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Estimating the Changing Prevalence of Tuberculosis Infection in the United States, 1971–2015

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An abstract of

A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in

Epidemiology

2019

Abstract

Estimating the Changing Prevalence of Tuberculosis Infection in the United States, 1971–2015

By Maryam B. Haddad

This dissertation examines the U.S. prevalence of latent tuberculosis infection (LTBI), and the relationship of LTBI with diabetes, during 1971–2015. The only LTBI test for which we have longitudinal results is the tuberculin skin test (TST), which was part of the National Health and Nutrition Examination Survey (NHANES) in 1971–1972, 1999–2000, and 2011–2012.

Based on NHANES 1971–1972, approximately 14% of the noninstitutionalized civilian adult population, more than twice the currently estimated 3%–6, would have a positive result if administered a TST. Simultaneously, the prevalence of diabetes increased sharply and is now more prevalent than LTBI.

NHANES is designed to provide accurate and stable estimates of conditions with prevalence of ≥10%. Because NHANES samples approximately 30 counties in each 2-year cycle, a single cycle may be inadequate for uncommon health conditions with geographic variation. Additionally, TST results are missing for 1 in 5 eligible participants across all 3 cycles. We assessed several potential sources of bias in NHANES-based estimates of LTBI prevalence. We also scrutinized LTBI's relationship with diabetes in 2011–2012.

Back-calculating from genotyping results in the National Tuberculosis Surveillance System in 2011–2015, we derived a non-NHANES estimate of LTBI prevalence for all 3,143 U.S. counties (or equivalents). Similar to the conventional NHANES 2011–2012 estimate, our overall estimate is that 8.9 million (uncertainty limits = 6.3–14.8 million) of the U.S. population has LTBI.

We found no evidence that county sampling biased NHANES-based estimates of LTBI prevalence. Estimates changed little in an analysis that accounted for the selection of multiple participants from the same household, reclassified borderline-positive TST results, adjusted for TST item nonresponse, and considered non-U.S. birth distributions.

We concluded that a conventional analysis for examining LTBI in previous NHANES cycles appears robust. On the other hand, analysis of the overall association between diabetes and a positive TST in 2011–2012 would miss the finding that the association was driven by findings among Hispanic and Asian NHANES participants and thus might not generalize to the entire U.S. population.

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Abbreviations

ACS	U.S. Census Bureau American Community Survey (used for NHANES 2011–2012 design and to enumerate the Hispanic and Asian populations for dissertation aim 2)
CDC	Centers for Disease Control and Prevention
CPS	U.S. Census Bureau Current Population Survey (used for NHANES 1999–2000 design and to enumerate county-level non-U.S.–born denominators for aim 1)
DTBE	Division of Tuberculosis Elimination at CDC
FDA	U.S. Food and Drug Administration
HANES I	Health and Nutrition Examination Survey (original name for NHANES in 1971–1974)
IGRA	interferon-gamma release assay (blood test for TB infection), such as QuantiFERON-TB Gold In-Tube test used in NHANES 2011–2012
LTBI	latent tuberculosis infection
MAR	missing at random (1 of 3 possible descriptions of patterns of missing data)
MCAR	missing completely at random (1 of 3 possible descriptions of patterns of missing data)
MNAR	missing not at random (1 of 3 possible descriptions of patterns of missing data)
MEC	NHANES mobile examination center
NCHS	National Center for Health Statistics, CDC
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Information Survey (sampling frame used for NHANES 1999–2000)
NTGS	National Tuberculosis Genotyping Service
NTSS	National Tuberculosis Surveillance System
PPD	purified protein derivative (antigen used in the tuberculin skin test)
PSU	primary sampling unit in NHANES
RDC	Research Data Center of NCHS
SP	NHANES survey participant
TB	tuberculosis
TST	tuberculin skin test

CHAPTER 1 — Introduction

Dissertation motivation and overview of aims

Latent tuberculosis infection (LTBI) is an asymptomatic condition that is typically undiagnosed, yet its effective detection and treatment are essential elements of the national and global goal to eliminate tuberculosis (TB). This dissertation examines the U.S. population prevalence of LTBI and its association with diabetes during 1971–2015. No nationwide public health surveillance for LTBI exists. The only LTBI screening test for which we have longitudinal results is the tuberculin skin test (TST), which was part of the National Health and Nutrition Examination Survey (NHANES) in 1971–1972, 1999–2000, and 2011–2012. Based on TST results in NHANES, approximately 14% of the noninstitutionalized civilian adult population had LTBI in 1971–1972, more than twice the currently estimated 3%–6% prevalence. The prevalence of diabetes simultaneously doubled to about 9% of the U.S. population. In NHANES 2011–2012, hemoglobin A1C (a marker for diabetes) and LTBI appear to have a dose-dependent relationship, but a similar association had not been previously observed. Approximately 20% of incident TB disease in the United States occurs in persons living with diabetes, whereas <6% occurs in persons living with HIV. Diabetes and HIV are both established risk factors for progression from LTBI to active TB disease. Given the higher prevalence of diabetes (about 30 million adults and growing) compared to HIV (about 1.1 million and stable), diabetes may be surpassing HIV in importance in the epidemiology of TB in the United States. Although NHANES-based estimates for LTBI prevalence seem reasonable, no analysis of potential influence of systematic error in the survey design, data collection, or data analysis has been previously undertaken. As part of this dissertation, a new genotyping-derived back-calculation method for estimating LTBI prevalence independently from NHANES was also developed.

Aim 1 (geographic representativeness) focuses on the counties selected for NHANES participation during 1971–1972, 1999–2000, and 2011–2012. Although both TB disease incidence and LTBI

prevalence have declined nationally, they retain notable geographic heterogeneity, suggesting that LTBI prevalence may no longer lend itself well to study with TST results from the approximately 30 counties sampled for a single 2-year NHANES cycle. We worked with the National Center for Health Statistics for masked access to restricted geographic variables within the Research Data Center. Doing so enabled us to examine the similarity with respect to TB of the counties selected for NHANES participation when compared to the counties in the rest of the United States. As part of the external validation dataset created for this aim, we also used genotyping results from TB disease cases routinely reported to the National Tuberculosis Surveillance System to back-calculate a non-NHANES estimate of LTBI prevalence for the 3,143 U.S. counties (or equivalents) during 2011–2015. Similar to the conventional NHANES 2011–2012 estimate, our overall estimate based on this back calculation is that 8.9 million (uncertainty limits = 6.3–14.8 million) of the U.S. population has LTBI. Our masked analysis found no evidence that county sampling biased national estimates of LTBI prevalence.

Aim 2 (additional participant factors) examines the extent to which estimates of the national prevalence of a positive TST might change with an analysis that considered factors not included in a conventional NHANES analysis. A conventional NHANES analysis accounts for correlation of measured health conditions within masked counties, which themselves are nested within major strata of similar counties — but not at later sampling stages, such as within households. We found no evidence of bias due to the selection of multiple participants per household. Further, in each of the 3 NHANES cycles with a TB component, TST results are missing for approximately 1 in 5 eligible participants; in the most recent cycle, there was digit preference for borderline-positive TST results. After using record-level reclassification informed by interferon-gamma release assay (IGRA blood test for TB infection) results to address the digit preference, we examined TST item nonresponse patterns within the standard 1999–2000 and 2011–2012 age/race/ethnicity groupings (i.e., NHANES analytic subdomains). Invoking a missing-at-random assumption, we imputed the missing TST results based on a Bernoulli trial, where the individual participant's probability of a positive TST was the weighted proportion of a positive TST among persons in the same subdomain who had self-reported a similar TB history. Finally, because non-U.S. birth is a risk factor for

LTBI, we examined whether to create an additional post-stratification adjustment to the standard NHANES participant weights to better reflect the non-U.S. birth distributions of Hispanic and Asian persons in the U.S. population. Their weighted proportions were similar to that seen in the U.S. population at large, so further adjustment was unnecessary. In summary, the estimated U.S. population prevalence of a positive TST was robust to all these bias adjustments, reinforcing our confidence in the validity of LTBI prevalence estimates based on a conventional analysis of the public use datasets in 1971–1972, 1999–2000, and 2011–2012.

Aim 3 (diabetes/LTBI relationship) examines whether race/ethnicity modifies the association between diabetes and a positive TST among adult NHANES participants. Although hemoglobin A1C (a marker for diabetes) and LTBI and appear to have a dose-dependent relationship in NHANES 2011–2012, this apparent relationship had not been previously observed. Oversampling of black non-Hispanic persons occurs in all NHANES cycles, oversampling of persons of Mexican-American descent occurred in NHANES 1999–2000, and oversampling of Asian persons occurred in NHANES 2011–2012. Nearly all the study participants with both conditions of interest (i.e., both diabetes and positive TST) were nonwhite, suggesting that conclusions about the diabetes/LTBI relationship might not generalize to the entire noninstitutionalized U.S. civilian population. We found that the overall association between diabetes and a positive TST in NHANES 2011–2012 was driven by findings among the Hispanic and Asian adult participants with diabetes: approximately 1 in 4 also had evidence of infection with *M. tuberculosis*.

Assumptions

Self-identified race/ethnicity is a subdomain characteristic used in NHANES sampling, and both aims 2 and 3 stratify NHANES participants on the basis of race/ethnicity. However, the conceptual framework for this dissertation does not assume that race/ethnicity is a causal mechanism for risk of LTBI or even a meaningful biologic entity in and of itself. Rather, the American construct of race/ethnicity can be closely tied to economic class and social experiences, so race/ethnicity is then associated with the cumulative lifetime risk of having acquired *M. tuberculosis* infection *(Link 1995, Kaufman 2001)*. In addition, in the context

of public health surveillance, stratifying U.S. residents by race/ethnicity is a way to draw attention to persistent health disparities *(Kaufman 2001),* including LTBI prevalence, and to suggest interventions for specific subpopulations at greater risk of LTBI and diabetes-associated LTBI.

Because we wished to examine prevalence over time, we defined LTBI on the basis of TST, the only test for TB infection for which we have longitudinal data. Blood-based IGRA tests for TB infection were not approved by the Food and Drug Administration (FDA) for commercial use in the United States until 2001. Although IGRAs appear more accurate (at least in populations at high risk for LTBI), they did not appear in NHANES until 2011. Therefore, we used a TST recorded in NHANES public-use datasets as measuring ≥10 mm as a proxy measurement for LTBI at the time of the examination.

A related assumption was that any detected evidence of *M. tuberculosis* infection in a NHANES participant was latent rather than active TB. Although a small number of the survey participants with positive TST results possibly had TB disease, an active TB diagnosis requires a more complete examination, and participant chest x-rays were only performed during NHANES 1971–1972. This assumption seems validated by the small and generally declining incidence of active TB disease in the United States, as well as the medical histories of NHANES participants: 12 (1.4%) of the 1,891 participants aged ≥25 years examined during April 1971–October 1972 self-reported a current diagnosis of TB. In 1999–2000 and 2011–2012, one study participant per cycle was taking multidrug therapy for a current diagnosis of TB disease. Only 34 (0.4%) of 8,832 examined participants aged ≥1 year in 1999–2000 reported any history of active TB, similar to the 42 (0.5%) of the 7,821 examined participants aged ≥6 years in 2011–2012.

Finally, it was outside the scope of this dissertation to determine the validity of the readings in the public-use dataset. However, the TST measurements in NHANES 2011–2012 had unusual TST peaks at 2, 8, and 9 mm. While the 2 mm peak is inconsequential (i.e., the TST result would still be classified as negative), the digit preference for 8 or 9 mm suggested some degree of systematic under-measurement (i.e., recording ≥10 mm positive results as 8 or 9 mm borderline-positive results), possibly to avoid having to notify those

participants about their potential LTBI status. We therefore in aims 2 and 3 used IGRA results among those participants to address this apparent misclassification.

Anticipated contributions and overview of this research

To monitor progress toward the goal of TB elimination, accurate LTBI prevalence estimation is in the national interest. No nationwide public health surveillance for LTBI exists. Until now, single 2-year NHANES cycles occurring 11 and 27 years apart have provided the only nationwide estimates of LTBI prevalence, so findings from this dissertation could help improve the design and execution of future TB components of NHANES. However, because NHANES visits only about 30 counties in each 2-year cycle, this national survey is not designed to provide estimates of health measures for individual states or counties. Another contribution of this dissertation is development of a method that independently of NHANES uses existing, routinely collected surveillance data to estimate national LTBI prevalence, as well as estimates for smaller geographic units or subpopulations.

Aims 1 and 2 of this dissertation use quantitative bias analysis methods to examine potential sources of systematic error in previous NHANES-based estimates of LTBI prevalence. Although none proved to be influential on overall estimates of LTBI prevalence, misclassification and other sources of potential error would ideally be prevented in the study design, rather than addressed in the analysis phase. Aim 3 of this dissertation also underscores the importance of considering race/ethnicity when studying the relationship between diabetes and LTBI in the United States; the strikingly high LTBI prevalence among the estimated 6 million Hispanic and 1.5 million Asian adults with diabetes in the United States suggests targeted interventions for this subpopulation as an efficient strategy to prevent future TB cases.

CHAPTER 2 — Literature review for tuberculosis (TB) infection

Conceptualization of TB infection

Origins of modern understanding of latent TB infection (LTBI)

One hundred years ago, the Great Flu pandemic of 1918 supplanted TB as the greatest single cause of death in the United States for the first time in decades (*US Dept. of Labor 1912*, *Noymer 2011*). Overstating TB's impact on recent and ancient human history would be difficult. From the Middle Ages until as late as 1820, European monarchs offered their subjects the divine healing power of "le toucher royal" or "king's touch" — laying hands on scrofula (neck lymphadenopathy caused by TB), which were correspondingly called "mal du roi" or the "king's evil" (*Perez 2006*). Evidence of TB can be found in human remains, artwork, and literature from ancient China, Egypt, India, Peru, and Turkey, which helps explain the genetic diversity among *Mycobacterium tuberculosis* strains in the modern era (*Dubos 1952*, *Keers 1978*, *Brosch 2002*).

The 4th century B.C. Hippocratic Oath mentions TB by the term *phthisis* ("decay" in Greek), and Aristotle is credited as first inferring TB's airborne infectious nature (*Young 1817*). The writings of Galen and other physicians during the Roman Empire describe a disease process involving progressive weakness, weight loss, nocturnal fever and sweats, and a contagious cough that posed a danger for other members of the household (*Keers 1978*). In 1720's *A New Theory of Consumptions: More Especially of a Phthisis or Consumption of the Lungs*, Benjamin Marten speculated with remarkable prescience:

> [The] "prime, essential, and hitherto accounted inexplicable cause of that disease. . . may possibly be some certain species of *Animalcula* or wonderfully minute living Creatures. . .capable of subsisting in our Juices and Vessels, and which being drove to the Lungs by the Circulation of the Blood. . .or which possibly carried about by the Air, may be immediately covey'd to the Lungs by that we draw in, and being there deposited, as in a proper *Nidus* or Nest, and being produced to Life, coming to Perfection, or increasing in Bigness. . .and perhaps wounding or gnawing the tender Vessels of the Lungs" (as quoted in *Doetsch 1978*).

The 17th century Dutch physician Franciscus Sylvius apparently coined the term *tubercles* from the Latin *tuberculum* ("small firm nodule") to describe TB's characteristic lesions in the lungs. Similar findings and

continued use of the term were seen in autopsy reports written by William Stark and Matthew Baillie in London and René Laënnec in Paris. These revealed various stages of the disease process, often associated with a "thick curdly pus" that today we would call *caseous granuloma*. In 1804, Laënnec further proposed the unitary theory that all forms of TB, whether pulmonary or extrapulmonary, could have the same underlying cause. Subsequent autopsies by Pierre-Charles-Alexandre Louis led to the conclusion that nearly every Parisian past the age of 15 had granulomatous lesions in the lungs, even if that person had died of other causes. Louis also advanced the modern understanding that the typical mode of initial *Mycobacterium tuberculosis* infection is airborne inhalation via the lungs (*Dubos 1952*, *Keers 1978*, *PJB 1956*, *Baillie 1795*, *Daniel 2000*).

At a scientific conference in Berlin on March 24, 1882, Robert Koch announced that a slowly replicating bacterium, which he termed the *tubercle bacillus*, was the etiologic causal agent for TB. In announcing this infectious cause, he hoped that future cure and prevention efforts could be directed at that bacterium, rather than the hitherto widely held belief that TB was "a manifestation of social misery" (*Dubos 1952*, *Keers 1978*, *PJB 1956*, *Baillie 1795*, *Daniel 2000*, *Daniel 1999*).

Development of the tuberculin skin test for detecting TB infection

Eight years later, on August 4, 1890, Koch prematurely announced his creation of a vaccine that purportedly both prevented TB in susceptible guinea pigs and cured TB in sick guinea pigs (*Dubos 1952*, *Keers 1978*, *Daniel 2000*, *Daniel 1999*). Although that "brownish transparent fluid" extract from *M. tuberculosis*, subsequently termed "tuberculin," was unable to reproduce those desirable effects in humans, it later became crucially important as the 20th century's only diagnostic tool for detecting TB infection in asymptomatic cattle and humans (*Snider 1982*). Further work in the early 1900s by Clemens von Pirquet in Austria and Charles Mantoux in France led to establishment of the tuberculin skin test (TST) (*Gauvain 1937*).

However, the exact composition of tuberculin was unreliable, subject to impurities, and difficult to reproduce, which meant it was difficult to compare TST induration measurements across populations or even in the same individual across time. It was only through the work of Florence B. Siebert during the 1930s that

an international standard for tuberculin tests, called the purified-protein derivative (PPD), was developed, ultimately replacing Koch's "Old Tuberculin" standard (*Snider 1982*, *Seibert 1934*, *Seibert 1941*, *Seibert 1954*, *WHO 1953*, *WHO 1963*, *Edwards 1960*, *Edwards 1968*, *Edwards/Palmer 1969*, *Affronti 1969*). Her 1940/1941 PPD-Standard (PPD-S) batch has been the reference that the World Health Organization since 1952 and the U.S. Food and Drug Administration (FDA) since 1978 have required all other tuberculin products to emulate as "equipotent" (*WHO 1953*, *WHO 1963*, *Guld 1958*, *FDA 1978*). However, that PPD-S batch stored at FDA has depleted, requiring development of a new standard, termed PPD-S2 (*Villarino 2000*).

Palpable induration around the tuberculin injection site 48–72 hours after TST administration is considered evidence of infection: a previous exposure to *M. tuberculosis* antigens has triggered an adaptive (but not protective) immune system response. The immune system sensitization takes 2–10 weeks after which, if not treated, the infection becomes chronic. Even successfully treated persons can retain a positive TST reaction, and if they inhale *M. tuberculosis* again, they can become infected again. The TST works by eliciting a cell-mediated hypersensitivity response: "helper" CD4 T lymphocytes, activated upon recognition of *M. tuberculosis* antigens in the tuberculin, secrete substances, including interleukin and interferon-gamma, to activate the macrophages and bring "killer" CD8 lymphocytes to the injection site on the forearm, resulting in a palpable induration at the injection of the infected human. In the United States, indurations measuring ≥10 mm are interpreted as evidence of infection with *M. tuberculosis* (with a more sensitive cutoff of ≥5 mm suggestive of infection in immunocompromised or recently exposed persons) (*Snider 1982*, *Edwards 1968*, *Edwards/Palmer 1969*, *ATS/CDC 2000*, *Edwards et al. 1969*, *Comstock 1974a*, *Comstock 1975a*).

In the United States, 5 tuberculin units (TU) within 0.1 mL, equivalent to 0.1 μg of PPD-S, is considered the standard dose for tuberculin skin testing to detect TB infection (*Snider 1982*, *FDA 1978*, *ATS/CDC 2000*, *Comstock 1975b*, *Rieder 1995*). The U.S. Public Health Service studies of college students and Naval recruits in the 1940s–1960s all used Dr. Siebert's original PPD-S (*Edwards 1968*, *Edwards/Palmer 1969*, *Edwards et al. 1969*, *Comstock 1974a*, *Comstock 1975a*, *Edwards 1950*, *Palmer 1950*, *Palmer 1956*, *Edwards 1964*), as did NHANES 1971–1972 and NHANES 1999–2000 (*Engel 1977*, *Bennett 2008*, *Khan 2008*). However,

because obtaining the diminishing supply of PPD-S from FDA had become increasingly difficult (i.e., requires an Investigational New Drug application), NHANES 2011–2012 used the commercially available Tubersol (Sanofi Pasteur product), which is considered an equipotent equivalent of PPD-S when using the 10 mm cutoff (*Villarino 1999*, *Miramontes 2015, Mancuso 2016*).

Development of interferon-gamma release assays for detecting TB infection

Until 2001, the only commercially available test for LTBI approved for use in the United States was the TST, which is essentially the same approach as the von Pirquet subcutaneous test or Mantoux intradermal test from the early 1900s: an *in vivo* diagnostic test of the cell-mediated immune response within the forearm of the person being screened (*Gauvain 1937*, *FDA 1978*, *ATS/CDC 2000*). That diagnostic approach has changed with the advent of *in vitro* interferon-gamma release assay (IGRA) tests, which are instead based on drawn blood (*Pottumarthy 1999*, *Doan 2017*).

In 2001, FDA approved the first IGRA, the QuantiFERON-TB test developed by Cellestis (Australia). That IGRA was subsequently replaced by improved versions called the QuantiFERON-TB Gold and then the QuantiFERON-TB Gold In-Tube, with FDA approval in 2005 and 2007, respectively. In 2011, Cellestis was acquired by the Dutch company QIAGEN. NHANES 2011–2012 participants had blood drawn for the QuantiFERON-TB Gold In-Tube test, in addition to receiving a TST with Tubersol brand PPD (*Miramontes 2015, Mancuso 2016*). As of October 2018, the only other IGRA on the commercial market in the United States is called the T-SPOT.*TB* test, manufactured by Oxford Immunotec (England) and approved by FDA in 2008 (*Doan 2017*, *Mazurek 2005*, *Mazurek 2010*).

IGRAs directly measure either the amount of interferon-gamma that is released (QuantiFERON-TB) or the number of cells that produce interferon-gamma (T-SPOT.*TB*) after the drawn blood is exposed to synthetic peptides mimicking *M. tuberculosis*. This peptide mixture mimics the CFP-10/ESAT-6 protein structure within *M. tuberculosis* and is considered more specific than the "purified-protein derivative" formulation in the TST. For non-U.S.-born persons who as young children received the bacille Calmette-

Guerin (BCG) vaccine to prevent TB meningitis and other severe forms of TB disease, this advantage is meaningful, because IGRAs do not cross-react with the *M. bovis* antigens in the BCG vaccine. That cross-reactivity is why persons born outside the United States, particularly recently vaccinated children, are more prone to false-positive TST results (*ATS/CDC 2000*, *Rieder 1995*, *Doan 2017*, *Mazurek 2005*, *Mazurek 2010*).

IGRAs also offer a number of practical advantages. As laboratory-based assays, IGRAs do not have the subjectivity associated with measuring the TST induration, and they require only a single patient encounter (*Mazurek 2005*, *Mazurek 2010*). Further, the T-SPOT.*TB* developers claim that T-SPOT.*TB* is more sensitive than either the TST or QuantiFERON-TB Gold in immunocompromised persons, and a recent meta-analysis also suggests better sensitivity in immunocompetent persons (*Doan 2017*). Latent class analysis of concurrent TST, QuantiFERON-TB Gold-in-Tube, and T-SPOT.*TB* results from 10,740 persons at high risk for LTBI estimated that positive predictive values for the IGRAs were higher than for the TST, particularly among non-U.S.-born persons without HIV infection. Among HIV-negative persons aged ≥5 years, the positive predictive value of the TST ranged 56.5%–75.4% for U.S.-born persons and 52.8%–61.3% for non-U.S.-born persons; negative predictive values ranged 89.9%–97.3% and 79.9%–95.0%, respectively. Among HIV-negative persons aged ≥5 years, the positive predictive value of QuantiFERON-TB Gold ranged 78.6%–97.0% for U.S.-born persons and 90.0%–99.5% for non-U.S.-born persons; negative predictive values ranged 91.1%–98.5% and 83.6%–96.3%, respectively. The lower bound of the positive predictive value for T-SPOT.*TB* (using the international cut-off of ≥6 spots) was somewhat higher (*Stout 2018*). T-SPOT.*TB* has not been used in NHANES.

Typical diagnostic dichotomy between "latent" infection and "active" disease

An estimated one fourth of the world's population is infected with *M. tuberculosis* (*Houben 2016*, *Pai 2016*, *WHO 2017*), although the validity of that estimate has been questioned, because few persons infected >2 years prior will experience progression to active TB disease (*Behr 2018*). Modlin and Bloom provide an evolutionary explanation:

> "[*M. tuberculosis*] has almost certainly evolved to exist in the human population, with only sufficient number of individuals developing major lung pathology to ensure transmission and survival of the pathogen, the remainder being contained by immune responses that often allows the pathogen to exist but ensures the survival of the hosts past reproductive age" (*Modlin 2013*).

Because the *M. tuberculosis* bacteria in LTBI replicate more slowly than in active TB disease, LTBI is able to be treated with fewer drugs. Therefore, excluding (i.e., clinically ruling out) an active case of TB before commencing therapy for LTBI is crucial to prevent acquisition of drug resistance. However, some have argued that this "latent" and "active" dichotomy, while useful clinically, is too simplistic from the epidemiologic or research perspective (*Modlin 2013*, *Achkar 2011*). For example, most persons exposed to a contagious case of TB, even heavily exposed persons, never get infected, suggesting some innate host immunity capable of destroying *M. tuberculosis* bacteria soon after initial contact in the lung alveoli (*Stein 2018*). Others, arguing that "latent TB" is too broad, propose a distinction between "incipient TB" (i.e., infection that is truly contained) or "subclinical TB" (i.e., progression in an as-yet asymptomatic host) (*Achkar 2011*).

Dynamic state of "latent" TB infection

The vast majority of humans with LTBI have immune systems that are able to suppress the *M. tuberculosis* infection via a lifelong dynamic process involving engulfment by macrophages and granulomas, vitamin D-dependent microbicidal pathways, tumor necrosis factor and other cytokines, and other processes still imperfectly understood. Any residual *M. tuberculosis* bacteria, however, retain the capacity to "reactivate" and replicate in larger numbers, leading to active TB disease, particularly in immunocompromised hosts (*Iseman 2000*).

Basic public health strategies for TB control and prevention

For over a century, TB control efforts in the United States and elsewhere have emphasized the early detection and isolation of active TB cases to prevent additional transmission within the community. Before 1952, TB control was accomplished by removing persons with infectious TB from their workplaces, schools, and even homes (i.e., placing them into TB sanatoria). Once curative treatment of active TB became available in 1952, infectivity and transmission were stopped by providing multiple-drug therapy, instead. Indeed, early

and effective treatment of TB benefits not only individuals and their families but also the entire community (*US Dept. of Labor 1912*, *Frost 1937*, *Taylor 2005*).

Beginning in 1965, the American Thoracic Society also began to encourage preventive therapy (i.e., treatment of LTBI) for recently exposed children under age 3, for adolescents and young adults under age 25 whose TST measured ≥10 mm, and for pregnant women, diabetics, and other persons with old "inactive TB" from the ineffective treatments that had been available prior to 1952 (*Corpe 1965*). TB control efforts in the United States also focus on identifying and treating TB and LTBI in contacts of persons with infectious TB (*ATS/CDC 2000*, *Taylor 2005*). Now there is renewed emphasis in the United States and other parts of the world to detect and treat more longstanding LTBI as a third strategy to prevent future cases of active TB (*ATS/CDC 2000*, *Taylor 2005*, *Corpe 1965*, *Davidow 2015*, *Esmail 2014*, *USPSTF 2016*, *WHO 2015*, *WHO 2018*), although some question the wisdom of this strategy in settings with ongoing TB transmission and high HIV prevalence (*Behr 2018*).

Biologic mechanisms for relationship between TB risk and other conditions

Consideration of risk factors in prioritizing LTBI treatment

The dilemma for individual patients, clinicians, and public health programs is that very few persons with longstanding LTBI will actually benefit from treatment (*Behr 2018*, *Horsburgh 2004*, *Shea 2014*, *Menzies 2018*, *Mirzazadeh 2018*). The concept of risk factors was first applied to TB in 1974. Discussion of risk should ideally distinguish between risk factors for becoming infected (e.g., birth in a country with high TB prevalence) and risk factors for having an infection that will progress to active TB disease (e.g., HIV, diabetes) (*ATS/CDC 2000*, *Behr 2018*, *Iseman 2000*, *Horsburgh 2004*, *Menzies 2018*). This distinction is important when considering TB control interventions (*Frost 1937*, *Horsburgh 2004*, *Comstock 1974b*).

Recent infection as the strongest risk factor for progression

Because the risk of progression to active TB disease is highest in the 2 years following initial *M. tuberculosis* infection, TB control efforts in the United States focus on identifying contacts of persons with infectious TB (*ATS/CDC 2000*, *Taylor 2005*). "TST conversion" signals recent infection; contacts of any age who "convert" their TST result from negative to positive following exposure to an active TB case are also at greater risk for developing TB (*ATS/CDC 2000*, *Corpe 1965*, *Horsburgh 2004*).

Youth as a strong risk factor for progression

Very young children with their immature immune systems have an extremely high risk of experiencing rapid progression to active TB (i.e., having primary disease) following infection (i.e., without passing through an intermediary LTBI phase). This rapid progression in children aged <5 years is why protective measures such as BCG vaccination in other countries and window prophylaxis in the United States are generally uncontested recommendations (*ATS/CDC 2000*, *Iseman 2000*).

For intrinsic biological reasons still poorly understood, there has always been a much lower risk of LTBI progression among children who were infected at age 5 years through the onset of puberty. Then, adolescents and young adults again seem more predisposed to primary disease (and, historically, TB mortality) across cohorts and decades, based on TB surveillance records in both North America and Europe (*US Dept. of Labor 1912*, *ATS/CDC 2000*, *Iseman 2000*, *Frost 1937*, *Corpe 1965*, *Comstock 1974b*, *Frost 1939*).

HIV infection as a risk factor for progression and possibly for infection

For an individual person, HIV is one of the strongest medical risk factors for progression to active TB following infection (*ATS/CDC 2000*, *Behr 2018*, *Iseman 2000*, *Horsburgh 2004*, *Shea 2014*, *Cantwell 1994*). High HIV viral loads are also plausibly associated with greater risk of infection following an exposure (*Iseman 2000*). The HIV epidemic contributed to the 1985–1992 TB resurgence; in 1993, HIV was reported for 13% of active TB disease (*Cantwell 1994*, *CDC 2018a*). In 2017, <6% of TB disease in the United States occurred

in persons living with HIV (*CDC 2018a*). While HIV-associated TB disease has declined, national HIV prevalence appears stable. The U.S. population prevalence of HIV infection is currently estimated as 1.1 million persons, similar to the estimated 1 to 1.5 million in 1990 (*CDC 2018b*), well below 1% of the U.S. population.

Diagnosing LTBI in persons living with HIV is complicated because of "anergy" (i.e., a tendency to have false-negative results due to impaired immune response) (*ATS/CDC 2000*, *Doan 2017*). Although HIV testing was part of NHANES 1999–2000 and 2011–2012, there were too few HIV-infected (e.g., only 19 participants in NHANES 2011–2012) to be able to examine its association with a positive TST result (*Bennett 2008*, *Khan 2008*, *Miramontes 2015, Mancuso 2016*).

Diabetes as a risk factor for progression and possibly for initial infection

One thousand years ago, Avicenna recognized that diabetes and TB often co-occurred, and in the 1930s–1950s, Dr. Andrew Banyai published a case series advocating for careful management of diabetes to achieve optimal TB disease outcomes (*Iseman 2000*, *Banyai 1959*). As the international prevalence of diabetes continues to grow, interest in the "converging epidemics of tuberculosis and diabetes" has also grown (*Magee 2013*, *Lönnroth 2014*, *Harries 2016*, *Al-Rifai 2017*, *Magee 2018*, *Ronacher 2017*).

Worldwide, an estimated 15% of TB cases are attributable to diabetes, and that population attributable fraction is growing (*Lönnroth 2014*). In the United States, diabetes may be surpassing HIV in importance in the epidemiology of TB. Like HIV, diabetes is an established individual risk factor for progression from LTBI to active TB disease (*Al-Rifai 2017*, *Jeon 2008*). Unlike HIV, diabetes prevalence in the United States is increasing. An estimated 30 million persons have diabetes, and another 84 million are estimated to have prediabetes, a precursor of type 2 diabetes (*CDC 2017*). In 2017, 20% of incident TB disease in the United States occurred in persons living with diabetes (*CDC 2018a*), twice the estimated 9% of the U.S. population with diabetes (*CDC 2017*), and far surpassing the <6% of TB disease cases that occur in persons living with HIV (*CDC 2018a*).

It is well understood that having diabetes impairs the host's ability to contain *M. tuberculosis* infection (*Iseman 2000*, *Banyai 1959*, *Magee 2013*, *Harries 2016*, *Al-Rifai 2017*, *Ronacher 2017*, *Jeon 2008*). Less clear is whether diabetes is also associated with incident infection itself. Cross-sectional studies in different populations have suggested a modest association between diabetes and LTBI (*Hensel 2016*, *Martínez-Aguilar 2015*, *Lee 2017*, *Webb 2009*, *Leow 2014*). However, confounding might induce a spurious association between the two conditions. A recent meta-analysis showed that the odds ratios for having both conditions consistently approached 1.0 after adjustment for age and other measured variables (pooled crude OR = 1.64, pooled adjusted OR = 1.18) (*Lee 2017*).

In NHANES 2011–2012, hemoglobin A1C (a marker for diabetes) and a positive test for LTBI appeared to have a dose-dependent relationship. As hemoglobin A1C levels increased (from <5.7 [no diabetes] to 5.7–6.4 [prediabetes] to >6.4 [diabetes]), prevalence of a TST ≥10 mm also increased. However, this dose-dependent relationship had not been seen in 1999–2000 (*Miramontes 2015*):

Estimated proportion of noninstitutionalized U.S. civilian population with LTBI, based on TST ≥10 mm in persons aged ≥6 years (weighted percent and 95% CI), by diabetes status		
Miramontes 2015 results	1999–2000	2011–2012
A1C <5.7	4.0% (3.1%–5.1%)	4.1% (3.0%–5.6%)
A1C of 5.7–6.4	9.1% (6.6%–12.4%)	6.7% (4.1%–10.7%)
A1C >6.4	6.9% (4.6%–10.3%)	8.7% (6.0%–12.4%)

A second NHANES 2011–2012 study using a more sensitive definition for classifying diabetes (i.e., also taking into account a self-reported diabetes diagnosis) observed a similar dose-dependent relationship with positive IGRA results (*Barron 2018*):

Estimated proportion of noninstitutionalized U.S. civilian population with LTBI, based on positive QuantiFERON®-TB Gold (QFT) IGRA blood test in persons aged ≥20 years (weighted percent and 95% CI), by diabetes status	
Barron 2018 results	2011–2012
A1C <5.7	4.6% (3.7%–5.6%)
A1C of 5.7–6.4	7.0% (5.2%–8.7%)
A1C >6.4 or self-reported diabetes	11.6% (7.9%–15.3%)

A third study of NHANES 2011–2012 data that used a yet more expansive definition to classify diabetes concluded that uncontrolled diabetes and diabetes not treated with insulin was associated with an even greater prevalence of a positive TST (*Martinez 2017*):

Estimated proportion of noninstitutionalized U.S. civilian population with LTBI, based on TST ≥10 mm in persons aged ≥20 years (weighted percent), by diabetes status	
Martinez 2017 results	2011–2012
A1C <5.7	4.1%
A1C of 5.7–6.4 or fasting glucose or OGTT**	5.5%
A1C >6.4 or self-reported diabetes or fasting glucose or OGTT*	7.6%

*Person classified as having diabetes if fasting plasma glucose ≥126 mg/dL or oral glucose tolerance test (OGTT) glucose of ≥200 mg/dL after 2 hours.
**Person classified as having prediabetes if a fasting glucose of 100–125 mg/dL or a 2-hour OGTT result of 140–199 mg/dL.

However, similar to the meta-analysis findings (*Lee 2017*), the odds ratios for the diabetes/LTBI relationship in NHANES 2011–2012 approached null as more variables were considered (*Barron 2018*, *Martinez 2017*):

Association between diabetes and positive QFT in noninstitutionalized U.S. civilian population aged ≥20 years (weighted odds ratio and 95% CI) from *Barron 2018*			
Crude model	No diabetes Prediabetes Diabetes	1.00 1.54 (1.24–1.91) 2.70 (1.76–4.14)	No covariates considered as confounders
Model presented in main paper	No diabetes Prediabetes Diabetes	1.00 1.15 (0.90– 1.47) 1.90 (1.15– 3.14)	Adjusting for age, sex, smoking status, history of active TB, and foreign birth
Model in supplement	No diabetes Prediabetes Diabetes	1.00 1.06 (0.81 – 1.35) 1.49 (0.84 – 2.64)	Adjusting for age, sex, education, ethnicity, and income to poverty ratio.

Association between diabetes and TST ≥10 mm in noninstitutionalized U.S. civilian population aged ≥20 years (weighted odds ratio and 95% CI) from *Martinez 2017*			
Model presented in main paper	No diabetes Prediabetes Diabetes	1.00 1.3 (0.8– 2.1) 1.5 (1.0– 2.2)	Adjusting for age, sex, smoking status, history of household TB exposure, family size, and foreign birth

If the posited diabetes/LTBI relationship is causal (which is not a settled question), each condition might amplify the other in a "two-way street" (*Magee 2018*). The more conventional explanation for a diabetes/LTBI association is that chronic hyperglycemia is a risk factor for incident infection, due to an impaired or delayed immunologic response that enables survival and persistence of the *M. tuberculosis* bacteria

beyond their initial entry into the lungs (*Magee 2018*, *Ronacher 2017*, *Lee 2017*, *Martinez 2016*). In what appears to be only one prospective study examining the diabetes/LTBI association, a group of Spanish researchers examined recent contacts of persons with infectious TB. They concluded that pre-existing diabetes was associated with incident infection (i.e., greater risk of tuberculin skin test conversions among contacts with diabetes) (*Arnedo-Pena 2015*). An alternative explanation for a causal association between diabetes and LTBI would suggest temporality in the opposite direction. Biologic plausibility for this hypothesis is supported by the macrophage stimulation that is common to both conditions. *M. tuberculosis* bacilli can survive in a lifelong latent state in the human body. *M. tuberculosis* bacilli persist within the macrophages of the lungs and lymph nodes, and plausibly in other reservoirs, which might include adipose (fat) tissue. Type 2 diabetes is often precipitated by obesity, where the pathway to peripheral insulin resistance appears to involve overstimulation of macrophages in adipose tissue. Having macrophages chronically infected with *M. tuberculosis* could thus lead to persistent inflammation that manifests as hyperglycemia, contributing to the development of prediabetes and diabetes (*Magee 2018*, *Barron 2018*, *Kim 2011*, *Boutens 2016*).

Chapter 8 (aim 3) focuses on the diabetes/LTBI association is NHANES.

Genetic susceptibility and race as potential risk factors for either infection or progression

Some human genetic factors are almost certainly associated with successful suppression of TB infection to prevent progression to active disease and possibly to prevent TB infection in the first place (*Iseman 2000*, *van Crevel 2002*). Much current research, including that of Emory University's NIH-funded Tuberculosis Research Unit, aims to identify the subset of infected persons with the highest individual risk of experiencing progression to active TB so that they can be prioritized for preventive efforts.

Before genomic studies were feasible, the 1952–1956 Prophit study of twins in England (*Comstock 1978*) and William Stead's examination of TST results and TB incidence in 227 Arkansas nursing homes following desegregation (*Stead 1990*) had suggested the potential relevance of hereditary or racial factors for infection and progression. Important concerns about missing aspects (e.g., unmeasured confounding

associated with racial discrimination) of these analyses, however, were subsequently raised (*van der Eijk 2007*; also multiple letters to the *New England Journal of Medicine* editors in response to *Stead 1990*). A more recent study estimated that the risk of progression from LTBI to active TB disease was similar for U.S.-born whites and blacks (<0.10% annual risk if HIV-uninfected), but elevated for Hispanics (0.17%–0.19%) and Asians (0.13%–0.15%) (*Shea 2014*).

Older age cohort as a risk factor for infection

At an aggregate level, elevated rates of active TB disease among the elderly can be somewhat attributed to a higher prevalence of LTBI among the elderly, given their having lived through time periods with much higher rates of TB (*Comstock 1975a*, *Frost 1939*, *Winston 2010*). This birth cohort effect was first demonstrated in Wade Hampton Frost's final manuscript, "The age selection of mortality from tuberculosis in successive decades." Examining Massachusetts mortality records, Frost grouped persons whose deaths were attributed to active TB disease into cohorts by birth decade, starting in 1880 and continuing through 1930. Then he plotted their age-specific mortality rates on the same graph. Consistently across all 6 age cohorts, TB mortality peaked in infancy, dropped rapidly during later childhood, and then peaked again for young adults in their 20's. However, across ages, the 1880 birth cohort's TB mortality rates were higher than the 1890 birth cohort's rates, which were higher than the 1900 birth cohort's rates, and so forth (*Frost 1939*).

Several decades later, George Comstock demonstrated similar birth cohort effects, but with LTBI prevalence rather than TB mortality, using cross-sectional TST results from a population-wide screening conducted in Muscogee County, GA, and Russell County, AL, in 1950. Citing similar findings in the Navy recruit studies, Comstock concluded, "current evidence favors the hypothesis that [incident] infection has been decreasing with time, so that younger persons had been exposed to lower rates of infection" (*Comstock 1975a*, p. 371). More recent analysis of NHANES 1971–1972 and 1999–2000 by 5-year birth cohorts similarly demonstrated highest prevalence of a positive TST among persons born before 1922, with successively lower prevalence for the 1922–1926, 1927–1931, and 1932–1936 birth cohorts (*Winston 2010*).

Being underweight, tall, and malnourished as risk factors for progression

Susan Sontag's *Illness as Metaphor* explains how TB in the 19th century was often romantically considered an artist's disease — an illness that afflicted the young, slender, and sensitive. The direction of this relationship, of course, is uncertain, as a classic symptom of active TB is unintentional weight loss. However, the importance of good nutrition was well appreciated by the early TB sanatoria. Wade Hampton Frost, noting the link between poverty and TB, described "better nutrition and relief from physical stress" as key TB control measures, describing the importance of "a generous plan of social assistance" for families affected by TB (*Frost 1937*), something which other industrialized nations such as Germany were already providing (*US Dept. of Labor 1912*).

The 1949–1951 Naval studies examined the anecdotal observation that tall, thin U.S. Army soldiers had been more prone to developing active TB disease during World War II. Although Naval recruits over 6'2" or weighing less than 130 lb. were no more likely to have positive TST results upon arrival for basic training, they had higher rates of TB progression during the first 2 years of service, when presumably diet among recruits was similar (*Palmer 1957*).

These risk factors may be impossible to study and increasingly irrelevant in the United States: in NHANES 1999–2000 and 2011–2012, too few participants had a body mass index under 18.5 to be able to estimate the prevalence of LTBI among underweight persons (*Miramontes 2015*).

Chronic kidney disease and dialysis as risk factors for progression

Chronic kidney disease is also recognized as an increasingly important risk factor for progression to active TB, which is why CDC added renal failure to the standard list of risk factors in the National Tuberculosis Surveillance System in 2009. Although renal failure is closely related to diabetes and malnutrition, the process of hemodialysis impairs macrophage function, making renal failure an independent risk factor (*Iseman 2000*). Whether kidney disease is also associated with risk of incident infection is uncertain.

Treatment for autoimmune diseases as a risk factor for progression

As explained in a previous section, tumor necrosis factor (TNF) and other cytokines play important roles in actively suppressing LTBI. However, immunosuppressive medications that antagonize TNF-alpha are a key treatment modality for persons suffering with rheumatoid arthritis and other autoimmune diseases. A known side effect of these medications is increased risk of progression from latent to active TB, which is why rheumatologists typically test and treat for LTBI before starting a patients on immunosuppressing agents. CDC added use of TNF-alpha blockers to the standard list of risk factors in the National Tuberculosis Surveillance System in 2009. Whether these medications are also associated with LTBI itself is uncertain, but with only five NHANES 2011–2012 participants reporting use of TNF-alpha blocker or interleukin inhibitor therapy, this question cannot be examined using NHANES data.

Vitamin D deficiency as an uncertain risk factor for TB

In addition to good nutrition, the early TB sanatoria emphasized the importance of sunlight exposure. Some of the criticism of earlier studies suggesting that black race might be a risk factor for TB posited that the true risk factor might be vitamin D deficiency (e.g., mentioned in several letters to the editors of the *New England Journal of Medicine* in response to *Stead 1990*). Patients newly diagnosed with active TB are often vitamin D deficient. Suppression of LTBI involves vitamin D-dependent microbicidal pathways, so it is plausible but not yet established that vitamin D deficiency is associated with progression to active TB disease.

Whether vitamin D is also associated with incident infection has not been as closely studied. NHANES collected blood for vitamin D level determination in 2000 (available only in the Research Data Center) and 2011–2012 (available in the public-use dataset). NHANES 2011–2012 participants with sufficient (20–29 ng/mL) and optimal (≥30 ng/mL) vitamin D levels had a weighted 5.8% (4.2%–8.0%) and 2.3% (1.5%–3.4%) prevalence of a positive TST, respectively. Conversely, persons with insufficient (10–19 ng/mL) and low (<10 ng/mL) levels had a weighted positive TST prevalence of 8.5% (3.5%–18.9%) and 8.2% (5.5%–11.9%). In summary, preliminary cross-sectional results from NHANES 2011–2012 suggest an

association between vitamin D and LTBI, but the direction of the relationship is uncertain. Examining this relationship further is outside the scope of this dissertation.

Tobacco and other substance use as risk factors for infection and progression

Although cigarette smoking has received much attention as a TB risk factor internationally (*Bates 2007*, *Lin 2007*), tobacco is not a variable in the U.S. National Tuberculosis Surveillance System, and its association with TB in the United States is difficult to estimate. Tobacco and other inhaled substances disrupt macrophage function in the lung alveoli (i.e., a nonspecific first line of immune defense), potentially predisposing persons to infection when they are exposed to somebody with active pulmonary TB. Substance abuse, including alcohol, also appears to foster progression to active TB disease. However, whether substance abuse directly causes progression or is mediated by concomitant malnutrition is less clear.

Estimating the national prevalence of TB infection

No ongoing population-based national surveillance for LTBI

In 1952, curative treatment for active TB first became available, heralding the closure of sanatoria all over the United States. The following year, incident TB became nationally notifiable. In 1953, a total of 84,304 active TB cases were reported by the 50 U.S. states and District of Columbia, corresponding to an annual incidence of 53 cases per 100,000 population (*CDC 2018a*). Except for a leveling in 1979–1981, which was attributed to an influx of Vietnamese immigrants; a resurgence in 1985–1992, which was attributed to HIV comorbidity, more immigration, and domestic transmission; and the more recent 2013–2015 leveling, which has not yet been fully explained, annual TB case counts have declined to about 9,500 total active TB cases, corresponding to 3 cases per 100,000 population (*Cantwell 1994*, *CDC 2018a*, *CDC 1981*, *CDC 1982*, *Salinas 2016*).

However, it was not until 2017 that the Council of State and Territorial Epidemiologists established a

case definition for LTBI (position statement 17-ID-09), explaining that as more jurisdictions in the United States make LTBI a reportable condition (i.e., 16 U.S. states as of August 2018), a "highly logical first step" is creating a standardized case definition: a positive TST or IGRA, no clinical or laboratory evidence of TB disease, and no previous diagnosis or treatment for either LTBI or TB disease (*CSTE 2017*).

Numerous studies in the 1950s, before treatment for LTBI was promoted, concluded that "positive tuberculin reactors" gave rise to most new TB cases (*Palmer 1956*). In 1965, one third of cases were estimated to be attributable to LTBI rather than recent transmission (*Corpe 1965*). But now, recent transmission accounts for approximately 14% of active TB cases in the United States (*France 2015*, *Yuen 2016*, *CDC 2018a*), suggesting that approximately 86% of annual cases arise from an underlying reservoir of untreated LTBI (see **chapter 5**). Accurate detection and treatment of LTBI has become an essential element of the global goal to eliminate TB by 2050 (*Esmail 2014*, *USPSTF 2016*, *WHO 2015*, *WHO 2018*, *Salinas 2016*, *Hill 2012*).

First LTBI prevalence surveys in United States: Framingham in 1917, Minnesota in early 1930s

In the early 1900s, virtually everybody surviving to adulthood in the United States had become infected during childhood by inhaling *M. tuberculosis* in airspace shared with a TB patient or by ingesting cow milk contaminated with *Mycobacterium bovis* (bovine TB). Over 90% of adults had a positive TST reaction, limiting its diagnostic utility among U.S. adults (*Edwards 1960*, *Edwards 1968*).

The first documented cross-sectional TST survey using the subcutaneous von Pirquet tuberculin was conducted among 500 children without any clinical or radiographic evidence of TB in Framingham, Massachusetts, during 1917. This Framingham Health and Tuberculosis Demonstration survey (which lay the groundwork for the later heart studies) demonstrated that the prevalence of a positive TST reaction increased with age, from 15% of 1-year-old children to 54% of 6-year-old children, with little overall difference between boys (32%) and girls (35%). The poorest district of the town, where most of the families of Italian ancestry resided, had the highest prevalence of positive TST reactions. The children of "Italian nationality" were much more likely to have a positive TST reaction (51%) than children with "Jewish or Irish nationality" (30%) or

"American nationality" (18%) (*Framingham 1918*).

By the 1930s, there was increasing interest in performing TST surveys among apparently healthy persons in different age groups and populations. TST surveys using the intradermal Mantoux tuberculin in Minnesota, for example, involved thousands of persons: 92% of sanatorium patients had positive test results, well above the 15%–20% of rural schoolchildren (*Mariette 1932*).

LTBI prevalence among nursing students in 1943–1949: geographic variability first noted

During 1943–1949, the American Trudeau Society funded a project to evaluate 20,000 young women (described as "white girls") for TB as they started nursing school. The examination include a TST using Dr. Siebert's PPD-S. Notable geographic patterns emerged (see Literature review appendix 1), with <10% of nursing students from the Midwest, 17% of those from the East coast, and 20% in Oklahoma, Texas, and Indiana having positive results (defined as ≥5 mm induration) (*Palmer 1950*).

LTBI prevalence in 1949–1951: overall declines but persistent geographic variability

To better understand this apparent geographic variability, the same procedures were subsequently replicated in a national study coordinated by the U.S. Public Health Service, with the support of the American Student Health Association and U.S. Navy, during 1949–1951. This 3-year study ultimately tested 38,070 white students (primarily freshmen) on 35 college campuses and 83,559 white Navy recruits as they arrived at the U.S. Naval Training Center in San Diego. A key component of this large scale study was careful interviewing to determine the young person's complete residence history. Persons were classified as lifelong "one-state residents" if they had not lived anywhere else for more than 6 months (i.e., 26,398, or 69% of the students, and 56,481, or 68% of the recruits). In fact, 49,404 (59%) of the recruits had lived in the same "section" (county grouping) of their home state for their whole lives (*Palmer 1956*).

As had been observed among the Framingham children in 1917 (*Framingham 1918*), this 1949–1951 national study showed that the prevalence trend of a positive TST reaction (defined as ≥5 mm induration)

increased steadily with age: from 7.9% of 17-year-old participants to 12.0% of 21-year-old participants. The authors interpreted this prevalence as the cumulative result of incident TB infections that occurred during the 1930s and 1940s, but they heralded the results as encouraging evidence that "most of our children can now be expected to reach adulthood without having acquired a tuberculous infection" (*Palmer 1956*). This secular trend was a notable change from when the TST was introduced in the early 1900s, and it predates 1952, when isoniazid trials at Staten Island's Seaview Hospital would first demonstrate that TB was curable.

Across all geographic areas in 1949–1951, female college students had the lowest prevalence of a positive TST reaction (6.8%), which the authors speculated as likely associated with a "higher social stratum" than the male college students and Naval recruits whose prevalence of a positive TST reaction was 8.6% and 9.1%, respectively. However, other differences were notable. In all three groups, persons from metropolitan areas had nearly twice the prevalence of infection than persons who had grown up on farms in rural areas. Young persons who had lived in more than one state were also more likely to be infected (*Palmer 1956*).

The geographic variability in results among "one-state" and "one-section" residents was notable and resulted in numerous subsequent publications and related studies (*Edwards/Palmer 1969*, *Edwards et al. 1969*, *Comstock 1974a*, *Comstock 1975a*, *Palmer 1950*). Briefly, the U.S. Southwest, where apparently there was a "well-known tendency [for] tuberculosis patients to move," had up to 20% of 1949–1951 TST participants testing positive, as did 16.7% of Kentucky participants, with neighboring states having 12%–15% positivity. The authors considered whether these regional differences were driven by the distribution of college student versus Naval recruits, or metropolitan versus rural residence, but adjustment did not substantially change these findings. They also noted that TB death rates in the white populations in those states during 1939–1941 (i.e., approximately 10 years prior) correlated strongly (r=0.88) with the proportion of white Naval recruits with a positive TST result in 1949–1951 (*Palmer 1956*).

LTBI prevalence among Navy recruits in 1958–1969, 1990: differences by national origin, race

Strikingly similar geographic trends were noted during subsequent studies of 1,216,425 Naval recruits

in 1958–1969. A change in this later Naval survey was that it used a more specific criterion of ≥10 mm (previous studies had used ≥5 mm) to define a positive result. Again, compared to Naval recruits who had grown up on farms, those from metropolitan areas had higher likelihood of a positive TST result. In addition, lifetime one-county residents of southern California, Arizona, New Mexico, Colorado, and Texas, and those in a band across Kentucky, West Virginia, and Maryland, again had the highest prevalence of positive TST reactions (*Edwards 1960*, *Edwards/Palmer 1969*, *Edwards et al. 1969*, *Comstock 1974a*). In 1944, Dr. Russell E. Teague of the Kentucky Division of Tuberculosis Control compiled mortality data showing that Arizona and New Mexico had the highest TB death rates. Setting those two states (which he termed "health resort states") aside, he reported that Kentucky, with 2,000 annual deaths attributed to TB, had the highest TB death rate in the United States (*Schulman 1944*).

Another potential explanation for the pronounced regional differences in positive TST prevalence observed in that 1958–1965 map (see Literature review appendix 2) is regional variations in uptake of milk pasteurization. Mandatory pasteurization of cow milk began in U.S. cities: Cincinnati (1897), New York City (1898), Philadelphia (1899), St. Louis (1900), Milwaukee (1903), Boston (1908), Chicago (1908), and Detroit (1910) (*Steele 2000*). After milk pasteurization began in New York City, nonpulmonary forms of active TB disease (particularly in the throat, neck, and stomach) declined sharply. Likewise, sharp declines in TB mortality among European children during the 1930s and 1940s were attributed to milk pasteurization (*Good 2018*). Despite advocacy by the U.S. Public Health Service for all part of the country to enforce FDA's Grade A Milk Safety Program standards, uptake of milk pasteurization in the United States took longer. The first U.S. state to enact mandatory statewide milk pasteurization was Michigan in 1948 (*Steele 2000*, *Langer 2012*). Two of the last states to require Grade A milk pasteurization were West Virginia (1968) and Kentucky (1973) (*West Virginia 1968*, *Beck 1982*). The higher prevalence of a positive TST among young white men from those states in 1958–1965 suggests higher LTBI prevalence through either inhalation of *M. tuberculosis* or ingestion of milk contaminated with *M. bovis* before entering the Navy (*Edwards 1960*, *Edwards 1968*).

This 1958–1969 Naval study was apparently also the first since the 1917 Framingham Health and Tuberculosis Demonstration that considered national origin or race. Among white Naval recruits aged 17–21, 3.8% had positive TST results. When these white young men were stratified by birthplace, 19.9% of those born abroad had a positive TST result; many had originated in countries with high rates of TB disease following World War II. Further, the U.S.-born who had lived abroad at least 6 months before joining the Navy also had slightly higher TST positivity. Finally, although approximately 92% of Naval recruits were classified as white, there were also 6% classified as black (primarily U.S.-born), and 2% as Asian (primarily Philippines-born). In these minority groups, the proportion with a positive TST result was 12.4% among blacks and 60.2% among Asians (*Edwards/Palmer 1969*, *Comstock 1974a*, *Comstock 1975a*).

A subsequent analysis focused on the 37 U.S. counties (or equivalents) with at least 25 black lifetime one-county residents joining the Navy during 1958–1961 (*Edwards 1964*). Working with the TST results from the total 3,052 black and 30,098 white recruits from those counties, the authors noted that TST positivity (which they defined as ≥8 mm induration) was consistently higher among the black recruits in 34 of 37 jurisdictions. In only Indianapolis and Kansas City were the infected proportions similar, and only in Little Rock did white Naval recruits have higher TST positivity than their black counterparts (see Literature review appendix 3). County-level positive TST prevalence ranged from 2.0% to 13.5% among the white recruits and from 3.8% to 25.5% among the black recruits. The authors commented on a study strength:

> "A word might be added here about the implications of the way in which this material was collected. Not only was the same product used, and the tests given and read by the same persons, but over a period of several years an almost continuous stream of recruits has been flowing through the skin-test area at both training centres without any segregation of the men as they come down the line. No attention is paid to the colour of skin, worldly wealth, social or educational background, farm or city residence, or what part of the USA or any other country the recruits call home. So, whatever the limitations of the data because of the relatively small numbers of men from some regions, the skin testing was done with the kind of uniformity and freedom from bias that make the material nearly ideal for studying the influence of numerous factors" (*Edwards 1964*).

In contrast to the racial disparities demonstrated by the TST results, these men were simultaneously also skin-tested for histoplasmin sensitivity, where the county-level results were "remarkably alike" between the two races (*Edwards 1964*).

For 2 months in 1990, the U.S. Navy sought to replicate the techniques used in 1958–1961 by asking 2,214 new recruits arriving at basic training in San Diego, Orlando, and Great Lakes, IL, to complete a demographic questionnaire as they received their TSTs. Male and female recruits had essentially the same prevalence of infection (again defined as a TST of ≥10 mm induration). Among the U.S.-born, the prevalence of infection was 1.6%, down from the 3.9% observed 3 decades previously. Among the non-U.S.–born, prevalence was 17.4%. Racial disparities persisted, with 1.2% of white or Hispanic recruits infected, compared with 4.9% of black or other non-Asian recruits. For the U.S.-born, home state was apparently not associated with prevalence of infection, but the Great Lakes recruits, for unclear reasons, had a higher prevalence of a positive TST (*Trump 1993*).

CHAPTER 3 — National Health and Nutrition Examination Survey (NHANES)

NHANES overview

Other than the 1940s–1960s college student and U.S. Navy studies described in the previous chapter, the only national estimates of LTBI prevalence have been provided by the National Health and Nutrition Examination Survey (NHANES). Sponsored by the National Center for Health Statistics (NCHS), NHANES was first authorized by the National Health Survey Act in 1956. The first examination cycle in 1960–1962, the National Health Examination Survey I, focused on chronic diseases in adults. The National Health Examination Survey II in 1963–1965 and National Health Examination Survey III in 1966–1970 focused on children and youth. When a nutritional component was added for the fourth cycle in 1971–1974, the survey was renamed the Health and Nutrition Examination Survey (HANES I). Then after 3 more cycles in 1976–1980, 1982–1984, and 1988–1994, NHANES relaunched in 1999 as what is now a continuously operating series of cross-sectional surveys (*NAPA 1981*, *NCHS 1971*, *Curtin 2012*, *Johnson 2014*, *Paulose-Ram 2017*).

Over a 2-year period, multistage stratified area probability sampling is used to select a self-weighting sample of approximately 10,000 participants who, once their individual weights have been summed, represent the entire noninstitutionalized civilian U.S. population at the time of the survey. NCHS makes the deidentified NHANES public-use datasets broadly available, including participant weights and masked sampling design parameters, with instructions about how to account for the complex, multistage, probability sample design when generating national estimates. NHANES is not a simple random sample, so appropriate analysis of this complex survey requires incorporation of the participant weights and sampling design parameters, as well as care not to subset data in a way that compromises variance estimation (*NCHS 2006*, *Johnson 2012*, *NCHS 2013a*, *Heeringa 2010*). Subject to research proposal approval by NCHS, certain restricted variables considered too sensitive for public access are available via the NCHS Research Data Center (RDC).

Three NHANES cycles with a tuberculin skin test (TST)

NHANES included a tuberculin skin test (TST) during 1971–1972, 1999–2000, and 2011–2012, and an interferon-gamma release assay (IGRA) blood test for TB infection in 2011–2012 (*Engel 1977*, *Bennett 2008*, *Khan 2008*, *Miramontes 2015, Mancuso 2016*, *NCHS 1991*). NHANES appendices 1 and 2 list the TB-related variables collected across those 3 NHANES cycles.

NHANES applicability for rare conditions

While the primary emphasis of the NHANES in-home interviews and detailed medical examinations is to monitor the prevalence of major health conditions and nutritional status over time, additional components for other conditions of interest are occasionally added to a single cycle (*NAPA 1981*, *NCHS 1971*, *Curtin 2012*, *Johnson 2014*). Prevalence estimates in NHANES are thought to be statistically reliable (adequately precise) if at least 2 years of sequential data are examined. That guideline is based, however, on a threshold prevalence of ≥10% for any given condition (*Johnson 2012*, *Curtin 2006*). Additionally, NHANES advises researchers to combine more than one sequential 2-year cycle "for rare events, for preparing estimates for very detailed demographic subdomains, and for measures that may have considerable geographic variation" (pp. 2–3 of *Curtin 2012*).

Sampling design parameters: major strata and primary sampling units (PSUs)

The NHANES major strata are mutually exclusive groups of counties with approximately the same total population size in each stratum. They are also thought to be relatively homogeneous in terms of health, because the intent is that the first sampling stage draw PSUs from strata that are "homogenous within" and "heterogenous between" (*Heeringa 2010*). The 1971–1972 and 1999–2000 major strata designations are not publicly available, but are shown in NHANES appendix 3 for NHANES 2011–2012.

PSUs generally correspond to single counties. NHANES is currently designed to visit 14 PSUs, corresponding to 1 PSU from each of the 14 major strata, per year. As in 1971–1972, the study locations

("stands") tend to be in northern states in summer and southern states in winter. Some large-population counties are selected "with certainty," but with a few exceptions (*Landis 1982*, *Porter 2011*), their identities are rarely disclosed. Otherwise, each county's probability of selection is proportional to that county's population size relative to the entire population of the major stratum in which that PSU is located. Because the stratum populations are so large, NHANES analytic guidelines recommend that the finite population corrections can be ignored and a "with replacement" design be used when employing a Taylor series linearization to estimate variance (*NCHS 2006*, *Johnson 2012*, *NCHS 2013a*, *Landis 1982*).

Unmasked versus masked design parameters

To provide an additional layer of anonymity for participants while preparing the public-use datasets, NCHS collapses the NHANES PSUs into 14 "pseudo" strata that do not necessarily correspond to their true major stratum (i.e., T_VSTRA in the restricted dataset becomes SDVSTRA in the public-use dataset). In addition, some of the secondary sampling units ("segments") within PSUs are swapped across PSUs, which are also presented in the public-use dataset as a masked variable (i.e., T_VPSU in the restricted dataset becomes SDMVPSU in the public-use dataset). The concept is that any complex survey analysis based on the swapped and masked strata and PSUs will estimate a variance that closely approximates the variance that would have been produced had the true sampling design parameters been used (*NCHS 2006*, *Johnson 2012*, *NCHS 2013a*, *Landis 1982*).

NHANES participant weights

Because NHANES is not a simple random sample, appropriate analysis of NHANES data must include the self-weighting participant weights that are assigned to each person. Otherwise, any national estimates that are produced using NHANES data will be biased. Approximately 13,000 persons are selected for participation in each 2-year NHANES cycle, with the goal that 10,000 will agree to participate. The NHANES public-use dataset includes weights for each interviewed (i.e., WTINT2YR) and examined (i.e., WTMEC2YR) study participant. Because not all who are interviewed return for the examination, the

examination weights are somewhat higher than the interview weights. Each participant typically represents between 5,000 and 40,000 other persons deemed similar in terms of their demographic subdomain (i.e., characteristics such as age, gender, race/ethnicity, and income).

A participant's *base* weight (not the final weight in the public-use dataset) is the reciprocal of the product of four selection probabilities:

(probability of being in a *PSU* that was selected in 1st stage of multistage sampling)
× (probability of being in a selected *segment* within that PSU in 2nd stage)
× (probability of being in a selected *household* within that segment in 3rd stage)
× (probability of being a selected *individual* within that household in 4th stage).

For these sampled persons to represent the entire population, this cumulative probability of selection is inverted and turned into a base weight. For example, a participant with a 0.0000851 probability of selection would have a base weight of 11,750 persons (i.e., 1/0.0000851).

Weights are further refined based on an adjustment for nonparticipation or unit nonresponse. Essentially, a response propensity model is invoked, in which NCHS considers the missing participant in a fifth stage (or selection probability) in the NHANES sample selection process. A key difference is that this stage (unlike the previous 4 selection probabilities involved in creating the base weight) is no longer under the complete control of NCHS staff; judgments must be made about the propensity of a person, conditional on being selected for the survey, to agree to be involved in the survey (*Heeringa 2010*).

Finally, there is a post-stratification adjustment to ensure that the weighted sample matches the distribution of the gender, age group, and race/ethnicity subdomains of interest in the overall noninstitutionalized civilian U.S. population. This population distribution is obtained from the U.S. Census Bureau (i.e., the Current Population Survey for NHANES 1999–2000 and the American Community Survey for NHANES 2011–2012) (*Curtin 2012*, *Johnson 2014*).

In summary, the WTINT2YR and WTMEC2YR participant weights are based on 3 factors: base weight based on known sampling probabilities, adjustment for unit non-response, and post-stratification

adjustment to match the population distributions for the predefined demographic subdomains of interest in that 2-year cycle.

American Community Survey (ACS) and Current Population Survey (CPS) population distributions

NCHS works carefully with the most current U.S. Census Bureau data to create the initial NHANES sampling frame, at each stage of the sampling process, and when creating post-stratification adjustments for the original sampling weights. For the first NHANES, the April 1, 1970, Census enumeration of noninstitutionalized civilian persons was used to create the NHANES participant weights.

For NHANES 1999–2000, NCHS used Current Population Survey (CPS) totals for the target population size and breakdown by race/ethnicity (*Curtin 2012*). The CPS is a monthly survey of about 60,000 households that is jointly administered by the U.S. Census Bureau and the U.S. Bureau of Labor Statistics. Because the CPS focus is labor force data, it collects information on birth country and U.S. residency status for surveyed persons aged ≥15 years. However, the CPS intercensal estimate for the U.S. population size on July 1, 1999, was actually nearly 10 million persons short of the actual population census on April 1, 2000, because of faster-than-anticipated population growth. The CPS had originally projected a total of 27.9 million non-U.S.-born as part of the U.S. civilian noninstitutionalized population in March 2000. However, that estimate was revised upward following the 2000 Census, which had enumerated 31.1 million (including noncivilian and in group quarters) (*Schmidley 2003*, *Lollock 2001*). Another population estimate that had to be revised upward was the total number of persons in the United States who were of Hispanic origin. The original estimate of 32.2 million (used to design NHANES 1999–2000) was later increased to 32.8 million (*Curtin 2012*, *Johnson 2012*, *Therrien 2001*).

The American Community Survey (ACS), also known as the "long form" on the Census, is administered to about 3.5 million households annually, and provides detailed demographic and social statistics about each county, typically as estimates across 5 years. ACS data is available later than CPS data, but is based on more households and has better geographic coverage. Unlike CPS, the ACS also includes group quarters

such as prisons and federal detention centers. Because it has a larger sample size than the CPS, the ACS was thought to have more reliable population estimates for Asians, the subdomain of interest for NHANES 2011–2012, and so the ACS has been used for NHANES since 2011 (*Johnson 2014*, *Paulose-Ram 2017*).

Oversampling for the NHANES subdomains of interest

Within geographic locations, participant selection is influenced by a "measure of size" based on the pre-determined analytic subdomains of interest for that cycle. NHANES appendix 1 shows which subpopulations were emphasized across the 3 cycles with a TB component. Deliberate oversampling generally decreases the weights assigned to individual subpopulation members but improves the precision of any analysis within that subpopulation. In 1971–1972, groups at risk for malnutrition were deliberately oversampled: low-income persons, children, women, and the elderly. In later cycles, black persons, low-income white persons, and persons aged ≥80 years have been oversampled. In 1999–2000, persons of Mexican-American descent were also oversampled; in subsequent cycles, this oversampled subdomain has been more broadly defined on the basis of any Hispanic ethnicity. Starting in 2011–2012, NHANES has oversampled Asian persons (*Curtin 2012*, *Johnson 2014*, *Paulose-Ram 2017*, *NCHS 2006*, *Johnson 2012*, *NCHS 2013a*, *Landis 1982*).

Target population and sampling frame for the 35 PSUs selected in 1971–1972

To create the HANES-1 sampling frame, the 1960 U.S. Census was used to partition the 48 mainland U.S. states and District of Columbia into 40 superstrata. Fifteen superstrata were metropolitan areas, and the other 25 were nonmetropolitan. NHANES documentation appears to explain that New York City was so populous that its 5 boroughs corresponded to 5 of the 15 metropolitan superstrata and that these were all included with certainty. The remaining 10 U.S. superstrata with a population of >2 million in 1960 were grouped into 5 pairs, where one half of the pairs (i.e., 5 metropolitan areas) were selected for 1971–1972 and the other half (i.e., the other 5 metropolitan areas) were selected for 1973–1974 (*NCHS 1991*, *Landis 1982*).

The remaining 25 less densely populated superstrata were partitioned into a sampling frame of 1,890 PSUs, each representing a metropolitan statistical area, a single large county, or 2–3 contiguous smaller counties. Probability sampling was used to select 2 PSUs from each stratum with the probability proportional to PSU size relative to total stratum population in 1960 (*Landis 1982*).

This sampling process resulted in a total of 65 PSUs selected for the 4-year survey (*NCHS 1991*). For the 1971–1972 dataset, the 2 years that included a TB component, only 1 PSU per nonmetropolitan stratum was able to be included, for a total of 10 metropolitan and 25 nonmetropolitan study locations. NCHS has provided documentation explaining how to collapse and recode the stratum, PSU, and segment variables in order to estimate variance accurately with this abridged dataset (*NCHS 1991*; see NHANES appendix 3).

Once the PSUs were selected, their Census Enumeration Districts were examined, with each *segment* (secondary sampling unit, somewhat analogous to a city block) categorized as poverty or non-poverty based on Census data. Disproportional higher selection of poverty segments allowed for better precision of estimates within populations living in poverty. Then all households within selected segments were visited, with the age and gender of each occupant recorded, to enable deliberately oversampling of those aged <5 or 65–74 years, and of women ages 20–44. The outcome was generally one person from each household being selected for the health interview. A systematic subsample of adults aged 25–74 years also received a detailed medical examination, including a chest x-ray and TST (*Engel 1977*, *NCHS 1991*, *Landis 1982*).

LTBI component of NHANES 1971–1972: primarily white U.S.-born cohort born before TB treatment available

At the first 35 study locations to host NHANES during April 1971–October 1972, a total of 1,891 examined participants aged 25–74 years were eligible for a TST (using Dr. Siebert's PPD-S). Those participants were subsequently weighted to represent approximately 104 million adults, corresponding to the cohort born in the first half of the 1900s, before treatment for TB was available, and still alive. Weighted race/ethnicity for this cohort was the 89% white, 10% black, and 1% "other" population of the United States in 1972.

Originally, TSTs were going to be part of the examination at all 65 PSUs in the full 4-year cycle, but the TST component of the examination ceased in the second year after only 35 PSUs (i.e., on October 5, 1972) "because of the burden imposed on the examinee by the necessity of a second visit" (*Engel 1977*). The missing data and NHANES 1971–1972 appendix also demonstrates how even before October 5, 1972, some study locations (notably Midwest locations 7 and 16) had unexplained high proportions of missing TST results among adults with otherwise complete examinations (i.e., an example of item nonresponse).

The national prevalence of LTBI based on NHANES 1971–1972 was initially estimated at 16.1% (95% CI: 14.8%–17.4%), with prevalence highest in the Northeast metropolitan cities (*Engel 1977*). Replicating that result has proved difficult and is potentially influenced by the original authors' assumption that persons with a history of TB disease or a previous positive TST result or previous LTBI treatment with isoniazid were "assumed [to] have had a positive reaction" (*Engel 1977*). When a definition based strictly on having a documented NHANES TST result ≥10 mm was later applied, the estimate was lowered to 14.3% (95% CI: 11.3%–18.0%) (*Bennett 2008*) or 14.4% (95% CI: 11.6%–17.7%) with the public-use dataset (*Khan 2008*).

Target population and sampling frame for the 27 PSUs selected in 1999–2000

When NHANES was relaunched as a continuous survey starting in 1999, NHANES used the National Health Information Survey (NHIS) sampling frame. NHIS had divided the 50 U.S. states and D.C. into 4 panels that were individually considered to be representative of the entire country. NHIS took the first and second panel, and NHANES took the third and fourth panel, to avoid inadvertently burdening the same community with both surveys (*Curtin 2012*, *Botman 2000*).

Because persons of Mexican-American descent ("Mexican Americans") were the subdomain of interest in NHANES 1999–2000 who needed to be oversampled, the probability of PSU selection was not based solely on the PSU's population size but also on the local Hispanic population. The 27 PSUs ultimately selected for NHANES 1999–2000 were based on the U.S. Census projections for population size and

Hispanic origin proportions in 2000. As in previous cycles, every household within selected secondary sampling units was visited ("screened") to obtain age, gender, and race/ethnicity of each household member and determine which were eligible for participation in NHANES, but a change with this cycle was that households with multiple eligible participants were given priority for selection, in an effort to improve participation (i.e., to reduce unit nonresponse). Unlike NHANES 1971–1972, which excluded persons age >74, NHANES no longer had an upper age limit, but the oldest participants from 1999–2000 were all "topcoded" as 85 years old (*Curtin 2012*).

LTBI component of NHANES 1999–2000: a more diverse cohort born at any time during 1900s

Twenty-seven years after HANES-1, NHANES relaunched as a continuously operating survey in 1999. NHANES 1999–2000 represented the birth cohort born at any time during the 1900s, and still alive at the end of the century — an estimated target population of 268 million persons aged ≥1 year, with 71% of the noninstitutionalized civilian U.S. population classified as white non-Hispanic, 13% as black non-Hispanic, 12% as Hispanic, and 5% as some other non-Hispanic race (*Curtin 2012*, *NCHS 2006*, *Johnson 2012*).

During the 1970s–1990s, the U.S. population had grown from approximately 200 million to nearly 300 million, and the non-U.S.-born proportion of the population more than doubled from 4.7% (a historic low) to 11% of the U.S. population. Further, because of quota changes following the 1965 Immigration and Naturalization Act, there were fewer immigrants from Europe and Canada, and more immigrants from Asia and Africa. Immigration from Mexico and Central America also increased (*Schmidley 2003*, *Lollock 2001*, *Gibson 2006*). Meanwhile, a national resurgence of TB occurred and then began to subside (*CDC 2018a*).

All 8,832 examined NHANES 1999–2000 participants age ≥1 year were eligible for a TST (again using Dr. Siebert's PPD-S), but many children with otherwise complete examinations did not have TSTs placed, suggesting that guardians of young children tended to decline consent for that component of the examination (i.e., a different example of item nonresponse).

After the 2-year examination weights were applied, the 95% confidence interval for the national prevalence of LTBI was estimated as 4.2% (95% CI: 3.3% to 5.2%) with the original dataset, with the 95% confidence interval ranging 1.4% to 2.1% for the U.S.-born and 13.5% to 25.2% for the non-U.S.–born (*Bennett 2008*). When later reanalyzed to limit to those aged ≥6, the estimates were essentially identical: 3.5% to 5.3% overall, with the 95% confidence interval ranging 1.5% to 2.5% for the U.S.-born and 13.5% to 23.8% for the non-U.S.–born (*Miramontes 2015*). Similar estimates were also obtained by others examining the public-use dataset: 4.1% (95% CI: 3.3%–5.1%) for the overall population (*Khan 2008*).

Target population and sampling frame for the 28 PSUs selected in 2011–2012

For the 2011–2014 cycle, NHANES had developed its own sampling frame of 14 major strata, with California strata 21 and 22 forming their own "stage grouping" and the remaining states being sorted into 4 groupings based on overall health, with major strata 11–13 considered the most healthy and major strata 51–53 the least healthy (see NHANES appendix 3). The 3,143 U.S. county equivalents were nested within 2,846 PSUs, because 328 small counties were combined into groups of ≥3 and treated as a single PSU. Eight of the total 60 PSUs for the 4-year cycle were large metropolitan areas (covering 6 counties) that were selected "with certainty." The PSUs not selected with certainty were sequentially stratified and "serpentine sorted" by county characteristics including minority population and poverty concentrations until they formed 52 smaller strata; then one PSU was selected from each. Twenty-eight PSUs participated in 2011–2012 (*Curtin 2012*, *Johnson 2014*, *Paulose-Ram 2017*).

As in 1999–2000, households with multiple eligible participants were given priority for selection. Asians were the oversampled subdomain of interest in this cycle. Again, this NHANES cycle had no upper age limit, but now the oldest participants were "topcoded" as age 80 rather than 85 (*Johnson 2014*).

LTBI component of NHANES 2011–2012: widening disparity between U.S.- and non-U.S.-born

Between 2000 and 2010, approximately 14 million non-U.S.-born persons came to live in the United

States, pushing their proportion of the total U.S. population from the 11% in 2000 to 13% in 2010 (*Lollock 2001*, *Grieco 2012*). Meanwhile, annual TB disease incidence in the United States steadily declined but notably shifted to involve more non-U.S.-born persons, particularly from Mexico, the Philippines, Vietnam, India, and China (*CDC 2018a*). NHANES 2011–2012 was designed to represent an estimated projected target population of 282 million persons ages ≥6, with 63% of the noninstitutionalized civilian U.S. population classified as white non-Hispanic, 12% as black non-Hispanic, 17% as Hispanic, 5% as Asian non-Hispanic, and 3% as some other non-Hispanic race (*Johnson 2014*, *NCHS 2013a*). In contrast to many of their Hispanic and Asian counterparts, most U.S.-born participants had been born and still lived in U.S. counties and states where active TB disease incidence had been largely in decline their entire lives (*Scales 2014*).

Perhaps due to the TST item nonresponse pattern in NHANES 1999–2000, the age group eligible for a TST was increased to ≥6 years in NHANES 2011–2012. All 7,821 examined NHANES participants aged ≥6 years in 2011–2012 were eligible, but this time with Tubersol brand PPD instead of PPD-S. In addition, participants aged ≥6 years had blood drawn for the QuantiFERON-TB Gold In-Tube IGRA test.

After the participant weights were applied, the 95% confidence interval for the national prevalence of LTBI in the U.S. population aged ≥6 year was estimated as 3.4% to 6.3% overall, with the 95% confidence interval ranging 0.9% to 2.6% for the U.S.-born and 16.1% to 25.8% for the non-U.S.–born (*Miramontes 2015*). Similar estimates were also obtained by others examining the public-use dataset: 4.4% (95% CI: 3.1%–6.1%) for the overall population (*Mancuso 2016*).

Because these results showed no evidence to support the presumed continued decline in LTBI prevalence, they were considered a surprise (*Miramontes 2015*). In fact, compared to 1999–2000, an estimated net 2.6 million *more* persons in the United States had LTBI: while the estimated number of U.S.-born persons with LTBI had decreased from 4.2 million to 3.6 million, the estimated number of non-U.S.–born with LTBI had increased from 5.4 million to 8.1 million (*Miramontes 2015*).

CHAPTER 4 — NHANES missing data

Unit versus item nonresponse

Not all persons who are selected and invited to participate in surveys will agree to do so. *Unit* represents an entire record, when a subset of sampled participants do not participate in the interview and/or examination, causing an entire row in the dataset to be missing. Unit non-response requires further adjustment to the original design's base sampling weights (*Heeringa 2010*, *Rubin 1987*, *Little 2002*, *Allison 2002*). NCHS has a series of procedures that are applied to the NHANES datasets before their public release; participant weights provided in the public-use datasets are thought to have adequately addressed unit nonresponse (*Curtin 2012*, *Johnson 2014*, *Johnson 2012*, *NCHS 2013a*, *Chen 2018*, *Westat 1974*).

In contrast, each individual NHANES analyst must determine how to address any *item* nonresponse for their outcome of interest. Item nonresponse occurs when someone who agrees to participate in a survey does not answer every interview question or does not participate in all aspects of the examination. The record/row for that participant will be present in the dataset, but one or more of variables/columns will be missing. Unless items are missing completely at random, item nonresponse can introduce bias (*Rubin 1987*, *Little 2002*, *Allison 2002*, *Perkins 2018*).

As introduced in the previous chapter and addressed in more detail with aim 2, missing TST results are an analytic problem in NHANES, affecting approximately 1 in 5 of the records that should have had a TST result. Further, the reasons for TST item nonresponse appear to differ across cycles (i.e., late examination timing and Midwest geography in NHANES 1971–1972; younger age in NHANES 1999–2000; and older age, Asian race, and personal TB history in NHANES 2011–2012).

NHANES design strategies to improve participation: increasing amounts of remuneration and preferential selection of households with multiple eligible participants

The original 1971 NHANES protocol was to offer "a free health examination at our special examination center" without any remuneration. Following what was deemed insufficient participation at the first 18 stands, a demonstration project showed that $10 helped increase MEC exam participation from 70% to 82%. Consequently, starting in March 1972, remuneration became standard for the remaining 15 stands (*NCHS 1975*). All NHANES 1999–2000 and 2011–2012 participants also received reimbursement of up to $70 for transportation, up to $31.50 for child/elder care, and up to $125 as "a token of thanks for your time and effort"; additional remuneration of $30 was given if they returned for TST readings (*Zipf 2012*).

Citing increased response rates from multiple-participant households during the 1982–1984 and 1988–1994 cycles, NHANES has changed its fourth sampling stage to increase the number of participants per household. Starting in 1999, NHANES sampling preferentially selects households with more than one eligible participant (*Curtin 2012*, *Johnson 2014*, *Zipf 2012*).

Differential nonparticipation (unit nonresponse) across race/ethnic subdomains

NCHS has noted that Hispanic participants, as a group, have better participation (i.e., lower unit nonresponse) than white and black non-Hispanic participants (*Paulose-Ram 2017*). On the other hand, despite having bilingual Asian staff and translating NHANES materials into Mandarin, Korean, and Vietnamese, the plan to oversample Asians in 2011–2012 required more extensive household screening efforts than had been anticipated. In spite of these efforts, Asian participants had the lowest participation (i.e., highest unit nonresponse), so their individual participant weights received proportionally more adjustment for nonparticipation (*Johnson 2014*, *Paulose-Ram 2017*).

As will be discussed in chapter 7, not only was there Asian *unit* nonresponse in 2011–2012, differential nonparticipation by Asians might have also extended to *item* nonresponse for the TST component of the medical examination (see **Aim 2 Table 1**).

Differential nonparticipation (unit nonresponse) based on income level

Refusal to participate in NHANES dates back to the early 1970s, when despite >98% participation in the household interview, only 74% of persons invited to participate in NHANES were also examined. Additionally, concern about poor response rates led NHANES to commission a follow-up study of the potential nonresponse bias, which traced 116 interviewed but unexamined persons from 1971–1972 substudy and asked why they did not return. Most explained that they did not perceive the "need" for a physical exam, and others cited competing schedule demands. Only 9% did not return because of illness or fear of results (*Westat 1974*).

Because within 5 broad income strata, self-reported health problems were similar between the examined and unexamined participants, the investigators concluded that the effect of nonresponse could be controlled by correspondingly increasing the weights of examined persons in the same income category (i.e., the assumption was that within each income category, examined and unexamined respondents were exchangeable) (*Westat 1974*). Adjustment for this unit nonresponse was thus based on 5 levels of income, where the base sampling weights were multiplied by the reciprocals of the probability of selection for each of those income levels (*Landis 1982*).

Additionally, concern about unexpectedly poor interview acceptance rates in 2011–2012 (i.e., 73%, as compared with 82% in 1999–2000 and >98% in 1971–1972) led NHANES to commission a follow-up study of the potential nonresponse bias. That nonresponse analysis similarly concluded that the characteristics "significantly related to response status were either used or highly correlated with those used in the weighting adjustments" and that "the weighting adjustments reduced this bias" (*NCHS 2013a*).

Patterns of item nonresponse: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR)

Across all 3 NHANES cycles, TST results were not recorded for approximately 1 in 5 examined participants within the age groups eligible for a TST. To assess whether item nonresponse has introduced bias or just imprecision, trying to discern the reasons that TST results are missing is important. In 1976, the statistician Donald Rubin introduced these 3 concepts as explaining item nonresponse, and they continue to be standard (*Rubin 1987*, *Little 2002*, *Allison 2002*, *Perkins 2018*, *NRC 2010*, *Little 2012*).

- *MCAR, missing completely at random*, where the missing TST is solely attributable to study-related logistical issues (e.g., inclement weather or power failure), and not associated with what the TST result would have been **or** to any participant characteristics. With this extreme but unlikely explanation, a complete-case analysis (simply dropping from the analysis all the records with missing TST results) does not introduce bias, but statistical precision is lost (*Rubin 1987*, *Little 2002*, *Allison 2002*).

- *MAR, missing at random*, where the missing TST is attributable to measured participant-related factors such as young age, rather than being related to what the TST would have been. When this assumption for the missing data mechanism is invoked, the analyst is asserting that other measured characteristics in the dataset (covariates) can predict both missingness and what the unobserved TST results would have been. In that way, the analyst can control for any bias created by the patterns of missingness. Creating higher weights for the participants with missing TST results is one example of invoking the MAR assumption; this approach was typically used in previous analyses of TST results in NHANES (*Bennett 2008*, *Miramontes 2015, Mancuso 2016*, see **Aim 2 Figure** footnotes for details). Multiple imputation is another potential approach (*Rubin 1987*, *Little 2002*, *Allison 2002*, *Perkins 2018*, *Berglund 2014*, *Schafer 2014*, *Harel 2018*) and will be used in aim 2.

- *MNAR, missing not at random*, where the missing TST **is** related to what the TST result would have been, had it been measured and recorded in the dataset. Determining whether data are MNAR is not possible with only the observed data. Sensitivity analyses, including imputation of extreme scenarios, are the preferred approach to examine the degree to which a MNAR missing data mechanism might have introduced bias (*Rubin 1987*, *Little 2002*, *Allison 2002*, *Perkins 2018*, *NRC 2010*, *Little 2012*) and will also be used in aim 2.

Missing TST results (21% item nonresponse) in NHANES 1971–1972

As previously explained, TSTs were going to be part of the HANES-1 examination of adults at all 65 PSUs in the full 4-year cycle, but the TST component ceased after 35 PSUs. The same 4 staff nurses placed and read 80% of the TSTs between April 27, 1971, and October 5, 1972 (*Engel 1977*). Of the 1,891 examined NHANES participants aged 25–74 in the 35 PSUs where a TST was part of the medical examination, 1,494 (79%) had a valid TST result.

As in later NHANES cycles, the 1971–1972 survey procedures allowed for TST readings to be performed offsite, such as homes or workplaces, to improve participation. In 1971–1972, at least 11% of readings occurred offsite. Among the 397 participants with missing TST results, just under a third, or 124 (31%), were "not given the test because their examination was done a day or two before the mobile examining unit was scheduled to move to the next location and survey personal would not have been available to read the reaction" (*Engel 1977*). Explanations for the other 273 were that a TST was placed, but the participant did not return for the reading (96 participants), or the participant refused the initial TST placement due to an anticipated inability to return for the reading (140 participants). A small number also had a history of TB disease (9 participants) or declined because of a previous positive TST (28 participants) (*Engel 1977*). As the missing data and NHANES 1971–1972 appendix (created with public-use data) also shows, among adults with otherwise complete examinations, Midwest study locations 7 and 16 had unexplained high

proportions of missing TST results. Other examined persons missing proportionately more TST results in NHANES 1971–1972 included persons aged 25–34 years (compared to older age groups) and black (compared to white) participants.

In general, the 1,494 participants with valid TSTs appeared demographically more similar to the 124 missing TSTs toward the end of a stand than to the 273 missing TSTs at earlier dates, seeming to support a hypothesis that the 124 could be *missing completely at random* — affecting precision but not introducing bias.

Missing TST results (16% item nonresponse) in NHANES 1999–2000

In NHANES 1999–2000, the staff who placed the TSTs (phlebotomists) were different from those who read them (technicians). All 8,832 examined participants aged ≥1 year during the 1999–2000 cycle were eligible for a TST; 7,386 (84%) had a valid TST result.

Unlike 1971–1972, there are no documented reasons that 1,219 examined persons aged ≥1 did not have a TST placed in 1999–2000 (see **Aim 2 Table 1**). Survey procedures again allowed for TST readings to be performed offsite, such as homes or workplaces, to improve participation, but whether readings occurred offsite is not in the public-use datasets, nor is examination date. Analysis performed with restricted data in the NCHS Research Data Center for this dissertation (i.e., RDC proposal Haddad 1554) ruled out having an examination scheduled toward the end of a "stand" in a county as being associated with not having a TST placed (i.e., TST completeness was uniform across the entire time in the county).

However, as **Aim 2 Table 1** demonstrates, nearly one third of examined children aged 1–5 years during NHANES 1999–2000 did not have a TST placed, even though it was in the examination protocol to offer a TST to this age group. (No TST placement was inferred by the lack of *any* response to the question, "Have you ever had a severe reaction to a TB skin test?" [TBQ070], which was supposed to be asked just before the TST was placed during the medical examination.) In addition, simply having a self-reported history of a positive TST (ascertained during the previous interview, "Have you ever been told that had a

positive TB skin test?" [TBQ020]) was not supposed to be a contraindication to having a TST placed for NHANES. Nevertheless, only 73% of persons who said yes to having had a previous positive TST had a recorded TST result in NHANES 1999–2000.

Missing TST results (22% item nonresponse) in NHANES 2011–2012

Again in NHANES 2011–2012, the staff who placed the TSTs (phlebotomists) were different from those who read them (technicians). All 7,821 examined participants aged ≥6 years during the 1999–2000 cycle were age-eligible for a TST; 6,128 (78%) had a valid TST result. Even with the exclusion of children aged 1–5 years in this cycle, having 22% TST item nonresponse was considerably worse than the 16% in NHANES 1999–2000.

Again in this cycle, there are no documented reasons for 1,384 examined persons aged ≥6 not to have TSTs placed (see **Aim 2 Table 1**). Whether readings occurred offsite is not in the public-use datasets, nor is examination date. However, analysis performed with restricted data (i.e., RDC proposal Haddad 1554) again ruled out having an examination scheduled toward the end of a "stand" as being associated with not having a TST placed.

But one notable change from 1999–2000 is evident. Again, the survey protocol was to ask all examinees, "Have you ever had a severe reaction to a TB skin test?" [TBQ070], just before the TST was placed. When this question had been asked 7,613 times during NHANES 1999–2000 cycle, no participant had ever said yes. In 2011–2012, 87 participants said yes, so no TST was placed; oddly, only 45 of those 87 had said yes some days earlier when asked about *any* history of a positive TST [TBQ020]. In total, only 65% of persons with a self-reported previous positive TST had a valid TST result in NHANES 2011–2012.

CHAPTER 5 — Development of external validation dataset for use in aim 1

Note: a published manuscript corresponding to a shorter version of this chapter is in the public domain (Haddad 2018).

3,143 county equivalents in the United States

The 50 U.S. states and District of Columbia partition into 3,143 U.S. county equivalents, of which approximately 28–30 participate in each 2-year NHANES cycle. Aim 1 of this dissertation relied on several non-NHANES data sources to develop an external validation dataset for examining the representativeness with respect to TB of the counties selected to participate in NHANES in 1971–1972, 1999–2000, and 2011–2012. This external dataset was then used within the Research Data Center (i.e., RDC proposal Haddad 1520, see Aim 1 appendix 1).

County population size in 1970

The source for this variable in the county dataset is the U.S. Census Bureau (co-asr-1970 file).

County population size in 2000

For this variable in the county dataset, resident population size on April 1, 2000, came from the U.S. Census of Population and Housing, Table B-1 (co-est000int-01 file). The Current Population Survey provided an enumeration of both the U.S.-born and non-U.S.-born residents of all 3,153 county equivalents.

County population size in 2010

For this variable in the county dataset, population size on April 1, 2010, was the "estimates base" from the U.S. Census Bureau, Population Division. In contrast to 2000, the Current Population Survey provided an estimate of the non-U.S.-born population size for only 801 counties, so an imputed # of non-U.S.-born persons for the other counties was calculated as (proportion of 2000 county population that was non-U.S.-born) x (total 2010 population).

U.S. Department of Agriculture Rural-Urban Continuum Codes

The U.S. Department of Agriculture published Rural-Urban Continuum Codes for U.S. counties in 1974, 1993, 2003, and 2013. To classify the 3,143 U.S. counties as urban or rural at the time of the three NHANES cycles, these Rural-Urban Continuum Codes were dichotomized (i.e., Codes 4–9 considered rural and Codes 0–3 considered metropolitan). However, due to changes to the metropolitan-nonmetropolitan and urban-rural criteria that were implemented after the 2000 Census, the 1974 and 1993 Rural-Urban Continuum Codes are not directly comparable to those in 2003 and 2013.

U.S. Census Bureau Small Area Income and Poverty Estimates

The U.S. Census Bureau used Small Area Income and Poverty Estimates to summarize what proportion of a county's population was living in poverty in 1999 and 2011. For 1971, poverty was estimated for only certain counties, so state poverty rate was used in the external dataset.

National TB Surveillance System (NTSS)

Since 1953, health departments in the 50 states and District of Columbia have reported verified cases of active TB disease (i.e., meeting the CDC and Council of State and Territorial Epidemiologists case definition) to the NTSS. Essentially a national TB registry, NTSS collects clinical, demographic, and risk factor data for all reported TB cases in the United States.

CDC's Division for Tuberculosis Elimination works closely with U.S. Census Bureau's postcensal resident population data when creating denominators for annual TB incidence, which is defined as "per 100,000" population by international convention. Unlike NHANES, the NTSS does not exclude the institutionalized or military population from the population denominators. All persons born outside the United States to parents who are not U.S. citizens are considered "non-U.S.-born," regardless of current U.S. residency status. To be counted as having a TB case in the United States, persons must have been or plan to remain in the United States for at least 3 months.

Method for estimating LTBI prevalence

The National TB Surveillance System contains 48,955 verified TB disease cases for 2011–2015. In the subset of 37,723 cases that were confirmed by culture (77.1% of the total), 36,104 (95.7%) had an *M. tuberculosis* isolate genotyped through the National TB Genotyping Service. We used each county's U.S. Census 2010 population denominator, annual TB disease incidence averaged over 2008–2015, and the assumptions described below to derive an estimated prevalence of LTBI among the residents of each county or county equivalent (i.e., Alaska boroughs, District of Columbia, Louisiana parishes, and Virginia independent cities).

For the 1,360 counties with zero genotyped TB cases during those 5 years, corresponding to 8% of the U.S. population, we estimated local LTBI prevalence as <1%. For the other counties, our assumptions were that all genotyped TB cases not attributed to recent *M. tuberculosis* transmission arose from preexisting LTBI and that the same recent versus preexisting proportions among genotyped cases would apply to each county's nongenotyped TB cases. The previously field-validated plausible source-case method (*France 2015*, *Yuen 2016*, *CDC 2018a*) was used to attribute cases to recent transmission (i.e., plausible source case within 10 miles within previous 2 years having infectious TB and the same spoligotyping and 24-locus mycobacterial interspersed repetitive unit–variable number tandem repeat typing results) for the District of Columbia and 49 U.S. states. All cases diagnosed in non-U.S.-born persons within 100 days of entry into the United States were excluded, because the presumption was that these cases did not represent infection acquired in the United States, even if their *M. tuberculosis* genotype happened to match that of another TB case within 10 miles of their current U.S. residence. Because some Oklahoma cases were missing geographic identifiers such as zip code that are used for identifying the 10-mile radius, a modification for Oklahoma cases in this analysis was that the plausible source case could have occurred anywhere in the same county.

Based on *Shea 2014*'s estimate of approximately 0.084 cases of reactivation TB per 100 person-years among U.S. residents with LTBI, we then applied a uniform 0.10% annual risk of progression to active disease to derive an estimated number of county residents with LTBI. [Chapter 5 note: because of *Emerging*

Infectious Diseases limitations on the number of permitted references, only *Shea 2014* is listed in support of the assumption of 0.1% annual risk of reactivation; other references that could have been included as support for this assumption are *Horsburgh 2004*, *Menzies 2018*, and *Mirzazadeh 2018*.]

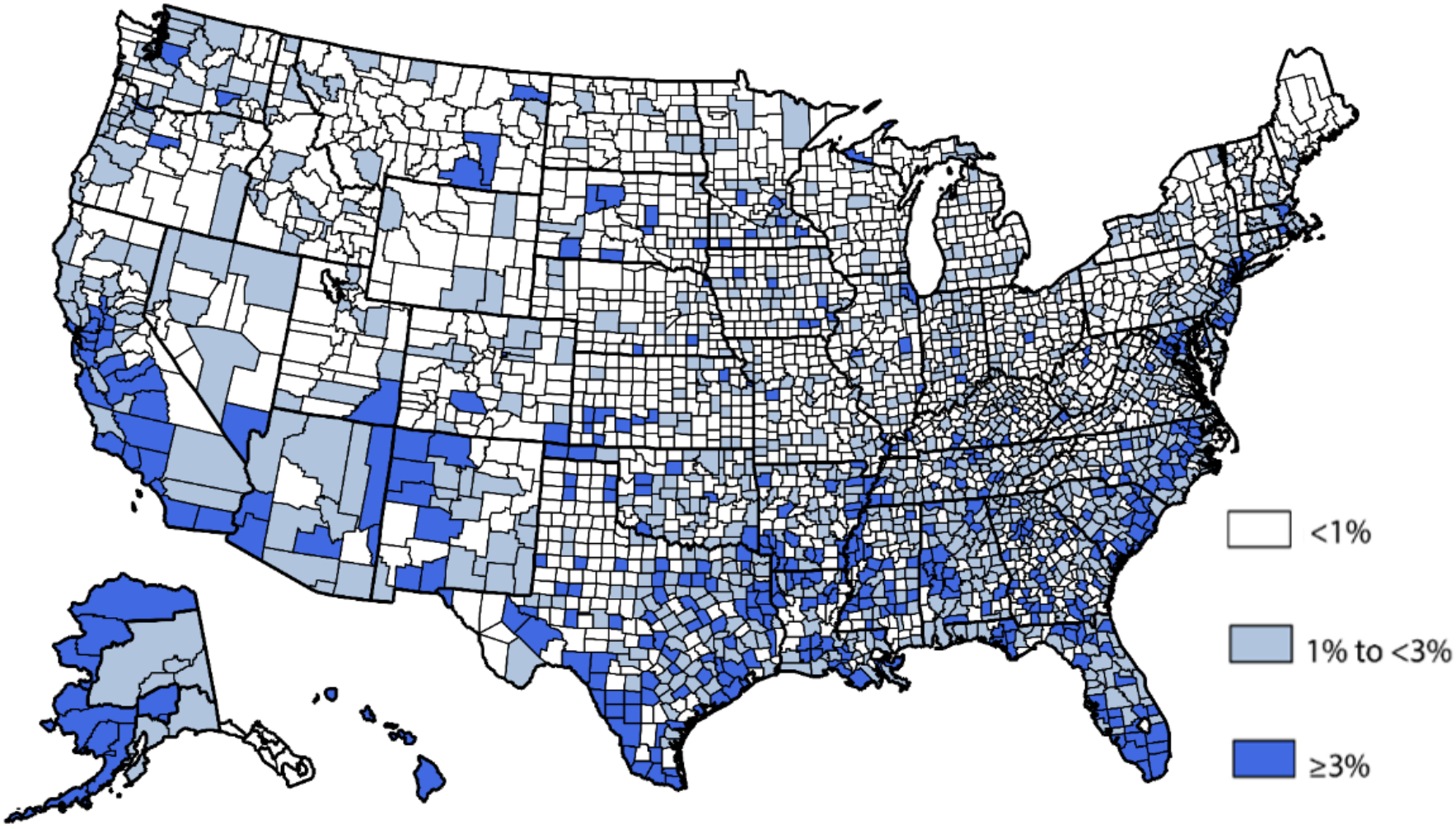
As sensitivity analyses, we examined how that LTBI prevalence estimates would decrease with a higher 0.14% uniform annual risk and how estimates would increase with a lower 0.06% uniform annual risk (*Shea 2014*); these are presented as uncertainty limits. We provide the formula and examples of this method in Aim 1 appendix 2.

County-level LTBI prevalence estimates

We estimated that 3.1% (uncertainty limits 2.2%–5.2% based on higher or lower annual risk assumptions) of the U.S. population, corresponding to 8.9 (6.3–14.8) million persons, were latently infected with *M. tuberculosis* during 2011–2015. County-level estimates varied widely, with an estimated LTBI prevalence of <1% in 1,981 counties, 1% to <3% in 785 counties, and ≥3% in 377 counties (**Map**). In 146 (72%) of the 202 rural counties and 62 (35%) of the 175 metropolitan counties with an estimated LTBI prevalence ≥3%, at least a fifth of the county population lives in poverty, as defined by the U.S. Census Bureau's Small Area Income and Poverty Estimates (**Table**).

National map of county-level LTBI prevalence estimates.
Estimated prevalence of latent *Mycobacterium tuberculosis* infection, by U.S. county (or equivalent), as derived from genotyped cases of tuberculosis disease reported to the U.S. National Tuberculosis Surveillance System during 2011–2015.

This public domain figure appears in Haddad MB, Raz KM, Lash TL, Hill AN, Kammerer JS, Winston CA, Castro KG, Gandhi NR, Navin TR. Simple estimates for the local prevalence of latent tuberculosis infection, United States, 2011–2015. *Emerg Infect Dis* 2018; 24(10): 1930–1933.



Selected characteristics of the 1,976 rural and the 1,167 metropolitan U.S. counties by estimated prevalence of latent *Mycobacterium tuberculosis* infection — United States, 2011–2015.

This public domain table appears in Haddad MB, Raz KM, Lash TL, Hill AN, Kammerer JS, Winston CA, Castro KG, Gandhi NR, Navin TR. Simple estimates for the local prevalence of latent tuberculosis infection, United States, 2011–2015. *Emerg Infect Dis* 2018; 24(10): 1930–1933.

	1,976 rural counties*					
County* characteristic	1,454 with estimated prevalence of <1%		320 with estimated prevalence of 1% to <3%		202 with estimated prevalence of ≥3%	
U.S. Census 2010						
Total combined population of counties in this column	28,727,127		11,750,121		5,816,158	
Median county population (rounded to thousands)	13,000		32,000		23,000	
Estimated prevalence of *M. tuberculosis* infection						
Total No. estimated infected in all counties in column	126,140		191,707		329,547	
Median No. estimated infected per county	0		500		1,112	
Proportion of county population living in poverty†, No. (%)						
<10%	95	(7)	13	(4)	2	(1)
10%–15.5%	564	(39)	78	(24)	29	(14)
15.6%–19.9%	378	(26)	95	(30)	25	(12)
≥20%	417	(29)	134	(42)	146	(72)
Race/ethnic group in county with the largest number of active tuberculosis cases reported in 2011–2015, No. (%)						
Black non-Hispanic	81	(15)	42	(13)	60	(30)
White non-Hispanic	241	(45)	109	(34)	34	(17)
Hispanic	74	(14)	58	(18)	60	(30)
Alaska Native/Native American or Pacific Islander	36	(7)	14	(4)	15	(7)
Asian	43	(8)	24	(8)	8	(4)
No one race/ethnic group predominated in case counts	979	(67)	73	(23)	24	(12)
	1,167 metropolitan counties*					
County* characteristic	527 with estimated prevalence of <1%		465 with estimated prevalence of 1% to <3%		175 with estimated prevalence of ≥3%	
U.S. Census 2010						
Total combined population of counties in this column	37,413,210		115,341,399		109,697,523	
Median county population (rounded to thousands)	38,000		144,000		291,000	
Estimated prevalence of *M. tuberculosis* infection						
Total No. estimated infected in all counties in column	212,563		2,300,435		5,772,136	
Median No. estimated infected per county	124		2,376		12,388	
Proportion of county population living in poverty†, No. (%)						
<10%	112	(21)	63	(14)	25	(14)
10%–15.5%	221	(42)	171	(37)	30	(17)
15.6%–19.9%	124	(24)	144	(31)	58	(33)
≥20%	70	(13)	87	(19)	62	(35)

Race/ethnic group in county with the largest number of active tuberculosis cases reported in 2011–2015, No. (%)						
Black non-Hispanic	45	(14)	86	(18)	57	(33)
White non-Hispanic	142	(44)	110	(24)	17	(10)
Hispanic	25	(8)	82	(18)	43	(25)
Alaska Native/Native American or Pacific Islander	8	(2)	8	(2)	3	(2)
Asian	48	(14)	118	(25)	46	(26)
No one race/ethnic group predominated in case counts	259	(49)	61	(13)	9	(5)

* Or county equivalents (i.e., Alaska boroughs, District of Columbia, Louisiana parishes, and Virginia independent cities). U.S. Department of Agriculture 2013 Rural-Urban Continuum Codes were dichotomized (i.e., Codes 4–9 considered rural and Codes 0–3 considered metropolitan).

† County's all-ages poverty level in 2011 as determined by the U.S. Census Bureau's Small Area Income and Poverty Estimates.

Conclusions about county-level LTBI prevalence estimates

We used routinely collected TB surveillance and genotyping data to derive LTBI prevalence estimates for all U.S. counties. Preventing TB is a growing focus of TB control strategies both in the United States and internationally. As governments, public health departments, and private sector partners intensify TB prevention activities, having a tool to understand local variations in LTBI prevalence could help prioritize resources (*Taylor 2005*, *USPSTF 2016*, *WHO 2018*).

This new method (Aim 1 appendix 2) for estimating LTBI prevalence is designed to be simple. By excluding the contribution of any TB cases attributed to recent transmission, our estimates disregard the small number of recent infections and instead draw attention to more longstanding LTBI prevalence. Because time since initial *M. tuberculosis* infection was unknown, a uniform population-level 0.10% annual risk of experiencing progression to active disease was assumed. Changing that uniform risk to 0.14% or 0.06% would have changed the number of counties with an estimated LTBI prevalence of ≥3% to 113 or 516 counties, respectively. A more sophisticated approach to estimate local LTBI prevalence might consider individual characteristics and differentiate risk of progression based on HIV status, age group, and possibly geographic region, nativity, and recent migration (*Shea 2014*). For example, a person receiving a TB diagnosis soon after arrival in a county would increase the LTBI prevalence estimates for that county, even if the TB was caused by an infection that had been acquired in another jurisdiction. On the other hand, our overall estimate that 2.2%–5.2% of the U.S. population is infected is similar to estimates from the 2011–2012 National Health and Nutrition Examination Survey (*Miramontes 2015, Mancuso 2016*).

In the United States, the last published nationwide county-level estimates of LTBI prevalence are based on 1958–1965 data, when 275,558 white men aged 17–21 years who had lived all their lives in one county were examined as they entered the U.S. Navy. Men from poor counties in the U.S. Southwest and Appalachian Mountains were more likely to have positive tuberculin skin test results (*Edwards et al. 1969*). Compared with those estimates of 5 decades ago, our estimates show a more diffuse pattern of higher LTBI

prevalence counties (**Map**). However, poverty remains a frequent characteristic of counties that we estimated as having higher LTBI prevalence.

This simple method for deriving an estimate of LTBI prevalence has limitations. We applied the county's proportion of genotyped TB cases estimated to arise from preexisting LTBI to all the county's nongenotyped TB cases. This proportion could overestimate the prevalence of LTBI in counties with many pediatric TB cases, which tend to be more difficult to confirm via culture techniques (i.e., cannot be genotyped), yet are sentinel events for recent transmission. Conversely, the routine genotyping methods (spoligotyping and 24-locus mycobacterial interspersed repetitive unit–variable number tandem repeat typing) used during 2011–2015 may have overestimated recent TB infections (i.e., underestimated LTBI prevalence) in certain localities with longstanding genotyping clusters; this limitation should diminish as the National TB Genotyping Service transitions to universal whole-genome sequencing in 2018.

This method for estimating LTBI prevalence also has several advantages. The simple approach could be applied in jurisdictions without TB genotyping services given an assumption or range of assumptions about the jurisdiction's proportion of active TB cases arising from LTBI and, if deemed applicable, an adjustment for underreported TB cases. Rather than relying on costly and imperfect LTBI screening methods, its starting point is verified cases of TB disease that are already routinely reported to established TB surveillance systems. Most importantly, these reported cases represent infected persons who progressed to active TB disease — the populations most likely to benefit from interventions to prevent future TB cases.

CHAPTER 6 — Aim 1: GEOGRAPHIC REPRESENTATIVENESS

This manuscript completed CDC clearance in September 2018 and is being submitted for publication.

Influence of geography on national estimates of *M. tuberculosis* infection prevalence

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Aim 1 Abstract

Objectives. To examine how county sampling might have influenced national estimates of LTBI prevalence.

Methods. After stratifying U.S. counties (or equivalents) based on population size and composition, rural versus urban classification, and poverty prevalence, we compared TB disease incidence and genotyping-derived estimates of LTBI prevalence between the counties selected and not selected for NHANES participation in 1971–1972, 1999–2000, and 2011–2012. Each county's genotyping-derived LTBI prevalence estimate was also compared to the unweighted prevalence of a positive TST among that county's NHANES participants in 2011–2012.

Results. After accounting for demographic differences, tuberculosis disease incidence and estimated LTBI prevalence were similar between selected and nonselected counties. In the selected counties, 90% of the genotyping-derived estimates of LTBI prevalence were within 1% of the unweighted prevalence of a positive TST.

Conclusions. This analysis reinforces confidence in estimates of national LTBI prevalence that are based on these 3 NHANES cycles.

Aim 1 Background

Geographic heterogeneity is a hallmark of TB epidemiology in the United States (*Cherng 2018*, *CDC 2018a*). Intake examinations among US Navy recruits in 1958–1969 and 1990 and more recent genotyping-derived estimates suggest that the prevalence of LTBI also varies by U.S. state and by county within states (*Edwards et al. 1969*, *Comstock 1974a*, *Trump 1993*, *Haddad 2018*).

In the United States, annual incidence of TB disease declined from 17.0 cases per 100,000 persons in 1971 to 3.2 cases per 100,000 in 2012 (*CDC 2018a*). During that 42-year time span, NHANES provided data to estimate LTBI prevalence among the U.S. noninstitutionalized civilian population 3 times. Based on NHANES TST results in 1971–1972, the estimated prevalence of LTBI among adults aged 25–74 years was 11%–18% (*Engel 1977*). In NHANES 1999–2000 and 2011–2012, estimated LTBI prevalence among persons aged ≥6 years was 3%–6% (*Bennett 2008*, *Miramontes 2015*).

A single 2-year NHANES cycle may no longer be sufficient for reliably estimating LTBI prevalence (*Curtin 2006*). The National Center for Health Statistics advises researchers to combine sequential NHANES cycles "for rare events. . . .and for measures that may have considerable geographic variation" (*Curtin 2012*, pp. 2–3). NHANES is designed to be nationally representative; in the first stage of the 4-stage probability sampling process, approximately 30 individual counties or groups of adjacent counties are selected for each 2-year cycle (*Curtin 2012*). If persons in the counties selected for NHANES participation were systematically more or less likely to have a positive tuberculin skin test than their counterparts in the rest of the national sampling frame, NHANES-based estimates might not be as nationally representative for LTBI as they are for more common health conditions. Because this hypothesis cannot be tested with NHANES data alone, we combined masked NHANES data with non-NHANES TB data to examine how county sampling might have influenced national LTBI prevalence estimates.

Aim 1 Methods

Creation of dataset with non-NHANES variables for each county

Demographic characteristics pertinent to TB. The U.S. Census Bureau and U.S. Department of Agriculture websites provided variables to create demographic profiles for all 3,143 U.S. county equivalents. These included population size and composition, rural versus urban classification, and poverty prevalence for 1970 through 2013.

Reported TB disease incidence. By international convention, annual TB disease incidence is defined per 100,000 population (*CDC 2018a*). Using National TB Surveillance System data, we determined each county's average annual TB disease incidence during 1999–2000 and during 2011–2012. County-level incidence is not calculable nationally until 1993 and later, so we used state-level incidence for 1971–1972.

Genotyping-derived LTBI prevalence estimates. We used genotyping results from the National TB Surveillance System data to derive an estimate of LTBI prevalence for each county (*Haddad 2018*). Median estimated LTBI prevalence among the US-born was 0.7% (lower and upper quartiles: 0.4%, 1.3%) and among the non-US–born was 13.1% (lower and upper quartiles: 8.8%, 18.5%), similar to previous national NHANES-based estimates (*Bennett 2008*, *Miramontes 2015*).

Access to restricted data

Because of disclosure risk, county of residence is restricted and not included in the NHANES public-use datasets. Following Research Data Center procedures (https://www.cdc.gov/rdc/), the National Center for Health Statistics allowed us to submit the non-NHANES county dataset to merge with county-masked NHANES data. We also provided the NHANES 1971–1972, 1999–2000, and 2011–2012 public-use datasets, which we had obtained from https://www.cdc.gov/nchs/nhanes/. Using the restricted county of residence

variable as the matching variable, Research Data Center staff merged the datasets and then removed the county identifiers.

Masked analysis of the TB experience in selected versus not selected counties

All subsequent analysis took place with the merged, deidentified datasets within the Research Data Center (i.e., RDC proposal Haddad 1520). We examined how reported TB disease incidence and estimated LTBI prevalence compared between counties selected and not selected for NHANES participation. We grouped counties into discrete categories based on population size and composition, rural versus urban classification, and poverty prevalence, within which we executed a series of statistical tests for differences in mean TB disease incidence and mean estimated LTBI prevalence. Nonsignificant differences in mean values between counties within demographically similar strata were interpreted as equivalent TB experiences between selected and nonselected counties in 1971–1972, 1999–2000, and 2011–2012.

Comparison of non-NHANES genotyping-derived LTBI prevalence estimates with NHANES TST results

NHANES participants are selected and weighted to be nationally representative. Because participants were never selected with the intention that they be representative of their individual counties, we considered them to be only a convenience sample from that county. These convenience samples were used for an approximate assessment of the validity of the genotyping-derived LTBI prevalence estimates for that county. Within each county selected for NHANES 2011–2012 participation, we determined the unweighted prevalence of a positive tuberculin skin test (i.e., public-use dataset result ≥10 mm of induration) among participants with skin test results.

Aim 1 Results

The demographics of the counties selected for NHANES participation in 1971–1972, 1999–2000, and 2011–2012 were similar across time, except that the counties selected in 2011–2012 had higher proportions of residents living in poverty, consistent with the recent national trend.

Among the counties selected for NHANES 1999–2000, median annual TB disease incidence was 4.9 cases per 100,000 persons, while national TB incidence was 6.3 per 100,000 in 1999 and 5.8 per 100,000 in 2000 (*CDC 2018a*). Among the counties selected for NHANES 2011–2012, median annual TB disease incidence was 3.6 cases per 100,000, while national TB incidence was 3.4 per 100,000 in 2011 and 3.2 per 100,000 in 2012 (*CDC 2018a*). Within strata of counties with similar population size, composition, rural versus urban classification, and poverty prevalence, mean TB disease incidence was similar between the selected and nonselected counties ($p > 0.05$ for each test of equivalence).

In 90% of the counties selected for NHANES 2011–2012, the genotyping-derived LTBI prevalence estimates (*Haddad 2018*) were within 1% of the unweighted prevalence of a positive tuberculin skin test among the NHANES participants from that county with skin test results.

Aim 1 Discussion

No published analysis is available of how the NHANES geographic sampling process might have influenced national LTBI prevalence estimates. We found no evidence that counties selected in 1971–1972, 1999–2000, and 2011–2012 had different TB experiences (i.e., reported TB incidence or estimated LTBI prevalence) from the counties that were not selected for NHANES participation. Our findings also imply that genotyping-derived estimates of county-level LTBI prevalence could continue to prove useful in the future (*Haddad 2018*).

This analysis reinforces confidence in national LTBI prevalence estimates based on previous NHANES cycles. However, both the low prevalence (≤6%) and geographic heterogeneity of this condition in the United States suggest that incorporating TB-related components into future NHANES cycles for >2 consecutive years would help achieve more stable population estimates (*Curtin 2006, Curtin 2012*, *Johnson 2012*).

CHAPTER 7 — Aim 2: ADDITIONAL PARTICIPANT FACTORS

Robustness of NHANES estimates of the U.S. prevalence of a positive tuberculin skin test

This manuscript completed CDC clearance in September 2018 and is being submitted for publication.

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Aim 2 Abstract

Background: A single 2-year National Health and Nutrition Examination Survey (NHANES) cycle is designed to provide accurate and stable estimates of conditions with prevalence of at least 10%. Recent NHANES-based estimates of a tuberculin skin test (TST) ≥10 mm in the noninstitutionalized U.S. civilian population are at most 6.3%.

Methods: NHANES included a TST in 1971–1972, 1999–2000, and 2011–2012. We examined the robustness of NHANES-based estimates of the U.S. population prevalence of a TST ≥10 mm with an analysis that considered the influence of the selection of multiple participants per household, reclassified borderline-positive TST results, adjusted for TST item nonresponse, and reweighted for non-U.S. birth distributions.

Results: We found no evidence of bias due to the selection of multiple participants per household. Prevalence estimates changed 0.3% with reclassification of borderline-positive TST results and 0.2%–0.3% with adjustment for TST item nonresponse. The weighted non-U.S. birth distribution among NHANES participants was similar to that in the overall population; further adjustment was unnecessary.

Conclusions: For estimating the national prevalence of a TST ≥10 mm during these 3 survey cycles, a conventional NHANES analysis using the masked design parameters and 2-year examination participant weights that are provided in the public-use datasets appears robust.

Aim 2 Background

Although it is fundamentally a general health and nutrition survey, the National Health and Nutrition Examination Survey (NHANES) can add infectious disease components, such as tuberculosis (TB), to a 2-year survey cycle. A tuberculin skin test (TST) was part of NHANES 1971–1972, 1999–2000, and 2011–2012 (*Engel 1977*, *Bennett 2008*, *Khan 2008*, *Miramontes 2015*, *Mancuso 2016*), leading to estimates that between 3.1% and 6.3% of the noninstitutionalized U.S. civilian population were latently infected with *Mycobacterium tuberculosis* in 1999–2000 and 2011–2012 (*Bennett 2008*, *Khan 2008*, *Miramontes 2015*, *Mancuso 2016*). However, a single 2-year NHANES cycle is designed to provide accurate and stable estimates of conditions with ≥10% prevalence (*Johnson 2012*, *Curtin 2006*). Furthermore, a conventional NHANES analysis accounts for correlations of health outcomes within primary sampling units (i.e., typically single counties), but does not account for correlations within later sampling stages, such as households. NHANES participants are selected at established rates to ensure that target sample sizes for predetermined analytic subdomains (based on gender, age, and race/ethnicity) are achieved. A method of subsampling is also used that maximizes the number of sampled participants per household. Because most NHANES analyses are done within the subdomains, within-household clustering at the subdomain level is considered generally small (*Curtin 2012*, *Johnson 2014*). However, this might not be the case for TB, where same-household NHANES participants might have correlated latent TB status. Additionally, sample weights account for the participant's gender, age, and race/ethnicity, but do not account for birth outside the United States, which is an established risk factor for TB infection (*ATS/CDC 2000*, *Bennett 2008*, *Khan 2008*, *Miramontes 2015*, *Mancuso 2016*, *Curtin 2012*, *Johnson 2014*, *NCHS 2006*, *Johnson 2012*, *NCHS 2013a*, *Curtin 2006*). A concern, therefore, is that conventional analyses using the NHANES-provided participant weights might inaccurately estimate the overall population prevalence of latent TB, as measured by a positive TST.

Another analytic challenge is item nonresponse. Across all 3 NHANES cycles, TST results were not recorded for approximately 1 in 5 examined participants within the age groups eligible for a TST. Some previous analysts have addressed this challenge by excluding participants without TST results and then

creating higher weights for participants with results (*Bennett 2008*, *Miramontes 2015*, *Mancuso 2016*). That reweighting approach assumes that TST results are missing at random. To be missing at random, TST item nonresponse must not have been influenced by what the (unobserved) TST results would have been, conditional on measured covariates. However, if the probability of a positive TST influenced TST participation, the missing-at-random assumption does not hold. Sensitivity analyses, including imputation of extreme scenarios, are the preferred approach to examine the degree to which a missing-not-at-random mechanism might have introduced bias (*Rubin 1987*, *Little 2002*, *Allison 2002*, *Perkins 2018*, *NRC 2010*).

A third analytic challenge for the 2011–2012 cycle is the digit preference for TST results being recorded as borderline-positive 8 or 9 mm readings. Digit preference for positive 10 mm measurements are more typical and had been observed in the 1999–2000 cycle (*Comstock 1975b*, *Rieder 1995*, *Bennett 2008*, *Khan 2008*, *Miramontes 2015*). Miramontes et al. addressed these digit preferences with smoothing techniques that yielded fewer 10 mm results in 1999–2000 and more 10 mm results in 2011–2012 (*Miramontes 2015*).

Given these challenges, we sought to evaluate the extent to which NHANES-based estimates for the national prevalence of a positive TST, as a proxy measurement for LTBI (*Engel 1977*, *Bennett 2008*, *Khan 2008*, *Miramontes 2015*, *Mancuso 2016*), might change with an analysis that examines the influence of the selection of multiple participants per household, and, where appropriate, reclassifies borderline-positive TST results, adjusts for TST item nonresponse, and reweights for non-U.S. birth distributions among Hispanic and Asian participants.

Aim 2 Methods

Data sources and target populations

Each 2-year NHANES cycle is designed to be nationally representative of the noninstitutionalized U.S. civilian population. Most of the data used for this analysis are publicly available at https://www.cdc.gov/nchs/nhanes/. Examination dates and sampling units beyond the primary sampling

unit are restricted variables that are not released publicly. However, the National Center for Health Statistics, subject to proposal approval, can allow a researcher to access masked versions of restricted variables through the Research Data Center (https://www.cdc.gov/rdc/).

NHANES examinations included a TST component in 1971–1972, 1999–2000, and 2011–2012, and an interferon-gamma release assay (IGRA) blood test for TB infection in 2011–2012. The age groups eligible for tests of TB infection changed in each cycle: participants aged 25–74 in 1971–1972, when NHANES represented 103 million adults, aged ≥1 year in 1999–2000 to represent 268 million, and aged ≥6 years in 2011–2012 to represent 282 million (*Engel 1977*, *Bennett 2008*, *Khan 2008*, *Miramontes 2015*, *Mancuso 2016*, *Curtin 2012*, *Johnson 2014*, *NCHS 2006*, *NCHS 2013a*, *NCHS 1991*).

Outcome of interest and frequency of item nonresponse

Following precedent, we defined our outcome of interest as a TST measurement in the public-use NHANES dataset of ≥10 mm (*Engel 1977*, *Bennett 2008*, *Khan 2008*, *Miramontes 2015*, *Mancuso 2016*, *ATS/CDC 2000*). TST results were missing for 397 (21%) of the 1,891 age-eligible examined participants in 1971–1972, for 1,466 (16%) of the 8,832 in 1999–2000, and for 1,693 (22%) of the 7,821 in 2011–2012.

Statistical approach

NHANES public-use datasets include masked design variables and participant weights to account for the complex, multistage, probability sampling design when generating national estimates (*NCHS 2006*, *Johnson 2012*, *NCHS 2013a*, *NCHS 1991*, *NCHS 2013b*). We used the PROC DESCRIPT procedure in SAS-callable SUDAAN (Research Triangle Institute, Research Triangle Park, NC) to estimate the population prevalence of a TST ≥10 mm. By default, SUDAAN uses Taylor linearization methods to estimate standard errors. We specified a with-replacement design and used SUDAAN's SUBPOPX option to subset to age-eligible participants with non-missing TST results (*Heeringa 2010*, *RTI 2008a*, *RTI 2008b*). When we specified more

than 2 levels of nesting, we used SUDAAN's /PSULEV = and /MISSUNIT options (*RTI 2008a*, *RTI 2008b*). See Aim 2 appendix 3. SAS and SUDAAN code for more details.

Conventional analysis and analysis using additional sampling design parameters

First, we conducted a conventional NHANES analysis using only variables in the public-use datasets — that is, with the provided 2-year examination weights and the masked major stratum and primary sampling units as the only levels of nesting (*NCHS 2006*, *Johnson 2012*, *NCHS 2013a*, *NCHS 1991*, *NCHS 2013b*). Within the Research Data Center (i.e., RDC proposal Haddad 1555), we substituted the public-use masked variables with the unmasked (true) major stratum and primary sampling unit variables and replicated the conventional NHANES analysis. Next we addressed whether to take into account additional sample design parameters: we sequentially added the Census tract, then block group, then block, and, finally, household. Doing so allowed us to examine the effect of multilevel clustering on the estimated population prevalence of a TST ≥10 mm.

Influence of preferential selection of multiple participants from same household

Starting in 1999, NHANES aimed to increase the number of persons surveyed per household. Selected households had an average of 1.6 surveyed persons (*Curtin 2012*, *Johnson 2014*). Because TB is an infectious disease, we hypothesized that households with multiple participants might have correlated TST results and thus be a source of bias: if large households with multiple infected persons were more likely to be selected, prevalence estimates could be biased upward. We separately examined TST results in households with only 1 examined participant and households with multiple examined participants.

Record-level reclassification to address digit preference for borderline-positive TST results

Although we had defined our outcome of interest as a positive TST measurement of ≥10 mm, the digit preference for TST results being measured as borderline-positive 8 or 9 mm during the 2011–2012 cycle suggested systematic under-measurement (*Miramontes 2015*). To correct for this potential bias, we reclassified

40 participants with positive IGRA blood test results and ≥8 mm but <10 mm TST results as having positive TSTs. This record-level reclassification remained in place for all subsequent analyses.

TST item nonresponse patterns

We observed that 124 (31%) of the 397 missing TST results during 1971–1972 occurred among participants examined during the final 2–3 days that NHANES examinations were scheduled in that county (see missing data and NHANES 1971–1972 appendix). Their TST results presumably were not recorded because of logistical difficulties in scheduling the TST reading after the examination center in that county had closed. However, our analysis within the Research Data Center (i.e., RDC proposal Haddad 1554) demonstrated that being scheduled for a later examination date did not influence the likelihood of having a TST result in 1999–2000 or 2011–2012. Excluding that possibility allowed us to focus on other potential predictors of TST item nonresponse.

Among the participants with TST item nonresponse in 1999–2000 and 2011–2012, we used responses to the question, "Have you ever had a severe reaction to a TB skin test?" (TBQ070), which was asked just before the TST was administered during the examination, to discriminate between the small number who did not have a TST placed due to an affirmative response, the moderate number who had a TST placed but did not return for it to be measured, and the large number of examined participants who did not receive a TST (see **Aim 2 Table 1**).

Participant profiles based on NHANES analytic subdomains

Previous NHANES analyses had noted that TST item nonresponse was more common among younger participants and among non-U.S.–born persons (*Bennett 2008*, *Miramontes 2015*). To better understand the associations of age, race/ethnicity, and U.S. versus non-U.S. birth with TST results, we divided participants into 4 age-based groupings, then into the 3 major race/ethnicity categories used in NHANES 1999–2000 and the 4 used in NHANES 2011–2012 (see NHANES appendix 1), and then by U.S. versus

non-U.S. birth, yielding a total of 24 distinct participant profiles in 1999–2000 and 32 in 2011–2012 (see **Aim 2 Table 2**).

Aim 2 Table 1. Unweighted participation in tuberculin skin test (TST) component of the National Health and Nutrition Examination Survey (NHANES) Examination, by response to interview questions — 1999–2000 and 2011–2012

Participant's Self-Reported Tuberculosis (TB) History and Other Response to NHANES Interview Questions	8,832 Examined Participants Aged ≥1 Year, 1999–2000						7,821 Examined Participants Aged ≥6 Years, 2011–2012							
	Complete TST Results		TST Item Nonresponse (n = 1,446)				Complete TST Results		TST Item Nonresponse (n = 1,693)					
			No TST Placed But Reason Unknown (n = 1,219)		TST Placed But No Result Recorded (n = 227)				No TST Placed But Reason Unknown (n = 1,384)		No TST Placed Due to Past Severe Reaction [a] (n = 87)		TST Placed But No Result Recorded (n = 222)	
	(n = 7,386)						(n = 6,128)							
	No.	Row %	No.	Row %	No.	Row %	No.	Row %	No.	Row %	No.	Row %	No.	Row %
No history to suggest previously diagnosed TB infection or active disease	6,898	84.1	1,088	13.3	212	2.6	5,720	78.9	1,288	17.8	34	0.5	208	2.9
Reported *any* previous TST	4,922	83.8	806	13.7	146	2.5	3,748	78.6	806	16.9	79	1.1	137	2.9
Reported previous *positive* TST	275	72.9	93	24.7	[b]		203	65.1	57	18.3	45	14.4	[b]	
Self-reported history of active TB	23	67.6	10	29.4	[b]		32	76.2	[b]		[b]		[b]	
No personal history of either positive TST or active TB but was in household with active TB	190	85.2	28	12.6	[b]		144	80.4	22	12.3	[b]		[b]	
Self-reported race/ethnicity/birthplace														
White non-Hispanic U.S.-born	2,366	85.1	380	13.7	33	1.2	1,960	81.3	374	15.5	16	0.7	62	2.6
Black non-Hispanic U.S.-born	1,600	84.8	244	12.9	42	2.2	1,567	79.9	324	16.5	16	0.8	53	2.7
Hispanic U.S.-born	1,773	81.7	197	13.7	100	4.6	748	81.5	143	15.6	[b]		26	2.8
Hispanic non-U.S.–born	1,134	83.8	176	13.0	43	3.2	720	81.0	134	15.1	11	1.2	24	2.7
Asian U.S.-born	Asian race not a category during 1999–2000 NHANES						221	67.4	94	28.7	[b]		11	3.4
Asian non-U.S.–born	Asian race not a category during 1999–2000 NHANES						496	67.9	181	24.8	24	3.3	30	4.1
Other U.S.-born	200	81.0	41	16.6	[b]		188	77.4	44	18.1	[b]		[b]	
Other non-U.S.–born	313	78.8	81	20.4	[b]		228	68.1	90	26.9	[b]		[b]	
Age group														
<1 year	TST offered to only participants aged ≥1 year in 1999–2000						TST offered to only participants aged ≥6 years in 2011–2012							
1–5 years	707	69.8	291	28.7	15	1.5	TST offered to only participants aged ≥6 years in 2011–2012							
6–11 years	853	80.4	191	18.0	17	1.6	876	68.9	366	28.8	[b]		30	2.4
12–15 years	1,025	84.8	142	11.7	42	3.5	519	82.4	100	15.9	[b]		10	1.6
16–19 years	958	86.7	93	8.4	54	4.9	472	78.7	93	15.5	[b]		33	5.5
20–29 years	679	85.1	88	11.0	31	3.9	750	78.6	149	15.6	[b]		48	5.0
30–39 years	664	86.1	94	12.2	13	1.7	743	80.4	137	14.8	17	1.8	27	2.9
40–49 years	622	86.5	84	11.7	13	1.8	715	81.7	118	13.5	17	1.9	25	2.9
50–59 years	480	87.3	61	11.1	[b]		718	81.7	132	15.0	11	1.3	18	2.0
60–69 years	649	85.6	89	11.7	20	2.6	688	79.3	142	16.4	18	2.1	20	2.3
70–79 years	459	87.3	56	10.6	11	2.1	400	81.1	81	16.4	[b]		[b]	
≥80 years	290	90.1	30	9.3	[b]		247	75.8	66	20.2	[b]		[b]	

[a] According to the survey protocol, which did not change between 1999–2000 and 2011–2012, affirmative responses to any of the TB-related questions during the NHANES interview were not exclusion criteria for being offered a TST as part of the NHANES examination. However, an affirmative response to the question, "Have you ever had a *severe* reaction to a TB skin test?" (TBQ070), which was asked just before the TST was placed during the NHANES medical examination, was a contraindication to offering the TST. In 1999–2000, the same question was asked just before the TST was placed, but no participant was recorded as answering it affirmatively.

[b] Some cell contents suppressed due to small numbers.

Aim 2 Table 2. Stratified participant profiles created for this NHANES analysis, showing weighted TST results, including effects of reclassification of borderline-positive and adjustments for missing TST results, 1999–2000 and 2011–2012

Within each 1999–2000 participant profile,
Row 1 denotes unweighted number of examined persons in that participant profile [a]
Row 2 denotes average 2-year examination weight per participant (i.e., how many noninstitutionalized U.S. civilians represented by that participant) [b]
Row 3 denotes weighted percent with complete tuberculin skin test (TST) result, using the 2-year examination weights provided in the NHANES public-use datasets
Row 4 denotes weighted percent with positive TST, without any adjustment
Row 5 denotes sensitivity analysis: lower and upper limits, using most extreme missing-not-at-random mechanisms (i.e., as if missing TSTs were all negative or all positive)
Row 6 denotes weighted percent with positive TST, after adjustment for TST item nonresponse based on self-reported TB history and the missing-at-random assumption [d]

	24 Participant Profiles Created for this NHANES 1999–2000 Analysis					
Row	**Black non-Hispanic participants aged 6–19 yrs**		**Mexican-American[a] participants aged 6–19 yrs**		**White/other[a] participants aged 6–19 yrs**	
1	934 U.S.-born	40 non-U.S.–born	1,072 U.S.-born	362 non-U.S.–born	869 U.S.-born	96 non-U.S.–born
2	9,000	8,000	4,000	3,000	44,000	37,000
3	85.1	90.5	82.2	86.1	79.8	78.0
4	0.6	11.5 [e]	1.6	11.8	0.2	6.3
5	0.5, 15.4	10.8, 19.8	1.3, 19.0	10.2, 24.1	0.2, 20.4	4.9, 26.9
6	**remained 0.6**	**remained 11.5** [e]	**similar 1.7**	**remained 11.8**	**remained 0.2**	**similar 6.1**
	Black non-Hispanic participants aged 20–39 yrs		**Mexican-American[a] participants aged 20–39 yrs**		**White/other[a] participants aged 20–39 yrs**	
1	262 U.S.-born	42 non-U.S.–born	161 U.S.-born	277 non-U.S.–born	674 U.S.-born	153 non-U.S.–born
2	35,000	33,000	18,000	16,000	83,000	69,000
3	86.4	90.4	86.3	84.4	89.1	81.1
4	5.1	18.9 [e]	4.4	17.3	0.3	19.7
5	4.4, 18.0	17.1, 26.6	3.8, 17.4	14.6, 30.3	0.2, 11.2	16.0, 34.8
6	**similar 5.5**	**similar 18.7** [e]	**remained 4.4**	**similar 17.6**	**remained 0.3**	**similar 19.6**
	Black non-Hispanic participants aged 40–59 yrs		**Mexican-American[a] participants aged 40–59 yrs**		**White/other[a] participants aged 40–59 yrs**	
1	227 U.S.-born	49 non-U.S.–born	146 U.S.-born	211 non-U.S.–born	526 U.S.-born	109 non-U.S.–born
2	26,000	23,000	11,000	10,000	90,000	69,000
3	85.0	73.0	86.3	87.8	90.0	84.9
4	10.7	22.9 [e]	2.0	27.0	1.6	25.3
5	9.1, 24.1	16.8, 43.8	1.7, 15.4	23.7, 35.9	1.4, 11.5	21.5, 36.6
6	**similar 11.6**	**↑ to 30.8** [e]	**similar 1.9**	**similar 27.9**	**similar 1.9**	**similar 25.2**
	Black non-Hispanic participants aged ≥60 yrs		**Mexican-American[a] participants aged ≥60 yrs**		**White/other[a] participants aged ≥60 yrs**	
1	257 U.S.-born	24 non-U.S.–born	195 U.S.-born	209 non-U.S.–born	774 U.S.-born	144 non-U.S.–born
2	12,000	11,000	3,000	3,000	42,000	34,000
3	85.9	72.0	87.1	86.1	90.5	76.8
4	16.6	25.1 [e]	13.3	21.9	3.4	10.9
5	14.3, 28.4	18.1, 46.0	11.6, 24.5	10.8, 32.8	2.2, 12.5	8.3, 31.6
6	**similar 17.0**	**similar 28.0** [e]	**similar 13.9**	**similar 22.1**	**similar 3.6**	**similar 11.5**

Within each 2011–2012 participant profile,
Row 1 denotes unweighted number of examined persons in that participant profile [a]
Row 2 denotes average 2-year examination weight per participant (i.e., how many noninstitutionalized U.S. civilians represented by that participant) [b]
Row 3 denotes weighted percent with complete tuberculin skin test (TST) result, using the 2-year examination weights provided in the NHANES public-use datasets
Row 4.a denotes weighted percent with positive TST, without any adjustment
Row 4.b denotes, if applicable, weighted percent with positive TST after reclassification of borderline-positive results [c]
Row 5 denotes sensitivity analysis: lower and upper limits, using most extreme missing-not-at-random mechanisms (i.e., as if missing TSTs were all negative or all positive)
Row 6 denotes weighted percent with positive TST, after adjustment for TST item nonresponse based on self-reported TB history and the missing-at-random assumption [d]

	32 Participant Profiles Created for this NHANES 2011–2012 Analysis							
Row	**Black non-Hispanic participants aged 6–19 yrs**		**Hispanic participants aged 6–19 yrs**		**Asian participants aged 6–19 yrs**		**White/other participants aged 6–19 yrs**	
1	716 U.S.-born	26 non-U.S.–born	595 U.S.-born	156 non-U.S.–born	212 U.S.-born	93 non-U.S.–born	683 U.S.-born	21 non-U.S.–born
2	12,000	12,000	17,000	19,000	9,000	9,000	48,000	44,000
3	79.1	48.9	81.1	79.5	64.3	72.7	71.3	76.9
4.a	1.1	47.1 [e]	0.5	7.4	1.4	11.5	0.0	4.6 [e]
4.b	not applicable	not applicable	0.6 [c]	not applicable	not applicable	not applicable	not applicable	not applicable
5	0.9, 21.8	23.0, 74.1	0.5, 19.4	5.9, 26.4	0.9, 36.6	8.4, 35.7	0.0, 28.7	3.5, 26.6
6	**remained 1.1**	**similar 49.0** [e]	**remained 0.6**	**similar 7.2**	**remained 1.4**	**similar 11.7**	**remained 0.0**	**remained 4.6** [e]
	Black non-Hispanic participants aged 20–39 yrs		**Hispanic participants aged 20–39 yrs**		**Asian participants aged 20–39 yrs**		**White/other participants aged 20–39 yrs**	
1	397 U.S.-born	48 non-U.S.–born	155 U.S.-born	239 non-U.S.–born	82 U.S.-born	231 non-U.S.–born	671 U.S.-born	55 non-U.S.–born
2	24,000	22,000	45,000	40,000	16,000	17,000	68,000	67,000
3	82.8	62.1	84.4	83.1	75.5	69.9	81.2	63.9
4.a	2.8	22.1	4.8	15.5	3.8	26.3	0.8	4.8 [e]
4.b	3.0 [c]	24.2 [c]	not applicable	16.4 [c]	not applicable	28.4 [c]	not applicable	not applicable
5	2.5, 19.7	15.0, 52.9	4.1, 19.6	13.6, 30.5	3.0, 24.4	19.1, 51.8	0.7, 19.4	3.0, 39.2
6	**similar 3.1**	**similar 28.3**	**similar 5.1**	**similar 16.2**	**similar 3.7**	**similar 28.0**	**similar 0.9**	**similar 5.9** [e]
	Black non-Hispanic participants aged 40–59 yrs		**Hispanic participants aged 40–59 yrs**		**Asian participants aged 40–59 yrs**		**White/other participants aged 40–59 yrs**	
1	430 U.S.-born	68 non-U.S.–born	83 U.S.-born	268 non-U.S.–born	15 U.S.-born	254 non-U.S.–born	598 U.S.-born	35 non-U.S.–born
2	21,000	19,000	35,000	30,000	18,000	16,000	96,000	60,000
3	80.6	71.7	92.0	83.0	78.6	67.3	87.3	81.0
4.a	6.7	23.8	3.6	25.7	0.0 [e]	34.1	0.6	13.0 [e]
4.b	6.9 [c]	25.3 [c]	not applicable	28.4 [c]	not applicable	37.4 [c]	0.6 [c]	not applicable
5	5.6, 24.9	18.1, 46.4	3.4, 11.4	23.6, 40.6	0.0, 24.5	26.1, 56.2	0.6, 13.2	10.5, 29.5
6	**similar 7.2**	**↑ to 30.1**	**remained 3.6**	**similar 28.5**	**remained 0.0** [e]	**similar 37.8**	**similar 0.7**	**remained 13.0** [e]
	Black non-Hispanic participants aged ≥60 yrs		**Hispanic participants aged ≥60 yrs**		**Asian participants aged ≥60 yrs**		**White/other participants aged ≥60 yrs**	
1	417 U.S.-born	45 non-U.S.–born	85 U.S.-born	226 non-U.S.–born	19 U.S.-born	153 non-U.S.–born	703 U.S.-born	37 non-U.S.–born
2	11,000	10,000	15,000	14,000	14,000	13,000	64,000	37,000
3	80.5	62.5	78.0	80.0	72.5	61.1	83.2	77.7
4.a	12.1	29.8	11.0	25.9	0.0 [e]	26.0	1.2	13.9 [e]
4.b	13.0 [c]	34.5 [c]	12.1 [c]	30.1 [c]	not applicable	30.0 [c]	1.3 [c]	not applicable
5	10.5, 29.9	21.6, 59.1	9.4, 31.4	24.1, 44.0	0.0, 27.5	18.3, 57.2	1.0, 17.8	10.8, 33.1
6	**similar 13.6**	**similar 35.3**	**similar 12.8**	**similar 30.9**	**remained 0.0** [e]	**similar 30.1**	**similar 1.4**	**similar 13.1** [e]

[a] To enable more precise prevalence estimates within subpopulations, elderly persons and persons either born in Mexico or of Mexican heritage (i.e., "Mexican-Americans") were deliberately oversampled in 1999–2000, and persons of Asian heritage were deliberately oversampled in 2011–2012; oversampled subpopulations have lower average participant weights. The white/other person category in 1999–2000 included Hispanic persons not of Mexican heritage (i.e, 287 U.S.-born and 301 non-U.S.–born). In addition, the 1999–2000 participant profiles exclude 6 examined participants aged ≥6 years whose birthplace was not recorded. The 2011–2012 profiles exclude 5 examined Hispanic participants aged ≥6 years whose birthplace was not recorded.

[b] Average 2-year examination weights were rounded to the thousands for this figure. Selection probabilities are not directly influenced by birthplace, but non-U.S.–born persons could, for example, be more likely to reside in densely populated counties having a higher probability of selection during the first NHANES sampling stage, which would contribute downstream to a lower participant weight.

[c] NHANES 2011–2012 was marked by a digit preference for TST measurements being recorded as borderline-positive 8 and 9 mm readings. We used interferon-gamma release assay (IGRA) blood test results to address this potential misclassification. Any participant whose IGRA result was positive and whose TST result in the public-use NHANES dataset was ≥8 mm but <10 mm was reclassified as having a positive TST. This rule resulted in 40 of the 60 total participants with TST results ≥5 mm but <10 mm being reclassified as TST-positive. Eight of these 40 reclassified participants also had some element of self-reported TB history, in contrast to 1 of the 20 IGRA-negative with TST results ≥5 mm but <10 mm who remained classified as TST-negative. This record-level reclassification remained in place for all subsequent analyses.

[d] For the missing-at-random adjustment, the individual participant's probability of a positive TST was the weighted proportion of a positive TST among persons in the same participant profile who had self-reported a similar TB history. Self-reported personal TB history was defined as a previous positive TST or IGRA blood test, or any previous treatment for either active or latent TB.

[e] Imprecise estimates due to small number of non-U.S.–born black non-Hispanic participants during NHANES 1999–2000, and small numbers of non-U.S.–born black non-Hispanic participants aged 6–19, U.S.-born Asian participants aged ≥40, and non-U.S.–born white/other participants of all ages during NHANES 2011–2012.

Imputation for TST item nonresponse

Our sensitivity analysis for the most extreme missing-not-at-random mechanisms used a single imputation to examine what would happen if all NHANES participants with TST item nonresponse had either all negative or all positive TST results (*Perkins 2018*, *NRC 2010*). We also created 30 replicates of each NHANES dataset based on a less extreme missing-at-random assumption. For each replicate, the missing TST result was replaced with an imputed positive or negative TST result based on a Bernoulli trial, where the individual participant's probability of a positive TST was the weighted proportion of a positive TST among persons in the same participant profile who had self-reported a similar TB history (defined as a previous positive TST or IGRA, or previous treatment for either active or latent TB). We used SUDAAN's MI_FILES option so that the estimated variance would incorporate the additional uncertainty added by the imputations (*Heeringa 2010*, *Allison 2002*, *Perkins 2018*, *NRC 2010*, *Berglund 2014*, *RTI 2008a*, *RTI 2008b*). For the code used, see the Aim 2 appendix 3. SAS and SUDAAN code.

Birth distributions among Hispanic and Asian participants

As a final step in examining the robustness of NHANES-based estimates of TB infection prevalence, we used the March 2000 Current Population Survey and March 2010 American Community Survey to compare the weighted U.S.- versus non-U.S. birth distributions of Hispanic and Asian participants to their corresponding relative proportions in the general population. If they differed, our plan was to create an additional post-stratification adjustment to the 2-year examination weights.

NHANES 1999–2000 oversampled persons of Mexican heritage (i.e., "Mexican-Americans") (*Curtin 2012*, *Johnson 2014*), when approximately half of the Mexican-Americans in the United States were non-U.S.–born (*Schmidley 2003*, *Lollock 2001*, *Therrien 2001*). In NHANES 2011–2012, the broader "Hispanic" category was used, and approximately 60% were non-U.S.–born (*Grieco 2012*). NHANES 2011–2012 also oversampled

persons of Asian heritage (i.e., "Asians") (*Johnson 2014*, *NCHS 2013a*), when approximately two-thirds of Asians in the United States were non-U.S.–born (*Grieco 2012*).

Aim 2 Results

Similar estimates with masked and unmasked datasets, and with additional design parameters

The estimated population prevalence of a TST result ≥10 mm remained the same using the unmasked 1999–2000 and 2011–2012 major stratum and primary sampling unit parameters. As expected, incorporation of additional sample design parameters (i.e., Census tract, Census block group, Census block, and household) improved precision (Aim 2 appendix 2).

No evidence of bias due to preferential selection of households

A weighted 56% of 1999–2000 participants and 58% of 2011–2012 participants shared a household with other examined participants. However, contrasting their TST results to those of participants who were their household's only representative did not reveal any differences in the prevalence of a positive TST result (Aim 2 appendix 2).

Patterns of TST item nonresponse as a potential source of bias

Differences were observed between NHANES participants with complete TST results and those with TST item nonresponse. In all 3 cycles, a self-reported previous positive test for TB infection or previous treatment for either active or latent TB was associated with TST item nonresponse (1971–1972 shown in missing data and NHANES 1971–1972 appendix; 1999–2000 and 2011–2012 shown in **Aim 2 Table 1**). Among participants with complete results, personal TB history was also associated with current evidence of TB infection (see Aim 2 appendix 1).

Persons aged ≥60 years were oversampled for NHANES 1999–2000 and had some of the most complete TST results in that cycle. Mexican-Americans were also oversampled and had a level of participation in the TB component of the examination like that of non-Hispanic persons (**Aim 2 Table 1**). In contrast, Asians, who were oversampled for NHANES 2011–2012, had some of the lowest participation in the TB component of the examination (**Aim 2 Table 1**), with missing TST results most pronounced among Asians aged ≥60 years (**Aim 2 Table 2**).

Modest effect from reclassification of borderline-positive TST results

The 40 reclassified borderline-positive TST results in 2011–2012 occurred within 16 of the 32 participant profiles (i.e., row 4.b. in **Aim 2 Table 2**). The pooled effect of these record-level reclassifications on the estimate of the overall noninstitutionalized U.S. civilian population being TST-positive was a modest change from the conventional NHANES analysis estimate of 4.3% (95% confidence interval [CI]: 3.0%, 5.9%) to 4.6% (95% CI: 3.3%, 6.3%) (**Aim 2 Figure**).

Modest effects of imputation for TST item nonresponse

To demonstrate the extreme bounds of the potential influence of missing-not-at-random TST results (*Perkins 2018*, *NRC 2010*), **Aim 2 Table 2** (row 5) shows how weighted prevalence estimates would change if NHANES participants with TST item nonresponse had either all negative or all positive TST results. Under a less extreme missing-at-random assumption, the estimated population prevalence of a positive TST slightly increased across most groups (row 6). However, the new prevalence estimates were only markedly different among black non-Hispanic non-U.S.–born participants aged 40–59 years, and there were relatively few of them, so these estimates were unstable.

The pooled effects of all these missing-at-random adjustments (i.e., where the individual participant's probability of a positive TST was the weighted proportion of a positive TST among persons in the same profile who had self-reported a similar TB history) are shown as the final set of estimates for 1999–2000 and

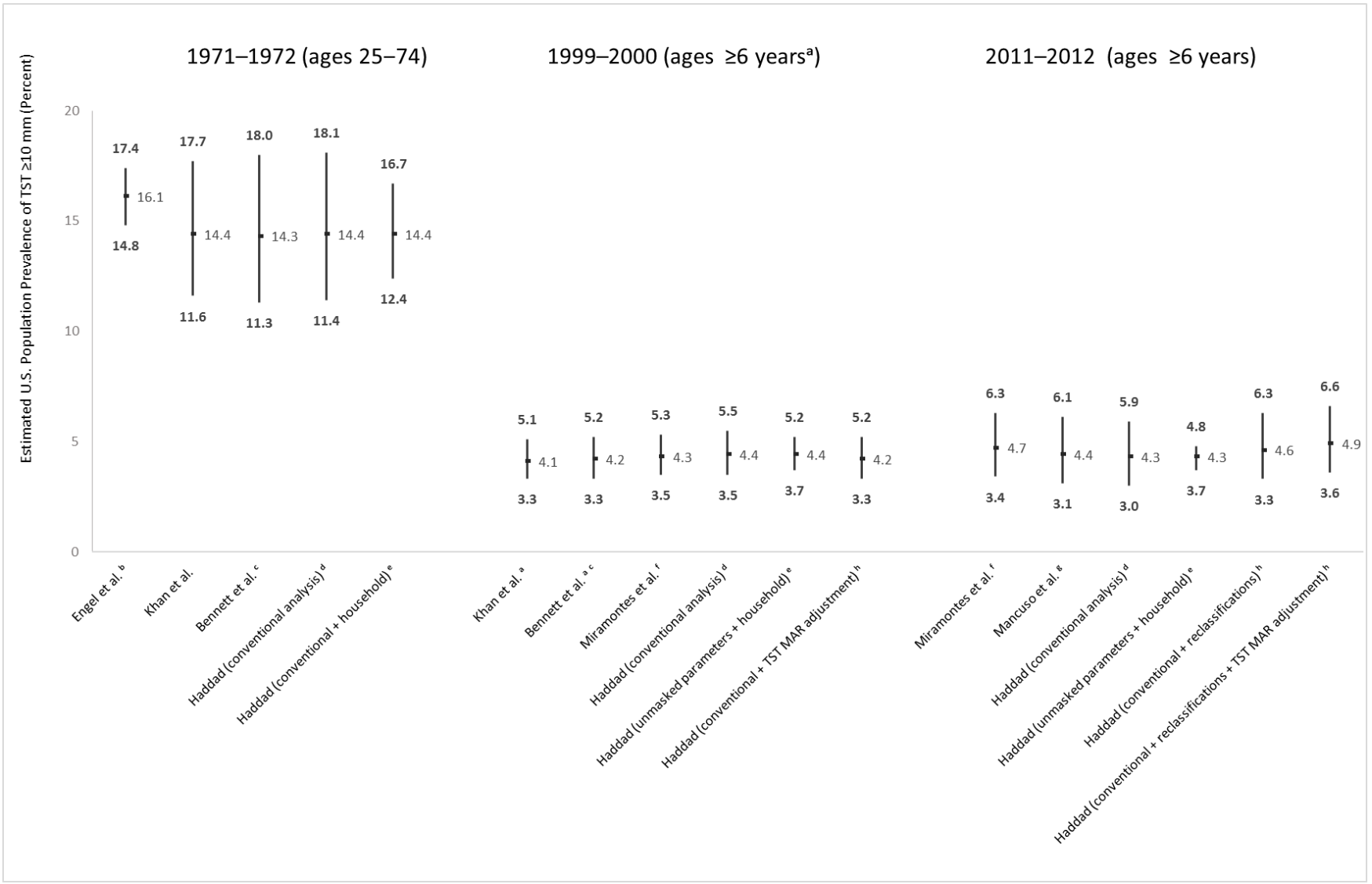
2011–2012 in the **Aim 2 Figure**. With these imputations for the missing TST results, the estimated point prevalence of a positive TST in the population decreased by 0.2% for 1999–2000 and increased by 0.3% for 2011–2012. However, the 95% confidence intervals (i.e., 3.3%, 5.2%, and 3.6%, 6.6%, respectively) remained similar to estimates without any adjustment for TST item nonresponse. Confidence intervals also overlapped across both cycles.

No need to reweight for non-U.S. birth among Hispanic and Asian participants

A weighted 46% of Mexican-American participants in NHANES 1999–2000 were non-U.S.-born. This proportion was similar to that seen in the U.S. population at large, according to the Current Population Survey (*Schmidley 2003*, *Lollock 2001*, *Therrien 2001*). A weighted 53% of Hispanic and 74% of Asian participants in NHANES 2011–2012 were non-U.S.-born. These proportions were similar to that seen in the U.S. population at large, according to the American Community Survey (*Grieco 2012*). Therefore, no further adjustments were made to the NHANES 2-year examination weights provided in the public-use dataset.

Aim 2 Figure. Pooled 95% confidence intervals and point estimates for prevalence of tuberculin skin test (TST) ≥10 mm in overall U.S. noninstitutionalized civilian population based on NHANES in 1971–1972, 1999–2000, and 2011–2012.

This figure summarizes previously published analyses, as well as the aim 2 analyses described in this dissertation.



[a] The Khan et al. and Bennett et al. 1999–2000 estimates were for participants aged ≥1 year.

[b] The Engel et al. 1971–1972 "tuberculin positive" estimates for participants aged 25–74 years apparently included examinees not given a TST because they reported a "history of a positive reaction, tuberculosis, or isoniazid prophylaxis."

[c] Bennett et al. addressed missing TST results in 1971–1972 and 1999–2000 by excluding participants without TST results and then creating higher weights for participants with results by multiplying the NHANES-provided 2-year examination weight by the inverse of the probability of having a result. In 1971–1972, this inverse probability reweighting approach was based on the 73% of examined participants aged 25–34 and 80% of those aged 35–74 with TST results. In 1999–2000, it was 75% of U.S.-born and 66% of the non-U.S.–born examined participants aged 1–14 years, and 88% of the U.S.-born and 83% of the non-U.S.–born aged ≥15.

[d] The Haddad et al. 1971–1972, 1999–2000, and 2011–2012 "conventional analysis" estimates are based entirely on NHANES data publicly available at https://www.cdc.gov/nchs/nhanes/, including the masked major strata and primary sampling units, and no changes to the standard NHANES-provided 2-year examination weights. Instead of addressing TST item nonresponse with a reweighting approach, SUDAAN's SUBPOPX option within PROC DESCRIPT was used to subset to age-eligible participants with complete TST results.

[e] The Haddad et al. 1971–1972 "conventional + household" estimate was possible using the masked household ID that is available in the public-use NHANES dataset for 1971–1972. In addition to nesting participants by masked major strata and primary sampling unit, household was added as a third level of nesting to account for the possibility of within-household clustering of TST results. However, in 1971–1972, only 49 (3%) of 1,842 households with TST results had >1 participant with TST results, in contrast to over half of participants in the later cycles. The 1999–2000 and 2011–2012 "unmasked parameters + household" estimates required access to restricted variables not in the public-use datasets. These replicated the conventional analysis but used the unmasked major strata and primary sampling units while also accounting for the possibility of within-household clustering of TST results. For more detailed results of what happened when the other restricted variables of Census tract, block group, and block were added, as well as results stratified between participants who shared households and participants who were the only household representative, see Aim 2 appendix 2.

[f] The Miramontes et al. estimates for 1999–2000 used the same Bennett et al. inverse probability reweighting approach for missing TST results, except that Miramontes et al. subsetted the 1999–2000 participants to those aged ≥6 years (i.e., excluding those aged 1–5 years), to enable better comparison to 2011–2012, when only participants aged ≥6 years were offered a TST. For 2011–2012, Miramontes et al. increased the NHANES-provided 2-year examination weights based on the 73% of the U.S.-born and 69% of the non-U.S.–born aged 6–14 years, and 83% of the U.S.-born and 74% of the non-U.S.–born aged ≥15 years, with TST results. The Miramontes et al. estimates also employed smoothing techniques to address the digit preferences for 10 mm measurements in 1999–2000 and 8 and 9 mm measurements in 2011–2012.

[g] Mancuso et al. 2011–2012 report that the standard NHANES-provided 2-year examination "weights were further adjusted for nonparticipation in TB testing so that it would represent the applicable study population" but do not provide further detail.

[h] The Haddad et al. 1999–2000 and 2011–2012 "conventional + TST MAR adjustment" analyses employed the conventional analysis of masked public-use NHANES datasets with further adjustment for TST item nonresponse (i.e., summarizing the overall population effect of the stratified results presented in **Table 2**). The missing TST result was replaced with 30 imputed positive or negative TST results based on a Bernoulli trial, where the individual participant's probability of a positive TST was the weighted proportion of a positive TST among persons in the same participant profile who had self-reported a similar TB history. Additionally for 2011–2012, the "+ reclassifications" analysis addressed the digit preference for 8 and 9 mm rather than 10 mm TST measurements in that cycle. Any participant whose interferon-gamma release assay (IGRA) blood test result was positive and whose TST result in the public-use NHANES dataset was ≥8 mm but <10 mm was reclassified as having a positive TST.

Aim 2 Discussion

The estimated U.S. population prevalence of a positive TST was robust to a variety of different bias adjustments, reinforcing our confidence in the validity of estimates based on a conventional analysis of the public-use NHANES datasets for 1971–1972, 1999–2000, and 2011–2012 (*Engel 1977*, *Bennett 2008*, *Khan 2008*, *Miramontes 2015*, *Mancuso 2016*, *Johnson 2012*, *Curtin 2006*, *Lash 2009*, *Lash 2015*). Consistent with the intent when masked design parameters are created for the public-use datasets, none of the restricted variables that we accessed within the Research Data Center proved to have any substantial influence on results (*NCHS 2006*, *Johnson 2012*, *NCHS 2013a*). We found no evidence of bias due to the selection of multiple participants per household. Incorporation of additional NHANES design parameters beyond the primary sampling unit simply improved precision, which is consistent with the NHANES design (i.e., based on sampling from strata that are "homogeneous within" and "heterogeneous between" (*Heeringa 2010*, page 32)).

Despite lower participation in the TST component of the medical examination by Asian adults in NHANES 2011–2012 (**Aim 2 Table 1**), their TST results remained similar after a missing-at-random adjustment based on self-reported TB history (**Aim 2 Table 2**). Although the estimated population prevalence of a positive TST increased across most age groups and most race/ethnic subdomain groupings following adjustment for TST item nonresponse, the pooled effect on overall population prevalence estimates was negligible (**Aim 2 Figure**).

A limitation of this analysis is that we do not know whether questions were systematically asked differently between the 2 most recent cycles, despite the use of nearly identical TB protocols. One finding that remains inexplicable is the different responses to the TBQ070 question, "Have you ever had a severe reaction to a tuberculosis skin test?" When asked of 7,613 respondents during NHANES 1999–2000 examinations, just prior to the TST placement, the recorded response was always "no." When in 2011–2012 the same question was asked of 6,437 respondents, 87 participants said "yes," even though only 45 of those

87 had reported a previous positive TST during the NHANES interview some days beforehand (**Aim 2 Table 1**).

We defined our outcome of interest as a TST measurement in the public-use NHANES dataset of ≥10 mm. With some known limitations, use of this cutoff is thought to provide a reasonable proxy measure for the prevalence of LTBI in the U.S. population (*ATS/CDC 2000*, *Comstock 1975a*). We used IGRA results to inform our reclassification of borderline-positive TST results in the 2011–2012 dataset; another option is smoothing, as employed by Miramontes et al. (*Miramontes 2015*). Ideally, misclassification and other sources of potential error such as digit preference would be prevented in the study design, rather than addressed in the analysis phase (*Perkins 2018*, *NRC 2010*, *Lash 2009*). The TST reader, for example, could use calipers that demarcate the TST induration but do not reveal the measurement (i.e., blind the reader to the measurement in mm units) until after the caliper jaws have been locked (*Comstock 1975b*).

Although none of the additional variables that we considered in our analysis proved to be influential on population prevalence estimates for TB infection, some aspects of our approach might have relevance for other health conditions. Any researcher working with publicly available survey data should carefully read all provided documentation (*Curtin 2012*, *Johnson 2014*, *NCHS 2006*, *Johnson 2012*, *NCHS 2013a*, *Heeringa 2010*, *NCHS 2013b*), not only to understand how participants were recruited and data were collected but also to consider, for example, whether a survey that is designed select multiple persons from households with >1 eligible participant might skew results for the health condition of interest. Another consideration is sample size and the anticipated population prevalence of the condition. A single 2-year NHANES cycle is designed to estimate conditions with ≥10% prevalence with a relative standard error of ≤30%. Nevertheless, Curtin et al. have pointed out that NHANES collects so many detailed measures that a "rare event" is not uncommon (*Curtin 2006*). Should any TB component be implemented into future NHANES cycles, having that be an ongoing component for ≥4 consecutive years would help achieve more stable prevalence estimates (*NCHS 2006*, *Johnson 2012*, *NCHS 2013a*, *Curtin 2006*).

Following decades of declines, the estimated U.S. population prevalence of a positive TST remained essentially the same between 1999–2000 and 2011–2012 (**Aim 2 Figure**). Given concomitant U.S. population growth, stable prevalence means that a growing number of persons residing in the United States are infected with *Mycobacterium tuberculosis*. Being able to accurately measure the prevalence of LTBI is arguably more important now than ever.

CHAPTER 8 — Aim 3: DIABETES/LTBI RELATIONSHIP

Aim 3 background

Worldwide, an estimated 15% of active TB cases are attributable to diabetes, and that population attributable fraction is growing (*Magee 2013*, *Lönnroth 2014*, *Harries 2016*, *Al-Rifai 2017*, *Magee 2018*, *Ronacher 2017*). In the United States, diabetes may be surpassing HIV in importance in the epidemiology of TB. Like HIV, diabetes is an established individual risk factor for progression from LTBI to active TB disease (*Al-Rifai 2017*, *Jeon 2008*). Unlike HIV, diabetes prevalence in the United States is increasing. While the estimated prevalence of HIV infection in the United States has remained stable at approximately 1.1 million persons (*CDC 2018b*), an estimated 30 million persons have diabetes, and another 84 million are estimated to have prediabetes, a precursor of type 2 diabetes (*CDC 2017*). In 2017, 20% of incident TB disease in the United States occurred in persons living with diabetes (*CDC 2018a*), twice the estimated 9% of the U.S. population with diabetes (*CDC 2017*), and far surpassing the <6% of TB disease cases that occur in persons living with HIV (*CDC 2018a*).

It is well understood that having diabetes impairs the host's ability to contain *M. tuberculosis* infection (*Iseman 2000*, *Banyai 1959*, *Magee 2013*, *Harries 2016*, *Al-Rifai 2017*, *Ronacher 2017*, *Jeon 2008*). Less clear is whether diabetes is also associated with incident *M. tuberculosis* infection itself. Cross-sectional studies in different populations have suggested a modest association between diabetes and LTBI (*Hensel 2016*, *Martínez-Aguilar 2015*, *Lee 2017*, *Webb 2009*, *Leow 2014*). However, confounding might induce a spurious association between the two conditions. A recent meta-analysis showed that the odds ratios for having both conditions consistently approached 1.0 after adjustment for age and other measured variables (pooled crude OR = 1.64, pooled adjusted OR = 1.18) (*Lee 2017*).

Three previous NHANES 2011–2012 analyses found a positive association between diabetes and a positive TST (*Miramontes 2015*, *Martinez 2017*) or positive IGRA (*Barron 2018*) in the noninstitutionalized U.S. civilian population represented by the survey. However, very few participants had both diabetes and a TST

≥10 mm: of the total 5,560 adult NHANES 2011–2012 participants, only 247 had both. Further, only 2 of the 247 were white non-Hispanic adults, suggesting that any NHANES-based conclusions about the diabetes/LTBI relationship might not generalize to the entire U.S. population.

Understanding whether and how diabetes and LTBI are associated within race/ethnicity strata in the United States has not, to our knowledge, been studied previously. Because diabetes increases the risk of progression from LTBI to active TB, identifying subpopulations at greatest risk of diabetes-associated LTBI can help target public health TB prevention efforts.

Aim 3 objective

We examined whether race/ethnicity modifies the association between diabetes and a positive TST during NHANES 1999–2000 and NHANES 2011–2012.

Aim 3 methods

Conceptual approach

This analysis of cross-sectional NHANES data defined the more prevalent conditions (diabetes and prediabetes) as the exposures of interest and the more rare condition (a positive TST) as the outcome of interest. Regardless, all measures of association are described as odds ratios without implying which condition occurred first.

Data source and study population

This analysis uses existing public-use NHANES datasets, focusing on participants aged ≥20 years. The analytic subdomains for NHANES 1999–2000 and NHANES 2011–2012 used age ≥20 years as a cutoff for adult participants, and diabetes is predominantly a condition affecting adults. Race/ethnicity in NHANES is based on self-report and is necessary during the sampling phase for allocating participants into the subdomains, which are based on age, gender, race/ethnicity and, in some cases, income. NHANES added

Hispanic ethnicity as a race/ethnicity category in 1999–2000. Asian race was added in NHANES 2011–2012. During 1999–2000, any Asian participants would have been classified as "other" race/ethnicity.

The public-use NHANES datasets dichotomize participants as U.S.-born or non-U.S.-born, without specifying country of birth. Participants born in the 50 U.S. states or District of Columbia are classified as U.S.-born. For the remaining participants, specific country of birth is available only within the Research Data Center, where the Yelk Woodruff et al. analysis demonstrated similar LTBI prevalence estimates among non-U.S.-born Asian participants in NHANES 2011–2012, ranging approximately 20% to 30%, regardless of whether they were born in China, India, the Philippines, or Vietnam. The majority of Hispanic NHANES participants not born in the 50 U.S. states or District of Columbia were born in Mexico, and their estimated LTBI prevalence ranged approximately 10% to 20% (*Yelk Woodruff 2018*).

Definition of exposures and outcomes of interest

All NHANES cycles have asked participants about a previous diagnosis of diabetes. In 1999–2000 and 2011–2012, hemoglobin A1C and serum glucose (random and in some cases fasting) were assessed in participants aged ≥12 years. The 2011–2012 cycle added an oral glucose tolerance test (OGTT). This analysis defines **diabetes** on the basis of a self-reported previous diagnosis of diabetes (excluding gestational diabetes only), current diabetic medications, or an A1C level of ≥6.5. Otherwise, **prediabetes** is defined on the basis of a self-reported previous diagnosis of "borderline" diabetes or, in the absence of any known history or diabetic medications, an A1C level of 5.7–6.4. The sensitivity of estimates to different definitions is shown in the Aim 3 appendix. In brief, adding OGTT and fasting glucose results would have minimal influence on the proportions of NHANES participants classified as having diabetes, but adding fasting glucose results would substantively increase the proportions classified as having prediabetes (**Aim 3 Table 1**).

As in aims 1 and 2, a positive TST is defined as ≥10 mm of induration in the public-use dataset, with aim 2's record-level reclassification from borderline-positive to positive of TST results for 39 adult NHANES

participants in 2011–2012. These were TST results that were recorded as ≥8 mm but <10 mm in someone with a positive IGRA blood test for TB infection.

Statistical approach

NHANES public-use datasets provided the masked design variables (major stratum and primary sampling unit) and individual participant weights that were used in this analysis. SAS-callable SUDAAN (Research Triangle Institute, Research Triangle Park, NC) uses Taylor linearization methods to generate nationally representative estimates with a 95% confidence interval (CI) that accounts for the complex, multistage, probability sampling design of NHANES. SUDAAN's PROC DESCRIPT procedure was used to estimate the population prevalence of diabetes and prediabetes (using the 2-year interview weights) and the population prevalence of a positive TST (using the 2-year examination weights). For measuring the weighted crude association between diabetes status and a positive TST, the PROC CROSSTAB procedure was used to generate unadjusted odds ratios. The PROC RLOGIST procedure was subsequently used to replicate those PROC CROSSTAB results before adding other variables associated with both diabetes and a positive TST to generate weighted adjusted odds ratios. The SUBPOPX command was used to limit to adults aged ≥20 years with valid TST results without impairing variance calculations. For the odds ratio calculations, the referent group was persons with neither diabetes nor prediabetes (i.e., persons with prediabetes were excluded from the diabetes/positive TST calculations, and persons with diabetes were excluded from the prediabetes/positive TST calculations).

Determine unweighted and weighted prevalence of diabetes, prediabetes, and a positive TST

The first step in this analysis was to generate descriptive tables showing the overall proportions of NHANES 1999–2000 and 2011–2012 participants, unweighted and weighted, with diabetes or prediabetes. How prevalence estimates changed when participant weights were applied was noted.

The unweighted and weighted prevalence of a TST ≥10 mm was also estimated, along with the patterns of where and how prevalence estimates increased after reclassification of the NHANES 2011–2012 borderline-positive TSTs.

Arrange participants by age group, diabetes status, and TST results — overall and stratified by race/ethnicity

Because the main objective of this aim was to examine the influence of race/ethnicity on the association between diabetes and a positive TST, the next step of this analysis was to examine how weighted TST results changed as diabetes status (i.e., diabetes, prediabetes, or no diabetes) changed. After showing this for the overall population in 1999–2000 and 2011–2012, a series of aim 3 stratified tables enabled examination of whether and how prevalence estimates varied across race/ethnicity strata (i.e., black non-Hispanic, Hispanic, Asian, and white non-Hispanic).

Consider influence of birthplace on diabetes/LTBI association

The aim 3 stratified tables demonstrated that the majority of adult NHANES participants who were Hispanic and Asian were non-U.S.-born, whereas the majority who were non-Hispanic black or white were U.S.-born. Aim 2 had found that non-U.S.-birth distributions (both unweighted and weighted) among Hispanic and Asian NHANES participants were similar to their distributions in the overall U.S. population, suggesting that additional stratification or reweighting by birthplace was unnecessary. However, given that false-positive results can occur among non-U.S.–born persons who have received the BCG vaccine (*ATS/CDC 2000*, *Rieder 1995*, *Doan 2017*, *Mazurek 2005*, *Mazurek 2010*), the weighted prevalence of a positive IGRA blood test is presented alongside the weighted prevalence of a positive TST result.

Determine odds ratios for association between diabetes/prediabetes and a positive TST

Given the stratified findings, the relevance of also modeling the overall association between diabetes/prediabetes and a positive TST is uncertain. Nonetheless, odds ratios for this association were

calculated within strata of birthplace, age group, race/ethnicity, and education level, as well as an overall weighted odds ratios that adjusted for these characteristics. Income and smoking were excluded because of their strong correlations with education level. Body mass index is not presented because it was associated with only diabetes status (not with TST results). Vitamin D level is not presented because it was associated only with TST results (not with diabetes status).

Rationale for adjusting for age when examining diabetes/LTBI association in NHANES

The analysis subsets to persons aged ≥20 years, and NHANES weighting already assures that age distributions match the underlying population. However, Lee et al. (2017) consider age to be the most important confounder of the diabetes/LTBI relationship (because advanced age is an established risk factor for both conditions), and they excluded from their systematic review any cross-sectional studies that did not control for age in their adjusted models (*Lee 2017*). For this reason, it was necessary to further demonstrate that age was not a confounder by presenting the overlapping weighted odds ratios for associations within the age 20–39, 40–59, and ≥60 years subpopulations and by including age group in the final adjusted model.

Aim 3 results

Unweighted and weighted prevalence of diabetes and prediabetes, and of a positive TST

In 1999–2000, an estimated 7.4% (95% CI = 6.4%–8.7%) of the overall U.S. civilian noninstitutionalized adult population had diabetes, and 11.5% (95% CI = 7.4%–12.1%) had prediabetes. Those proportions nearly doubled to 11.5% (95% CI = 10.1%–13.2%) and 22.6% (95% CI = 20.6%–24.8%), respectively, of the population in 2011–2012. Estimated diabetes prevalence increased as age increased, and was higher in nonwhite persons and in persons who had not completed high school. However, estimated diabetes prevalence did not differ based on birthplace (**Aim 3 Table 2**).

Based on NHANES 1999–2000, an estimated 5.3% (95% CI = 4.2%–6.6%) of the U.S. adult population, if tested, would have had a TST result ≥10 mm. In NHANES 2011–2012, that estimate remained essentially the same, 5.0% (95% CI = 3.5%–7.0%), increasing slightly to 5.4% (95% CI = 3.8%–7.5%), following record-level reclassifications of borderline TST results. In both cycles, estimated positive TST prevalence was similar across age groups, peaking somewhat for those aged 40–59 years. This evidence of LTBI was markedly higher among nonwhite persons and among persons who had not completed high school, as well as among non-U.S.-born persons (**Aim 3 Table 3**).

In no situations did the estimated U.S. population prevalence of diabetes (**Aim 3 Table 2**) or a positive TST (**Aim 3 Table 3**) increase after NHANES participant weights were applied. Weighted population prevalence estimates were generally lower than the corresponding unweighted proportions among NHANES participants. There was one exception: within race/ethnic strata, unweighted and weighted positive TST prevalence was remarkably similar (**Aim 3 Table 3**), suggesting that decreases seen elsewhere when participant weights were applied might be driven by race/ethnicity differences in those other strata.

Association between diabetes/prediabetes and LTBI only apparent among Hispanic and Asian participants

The aim 3 stratified tables illustrate TST results among NHANES participants by diabetes status, in the overall U.S. population as well as stratified by race/ethnicity, in 1999–2000 and 2011–2012. The weighted prevalence of a positive TST among NHANES participants was generally higher for persons with diabetes or prediabetes, a consistent finding in both cycles. However, the overall modest association between diabetes and a positive test for LTBI in NHANES 2011–2012 was replicated only among nonwhite participants, representing less than one third of the total adult population in the United States. Specifically, approximately 1 in 4 Hispanic and Asian participants with diabetes also had evidence of LTBI (aim 3 stratified tables).

Because nearly all the study participants with either diabetes or prediabetes and a positive TST were nonwhite, adjusting for race/ethnicity moved every odds ratio for that association down toward the null (i.e., associations between diabetes and a positive TST shown in **Aim 3 Table 4**, and associations between

prediabetes and a positive TST shown in **Aim 3 Table 5**). Consistent with the stratified tables, there was no longer any overall diabetes/LTBI association (OR = 1.3, 95% CI = 0.7–2.3) after adjustment for birthplace, age group, race/ethnicity, and education level.

Aim 3 discussion

This analysis demonstrates that in the United States, the race/ethnicity construct is important when considering the association between diabetes and LTBI. However, our results suggest that race/ethnicity does not act as a confounder but rather as an effect modifier. Simply comparing unadjusted and adjusted measures of association for diabetes and LTBI, or conducting a typical logistic regression that considers race/ethnicity to be a confounder, would miss the heterogeneity of that association within different race/ethnicity groupings in the United States. Compared to their nondiabetic counterparts, non-Hispanic white and non-Hispanic black persons with diabetes do not appear to have an elevated odds of LTBI. Hispanic and Asian persons do.

Nearly all the NHANES participants with both diabetes and a positive screening test for LTBI were black, Hispanic, or Asian, representing 70 million nonwhite adults in the U.S. population. African Americans are the race/ethnic group with the highest prevalence of diabetes and prediabetes — an estimated half of all black adults in the U.S. population, even employing the least sensitive definitions (**Aim 3 Table 1**). However, their odds of also having LTBI were not as markedly elevated as they were for the more circumscribed population of an estimated 6 million Hispanic and 1.5 million Asian adults with diabetes.

Based on both TST and IGRA blood test results in NHANES, approximately 1 in 4 Hispanic and Asian adults with diabetes in the United States is latently infected with *M. tuberculosis*. Enhanced screening among Hispanic and Asian adults with diabetes could be as a cost-effective strategy to detect LTBI, because this subpopulation has a higher prevalence of LTBI. In addition, these adults also have a greater risk of having LTBI progress to active TB (*Iseman 2000*, *Banyai 1959*, *Magee 2013*, *Harries 2016*, *Al-Rifai 2017*, *Ronacher 2017*, *Jeon 2008*). Furthermore, Shea et al.'s study estimated that the annual risk of progression from LTBI to active TB disease was higher among Hispanics (0.17%–0.19%) and Asians (0.13%–0.15%) than among U.S.-

born whites and blacks (<0.10% annual risk if HIV-uninfected) (*Shea 2014*). Therefore, prioritizing Hispanic and Asian adults with diabetes for LTBI treatment could be an efficient TB prevention strategy: compared to persons with longstanding LTBI in the general population, far fewer would need to be treated to avert future TB cases.

This analysis is also subject to misclassification bias. A strength of the NHANES examination is the systematic evaluation for diabetes in participants aged ≥12 years, so exposure misclassification in this analysis was unlikely. However, outcome misclassification is likely. The slight downward trend in positive TST prevalence in persons aged ≥60 years (**Aim 3 Table 3**) is a reminder that false-negative TST results among the elderly are a known phenomenon (*Hochberg 2016*). Because older persons are also more likely to have diabetes, this analysis likely underestimated the true strength of the diabetes/LTBI association in the elderly. (This was also one of the few measures that *increased* in magnitude when participant weights were applied in **Aim 3 Table 4** and **Aim 3 Table 5**.) Conversely, false-positive TST results likely caused some outcome misclassification for non-U.S.-born NHANES participants, many of whom were Hispanic or Asian who might have received the BCG vaccine as children. In these participants, the IGRA blood test results shown in the aim 3 stratified tables are more reliable (*Doan 2017*, *Mazurek 2005*, *Mazurek 2010*, *Stout 2018*).

Continuing to examine the influence of race/ethnicity on the diabetes/LTBI association in future population-based surveys will be important. Despite NHANES oversampling to improve precision of estimates in nonwhite subgroups, none of the measures of association is based on large numbers of persons with both conditions. For example, the elevated odds of a positive TST seen among Asians with prediabetes (**Aim 3 Table 5**) was not also present for Asians with diabetes (**Aim 3 Table 4**), even though this pattern did hold among Hispanic persons.

Although this analysis reaffirms the known finding that birth outside the United States is a risk factor for LTBI, diabetes and prediabetes were equally prevalent among the U.S.-born and non-U.S.–born. This analysis (**Aim 3 Table 2**) corroborated other national prevalence estimates showing that diabetes and

prediabetes are increasing at an alarming rate across all population groups (*CDC 2017*). As diabetes grows in importance in the epidemiology of TB in the United States, this analysis draws attention to the specific contributions of Hispanic and Asian persons to that changing epidemiology.

CHAPTER 9 — CONCLUSIONS AND FUTURE DIRECTIONS

Summary of findings and public health implications

This dissertation has examined the U.S. population prevalence of LTBI starting in 1971, the year NHANES began, through 2015, when *M. tuberculosis* genotyping results from routinely reported active TB cases were used to derive estimates of LTBI prevalence comparable to those obtained with NHANES. The epidemiology of TB and the population of the United States both changed substantially during these 45 years. However, the U.S. population prevalence of LTBI appears to have stabilized at ≥3% since 1999. Given concomitant U.S. population growth, stable prevalence means that a growing number of persons are infected with *M. tuberculosis*, delaying any prospect of TB elimination in the United States without better focus on LTBI detection and treatment. Because socioeconomic and related race/ethnicity inequities in LTBI distribution persist, health disparities related to TB will widen without effective interventions to eliminate LTBI in the populations at greatest risk.

A single 2-year NHANES cycle is designed to enable precise estimates for conditions with ≥10% prevalence and little geographic variability. LTBI fulfills neither criterion. TB's striking geographic and demographic heterogeneity motivated this dissertation. Nevertheless, this first analysis of how the NHANES county sampling process might have influenced national LTBI prevalence estimates for 1971–1972, 1999–2000, and 2011–2012 found no evidence of bias due to that aspect of the survey design (aim 1). Systematic under-measurement of positive TST results in the NHANES 2011–2012 public-use dataset was addressed through record-level reclassification, but the pooled effect on overall population prevalence estimates was negligible (aim 2). We also found little difference in 1971–1972, 1999–2000, and 2011–2012 LTBI prevalence estimates after accounting for the selection of multiple participants per household, missing TST patterns, and non-U.S.-birth distributions (aim 2).

Although our aim 1 and 2 findings reinforced confidence in previous NHANES-based estimates, we

concluded that TB components in future NHANES should be implemented as an ongoing component for ≥4 consecutive years to achieve more reliable prevalence estimates. NHANES 2011–2012 was likely the last national survey to include a TST. CDC's Division of Tuberculosis Elimination is working with the National Center for Health Statistics to incorporate the IGRA blood test for TB infection into NHANES 2019–2020, but the IGRA will be offered to non-U.S.-born participants only (personal communication, Roque Miramontes, October 2018).

Knowledge that TB disease and diabetes often co-occur dates back 1,000 years, and as early as 1965, the American Thoracic Society advocated treatment of LTBI among persons with diabetes. However, as diabetes prevalence increases, not only in the United States but worldwide, its importance in the epidemiology of TB has intensified. In 2017, 20% of incident TB disease in the United States occurred in persons living with diabetes. This dissertation adds to the growing body of evidence that diabetes might be associated with LTBI itself (in addition to the well-established risk of progression) — but potentially only in certain subpopulations (aim 3). Our findings suggest that enhanced screening of LTBI among the estimated 6 million Hispanic and 1.5 million Asian adults with diabetes in the United States could be a cost-effective strategy to detect LTBI (i.e., a predicted 1 in 4 is infected). In addition, prioritizing this subpopulation for LTBI treatment could be an efficient TB prevention strategy, because compared to persons with longstanding LTBI in the general population, far fewer would need to be treated to avert future TB cases.

U.S. population changes and NHANES changes, yet persistent inequities in LTBI distribution

Non-U.S.-born persons composed a historically low 5% of the population in 1970 and then a more typical 11% in 2000 and 13% in 2010 (*Schmidley 2003*, *Lollock 2001*, *Therrien 2001*, *Gibson 2006*, *Grieco 2012*, *Frey 2018*). As the U.S. population has diversified, NHANES has evolved to sample according to changing race/ethnic trends, adding Hispanic ethnicity in the 1990s and Asian race in 2011 (*Curtin 2012*, *Paulose-Ram 2017*, *NCHS 2006*, *Johnson 2012*). The self-weighting NHANES dataset automatically accounts for differences in health conditions by gender, age, and race/ethnicity, but not by birthplace, which is an established risk

factor for TB, but not for many of the other health conditions in the survey.

NHANES is currently designed to be as statistically efficient as possible with an annual sample of approximately 5,000 persons from 14 primary sampling units (i.e., about 15 counties). In calling for changes in how NHANES is designed in the future, the National Center for Health Statistics acknowledges that the small number of counties selected for participation results in a high level of design effects due to correlations of health conditions within those counties (*Porter 2018*, *Federal Register 2018*). Likewise, a conventional NHANES analysis cannot examine correlations within later sampling stages, such as within neighborhoods and households, which are important considerations with any infectious disease, but especially TB.

NHANES helps document a greater lifetime risk of acquiring *M. tuberculosis* infection among persons who have not completed high school, as well as persons of color and persons born outside the United States. Similar health disparities were seen 100 years ago. The 1917 Framingham Health and Tuberculosis Demonstration survey found the highest prevalence of a positive TST among children in the poorest district of the town who were of "Italian nationality" (51%) or "Jewish or Irish nationality" (30%) rather than "American nationality" (18%) (*Framingham 1918*). Wade Hampton Frost, continuing to note the link between poverty and TB, described "better nutrition and relief from physical stress" as key TB control measures, and urged for "a generous plan of social assistance" for families affected by TB (*Frost 1937*). TST surveys among Naval recruits in 1958–1969 and 1990 showed higher LTBI prevalence among non-U.S.-born recruits, noting that many had been born in countries with high rates of TB disease (*Edwards/Palmer 1969*, *Comstock 1974a*, *Comstock 1975a*, *Trump 1993*). But among men who had lived all their lives in the same U.S. county, black recruits have markedly higher TST positivity than their white counterparts, despite very similar histoplasmin sensitivity (*Edwards 1964*, see Literature review appendix 3).

On the other hand, some of the states with the highest LTBI prevalence estimates 5–6 decades ago (see Literature review appendix 2) have made remarkable strides in TB control. In the 1940s, over 2,000 of Kentucky's residents died annually from TB (*Schulman 1944*). During 1950, West Virginia reported over 2,000

new TB disease cases (*West Virginia 2011*). With 65 and 16 total cases of active TB disease reported statewide during 2017, respectively, these two states have achieved some of best TB control in the United States (*CDC 2018a*). Using the genotype-based LTBI prevalence estimation method developed for aim 1, Kentucky's estimated LTBI prevalence is only 0.9% among the U.S.-born, and West Virginia's is only 0.6% (see Aim 1 appendix 5).

Contribution to the field and future directions

An example of quantitative bias analysis applied to measures of prevalence

This dissertation provides an example of bias analysis methods applied to a measure of prevalence. Epidemiologists may typically think of bias analysis in the context of measures of association, such as Joseph Berkson's work "correcting the spurious association" that can occur when using hospitalized persons as controls in case-control studies (*Berkson 1946*), or Jerome Cornfield's counterarguments to R.A. Fisher about the minimum effect that an unmeasured confounder would have to exert in order to explain the observed association between smoking and lung cancer (*Cornfield 1954*).

Regardless of the measurement of interest, quantitative bias analysis can help guide an epidemiologist's thinking about the direction and magnitude of potential bias, or consider the most likely source of uncertainty, and how that might have influenced findings, even threatening their validity (*Lash 2009*, *Lash 2014*). This dissertation was not an exhaustive examination of all potential sources of systematic error with respect to TB in NHANES. Rather, each aim focused on one potential source of bias at a time, starting with the one initially thought to be the dominant source of uncertainty (i.e., sampling approximately 30 of the 3,143 counties to derive estimates for the whole United States) and then using record-level reclassification to correct for likely TST mismeasurement before moving on to address other potential sources of bias. Although missing data patterns can induce substantial bias into survey findings (*Rubin 1987*, *Little 2002*, *Allison 2002*, *Perkins 2018*), invoking a missing-at-random assumption and using multiple imputation to address item nonresponse within strata of similar participants is preferable to ignoring the missing data.

Consideration of race/ethnicity when examining diabetes/LTBI association

Although effect modification is not a bias, previous NHANES examinations of the diabetes/LTBI association appear to have overlooked heterogeneity of the association within different race/ethnicity groupings. Non-Hispanic white and non-Hispanic black persons with diabetes do not appear to have an elevated odds of LTBI, compared to their nondiabetic counterparts. Hispanic and Asian persons do. A typical logistic regression that instead considers race/ethnicity as a confounder of the diabetes/LTBI relationship would hide this heterogeneity and potentially either overlook stratum-specific associations or overgeneralize to the entire U.S. population an association that is only present in a more circumscribed population.

Awareness of caveats to consider when relying on NHANES data

Ideally, potential sources of systematic error are prevented in the study design, rather than addressed in the analysis phase (*Perkins 2018*, *NRC 2010*, *Lash 2009*). However, that ideal is seldom available to epidemiologists who are working with data collected by other people, often for other purposes. This work promotes more awareness of the caveats to consider when relying on NHANES for estimates of LTBI and other low-prevalence conditions with geographic variability. Any researcher working with data collected by others should understand how participants were recruited and how data were collected, as well as examine item nonresponse and other data patterns that suggest important analytic considerations. This counsel holds especially true for national survey data, where each individual participant represents thousands of other persons, and the survey designers might not have had the researcher's specific research topic in mind.

Alternative to NHANES for estimating LTBI prevalence for any given jurisdiction

With very few exceptions (*Landis 1982*, *Porter 2011*), NHANES was never intended to produce accurate county-level or state-level estimates. The county-level LTBI prevalence estimates created for aim 1 demonstrate that CDC's Division of TB Elimination could potentially be less reliant on periodic NHANES surveys and instead use existing National TB Surveillance System data on an ongoing basis to estimate not only national LTBI prevalence but also prevalence for any given jurisdiction or subpopulation.

TB need not remain "a manifestation of social misery"

The most expensive LTBI cure costs $700 (*Marks 2018*). In announcing his discovery of the *M. tuberculosis* bacterium in 1882, Robert Koch voiced optimism that TB need not remain "a manifestation of social misery." He hoped that the future "fight against this terrible plague of mankind will deal no longer with an undetermined something, but with a tangible parasite" (*Dubos 1952*, *Keers 1978*, *PJB 1956*, *Baillie 1795*, *Daniel 2000*, *Daniel 1999*). The concept of LTBI is notoriously intangible, yet with valid LTBI prevalence estimates to guide public health interventions, 12 doses of medication can kill the LTBI parasite and eliminate the misery of TB.

CHAPTER 10 — CONSOLIDATED BIBLIOGRAPHY

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APPENDICES

Pre-NHANES national surveys of TB infection prevalence

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- Number of NHANES participants (all ages) classified as having diabetes, prediabetes, or neither for aim 3.
- Aim 3 Table 1. Demonstration of sensitivity to various definitions of diabetes and prediabetes among NHANES participants aged ≥20 years, 1999–2000 and 2011–2012.
- Aim 3 Table 2. Weighted prevalence of diabetes and prediabetes among NHANES participants aged ≥20 years, 1999–2000 and 2011–2012.

Definitions and prevalence tables for a positive screening test for LTBI

- Aim 3 Table 3. Unweighted and weighted prevalence of a positive TST among NHANES participants aged ≥20 years, 1999–2000 and 2011–2012, based on TST results in public-use dataset, and after record-level reclassification of 39 borderline-positive TST results in 2011–2012.

- Aim 3 stratified tables — positive TST and IGRA results stratified by diabetes status and race/ethnicity among NHANES 1999–2000 and 2011–2012 participants aged ≥20 years

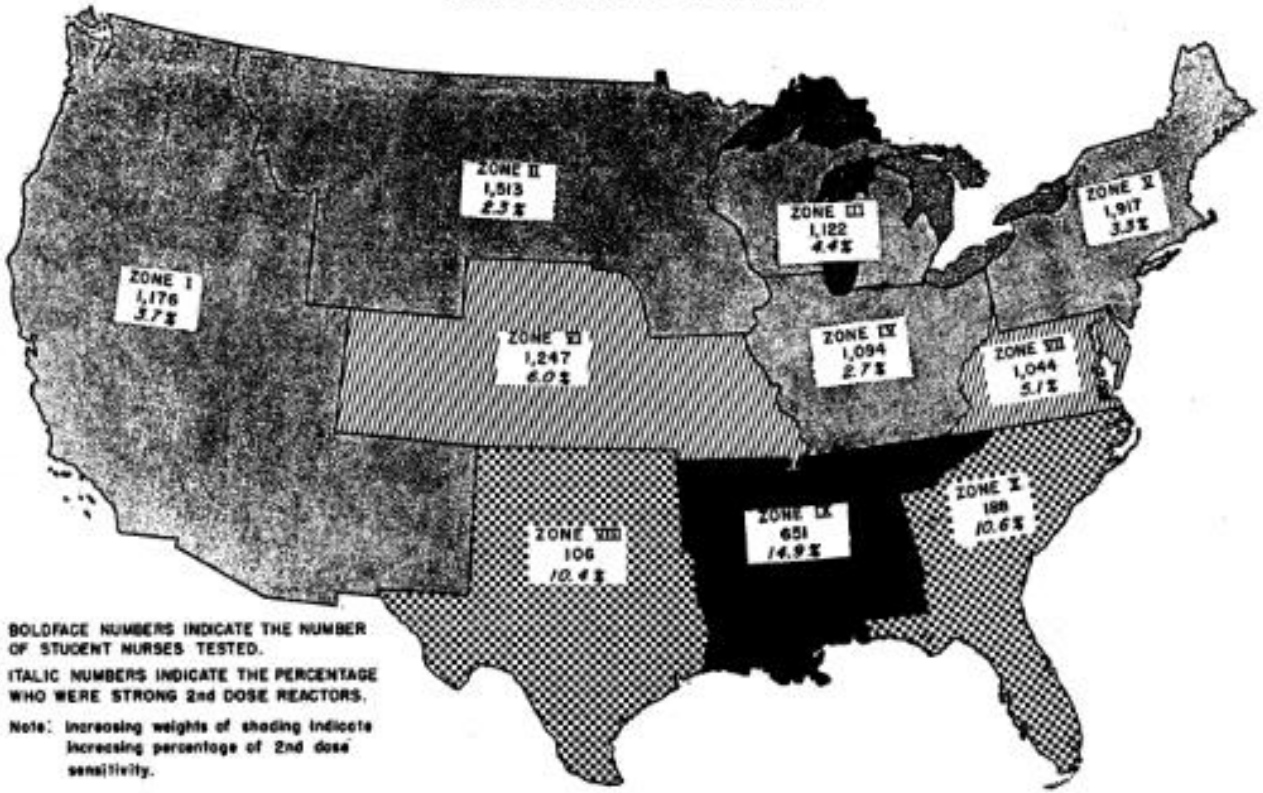
Measures of association between diabetes status and a positive test for LTBI

- Aim 3 Table 4. Unweighted and weighted odds ratios for association between a positive TST and diabetes among NHANES participants aged ≥20 years, 1999–2000 and 2011–2012.

- Aim 3 Table 5. Unweighted and weighted odds ratios for association between a positive TST and prediabetes among NHANES participants aged ≥20 years, 1999–2000 and 2011–2012.

Literature review appendix 1. Positive TST prevalence among nursing students by home state — 1943

Figure 1. Division of the United States into 10 zones, showing the numbers of lifetime residents tested and the percentage classified as strong 2d dose reactors in each zone.



City of training	Nurses tested	Strong 2d dose reactors percentage
Minneapolis	2,419	3.1
Columbus	1,330	3.3
Philadelphia	2,179	4.5
Los Angeles	1,778	5.0
San Francisco	1,111	4.0
Detroit	1,250	4.2
Total	10,067	4.0
Baltimore	1,971	5.7
Denver	1,329	5.1
Kansas City, Kans	532	7.7
Kansas City, Mo	1,131	5.4
New Orleans	1,290	14.3

State	Percentage
Indiana	0.0
Iowa	.8
Wisconsin	1.4
New Jersey	1.4
North Dakota	2.0
Minnesota	2.4
New York	2.5
Ohio	2.6
Wyoming	2.9
South Dakota	3.4
Pennsylvania	3.4
California	3.6
West Virginia	3.8
D. C.	3.8
Michigan	4.8
Maryland	5.4
Colorado	5.4
Illinois	5.4
Kansas-Missouri	6.0
Virginia	6.1
Nebraska	7.9
Texas	9.7
North Carolina	11.1
Florida	11.7
Oklahoma	11.8
Mississippi	13.1
Alabama	14.0
Louisiana	15.5
Arkansas	16.1

From Tables 1 and 4 and Figure 1 in Palmer CE, Ferebee SH, Strange Petersen O. Studies of pulmonary findings and antigen sensitivity among student nurses, VI: geographic differences in sensitivity to tuberculin as evidence of nonspecific allergy. *Pub Health Rep.* 1950; 65: 1111–1131. Figure is in public domain; *Public Health Reports* is published by the Association of Schools and Programs of Public Health on behalf of the U.S. Public Health Service.

Literature review appendix 2. Positive TST prevalence among Naval recruits by home county — 1958–1965

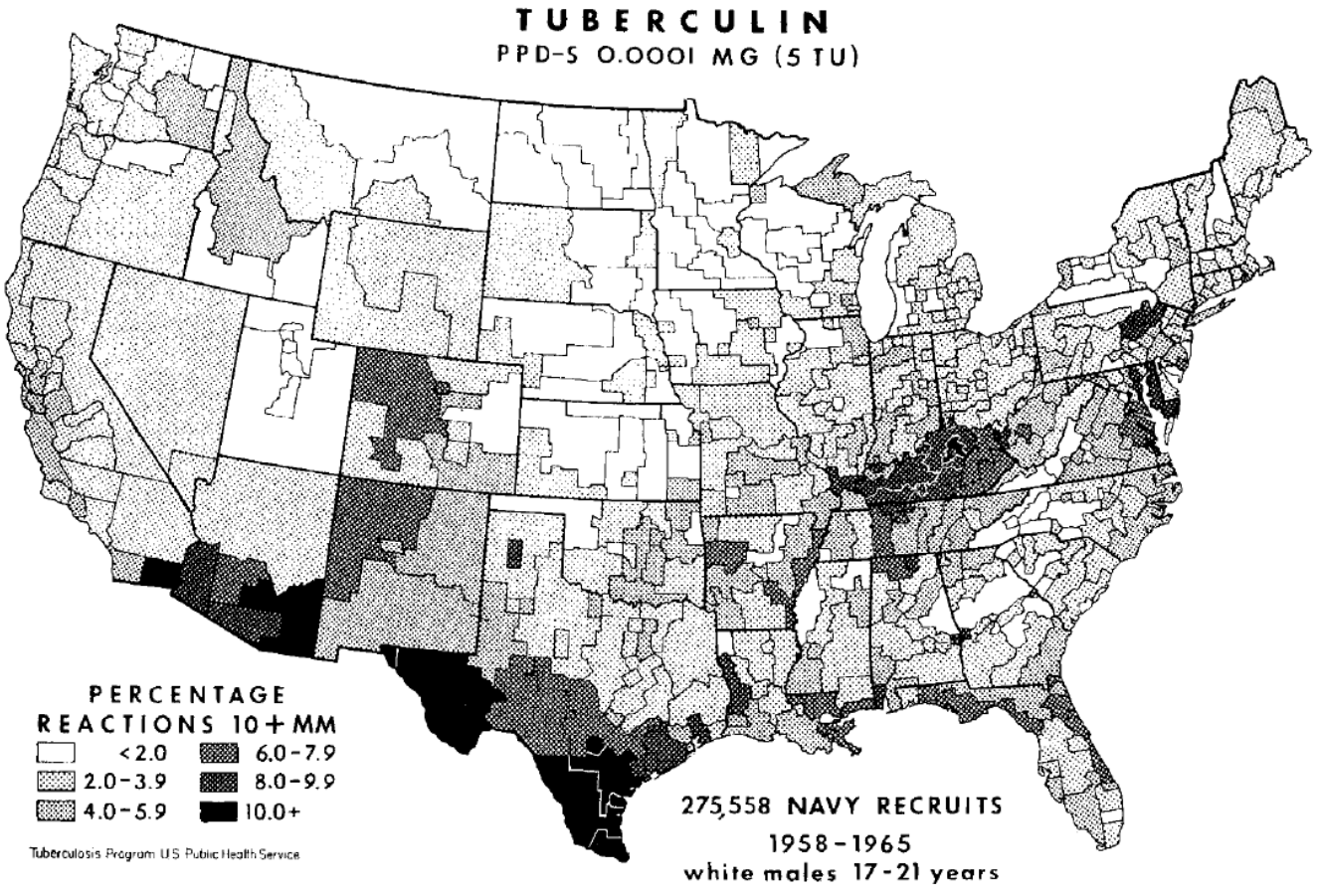


FIG. 10. Geographic variation in the frequency of reactors to 0.0001 mg PPD-S.

Figure 10 in Edwards LB, Acquaviva FA, Livesay VT, Cross FW, Palmer CE. An atlas of sensitivity to tuberculin, PPD-B, and histoplasmin in the United States. *Am Rev Respir Dis.* 1969; 99(4) Suppl: 1–132. In public domain under U.S. Public Health Service Contract No. HSM 21-69-502.

Literature review appendix 3. Positive TST prevalence among men aged 17–21 as they entered the U.S. Navy, stratified by their home county and race — 1958–1961

State	County equivalent (major city in that county if city not of same name)	Proportion with PPD-S tuberculin skin test induration of ≥8 mm		Relative prevalence
		White men	**Black men**	(Black/White)
Alabama	Jefferson (Birmingham)	19 (**4.7%**) of 404	5 (**15.2%**) of 33	3.2
Arkansas	Pulaski (Little Rock)	13 (**6.5%**) of 200	2 (**3.8%**) of 53	0.6
California	Los Angeles	143 (**4.2%**) of 3,383	17 (**11.0%**) of 154	2.6
District of Columbia		10 (**10.3%**) of 97	23 (**16.0%**) of 144	1.5
Georgia	Fulton (Atlanta)	9 (**3.0%**) of 299	7 (**10.9%**) of 64	3.6
Illinois	Cook (Chicago)	219 (**6.9%**) of 3,167	102 (**23.2%**) of 439	3.4
Indiana	Lake (Gary)	23 (**4.9%**) of 468	12 (**18.8%**) of 64	3.8
Indiana	Marion (Indianapolis)	20 (**3.9%**) of 518	2 (**3.8%**) of 53	1.0
Kansas	Wyandotte (Kansas City)	15 (**6.9%**) of 217	4 (**7.1%**) of 56	1.0
Kentucky	Jefferson (Louisville)	48 (**9.0%**) of 536	9 (**11.0%**) of 82	1.2
Louisiana	Baton Rouge	9 (**6.1%**) of 148	5 (**16.1%**) of 31	2.7
Louisiana	Orleans	65 (**13.5%**) of 482	30 (**22.6%**) of 133	1.7
Maryland	Baltimore	146 (**12.3%**) of 1,185	24 (**25.5%**) of 94	2.1
Michigan	Wayne (Detroit)	133 (**5.2%**) of 2,563	28 (**14.4%**) of 194	2.8
Missouri	Jackson (Kansas City)	26 (**4.6%**) of 560	6 (**12.5%**) of 48	2.7
Missouri	St. Louis	66 (**5.5%**) of 1,195	12 (**14.6%**) of 82	2.6
New Jersey	Atlantic (Atlantic City)	9 (**6.9%**) of 131	6 (**20.0%**) of 30	2.9
New Jersey	Essex (Newark)	39 (**5.9%**) of 659	7 (**16.7%**) of 42	2.8
New York	5 NYC boroughs	314 (**7.6%**) of 4,133	16 (**14.2%**) of 113	1.9
N. Carolina	Forsyth (Winston-Salem)	5 (**6.8%**) of 73	3 (**10.7%**) of 28	1.6
Ohio	Cuyahoga (Cleveland)	77 (**5.0%**) of 1,530	13 (**24.5%**) 53	4.9
Ohio	Franklin (Columbus)	34 (**6.3%**) of 544	6 (**14.0%**) of 43	2.2
Ohio	Hamilton (Cincinnati)	50 (**6.6%**) of 754	13 (**9.4%**) of 139	1.4
Ohio	Mahoning (Youngstown)	22 (**6.8%**) of 325	6 (**15.8%**) of 38	2.3
Ohio	Dayton (Montgomery)	21 (**4.8%**) of 442	3 (**12.0%**) of 25	2.5
Oklahoma	Oklahoma (Oklahoma City)	9 (**4.1%**) of 219	8 (**20.5%**) of 39	5.0
Pennsylvania	Allegheny (Pittsburgh)	152 (**7.9%**) of 1,921	12 (**17.1%**) of 70	2.2
Pennsylvania	Delaware (Chester)	20 (**5.3%**) of 374	4 (**13.8%**) of 29	2.6
Pennsylvania	Philadelphia	89 (**6.6%**) of 1,356	21 (**10.9%**) of 193	1.7
S. Carolina	Richland (Columbia)	3 (**3.2%**) of 93	5 (**14.7%**) of 34	4.6
Tennessee	Davidson (Nashville)	18 (**6.5%**) of 277	4 (**13.8%**) of 29	2.1
Tennessee	Shelby (Memphis)	6 (**3.1%**) of 192	20 (**15.9%**) of 126	5.1
Texas	Dallas	41 (**7.9%**) of 520	6 (**18.2%**) of 33	2.3
Texas	Harris (Houston)	47 (**6.8%**) of 696	9 (**8.6%**) of 105	1.3
Texas	Jefferson (Beaumont)	11 (**6.2%**) of 178	8 (**15.4%**) of 52	2.5
Virginia	Henrico (Richmond)	10 (**6.3%**) of 159	7 (**12.3%**) of 57	2.0
Virginia	Norfolk	2 (**2.0%**) of 100	11 (**22.0%**) of 50	11.0
Total "lifetime one-county" residents of these 37 counties		1,943 (**6.5%**) of 30,094	476 (**15.6%**) of 3,052	**2.4**

From Table 1 in Edwards PQ, Palmer CE. Sensitivity to histoplasmin among Negro and white residents of different communities in the USA. *Bull World Health Organ.* 1964; 30: 574–585.

NHANES appendix 1. Overview of the 3 NHANES cycles with a TB component

Overview of design changes

1971–1972

- **35 PSUs with a TST as part of examination during April 27, 1971–October 5, 1972**
  - Study locations 1–10 were the larger metropolitan areas selected with certainty
  - Study locations 11–35 were the smaller areas that were selected with probability proportional to size
  - Within study locations, deliberate oversampling of Census Enumeration Districts with higher poverty
- Deliberately oversampled ages <5, ages 65–74, and women ages 20–44
- Everyone classified as belonging to one of these three race groups:
  White (89.3%), Black (9.8%), Other (0.9%)

1999–2000

- **12 PSUs in 1999, 15 PSUs in 2000 (total of 27 PSUs)**
- Deliberately oversampled Mexican Americans, elderly, and pregnant women ages 15–39
- 76 subdomains with age/gender groupings based on three categories:
  - Black non-Hispanic
  - Mexican-American
  - White/Other
    - Included Hispanic persons other than Mexican Americans and Asians
    - Partitioned into low versus non-low income for the 15 PSUs in 2000

2011–2012

- **14 PSUs in 2011, 14 PSUs in 2012 (total of 28 PSUs)**
- Deliberately oversampled Asians
- 97 subdomains with age/gender groupings based on five categories
  - Black non-Hispanic
  - Mexican American and other Hispanic
  - White/Other and low income non-Hispanic
  - White/Other and non-low income non-Hispanic
  - Asian non-Hispanic (new addition for this cycle, 5% of the population)

76 analytic subdomains for NHANES 1999–2000

The U.S. Census Bureau's Current Population Survey for the national distribution of the civilian noninstitutionalized population into these 76 subdomains was used to sample participants and create their individual weights. Only non-Hispanic black persons and Mexican Americans were deliberately oversampled to allow for unbiased estimation within their self-reported race/ethnic group. The National Center for Health Statistics also cautions that sampling process was not intended to produce accurate population estimates for either "other Hispanics" or "all Hispanics" as a category in 1999–2000; Hispanics who are not Mexican American are included in the white/other group. Asians and other race groups are also included in the white/other category. The low versus non-low income distinction within the white/other category was not applied until 2000.

<table>
<tr><td colspan="2">Black non-Hispanic
both genders aged < 1 year</td><td colspan="2">Mexican American
both genders aged < 1 year</td><td colspan="2">Low income white/other (LIWO)
both genders aged < 1 year</td><td colspan="2">Non-low income white/other (Non-LIWO)
both genders aged < 1 year</td></tr>
<tr><td colspan="2">Black non-Hispanic
both genders aged 1–2 years</td><td colspan="2">Mexican American
both genders aged 1–2 years</td><td colspan="2">Low income white/other
both genders aged 1–2 years</td><td colspan="2">Non-low income white/other
both genders aged 1–2 years</td></tr>
<tr><td colspan="2">Black non-Hispanic
both genders aged 3–5 years</td><td colspan="2">Mexican American
both genders aged 3–5 years</td><td colspan="2">Low income white/other
both genders aged 3–5 years</td><td colspan="2">Non-low income white/other
both genders aged 3–5 years</td></tr>
<tr><td>Black non-Hispanic
males aged 6–11 yrs</td><td>Black non-Hispanic
females 6–11 yrs</td><td>Mexican American
males 6–11 yrs</td><td>Mexican American
females 6–11 yrs</td><td>LIWO
males 6–11 yrs</td><td>LIWO
females 6–11 yrs</td><td>Non-LIWO
males 6–11 yrs</td><td>Non-LIWO
females 6–11 yrs</td></tr>
<tr><td>Black non-Hispanic
males 12–15 yrs</td><td>Black non-Hispanic
females 12–15 yrs</td><td>Mexican American
males 12–15 yrs</td><td>Mexican American
females 12–15 yrs</td><td>LIWO
males 12–15 yrs</td><td>LIWO
females 12–15 yrs</td><td>Non-LIWO
males 12–15 yrs</td><td>Non-LIWO
females 12–15 yrs</td></tr>
<tr><td>Black non-Hispanic
males 16–19 yrs</td><td>Black non-Hispanic
females 16–19 yrs</td><td>Mexican American
males 16–19 yrs</td><td>Mexican American
females 16–19 yrs</td><td>LIWO
males 16–19 yrs</td><td>LIWO
females 16–19 yrs</td><td>Non-LIWO
males 16–19 yrs</td><td>Non-LIWO
females 16–19 yrs</td></tr>
<tr><td rowspan="2">Black non-Hispanic
males 20–39 yrs</td><td rowspan="2">Black non-Hispanic
females 20–39 yrs</td><td rowspan="2">Mexican American
males 20–39 yrs</td><td rowspan="2">Mexican American
females 20–39 yrs</td><td>LIWO
males 20–29 yrs</td><td>LIWO
females 20–29 yrs</td><td>Non-LIWO
males 20–29 yrs</td><td>Non-LIWO
females 20–29 yrs</td></tr>
<tr><td>LIWO
males 30–39 yrs</td><td>LIWO
females 30–39 yrs</td><td>Non-LIWO
males 30–39 yrs</td><td>Non-LIWO
females 30–39 yrs</td></tr>
<tr><td rowspan="2">Black non-Hispanic
males 40–59 yrs</td><td rowspan="2">Black non-Hispanic
females 40–59 yrs</td><td rowspan="2">Mexican American
males 40–59 yrs</td><td rowspan="2">Mexican American
females 40–59 yrs</td><td>LIWO
males 40–49 yrs</td><td>LIWO
females 40–49 yrs</td><td>Non-LIWO
males 40–49 yrs</td><td>Non-LIWO
females 40–49 yrs</td></tr>
<tr><td>LIWO
males 50–59 yrs</td><td>LIWO
females 50–59 yrs</td><td>Non-LIWO
males 50–59 yrs</td><td>Non-LIWO
females 50–59 yrs</td></tr>
<tr><td rowspan="3">Black non-Hispanic
males ≥60 yrs</td><td rowspan="3">Black non-Hispanic
females ≥60 yrs</td><td rowspan="3">Mexican American
males ≥60 yrs</td><td rowspan="3">Mexican American
females ≥60 yrs</td><td>LIWO
males 60–69 yrs</td><td>LIWO
females 60–69 yrs</td><td>Non-LIWO
males 60–69 yrs</td><td>Non-LIWO
females 60–69 yrs</td></tr>
<tr><td>LIWO
males 70–79 yrs</td><td>LIWO
females 70–79 yrs</td><td>Non-LIWO
males 70–79 yrs</td><td>Non-LIWO
females 70–79 yrs</td></tr>
<tr><td>LIWO
males ≥80 yrs</td><td>LIWO
females ≥80 yrs</td><td>Non-LIWO
males ≥80 yrs</td><td>Non-LIWO
females ≥80 yrs</td></tr>
</table>

97 analytic subdomains for NHANES 2011–2012

Technical notes about the 2011–2012 subdomains: The U.S. Census Bureau's American Community Survey for the national distribution of the civilian noninstitutionalized population into these 97 subdomains was used to sample participants and create their individual weights. Although the Current Population Survey had been used in previous NHANES cycles, the American Community Survey was thought to have better quality data for Asians, the race/ethnic group deliberately oversampled in this cycle.

<table>
<tr><td colspan="2">Black (non-Hispanic)
both genders aged < 1 year</td><td colspan="2">Hispanic
both genders aged < 1 year</td><td colspan="2">Asian (non-Black and non-Hispanic)
both genders aged < 1 year</td><td colspan="2">Low income white/other (LIWO)
both genders aged < 1 year</td><td colspan="2">Non-LIWO both genders aged < 1 year</td></tr>
<tr><td colspan="2">Black
both genders aged 1–2 years</td><td colspan="2">Hispanic
both genders aged 1–2 years</td><td colspan="2">Asian
both genders aged 1–2 years</td><td colspan="2">LIWO both genders aged 1–2 years</td><td colspan="2">Non-LIWO both genders aged 1–2 years</td></tr>
<tr><td colspan="2">Black
both genders aged 3–5 years</td><td colspan="2">Hispanic
both genders aged 3–5 years</td><td colspan="2">Asian
both genders aged 3–5 years</td><td colspan="2">LIWO both genders aged 3–5 years</td><td colspan="2">Non-LIWO both genders aged 3–5 years</td></tr>
<tr><td>Black males 6–11 yrs</td><td>Black females 6–11 yrs</td><td>Hispanic males 6–11 yrs</td><td>Hispanic females 6–11 yrs</td><td>Asian males 6–11 yrs</td><td>Asian females 6–11 yrs</td><td>LIWO males 6–11 yrs</td><td>LIWO females 6–11 yrs</td><td>Non-LIWO males 6–11 yrs</td><td>Non-LIWO females 6–11 yrs</td></tr>
<tr><td>Black males 12–19 yrs</td><td>Black females 12–19 yrs</td><td>Hispanic males 12–19 yrs</td><td>Hispanic females 12–19 yrs</td><td>Asian males 12–19 yrs</td><td>Asian females 12–19 yrs</td><td>LIWO males 12–19 yrs</td><td>LIWO females 12–19 yrs</td><td>Non-LIWO males 12–19 yrs</td><td>Non-LIWO females 12–19 yrs</td></tr>
<tr><td rowspan="2">Black males 20–39 yrs</td><td rowspan="2">Black females 20–39 yrs</td><td rowspan="2">Hispanic males 20–39 yrs</td><td rowspan="2">Hispanic females 20–39 yrs</td><td rowspan="2">Asian males 20–39 yrs</td><td rowspan="2">Asian females 20–39 yrs</td><td>LIWO males 20–29 yrs</td><td>LIWO females 20–29 yrs</td><td>Non-LIWO males 20–29 yrs</td><td>Non-LIWO females 20–29 yrs</td></tr>
<tr><td>LIWO males 30–39 yrs</td><td>LIWO females 30–39 yrs</td><td>Non-LIWO males 30–39 yrs</td><td>Non-LIWO females 30–39 yrs</td></tr>
<tr><td>Black males 40–49 yrs</td><td>Black females 40–49 yrs</td><td>Hispanic males 40–49 yrs</td><td>Hispanic females 40–49 yrs</td><td>Asian males 40–49 yrs</td><td>Asian females 40–49 yrs</td><td>LIWO males 40–49 yrs</td><td>LIWO females 40–49 yrs</td><td>Non-LIWO males 40–49 yrs</td><td>Non-LIWO females 40–49 yrs</td></tr>
<tr><td>Black males 50–59 yrs</td><td>Black females 50–59 yrs</td><td>Hispanic males 50–59 yrs</td><td>Hispanic females 50–59 yrs</td><td>Asian males 50–59 yrs</td><td>Asian females 50–59 yrs</td><td>LIWO males 50–59 yrs</td><td>LIWO females 50–59 yrs</td><td>Non-LIWO males 50–59 yrs</td><td>Non-LIWO females 50–59 yrs</td></tr>
<tr><td rowspan="3">Black males ≥60 yrs</td><td rowspan="3">Black females ≥60 yrs</td><td rowspan="3">Hispanic males ≥60 yrs</td><td rowspan="3">Hispanic females ≥60 yrs</td><td rowspan="3">Asian males ≥60 yrs</td><td rowspan="3">Asian females ≥60 yrs</td><td>LIWO males 60–69 yrs</td><td>LIWO females 60–69 yrs</td><td>Non-LIWO males 60–69 yrs</td><td>Non-LIWO females 60–69 yrs</td></tr>
<tr><td>LIWO males 70–79 yrs</td><td>LIWO females 70–79 yrs</td><td>Non-LIWO males 70–79 yrs</td><td>Non-LIWO females 70–79 yrs</td></tr>
<tr><td>LIWO males ≥80 yrs</td><td>LIWO females ≥80 yrs</td><td>Non-LIWO males ≥80 yrs</td><td>Non-LIWO females 50–≥80 yrs</td></tr>
</table>

Major data elements and participation overview across all 3 NHANES cycles

Survey component	1971–1972	1999–2000	2011–2012
Total no. SPs interviewed at home	n=2,279 age ≥25 from 35 PSUs	n=9,493 age ≥1 from 27 PSUs	n=8,161 age ≥6 from 31 PSUs
Demographics (DMQ)	asked of all SPs *but no Hispanic or Asian categories (all = "other")*	asked of all SPs *but no Asian category (all = "other")*	asked of all SPs
Socioeconomic variables	asked of all SPs	asked of all SPs	asked of all SPs
Housing (HOQ)	asked of all SPs	asked of all SPs	asked of all SPs
Family income (INQ)	asked of all SPs	asked of all SPs	asked of all SPs
Current health (HSQ)	asked of all SPs	asked if SP age ≥12	asked if SP age ≥12
Diet and nutrition (DBQ)	asked of all SPs	asked of all SPs	asked of all SPs
Medications (RXQ)	asked of all SPs	asked of all SPs	asked of all SPs
Medical conditions (MCQ)	asked of all SPs	asked if SP age ≥1	asked if SP age ≥1
Tobacco use (SMQ)	not asked	asked if SP age ≥20	asked if SP age ≥18
Alcohol use (ALQ)	asked of all SPs	asked if SP age ≥20	asked if SP age ≥18
Drug use (DUQ)	not asked	asked if SP age 12–59	asked if SP age 12–69
Diabetes (DIQ)	asked of all SPs	asked if SP age ≥1	asked if SP age ≥1
Kidney conditions (KIQ)	asked of all SPs	asked if SP age ≥20	asked if SP age ≥20
Respiratory health (RDQ)	asked of all SPs	asked if SP age ≥1	not asked
Tuberculosis history (TBQ)	asked all (even age <25)	**asked if SP age ≥1**	**asked if SP age ≥6**
Total no. SPs examined in MEC	n=1,891 age ≥25 (83% of interviewed)	n=8,832 age ≥1 (93% of interviewed)	n=7,821 age ≥6 (96% of interviewed)
Total no. examined SPs who had TST placed	**n=1,580 age ≥25** (84% of examinees)	n=7,613 age ≥1 (86% of examined)	n=6,350 age ≥6 (81% of examined)
Total no. examined SPs who had TST read	**n=1,494 age ≥25** (79% of examinees)	**n=7,386 age ≥1** (84% of examinees)	**n=6,128 age ≥6** (78% of examinees)
Total no. examined SPs with IGRA results	not obtained	not obtained	n=7,107 **age ≥6** (91% of examinees)
Body measurements	obtained from all SPs	obtained from all SPs	obtained from all SPs
Chest x-ray	obtained if SP age ≥25	not obtained	not obtained
Physician exam	obtained if SP age ≥25	obtained from all SPs	obtained from all SPs
Diabetes screening	Urine only (no blood test compoennt): dipstick glucose obtained if SP age ≥25	Blood tests: Random (and fasting, if examined in morning) glucose and Hgb A1C obtained if SP age ≥12	Blood tests: Random (and fasting, if morning) glucose, Hgb A1C, and oral glucose tolerance test if age ≥12
HIV test	not obtained	obtained if SP age 18–49	obtained if SP age 18–59
Vitamin D level	not obtained	obtained in 2000 only, only available in RDC	obtained if SP age ≥1

SP = survey participant, PSU = primary sampling unit, MEC = mobile examination center,
TST = tuberculin skin test, IGRA = interferon-gamma release assay blood test for tuberculosis infection

NHANES appendix 2. Data dictionary for public-use and restricted variables

NHANES public-use dataset variables

NHANES cycle	Filename	Variable name	Variable description
NHANES 1971–1972	D_4081	SEQN	Respondent sequence number
		N1AH0025	TOTAL SAMPLE PERSONS IN HOUSEHOLD
		N1AH0101	AGE AT INTERVIEW
		N1AH0104	SEX OF EXAMINED PERSON
		N1AH0144	AGE AT EXAMINATION
		N1AH0194	**STRATA 1/** variable corresponds to PSU for study locations 1–10, which were the larger metropolitan areas selected with certainty, and to stratum for study locations 11–35, which were the smaller areas selected with probability proportional to size
		N1AH0196	**PRIMARY SAMPLING UNITS 1/** variable corresponds to segment (secondary sampling unit) for locations 1–10 and to PSU for locations 11–35
	D_4091	SEQN	Respondent sequence number
		N1GM0718	HAVE YOU EVER BEEN TESTED FOR TB?
		N1GM0719	HOW WERE YOU TESTED? (SKIN TEST)
		N1GM0720	HOW WERE YOU TESTED? (CHEST X-RAY)
		N1GM0721	HOW WERE YOU TESTED? (SPUTUM EXAMINATION)
		N1GM0729	WHAT DID DOCTOR SAY THE CONDITION AFFECTING YOUR CHEST WAS?
		N1GM0739	OTHER DISEASES OF THE UPPER RESPIRATORY TRACT
		N1GM0743	WHEN YOU SEE THE DOCTOR ABOUT YOUR CONDITION, HOW OFTEN DO YOU RECEIVE CHEST XRAY?
		N1GM0744	DOES HE PRESCRIBE MEDICINE FOR THE CONDITION?
		N1GM0366	FIRST CONDITION THAT STAYED IN HOPSIITAL FOR
		N1GM0368	SECOND CONDITION THAT STAYED IN HOPSIITAL FOR
		N1GM0370	THIRD CONDITION THAT STAYED IN HOPSIITAL FOR
		N1GM0372	FIRST CONDITION HOW LONG WERE IN THE HOSPITAL
		N1GM0374	SECOND CONDITION HOW LONG IN THE HOSPITAL
		N1GM0376	THIRD CONDITION HOW LONG WERE IN THE HOSPITAL

NHANES 1971–1972	D_4233	SEQN	Respondent sequence number
		N1ME0020	HIGHEST GRADE ATTENDED-HEAD OF HOUSEHOLD
		N1ME0023	TOTAL NUMBER OF PERSONS IN HOUSEHOLD
		N1ME0034	TOTAL FAMILY INCOME GROUP
		N1ME0095	**FAMILY UNIT CODE**
		N1ME0103	(restricted variable **HHID** in later cycles)
		N1ME0110	RACE OF EXAMINED PERSON (white, black, other)
		N1ME0130	PLACE OF BIRTH (a dichotomized variable in later cycles)
		N1ME0132	CLASS OF WORKER BUSINESS OR INDUSTRY CODE
		N1ME0135	OCCUPATION CODE
		N1ME0138	**DATE OF EXAM** (restricted variable **RIAEXDT** in later cycles)
		N1ME0147	POVERTY INDEX (X.XX)
		N1ME0164	Interview weight, ALL SAMPLE PERSONS-LOCATIONS 1-35 **(equivalent of variable WTINT2YR in later cycles)**
		N1ME0158	Exam weight, DETAILED PERSONS-LOCATIONS 1-35 **(equivalent of variable WTMEC2YR in later cycles)**
	D_4251	SEQN	Respondent sequence number
		N1XR0552	**PPD-S INDURATION (MM) (LEFT ARM)**
		N1XR0556	WHERE WERE RESULTS READ?
		N1XR0557	DAYS BETWEEN TEST AND READING
		N1XR0558	TYPE OF READER
		N1XR0559	WAS TEST READ?
		N1XR0293	ETIOLOGY OF LUNG NODULES (INFECTIOUS OR NOT)
		N1XR0358	ETIOLOGY OF LUNG NODULES (INFECTIOUS OR NOT)
		N1XR0423	ETIOLOGY OF LUNG NODULES (INFECTIOUS OR NOT)
		N1XR0300	UNDERLYING CONDITIONS (GRANULOMATOUS)
		N1XR0365	UNDERLYING CONDITIONS (GRANULOMATOUS)
		N1XR0430	UNDERLYING CONDITIONS (GRANULOMATOUS)
NHANES 1999–2000 (SDDSRVYR = 1)	DEMO	SEQN	Respondent sequence number
		RIDSTATR	Interview/Examination Status
		RIAGENDR	Gender
		RIDAGEYR	Age at Screening Adjudicated - Recode
		RIDRETH2	Linked NH3 Race/Ethnicity - Recode
		DMDBORN	Country of Birth – **Recode** **(this has been recoded as a dichotomized variable)**
		DMDYRSUS	Length of time in US

		DMDEDUC2	Education Level - Adults 20+
		INDFMPIR	Family Poverty Income Ratio
		DMDHRBRN	HH Ref Person Country of Birth (also dichotomized)
		DMDHREDU	HH Ref Person Education Level
		DMDHSEDU	HH Ref Person's Spouse Education Level
		WTINT2YR	Full Sample 2 Year Interview Weight
		WTMEC2YR	Full Sample 2 Year MEC Exam Weight
		SDMVPSU	Masked Variance Pseudo-PSU
		SDMVSTRA	Masked Variance Pseudo-Stratum
	TBQ	SEQN	Respondent sequence number
		TBQ010	Ever had TB/tuberculosis skin test
		TBQ020	Ever told had positive TB skin test
		TBQ030	Prescribed medicine for preventing TB
		TBQ040	Ever told you had active TB
		TBQ050	Prescribed medicine for active TB
		TBQ060	Lived in household TB sick person
	TB	SEQN	Respondent sequence number
		TBQ070	Ever had a severe reaction to TB test?
		TBDPPDS	**PPDS induration (mm)**
NHANES 2011–2012 (SDDSRVYR = 7)	DEMO_G	SEQN	Respondent sequence number
		RIDSTATR	Interview/Examination status
		RIAGENDR	Gender
		RIDAGEYR	Age in years at screening
		RIDRETH3	Race/Hispanic origin w/ NH Asian
		RIDEXAGY	Age in years at exam - 2 to 19 years
		DMDBORN4	**Country of birth (recoded as dichotomized variable)**
		DMDYRSUS	Length of time in US
		DMDEDUC2	Education level - Adults 20+
		WTINT2YR	Full sample 2 year interview weight
		WTMEC2YR	Full sample 2 year MEC exam weight
		SDMVPSU	Masked variance pseudo-PSU
		SDMVSTRA	Masked variance pseudo-stratum
		INDFMPIR	Ratio of family income to poverty
		DMDHRBR4	HH ref person's country of birth (also dichotomized)
			HH ref person's education level
		HMDHREDU	HH ref person's spouse's educ level
		DMDHSEDU	
	TBQ_G	SEQN	Respondent sequence number
		TBQ010	Ever had TB/tuberculosis skin test
		TBQ015a	Did you receive the skin test
		TBQ022	Told your skin test was positive for TB
		TBQ030	Prescribed medicine for preventing TB
		TBQ040	Ever told you had active TB
		TBQ050	Prescribed medicine for active TB
		TBQ060	Lived in household TB sick person
	TBX_G	SEQN	Respondent sequence number
		TBQ070	Had a severe reaction to a TB skin test?
		TBDRUIND	**Induration in mm of the tuberculin skin test**
	TB_G	SEQN	Respondent sequence number
		LBXTBIN	**TB coded result of the IGRA blood test**

NHANES restricted variables available only in the NCHS Research Data Center

NHANES cycle	**Variable name**	**Variable description** (only accessed in the NCHS Research Data Center as part of approved RDC proposals 1520, 1554, and 1555 and even then, some of these were masked by NCHS)
NHANES 1999–2000 and NHANES 2011–2012	SEQN	Respondent sequence number
	T_VSTRA	Unmasked equivalent of SDMVSTRA (major stratum)
	T_VPSU	Unmasked equivalent of SDMVPSU (primary sampling unit)
	STATE2K	2-digit FIPS code for state
	CNTY2K	3-digit FIPS code for county (or county equivalent)
	TRACT2K	6-digit FIPS code for Census tract
	BG2K	1-digit Census block group code
	BLOCK2K	4-digit Census block code
	HHID	NHANES household unit ID
	RIAEXDT	Date of MEC examination (when TST would be placed)

NHANES appendix 3. NHANES sampling frame details

NHANES instructions for how to collapse and recode 1971–1972 study locations to enable accurate variance estimation.

In the NHANES 1971–1972 public-use dataset, variable N1AH0194 corresponds to PSU for the metropolitan PSUs numbered 1–10 but to major stratum for the nonmetropolitan PSUs. Variable N1AH0196 corresponds to segment (secondary sampling unit) within the metropolitan PSUs but to PSU within the nonmetropolitan major strata 11–35. HANES I ran from April 1971 through June 1974. However, TSTs were aborted on October 5, 1972. To estimate variance accurately with this aborted dataset, NCHS provided documentation (*NCHS 1991*) explaining how to collapse and recode the sampling design parameters:

Metropolitan PSUs selected with certainty or with 0.5 probability for NHANES 1971–1972

- Recode Northeast study locations 1 and 2 as PSUs 1 and 2 within major stratum 1
- Recode Northeast study locations 3 and 6 as PSUs 1 and 2 within major stratum 3
- Recode Midwest location 4 and West location 5 as PSUs 1 and 2 within major stratum 4
- Retain original PSU and segment identities for Midwest locations 7, Northeast locations 8 and 9, and West location 10, but recode location #s as strata #s, and recode the segment #s as PSU #s

Nonmetropolitan PSUs 11–35 selected with probability proportional to population size

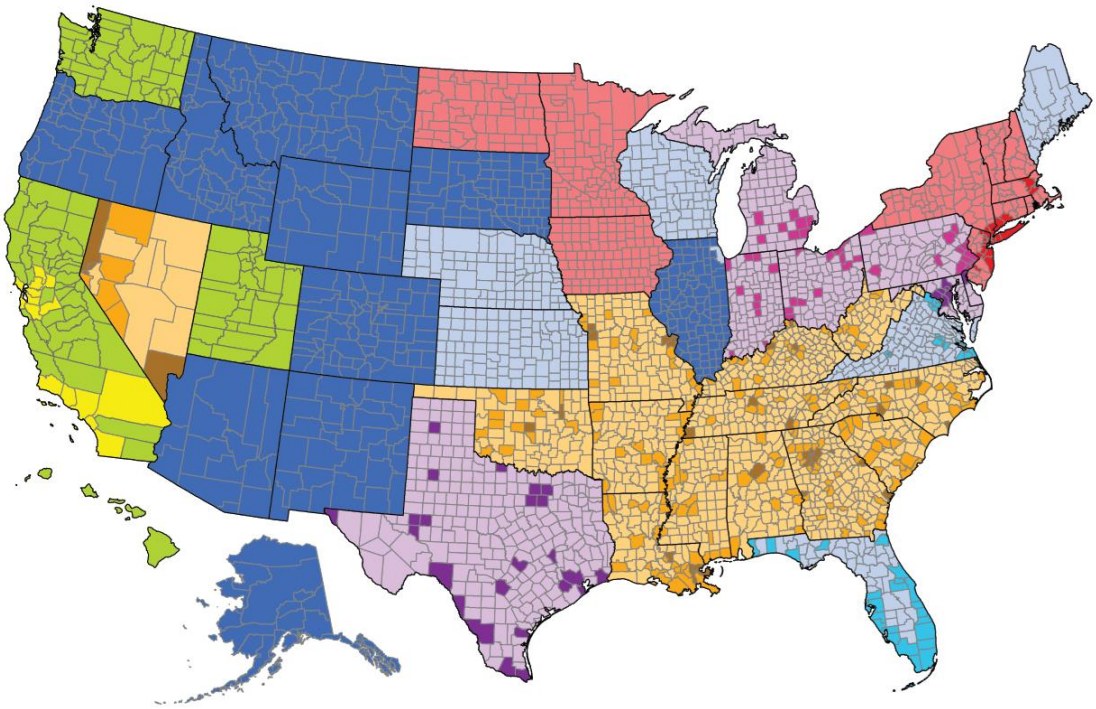
- Recode Northeast study locations 11 and 12 as PSUs 1 and 2 in major stratum 11
- Retain original PSU and segment identities for Northeast location 13, but recode PSU # as stratum 13, and recode segment #s as the PSU #s
- Recode Northeast location 14 and Midwest location 21 as PSUs 1 and 2 in stratum 14
- Recode Midwest locations 15 and 16 as PSUs 1 and 2 in stratum 15
- Recode Midwest locations 17 and 20 as PSUs 1 and 2 in stratum 17
- Recode Midwest locations 18 and 19 as PSUs 1 and 2 in stratum 18
- Recode Southeast locations 22 and 25 as PSUs 1 and 2 in stratum 22
- Recode Southeast locations 23 and 24 as PSUs 1 and 2 in stratum 23
- Recode Southeast locations 26 and 27 as PSUs 1 and 2 in stratum 26
- Recode Southeast locations 28 and 29 as PSUs 1 and 2 in stratum 28
- Recode West locations 30 and 35 as PSUs 1 and 2 in stratum 30
- Recode West locations 31 and 32 as PSUs 1 and 2 in stratum 31
- Recode West locations 33 and 34 as PSUs 1 and 2 in stratum 33

* National Center for Health Statistics. Public Use Data Tape Documentation: Chest X-Ray, Pulmonary Diffusion, and Tuberculin Skin Test Results, Ages 25–74, Tape Number 4251, National Health and Nutrition Examination Survey, 1971–75. Hyattsville, MD: National Center for Health Statistics, 1991.

NHANES sampling frame for 2011–2012

Note: Geographic documentation is unusually detailed this cycle. No map like this available previously.

Map showing the 14 major strata used in the design of NHANES 2011–2012.



Major stratum	Description
11	PSUs in state group 1† with less than 4.7% of the population living in rural areas of the Northeast
12	PSUs in state group 1†: – with 4.7% or more of the population living in rural areas of the Northeast; or, – in the Midwest
13	PSUs in state group 1† in the West
21	PSUs in California (state group 2) with less than 10.0% of the population living in rural areas
22	PSUs in California (state group 2) with 10.0% or more of the population living in rural areas, with the exception of two PSUs with rural population less than 10.0%
31	PSUs in state group 3† with less than 20.0% of the population living in rural areas of the South
32	PSUs in state group 3† in South Dakota, Illinois (except for Cook County), and all others in the West
33	PSUs in state group 3†: – with 20.0% or more of the population living in rural areas of the South; or, – in the Northeast; or, – in the Midwest and not included in major stratum 32

Major stratum	Description
41	PSUs in state group 4† with less than 13.3% of the population living in rural areas of the South
42	PSUs in state group 4†: – with less than 21.0% of the population living in rural areas of the Northeast; or, – with less than 21.6% of the population living in rural areas of the Midwest
43	PSUs in state group 4†: – with 21.0% or more of the population living in rural areas of the Northeast; or, – with 21.6% or more of the population living in rural areas of the Midwest; or, – with 13.3% or more of the population living in rural areas of the South
51	PSUs in state group 5† with less than 11.0% of the population living in rural areas of the South, Midwest, or West
52	PSUs in state group 5† with 11.0% to less than 42.0% of the population living in rural areas of the South, Midwest, or West
53	PSUs in state group 5† with 42.0% or more of the population living in rural areas of the South, Midwest, or West

 From Figure on page 25, Johnson CL, Dohrmann SM, Burt VL, Mohadjer LK. National Health and Nutrition Examination Survey: sample design, 2011–2014. *Vital Health Stat.* 2014; 2(162): 1–25. Available at: http://www.cdc.gov/Nchs/Data/Series/Sr_02/Sr02_162.Pdf.

Missing data and NHANES 1971–1972 appendix

TST completeness by exam date and study location, as recorded in the NHANES 1971–1972 public-use dataset.

Study location*	MEC dates when TST part of exam**	Total no. inter-viewed **N=5,595**	Total no. examined in MEC** **N=1,891**	Total no. with valid TST **N=1,494**	Date last TST placed (No. days before last MEC date)	**Participants missing TST results (N=397)**	
						No. (%) participants despite exam date ≤ date last TST was placed *(missingness unexplained)* **n=273**	No. (%) participants whose exam date > date last TST was placed *(missingness explained)* **n=124**
3	4/27/71–5/26/71	145	45	39	5/25/71 (–1 day)	3	3
8	5/24/71–6/12/71	97	42	29	6/10/71 (–2 days)	6	7
11	6/4/71–6/25/71	99	34	33	6/24/71 (–1 day)	0	1
14	6/16/71–7/3/71	116	42	32	6/28/71 (–5 days)	2	8
9	7/31/71–8/12/71	165	57	49	8/10/71 (–2 days)	6	2
7	7/13/71–8/25/71	188	71	50	8/24/71 (–1 day)	**19**	2
6	8/18/71–9/29/71	135	48	42	9/25/71 (–4 days)	4	2
12	8/19/71–9/11/71	93	34	31	9/9/71 (–2 days)	0	3
18	9/4/71–9/24/71	117	37	33	9/23/71 (–1 day)	3	1
2	9/18/71–11/2/71	119	44	41	10/30/71 (–3 days)	1	2
20	10/2/71–10/23/71	109	41	28	10/21/71 (–2 days)	10	3
19	10/14/71–11/6/71	111	35	20	11/4/71 (–2 days)	9	6
5	11/5/71–12/18/71	209	72	52	12/15/71 (–3 days)	15	5
27	11/11/71–12/8/71	132	40	39	12/7/71 (–1 day)	0	1
24	11/16/71–12/14/71	113	26	17	12/11/71 (–3 days)	8	1
25	1/20/72–2/26/72	212	76	62	2/23/72 (–3 days)	10	4
31	1/20/72–2/12/72	144	51	44	2/10/72 (–2 days)	1	6
30	1/27/72–3/11/72	215	80	65	3/9/72 (–2 days)	12	3
32	2/19/72–3/17/72	146	46	40	3/14/72 (–3 days)	3	3
Note that in March 1972, NHANES began giving participants $10 remuneration for participating in the medical examination.							

28	3/4/72–4/18/72	279	99	85	4/15/72 (–3 days)	11	3
35	3/4/72–4/29/72	301	108	92	4/27/72 (–2 days)	10	6
10	3/24/72–5/2/72	251	84	79	4/29/72 (–3 days)	4	1
23	4/25/72–5/16/72	110	38	30	5/11/72 (–5 days)	3	5
26	5/6/72–6/7/72	189	58	49	6/3/72 (–4 days)	7	2
33	5/12/72–6/3/72	168	58	54	6/3/72	4	0
1	5/31/72–7/8/72	180	62	40	7/1/72 (–7 days)	15	7
34	6/10/72–7/1/72	122	42	34	6/28/72 (–3 days)	5	3
17	6/16/72–7/7/72	131	40	33	7/5/72 (–2 days)	3	4
21	7/13/72–8/3/72	177	56	40	8/1/72 (–2 days)	8	8
13	7/15/72–8/5/72	143	46	31	8/2/72 (–3 days)	9	6
4	7/15/72–8/26/72	192	70	53	8/24/72 (–2 days)	13	4
22	8/9/72–9/16/72	147	52	33	9/14/72 (–2 days)	15	4
29	8/12/72–9/7/72	256	54	44	9/2/72 (–5 days)	5	5
16	9/2/72–9/30/72	176	63	25	9/30/72	**38**	0
15	9/16/72–10/7/72	108	40	26	10/5/72 (–2 days)	11	3

* Study location number as denoted in the public-use dataset (not chronologic). According to study design documentation, study locations 1–10 corresponded to metropolitan PSUs 1–10, cities with populations of ≥2 million population that were selected with certainty. Metropolitan PSUs 1–3, 6, 8–9 were located in the Northeast; metropolitan PSUs 4 and 7 in the Midwest; and metropolitan PSU 5 in the West. The less densely populated study locations 11–35 were selected with probability proportional to population size from the rest of the national sampling frame of 1,890 PSUs sorted into 25 strata that were classified into four regions: nonmetropolitan PSUs 11–14 were the Northeast (Region 1); PSUs 15–21 in the Midwest (Region 2); PSUs 22–29 in the Southeast (Region 3); and PSUs 30–35 in the West (Region 4).

** This 1,891 reflects examined adults aged 25–74 years beginning April 27, 1971, through October 5, 1972, while the TST was still a standard component of the HANES I medical examination (i.e., examined adult participants with SEQN=228 through SEQN=10127, but excluding study location 4 participant with SEQN=9045 who was not examined until 1973). Additional examinations at these PSUs that occurred after October 7, 1972, are excluded.

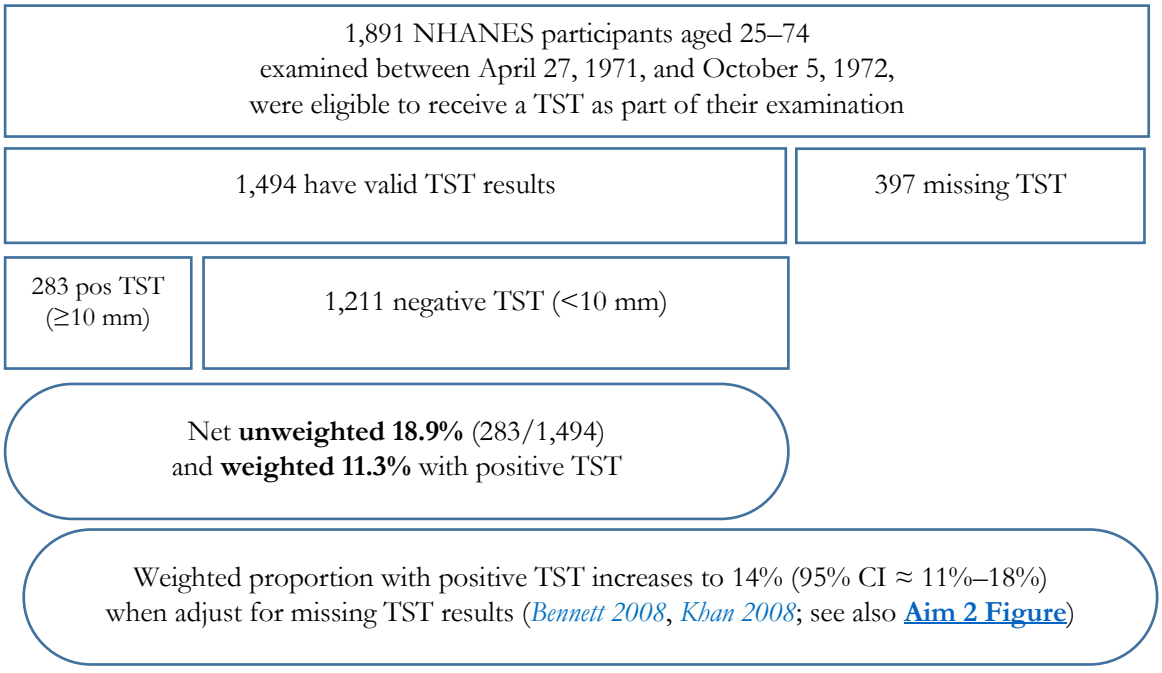
Demographic characteristics of NHANES participants with and without TST results, 1971–1972

Characteristic (due to rounding some **column** percentages do not sum to 100%)	Participants with TST results **N=1,494***	**Examined participants missing TST results (N=397)**	
		despite exam date ≤ date of last TST placement *(missingness unexplained)* **N=273**	**with exam date > date of last TST** *(missingness explained)* **N=124**
Age 25–34 years**	252 **(17%)**	62 **(23%)**	24 **(19%)**
35–44 years	240 (16%)	45 (16%)	23 (19%)
45–54 years	370 (25%)	66 (24%)	25 (20%)
55–64 years	297 (20%)	48 (18%)	30 (24%)
65–74 years	333 (22%)	52 (19%)	30 (24%)
U.S.-born**	1,353 (91%)	246 (92%)	110 (90%)
Not U.S-born	129 (9%)	23 (9%)	12 (10%)
White race	1,171 (78%)	191 (70%)	100 (81%)
Black race	307 **(21%)**	81 **(30%)**	23 **(19%)**
Other race	16 (1%)	1 (<1%)	1 (<1%)

*Of the 1,494 participants with TST results, 283 were positive (TST recorded as measuring ≥10 mm), and the remaining 1,211 were negative. See next table for more information.

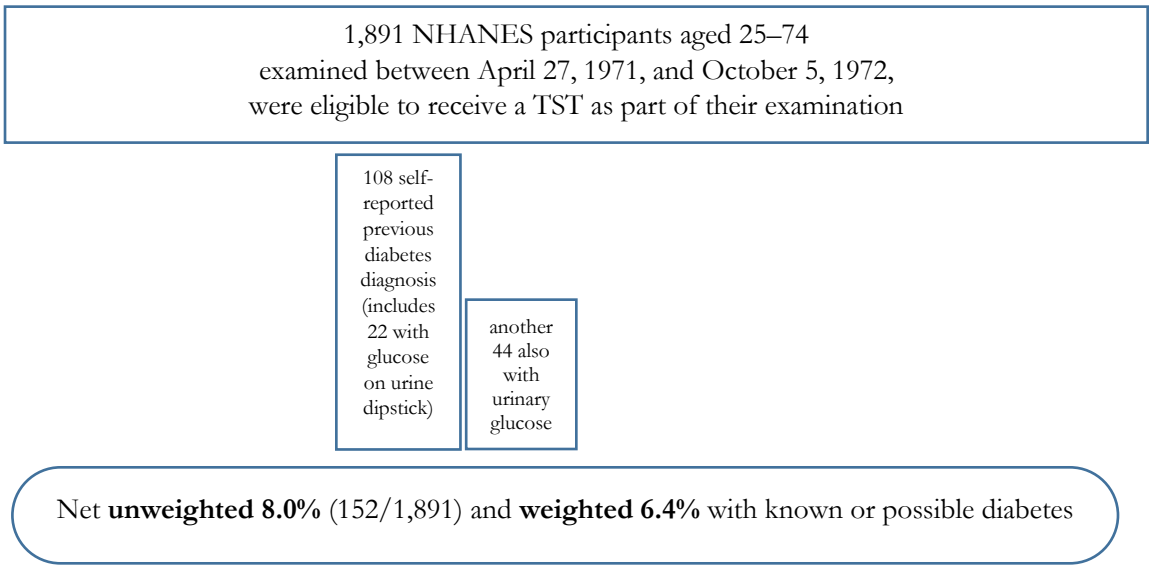
** Age not available for 2 participants and birthplace not available for 18 participants.

Overview of TST results in 1971–1972



Overview of diabetes screening results in 1971–1972

Known diabetes was defined on the basis of a self-reported previous diagnosis of diabetes, and **possible diabetes** was defined on the basis of urinary glucose without a self-reported previous diagnosis (i.e., possibly undiagnosed).



TST results among NHANES 1971–1972 adult participants by diabetes status and race

See aim 3 introduction	283 with positive TST (≥10 mm		1,211 with negative TST (<10 mm		397 participants missing TST results	
	White	**Black**	**White**	**Black**	**White**	**Black**
No diabetes (n=1,739)	172	78	923	190	265	96
Diabetes known (n=108)	8	**12**	52	**11**	18	**6**
Diabetes possible (n=44)	1	**4**	15	**12**	8	**2**
Total	181 (unweighted 15% and weighted 9% of those with TST results	**94** (unweighted 31% and weighted 16% of those with TST results)	990	**213**	291	**104**

In NHANES 1971–1972, diabetes was more prominent among African Americans: 47 (11%) of the 411 black participants had known or possible diabetes, compared with 102 (7%) of the 1,462 white participants. When the examination weights were applied, each prevalence decreased somewhat, to 9% and 5%, respectively.

Without adjustment for missing TST results, the prevalence of a positive TST was also higher among black participants (unweighted 31%, weighted 16%) than among white participants (unweighted 15%, weighted 9%).

The unweighted proportion of white participants with a positive TST was 16% among those without diabetes and 12% among those with diabetes. The unweighted proportion of black participants with a positive TST was 29% among those without diabetes and 41% among those with diabetes.

Aim 1 appendix 1. County-level variables developed for Aim 1 in the NCHS Research Data Center

The purpose of these discrete categories was to be able to stratify all 3,143 counties based on size, urbanity, poverty, racial/ethnic composition, and U.S. versus non-U.S. birth proportions, and to be able to conduct the analysis in the Research Data Center without knowing or inadvertently disclosing county identities.

County-level variables derived from U.S. Census (American Community Survey and Current Population Survey) and U.S. Department of Agriculture public-use datasets	
Pop1970_cty	0 = county pop < 10,000, 1 = 10,001–24,999, 2 = 25,000–99,999, 3 = 100,000+
Pop2000_cty	0 = county pop < 10,000, 1 = 10,001–24,999, 2 = 25,000–99,999, 3 = 100,000+
Pop2010_cty	0 = county pop < 10,000, 1 = 10,001–24,999, 2 = 25,000–99,999, 3 = 100,000+
Metro74	Dichotomous recode of the USDA's Rural-Urban Continuum Code (0–9) for 1974, where this variable: 0 = nonmetro (codes 4–9), 1 = metro (codes 0–3)
Metro93	Dichotomous recode of the USDA's Rural-Urban Continuum Code (0–9) for 1993, where this variable: 0 = nonmetro (codes 4–9), 1 = metro (codes 0–3)
Metro03	Dichotomous recode of the USDA's Rural-Urban Continuum Code (0–9) for 2003, where this variable: 0 = nonmetro (codes 4–9), 1 = metro (codes 0–3)
Metro13	Dichotomous recode of the USDA's Rural-Urban Continuum Code (0–9) for 2013, where this variable: 0 = nonmetro (codes 4–9), 1 = metro (codes 0–3)
Pov1970_st	Recode of Current Population Survey, 1971, State Poverty Rate (proportion per 100): 0 = <10%, 1 = 10%–15.5%, 2 = 15.6%–19.9%, 3 = 20% or more in poverty
Pov1999_cty	Recode of Small Area Income and Poverty Estimates for county's 1999 all ages in poverty, 0 = <10%, 1 = 10%–15.5%, 2 = 15.6%–19.9%, 3 = ≥20% in poverty
Pov2011_cty	Recode of Small Area Income and Poverty Estimates for county's 2011 all ages in poverty, 0 = <10%, 1 = 10%–15.5%, 2 = 15.6%–19.9%, 3 = ≥20% in poverty
RE	Race/ethnicity recode of U.S. Census totals in 1970/2000/2010 to partition counties: = 'O' for 342 counties with sizable American Indian/Alaska Native or Pacific Islander populations (≥4% of total pop), else = 'A' for 95 counties with sizable Asian populations (≥4%), else = 'H' for 377 counties with sizable Hispanic populations (≥15%), else = 'B' for 536 counties with sizable Black-non-Hispanic populations (≥15%), else = 'W' for 1,793 counties with primarily White non-Hispanic populations (≥70%).
FBprop	Non-U.S.-born proportion recode to partition counties: = 0 for the 1,702 counties with <2% of their population non-U.S.–born = 1 for the 832 counties with 2%–4.9% of their population non-U.S.–born = 2 for the 376 counties with 5%–9.9% of their population non-U.S.–born = 3 for the 233 counties with ≥10% of their population non-U.S.–born

County-level variables derived from National Tuberculosis Surveillance System (NTSS) and National Tuberculosis Genotyping Service (NTGS) datasets at CDC's Division of Tuberculosis Elimination	
RE_TB	Counties partitioned based on which race/ethnicity group in that county had the highest proportion of active TB cases reported to the NTSS during 1993–2015: = 'W' for 1,530 counties where white non-Hispanic persons had largest proportion = 'B' for 530 counties where it was black-non-Hispanic persons = 'H' for 372 counties where it was Hispanic persons = 'A' for 145 counties where it was Asian persons = 'O' for 109 counties where most TB cases occurred in persons of other race/ethnicity = 'N' for the 457 counties where no one race/ethnic group had largest proportion of TB (this 457 includes the 280 counties with no active TB cases reported in 1993–2015)
TBHx_state	County classification based on historic TB incidence data for that state: = 0 in the 12 states that had achieved <15 TB cases per 100,000 population in 1960/70s = 1 in the 11 states with 15–20 TB cases per 100,000 in in 1960/70s = 2 in D.C. and the 27 states with ≥20 cases per 100,000 in in 1960/70s (*must use state as proxy because county-level TB rates not available until 1993*)
cty9900_incid	County's average annual TB disease rate per 100,000 residents, 1999–2000
cty9900_incid_US	County's average annual TB disease rate per 100,000 U.S.-born, 1999–2000
cty9900_incid_FB	County's average annual TB disease rate per 100,000 foreign-born, 1999–2000
cty1112_incid	County's average annual TB disease rate per 100,000 residents, 2011–2012
cty1112_incid_US	County's average annual TB disease rate per 100,000 U.S.-born, 2011–2012
cty1112_incid_FB	County's average annual TB disease rate per 100,000 foreign-born, 2011–2012
cty_anyTB	Variable to denote the 280 counties with no active TB cases reported in 1993–2015 (*these counties have essentially achieved TB elimination, virtually no LTBI expected*)
USrate_pre	Ordinal recode based on 1996–2003 county TB incidence among U.S.-born: = 0 in the 622 counties with zero TB among U.S.-born persons in those 8 years = 1 in the 2,339 counties averaging <10 annual TB cases per 100,000 U.S.-born = 2 in the 182 counties averaging ≥10 annual TB cases per 100,000 U.S.-born (*to use when examining NHANES 1999–2000 to estimate how much LTBI expected*)
FBrate_pre	Ordinal recode based on 1996–2003 county TB incidence among foreign-born: = 0 in the 1,641 counties with zero TB among foreign-born persons in 8 years = 1 in the 173 counties averaging <10 annual TB cases per 100,000 foreign-born = 2 in 1,329 counties averaging ≥10 annual TB cases per 100,000 foreign-born (*to use when examining NHANES 1999–2000 to estimate how much LTBI expected*)
USrate_post	Ordinal recode based on 2008 –2015 county TB incidence among U.S.-born: = 0 in the 1,041 counties with zero TB among U.S.-born persons in those 8 years = 1 in the 2,076 counties averaging <10 annual TB cases per 100,000 U.S.-born = 2 in the 26 counties averaging ≥10 annual TB cases per 100,000 U.S.-born (*to use when examining NHANES 2011–2012 to estimate how much LTBI expected*)

FBrate_post	Ordinal recode based on 2008 –2015 county TB incidence among foreign-born: = 0 in the 1,607 counties with zero TB among foreign-born persons in 8 years = 1 in the 275 counties averaging <10 annual TB cases per 100,000 foreign-born = 2 in 1,261 counties averaging ≥10 annual TB cases per 100,000 foreign-born (*to use when examining NHANES 2011–2012 to estimate how much LTBI expected*)
	Based on the National TB Surveillance System and National TB Genotyping Service, LTBI background prevalence in the total population at the start of 2011 was able to be estimated for 1,783 counties with any TB cases (the counties with no TB cases assumed to have LTBI prevalence <1%). The 2010 Current Population Survey provided an estimate of the foreign-born population proportion for only 801 counties (including 753 with any TB cases).
Lest_cty2	= 1 in the 446 counties with an estimated LTBI prevalence < 1%, overall = 2 in the 574 counties with an estimated LTBI prevalence of 1% to < 2%, overall = 3 in the 322 counties with an estimated LTBI prevalence of 2% to < 3%, overall = 4 in the 189 counties with an estimated LTBI prevalence of 3% to < 4%, overall = 5 in the 252 counties with an estimated LTBI prevalence of 4% or more, overall
Lest_cty2_US	= 1 in the 217 counties with an estimated prevalence <0.5%, among U.S.-born = 2 in the 242 counties with an estimated prevalence of 0.5% to <1%, U.S.-born = 3 in the 207 counties with an estimated prevalence of 1% to <2%, U.S.-born = 4 in the 87 counties with an estimated prevalence of 2% or more, U.S.-born
Lest_cty2_FB	= 1 in the 70 counties with an estimated prevalence <5%, among foreign-born = 2 in the 162 counties with an estimated prevalence of 5% to <10%, foreign-born = 3 in the 221 counties with estimated prevalence of 10% to <15%, foreign-born = 4 in the 300 counties with an estimated prevalence of 15% or more, foreign-born *All of the counties selected for NHANES 2011–2012 had at least 1 TB case, and all except 2 rural counties had a foreign-born population proportion in the 2010 Current Population Survey.*

Aim 1 appendix 2. Formula and examples of method for back-calculating an estimate for the prevalence of latent *Mycobacterium tuberculosis* infection

$$\frac{\left(\begin{array}{c}\text{county's average no. active TB cases each year} \\ \text{x proportion of cases attributed to LTBI} \\ \text{x 1,000}\end{array}\right)}{\text{county population size}}$$

Let a = jurisdiction population,

b = average annual No. TB cases in that jurisdiction, and

c = proportion of TB cases attributed to recent transmission (i.e., [1 – c] = proportion attributed to latent TB infection).

Then if $b = 0$, $d = 0$ and $f = < 1\%$

Otherwise, $d = b \times (1 - c)$ and $e = \frac{d}{0.0010}$ if assume uniform 0.10% annual risk and $f = \frac{e}{a}$ (× 100 if wish to express as percentage)

or $\frac{\left(\frac{d}{0.0014}\right)}{a}$ for lower uncertainty limit or $h = \frac{\left(\frac{d}{0.0006}\right)}{a}$ for upper uncertainty limit

Variable	a	b	c	d	e	f	g	h
Jurisdiction	Jurisdiction Population	Average Annual No. TB cases	Proportion of TB cases attributed to recent transmission	Annual No. TB cases attributed to latent infection	Estimated No. residents with infection if 0.10% annual risk of progression	Estimated prevalence of infection if 0.10% annual risk of progression	Sensitivity analysis for estimated prevalence of infection: Lower uncertainty limit based on 0.14% annual risk of progression	Sensitivity analysis for estimated prevalence of infection: Upper uncertainty limit based on 0.06% annual risk of progression
Example X	any size	0		0		<1%		
Example Y	150,000	1	0	1	1,000	0.7%	0.5%	1.1%
Example Z	2,000,000	50	0.2	40	40,000	2.0%	1.4%	3.3%

Aim 1 appendix 3. Demographic characteristics pertinent to TB, and historic, recent, and modern TB disease incidence, among all 3,143 counties during NHANES 1971–1972, 1999–2000, and 2011–2012

Note: Originally in the RDC, this table contained additional columns to compare the overall national distribution to the distribution among the counties selected for NHANES participation in each of these cycles, but those columns were suppressed due to disclosure concerns.

	1971–1972	**1999–2000**	**2011–2012**
	All 3,143 counties (percent)	All 3,143 counties (percent)	All 3,143 counties (percent)
County size			
≤10,000 population at time of NHANES cycle	876 (28)	697 (22)	698 (22)
10,001–24,999	1,016 (32)	886 (28)	845 (27)
25,000–99,999	902 (29)	1,036 (33)	1,022 (33)
≥100,000	349 (11)	524 (17)	578 (18)
Non-U.S.-born population			
<2% of county's total population in 2000*	[a]	1,702 (54)	[a]
2.0%–4.9% of county's total population in 2000*		832 (26)	
5.0%–9.9% of county's total population in 2000*		376 (12)	
≥10% of county's total population in 2000*		233 (7)	
Metropolitan/urban[b]	2,495 (79)[b]	2,053 (65)	1,976 (63)
Nonmetropolitan/rural[b]	648 (21)[b]	1,090 (35)	1,167 (37)
Poverty level[c]			
<10% of population[c] in poverty	322 (10)[c]	851 (27)	310 (9)
10%–15.5% in poverty	1,407 (45)[c]	1,362 (43)	1,092 (35)
15.6%–19.9% in poverty	518 (16)[c]	558 (17)	825 (26)
≥20% in poverty	896 (29)[c]	372 (12)	916 (29)
Historic TB incidence (1963–1972)[c] based on state's total population			
Low (in state averaging <15 annual cases per 100,000)	631 (20)	—	—
Medium (15–20 cases per 100,000)	488 (16)	—	—
High (≥20 cases per 100,000)	2,024 (64)	—	—

Recent TB incidence (1996–2003)			
among county's U.S.-born population			
None (in county with 0 cases among U.S.-born)	—	622 (20)	—
Low/Medium (averaging <10 annual cases per 100,000)	—	2,339 (74)	—
High (≥10 annual cases per 100,000)	—	182 (6)	—
among county's non-U.S.–born population			
None (in county with 0 cases among non-U.S.–born)	—	1,641 (52)	—
Low/Medium (averaging <10 annual cases per 100,000)	—	173 (6)	—
High (≥10 annual cases per 100,000)	—	1,329 (42)	—
Modern TB incidence (2008–2015)			
among county's U.S.-born population			
None (in county with 0 cases among U.S.-born)	—	—	1,041 (33)
Some TB (in county with ≥1 case among U.S.-born)[d]	—	—	2,102 (67)
among county's non-U.S.–born population			
None (in county with 0 cases among non-U.S.–born)	—	—	1,607 (51)
Low/Medium (averaging <10 annual cases per 100,000)	—	—	275 (9)
High (≥10 annual cases per 100,000)	—	—	1,261 (40)

[a] U.S. Census provided an estimate of the foreign-born population size for all counties in 2000 but in other years is only available for a subset of counties.

[b] Rural-Urban Continuum Codes from the U.S. Department of Agriculture for 1974, 2003, and 2013 were dichotomized into these two categories. Note that due to changes to the metropolitan-nonmetropolitan and urban-rural criteria that were implemented after the 2000 Census, the 1974 Rural-Urban Continuum Codes are not directly comparable with those in 2003 and 2013.

[c] Measures of poverty in 1970 and TB disease incidence in 1963–1972 only available at the state level; later measures are at the county level.

[d] In 2,102 counties, at least 1 TB case occurred; this included 26 counties with an average of ≥10 cases annually per 100,000 U.S.-born persons.

Aim 1 appendix 4. Median TB disease incidence, by NHANES 2011–2012 major strata, PSUs, and counties

Major stratum description	Major stratum number (see NHANES 2011–2012 sampling frame)	Number of PSUs in stratum (n=2,840)	Number of counties in stratum (n=3,143)	Median county-level TB incidence* and 95% confidence interval		
				in total county population	among U.S.-born in county	among non-U.S.-born in county
metropolitan Northeast	**11**	23	24	**4.0 (1.9–8.1)**	**1.0 (0.4–2.7)**	**13.8 (8.4–21.5)**
Hawaii, Washington, Utah	**12**	313	349	0.0 (0.0–4.7)	0.4 (0.0–1.3)	11.4 (0.0–41.5)
rural Northeast, Midwest	**13**	66	73	0.0 (0.0–6.7)	0.5 (0.0–2.0)	14.0 (0.0–28.6)
metropolitan California	**21**	14	16	**5.9 (1.5–13.9)**	**1.7 (0.4–4.1)**	**18.5 (5.0–31.7)**
rural California	**22**	40	42	2.2 (0.0–6.4)	1.3 (0.2–3.7)	11.6 (0.0–21.5)
metropolitan Florida and Virginia	**31**	34	52	**2.9 (0.0–7.8)**	**1.5 (0.3–3.2)**	**11.1 (3.2–24.8)**
Alaska, Arizona, Colorado, Idaho, Montana, New Mexico, Oregon, South Dakota, Wyoming, and (except for Cook County) Illinois	**32**	378	467	0.0 (0.0–7.8)	0.6 (0.0–3.4)	7.3 (0.0–39.6)
rural Florida and Virginia; all of Kansas, Maine, Minnesota, and Nebraska; and metropolitan Illinois	**33**	353	436	0.0 (0.0–5.4)	0.4 (0.0–2.0)	9.2 (0.0–35.0)
metropolitan Texas	**41**	30	32	**4.5 (1.8–14.3)**	**2.0 (0.6–5.4)**	**18.6 (3.0–27.2)**
metropolitan Northeast and Midwest	**42**	42	44	1.5 (0.0–4.0)	0.7 (0.0–1.9)	12.7 (3.1–33.3)
rural Texas	**43**	499	535	0.0 (0.0–7.6)	0.4 (0.0–2.5)	7.5 (0.0–43.8)
metropolitan Southeast and Nevada	**51**	35	35	**3.0 (1.0–11.3)**	**1.8 (0.3–4.6)**	**17.4 (10.7–45.3)**
intermediate Southeast and Nevada	**52**	192	194	1.9 (0.0–7.7)	1.3 (0.0–4.7)	12.7 (0.0–42.9)
rural Southeast and Nevada	**53**	821	844	0.0 (0.0–8.2)	1.2 (0.0–5.9)	0.0 (0.0–38.4)

*per 100,000 population, as determined at the county level by taking average of all cases reported by that county (or country equivalent) to the National Tuberculosis Surveillance System during 2011 and 2012

Aim 2 appendix 1. Unweighted TB infection test results by TB history — as recorded in NHANES public-use datasets, 1999–2000 and 2011–2012

Among the 7,386 NHANES Examined Participants With Complete TST Results, 1999–2000		
Self-Reported TB History	**NHANES Test for TB Infection**	
	TST ≥10 mm Unweighted No. ()	**Positive IGRA**
History of active TB (*n* = 23)	7 (30.4)	Test not available in 1999–2000
History of positive TST but no active TB (*n* = 275)	97 (35.3)	Test not available in 1999–2000
No personal TB/positive TST history but lived in household of someone with active TB (*n* = 190)	25 (13.2)	Test not available in 1999–2000
None of the above (*n* = 6,898)	281 (4.1)	Test not available in 1999–2000

Among the 6,128 NHANES Examined Participants With Complete TST Results, 6,068 (99.0) Also Had IGRA Blood Test Results, 2011–2012		
Self-Reported TB History	**NHANES Test for TB Infection**	
	TST ≥10 mm Unweighted No. ()	**Positive IGRA Unweighted No. ()**
History of active TB (*n* = 32)	14 (43.8)	18 (56.3) of 32 tested
History of positive TST but no active TB (*n* = 203)	87 (42.9)	63 (31.2) of 202 tested
No personal TB/positive TST history but lived in household of someone with active TB (*n* = 144)	13 (9.0)	12 (8.3) of 144 tested
None of the above (*n* = 5,749)	322 (5.6)	336 (5.9) of 5,690 tested

Among the 1,693 Examined NHANES Participants with TST Item Nonresponse, 1,024 (60.5) Had IGRA Blood Test Results, 2011–2012		
Self-Reported TB History	**NHANES Test for TB Infection**	
		Positive IGRA Unweighted No. ()
History of active TB (*n* = 10)	TST item nonresponse	2 (28.6) of 7 tested
History of positive TST but no active TB (*n* = 109)	TST item nonresponse	32 (36.4) of 88 tested
No personal TB/positive TST history but lived in household of someone with active TB (*n* = 32)	TST item nonresponse	3 (14.3) of 21 tested
None of the above (*n* = 1,542)	TST item nonresponse	70 (7.7) of 908 tested

Aim 2 appendix 2. Influence of using different NHANES sampling design parameters on the estimated population prevalence of a TST result ≥10 mm.

NHANES cycle, participants with complete TST results, and corresponding noninstitutionalized U.S. civilian population	**Nesting variables used in the analysis**	**Weighted percent prevalence and 95% CI using the standard masked design variables in public-use dataset**	**Weighted percent prevalence and 95% CI using the unmasked true design variables** (only available in the Research Data Center for 1999–2000 and 2011–2012)
NHANES 1971–1972 **All participants aged 25–74 years** n=1,494 weighted to represent 81 million persons	***conventional 2-level analysis*** **major stratum, primary sampling unit (PSU)**		14.4 (11.4–18.1)
	3-level, adding level of household major stratum, PSU, household ID		**14.4** **(12.4–16.7)**
NHANES 1999–2000 **All participants aged 25–74 years** n=3,012 participants weighted to represent 140 million persons	***conventional 2-level analysis*** **major stratum, PSU**	5.5 (4.4–7.0)	5.5 (3.9–7.8)
	3-level, adding level of Census tract major stratum, PSU, Census tract		5.5 (4.6–6.7)
	4-level, adding level of block group major stratum, PSU, Census tract, block group		5.5 (4.7–6.5)
	5-level, adding individual block major stratum, PSU, tract, block group, block		5.5 (4.7–6.5)
	6-level, adding household stratum, PSU, tract, block group, block, household		5.5 (4.6–6.6)
NHANES 2011–2012 **All participants aged 25–74 years** n=3,439 participants weighted to represent 154 million persons	***conventional 2-level analysis*** **major stratum, PSU**	5.3 (3.7–7.5)	5.3 (3.7–7.5)
	3-level, adding level of Census tract major stratum, PSU, Census tract		5.3 (4.5–6.2)
	4-level, adding level of block group major stratum, PSU, Census tract, block group		5.3 (4.5–6.2)
	5-level, adding individual block major stratum, PSU, tract, block group, block		5.3 (4.6–6.1)
	6-level, adding household stratum, PSU, tract, block group, block, household		5.3 (4.6–6.1)

NHANES cycle, participants with complete TST results, and corresponding noninstitutionalized U.S. civilian population	**Nesting variables used in the analysis**	**Weighted percent prevalence and 95% CI using the standard masked design variables in public-use dataset**	**Weighted percent prevalence and 95% CI using the unmasked true design variables** (only available in the Research Data Center for 1999–2000 and 2011–2012)
NHANES 1999–2000 All participants aged ≥1 year n=7,386 participants weighted to represent 228 million persons	***conventional 2-level analysis*** **major stratum, PSU**	4.2 (3.3–5.2)	4.2 (3.0–5.7)
	3-level, adding level of Census tract major stratum, PSU, Census tract		4.1 (3.4–5.0)
	4-level, adding level of block group major stratum, PSU, Census tract, block group		4.2 (3.5–4.9)
	5-level, adding individual block major stratum, PSU, tract, block group, block		4.2 (3.5–4.9)
	6-level, adding household stratum, PSU, tract, block group, block, household		4.2 (3.5–4.9)
NHANES 1999–2000 All participants aged ≥6 years n=6,679 participants weighted to represent 215 million persons	***conventional 2-level analysis*** **major stratum, PSU**	4.4 (3.5–5.5)	4.4 (3.1–6.0)
	3-level, adding level of Census tract major stratum, PSU, Census tract		4.4 (3.6–5.3)
	4-level, adding level of block group major stratum, PSU, Census tract, block group		4.4 (3.7–5.2)
	5-level, adding individual block major stratum, PSU, tract, block group, block		4.4 (3.7–5.1)
	6-level, adding household stratum, PSU, tract, block group, block, household		**4.4** **(3.7–5.2)**
NHANES 2011–2012 All participants aged ≥6 years n=6,128 participants weighted to represent 228 million persons	***conventional 2-level analysis*** **major stratum, PSU**	4.3 (3.0–5.9)	4.3 (3.0–6.1)
	3-level, adding level of Census tract major stratum, PSU, Census tract		4.3 (3.7–4.9)
	4-level, adding level of block group major stratum, PSU, Census tract, block group		4.3 (3.7–5.0)
	5-level, adding individual block major stratum, PSU, tract, block group, block		4.3 (3.7–4.9)
	6-level, adding household stratum, PSU, tract, block group, block, household		**4.3** **(3.7–4.8)**

NHANES 1971–1972 U.S.-born participants aged 25–74 years n=1,353 weighted to represent 74 million persons	***conventional 2-level analysis*** **major stratum, PSU**		12.5 (9.6–16.2)
	3-level, adding level of household major stratum, PSU, household ID		12.5 (10.6–14.7)
NHANES 1999–2000 U.S.-born participants aged ≥6 years n=5,252 weighted to represent 183 million persons unless otherwise noted	***conventional 2-level analysis*** **major stratum, PSU**	1.9 (1.4–2.6)	1.9 (1.4–2.7)
	3-level, adding level of Census tract major stratum, PSU, Census tract		1.9 (1.5–2.5)
	4-level, adding level of block group major stratum, PSU, Census tract, block group		1.9 (1.5–2.5)
	5-level, adding individual block major stratum, PSU, tract, block group, block		1.9 (1.6–2.4)
	6-level, adding household stratum, PSU, tract, block group, block, household		1.9 (1.6–2.4)
	6-level results when subset to those participants who were the only household member to be examined (unweighted 79 percent with complete TST results, representing 80 million)		1.9 (1.4–2.7)
	6-level results when subset to participants who were in same household as other examined participants (unweighted 82 percent with complete TST results, representing 103 million)		2.0 (1.4–2.7)
NHANES 2011–2012 U.S.-born participants aged ≥6 years n=4,684 weighted to represent 193 million persons unless otherwise noted	***conventional 2-level analysis*** **major stratum, PSU**	1.5 (0.9–2.5)	1.5 (0.8–2.7)
	3-level, adding level of Census tract major stratum, PSU, Census tract		1.5 (1.1–1.9)
	4-level, adding level of block group major stratum, PSU, Census tract, block group		1.5 (1.1–2.0)
	5-level, adding individual block major stratum, PSU, tract, block group, block		1.5 (1.1–2.0)
	6-level, adding household stratum, PSU, tract, block group, block, household		1.5 (1.1–1.9)
	6-level results when subset to those participants who were the only household member to be examined (unweighted 76 percent with complete TST results, representing 82 million)		1.9 (1.3–2.6)
	6-level results when subset to participants who were in same household as other examined participants (unweighted 77 percent with complete TST results, representing 111 million)		1.2 (0.8–1.7)

NHANES 1971–1972 Non-U.S.–born participants aged 25–74 years n=129 weighted to represent 6 million persons	***conventional 2-level analysis*** **major stratum, PSU**		39.3 (28.0–51.8)
	3-level, adding level of household major stratum, PSU, household ID		39.3 (28.3–51.4)
NHANES 1999–2000 Non-U.S.–born participants aged ≥6 years n=1,423 weighted to represent 31 million persons unless otherwise noted	***conventional 2-level analysis*** **major stratum, PSU**	18.5 (13.5–24.8)	18.5 (13.0–25.6)
	3-level, adding level of Census tract major stratum, PSU, Census tract		18.5 (14.9–22.7)
	4-level, adding level of block group major stratum, PSU, Census tract, block group		18.5 (15.2–22.4)
	5-level, adding individual block major stratum, PSU, tract, block group, block		18.5 (15.4–22.0)
	6-level, adding household stratum, PSU, tract, block group, block, household		18.5 (14.9–22.8)
	6-level results when subset to those participants who were the only household member to be examined (unweighted 76 percent with complete TST results, representing 14 million)		17.8 (13.1–23.8)
	6-level results when subset to participants who were in same household as other examined participants (unweighted 78 percent with complete TST results, representing 18 million)		19.0 (14.6–24.4)
NHANES 2011–2012 Non-U.S.–born participants aged ≥6 years n=1,441 weighted to represent 35 million persons unless otherwise noted	***conventional 2-level analysis*** **major stratum, PSU**	19.8 (15.1–25.5)	19.8 (15.1–25.5)
	3-level, adding level of Census tract major stratum, PSU, Census tract		19.8 (17.5–22.3)
	4-level, adding level of block group major stratum, PSU, Census tract, block group		19.8 (17.2–22.6)
	5-level, adding individual block major stratum, PSU, tract, block group, block		19.8 (17.3–22.5)
	6-level, adding household stratum, PSU, tract, block group, block, household		19.8 (17.5–22.3)
	6-level results when subset to those participants who were the only household member to be examined (unweighted 69 percent with complete TST results, representing 15 million)		19.7 (16.7–23.0)
	6-level results when subset to participants who were in same household as other examined participants (unweighted 71 percent with complete TST results, representing 19 million)		19.9 (16.7–23.5)

Aim 2 appendix 3. SAS and SUDAAN code for replicating Aim 2 analysis.

SAS (SAS Institute, Cary, NC) and SAS-callable SUDAAN (Research Triangle Institute, Research Triangle Park, NC) code for NHANES 1999–2000 and NHANES 2011–2012 analysis, including reclassifications for borderline-positive TST results and imputations for missing TST results.

```
libname nhanes '\\ place libname path here ';

data work.nh9900_9282;
          set nhanes.nh9900;

          if RIDSTATR = 2 ;   /*to subset to the 9282 survey participants
                                                    undergoing 1999-2000 NHANES exam*/
                                                /*but note that only those age 1+ eligible for TST (n=8956)
                              --> interested in the subset of 7819 age 6+ for better comparison to 2011-2012*/

/* from TB data file in 1999-2000 NHANES
          • TBDPPDS - PPDS induration (mm)                                        */

                              if TBDPPDS = 0 then TST1 = 1;
                                        else if 0 < TBDPPDS < 10 then TST1 = 2;
                                        else if 10 le TBDPPDS < 77 then TST1 = 3;
                                        else TST1 = 9;

                              if TST1 ne 9 then VALID_TST = 1; else VALID_TST = 2;

/* from TBQ data file in 1999-2000 NHANES
          • TBQ020 - Ever told had positive TB skin test                          equiv is TBQ022 in 2011-2012
          • TBQ030 - Prescribed medicine for preventing TB
          • TBQ040 - Ever told you had active TB
          • TBQ050 - Prescribed medicine for active TB
          • TBQ060 - Lived in household TB sick person      */

                              if TBQ040 = 1 then Hx = 'active TB';
                                        else if TBQ050 = 1 then Hx = 'active TB';
                                                  /*though turns out unnecessary because they are a subset*/
                                        else if  TBQ020 = 1 then Hx = 'pos TST';
                                        else if TBQ030 = 1 then Hx = 'LTBI Tx';
                                                  /*also unnecessary because they are a subset*/
                                        else if  TBQ060 = 1 then Hx = 'household';
                                        else Hx = 'none';


/*create new var SRTH = self-reported TB Hx*/
                              if Hx in ('LTBI Tx', 'active TB',  'pos TST') then SRTH = 1;
                                        else SRTH = 2;


/* from DEMO data file in 1999-2000 NHANES
          • RIDAGEYR - Age in years at screening
          • RIDRETH2 - Linked NH3 Race/Ethnicity
          • DMDBORN - Country of Birth                                            */

                    if RIDAGEYR > 5 then AGE6up = 1; else AGE6up = 0;

                    if RIDAGEYR < 1 then AGEGP_SUBD = 0;                                    /*age < 1 yr*/
                              else if RIDAGEYR <  6 then AGEGP_SUBD = 10;                   /*ages  1- 5*/
                              else if RIDAGEYR < 12 then AGEGP_SUBD = 11;                   /*ages  6-11*/
                              else if RIDAGEYR < 16 then AGEGP_SUBD = 12;                   /*ages 12-15*/
                              else if RIDAGEYR < 20 then AGEGP_SUBD = 16;                   /*ages 16-19*/
                              else if RIDAGEYR < 30 then AGEGP_SUBD = 20;                 /*ages 20-29*/
                              else if RIDAGEYR < 40 then AGEGP_SUBD = 30;           /*ages 30-39*/
                              else if RIDAGEYR < 50 then AGEGP_SUBD = 40;           /*ages 40-49*/
                              else if RIDAGEYR < 60 then AGEGP_SUBD = 50;           /*ages 50-59*/
                              else if RIDAGEYR < 70 then AGEGP_SUBD = 60;           /*ages 60-69*/
                              else if RIDAGEYR < 80 then AGEGP_SUBD = 70;                 /*ages 70-79*/
                              else AGEGP_SUBD = 80;                                                 /*age 80+ yrs*/


if AGEGP_SUBD in (0, 10)then GROUPING = 'tooyoung';
else if ( AGEGP_SUBD in (11,12,16) and RIDRETH2 = 2 and DMDBORN = 1  ) then GROUPING = 'B0619_US';
else if ( AGEGP_SUBD in (20,30) and RIDRETH2 = 2 and DMDBORN = 1 ) then GROUPING = 'B2039_US';
else if ( AGEGP_SUBD in (40,50) and RIDRETH2 = 2 and DMDBORN = 1 ) then GROUPING = 'B4059_US';
else if ( AGEGP_SUBD in (60,70,80) and RIDRETH2 = 2 and DMDBORN = 1 ) then GROUPING = 'B6000_US';
else if ( AGEGP_SUBD in (11,12,16) and RIDRETH2 = 2 and DMDBORN = 2  ) then GROUPING = 'B0619_FB';
else if ( AGEGP_SUBD in (20,30) and RIDRETH2 = 2 and DMDBORN = 2 ) then GROUPING = 'B2039_FB';
else if ( AGEGP_SUBD in (40,50) and RIDRETH2 = 2 and DMDBORN = 2 ) then GROUPING = 'B4059_FB';
else if ( AGEGP_SUBD in (60,70,80) and RIDRETH2 = 2 and DMDBORN = 2 ) then GROUPING = 'B6000_FB';
else if ( AGEGP_SUBD in (11,12,16) and RIDRETH2 = 3 and DMDBORN = 1 ) then GROUPING = 'M0619_US';
else if ( AGEGP_SUBD in (20,30) and RIDRETH2 = 3 and DMDBORN = 1 ) then GROUPING = 'M2039_US';
else if ( AGEGP_SUBD in (40,50) and RIDRETH2 = 3 and DMDBORN = 1 ) then GROUPING = 'M4059_US';
else if ( AGEGP_SUBD in (60,70,80) and RIDRETH2 = 3 and DMDBORN = 1 ) then GROUPING = 'M6000_US';
else if ( AGEGP_SUBD in (11,12,16) and RIDRETH2 = 3 and DMDBORN = 2  ) then GROUPING = 'M0619_FB';
else if ( AGEGP_SUBD in (20,30) and RIDRETH2 = 3 and DMDBORN = 2 ) then GROUPING = 'M2039_FB';
else if ( AGEGP_SUBD in (40,50) and RIDRETH2 = 3 and DMDBORN = 2 ) then GROUPING = 'M4059_FB';
else if ( AGEGP_SUBD in (60,70,80) and RIDRETH2 = 3 and DMDBORN = 2  ) then GROUPING = 'M6000_FB';
else if ( AGEGP_SUBD in (11,12,16)  and DMDBORN = 1 ) then GROUPING = 'W0619_US';
```

```
else if ( AGEGP_SUBD in (20,30) and DMDBORN = 1 ) then GROUPING = 'W2039_US';
else if ( AGEGP_SUBD in (40,50) and DMDBORN = 1 ) then GROUPING = 'W4059_US';
else if ( AGEGP_SUBD in (60,70,80) and DMDBORN = 1) then GROUPING = 'W6000_US';
else if ( AGEGP_SUBD in (11,12,16)  and DMDBORN = 2 ) then GROUPING = 'W0619_FB';
else if ( AGEGP_SUBD in (20,30) and DMDBORN = 2 ) then GROUPING = 'W2039_FB';
else if ( AGEGP_SUBD in (40,50) and DMDBORN = 2 ) then GROUPING = 'W4059_FB';
else if ( AGEGP_SUBD in (60,70,80) and DMDBORN = 2) then GROUPING = 'W6000_FB';
else GROUPING = 'unclass';


/*IMPUTATIONS for missing TST results:

          IMP_2 (best estimate if MAR) -
          within the subgroup of profile participants who had the same
          (binary variable) SRTH / self-reported personal TB history

          IMP_3 and IMP_4 (extreme MNAR assumptions)        -
           IMP_3 - all persons had positive instead of missing TST results
           IMP_4 - and all persons had negative instead of missing TST results*/


if (TST_VALID = 1 and TST1 = 3)                then do;   IMP_2 = 1 ;          IMP_3 = 1 ;  IMP_4 = 1 ; end;
else if (TST_VALID = 1 and TST1 in (1,2))         then do;   IMP_2 = 0 ;        IMP_3 = 0 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B0619_US' and SRTH = 1) then do;   IMP_2 = 0.140 ;        IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B0619_US' and SRTH = 2) then do;   IMP_2 = 0.005 ;        IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B0619_FB' and SRTH = 1) then do;   IMP_2 = 0     ;        IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B0619_FB' and SRTH = 2) then do;   IMP_2 = 0.117 ;        IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B2039_US' and SRTH = 1) then do;   IMP_2 = 0.362 ;        IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B2039_US' and SRTH = 2) then do;   IMP_2 = 0.042 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B2039_FB' and SRTH = 1) then do;   IMP_2 = 0.469 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B2039_FB' and SRTH = 2) then do;   IMP_2 = 0.159 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B4059_US' and SRTH = 1) then do;   IMP_2 = 0.468 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B4059_US' and SRTH = 2) then do;   IMP_2 = 0.073 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B4059_FB' and SRTH = 1) then do;   IMP_2 = 1     ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B4059_FB' and SRTH = 2) then do;   IMP_2 = 0.210 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B6000_US' and SRTH = 1) then do;   IMP_2 = 0.577 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B6000_US' and SRTH = 2) then do;   IMP_2 = 0.129 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B6000_FB' and SRTH = 1) then do;   IMP_2 = 0.590 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'B6000_FB' and SRTH = 2) then do;   IMP_2 = 0.206 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M0619_US' and SRTH = 1) then do;   IMP_2 = 0.285 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M0619_US' and SRTH = 2) then do;   IMP_2 = 0.012 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M0619_FB' and SRTH = 1) then do;   IMP_2 = 0.406 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M0619_FB' and SRTH = 2) then do;   IMP_2 = 0.085 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M2039_US' and SRTH = 1) then do;   IMP_2 = 0.415 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M2039_US' and SRTH = 2) then do;   IMP_2 = 0.030 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M2039_FB' and SRTH = 1) then do;   IMP_2 = 0.347 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M2039_FB' and SRTH = 2) then do;   IMP_2 = 0.159 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M4059_US' and SRTH = 1) then do;   IMP_2 = 0.075 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M4059_US' and SRTH = 2) then do;   IMP_2 = 0.015 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M4059_FB' and SRTH = 1) then do;   IMP_2 = 0.593 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M4059_FB' and SRTH = 2) then do;   IMP_2 = 0.227 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M6000_US' and SRTH = 1) then do;   IMP_2 = 0.381 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M6000_US' and SRTH = 2) then do;   IMP_2 = 0.113 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M6000_FB' and SRTH = 1) then do;   IMP_2 = 0.399 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'M6000_FB' and SRTH = 2) then do;   IMP_2 = 0.208 ;    IMP_3 = 1 ;  IMP_4 = 0 ; end;
else if (GROUPING = 'W0619_US' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W0619_US' and SRTH = 2) then do;  IMP_2 = 0.002 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W0619_FB' and SRTH = 1) then do;  IMP_2 = 0.453 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W0619_FB' and SRTH = 2) then do;  IMP_2 = 0.038 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W2039_US' and SRTH = 1) then do;  IMP_2 = 0.029 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W2039_US' and SRTH = 2) then do;  IMP_2 = 0.002 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W2039_FB' and SRTH = 1) then do;  IMP_2 = 0.402 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W2039_FB' and SRTH = 2) then do;  IMP_2 = 0.176 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W4059_US' and SRTH = 1) then do;  IMP_2 = 0.307 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W4059_US' and SRTH = 2) then do;  IMP_2 = 0.006 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W4059_FB' and SRTH = 1) then do;  IMP_2 = 0.367 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W4059_FB' and SRTH = 2) then do;  IMP_2 = 0.237 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W6000_US' and SRTH = 1) then do;  IMP_2 = 0.268 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W6000_US' and SRTH = 2) then do;  IMP_2 = 0.024 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W6000_FB' and SRTH = 1) then do;  IMP_2 = 0.271 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W6000_FB' and SRTH = 2) then do;  IMP_2 = 0.093 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
run;



data work.nh1112_9338;
          set nhanes.nh1112;

          if RIDSTATR = 2 ;             /*to subset to the 9338 survey participants
                                                                        undergoing 2011-2012 NHANES exam*/
                    /*but note that only those age 6+ eligible for TST
                              --> interested in that subset of 7821 SPs*/


/* from TBX_G data file in 2011-2012 NHANES
          • TBDRUIND - Induration in mm                                 */

                              if TBDRUIND = 0 then TST1 = 1;
                                        else if 0 < TBDRUIND < 10 then TST1 = 2;
                                        else if 10 le TBDRUIND < 77 then TST1 = 3;
                                        else TST1 = 9;

                              if TST1 ne 9 then VALID_TST = 1; else VALID_TST = 2;
```

```
/***reclassification of borderline TST results***/
/* from TB_G data file in 2011-2012 NHANES
          • LBXTBIN - TB coded result             (from QuantiFERON-TB Gold In Tube test)    */

                              if (LBXTBIN = 1 and TST1 = 2 and (8 le TBDRUIND lt 10)) then TST_reclassify = 3;
                                        else TST_reclassify = TST1;


/* from TBQ_G data file in 2011-2012 NHANES
                    • TBQ010 - Ever had TB/tuberculosis skin test
                    • TBQ015a - Did you receive the skin test
                    • TBQ015b - Did you receive the blood test
                    • TBQ015c - Did you receive the tine test
                    • TBQ022 - Told your skin test was positive for TB          equiv is TBQ020 in 1999-2000
                    • TBQ025 - Told your blood test was positive for TB
                    • TBQ028 - Told your tine test was positive for TB
                    • TBQ030 - Prescribed medicine for preventing TB
                    • TBQ035 - Did you/SP complete this treatment?
                    • TBQ040 - Ever told you had active TB
                    • TBQ050 - Prescribed medicine for active TB
                    • TBQ060 - Lived in household TB sick person      */

                              if TBQ040 = 1 then Hx = 'active TB';
                                        else if TBQ050 = 1 then Hx = 'active TB';
                                        /*though again turns out unnecessary because they are a subset*/
                                        else if  TBQ022 = 1 then Hx = 'pos TST';
                                        else if TBQ030 = 1 then Hx = 'LTBI Tx';
                                                  /*again also unnecessary because they are a subset*/
                                        else if TBQ025 = 1 then Hx = 'pos IGRA';
                                        else if TBQ028 = 1 then Hx = 'pos Tine';
                                        else if  TBQ060 = 1 then Hx = 'household';
                                        else Hx = 'none';


          if TBQ022 = 1 then testHx = 'TST  pos'; /*equiv is TBQ020 in 1999-2000*/

                    else if TBQ025 = 1 then testHx = 'IGRA pos';      /*only relevant for 2011-2012*/
                    else if TBQ028 = 1 then testHx = 'TINE pos';      /*only relevant for 2011-2012*/
                                        else testHx = 'no pos';


/*create new var SRTH = self-reported TB Hx*/

          if Hx in ('LTBI Tx', 'active TB', 'pos IGRA', 'pos TST', 'pos Tine') then SRTH = 1;
                                        else SRTH = 2;


/*from DEMO_G data file in 2011-2012 NHANES
          • RIDAGEYR - Age in years at screening
          • RIDRETH3 - Race/Hispanic origin w/ NH Asian
          • DMDBORN4 - Country of birth */

                    if RIDAGEYR > 5 then AGE6up = 1; else AGE6up = 0;

                    if RIDAGEYR < 1 then AGEGP_SUBD = 0;                                                  /*age < 1 yr*/
                              else if RIDAGEYR <  6 then AGEGP_SUBD = 10;                                 /*ages  1- 5*/
                              else if RIDAGEYR < 12 then AGEGP_SUBD = 11;                                 /*ages  6-11*/
                              else if RIDAGEYR < 16 then AGEGP_SUBD = 12;                                 /*ages 12-15*/
                              else if RIDAGEYR < 20 then AGEGP_SUBD = 16;                                 /*ages 16-19*/
                              else if RIDAGEYR < 30 then AGEGP_SUBD = 20;                                 /*ages 20-29*/
                              else if RIDAGEYR < 40 then AGEGP_SUBD = 30;                       /*ages 30-39*/
                              else if RIDAGEYR < 50 then AGEGP_SUBD = 40;                       /*ages 40-49*/
                              else if RIDAGEYR < 60 then AGEGP_SUBD = 50;                       /*ages 50-59*/
                              else if RIDAGEYR < 70 then AGEGP_SUBD = 60;                       /*ages 60-69*/
                              else if RIDAGEYR < 80 then AGEGP_SUBD = 70;                                 /*ages 70-79*/
                              else AGEGP_SUBD = 80;                                                                 /*age 80+ yrs*/


if AGEGP_SUBD in (0, 10)then GROUPING = 'tooyoung';
else if ( AGEGP_SUBD in (11,12,16) and DMDBORN4 = 1 and RIDRETH3 = 4 )then GROUPING = 'B0619_US';
else if ( AGEGP_SUBD in (20,30) and DMDBORN4 = 1 and RIDRETH3 = 4 ) then GROUPING = 'B2039_US';
else if ( AGEGP_SUBD in (40,50) and DMDBORN4 = 1 and RIDRETH3 = 4 ) then GROUPING = 'B4059_US';
else if ( AGEGP_SUBD in (60,70,80) and DMDBORN4 = 1 and RIDRETH3 = 4 ) then GROUPING = B6000_US';
else if ( AGEGP_SUBD in (11,12,16) and DMDBORN4 = 2 and RIDRETH3 = 4 )then GROUPING = 'B0619_FB';
else if ( AGEGP_SUBD in (20,30) and DMDBORN4 = 2 and RIDRETH3 = 4 ) then GROUPING = 'B2039_FB';
else if ( AGEGP_SUBD in (40,50) and DMDBORN4 = 2 and RIDRETH3 = 4 ) then GROUPING = 'B4059_FB';
else if ( AGEGP_SUBD in (60,70,80) and DMDBORN4 = 2 and RIDRETH3 = 4 )then GROUPING = 'B6000_FB';
else if ( AGEGP_SUBD in (11,12,16) and DMDBORN4 = 1 and(RIDRETH3 in (1,2)))then GROUPING = 'H0619_US';
else if ( AGEGP_SUBD in (20,30) and DMDBORN4 = 1 and (RIDRETH3 in (1, 2) )) then GROUPING = 'H2039_US';
else if ( AGEGP_SUBD in (40,50) and DMDBORN4 = 1 and (RIDRETH3 in (1, 2) )) then GROUPING = 'H4059_US';
else if ( AGEGP_SUBD in (60,70,80) and DMDBORN4 =1 and (RIDRETH3 in (1, 2))) then GROUPING = 'H6000_US';
else if ( AGEGP_SUBD in (11,12,16) and DMDBORN4 =2 and (RIDRETH3 in (1, 2))) then GROUPING = 'H0619_FB';
else if ( AGEGP_SUBD in (20,30) and DMDBORN4 = 2 and (RIDRETH3 in (1, 2) )) then GROUPING = 'H2039_FB';
else if ( AGEGP_SUBD in (40,50) and DMDBORN4 = 2 and (RIDRETH3 in (1, 2) )) then GROUPING = 'H4059_FB';
else if ( AGEGP_SUBD in (60,70,80) and DMDBORN4 =2 and (RIDRETH3 in (1, 2))) then GROUPING = 'H6000_FB';
else if ( AGEGP_SUBD in (11,12,16) and DMDBORN4 = 1 and RIDRETH3 = 6 ) then GROUPING = 'A0619_US';
else if ( AGEGP_SUBD in (20,30) and DMDBORN4 = 1 and RIDRETH3 = 6 ) then GROUPING = 'A2039_US';
else if ( AGEGP_SUBD in (40,50) and DMDBORN4 = 1 and RIDRETH3 = 6 ) then GROUPING = 'A4059_US';
else if ( AGEGP_SUBD in (60,70,80) and DMDBORN4 = 1 and RIDRETH3 = 6 ) then GROUPING = 'A6000_US';
else if ( AGEGP_SUBD in (11,12,16) and DMDBORN4 = 2 and RIDRETH3 = 6  ) then GROUPING = 'A0619_FB';
else if ( AGEGP_SUBD in (20,30) and DMDBORN4 = 2 and RIDRETH3 = 6 ) then GROUPING = 'A2039_FB';
else if ( AGEGP_SUBD in (40,50) and DMDBORN4 = 2 and RIDRETH3 = 6 ) then GROUPING = 'A4059_FB';
else if ( AGEGP_SUBD in (60,70,80) and DMDBORN4 =2 and RIDRETH3 = 6  ) then GROUPING = 'A6000_FB';
else if ( AGEGP_SUBD in (11,12,16) and DMDBORN4 =1 and (RIDRETH3 in (3, 7))) then GROUPING = 'W0619_US';
```

```
else if ( AGEGP_SUBD in (20,30) and DMDBORN4 = 1 and (RIDRETH3 in (3, 7))) then GROUPING = 'W2039_US';
else if ( AGEGP_SUBD in (40,50) and DMDBORN4 = 1 and (RIDRETH3 in (3, 7))) then GROUPING = 'W4059_US';
else if ( AGEGP_SUBD in (60,70,80) and DMDBORN4 =1 and (RIDRETH3 in (3, 7))) then GROUPING = 'W6000_US';
else if ( AGEGP_SUBD in (11,12,16) and DMDBORN4 =2 and (RIDRETH3 in (3, 7))) then GROUPING = 'W0619_FB';
else if ( AGEGP_SUBD in (20,30) and DMDBORN4 = 2 and (RIDRETH3 in (3, 7))) then GROUPING = 'W2039_FB';
else if ( AGEGP_SUBD in (40,50) and DMDBORN4 = 2 and (RIDRETH3 in (3, 7))) then GROUPING = 'W4059_FB';
else if ( AGEGP_SUBD in (60,70,80) and DMDBORN4 =2 and (RIDRETH3 in (3, 7))) then GROUPING = 'W6000_FB';
else GROUPING = 'unclass';          /* 2 unk origin Mex American and 3 unk origin oth Hisp*/


/*IMPUTATIONS for missing TST results:

          IMP_2 (best estimate if MAR) - within the subgroup of profile participants who had the same
          (binary variable) SRTH / self-reported personal TB history

          IMP_3 and IMP_4 (extreme MNAR assumptions) IMP_3 = all had positive instead of missing TST
                                                     IMP_4 = all had negative instead of missing TST */

if (TST_reclassify = 3)                then do;              IMP_2 = 1 ;       IMP_3 = 1 ;    IMP_4 = 1 ;   end;
else if (TST_reclassify in (1,2))      then do;              IMP_2 = 0 ;       IMP_3 = 0 ;    IMP_4 = 0 ;   end;
else if (GROUPING = 'B0619_US' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B0619_US' and SRTH = 2) then do;  IMP_2 = 0.011 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B0619_FB' and SRTH = 1) then do;  IMP_2 = 1     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B0619_FB' and SRTH = 2) then do;  IMP_2 = 0.420 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B2039_US' and SRTH = 1) then do;  IMP_2 = 0.254 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B2039_US' and SRTH = 2) then do;  IMP_2 = 0.024 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B2039_FB' and SRTH = 1) then do;  IMP_2 = 0.599 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B2039_FB' and SRTH = 2) then do;  IMP_2 = 0.167 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B4059_US' and SRTH = 1) then do;  IMP_2 = 0.449 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B4059_US' and SRTH = 2) then do;  IMP_2 = 0.044 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B4059_FB' and SRTH = 1) then do;  IMP_2 = 0.866 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B4059_FB' and SRTH = 2) then do;  IMP_2 = 0.137 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B6000_US' and SRTH = 1) then do;  IMP_2 = 0.513 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B6000_US' and SRTH = 2) then do;  IMP_2 = 0.094 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B6000_FB' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'B6000_FB' and SRTH = 2) then do;  IMP_2 = 0.383 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H0619_US' and SRTH = 1) then do;  IMP_2 = 0.098 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H0619_US' and SRTH = 2) then do;  IMP_2 = 0.005 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H0619_FB' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H0619_FB' and SRTH = 2) then do;  IMP_2 = 0.077 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H2039_US' and SRTH = 1) then do;  IMP_2 = 0.536 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H2039_US' and SRTH = 2) then do;  IMP_2 = 0.026 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H2039_FB' and SRTH = 1) then do;  IMP_2 = 0.422 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H2039_FB' and SRTH = 2) then do;  IMP_2 = 0.148 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H4059_US' and SRTH = 1) then do;  IMP_2 = 1     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H4059_US' and SRTH = 2) then do;  IMP_2 = 0.028 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H4059_FB' and SRTH = 1) then do;  IMP_2 = 0.543 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H4059_FB' and SRTH = 2) then do;  IMP_2 = 0.250 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H6000_US' and SRTH = 1) then do;  IMP_2 = 0.413 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H6000_US' and SRTH = 2) then do;  IMP_2 = 0.099 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H6000_FB' and SRTH = 1) then do;  IMP_2 = 0.648 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'H6000_FB' and SRTH = 2) then do;  IMP_2 = 0.257 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A0619_US' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A0619_US' and SRTH = 2) then do;  IMP_2 = 0.014 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A0619_FB' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A0619_FB' and SRTH = 2) then do;  IMP_2 = 0.121 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A2039_US' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A2039_US' and SRTH = 2) then do;  IMP_2 = 0.038 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A2039_FB' and SRTH = 1) then do;  IMP_2 = 0.643 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A2039_FB' and SRTH = 2) then do;  IMP_2 = 0.230 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A4059_US' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A4059_US' and SRTH = 2) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A4059_FB' and SRTH = 1) then do;  IMP_2 = 0.506 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A4059_FB' and SRTH = 2) then do;  IMP_2 = 0.351 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A6000_US' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A6000_US' and SRTH = 2) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A6000_FB' and SRTH = 1) then do;  IMP_2 = 0.459 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'A6000_FB' and SRTH = 2) then do;  IMP_2 = 0.262 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W0619_US' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W0619_US' and SRTH = 2) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W0619_FB' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W0619_FB' and SRTH = 2) then do;  IMP_2 = 0.046 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W2039_US' and SRTH = 1) then do;  IMP_2 = 0.233 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W2039_US' and SRTH = 2) then do;  IMP_2 = 0.005 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W2039_FB' and SRTH = 1) then do;  IMP_2 = 1     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W2039_FB' and SRTH = 2) then do;  IMP_2 = 0.037 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W4059_US' and SRTH = 1) then do;  IMP_2 = 0.111 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W4059_US' and SRTH = 2) then do;  IMP_2 = 0.005 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W4059_FB' and SRTH = 1) then do;  IMP_2 = 0     ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W4059_FB' and SRTH = 2) then do;  IMP_2 = 0.131 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W6000_US' and SRTH = 1) then do;  IMP_2 = 0.191 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W6000_US' and SRTH = 2) then do;  IMP_2 = 0.007 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W6000_FB' and SRTH = 1) then do;  IMP_2 = 0.366 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
else if (GROUPING = 'W6000_FB' and SRTH = 2) then do;  IMP_2 = 0.106 ;   IMP_3 = 1 ;   IMP_4 = 0 ;  end;
run;


proc freq data=work.nh9900_9282;
          tables age6up * TST1 / norow nocol nopercent missing ;               /*7819 with TST results*/
run;

proc freq data=work.nh1112_9338;
          tables age6up * TST1 / norow nocol nopercent missing ;               /*7821 with TST results*/
          tables TST1*TST_reclassify / nopercent norow nocol missing;
run;                                                  /*resulted in 40 being reclassified as having pos TST*/
```

```
/****conventional analyses with public-use data vars in SAS-callable SUDAAN****/


proc sort data = work.nh9900_9282;                by SDMVSTRA SDMVPSU;                                run;

proc sort data = work.nh1112_9338;                by SDMVSTRA SDMVPSU;                                run;



/*using the public-use TSTs*/

                    proc descript data=work.nh9900_9282  design=wr ;
                              subpopx AGE6UP = 1 and VALID_TST = 1 ;
                              nest SDMVSTRA SDMVPSU;
                              weight wtmec2yr;
                              catlevel 3  ;
                              var TST1 ;
                              print PERCENT LOWPCT UPPCT SEPERCENT / style=nchs;
                              rtitle "conventional analysis: Positive TST results in US pop age 6+,
                              1999-2000 - based only on those with valid TST results";
                    run;

                    proc descript data=work.nh1112_9338  design=wr ;
                              subpopx AGE6UP = 1 and VALID_TST = 1 ;
                              nest SDMVSTRA SDMVPSU;
                              weight wtmec2yr;
                              catlevel 3  ;
                              var TST1 ;
                              print PERCENT LOWPCT UPPCT SEPERCENT / style=nchs;
                              rtitle "conventional analysis: Positive TST results in US pop age 6+,
                               2011-2012 - based only on those with valid TST results";
                    run;
/*using the 40 reclassified TSTs for 2011-2012*/

                    proc descript data=work.nh1112_9338  design=wr ;
                              subpopx AGE6UP = 1 and VALID_TST = 1 ;
                              nest SDMVSTRA SDMVPSU;
                              weight wtmec2yr;
                              catlevel 3  ;
                              var TST_reclassify ;
                              print PERCENT LOWPCT UPPCT SEPERCENT / style=nchs;
                              rtitle "conventional analysis for 2011-2012 after reclassifying
                                             40 borderline TST results as positive";
                    run;

/***  probabilistic bias analysis (better than simple deterministic reclassification) *********/

/******for RECORD-LEVEL correction to potential misclassification*******/

/***  rationale, per Tim Lash bias analaysis course, lecture 10:
Record level data turns the Se and Sp into PPV and NPV and uses those values in Bernoulli trials to decide which individual to
“correct”
Accounts for uncertainty in the bias parameters plus random error in who is reassigned    ***/



/*use an array to do this 30 times*/

data work.reps_9900;
          set work.nh9900_9282;

          array TST_rep[30] ;

          do i = 1 to 30;

                    if seed11 eq .  then do seed11 =  403712+SEQN;    end;

                                        if                  TST1 in (1,2,3) then TST_rep[i] = TST1+5;
                                        /*so now 6-7 are neg, 8 is pos, and 9 still unkn*/

                                        else if    TST1 in (9) then
                                                                                  call ranbin (seed11, 1, (IMP_2), TST_rep[i]);               /*this
should apply to the 1,693 examined age 6+ missing TST results in 2011-2012*/

                                        if TST_rep[i] = 1 then TST_rep[i] = 8;
                                        else if TST_rep[i] in (6,7,8) then TST_rep[i] = TST_rep[i];
                                                                                                  else TST_rep[i] = 6;

          end;

          drop i;
run;

proc freq data = work.reps_9900;
          tables TST1 * (TST_rep1--TST_rep30) /norow nocol nopercent ;
                                                                                                  /*between 459 and 490 instead of 410 pos*/
run;


/*now make them go back to familiar where 3 = pos (now no missings)*/

data work.rep01_9900;                    set work.reps_9900;           TST8 = TST_rep1 - 5;                    rep = 01;
          SEQ = ((100 + rep) * 10000 ) + SEQN;
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
```

```
data work.rep02_9900;                   set work.reps_9900;           TST8 = TST_rep2 - 5;                    rep = 02;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep03_9900;                   set work.reps_9900;           TST8 = TST_rep3 - 5;                    rep = 03;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep04_9900;                   set work.reps_9900;           TST8 = TST_rep4 - 5;                    rep = 04;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep05_9900;                   set work.reps_9900;           TST8 = TST_rep5 - 5;                    rep = 05;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep06_9900 ;                  set work.reps_9900;           TST8 = TST_rep6 - 5;                    rep = 06;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep07_9900;                   set work.reps_9900;           TST8 = TST_rep7 - 5;                    rep = 07;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep08_9900;                   set work.reps_9900;           TST8 = TST_rep8 - 5;                    rep = 08;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep09_9900;                   set work.reps_9900;           TST8 = TST_rep9 - 5;                    rep = 09;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep10_9900;                   set work.reps_9900;           TST8 = TST_rep10 - 5;                   rep = 10;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep11_9900;                   set work.reps_9900;           TST8 = TST_rep11 - 5;                   rep = 11;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep12_9900;                   set work.reps_9900;           TST8 = TST_rep12 - 5;                   rep = 12;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep13_9900;                   set work.reps_9900;           TST8 = TST_rep13 - 5;                   rep = 13;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep14_9900;                   set work.reps_9900;           TST8 = TST_rep14 - 5;                   rep = 14;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep15_9900;                   set work.reps_9900;           TST8 = TST_rep15 - 5;                   rep = 15;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep16_9900;                   set work.reps_9900;           TST8 = TST_rep16 - 5;                   rep = 16;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep17_9900;                   set work.reps_9900;           TST8 = TST_rep17 - 5;                   rep = 17;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep18_9900;                   set work.reps_9900;           TST8 = TST_rep18 - 5;                   rep = 18;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep19_9900;                   set work.reps_9900;           TST8 = TST_rep19 - 5;                   rep = 19;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep20_9900;                   set work.reps_9900;           TST8 = TST_rep20 - 5;                   rep = 20;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep21_9900;                   set work.reps_9900;           TST8 = TST_rep21 - 5;                   rep = 21;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep22_9900;                   set work.reps_9900;           TST8 = TST_rep22 - 5;                   rep = 22;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep23_9900;                   set work.reps_9900;           TST8 = TST_rep23 - 5;                   rep = 23;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep24_9900;                   set work.reps_9900;           TST8 = TST_rep24 - 5;                   rep = 24;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep25_9900;                   set work.reps_9900;           TST8 = TST_rep25 - 5;                   rep = 25;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep26_9900;                   set work.reps_9900;           TST8 = TST_rep26 - 5;                   rep = 26;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep27_9900;                   set work.reps_9900;           TST8 = TST_rep27 - 5;                   rep = 27;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep28_9900;                   set work.reps_9900;           TST8 = TST_rep28 - 5;                   rep = 28;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep29_9900;                   set work.reps_9900;           TST8 = TST_rep29 - 5;                   rep = 29;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep30_9900;                   set work.reps_9900;           TST8 = TST_rep30 - 5;                   rep = 30;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;

proc sort data = work.reps_9900;                        by SDMVSTRA SDMVPSU;                    run;

data work.reps9900_mini;
        set work.reps_9900;
        TST8 = TST1;
                keep SEQN  GROUPING AGE6UP DMDBORN4  VALID_TST   SDMVSTRA SDMVPSU  wtmec2yr  TST8 ;
run;
```

```
data work.reps_1112;
        set work.nh1112_9338;

        array TST_rep[30] ;

        do i = 1 to 30;

                if seed11 eq .  then do seed11 =  403712+SEQN;    end;

                        if                TST_reclassify in (1,2,3) then TST_rep[i] = TST_reclassify + 5;
        /*so now 6-7 are neg, 8 is pos, and 9 still unkn*/

                                  else if    TST_reclassify in (9) then
                                                call ranbin (seed11, 1, (IMP_2), TST_rep[i]);
        /*this should apply to the 1,693 examined age 6+ missing TST results in 2011-2012*/

                                  if TST_rep[i] = 1 then TST_rep[i] = 8;
                                  else if TST_rep[i] in (6,7,8) then TST_rep[i] = TST_rep[i];
                                                                          else TST_rep[i] = 6;

        end;
        drop i;
run;

proc freq data = work.reps_1112;
        tables TST1 * (TST_rep1--TST_rep50) /norow nocol nopercent ;
                                                                        /*between 600 and 634 instead of 442 pos*/
        tables TST_reclassify * (TST_rep1--TST_rep30) /norow nocol nopercent ;    /* instead of 482 pos*/
run;


/*now make them go back to familiar where 3 = pos (now no missings)*/

data work.rep01_1112;                  set work.reps_1112;                    TST8 = TST_rep1 - 5;                    rep = 01;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep02_1112;                  set work.reps_1112;           TST8 = TST_rep2 - 5;                      rep = 02;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep03_1112;                  set work.reps_1112;           TST8 = TST_rep3 - 5;                      rep = 03;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep04_1112;                  set work.reps_1112;           TST8 = TST_rep4 - 5;                      rep = 04;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep05_1112;                  set work.reps_1112;           TST8 = TST_rep5 - 5;                      rep = 05;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep06_1112;                  set work.reps_1112;           TST8 = TST_rep6 - 5;                      rep = 06;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep07_1112;                  set work.reps_1112;           TST8 = TST_rep7 - 5;                      rep = 07;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep08_1112;                  set work.reps_1112;           TST8 = TST_rep8 - 5;                      rep = 08;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep09_1112;                  set work.reps_1112;           TST8 = TST_rep9 - 5;                      rep = 09;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep10_1112;                  set work.reps_1112;           TST8 = TST_rep10 - 5;                     rep = 10;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep11_1112;                  set work.reps_1112;           TST8 = TST_rep11 - 5;                     rep = 11;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep12_1112;                  set work.reps_1112;           TST8 = TST_rep12 - 5;                     rep = 12;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep13_1112;                  set work.reps_1112;           TST8 = TST_rep13 - 5;                     rep = 13;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep14_1112;                  set work.reps_1112;           TST8 = TST_rep14 - 5;                     rep = 14;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep15_1112;                  set work.reps_1112;           TST8 = TST_rep15 - 5;                     rep = 15;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr  TST8 ; run;
data work.rep16_1112;                  set work.reps_1112;           TST8 = TST_rep16 - 5;                     rep = 16;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr  TST8 ; run;
data work.rep17_1112;                  set work.reps_1112;           TST8 = TST_rep17 - 5;                      rep = 17;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr  TST8 ; run;
data work.rep18_1112;                  set work.reps_1112;           TST8 = TST_rep18 - 5;                      rep = 18;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr  TST8 ; run;
data work.rep19_1112;                  set work.reps_1112;           TST8 = TST_rep19 - 5;                      rep = 19;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr  TST8 ; run;
data work.rep20_1112;                  set work.reps_1112;           TST8 = TST_rep20 - 5;                      rep = 20;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
        keep SEQN GROUPING  AGE6UP DMDBORN4  VALID_TST  SDMVSTRA SDMVPSU wtmec2yr  TST8 ; run;
data work.rep21_1112;                  set work.reps_1112;           TST8 = TST_rep21 - 5;                      rep = 21;
        SEQ = ((100 + rep) * 10000 ) + SEQN;
```

```
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep22_1112;                   set work.reps_1112;           TST8 = TST_rep22 - 5;                   rep = 22;
          SEQ = ((100 + rep) * 10000 ) + SEQN;
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep23_1112;                   set work.reps_1112;           TST8 = TST_rep23 - 5;                   rep = 23;
          SEQ = ((100 + rep) * 10000 ) + SEQN;
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep24_1112;                   set work.reps_1112;           TST8 = TST_rep24 - 5;                   rep = 24;
          SEQ = ((100 + rep) * 10000 ) + SEQN;
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep25_1112;                   set work.reps_1112;           TST8 = TST_rep25 - 5;                   rep = 25;
          SEQ = ((100 + rep) * 10000 ) + SEQN;
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep26_1112;                   set work.reps_1112;           TST8 = TST_rep26 - 5;                   rep = 26;
          SEQ = ((100 + rep) * 10000 ) + SEQN;
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep27_1112;                   set work.reps_1112;           TST8 = TST_rep27 - 5;                   rep = 27;
          SEQ = ((100 + rep) * 10000 ) + SEQN;
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep28_1112;                   set work.reps_1112;           TST8 = TST_rep28 - 5;                   rep = 28;
          SEQ = ((100 + rep) * 10000 ) + SEQN;
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep29_1112;                   set work.reps_1112;           TST8 = TST_rep29 - 5;                   rep = 29;
          SEQ = ((100 + rep) * 10000 ) + SEQN;
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;
data work.rep30_1112;                   set work.reps_1112;           TST8 = TST_rep30 - 5;                   rep = 30;
          SEQ = ((100 + rep) * 10000 ) + SEQN;
          keep SEQN GROUPING  AGE6UP DMDBORN4 VALID_TST  SDMVSTRA SDMVPSU wtmec2yr TST8 ; run;


proc sort data = work.reps_1112;                          by SDMVSTRA SDMVPSU;                  run;

data work.reps1112_mini;
          set work.reps_1112;
          TST8 = TST_reclassify;
          keep SEQN  GROUPING AGE6UP DMDBORN4  VALID_TST   SDMVSTRA SDMVPSU  wtmec2yr  TST8 ;
run;


/*redo pos TST prevalence estimates in SUDAAN using 30 imputed datasets for missing TST results*/

                    proc sort data = work.reps9900_mini;                      by SDMVSTRA SDMVPSU;                  run;

                    proc descript data=work.reps9900_mini  design=wr ;

                              subpopx AGE6UP = 1  ;
                              nest SDMVSTRA SDMVPSU;
                              weight wtmec2yr;

                              catlevel 3  ;
                              var TST8 ;

                              print PERCENT LOWPCT UPPCT SEPERCENT / style=nchs;

                              rtitle "Positive TST results in US pop age 6+, 1999-2000,
                                        using MAR to impute results for those without valid TST results";

                              mi_files  rep01_9900 rep02_9900 rep03_9900 rep04_9900 rep05_9900
                                                  rep06_9900 rep07_9900 rep08_9900 rep09_9900 rep10_9900
                                                  rep11_9900 rep12_9900 rep13_9900 rep14_9900 rep15_9900
                                                  rep16_9900 rep17_9900 rep18_9900 rep19_9900 rep20_9900
                                                  rep21_9900 rep22_9900 rep23_9900 rep24_9900 rep25_9900
                                                  rep26_9900 rep27_9900 rep28_9900 rep29_9900 rep30_9900;
                              run;



                    proc sort data = work.reps_1112_mini;             by SDMVSTRA SDMVPSU;                  run;

                    proc descript data=work.reps1112_mini  design=wr ;

                              subpopx AGE6UP = 1  ;
                              nest SDMVSTRA SDMVPSU;
                              weight wtmec2yr;

                              catlevel 3  ;
                              var TST8 ;

                              print PERCENT LOWPCT UPPCT SEPERCENT / style=nchs;

                              rtitle "Positive TST results in US pop age 6+, 2011-2012,
                                        using MAR to impute results for those without valid TST results";

                              mi_files  rep01_1112 rep02_1112 rep03_1112 rep04_1112 rep05_1112
                                                  rep06_1112 rep07_1112 rep08_1112 rep09_1112 rep10_1112
                                                  rep11_1112 rep12_1112 rep13_1112 rep14_1112 rep15_1112
                                                  rep16_1112 rep17_1112 rep18_1112 rep19_1112 rep20_1112
                                                  rep21_1112 rep22_1112 rep23_1112 rep24_1112 rep25_1112
                                                  rep26_1112 rep27_1112 rep28_1112 rep29_1112 rep30_1112;
                              run;
```

Aim 3 appendix

Effects of different criteria to define diabetes and prediabetes using NHANES data

Miramontes 2015 defined diabetes and prediabetes status based solely on hemoglobin A1C levels, without regard to diabetes diagnosis or medication use. *Barron 2018* also used A1C but further took into account self-reported diabetes diagnosis. *Martinez 2017* used A1C, self-reported diagnosis, but further took into account fasting blood glucose and OGTT results.

This dissertation also considered prescribed medications that NHANES participants were taking. A list of all prescribed medications is in the RXQ_RX file in NHANES 1999–2000 and the RXQ_RX_G file in 2011–2012. In 1999–2000, these included INSULIN and the oral medications ACARBOSE, GLIMEPIRIDE, GLIPIZIDE, GLYBURIDE, METFORMIN, NATEGLINIDE, PIOGLITAZONE, REPAGLINIDE, ROSIGLITAZONE, and TROGLITAZONE. With the exception of TROGLITAZONE (removed from the market in 2000), the same medications were being used by NHANES participants in 2011–2012, as well as a number of more recently developed oral medications for managing diabetes: EXENATIDE, GLICLAZIDE, LINAGLIPTIN, LIRAGLUTIDE, MIGLITOL, NATEGLINIDE, SAXAGLIPTIN, SITAGLIPTIN.

Examination of these files suggests that some persons who replied "no" to the **DIQ010** question, "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" were actually taking medications normally prescribed for diabetes management. In addition, some persons taking diabetes medications had replied "no" to the **DIQ070** question, "Are you now taking diabetic pills to lower your blood sugar? These are sometimes called oral agents or oral hypoglycemic agents," or to the **DIQ050** question, "Are you now taking insulin?", were taking medications that would normally be prescribed for diabetes management. Others were not asked the DIQ050 or DIQ070 questions because of the skip pattern if they answered "no" to DIQ010.

In 1999–2000

- 456 NHANES participants were taking a cumulative 573 medications to control diabetes (with 86 taking insulin only, 317 taking oral medications only, and 53 taking both).
  - 78 of the 138 participants who replied "yes" to the DIQ050 insulin question also listed or showed insulin to the NHANES interviewer. One other person who said he did not have diabetes (DIQ010) showed insulin containers to the NHANES interviewer; he has been reclassified as diabetic for Aim 3.
  - 277 of the 334 participants who replied "yes" to the DIQ070 diabetic pill question also listed or showed at least one of the above oral medications to the NHANES interviewer. However, an additional 36 listed or showed one of the above oral medications, so they were also reclassified as having diabetes.

In 2011–2012

- 670 NHANES participants were taking a cumulative 1,026 medications to control diabetes (with 100 taking insulin only, 457 taking oral medications only, and 113 taking both).
  - 158 of the 213 participants who replied "yes" to the DIQ050 insulin question also listed or showed insulin to the NHANES interviewer. Nobody who said "no" listed or showed insulin when asked to list all current medications.
  - 466 of the 546 participants who replied "yes" to the DIQ070 diabetic pill question also listed or showed ≥1 of the above oral medications to the NHANES interviewer. However, an additional 24 listed or showed ≥1 oral medications, so they were also reclassified as having diabetes for Aim 3.

This dissertation did not reclassify persons on the basis of other blood test results. After examining the potential impact of considering additional blood test results, only A1C levels were used. However, **Aim 3 Table 1** shows how prevalence would change with more inclusive definitions.

Potential impact of incorporating **random glucose** into **diabetes** classifications

- If a random glucose ≥200 mg/dL had also been considered diagnostic of diabetes:
  - No participants in NHANES 1999–2000 would have been reclassified.
  - Four participants in 2011–2012 would have changed how they are classified for Aim 3. Three participants with random glucose results of 208–243 mg/dL remained classified as prediabetic, and one with a random glucose of 202 mg/dL but an A1C of 5.5 and no history/medications related to diabetes remained classified as nondiabetic.

Potential impact of incorporating **fasting glucose** into **diabetes** classifications

- If a fasting glucose ≥126 mg/dL had also been considered diagnostic of diabetes:
  - Twenty-three participants in 1999–2000 would have been reclassified as having diabetes (i.e., 17 remained classified as prediabetic based on an A1C of 5.9–6.4, and 6 with no history/medications related to diabetes remained classified as nondiabetic based on an A1C of 5.1–5.6).
  - Fifty-two participants in 2011–2012 would have been reclassified as having diabetes (i.e., 41 remained classified as prediabetic based on A1C of 5.7–6.4, and 11 with no history/medications related to diabetes remained classified as nondiabetic based on an A1C of 5.0–5.6).

Potential impact of incorporating **oral glucose tolerance test (OGTT)** into **diabetes** classifications

- If an OGTT ≥200 mg/dL had also been considered diagnostic of diabetes:
  - Unable to assess if any of the 1999–2000 participants would have been reclassified because an OGTT was not part of that NHANES cycle.
  - Sixty-two participants in 2011–2012 would have been reclassified as having diabetes (i.e., 59 remained classified as prediabetic and 3 as nondiabetic).

Potential impact of incorporating **fasting glucose** into **prediabetes** classifications

- If a fasting glucose of 100–125 mg/dL had also been considered diagnostic of prediabetes:
  - 403 participants in 1999–2000 would have been reclassified as prediabetic but instead remained classified as nondiabetic based on a normal A1C of 5.1–5.6.
  - 476 participants in 2011–2012 would have been reclassified as prediabetic but instead remained classified as nondiabetic based on a normal A1C of 5.0–5.6.

Potential impact of incorporating **oral glucose tolerance test (OGTT)** into **prediabetes** classifications

- If an OGTT of 140–199 mg/dL had also been considered diagnostic of prediabetes:
  - 59 participants in NHANES 2011–2012 with an A1C of 4.1–5.6 and with no history/medications related to diabetes would have been reclassified as prediabetic.

Number of NHANES participants (all ages) classified as having diabetes, prediabetes, or neither for aim 3

No. NHANES participants classified as having diabetes based on interview, medications, and A1C findings Unweighted, all ages	**1999–2000** Total with diabetes = **610**	**2011–2012** Total with diabetes = **913**
Reported having previous diabetes diagnosis <u>and</u> currently taking medications	439	639
- A1C ≥7.0, diabetes not controlled, n (%)	247 (**56%**)	298 (**47%**)
- A1C <7.0, diabetes controlled, n (%)	123 (28%)	283 (44%)
- No A1C level available to assess diabetes control, n (%)	69 (16%)	58 (9%)
Did not report diabetes diagnosis <u>but</u> taking medications for diabetes	20	31
- A1C ≥7.0, diabetes not controlled, n (%)	8 (**40%**)	8 (**26%**)
- A1C <7.0, diabetes controlled, n (%)	9 (45%)	19 (61%)
- No A1C level available to assess diabetes control, n (%)	3 (15%)	4 (13%)
Reported having previous diabetes diagnosis <u>but not</u> currently taking medications	61	88
- A1C ≥7.0, diabetes not controlled, n (%)	18 (**30%**)	25 (**27%**)
- A1C <7.0, diabetes controlled, n (%)	33 (54%)	63 (68%)
- No A1C level available to assess diabetes control, n (%)	10 (15%)	
Reported being told had "borderline" diabetes but based on A1C ≥6.5 might actually have diabetes	11	34
No previous diabetes or "borderline" diagnosis but based on A1C ≥6.5 might actually have diabetes	79	117

No. NHANES participants classified as having prediabetes based on interview, medications, and A1C findings Unweighted, all ages	**1999–2000** Total with prediabetes = **627**	**2011–2012** Total with prediabetes = **1,514**
Reported being told had "borderline" diabetes (but not on meds)	34	191
- A1C 5.7–6.4 consistent with prediabetes diagnosis, n (%)	17 (50%)	49 (26%)
- A1C <5.7, diabetes controlled, n (%)	11 (32%)	123 (64%)
- No A1C level available to assess diabetes control, n (%)	6 (18%)	19 (10%)
No diabetes/prediabetes self-reported history but based on A1C 5.7–6.4 might have prediabetes	593	1,323

No. NHANES participants classified as having neither condition based on interview, medications, and A1C findings Unweighted, all ages	**1999–2000** Nondiabetic participants = **8,728**	**2011–2012** Nondiabetic participants = **7,333**
No diabetes/prediabetes self-reported history and based on A1C <5.7 appears nondiabetic (i.e., confirmed nondiabetic)	5,194	3,803
No diabetes/prediabetes self-reported history but A1C result is missing (i.e., probable nondiabetic)	3,534	3,530

Aim 3 Table 1. Demonstration of sensitivity to various definitions of diabetes and prediabetes among NHANES participants aged ≥20 years, 1999–2000 and 2011–2012.

Showing effects of using different definitions for diabetes and prediabetes	1999–2000		2011–2012	
	Percent with diabetes	**Percent with prediabetes**	**Percent with diabetes**	**Percent with prediabetes**
Unweighted prevalence of diabetes and prediabetes among NHANES participants aged ≥20 years Using aim 3 definitions (the definitions used in all subsequent tables), unweighted point prevalence among NHANES participants aged ≥20 years [purple font for more sensitive DM/PREDM definitions adding in fasting glucose, where ≥126 mg/dL as also diagnostic of DM, and 100–125 for PREDM] [green font for even more sensitive definitions that also considered in OGTT results, where ≥200 mg/dL also diagnostic of DM, and 140–199 for PREDM]				
Born in 50 U.S. states/D.C.	12.0 [12.6]	12.1 [18.1]	15.8 [16.6] [17.4]	25.0 [31.6] [31.7]
Born elsewhere	13.1 [13.2]	11.7 [19.0]	17.0 [18.1] [19.5]	25.1 [31.4] [30.9]
Age grouping				
20 to 39 years	1.8 [1.9]	3.5 [7.9]	3.5 [3.8] [3.9]	14.3 [22.4] [22.9]
40 to 59 years	10.7 [11.3]	13.6 [21.3]	16.7 [17.8] [18.2]	28.5 [35.0] [35.8]
60+ years	23.0 [23.8]	18.6 [25.7]	29.5 [30.9] [33.4]	33.2 [37.9] [36.4]
Race/ethnicity				
Non-Hispanic white	8.6 [9.2]	11.0 [18.0]	12.4 [13.4] [14.6]	23.4 [31.8] [31.7]
Non-Hispanic black	16.8 [17.2]	15.6 [19.4]	21.5 [22.1] [22.7]	29.2 [32.7] [32.7]
Hispanic	14.6 [15.0]	11.4 [18.7]	17.9 [19.1] [20.4]	24.9 [31.8] [31.5]
Asian			13.5 [14.6] [15.7]	23.3 [29.7] [29.9]
Education				
high sch/GED completed	8.2 [8.5]	10.7 [17.1]	13.6 [14.4] [15.2]	24.5 [31.3] [31.4]
no HS diploma/GED	18.7 [19.4]	14.0 [20.2]	24.5 [25.7] [27.2]	26.7 [32.3] [31.7]
Weighted prevalence estimates for diabetes and prediabetes in the overall U.S. population aged ≥20 years				
Weighted overall noninstutitionalized civilian U.S. population aged ≥ 20 yrs	**7.4 (6.4–8.7)**	**9.5 (7.4–12.1)**	**11.5 (10.1–13.2)**	**22.6 (20.6–24.8)**
Weighted overall with more sensitive DM/PREDM definitions adding in fasting glucose	**7.9 (6.8–9.1)**	**15.7 (13.6–18.0)**	**12.2 (10.8–13.8)**	**31.2 (28.8–33.8)**
Weighted overall with more sensitive DM/PREDM defs also adding in OGTT results	*No OGTT in 1999-2000*	*No OGTT in 1999-2000*	**13.0 (11.4–14.7)**	**31.5 (29.0–34.2)**

Aim 3 Table 2. Weighted prevalence of diabetes and prediabetes among NHANES participants aged ≥20 years, 1999–2000 and 2011–2012.

Using aim 3 definitions for diabetes and prediabetes	1999–2000		2011–2012	
	Weighted (95% CI) percent with **diabetes** (total = **598** of the 4,880 aged ≥20)	Weighted (95% CI) percent with **prediabetes** (total = **585** of the 4,880 aged ≥20)	Weighted (95% CI) percent with **diabetes** (total = **899** of the 5,560 aged ≥20)	Weighted (95% CI) percent with **prediabetes** (total = **1,391** of the 5,560 aged ≥20)
Born in 50 U.S. states/D.C.	7.4 (6.2–8.7)	9.4 (7.0–12.4)	11.2 (9.6–13.1)	22.7 (20.4–25.2)
Born elsewhere	7.8 (4.8–12.4)	10.0 (8.0–12.3)	12.9 (11.1–15.0)	22.1 (19.7–24.7)
Age group				
20 to 39 years	1.8 (1.4–2.6)	3.2 (2.2–4.5)	2.6 (1.7–4.1)	12.3 (10.7–14.2)
40 to 59 years	7.8 (6.0–10.7)	12.3 (8.9–16.8)	12.7 (10.3–15.6)	23.7 (20.0–27.9)
≥60 years	18.1 (15.7–20.9)	17.8 (13.9–22.5)	22.3 (19.5–25.4)	35.2 (31.0–39.7)
Race/ethnicity				
Non-Hispanic white	6.4 (5.2–7.9)	9.0 (6.4–12.6)	9.7 (8.1–11.6)	21.9 (19.0–25.0)
Non-Hispanic black	11.4 (9.8–13.3)	12.6 (10.1–15.7)	17.8 (14.7–21.3)	28.4 (25.7–31.3)
Hispanic	8.3 (5.3–12.8)	9.0 (7.0–11.6)	13.2 (10.9–15.8)	21.6 (19.4–24.0)
Asian			12.4 (9.6–15.7)	22.1 (18.3–26.4)
Education				
high sch/GED completed	5.7 (4.8–6.7)	8.5 (6.1–11.6)	10.2 (8.6–12.0)	21.8 (19.8–24.0)
no HS diploma/GED	13.0 (10.5–15.8)	12.6 (10.7–14.8)	18.3 (15.5–21.5)	26.8 (22.3–31.9)
Weighted prevalence estimates for diabetes and prediabetes in the overall U.S. population				
Weighted % of overall noninstutitionalized civilian U.S. population aged ≥ 20 yrs	**7.4 (6.4–8.7)**	**9.5 (7.4–12.1)**	**11.5 (10.1–13.2)**	**22.6 (20.6–24.8)**

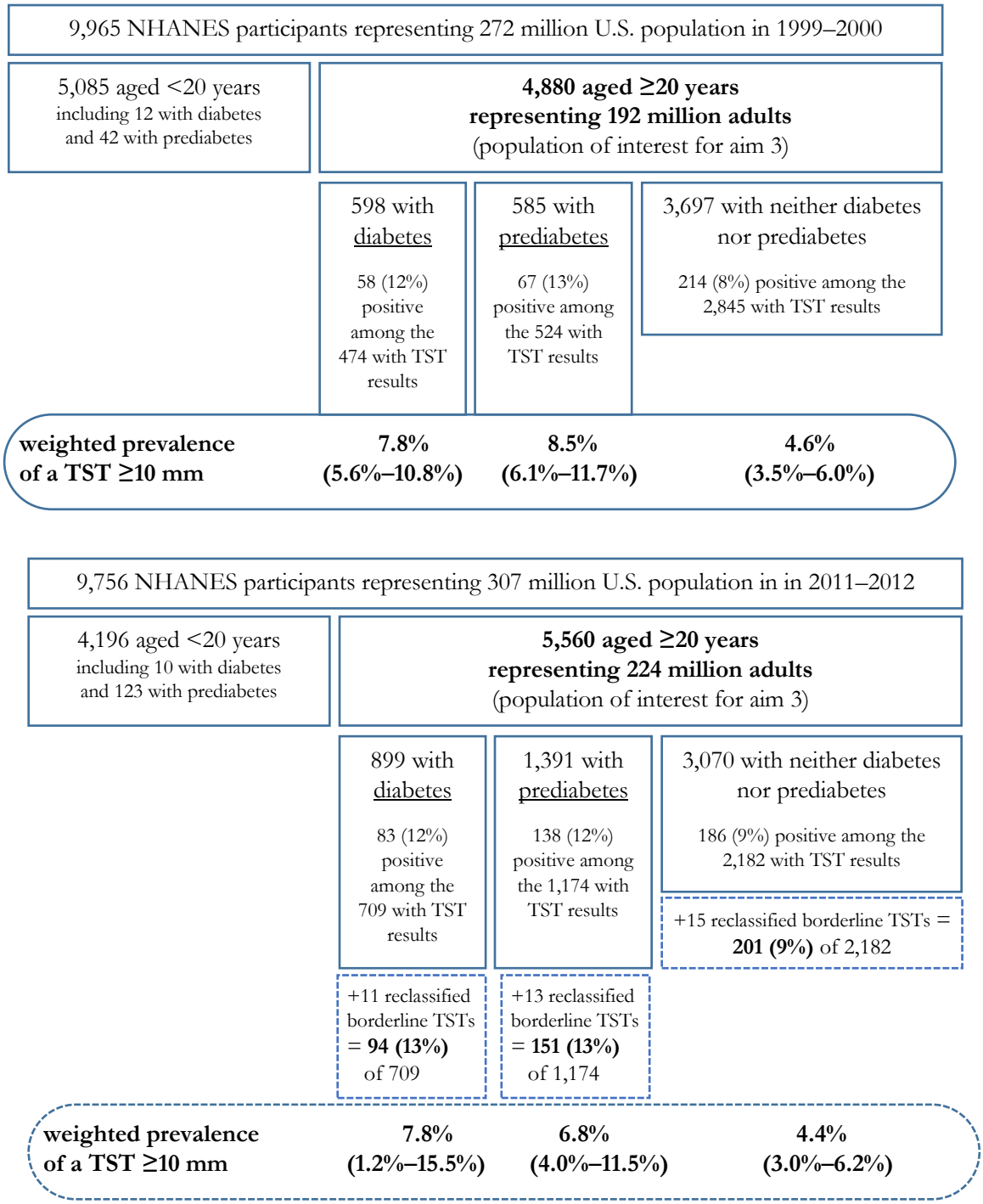
Blue font denotes where prevalence estimate decreased when participant weights were applied (i.e., as compared to unweighted prevalence in previous Aim 3 Table 1).

Aim 3 Table 3. Positive TST prevalence among NHANES participants aged ≥20 years, 1999–2000 and 2011–2012, based on TST results in public-use datasets and after record-level reclassification of 39 borderline-positive TST results in 2011–2012

	NHANES participants aged ≥20 yrs with positive TST					
	1999–2000		2011–2012			
	TST ≥10 mm in public-use dataset (total = 339 after subsetting to the 3,843 aged ≥20 with valid TST results)		**TST ≥10 mm in public-use dataset** (total = 409 after subsetting to the 4,261 aged ≥20 with valid TST results)		**TST ≥10 mm after 39 reclassifications** (total = 448 after subsetting to the 4,261 aged ≥20 with valid TST results)	
	Unweighted percent with TST ≥10 mm	**Weighted prevalence (95% CI)**	**Unweighted percent with TST ≥10 mm**	**Weighted prevalence (95% CI)**	**Unweighted percent with reclassified TST ≥10 mm** ↑ if higher	**Weighted prevalence (95% CI)** ↑ if higher
Born in 50 U.S. states or D.C.	4.8	2.4 (1.8–3.2)	3.7	1.8 (1.0–3.1)	↑3.9	↑1.9 (1.1–3.1)
Born elsewhere	20.1	20.1 (14.6–27.0)	24.3	21.1 (15.8–27.6)	↑26.8	↑23.0 (17.4–29.9)
Age grouping						
20 to 39 years	6.0	4.3 (2.7–6.8)	6.8	4.6 (3.2–6.7)	↑7.3	↑4.9 (3.4–6.9)
40 to 59 years	**10.3**	**6.1** (4.5–8.2)	**11.4**	**5.5** (3.7–8.1)	↑**12.4**	↑**6.0** (4.1–8.8)
60+ years	**10.4**	**5.7** (4.3–7.6)	**10.8**	**4.7** (3.1–7.0)	↑**12.1**	↑**5.1** (3.5–7.6)
Race/ethnicity						
Non-Hispanic white	2.4	2.2 (1.4–3.5)	1.5	1.1 (0.6–2.1)	↑1.6	1.1 (0.6–2.1)
Non-Hispanic black	11.9	10.4 (8.0–13.4)	9.3	7.8 (5.7–10.6)	↑10.0	↑8.3 (6.1–11.2)
Hispanic	15.5	14.2 (10.9–18.3)	17.4	15.3 (10.5–21.8)	↑19.2	↑16.7 (11.6–23.4)
Asian			24.2	24.9 (20.5–30.0)	↑26.7	↑27.3 (23.0–32.2)
Education						
High school/GED completed	4.8	3.6 (2.6–5.1)	8.0	3.8 (2.7–5.2)	↑8.5	↑3.9 (2.8–5.4)
No high school diploma/GED	15.3	10.4 (8.2–13.0)	14.8	11.2 (7.3–16.8)	↑17.2	↑12.8 (8.6–18.5)
Overall noninstutitionalized civilian U.S. population aged ≥ 20 yrs		**5.3 (4.2–6.6)**		**5.0 (3.5–7.0)**		↑**5.4 (3.8–7.5)**

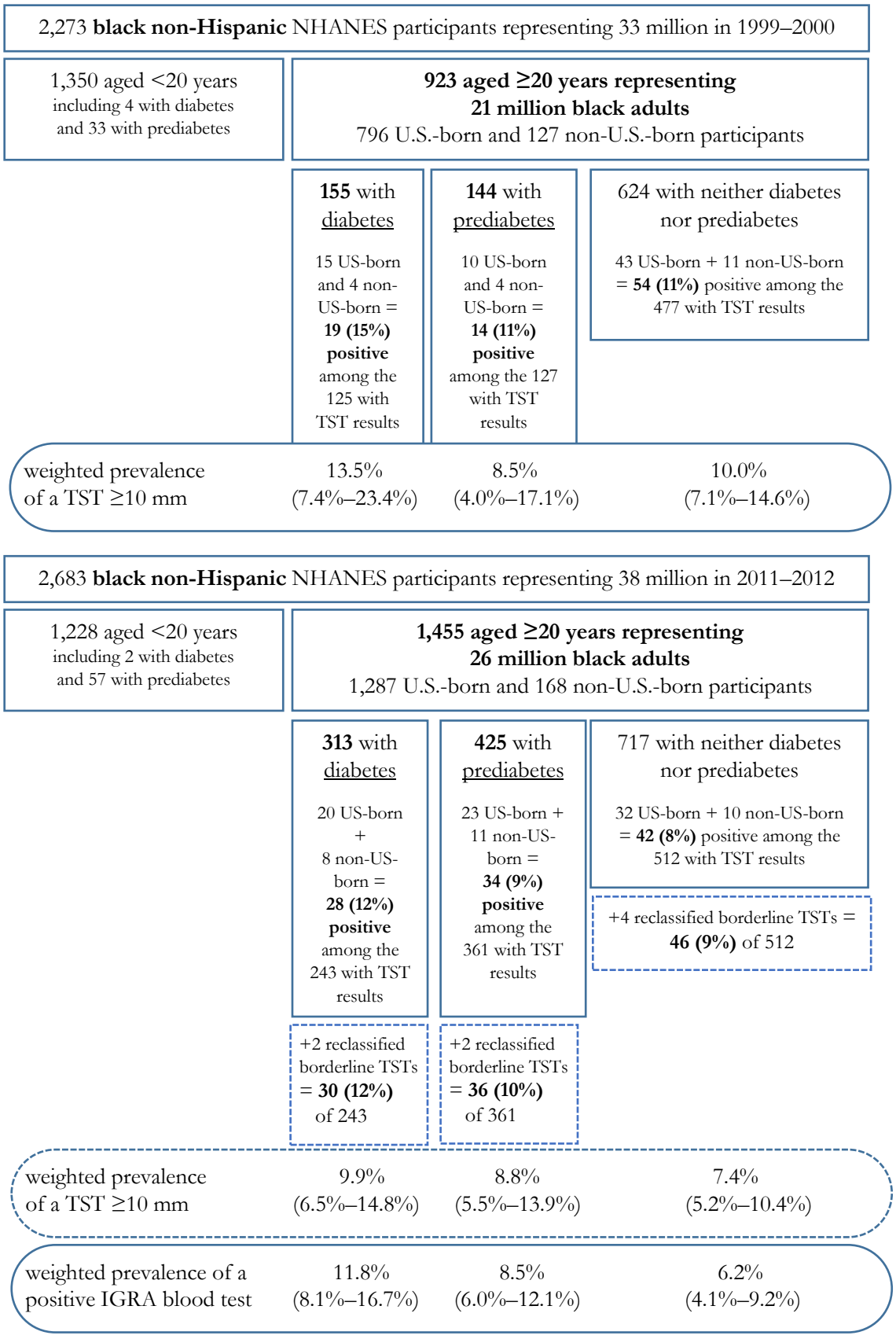
↑ Arrows show where weighted and unweighted estimates increased after borderline-positive TST results in NHANES 2011–2012 were reclassified. Blue font shows where weighted estimates decreased after the participant weights were applied to the unweighted %s (none increased).

Aim 3 stratified tables — positive TST and IGRA results stratified by diabetes status and race/ethnicity among NHANES 1999–2000 and 2011–2012 participants aged ≥20 years

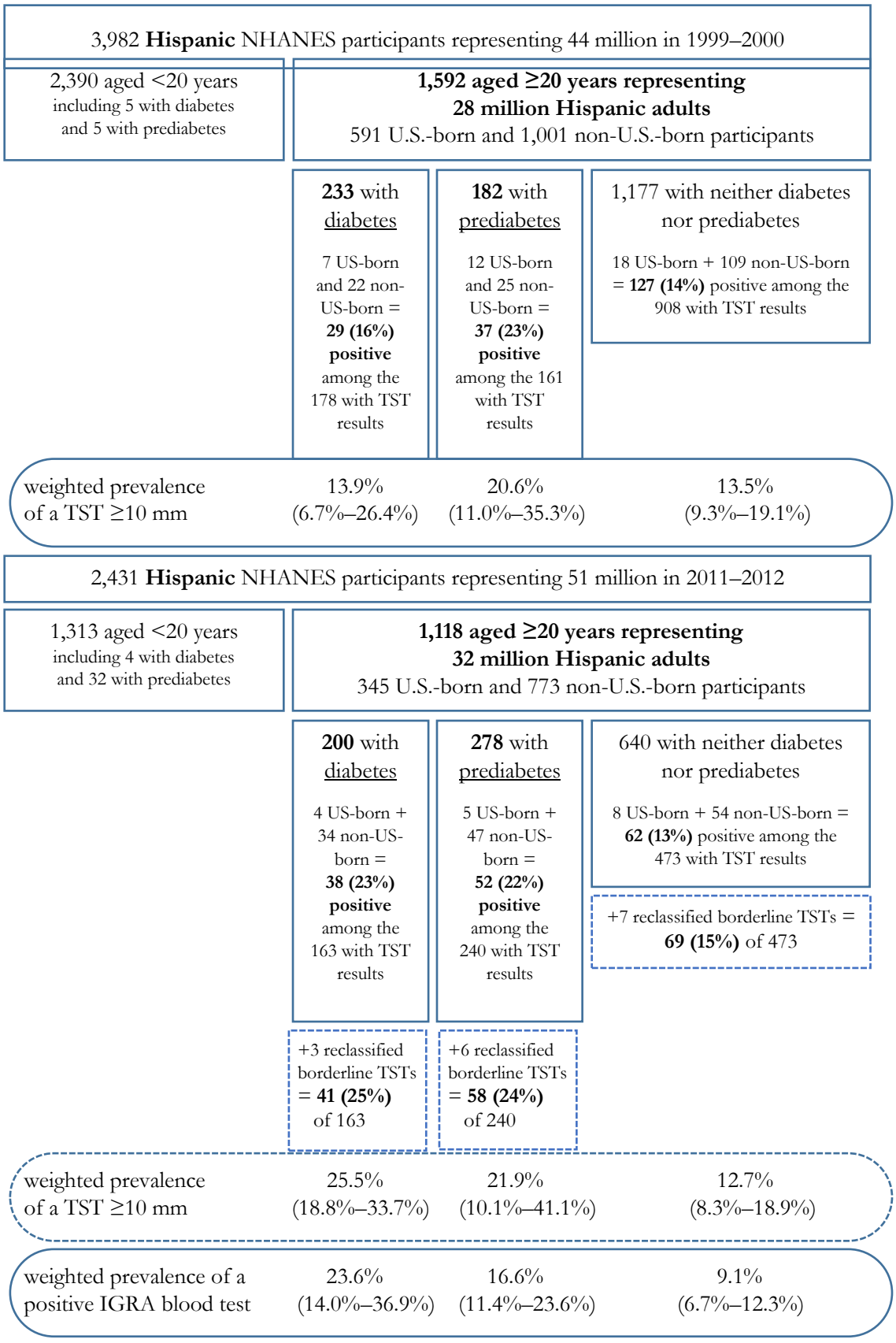


Note: The following series of stratified tables excluded 155 NHANES 1999–2000 participants aged <20 and 132 participants aged ≥20 years and whose race/ethnicity was not black, Hispanic, or white, and 235 NHANES 2011–2012 participants aged <20 and 152 participants aged ≥20 years whose race/ethnicity was not black, Hispanic, Asian, or white.

Stratified tables for black non-Hispanic NHANES participants in 1999–2000 and 2011–2012

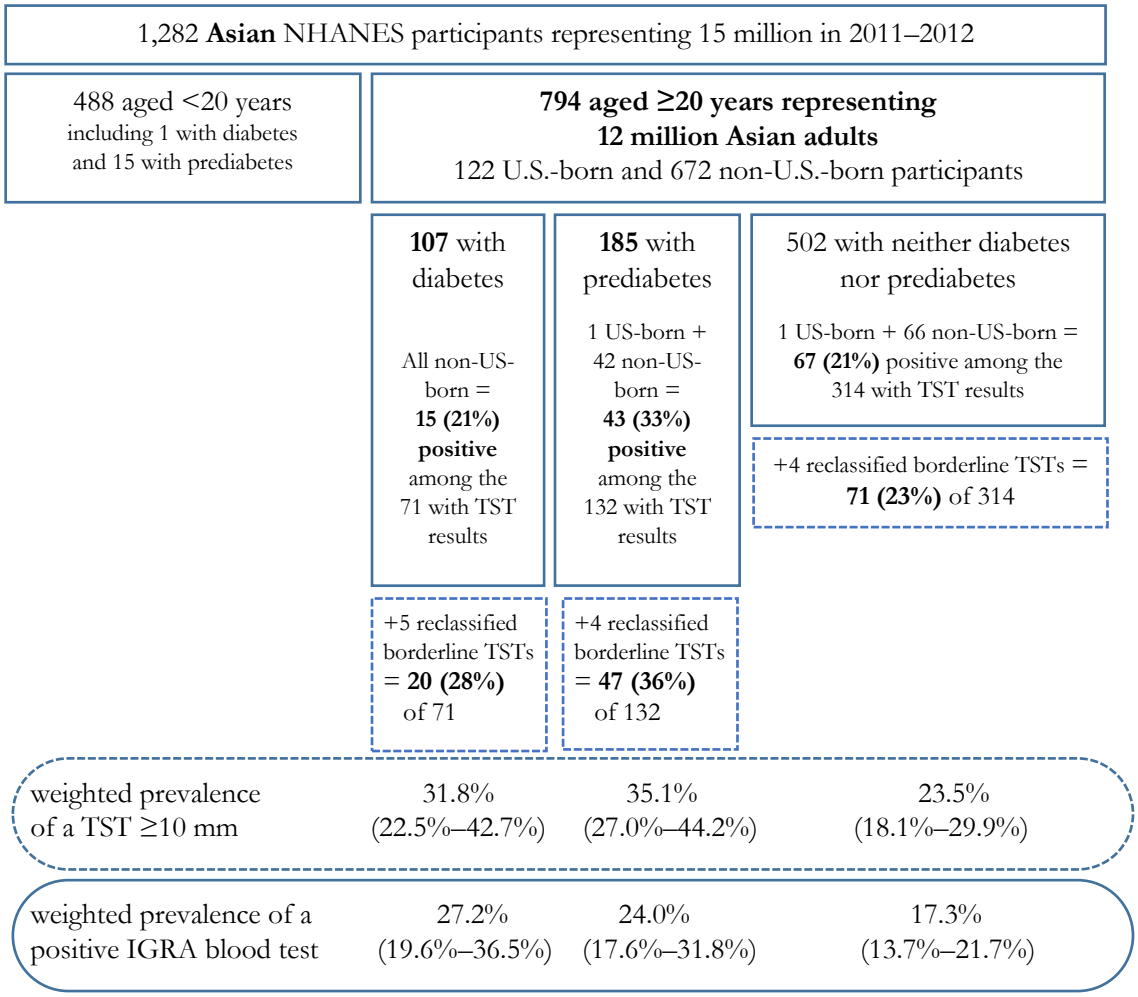


Stratified tables for Hispanic NHANES participants in 1999–2000 and 2011–2012

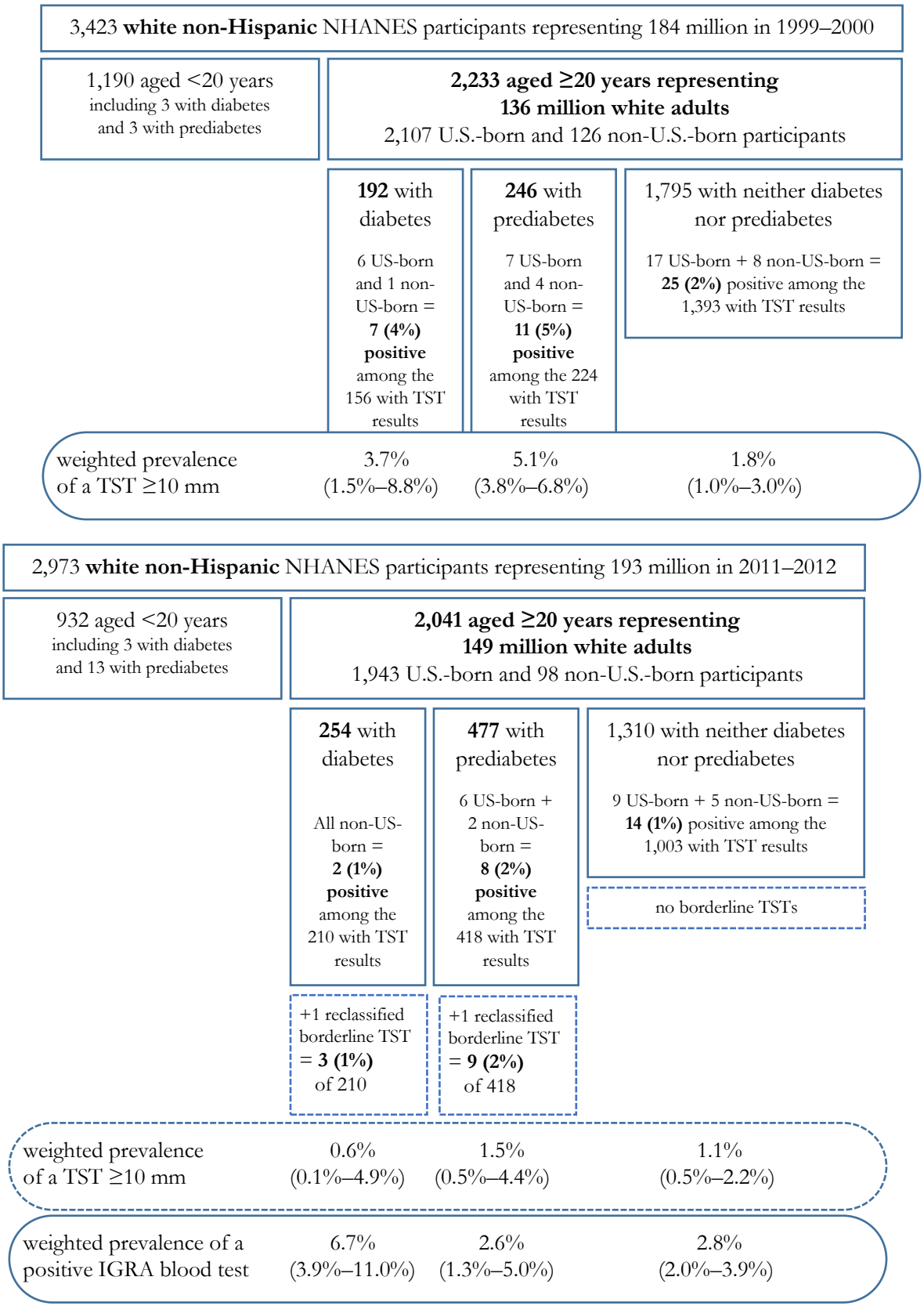


Stratified tables for Asian NHANES participants in 2011–2012

NHANES had no category for Asian race in 1999–2000.



Stratified tables for white non-Hispanic NHANES participants in 1999–2000 and 2011–2012



Aim 3 Table 4. Odds ratios for association between diabetes and a positive TST among NHANES participants aged ≥20 years, 1999–2000 and 2011–2012

	Odds Ratio (OR) showing association between diabetes and positive TST			
	1999–2000		2011–2012	
Unweighted and weighted crude (unadjusted) ORs within subpopulations				
Subpopulation	(no. with both conditions/ total no. participants*) unweighted OR	**Weighted OR (95% CI)**	(no. with both conditions/ total no. participants*) unweighted OR	**Weighted OR (95% CI)**
Born in 50 U.S. states or D.C.	(29/2,415) 2.5	3.0 (1.7–5.6)	(27/2,194) 1.7	1.2 (0.6–2.2)
Born elsewhere	(29/859) 1.3	1.1 (0.5–2.3)	(67/881) 1.4	1.9 (1.1–2.3)
Age grouping				
20 to 39 years†	(1/1,263) 0.7	0.7 (0.1–6.6)†	(8/1,247) 2.1	2.9 (1.4–6.3)†
40 to 59 years	(19/932) 1.6	1.8 (0.8–4.0)	(36/986) 1.4	1.9 (0.8–4.5)
60+ years	(38/1,079) 1.6	2.0 (1.0–4.2)	(50/842) 1.2	1.6 (0.9–3.0)
Race/ethnic origin				
Non-Hispanic white	(7/1,263) 2.5	2.1 (1.1–4.1)	(3/1,209) 0.7	0.4 (0.1–4.1)
Non-Hispanic black	(19/583) 1.5	1.4 (0.6–3.4)	(30/752) 1.5	1.5 (0.8–2.6)
Mexican/Hispanic	(29/1,079) 1.2	1.0 (0.4–2.8)	(41/632) 2.0	2.4 (1.3–4.2)
Asian			(20/385) 1.0	1.0 (0.5–2.2)
Education				
high sch/GED completed	(13/2,058) 1.7	2.1 (1.3–3.4)	(47/2,373) 1.4	1.4 (0.9–2.3)
no HS diploma/GED	(45/1,216) 1.1	1.0 (0.6–1.8)	(47/702) 1.4	1.5 (0.8–2.7)
Unweighted and weighted unadjusted OR in the overall U.S. population aged ≥20 years				
Aim 2 diabetes definitions	unweighted 1.7 (1.3–2.4)	weighted 1.7 (1.3–2.4)	unweighted 1.6 (1.0–2.5)	weighted 1.7 (1.1–2.7)
With more sensitive diabetes definition adding in fasting glucose	1.8 (1.4–2.5)	1.8 (1.3–2.4)	1.6 (1.2–2.1)	1.8 (1.2–2.7)
With more sensitive diabetes definition also adding in OGTT	*Not examined in 1999-2000*	*Not examined in 1999-2000*	1.6 (1.3–2.1)	1.9 (1.4–2.6)
Weighted adjusted OR for diabetes and positive TST in overall U.S. population aged ≥20 years				
Weighted adjusted OR in overall population adjusted for birthplace, age group, race/ethnicity, education	**1.2 (1.0–3.0)**		**1.3 (0.7–2.3)**	

*Total no. participants in these calculations includes everyone aged ≥20 years with TST results.
The referent group is persons with neither diabetes nor prediabetes (i.e., persons with prediabetes are excluded from these calculations).

†Estimates for the U.S. population aged 20–39 years are based on small numbers and less reliable:
In 1999–2000, only 1 participants in this group had both diabetes and a positive TST.
In 2011–2012, only 7 had both conditions.

Aim 3 Table 5. Odds ratios for association between prediabetes and a positive TST among NHANES participants aged ≥20 years, 1999–2000 and 2011–2012

	Odds Ratio (OR) showing association between prediabetes and positive TST			
	1999–2000		2011–2012	
Unweighted and weighted crude (unadjusted) ORs within subpopulations				
Subpopulation	(no. with both conditions/ total no. participants*) unweighted OR	**Weighted OR (95% CI)**	(no. with both conditions/ total no. participants*) unweighted OR	**Weighted OR (95% CI)**
Born in 50 U.S. states or D.C.	(31/2,465) 2.3	2.3 (1.3–4.0)	(40/2,536) 1.5	1.6 (0.8–3.3)
Born elsewhere	(36/859) 1.7	1.9 (1.2–3.1)	(112/1,005) 1.6	1.7 (1.0–2.8)
Age grouping				
20 to 39 years†	(8/1,296) 2.7	3.6 (2.2–5.8)†	(21/1,431) 1.3	1.4 (0.6–2.9)†
40 to 59 years	(14/967) 0.9	0.9 (0.3–2.5)	(65/1,186) 1.6	1.9 (0.9–3.8)
60+ years	(45/1,061) 2.0	3.0 (2.0–4.4)	(65/924) 1.3	1.6 (0.7–3.6)
Race/ethnic origin				
Non-Hispanic white	(11/1,599) 2.8	3.0 (1.7–5.2)	(9/1,417) 1.4	1.3 (0.3–4.9)
Non-Hispanic black	(14/585) 1.0	0.9 (0.3–2.2)	(37/870) 1.3	1.3 (0.8–2.1)
Mexican/Hispanic	(36/1,062) 1.8	1.7 (0.7–4.3)	(58/709) 1.8	2.0 (0.9–4.6)
Asian			(47/446) 1.7	1.6 (1.1–2.4)
Education				
high sch/GED completed	(23/2,142) 2.2	2.0 (1.3–3.0)	(93/2,797) 1.6	1.5 (1.0–2.2)
no HS diploma/GED	(44/1,182) 1.3	1.4 (0.8–2.6)	(58/744) 1.4	1.4 (0.6–3.4)
Unweighted and weighted unadjusted OR in the overall U.S. population aged ≥20 years				
Aim 2 prediabetes definition	unweighted 1.8 (1.4–2.4)	weighted 1.9 (1.3–2.8)	unweighted 1.6 (1.2–2.0)	weighted 1.6 (1.0–2.5)
With more sensitive prediabetes definitio adding in fasting glucose	1.8 (1.4–2.3)	1.8 (1.3–2.4)	1.4 (1.1–1.7)	1.4 (1.0–2.0)
With more sensitive prediabetes definitio also adding in OGTT	*No OGTT in 1999-2000*	*No OGTT in 1999-2000*	1.3 (1.1–1.7)	1.4 (0.9–2.0)
Weighted adjusted OR for prediabetes and positive TST in overall U.S. population aged ≥20 years				
Weighted adjusted OR in overall population adjusted for birthplace, age group, race/ethnicity, education	**1.6 (1.1–2.2)**		**1.4 (0.8–2.4)**	

*Total no. participants in these calculations includes everyone aged ≥20 years with TST results.
The referent group is persons with neither diabetes nor prediabetes
(i.e., persons with diabetes are excluded from these calculations).

†Estimates for the U.S. population aged 20–39 years are based on small numbers and less reliable:
In 1999–2000, only 8 participants in this group had both prediabetes and a positive TST.
In 2011–2012, only 19 had both conditions.