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Presentation and Treatment Outcomes by Diabetes Status among Patients with Tuberculosis in Guam, 2015–2018

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Health
2020

Abstract

Presentation and Treatment Outcomes by Diabetes Status
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By Stephanie O'Connor

Background: In areas with persistent tuberculosis (TB) incidence, increased prevalence of diabetes mellitus threatens TB elimination efforts. Previous studies have found that people with diabetes are at increased risk of developing TB, having more extensive TB disease manifestation, and suffering worse TB treatment outcomes. With a diabetes prevalence of 18.7% and TB incidence of 41.7 cases per 100,000 people, Guam's population is among those at risk of a dual epidemic.

Objectives: First, this analysis will describe the burden and distribution of TB with concomitant diabetes in Guam. Next, it will assess the association between diabetes status and several key presentation and treatment characteristics among patients with TB. Finally, it will examine the prevalence of diabetes among foreign-born patients with TB by length of residence.

Methods: Data were collected through routine TB surveillance from 2015–2018. Patients meeting the surveillance case definition for TB who were at least 15 years of age and presented with pulmonary, drug-susceptible TB were eligible for inclusion. Diabetes was the exposure of interest, and outcome variables included positive sputum smear, pulmonary cavitation, treatment duration, and treatment outcome. A secondary analysis including only foreign-born patients examined the odds of having diabetes based on length of residence. Multivariate logistic regression was used for both analyses.

Results: Of the 245 patients with TB eligible for inclusion, 38% had diabetes. The odds of being diabetic were 4.15 times higher among long-term immigrants compared to recent immigrants (CI 1.76–9.80). Overall, having diabetes was associated with both smear positivity and pulmonary cavitation (aOR 4.98, CI 2.63–9.44; aOR 3.61, CI 1.37–9.50). TB cases with diabetes were also more likely to have extended treatment duration and unfavorable treatment outcomes (aOR 5.69, CI 2.96–10.94; aOR 3.20, CI 1.36–7.52). The odds of death were 5.66 times higher among those with diabetes (CI 1.88–17.04).

Conclusion: There is a high burden of TB with concomitant diabetes in Guam. Diabetes was found to be associated with more severe presentation, worse treatment outcomes, and higher mortality. This analysis of Guam's TB surveillance data suggests that diabetes is an important factor to consider in TB prevention and treatment.

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Acknowledgements

In addition to the members of my thesis committee, I would like to thank Dr. Paul White and Dr. Christopher Murrill for their review of this work. I would also like to express my appreciate to Alice Cuenca, Kin Lam, Chima Mbakwem, Juanenrico Santiago, and the entire staff of the Guam Tuberculosis and Hansen's Disease Control Program for their commitment to promoting the health of the people of Guam. Finally, I would like to thank my family for their enduring support for all of my endeavors.

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Chapter 1 Introduction

Even as the burden of infectious disease declines in populations experiencing epidemiologic transition, tuberculosis (TB) remains an ongoing concern for many low- and middle-income countries. While incidence and mortality rates have declined modestly on the global level, progress has not been uniform across regions (1). Lower-income countries, which have historically borne a disproportionate TB burden (2), now face rising levels of some non-communicable diseases (3). Among populations with persistent TB incidence, increased prevalence of diabetes mellitus threatens TB elimination efforts.

Diabetes is on the rise in the 30 countries with the highest TB burden (1). As an immunosuppressive condition, diabetes may increase the risk of developing active TB disease, severe TB presentation, unfavorable TB treatment outcomes, multi-drug resistant TB, and TB relapse (4-6). Previous studies showed greater TB prevalence among those with diabetes (7, 8). One study found that having diabetes corresponded to a 12-fold increase in TB prevalence among overweight or obese adults, highlighting the role of body mass index (BMI) (9). Among those with diabetes, there is an estimated three-fold increase in the risk of developing TB (10). Patients with diabetes have been found to have more symptoms on average than those without diabetes (11). Other researchers found higher rates of specific clinical features, including cavitation, hemoptysis, fever, and cough (12, 13). Worse treatment outcomes have also been found among diabetic patients with TB when using response to TB medication, sputum culture conversion, and mortality as metrics (11, 14, 15).

According to estimates from the World Health Organization (WHO), 360,000 TB cases were attributable to diabetes in 2018, or 4% of total cases (1). Just as having diabetes can impact TB status and manifestation, having TB appears to alter glycemic control, a key indicator of diabetes (16). Consistent with the bidirectional relationship between TB and diabetes, there is evidence of higher diabetes prevalence among patients with TB than the general population (6, 13). A systematic review of TB/diabetes studies estimated that 16% of patients with TB had concomitant diabetes, and the regional prevalence for Oceania was estimated at 23% (7). The increased risk of diabetes in patients with TB may be due to poor glycemic control brought on by anti-tuberculosis medications or by temporary impairment of glucose tolerance attributable to TB infection itself (16-18).

Guam's population is among those at risk of a dual epidemic of TB and diabetes. In 2018, 35.7% of TB cases in Guam had diabetes, compared to 19.8% in the mainland U.S. (19). The island's geographic location, ethnic makeup, and cultural norms are among the risk factors that intersect to create complex challenges for TB treatment and control. Located in the Micronesian region, Guam is an island nation that had a population of 159,000 in the last census (20) and is similar in size to the city of Chicago. Guam is one of six U.S.-affiliated Pacific Islands (USAPI), a group that also includes the Commonwealth of the Northern Mariana Islands, the Federated States of Micronesia (FSM), Palau, the Marshall Islands, and American Samoa.

Estimates from 2018 indicate a TB rate of 41.7 cases per 100,000 population in Guam, while the U.S. rate was 2.8 per 100,000 (19). Although the rate of decline in TB cases has slowed, both incidence and prevalence have reached an all-time low in the mainland (21). TB incidence in Guam has fluctuated considerably over time, hitting a recent low of 17.2 cases per 100,000 in 2002 but rising to 62.7 cases per 100,000 just seven years later (22). This variation is partially a product of Guam's relatively small population size, but TB incidence has remained consistently higher on the island than in the mainland U.S.

Guam's relatively high TB incidence is part of a broader trend among nearby countries. The Philippines, one of Guam's closest neighbors, accounted for 6% of global TB cases in 2018 (1).

Rates are also high in other USAPI, notably 128.8 per 100,000 population in FSM, 111.1 in Palau, and 332.8 in the Marshall Islands (23). The frequency and volume of visitors and immigrants from neighboring countries create sustained opportunity for TB exposure.

Guam's overall age-adjusted comparative diabetes prevalence of 18.7% is considerably higher than the regional average of 11.4% (24), although comparably high rates have been documented in other Pacific Island countries and territories (PICTs) (25). Rising obesity and diabetes in the Pacific Islands may be partially attributable to the transition away from a traditional lifestyle characterized by active fishing and cultivation of fruits and vegetables. A study in FSM found a direct relationship between practicing a more traditional lifestyle and having better overall health (26). Another study assessing the relationship between body composition and modernization in Vanuatu found higher obesity rates among islands with greater levels of economic development, access to urban areas, and tourism (27). With the highest gross domestic product per capita among all PICTs (28), Guam may exemplify the impact of development on body composition among Pacific Islands experiencing modernization. Metabolic and behavioral risks make up nine of the island's ten causes of disability-adjusted life years (DALYs), with high BMI, dietary risks, and high fasting plasma glucose ranking as the top three (29). Residents who are not native to Guam may also be impacted by lifestyle-related health conditions, as immigrant health studies indicate that acculturation can have an obesogenic effect exacerbated by duration of residence (30, 31).

Despite the high burden of TB and diabetes in Guam and its neighboring islands, a systematic review of 94 studies reporting on both conditions included only four with data from the Pacific Islands (7). One was a case-control study conducted in Kiribati that found diabetes prevalence to be 37% among TB cases (32). In this study's adjusted model, the odds of having diabetes among those with TB were estimated to be 2.8 times the odds among those without TB (CI 2.0–4.1)

(32). A study in the Marshall Islands reported that 45% of TB patients had concomitant diabetes, although only 62 patients were enrolled (33). The two remaining studies were conducted in Fiji. The earlier study found that 13% of TB patients were known to be diabetic (34). Similar diabetes prevalence was reported in the second study, at 12% (35). Among the studies conducted in the Pacific Islands, the later study in Fiji was the only one that reported TB treatment outcomes, although it did not find that differences by diabetes status were statistically significant (35).

Aside from a report on risk factors for diabetes in Guam that included TB (36), there is no published literature reporting recent prevalence of diabetes among the island's TB cases. Furthermore, the extent to which clinical presentation and treatment outcomes differ based on diabetes status among patients with TB in Guam has yet to be assessed. Understanding this relationship is particularly important in Guam, as previous research suggests unique diabetes pathogenesis among Pacific Islanders and Southeast Asians, the island's majority ethnic groups (37, 38). The first aim of this thesis was to estimate the prevalence of diabetes among patients with TB disease in Guam. The second was to estimate the association between diabetes status and TB clinical presentation characteristics and TB treatment outcomes. The final objective was to estimate the association between length of residence in Guam and diabetes status among patients with TB.

Chapter 2 Methods

Data were collected through TB surveillance conducted by the Guam Tuberculosis and Hansen's Disease Control Program, which reports verified cases of TB to the U.S. Centers for Disease Control and Prevention (CDC) as part of the National Tuberculosis Surveillance System (39). For surveillance purposes, the CDC defines a clinical case as anyone with TB signs or symptoms who tests positive via interferon gamma release assay (IGRA) or tuberculin skin test (TST), receives diagnostic evaluation, and is treated for TB (40). Confirmed TB cases require laboratory criteria for diagnosis from clinical specimens, such as via isolation of *Mycobacterium tuberculosis*, detection of *M. tuberculosis* by nucleic acid amplification test (NAAT), or acid-fast bacilli (AFB) by microscopy (40). A case meeting either the clinical or laboratory criteria is considered confirmed (40).

Eligible participants in this study included all TB cases in Guam meeting the surveillance case definition from 2015–2018. Reported cases were either referred by a healthcare provider or detected directly by the TB Program. Patients with extrapulmonary TB and those under 15 years of age were excluded from analysis. Multi-drug resistant TB (MDR-TB) cases, defined as those with resistance to isoniazid and rifampin detected through initial drug susceptibility testing (1), were also removed.

Data used for this analysis were reported with the CDC's Report of Verified Case of Tuberculosis (RVCT) form, through which diabetes status is recorded as a dichotomous variable (40). Patients with TB were asked about diabetes status as part of routine TB surveillance procedures. For cases of unknown status, a determination was made based on measured glycated hemoglobin A1c (HbA1c) levels upon presentation at the TB Program clinic. Concomitant diabetes reported by a referring healthcare provider may not have been verified in all reported TB cases. Although patients' HbA1c levels are routinely monitored during TB treatment, this information is stored only in medical records. Because these records are not linked to the TB surveillance database, HbA1c could not be used in this analysis.

Outcome variables were selected based on a review of previous studies examining the relationship between diabetes and tuberculosis. Disease presentation was assessed based on sputum smear and the presence of pulmonary cavitation. A patient was treated as smear positive if any sputum sample detected AFB. In accordance with the CDC's TB surveillance guidelines, results of a sputum smear carried out using samples collected more than two weeks after TB treatment was initiated would not be reported (40). Pulmonary cavitation was considered separately based on detection through chest radiography or computerized tomography (CT) scan. Regardless of detection method, cavitation was defined as evidence of one or more cavities present in an initial examination.

Consistent with other studies examining this topic (41, 42), treatment outcome was defined as unfavorable if the patient was lost to follow-up, did not complete treatment, or died. Deaths included mortality from any cause. It is possible that some patients reported to have died were diagnosed with TB postmortem. Therapy duration was also included as a component of treatment outcome. Duration was measured as the number of days between the date multidrug therapy for TB was initiated and the date it was stopped, regardless of the reason for halting treatment. The minimum treatment period for TB is six months, but a three-month extension is recommended for those TB case-patients who present with cavitation and remain culture positive after the intensive phase of treatment (43). In this analysis, extension beyond six months (180 days) and nine months (270 days) were both included as outcome variables. Because underlying conditions such as diabetes are included in the decision process for selecting a treatment plan, these measures are considered to be one indication of treatment practice, not necessarily of disease severity.

A secondary analysis using diabetes as the outcome of interest was also conducted. Length of residence, measured as both a continuous and binary variable, was considered the main predictor. Only foreign-born patients with TB were included in this phase of the analysis. For the binary analysis, 15 years of residence was used as the cut point, because a previous study found that immigrants had similar health status to the native-born population after at least this length of time residing in the United States (44).

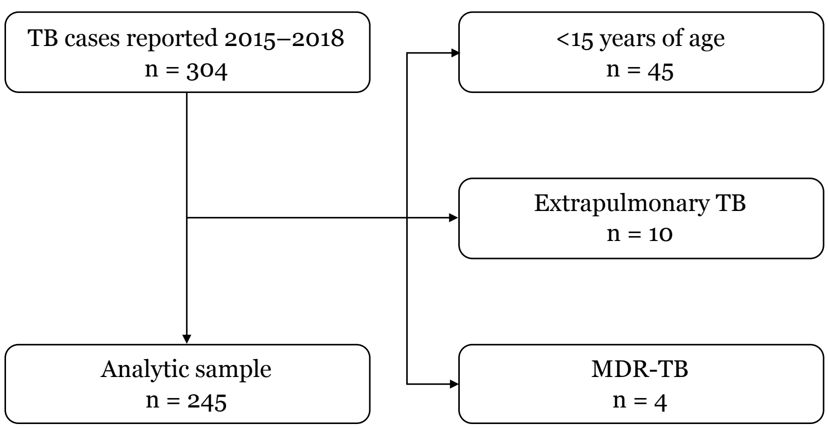
Chi-square tests were used to determine whether variable frequency differed by diabetes status in the primary analysis, and by length of residence in the secondary analysis. A two-sample t-test was used to compare mean age, and a Mann-Whitney *U* test was used for length of residence, which was not normally distributed. Adjusted odds ratios were calculated in SAS 9.4 using logistic regression. All odds ratios are expressed with the corresponding 95% confidence intervals. Multivariable analyses controlled for age, sex, and race. Race was self-reported according to the standard categorization used for federal statistics (45).

Surveillance records were de-identified prior to analysis. This project was determined to be exempt as non-human subjects research by the Institutional Review Board of Emory University.

Chapter 3 Results

Among the 304 cases of TB reported from 2015–2018, 45 were younger than 15 years of age. Another 10 cases were reported with extrapulmonary disease. Initial drug susceptibility results were available for 167 patients (67%) who met all other inclusion criteria. Of these, four were classified as having MDR-TB. The remaining 245 cases met the criteria for study inclusion. The mean age among cases was 49 years. Fifty-one percent of cases were Asian, and 45% identified as Native Hawaiian or other Pacific Islander. Overall diabetes prevalence was 38%. Mean age was significantly higher among diabetic patients with TB, at 58 years of age compared to 44 among those without diabetes ($p<0.001$) (Table 1). There were no statistically significant differences in diabetes status based on race or sex.

Figure 1: Eligibility for inclusion in the analytic sample



Clinical Presentation

Overall, 54% of cases were AFB smear positive, and those with concomitant diabetes were significantly more likely to have a positive sputum smear (cOR 4.92, CI 2.72–8.92). Based on chest x-ray results, 28% of cases presented with pulmonary cavitation. The unadjusted odds of cavitation among TB cases with diabetes were 1.72 times the odds among those without diabetes (CI 0.98–3.05). CT scan results were available for 39% of cases. Having diabetes was associated with both AFB smear positivity and cavitation detected using CT scan after controlling for age, sex, and race. Those with diabetes had 4.98 times higher odds of being smear positive compared to those without diabetes (CI 2.63–9.44). The odds of cavitation increased 3.61 times based on diabetes status (CI 1.37–9.50) (Table 2, Table 4).

Treatment Outcomes

Among all patients with TB, 81% had a treatment course longer than six months (180 days) and 42% longer than nine months (270 days). Therapy extension beyond six months was not significantly associated with diabetes status (cOR 0.55, CI 0.26–1.16). However, those with diabetes were at increased odds of remaining in treatment for at least nine months. Among TB cases with diabetes, the adjusted odds of requiring therapy for at least nine months were 5.69 times the odds among those without diabetes (CI 2.96–10.94). TB cases with diabetes were also more likely to experience an unfavorable treatment outcome. Overall, 82% of cases completed treatment. Controlling for age, sex, and race, TB cases with diabetes were 3.20 times more likely to have an unfavorable outcome (CI 1.36–7.52). Overall mortality among cases was 9%, with a mortality rate of 20% among those with diabetes and 3% among those without diabetes. Compared to patients with TB only, the adjusted odds of death were 5.66 times higher among those with diabetes (CI 1.88–17.04) (Table 3, Table 4).

Length of Residence

Three quarters of TB cases were not born in Guam, and 45% were originally from the Philippines. Among those with a recorded arrival date, the median length of residence in Guam was 18 years, with an inter-quartile range of 23 and range of less than a year to 81 years. Fourteen percent had lived in Guam for less than a year, and 56% had been residents for less than 15 years. Median length of residence among those with TB and diabetes was 28 years, more than twice as long as those with only TB ($p<0.001$). In the unadjusted model, there was a weak association between having diabetes and length of residence in Guam (cOR 1.06, CI 1.04–1.09).

After controlling for age, sex, and race, the association was nearly unchanged (aOR 1.06, CI 1.03-1.09), indicating a six-percent increase in the odds of having diabetes for every additional year of residence. Using 15 years as a cutoff, the odds of having diabetes among long-term immigrants with TB were 5.25 times the odds among recent immigrants (CI 2.40–11.49). In the adjusted model, the odds ratio remained statistically significant (aOR 4.15, CI 1.76–9.80) (Table 5, Table 6).

Chapter 4 Discussion

Among TB cases reported in Guam between 2015 and 2018, diabetes prevalence was found to be 38%, higher than the island's overall prevalence of 18.7% (24). Patients with TB and concomitant diabetes were older on average than those without diabetes. While people identifying as Asian make up only a third of Guam's population (20), they represented half of TB cases during the time period examined. This analysis provided evidence of differential disease presentation by diabetes status. Compared with reported TB patients who did not have diabetes, those with diabetes were nearly five times more likely to have a positive AFB sputum smear, and the odds of lung cavitation were 3.61 times higher. Differences in TB treatment outcomes were also observed. Diabetes was associated with higher odds of an unfavorable outcome and a five-fold increase in a patient's odds of continuing treatment duration for more than nine months. The observable effects of the interplay between TB and diabetes are evident in the findings of this analysis. Data from Guam contribute to the existing body of knowledge by elucidating how that complex relationship is expressed in a setting where biological and environmental factors create compounded risk. The following sections explore those factors in order to contextualize findings from analysis of Guam's TB surveillance data.

Regional Prevalence

Of the TB cases included in this analysis, 75% were born somewhere other than Guam. While foreign birth is a known risk factor for TB in low-burden countries, immigrants from high-incidence countries are at increased risk of developing active disease compared to those from countries with low incidence (46). Most (94%) of Guam's foreign-born patients with TB were from countries with TB incidence higher than Guam's (47). Because even higher rates of TB are found in most of Guam's closest neighboring countries, there is ongoing risk of disease importation. In 2019, over 40,000 visitors arrived in Guam from other USAPI and nearly 20,000 from the Philippines (48). Almost a third of Guam's population was classified as foreign-born in the last census, and of these, 58% were from the Philippines and 21% from FSM (20). According to more recent estimates, 19,000 immigrants from FSM, Palau, and the Marshall Islands reside in Guam, a greater number than in Hawaii or any other USAPI (49). These island nations have TB incidence ranging from 2-8 times higher than Guam's (1).

Beyond the infectious disease dynamics operating in the region, the prevalence of diabetes and its associated risk factors raise a different set of concerns for TB control efforts. Of the ten countries with the highest diabetes prevalence, seven are Pacific Islands (24). Guam is among them, currently ranking tenth but expected to have the seventh-highest diabetes prevalence globally by 2045 (24). A systematic review of diabetes studies conducted in the PICTs found high rates of diabetes and associated risk factors, including obesity and physical inactivity, across the Pacific (25). The WHO's STEPwise approach to surveillance (STEPS) is a tool that has been used to assess noncommunicable disease in countries around the world, including the Pacific region. Of the 16 Pacific Island countries that have conducted STEPS surveys, nine estimated diabetes prevalence to be above 20%, and one – American Samoa – reported that nearly half of its population was diabetic (25).

Ethnicity & Diabetes

The burden of diabetes in the Pacific is consistent with known associations between ethnicity and metabolic conditions. Both Pacific Islanders and Southeast Asians have been identified as ethnic groups at increased risk of diabetes, which is particularly concerning for Guam, where 49% of residents were Native Hawaiian/Pacific Islander, and 26% were Filipino in the last census (20). Although by no means homogenous, Pacific Islander and South Asian ethnic groups share a relatively close genetic relationship (50), allowing for some generalization across both groups in the absence of research that is specific to Micronesians.

The association between race and diabetes has been observed even outside of the geographic confines of the Pacific. Obesity, a risk factor for diabetes, is more prevalent among Native Hawaiian and other Pacific Islander ethnic groups compared to White and East Asian sub-groups in the U.S. (51). California residents who were ethnically Pacific Islander or Filipino were found to have the highest diabetes prevalence among all Asian sub-groups, at 18 and 16%, respectively (38). Another California-based study estimated that the odds of diabetes among Filipino residents were four times the odds among White residents (52). Studies conducted in Hawaii, another state with large numbers of Asian and Pacific Islander residents, found similar results. In one study, diabetes prevalence was higher among Filipinos and those who identified as Native Hawaiian or other Pacific Islander compared to White respondents (51). A cohort study of older adults found that a greater percentage of Native Hawaiians than Japanese or White Americans developed diabetes during the follow-up period (53). Although these studies were all conducted in the United States, similar results have been found within the Western Pacific. A study comparing prevalence of risk factors for cardiovascular disease among native-born and immigrant Australians found that those born in South Asia were more than twice as likely to have diabetes after controlling for age, sex, and socioeconomic factors (54).

Theories on Heterogenous Diabetes Risk

The higher prevalence of diabetes among Pacific Islanders and Southeast Asians may be partially explained by differences in metabolic function and body composition. Fasting insulin levels, percent body fat, abdominal adiposity, and visceral adipose tissue concentration have all been found to be higher among South Asians than other ethnic groups, both in the neonatal and later life stages (37). Genes linked to diabetes have been identified, but the degree to which diabetes risk can be attributed to genetic differences remains unclear (55) .

Although the relationship between these measures and diabetes risk is complex and not yet entirely understood, body composition has been incorporated into theories about ethnic differences in diabetes pathogenesis. Some posit that a combination of environmental factors linked to the region's climate, including periods of food scarcity and exposure to infectious agents, have influenced evolution of South Asian people groups (37). More proximal explanations point to studies in human and animal models suggesting that factors such as maternal undernutrition and psychosocial stress increase the risk that a fetus will go on to develop a metabolic disorder (55).

In combination with predisposing metabolic factors, lifestyle differences may help explain the high rates of obesity and diabetes in Guam and the broader Pacific and South Asia region. The traditional diet of the Chamorro people, the majority ethnic group of the Marianas archipelago, primarily consisted of fish and nutrient-rich fruits and vegetables, but children in Guam now consume less than half the recommended dietary allowance of calcium, vitamin A, and folate (56). A survey measuring nutrition intake using 24-hour dietary recall found evidence of excessive saturated fat, cholesterol, and sodium in the diets of Guam residents (57). In this study, those who identified as Chamorro reported higher energy intake from saturated fats than Asian and Filipino respondents (57). Another study comparing dietary habits among Chamorro and Filipino residents of Guam found that energy density and added sugar consumption were higher among Chamorro men than their Filipino counterparts (58). Daily fruit and vegetable intake were well below recommended quantities in both ethnic groups (58). STEPS surveys have been conducted in four jurisdictions among the USAPI – American Samoa, the Marshall Islands, and the Micronesian states of Chuuk and Pohnpei. The results indicated low physical activity in over 60% of the adult population in all jurisdictions surveyed, and daily fruit and vegetable consumption below the recommended number of daily servings in 82-91% (59-62).

Role of Immigration

While metabolic and lifestyle factors appear to put Guam and neighboring countries at increased risk, diabetes prevalence is not uniform across the Pacific and Southeast Asia. The Philippines and FSM, the two countries most represented among Guam's foreign-born patients with TB, both have lower prevalence of diabetes than Guam. Age-adjusted comparative diabetes prevalence is 11.9% in FSM and 7.1% in the Philippines (24). Among Filipino patients with TB, 53% had diabetes, while only 6% of those from FSM were diabetic. This heterogeneity raises questions about the role of immigration in understanding the burden of TB with concomitant diabetes in Guam. Some circumstances associated with being an immigrant, such as having less time for physical activity, are also risk factors for diabetes, and acculturation may entail adoption of obesogenic dietary habits (55).

One study attempting to understand how immigration affects lifestyle enrolled first- and second-generation Japanese Americans and non-immigrant residents of Japan (31). Higher BMI, as well as dietary habits and activity levels linked to diabetes, were most common among those born in the United States, followed by first-generation immigrants and then non-immigrants (31). Additional evidence for the obesogenic effect of immigration comes from a study that compared Vietnamese immigrants living in the United States to those who returned to Vietnam, as well as a third group of non-immigrants in Vietnam (30). U.S. residents were found to have higher BMI and waist-hip ratios than the other two groups (30).

The study of Vietnamese immigrants found that the length of time since a person immigrated was another important predictor of being overweight (30), a result observed in other studies as well (54). In a survey of California residents, BMI was significantly higher among those who had lived in the U.S. for more than 15 years compared to those who immigrated more recently (63). Among refugees resettled in the United States, every additional year of residence corresponded to 12.2% increased odds of diabetes (64), and a study of immigrants overall found that those who had lived in the U.S. for at least ten years were at increased odds of high BMI and diabetes (65). Another study estimated that the odds of diabetes among long-term immigrants from the Philippines were four times the odds among second-generation Filipino Americans (66).

Conclusions from these large-scale studies powered to detect differences in BMI and diabetes prevalence support the finding from this analysis that the odds of having diabetes were significantly higher among long-term immigrants with TB compared to those who immigrated to Guam within the last 15 years. Although these results suggest that there is an obesogenic effect associated with immigration to Guam, it is unclear whether acculturation results in major lifestyle and dietary changes among immigrants to Guam from neighboring countries, and the extent to which living on the island has a Westernizing influence remains under-studied.

Chapter 5 Limitations

The primary limitation of this analysis is that the data used were collected as part of routine TB surveillance. The implications of this statement are twofold – first, that case information may not have been recorded as systematically as it would be for the purposes of a formal study. Treatment of existing cases and prevention of disease transmission were prioritized, possibly at the expense of data completeness. Decisions made based on clinical judgements may have introduced bias, as the choice to order a chest CT scan, for example, would be made based on healthcare provider discretion rather than according to study protocol.

Second, the data are concentrated around clinical features, diagnostic evaluation, and risk factors associated with TB, not diabetes. Diabetes is only one of many underlying conditions considered important in TB treatment. As a result, some measures that could have helped orient the findings of this analysis in relation to prior research were not collected. A measure of BMI or percent body fat would have been particularly informative. Prior studies linking diabetes pathogenesis to various metabolic indicators allow for inference that body composition, for example, may play a role in the high burden of diabetes among TB patients in Guam, but in the absence of additional anthropometric measures, this analysis cannot provide supporting evidence.

Because data were collected through the TB Control Program, diabetes status was not ascertained or verified systematically. Ideally, systematic measures and recordings of HbA1c would have provided accurate ascertainment of glycemic control in these reported TB cases, and its association with clinical features and treatment outcomes. Although HbA1c levels were measured and included in medical records for some patients, this information was not linked to TB surveillance data and could not be incorporated into analysis. Cases not reported to be diabetic were assumed to be diabetes-negative. It is possible that some patients with undiagnosed diabetes were included among those without diabetes. However, because diabetes status is required information for reporting TB, cases were generally tested through measurement of HbA1c levels. This type of exposure misclassification would attenuate the odds ratio, leading to a more conservative estimate.

Another important datapoint missing for some cases was initial drug susceptibility testing, which was reported for two-thirds of cases included in the analysis. Given that drug susceptibility results were not universally reported, it is possible that some cases of multidrug resistant TB were not classified as such.

Finally, the use of surveillance data precludes assessment of chronology to determine which of the two conditions of interest, TB or diabetes, occurred first, and its impact on the other. While this is a characteristic limitation of cross-sectional data, it is of particular relevance in the case of TB and diabetes. Having TB may be a factor in developing diabetes for some people, and having diabetes puts a person at increased risk of TB disease. Thus, knowing which condition was preexisting would provide a more nuanced understanding of how diabetes status impacts TB presentation and treatment outcomes.

Chapter 6 Implications

Consequences for TB Prevention and Control Practice

This analysis found diabetes prevalence among TB cases to be exceptionally high, at 38%. This finding has implications for both clinical management and prevention of disease transmission. The association between having diabetes and presenting with more extensive disease highlights the importance of early TB detection in Guam. Lung cavitation, positive AFB sputum smear, and higher smear grade are associated with higher risk of transmission by those with TB disease to their close contacts (67). A systematic review of TB transmission patterns found that patients who were AFB smear positive or presented with cavitation were more likely to infect contacts (68). Another study focused on children found that risk of infection was higher among those who were household contacts of an AFB smear-positive adult (69). Because smear-positive TB cases and those with cavitation are more infectious, identifying and treating cases before they reach this stage of disease manifestation is a key TB control measure.

The disproportionate number of TB cases with diabetes who had unfavorable treatment outcomes suggests a need for tailored clinical management in this high-risk group. Identifying TB cases with undiagnosed diabetes through systematic screening is a necessary precursor. Existing recommendations are in place for baseline diabetes screening for those at risk, based on factors such as age, BMI, and ethnicity (43). The higher rate of therapy extension among TB cases with diabetes indicates that there is already differentiation in treatment course that correlates with diabetes status, although this may be because diabetic TB patients were more likely to present with cavitation. One strategy for providing increased monitoring of cure progression and treatment adherence among TB patients with concomitant diabetes is directly observed therapy (DOT). A study in Taiwan found that a six-month course of directly observed therapy reduced TB recurrence among patients with concomitant diabetes (70). Although recurrence was not captured in the data from Guam, findings from Taiwan suggest that more favorable treatment outcomes may be achieved if DOT is widely implemented.

Recommendations for Further Study

While this analysis provides support for previous research indicating differential TB presentation and treatment outcomes in people with concomitant diabetes, future studies are needed to better understand the role of contextual factors present in Guam, including the island's majority ethnic groups and significant contact with countries that have higher TB incidence. By incorporating measures of body composition and metabolic function, additional research could provide new insights regarding how observed differences in diabetes risk, as well as possible underlying mechanisms, may exacerbate the detrimental effect of having diabetes on TB manifestation and treatment outcomes. For Guam in particular, it may be important to further investigate the root causes of unfavorable treatment outcomes in order to distinguish between failure to adhere to recommended treatment and failure of the treatment itself. A key component of a follow-up study would be ensuring identification of all multidrug resistant TB cases.

Conclusion

This analysis provides evidence of a high burden of TB disease with concomitant diabetes among a population that is primarily of Pacific Islander and Southeast Asian ethnicity. There are many possible contributors to Guam's TB/diabetes burden, including immigration and regional lifestyle patterns, as well as biological mechanisms fueling a reciprocal relationship between these two conditions. More extensive disease manifestation, as measured by AFB sputum smear positivity and pulmonary cavitation, was found among TB patients with concomitant diabetes. Those with both conditions were also more likely to be treated for more than nine months and have unfavorable treatment outcomes. Among foreign-born persons, who made up the majority of TB cases, there was an association between length of residence in Guam and having diabetes. This analysis of Guam's TB surveillance data suggests that diabetes is an important factor to consider in TB prevention and treatment.

Chapter 7 Tables

Table 1: Demographic characteristics of patients with TB in Guam by diabetes status

	TB Only n=153	TB & Diabetes n=92	Total n=245	P-value
Age mean (SD)	44 (18)	58 (11)	49 (17)	<0.001*
Sex n (%)				0.433**
Male	87 (57)	57 (62)	144 (59)	
Female	66 (43)	35 (38)	101 (41)	
Race n (%)				0.438**
Asian	74 (48)	50 (54)	124 (51)	
Native Hawaiian/ Other Pacific Islander	71 (47)	40 (44)	111 (45)	
Other/Unknown	8 (5)	2 (2)	10 (4)	
Nativity n (%)				0.358**
Guam-born	36 (23)	26 (28)	62 (25)	
Foreign-born	116 (76)	66 (72)	182 (75)	
Philippines	61 (40)	49 (53)	110 (45)	
FSM	42 (27)	5 (6)	47 (19)	
Other	13 (9)	12 (13)	25 (11)	
Unknown	1 (1)	0 (0)	1 (0)	

*Two-sample t-test used to compare difference in means
**Chi-square test used to compare difference in frequency distribution

Table 2: Presentation characteristics of patients with TB in Guam by diabetes status

	TB Only n=153	TB & Diabetes n=92	Total n=245	P-value
AFB sputum smear n (%)				<0.001*
Positive	62 (41)	71 (77)	133 (54)	
Negative	86 (56)	20 (22)	106 (43)	
Unknown	5 (3)	1 (1)	6 (3)	
Lung cavitation (x-ray) n (%)				0.060*
Yes	36 (24)	33 (36)	69 (28)	
No	109 (71)	58 (63)	167 (68)	
Unknown	8 (5)	1 (1)	9 (4)	
Lung cavitation (CT) n (%)				0.004*
Yes	22 (14)	35 (38)	57 (23)	
No	26 (17)	12 (13)	38 (16)	
Unknown	105 (69)	45 (49)	150 (61)	

*Chi-square test used to compare difference in frequency distribution

Table 3: Treatment characteristics of patients with TB in Guam by diabetes status

	TB Only n=153	TB & Diabetes n=92	Total n=245	P-value
Therapy >6 months n (%)				0.113*
Yes	131 (86)	68 (74)	199 (81)	
No	17 (11)	16 (17)	33 (14)	
Unknown	5 (3)	8 (9)	13 (5)	
Therapy >9 months n (%)				<0.001*
Yes	47 (31)	56 (61)	103 (42)	
No	101 (66)	28 (30)	129 (53)	
Unknown	5 (3)	8 (9)	13 (5)	
Treatment outcome n (%)				<0.001*
Unfavorable	11 (7)	21 (23)	32 (13)	
Died	5 (3)	18 (20)	23 (9)	
Other	6 (4)	3 (3)	9 (4)	
Favorable	135 (88)	65 (71)	200 (82)	
Unknown	7 (5)	6 (6)	13 (5)	
Mortality n (%)				
Died	5 (3)	18 (20)	23 (10)	<0.001*
Other outcome	141 (92)	68 (73)	209 (85)	
Unknown	7 (5)	6 (7)	13 (5)	

*Chi-square test used to compare difference in frequency distribution

Table 4: Logistic regression analysis of the odds of presentation and treatment characteristics among TB patients with concomitant diabetes compared to those with TB only

Model	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio* (95% Confidence Interval)	n**
1. AFB smear positive	4.92 (CI 2.72–8.92)	4.98 (CI 2.63–9.44)	239
2. Lung cavitation (x-ray)	1.72 (CI 0.98–3.05)	1.74 (CI 0.93–3.26)	236
3. Lung cavitation (CT)	3.45 (CI 1.45–8.21)	3.61 (CI 1.37–9.50)	95
4. Therapy >6 months	0.55 (CI 0.26–1.16)	0.76 (CI 0.34–1.67)	232
5. Therapy >9 months	4.30 (CI 2.43–7.60)	5.69 (CI 2.96–10.94)	232
6. Unfavorable treatment outcome	3.97 (CI 1.81–8.71)	3.20 (CI 1.36–7.52)	232
7. Death	7.47 (CI 2.66–20.96)	5.66 (CI 1.88–17.04)	232

*Adjusted for age, sex, race
**Number of observations used in model

Table 5: Length of Residence of Foreign-born Patients with TB in Guam by Diabetes Status

	TB Only n=117	TB & Diabetes n=66	Total n=183	P-value
Length of residence median (IQR)	12 (24)	28 (25)	18 (23)	<0.001*
Residence ≥15 years n (%)				<0.001**
No	51 (44)	11 (17)	62 (34)	
Yes	38 (32)	43 (65)	81 (44)	
Unknown	28 (24)	12 (18)	40 (22)	

*Mann-Whitney *U* test used to compare difference in medians
**Chi-square test used to compare difference in frequency distribution

Table 6: Logistic regression analysis of the odds of diabetes among foreign-born patients with TB in short- and long-term residents

Model	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio* (95% Confidence Interval)	n**
8. Length of residence	1.06 (1.04–1.09)	1.06 (1.03–1.09)	143
9. Residence ≥15 years	5.25 (2.40–11.49)	4.15 (1.76–9.80)	143

*Adjusted for age, sex, race
**Number of observations used in model

References

1. World Health Organization. Global Tuberculosis Report 2019.
2. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. Lancet Infect Dis. 2018;18(3):261-84.
3. Institute for Health Metrics and Evaluation (IHME). Findings from the Global Burden of Disease Study 2017. Seattle, WA: IHME; 2018.
4. Jimenez-Corona ME, Cruz-Hervert LP, Garcia-Garcia L, Ferreyra-Reyes L, Delgado-Sanchez G, Bobadilla-Del-Valle M, et al. Association of diabetes and tuberculosis: impact on treatment and post-treatment outcomes. Thorax. 2013;68(3):214-20.
5. Perez-Navarro LM, Restrepo BI, Fuentes-Dominguez FJ, Duggirala R, Morales-Romero J, Lopez-Alvarenga JC, et al. The effect size of type 2 diabetes mellitus on tuberculosis drug resistance and adverse treatment outcomes. Tuberculosis (Edinb). 2017;103:83-91.
6. Kubiak RW, Sarkar S, Horsburgh CR, Roy G, Kratz M, Reshma A, et al. Interaction of nutritional status and diabetes on active and latent tuberculosis: a cross-sectional analysis. BMC Infectious Diseases. 2019;19(1):627.
7. Workneh MH, Bjune GA, Yimer SA. Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review. PloS one. 2017;12(4):e0175925.
8. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health. 2007;7:234.
9. Kubiak RW, Sarkar S, Horsburgh CR, Roy G, Kratz M, Reshma A, et al. Interaction of nutritional status and diabetes on active and latent tuberculosis: a cross-sectional analysis. BMC Infect Dis. 2019;19(1):627.
10. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008;5(7):e152.
11. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff TH, et al. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clin Infect Dis. 2007;45(4):428-35.
12. Magee MJ, Kempker RR, Kipiani M, Gandhi NR, Darchia L, Tukvadze N, et al. Diabetes mellitus is associated with cavities, smear grade, and multidrug-resistant tuberculosis in Georgia. Int J Tuberc Lung Dis. 2015;19(6):685-92.
13. Restrepo BI, Fisher-Hoch SP, Crespo JG, Whitney E, Perez A, Smith B, et al. Type 2 diabetes and tuberculosis in a dynamic bi-national border population. Epidemiol Infect. 2007;135(3):483-91.
14. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg. 2009;80(4):634-9.
15. Heysell SK, Moore JL, Keller SJ, Houpt ER. Therapeutic drug monitoring for slow response to tuberculosis treatment in a state control program, Virginia, USA. Emerg Infect Dis. 2010;16(10):1546-53.
16. Niazi AK, Kalra S. Diabetes and tuberculosis: a review of the role of optimal glycemic control. J Diabetes Metab Disord. 2012;11(1):28.
17. Yorke E, Atiase Y, Akpalu J, Sarfo-Kantanka O, Boima V, Dey ID. The Bidirectional Relationship between Tuberculosis and Diabetes. Tuberc Res Treat. 2017;2017:1702578.
18. Krishnappa D, Sharma SK, Singh AD, Sinha S, Ammini AC, Soneja M. Impact of tuberculosis on glycaemic status: A neglected association. Indian J Med Res. 2019;149(3):384-8.
19. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2018 Atlanta, GA: US Department of Health and Human Services, CDC; 2019 [
20. U.S. Census Bureau. Guam Demographic Profile Summary File. 2012.

21. Schwartz NG, Price SF, Pratt RH, Langer AJ. Tuberculosis - United States, 2019. MMWR Morb Mortal Wkly Rep. 2020;69(11):286-9.
22. Centers for Disease Control and Prevention. NCHHSTP AtlasPlus [updated 2019. Available from: https://www.cdc.gov/nchhstp/atlas/index.htm.
23. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2017. Atlanta, GA: US Department of Health and Human Services, CDC; 2018.
24. International Diabetes Federation. IDF Diabetes Atlas, 9th edn Brussels, Belgium2019 [Available from: http://www.diabetesatlas.org.
25. Tin ST, Lee CM, Colagiuri R. A profile of diabetes in Pacific Island Countries and Territories. Diabetes Res Clin Pract. 2015;107(2):233-46.
26. Balick MJ, Lee RA, De Gezelle JM, Wolkow R, Cohen G, Sohl F, et al. Traditional lifestyles, transition, and implications for healthy aging: An Example from the remote island of Pohnpei, Micronesia. PLoS One. 2019;14(3):e0213567.
27. Olszowy KM, Pomer A, Dancause KN, Sun C, Silverman H, Lee G, et al. Impact of modernization on adult body composition on five islands of varying economic development in Vanuatu. Am J Hum Biol. 2015;27(6):832-44.
28. World Bank. GDP per Capita (Current US$) [Available from: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?most_recent_value_desc=true.
29. Institute for Health Metrics and Evaluation (IHME). Country Profile: Guam 2017 [Available from: http://www.healthdata.org/guam.
30. Fu H, VanLandingham MJ. Disentangling the effects of migration, selection and acculturation on weight and body fat distribution: results from a natural experiment involving Vietnamese Americans, returnees, and never-leavers. J Immigr Minor Health. 2012;14(5):786-96.
31. Egusa G, Watanabe H, Ohshita K, Fujikawa R, Yamane K, Okubo M, et al. Influence of the extent of westernization of lifestyle on the progression of preclinical atherosclerosis in Japanese subjects. J Atheroscler Thromb. 2002;9(6):299-304.
32. Viney K, Cavanaugh J, Kienene T, Harley D, Kelly PM, Sleigh A, et al. Tuberculosis and diabetes mellitus in the Republic of Kiribati: a case-control study. Trop Med Int Health. 2015;20(5):650-7.
33. Nasa JN, Brostrom R, Ram S, Kumar AM, Seremai J, Hauma M, et al. Screening adult tuberculosis patients for diabetes mellitus in Ebeye, Republic of the Marshall Islands. Public Health Action. 2014;4(Suppl 1):S50-2.
34. Gounder S, Harries AD. Screening tuberculosis patients for diabetes mellitus in Fiji: notes from the field. Public Health Action. 2012;2(4):145-7.
35. Prasad P, Gounder S, Varman S, Viney K. Sputum smear conversion and treatment outcomes for tuberculosis patients with and without diabetes in Fiji. Public Health Action. 2014;4(3):159-63.
36. Ichiho HM, Anson R, Keller E, Lippwe K, Aitaoto N. An assessment of non-communicable diseases, diabetes, and related risk factors in the Federated States of Micronesia, State of Pohnpei: a systems perspective. Hawaii J Med Public Health. 2013;72(5 Suppl 1):49-56.
37. Bakker LE, Sleddering MA, Schoones JW, Meinders AE, Jazet IM. Pathogenesis of type 2 diabetes in South Asians. Eur J Endocrinol. 2013;169(5):R99-r114.
38. Karter AJ, Schillinger D, Adams AS, Moffet HH, Liu J, Adler NE, et al. Elevated rates of diabetes in Pacific Islanders and Asian subgroups: The Diabetes Study of Northern California (DISTANCE). Diabetes Care. 2013;36(3):574-9.
39. Yelk Woodruff RS, Pratt RH, Armstrong LR. The US National Tuberculosis Surveillance System: A Descriptive Assessment of the Completeness and Consistency of Data Reported from 2008 to 2012. JMIR Public Health Surveill. 2015;1(2):e15.
40. Centers for Disease Control and Prevention. Report of Verified Case of Tuberculosis (RVCT) Instruction Manual. 2009.

41. Lin Y, Enarson DA, Du J, Dlodlo RA, Chiang CY, Rusen ID. Risk factors for unfavourable treatment outcome among new smear-positive pulmonary tuberculosis cases in China. Public Health Action. 2017;7(4):299-303.
42. Mukhtar F, Butt ZA. Risk of adverse treatment outcomes among new pulmonary TB patients co-infected with diabetes in Pakistan: A prospective cohort study. PLoS One. 2018;13(11):e0207148.
43. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases. 2016;63(7):853-67.
44. Goel MS, McCarthy EP, Phillips RS, Wee CC. Obesity among US immigrant subgroups by duration of residence. Jama. 2004;292(23):2860-7.
45. U.S. Centers for Disease Control and Prevention. National Health Interview Survey Glossary [updated November 6, 2015. Available from: https://www.cdc.gov/nchs/nhis/rhoi/rhoi_glossary.htm.
46. Guthrie JL, Ronald LA, Cook VJ, Johnston J, Gardy JL. The problem with defining foreign birth as a risk factor in tuberculosis epidemiology studies. PLoS One. 2019;14(4):e0216271.
47. World Health O. Global tuberculosis report 2019. Geneva: World Health Organization; 2019 2019.
48. Guam Visitors Bureau. 2019 Annual Summary. 2020.
49. United States Census Bureau. 2018 Estimates of Compact of Free Association (COFA) Migrants. 2019.
50. Su B, Jin L, Underhill P, Martinson J, Saha N, McGarvey ST, et al. Polynesian origins: insights from the Y chromosome. Proc Natl Acad Sci U S A. 2000;97(15):8225-8.
51. Uchima O, Wu YY, Browne C, Braun KL. Disparities in Diabetes Prevalence Among Native Hawaiians/Other Pacific Islanders and Asians in Hawai'i. Prev Chronic Dis. 2019;16:E22.
52. Choi SE, Liu M, Palaniappan LP, Wang EJ, Wong ND. Gender and ethnic differences in the prevalence of type 2 diabetes among Asian subgroups in California. J Diabetes Complications. 2013;27(5):429-35.
53. Steinbrecher A, Erber E, Grandinetti A, Nigg C, Kolonel LN, Maskarinec G. Physical activity and risk of type 2 diabetes among Native Hawaiians, Japanese Americans, and Caucasians: the Multiethnic Cohort. J Phys Act Health. 2012;9(5):634-41.
54. Guo S, Lucas RM, Joshy G, Banks E. Cardiovascular disease risk factor profiles of 263,356 older Australians according to region of birth and acculturation, with a focus on migrants born in Asia. PLoS One. 2015;10(2):e0115627.
55. Golden SH, Brown A, Cauley JA, Chin MH, Gary-Webb TL, Kim C, et al. Health disparities in endocrine disorders: biological, clinical, and nonclinical factors--an Endocrine Society scientific statement. J Clin Endocrinol Metab. 2012;97(9):E1579-639.
56. Pobocik RS, Richer JJ. Estimated intake and food sources of vitamin A, folate, vitamin C, vitamin E, calcium, iron, and zinc for Guamanian children aged 9 to 12. Pac Health Dialog. 2002;9(2):193-202.
57. Pobocik RS, Boudreau NS. Nutrient analysis of the Guamanian diet: acceptable energy distribution with inadequate nutrient quality. Pac Health Dialog. 2005;12(2):65-77.
58. Guerrero RT, Paulino YC, Novotny R, Murphy SP. Diet and obesity among Chamorro and Filipino adults on Guam. Asia Pac J Clin Nutr. 2008;17(2):216-22.
59. Chuuk Department of Health Services (Micronesia) DoHaSAM, World Health Organization (WHO),. Micronesia - Chuuk STEPS Noncommunicable Disease Risk Factors Survey 2006.; 2012.
60. Centre for Physical Activity and Health UoSA, Department of Health and Social Affairs (Micronesia), Fiji School of Medicine, Micronesia Human Resources Development Center,

Pohnpei State Department of Health Services, World Health Organization (WHO),. Micronesia - Pohnpei STEPS Noncommunicable Disease Risk Factors Survey 2002. 2008.
61. Fiji School of Medicine MCfPHR, University of Tasmania (Australia), Ministry of Health (Marshall Islands), World Health Organization (WHO),. Marshall Islands STEPS Noncommunicable Disease Risk Factors Survey 2002. 2007.
62. Department of Health (American Samoa) MUA, World Health Organization (WHO). American Samoa STEPS Noncommunicable Disease Risk Factors Survey 2004. 2004.
63. Rosas LG, Sanchez-Vaznaugh EV, Sanchez BN. Nativity, US Length of Residence, and BMI Among Diverse Asian American Ethnic Groups. J Immigr Minor Health. 2015;17(5):1496-503.
64. Golub N, Seplaki C, Stockman D, Thevenet-Morrison K, Fernandez D, Fisher S. Impact of Length of Residence in the United States on Risk of Diabetes and Hypertension in Resettled Refugees. J Immigr Minor Health. 2018;20(2):296-306.
65. Commodore-Mensah Y, Ukonu N, Obisesan O, Aboagye JK, Agyemang C, Reilly CM, et al. Length of Residence in the United States is Associated With a Higher Prevalence of Cardiometabolic Risk Factors in Immigrants: A Contemporary Analysis of the National Health Interview Survey. J Am Heart Assoc. 2016;5(11).
66. Bayog MLG, Waters CM. Nativity, Chronic Health Conditions, and Health Behaviors in Filipino Americans. J Transcult Nurs. 2018;29(3):249-57.
67. Lohmann EM, Koster BF, le Cessie S, Kamst-van Agterveld MP, van Soolingen D, Arend SM. Grading of a positive sputum smear and the risk of Mycobacterium tuberculosis transmission. Int J Tuberc Lung Dis. 2012;16(11):1477-84.
68. Melsew YA, Doan TN, Gambhir M, Cheng AC, McBryde E, Trauer JM. Risk factors for infectiousness of patients with tuberculosis: a systematic review and meta-analysis. Epidemiol Infect. 2018;146(3):345-53.
69. Singh M, Mynak ML, Kumar L, Mathew JL, Jindal SK. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. Arch Dis Child. 2005;90(6):624-8.
70. Wang JY, Lee MC, Shu CC, Lee CH, Lee LN, Chao KM, et al. Optimal duration of anti-TB treatment in patients with diabetes: nine or six months? Chest. 2015;147(2):520-8.