-69.8)	<0.01
HepB Surface Ag ¹⁵ Positive Negative	0.34 (0.20-0.48) 99.7 (99.5-99.8)	8.6 (1.4-15.8) 11.2 (9.7-12.7)	27.7 (12.9-42.4) 22.0 (20.3-23.7)	63.8 (45.9-81.6) 66.9 (64.6-69.1)	<0.01
HepC Ab (confirmed) ¹⁶ Positive Negative	1.7 (1.0-2.3) 98.3 (97.7-99.0)	19.8 (7.1-32.5) 11.1 (9.7-12.5)	17.5 (11.4-23.6) 22.0 (20.2-23.9)	62.7 (46.9-78.4) 66.9 (64.6-69.2)	0.01
Self-reported Hypertension ¹⁷ Yes No	31.5 (28.4-34.7) 68.5 (65.3-71.6)	23.3 (20.8-25.9) 5.9 (4.8-7.0)	29.2 (26.6-31.8) 18.9 (17.2-20.6)	47.5 (44.1-50.8) 75.2 (73.2-77.3)	<0.01
Total Bilirubin (mg/dL) ¹⁸ Normal Not Normal	98.7 (98.0-99.4) 1.3 (0.59-2.0)	11.2 (9.6-12.7) 5.3 (0.21-10.4)	22.1 (20.5-23.7) 14.3 (1.7-26.9)	66.7 (64.4-69.1) 80.4 (67.0-93.9)	0.11
Total Cholesterol (mg/dL) ¹⁹ <200 200-239 ≥240	56.9 (55.0-58.8) 30.1 (28.4-31.7) 13.0 (11.4-14.7)	12.7 (11.2-14.1) 8.9 (6.6-11.3) 9.6 (6.4-12.9)	19.1 (17.0-21.2) 24.4 (20.8-28.1) 29.2 (24.9-33.7)	68.2 (65.4-71.0) 66.6 (61.9-71.3) 61.1 (56.1-66.1)	<0.01
HDL Cholesterol (mg/dL) ²⁰ <40 40 – 59 ≥60	17.4 (14.7-20.1) 54.7 (51.9-57.6) 27.9 (25.5-30.2)	18.9 (13.4-24.5) 11.8 (10.5-13.1) 5.1 (3.2-6.9)	25.4 (22.2-28.6) 23.3 (21.1-25.5) 17.5 (13.4-21.6)	55.7 (48.6-62.7) 64.9 (62.3-67.5) 77.4 (72.7-82.1)	<0.01

Table 1 Abbreviations: BMI-body mass index; LTBI-latent TB infection; HbA1c-glycated hemoglobin; TST-

tuberculin skin test; QFT-GIT-QuantiFERON®-TB Gold In-Tube; NH-Non-Hispanic; Anti-HBc-hepatitis B core

antibody; HBsAg-hepatitis B surface antigen; Anti-HCV-hepatitis C antibody

- 1: Diabetes determined by self-report (answered “yes” to having been told by a doctor or health professional that he/she had diabetes) and according to American Diabetes Association guidelines[61]; participants who self-reported diabetes were classified as having diabetes regardless of HbA1c.
- 2: Prediabetes determined according to American Diabetes Association guidelines[61].
- 3: All p-values obtained using Rao-Scott chi-square.
- 4: BMI categories defined according to CDC guidelines[64].
- 5: Foreign born individuals include those who reported being born in one of the five United States territories.
- 6: Positive LTBI defined by positive QFT-GIT result; negative LTBI defined by negative QFT-GIT result.
- 7: Positive TST defined as an induration >10mm[78].
- 8: HbA1c categories determined according to American Diabetes Association guidelines[61].
- 9: Current smokers defined as those who self-reported having smoked at least 100 cigarettes in their lifetime and currently smoking every day or some days; former smokers defined as those who self-reported having smoked at least 10 cigarettes in their lifetime but are not currently smoking at all; participants who reported not having smoked at least 100 cigarettes in their lifetime defined as never having smoked[65, 66].
- 10: Determined by participant’s response to “Were you ever told that you had active tuberculosis or TB?”[79]11: Determined by participant’s response to “Were you ever prescribed any medicine to treat active tuberculosis or TB?”; specific medicine type not asked[79].
- 12: Ratio of family income to poverty guidelines; poverty guidelines as determined by the Department of Health and Human Services used as poverty measure to calculate ratio of family income to poverty[80].
- 13: Categories for Albumin/Creatinine Ratio (ACR) defined according to National Kidney Foundation guidelines for albuminuria categories in chronic kidney disease (CKD)[67].
- 14: Anti-HBc; positive/negative result determined by response to VITROS Anti-HBc assay[81].
- 15 : HBsAg; only tested if participant had positive result for anti-HBc; positive/negative result determined by response to VITROS HBsAg assay; participants that tested negative for anti-HBc also coded as negative for HBsAg[81].
- 16: Anti-HCV; participants first screened for anti-HCV using VITROS Anti-HCV assay; participants with repeatedly positive reactions to Anti-HCV assay are then confirmed positive using the Chiron RIBA HCV 3.0 Strip[82].

17: Hypertension determined by self-report (answered “yes” to having been told by a doctor or health professional that he/she had hypertension/high blood pressure)[83].

18: Categories for Total Bilirubin defined according to Medline Plus guidelines[84].

19: Categories for Total Cholesterol defined according to National Institute of Health guidelines[69].

20: Categories for HDL Cholesterol defined according to Medline Plus guidelines as follows[70].

Table 2: Weighted prevalence of latent tuberculosis infection (LTBI) among the civilian, non-institutionalized United States population, adults 20 years and older, 2011-2012

Participant Characteristics	Totals for Population N=4,958 % (95% CI)	LTBI Positive¹ % (95% CI) 5.9 (4.9-7.0)	LTBI Negative² % (95% CI) 94.1 (93.0-95.1)	p-value³
Age (years)				
20 – 34	27.5 (23.1-31.9)	3.3 (2.5-4.1)	96.7 (95.9-97.5)	<0.01
35 – 64	54.9 (51.8-57.9)	6.4 (4.7-8.1)	93.6 (91.9-95.3)	
≥65	17.6 (15.3-19.9)	8.8 (6.6-10.9)	91.2 (89.1-93.4)	
BMI ⁴				0.68
<18.5	1.8 (1.3-2.2)	7.9 (2.0-13.9)	92.1 (86.1-98.0)	
18.5 – 24.9	29.4 (26.1-32.6)	6.4 (4.5-8.3)	93.6 (91.7-95.5)	
25.0-29.9	33.5 (30.7-36.3)	5.6 (4.3-6.9)	94.4 (93.1-95.7)	
≥30.0	35.4 (32.3-38.5)	5.8 (4.7-7.0)	94.2 (93.0-95.3)	
Foreign Born ⁵				<0.01
No	82.1 (77.9-86.3)	3.5 (2.5-4.6)	96.5 (95.4-97.5)	
Yes	17.9 (13.7-22.1)	17.2 (14.3-20.0)	82.8 (80.0-85.7)	
TST ⁶				<0.01
Positive	4.7 (3.0-6.4)	46.2 (40.1-52.4)	53.8 (47.6-59.9)	
Negative	95.3 (93.6-97.0)	3.6 (2.7-4.4)	96.4 (95.6-97.3)	
Diabetes ⁷				<0.01
No Diabetes	66.5 (64.2-68.8)	4.6 (3.7-5.6)	95.4 (94.4-96.3)	
Prediabetes	22.1 (20.5-23.8)	7.0 (5.2-8.7)	93.0 (91.3-94.8)	
Diabetes	11.4 (9.8-13.0)	11.6 (7.9-15.3)	88.4 (84.7-92.1)	
HbA1c (%) ⁸				<0.01
<5.7	67.1 (64.9-69.3)	4.7 (3.7-5.6)	95.3 (94.4-96.3)	
5.7-6.4	24.8 (22.7-26.9)	7.7 (6.0-9.5)	92.3 (90.5-94.0)	
≥6.5	8.1 (6.9-9.3)	10.9 (7.1-14.8)	89.1 (85.2-92.9)	
Education				<0.01
<9 th Grade	5.7 (4.5-7.0)	17.9 (13.2-22.7)	82.1 (77.3-86.8)	
9 th – 12 th	10.5 (7.6-13.5)	7.7 (5.4-10.0)	92.3 (90.0-94.6)	
HS Grad/GED	20.2 (17.2-23.2)	7.1 (4.7-9.5)	92.9 (90.5-95.3)	
Some College	32.2 (29.0-35.3)	3.5 (2.2-4.7)	96.5 (95.3-97.8)	
≥College Grad	31.4 (26.1-36.7)	5.0 (3.4-6.6)	95.0 (93.4-96.6)	
Race/Ethnicity				<0.01
Hispanic	14.7 (9.2-20.2)	12.9 (10.4-15.4)	87.1 (84.6-89.6)	
NH White	68.8 (60.2-77.3)	3.1 (2.2-4.1)	96.9 (95.9-97.8)	
NH Black	11.3 (6.5-16.1)	8.0 (6.0-9.9)	92.0 (90.1-94.0)	
NH Asian	5.2 (3.2-7.1)	20.3 (16.8-23.8)	79.7 (76.2-83.4)	
Sex				<0.01
Female	52.2 (50.5-53.9)	5.0 (3.9-6.2)	95.0 (93.8-96.1)	
Male	47.8 (46.1-49.5)	6.9 (5.7-8.2)	93.1 (91.8-94.3)	
Smoking Status ⁹				0.15
Current	19.5 (17.2-21.7)	6.7 (4.3-9.1)	93.3 (90.9-95.7)	
Former	24.3 (21.6-26.9)	7.1 (4.8-9.5)	92.9 (90.5-95.2)	
Never	56.2 (53.3-59.1)	5.2 (4.2-6.1)	94.8 (93.9-95.8)	
Previous TB ¹⁰				

Yes No	0.40 (0.22-0.58) 99.6 (99.4-99.8)	42.7 (24.1-61.2) 5.8 (4.8-6.8)	57.3 (38.8-75.9) 94.2 (93.2-95.2)	<0.01
TB Meds ¹¹ Yes No	0.24 (0.12-0.36) 99.8 (99.6-99.9)	48.2 (24.6-71.7) 5.8 (4.8-6.8)	51.8 (28.3-75.4) 94.2 (93.2-95.2)	<0.01
Ratio of Family Income to Poverty ¹² 0-0.99 1-1.99 2-2.99 3-3.99 4-4.99 ≥5	17.2 (13.8-20.6) 21.1 (18.1-24.2) 14.3 (12.1-16.4) 12.1 (9.1-15.1) 10.7 (8.5-12.9) 24.6 (19.6-29.6)	8.5 (6.3-10.7) 7.8 (6.1-9.5) 5.4 (2.3-8.5) 4.7 (2.7-6.6) 2.9 (0.94-4.9) 4.1 (2.3-5.9)	91.5 (89.3-93.7) 92.2 (90.5-93.9) 94.6 (91.5-97.7) 95.3 (93.4-97.3) 97.1 (95.1-99.1) 95.9 (94.1-97.7)	<0.01
Albumin/Creatinine Ratio (mg/g) ¹³ <30 30 – 300 >300	90.4 (89.2-91.6) 8.3 (7.4-9.2) 1.3 (0.94-1.7)	5.7 (4.6-6.8) 7.6 (4.3-10.8) 12.9 (6.7-19.2)	94.3 (93.2-95.4) 92.4 (89.2-95.7) 87.1 (80.8-93.3)	0.01
HepB Core Ab ¹⁴ Positive Negative	4.6 (3.6-5.5) 95.4 (94.5-96.4)	18.0 (11.6-24.4) 5.3 (4.3-6.3)	82.0 (75.6-88.4) 94.7 (93.7-95.7)	<0.01
HepB Surface Ag ¹⁵ Positive Negative	0.34 (0.20-0.48) 99.7 (99.5-99.8)	23.0 (8.2-37.7) 5.8 (4.8-6.8)	77.0 (62.3-91.8) 94.2 (93.2-95.2)	<0.01
HepC Ab (confirmed) ¹⁶ Positive Negative	1.7 (1.0-2.3) 98.3 (97.7-99.0)	5.1 (0.60-9.6) 5.9 (4.9-6.9)	94.9 (90.4-99.4) 94.1 (93.1-95.1)	0.71
Self-reported Hypertension ¹⁷ Yes No	31.5 (28.4-34.7) 68.5 (65.3-71.6)	7.3 (5.6-9.0) 5.3 (4.3-6.3)	92.7 (91.0-94.4) 94.7 (93.7-95.7)	<0.01
Total Bilirubin (mg/dL) ¹⁸ Normal Not Normal	98.7 (98.0-99.4) 1.3 (0.59-2.0)	5.9 (4.9-6.9) 3.6 (0-8.7)	94.1 (93.1-95.1) 96.4 (91.3-100)	0.45
Total Cholesterol (mg/dL) ¹⁹ <200 200-239 ≥240	56.9 (55.0-58.8) 30.1 (28.4-31.7) 13.0 (11.4-14.7)	5.8 (4.7-6.9) 6.2 (4.6-7.8) 5.6 (4.0-7.1)	94.2 (93.1-95.3) 93.8 (92.2-95.4) 94.4 (92.9-96.0)	0.74
HDL Cholesterol (mg/dL) ²⁰ <40 40 – 59 ≥60	17.4 (14.7-20.1) 54.7 (51.9-57.6) 27.9 (25.5-30.2)	7.1 (5.2-9.0) 5.8 (4.8-6.8) 5.3 (3.5-7.0)	92.9 (91.0-94.8) 94.2 (93.2-95.2) 94.7 (93.0-96.5)	0.23

Table 2 Abbreviations: BMI-body mass index; LTBI-latent TB infection; HbA1c-glycated hemoglobin; TST-

tuberculin skin test; QFT-GIT-QuantiFERON®-TB Gold In-Tube; NH-Non-Hispanic; Anti-HBc-hepatitis B core

antibody; HBsAg-hepatitis B surface antigen; Anti-HCV-hepatitis C antibody

- 1: Positive LTBI defined by positive QFT-GIT result.
- 2: Negative LTBI defined by negative QFT-GIT result.
- 3: All p-values obtained using Rao-Scott chi-square.
- 4: BMI categories defined according to CDC guidelines[64].
- 5: Foreign born individuals include those who reported being born in one of the five United States territories.
- 6: Positive TST defined as an induration >10mm[85].
- 7: Diabetes status determined by self-report (answered “yes” to having been told by a doctor or health professional that he/she had diabetes) and according to American Diabetes Association guidelines; participants who self-reported diabetes were classified as having diabetes regardless of HbA1c.
- 8: HbA1c categories determined according to American Diabetes Association guidelines[61].
- 9: Current smokers defined as those who self-reported having smoked at least 100 cigarettes in their lifetime and currently smoking every day or some days; former smokers defined as those who self-reported having smoked at least 10 cigarettes in their lifetime but are not currently smoking at all; participants who reported not having smoked at least 100 cigarettes in their lifetime defined as never having smoked[65, 85].
- 10: Determined by participant’s response to “Were you ever told that you had active tuberculosis or TB?”
- 11: Determined by participant’s response to “Were you ever prescribed any medicine to treat active tuberculosis or TB?”; specific medicine type not asked.
- 12: Ratio of family income to poverty guidelines; poverty guidelines as determined by the Department of Health and Human Services (HHS) used as poverty measure to calculate ratio of family income to poverty[85].
- 13: Categories for Albumin/Creatinine Ratio (ACR) defined according to National Kidney Foundation guidelines for albuminuria categories in chronic kidney disease (CKD)[67].
- 14: Anti-HBc; positive/negative result determined by response to VITROS Anti-HBc assay[85].
- 15: HBsAg; only tested if participant had positive result for anti-HBc; positive/negative result determined by response to VITROS HBsAg assay; participants that tested negative for anti-HBc also coded as negative for HBsAg[85].
- 16: Anti-HCV; participants first screened for anti-HCV using VITROS Anti-HCV assay; participants with repeatedly positive reactions to anti-HCV assay are then confirmed positive using the Chiron RIBA HCV 3.0 Strip[85].

17: Hypertension determined by self-report (answered “yes” to having been told by a doctor or health professional that he/she had hypertension/high blood pressure)[85].

18: Categories for Total Bilirubin defined according to Medline Plus guidelines[84].

19: Categories for Total Cholesterol defined according to National Institutes of Health guidelines[69].

20: Categories for HDL Cholesterol defined according to Medline Plus guidelines[70].

Table 3: Multivariable models for odds of latent tuberculosis infection by diabetes status in the civilian, non-institutionalized United States population aged 20 years and older, 2011-2012

Models	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) ¹
Model 1: No Diabetes ² Prediabetes Diabetes	1.00 1.54 (1.24 – 1.91) 2.70 (1.76 – 4.14)	1.00 1.15 (0.90 – 1.47) 1.90 (1.15 – 3.14)
Model 2: No Diabetes ³ Diabetes	1.00 2.38 (1.58 – 3.59)	1.00 1.80 (1.14 – 2.83)
Model 3: No Diabetes Undiagnosed Diabetes ⁴ Diagnosed Diabetes	1.00 3.06 (1.61 – 5.82) 2.22 (1.46 – 3.38)	1.00 1.96 (1.05 – 3.68) 1.75 (1.09 – 2.80)
Model 4: HbA1c (%) ⁵ <5.7% 5.7-6.4% ≥6.5%	1.00 1.71 (1.33 – 2.19) 2.50 (1.64 – 3.81)	1.00 1.30 (0.96 – 1.75) 1.67 (1.04 – 2.69)
Model 5: HbA1c (%) <5.7 5.7-6.4 6.5-7.5 7.6-8.5 >8.5	1.00 1.71 (1.33 – 2.19) 2.44 (1.48 – 4.01) 3.12 (1.62 – 6.02) 2.21 (1.08 – 4.51)	1.00 1.30 (0.96 – 1.75) 1.66 (0.99 – 2.80) 1.96 (1.06 – 3.63) 1.50 (0.70 – 3.22)

1: Models adjusted for age (categorized as 20-35 years, 35-65 years, and ≥65 years), sex (female, male), smoking status (current, former, never), history of active TB (yes, no), and foreign born status (yes, no).

2: Diabetes status determined by self-report (answered “yes” to having been told by a doctor or health professional that he/she had diabetes) and according to American Diabetes Association guidelines[61]; participants who self-reported diabetes were classified as having diabetes regardless of HbA1c.

3: Individuals classified as having prediabetes or no diabetes for Model 1 were classified as not having diabetes for Model 2.

4: Participants with diabetes who were unaware they had diabetes were classified as previously undiagnosed; these previously undiagnosed participants have no information for duration of diabetes[85].

5: Glycated hemoglobin (HbA1c) categories determined according to American Diabetes Association guidelines[61].

Bold indicates that the adjusted odds ratio (aOR) is statistically significant

Table 4: Weighted prevalence of latent tuberculosis (LTBI) infection among only those with diabetes¹ in the civilian, non-institutionalized United States population, adults 20 years and older, 2011-2012

Participant Characteristics	Totals for Population N=793 % (95% CI)	LTBI Positive² % (95% CI) 11.6 (7.9-15.3)	LTBI Negative³ % (95% CI) 88.4 (84.7-92.1)	p-value⁴
Age (years)				
20 – 34	4.8 (3.2-6.4)	9.2 (0-21.4)	90.8 (78.6-100)	0.71
35 – 64	59.9 (55.4-64.6)	10.9 (5.5-16.2)	89.1 (83.8-94.5)	
≥65	35.3 (30.8-39.8)	13.1 (9.0-17.3)	86.9 (82.7-91.0)	
Sex				
Female	50.7 (45.6-55.8)	11.1 (7.1-15.0)	88.9 (85.0-92.9)	0.59
Male	49.3 (44.2-54.4)	12.1 (7.6-16.6)	87.9 (83.4-92.4)	
Race/Ethnicity				
Hispanic	17.3 (9.5-25.2)	24.3 (12.4-36.2)	75.7 (63.8-87.6)	<0.01
NH White	58.4 (46.3-70.5)	6.9 (3.2-10.6)	93.1 (89.4-96.8)	
NH Black	18.3 (10.2-26.3)	11.7 (7.5-15.9)	88.3 (84.1-92.5)	
NH Asian	6.0 (3.4-8.7)	27.5 (19.0-35.9)	72.5 (64.1-81.0)	
Foreign Born ⁵				
No	79.3 (73.3-85.3)	6.8 (4.4-9.1)	93.2 (90.9-95.6)	<0.01
Yes	20.7 (14.7-26.7)	30.2 (18.8-41.6)	69.8 (58.4-81.2)	
Smoking Status ⁶				
Current	18.0 (14.7-21.3)	12.5 (7.1-17.8)	87.5 (82.2-92.9)	0.21
Former	32.2 (27.1-37.3)	14.5 (7.8-21.3)	85.5 (78.7-92.2)	
Never	49.9 (43.7-56.0)	9.4 (5.1-13.8)	90.6 (86.2-95.0)	
Diabetes Duration (years) ⁷				
Undiagnosed ⁸	19.9 (15.3-24.4)	14.4 (6.7-22.2)	85.6 (77.8-93.3)	0.32
<1	4.8 (2.3-7.2)	3.6 (0-8.0)	96.4 (92.0-100)	
1-3	16.5 (11.2-21.7)	9.3 (3.1-15.6)	90.7 (84.4-96.9)	
4-10	26.0 (22.7-29.4)	11.1 (6.0-16.3)	88.9 (83.7-94.0)	
≥10	32.9 (26.7-39.0)	12.5 (7.3-17.7)	87.5 (82.3-92.7)	
Diabetes Diagnosis Status				
Undiagnosed	19.9 (15.3-24.4)	14.4 (6.7-22.2)	85.6 (77.8-93.3)	0.24
Diagnosed	80.1 (75.6-84.7)	10.9 (7.4-14.4)	89.1 (85.6-92.6)	
Taking insulin				
Yes	23.5 (18.4-28.5)	7.3 (3.1-11.4)	92.7 (88.6-96.9)	0.03
No	76.5 (71.5-81.6)	12.9 (8.5-17.3)	87.1 (82.7-91.5)	
How long taking insulin (months) ⁹				
1-12	20.9 (13.9-27.9)	7.2 (0-15.5)	92.8 (84.5-100)	0.09
13-24	11.0 (4.7-17.4)	11.0 (0-29.4)	89.0 (70.6-100)	
25-36	6.3 (0-13.7)	23.0 (3.1-43.0)	77.0 (57.0-96.9)	
>36	61.8 (49.1-74.4)	4.7 (0.99-8.4)	95.3 (91.6-99.0)	
Oral Agents ¹⁰				
Yes	60.4 (55.1-65.6)	12.0 (7.5-16.4)	88.0 (83.6-92.5)	0.65
No	39.6 (34.4-44.9)	11.0 (6.8-15.2)	89.0 (84.8-93.2)	
HbA1c (%) ¹¹				

<5.7	5.4 (3.1-7.6)	9.1 (2.3-16.0)	90.9 (84.0-97.7)	0.71
5.7-6.4	23.4 (17.1-29.8)	14.1 (5.9-22.4)	85.9 (77.6-94.1)	
6.5-7.5	34.8 (28.8-40.7)	10.7 (6.2-15.2)	89.3 (84.8-93.8)	
7.6-8.5	14.5 (10.2-18.8)	13.3 (5.3-21.3)	86.7 (78.7-94.7)	
>8.5	21.9 (17.7-26.1)	9.8 (3.9-15.7)	90.2 (84.3-96.1)	
HepB Core Ab ¹²				0.04
Positive	7.8 (5.0-10.7)	20.8 (8.9-32.7)	79.2 (67.3-91.1)	
Negative	92.2 (89.3-95.0)	11.0 (7.2-14.9)	89.0 (85.1-92.8)	0.06
HepC Ab (confirmed) ¹³				
Positive	2.9 (0.80-5.1)	3.8 (0-10.4)	96.2 (89.6-100)	0.31
Negative	97.1 (94.9-99.2)	12.0 (8.3-15.8)	88.0 (84.2-91.7)	
Self-reported Hypertension ¹⁴				0.43
Yes	64.6 (60.8-68.3)	10.6 (6.7-14.5)	89.4 (85.5-93.3)	
No	35.4 (31.7-39.2)	13.4 (7.4-19.4)	86.6 (80.6-92.6)	
Total Cholesterol (mg/dL) ¹⁵				0.75
<200	64.6 (60.0-69.2)	10.4 (6.8-13.9)	89.6 (86.1-93.2)	
200-239	24.1 (20.2-28.0)	14.9 (6.9-22.9)	85.1 (77.1-93.1)	
≥240	11.3 (7.4-15.1)	13.4 (1.8-24.9)	86.6 (75.1-98.2)	
HDL Cholesterol (mg/dL) ¹⁶				
<40	29.6 (21.9-37.2)	11.9 (6.2-17.6)	88.1 (82.4-93.8)	
40-59	57.7 (49.7-65.7)	11.1 (6.7-15.5)	88.9 (84.5-93.3)	
≥60	12.7 (9.1-16.4)	14.5 (4.3-24.7)	85.5 (75.3-95.7)	

Table 4 Abbreviations: BMI-body mass index; LTBI-latent TB infection; HbA1c-glycated hemoglobin; TST-

tuberculin skin test; QFT-GIT-QuantIFERON®-TB Gold In-Tube; NH-Non-Hispanic; Anti-HBc-hepatitis B core antibody; Anti-HCV-hepatitis C antibody

1: Diabetes determined by self-report (answered “yes” to having been told by a doctor or health professional that he/she had diabetes) and according to American Diabetes Association guidelines as having an HbA1c (glycated hemoglobin) level ≥6.5%[61]; participants who self-reported diabetes were classified as having diabetes regardless of HbA1c.

2: Positive LTBI defined by positive QFT-GIT result.

3: Negative LTBI defined by negative QFT-GIT result.

4: All p-values obtained using Rao-Scott chi-square.

5: Foreign born individuals include those who reported being born in one of the five United States territories.

6: Current smokers defined as those who self-reported having smoked at least 100 cigarettes in their lifetime and currently smoking every day or some days; former smokers defined as those who self-reported having smoked at least 10 cigarettes in their lifetime but are not currently smoking at all; participants who reported not having smoked at least 100 cigarettes in their lifetime defined as never having smoked[65, 85].

- 7: Refers to how long participant has known they have diabetes; this was calculated using the age of the participant and his/her response to the survey question regarding how old he/she was when a doctor or other health professional first told him/her that he/she had diabetes or sugar diabetes[85].
- 8: Participants with diabetes who were unaware they had diabetes were classified as previously undiagnosed; these previously undiagnosed participants have no information for duration of diabetes[85].
- 9: Among participants who answered “yes” to taking insulin.
- 10: Determined by response to survey question “Are you now taking diabetic pills to lower your blood sugar?”; specific medications not determined[85].
- 11: HbA1c categories determined according to American Diabetes Association guidelines[61].
- 12: Anti-HBc; positive/negative result determined by response to VITROS Anti-HBc assay[85].
- 13: Anti-HCV; participants first screened for anti-HCV using VITROS Anti-HCV assay; participants with repeatedly positive reactions to anti-HCV assay are then confirmed positive using the Chiron RIBA HCV 3.0 Strip[85].
- 14: Hypertension determined by self-report (answered “yes” to having been told by a doctor or health professional that he/she had hypertension/high blood pressure)[85].
- 15: Categories for Total Cholesterol defined according to National Institute of Health guidelines[69].
- 16: Categories for HDL Cholesterol defined according to Medline Plus guidelines[70].

Supplemental Table 1: Multivariable models for odds of latent tuberculosis infection associated with diabetes status in the civilian, non-institutionalized United States population aged 20 years and older, 2011-2012:

Models	Adjusted Odds Ratio (95% CI)	Covariates¹
Model 1 No Diabetes ² Prediabetes Diabetes	1.00 0.95 (0.75 – 1.21) 1.49 (0.83 – 2.68)	age, sex, education, previous history of active TB, ethnicity, income to poverty ratio, ACR, HepB surface antigen, HepB core antibody, smoking status, foreign born status, and hypertension
Model 2 No Diabetes Prediabetes Diabetes	1.00 1.21 (0.90 – 1.62) 2.04 (1.17 – 3.57)	age, sex, ACR, HepB surface antigen, and HepB core antibody
Model 3 No Diabetes Prediabetes Diabetes	1.00 1.06 (0.81 – 1.35) 1.49 (0.84 – 2.64)	age, sex, education, ethnicity, and income to poverty ratio
Model 4 No Diabetes Prediabetes Diabetes	1.00 1.05 (0.82 – 1.35) 1.55 (0.91 – 2.65)	age, sex, ethnicity, country of birth, income to poverty ratio, smoking status, and education
Model 5 No Diabetes Prediabetes Diabetes	1.00 1.25 (0.93 – 1.68) 2.20 (1.22 – 3.96)	age, sex, BMI, ACR, HepB surface antigen, HepB core antibody and hypertension
Model 6 No Diabetes Prediabetes Diabetes	1.00 1.07 (0.83 – 1.37) 1.67 (1.01 – 2.74)	age, sex, smoking status, ethnicity, and country of birth
Model 7 No Diabetes Prediabetes Diabetes	1.00 1.09 (0.79 – 1.41) 1.61 (0.86 – 2.99)	age, sex, BMI, hypertension, ethnicity, and income to poverty ratio
Model 8 No Diabetes Prediabetes Diabetes	1.00 1.17 (0.92 – 1.49) 1.93 (1.17 – 3.21)	age, sex, country of birth, previous history of active TB, and smoking status
Model 9 No Diabetes Prediabetes Diabetes	1.00 1.22 (0.93 – 1.60) 1.86 (1.00 – 3.46)	age, sex, BMI, education, and income to poverty ratio
Model 10 No Diabetes Prediabetes Diabetes	1.00 1.12 (0.84 – 1.49) 1.76 (1.02 – 3.03)	age, sex, ethnicity, BMI, and country of birth

Supplemental Table 1 Abbreviations: TB-tuberculosis; ACR-albumin-creatinine ratio

1: Covariates controlled for in multivariable logistic model.

2: Diabetes status determined by self-report (answered “yes” to having been told by a doctor or health professional that he/she had diabetes) and according to American Diabetes Association guidelines[61]; participants who self-reported diabetes were classified as having diabetes regardless of HbA1c.

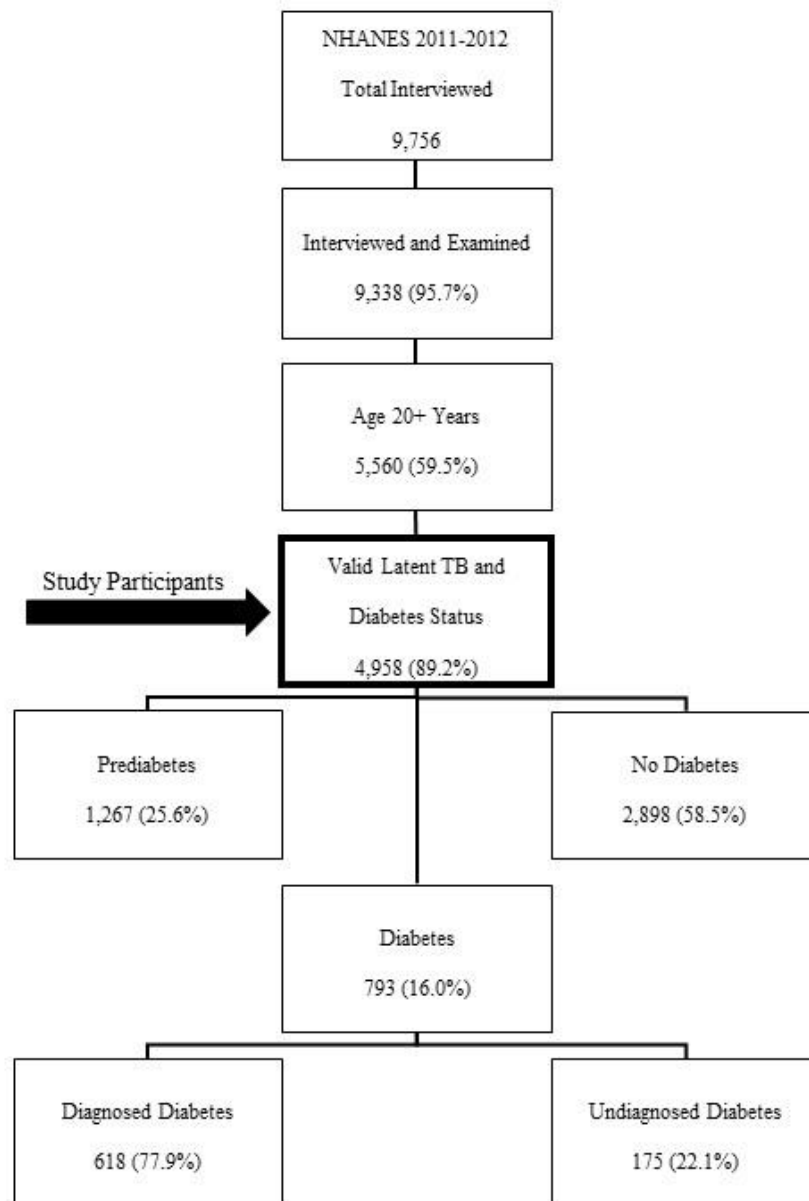


Figure 1: Flow chart showing process of selection for NHANES 2011-2012 participants eligible for study, including the categorization of eligible participants by diabetes status; raw numbers and percentages not weighted for NHANES sampling methodology.