Understanding the relationship between Diabetes and Tuberculosis in Kazakhstan: Implications for integrated care and management

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ABSTRACT

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The global increase in diabetes prevalence undermines public health efforts to eliminate TB globally by increasing TB morbidity and mortality. Emerging research suggests that diabetes has been found to increase likelihood of acquiring TB. However, there remains limited research on the multi-level risk and protective factors that are associated with these co-occurring problems and the long-term TB treatment outcomes for individuals who have both TB and diabetes. Using a matched case control study of 1600 participants in four regions of Kazakhstan, the findings from this dissertation show diabetes prevalence to be higher among those with TB than individuals without TB, at 7% and less than 1%, respectively. Multivariate logistic regressions noted that diabetes was roughly associated with nine times the odds of having both diabetes and TB (OR 8.6; 99% CI 4.13-17.85). Multilevel risk and protective factors significantly associated with both diseases included older age (45 years old and above); being obese (OR 8.19; P-value 0.015); having been to the doctor in the past 12 months (OR 4.80; P-value 0.006); urban residence (OR 3.34; P-value 0.021) and being born in a country other than Kazakhstan or Russia (OR 4.39; P-value 0.032). More importantly, the findings show that diabetes is not associated with unsuccessful TB treatment outcome as other studies have found. In general, the results of the current study point to the need to conduct robust, longitudinal studies that focus on the overlapping risk and protective factors associated with both diseases in order to better understand whether these risk factors are specific to particular settings or generalizable to all settings with high TB burdens.

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DEDICATION AND ACKNOWLEDGEMENT

First and foremost, I thank Almighty God for seeing me through this journey. I dedicate this dissertation to my late father, Rev. Henry Kwabena Aifah whose life experience with diabetes led me to this stage and whose unexpected passing has surprisingly been my source of motivation. I also extend this dedication to the rest of my immediate family: my dearest mother, Beatrice Ampofo-Aifah, my siblings (Josephine Aifah, Marian Aifah, Henry Aifah, Jr., and Edward Aifah) and youngest editions (Jared Emmanuel Aifah, Nadia Ama Aifah, Sophia Aifah, Gianna Aifah and Kobina Hemans) who have all been my biggest supporters. Thank you all for the words of encouragement, for the precious moments of laughter and for never giving up on me. May you all be blessed always.

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CHAPTER 1: INTRODUCTION

Over the past two decades, the global diabetes burden has proliferated in prevalence with current estimates reporting between 415 to 422 million people affected in 2015 and an expected increase of 642 million people in 2040 (Federation, 2015; Organization, 2016c). Explanations for this steady increase, particularly for Type 2 diabetes, are overwhelmingly focused on individual behaviors or lifestyle habits such as physical inactivity, poor diet, overweight or obese status, smoking, etc., as key risk factors (Organization, 2016c). While these individual-level risk factors are significant, limited research has addressed co-occurring diseases and the potential impact on diabetes burden worldwide (Baker et al., 2011a).

As a case in point, current reports show that the increasing burden of diabetes both negatively impacts and is affected by the burden of infectious diseases like tuberculosis (TB) (Alisjahbana et al., 2007; Baker et al., 2011a; A. Harries et al., 2015; M. J. Magee, Blumberg, & Narayan, 2011; Restrepo, 2007; Skowroński, Zozulińska-Ziółkiewicz, & Barinow-Wojewódzki, 2014; Sotgiu, Matteelli, & Migliori, 2015). Despite a global decrease in TB incidence in recent years, TB remains a major public health issue (Organization, 2015b). The latest global TB report by the World Health Organization (WHO) estimates that there were 10.4 million new TB cases in 2015 (Organization, 2016d) an increase from the previous year which reported 9.6 million new cases (Organization, 2015b). In addition to chronic diseases like diabetes posing a serious threat to TB care and management worldwide, known multi-level risk factors for TB include smoking, alcohol use, poverty, overcrowding and under-nutrition (Lönnroth, Jaramillo, Williams, Dye, & Raviglione, 2010).

Despite the negative effect on health outcomes as result of co-occurring diabetes and TB, research and prevention strategies remain limited in addressing this growing threat (Littleton &

Park, 2009) and the associated multi-level risk and protective factors (e.g. at the individual, community, macro, and structural levels). Historically, the relationship between diabetes and TB has been well established in clinical and epidemiological studies for over a century (Baker et al., 2011b; Jeon & Murray, 2008b). Recent studies found that in some settings diabetes and TB co-occurrence exceed that of TB and HIV (Sen, Joshi, & Udwadia, 2009). Although the individual risk for acquiring TB as result of HIV/AIDS is higher, the growing prevalence of diabetes worldwide makes it a stronger risk factor at the population level due to the increased population-attributable fraction (PAF) of TB (A. Harries et al., 2013; Lönnroth, Castro, et al., 2010). The PAF is an approximation of the relative reduction of TB incidence due to the eradication of particular risk factor (Organization, 2016d) e.g. diabetes.

Known risk factors for co-occurring diabetes and tuberculosis include age, gender, smoking, alcohol consumption, poor diabetes self-management and a family history of diabetes or TB (Viswanathan et al., 2012). Using dynamic tuberculosis transmission models to assess the potential effect of diabetes on TB epidemiology in 13 high TB burdened countries, Pan and colleagues (2015) found that at the current rate of prevalence, diabetes as a single risk factor could substantially undermine efforts to control TB or reverse the decline in TB incidence – i.e. increasing TB morbidity and mortality – within the next 20 years. Given this negative symbiosis and the increasing burden of multi-drug resistant tuberculosis (MDR-TB) social science research in high TB and or diabetes-burdened areas is urgently needed to better understand the multilevel risk and protective factors that are associated with and the implications of the relationship on current diabetes and TB management and treatment.

For high TB burdened countries, diabetes prevalence may be a potential threat to tuberculosis surveillance and control (A. Harries et al., 2015; A. D. Harries et al., 2010; Kapur, Harries, Lönnroth, Wilson, & Sulistyowati, 2016). In high tuberculosis incident countries (e.g. China and India) recent studies show diabetes prevalence was higher among TB patients than among non-TB patients (Heo et al., 2015). Studies in India and China, which are among the top 10 countries with the highest incidence of TB associated with diabetes, reveal that in countries with high tuberculosis prevalence, screening for tuberculosis in diabetes patients results in high TB detection rates (A. Harries et al., 2015). Conversely, diabetes screening in tuberculosis patients has identified high rates of diabetes (A. D. Harries et al., 2010; Jeon et al., 2010).

While few studies have found that diabetes is significantly associated with MDR-TB, several studies have noted the opposite (Fisher-Hoch et al., 2008). Using surveillance data, a cross border retrospective study conducted in Mexico and Texas found that Type 2 diabetes was significantly associated with MDR-TB in that TB patients with diabetes were more prone to drug resistance (Fisher-Hoch et al., 2008). Moreover, other studies have found that although most diabetes-TB patients were either cured or had completed treatment after TB treatment, their treatment duration was significantly longer than those with only TB (Chang et al., 2011). In settings where either illness is prevalent, research is lacking on multi-level factors such as migration and poverty that may contribute to the co-occurrence and possibly have negative implications for drug resistant tuberculosis treatment and prevention.

Similar to other former Soviet countries, Kazakhstan is among the list of 30 high MDR-TB burdened countries with the occurrence of MDR-TB among notified pulmonary TB cases estimated to be roughly 75% (Organization, 2015b, 2016d). Despite a decrease in TB incidence and prevalence during the Soviet Union era, sparse data show that the resurgence of TB in Kazakhstan and other Central Asian countries is associated with alcoholism, socioeconomic decline and gaps in TB control as well as other health services (Lönnroth, Jaramillo, et al., 2010;

Lönnroth, Jaramillo, Williams, Dye, & Raviglione, 2009). Like other Central Asian countries, the burden of increasing MDR-TB cases in Kazakhstan may be further compounded by the prevalence of co-morbidities with chronic diseases such as diabetes. Although diabetes research is quite limited in Kazakhstan, current estimates on age-standardized prevalence is reported to be 13.2% - much higher than the Russian Federation (9.0%) or all of Europe (8.3%) (Supiyev et al., 2016). Limited research on co-occurring diabetes-tuberculosis has mostly focused on settings where both are endemic but few have looked at this dual disease burden in settings where one is more common and the other is steadily increasing in incidence and prevalence. More importantly, these studies have failed to assess the ecological risk factors, i.e. to go beyond the individual level to also consider the multi-level risk and protective factors, that may impact the co-occurrence of diabetes and TB. Studies using an ecological systems perspective conceptualize the key factors at each level (e.g. individual, community, macro and structural) to consider the multiple levels of influence on the primary outcome, thereby providing relevant evidence in support of more comprehensive interventions (Sallis, Owen, & Fisher, 2008).

Through secondary analysis of a matched-case control study conducted in four TB burdened regions in Kazakhstan, that used the ecological systems theory for its design, the central goal of this dissertation is to contribute to existing research on diabetes prevalence and its co-occurrence with tuberculosis in TB burdened settings with growing diabetes incidence. Furthermore, this study extends current research on individual level risk factors and examines the multilevel risk and protective factors, i.e. encompassing the individual (i.e. modifiable and non-modifiable demographics), interpersonal networks (e.g. social support, smoking norms),community or environmental (e.g. urban or rural residence, migration, study site) and macro-structural (e.g. poverty, access to care, healthcare quality), associated with the co-occurrence of diabetes and TB, while providing relevant inquiry on the negative affect of diabetes on TB treatment outcomes. As noted previously, current research in regions doubly affected by both diseases (e.g. China and India) show that co-occurring diabetes and tuberculosis is not only increasing in prevalence but urgently requires integrated care and management that is challenging weak, siloed health systems (Cai et al., 2017; Viswanathan et al., 2012). With the proliferation of diabetes in high TB burdened settings throughout regions in Asia (Zheng, Hu, & Gao, 2017) and Africa (A. O. Ogbera et al., 2014), substantive examination of the relationship between diabetes and TB will advance intervention research on disease co-occurrence and the multilevel risk and protective factors that threaten prevention and treatment outcomes.

In the ensuing chapters, this dissertation systematically examines the associated risks and protective factors of co-occurring diabetes and TB. Additionally, the related factors of diabetes and TB treatment outcome are also examined. Chapter two includes a brief discussion on the current health system of Kazakhstan and the challenges that may impact negative health outcomes such as co-occurring diabetes and TB. The chapter then examines the known prevalence of both diseases, both globally and in Kazakhstan, as well as the established risk factors associated with the confluence of both diseases. In this section, a brief discussion on current global strategies for co-occurring diabetes and TB is provided. In chapter three, a discourse on the theoretical framework guiding this dissertation and the data used is provided. The application of the ecological framework is most useful for the current study as it considers the different mechanisms that may increase the diabetes-TB burden within the study population. Chapter four reviews the methods for data collection and analysis, while the following chapter provides the results for each of the four aims of the current study. Chapter six includes a discussion of the findings, study strengths and limitations as well as the conclusion. Finally, chapter seven considers the implications of the current study for social work practice as well as global health policy in general.

CHAPTER 2: LITERATURE REVIEW

Kazakhstan demographics

A former Soviet Union republic, the landlocked central Asian country of Kazakhstan borders Russia, China, Kyrgyzstan, Russia, Turkmenistan and Uzbekistan (Agency, 2016). Geographically, the country is divided into 14 provinces or oblasts and 2 major cities, Astana (the capital) and Almaty (Agency, 2016). It is considered by the World Bank (2016) to be an upper middle-income country. According to the Central Intelligence Agency (2016), Kazakhstan has a population of over 18 million and is ethnically diverse with the majority being Kazakh (roughly 63%), followed by Russian (estimated 24%) and the remainder consisting of Uzbek, Ukrainian, Uighur, Tatar, German and other. As of 2016, the estimated life expectancy at birth for the total population is 70.8 years while for males and females it is 65.6 and 75.7 years, respectively (Agency, 2016). The official language is Kazakh but Russian is predominantly spoken throughout the country (Agency, 2016).

Despite having a better economic profile in comparison to a neighboring country such as Kyrgyzstan, Kazakhstan's health profile is noticeably not on par with its economic situation that there remain challenges within the healthy lifestyles of the general population and public health's ability to respond to the ensuing poor health outcomes (Aringazina, Gulis, & Allegrante, 2012; Cockerham, Hinote, Abbott, & Haerpfer, 2004). Using survey research to compare the healthy lifestyles of Kyrgyztan and Kazakhstan, Cockerham and colleagues (2004) show that although Kyrgyzstan is a lower income country, it has a better health profile with the population living longer than their peers in Kazakhstan. Findings from the study highlight better practices in healthy lifestyle for the Kyrgyz population, including a healthier diet, smoking less, consuming alcohol less when compared to the Kazakh sample (Cockerham et al., 2004). Given the association of poor diet, smoking and alcohol consumption to diseases such as diabetes (Organization, 2016c) and tuberculosis (Organization, 2015b), more studies in countries like Kazakhstan offer a unique opportunity to examine how these noted risk factors relate to co-occurring non-communicable and communicable diseases.

More importantly, other studies note that in addition to poor Kazakhstani healthy lifestyle practices, the burden of non-communicable and communicable diseases are negatively impacted by its weak health systems performance (Adambekov, Kaiyrlykyzy, Igissinov, & Linkov, 2015; Aringazina et al., 2012). For countries or regions with weak health systems, the double burden of diabetes-TB and the associated joint management of both diseases may be considered one of the greatest health challenges to overcome (Critchley et al., 2017); however, the HIV-TB model offers an example of critical areas to consider for the integration of services. As noted by Riza and colleagues (Riza et al., 2014), the integration of HIV and TB has not only strengthened health systems response to the co-occurrence of both diseases but has also increased patient uptake of services, reduced mortality rates, and improved treatment outcomes.

Synopsis of health systems development in Post-Soviet countries

Although this study does not focus on health systems performance per se, considering the current state of health systems development in Kazakhstan is important as health outcomes related to co-occurring disease burden are impacted by the performance and ability of health systems to respond adequately (Adambekov et al., 2015). Similar to other former Soviet Union countries, Kazakhstan has gone through considerable changes in health systems development after the dissolution in the 1990s, contributing to disparities in health care utilization and health outcomes (SO, 2014). Most notably, these changes were triggered by the substantial decline in government expenditure in health systems development (Glonti & Rechel, 2013; SO, 2014) after the breakdown of the centralized health care system of the Soviet Union and the vacillating health care reforms that followed (Adambekov et al., 2015). The drastic decline in public health financing in the health sector led to increased private health expenditure through steep levels of out-of-pocket payments (OOP) by patients (SO, 2014). Rechel, Richardson, and McKee (2014) state that the resultant financial barriers caused by the over reliance on OOPs by patients led to individuals in need of health services not being able to access care because of high costs in addition to the within country regional variation in healthcare utilization.

While Kazakhstan has since the 1990s made noticeable strides in health systems development (Aringazina et al., 2012; SO, 2014), better understanding is warranted in regards to public health challenges and the dual burden of communicable and non-communicable diseases (Adambekov et al., 2015). Rechel et al. (2014) state that in examining health systems performance it is useful to evaluate "tracer conditions" such as diabetes which are prevalent and require coordinated input from a number of allied health professionals in addition to the accessibility of necessary medicines and the promotion of patient well-being. This fact is clearly evident throughout the Central Asian region, as limited and conflicting data on chronic condition like diabetes highlight a major challenge in public health response to the emerging burden associated with the epidemiological transition or the dual burden of communicable and non-communicable diseases (Adambekov et al., 2015). Rechel et al. (2014) also state that failures in infectious disease control, e.g. the challenge and emergence of multi-drug resistant TB (MDR-TB), are also key indicators of weak health system performance.

These considerations are important for the current study given the sparse data on diabetes prevalence and the increasing burden of MDR-TB in Kazakhstan. In the following sections of this chapter, an overview of the current literature of diabetes prevalence and TB incidence both globally and in Kazakhstan is discussed. In the final section of this chapter, the discussion on the co-occurrence of diabetes and TB includes key multilevel risk and protective factors such as healthcare utilization and access to care, which have considerable implications on the co-occurrence of both diseases within the population.

Diabetes prevalence globally

1980 to 2014 diabetes prevalence estimates and regional differences

In recent years, research has shown that the prevalence of type 2 diabetes is increasing globally (Esterson, Carey, Piette, Thomas, & Hawkins, 2014; Mendenhall, Norris, Shidhaye, & Prabhakaran, 2014) and contributes significantly to mortality, morbidity and health-system expenditures worldwide (Collaboration, 2016; Krug, 2016). Using a robust, pooled analysis of population based studies, the NCD Risk Factor Collaboration or NCD-RisC (2016) reports in the Lancet that the global trend in diabetes shows an increase in prevalence from 108 million in 1980 to 422 million in 2014.The authors also state that age-standardized prevalence for diabetes increased for both men and women in the same time period, from 4.3% to 9% and 5% to 7.9%, respectively (Collaboration, 2016). Moreover, the NCD-RisC group (2016) highlight that the trend in diabetes prevalence is more notable and has grown more rapidly in low-income and middle-income countries in comparison to high-income countries. Despite their findings, the researchers cite that a major limitation of their study is the challenge of having no or limited data sources on population based diabetes data from regions such as Central Asia and Sub-Saharan Africa (Collaboration, 2016). Consequently, this dissertation provides critical evidence on the current trend of diabetes in Kazakhstan, especially as it pertains to the continued burdened of TB in the country and throughout the Central Asian region.

Diabetes prevalence in the Central Asian region

The Central Asian region consists of five of the former Soviet Republics: Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan. Recent reports by the WHO provide disparate diabetes prevalence rates throughout the Central Asian region – the only similarity being is that each country in the region, from 1980 until 2014, has experienced a steady increase in diabetes prevalence (Organization, 2016). For the general population in Kazakhstan, diabetes prevalence is reported to be 11.5% with little gender difference between males and females as estimates are reported to be 11.3% and 11.7%, respectively (Organization, 2016f). Although Turkmenistan is also an upper-middle income country, diabetes prevalence among the general population, males and females differ slightly from Kazakhstan with current estimates at 10.2%, 9.9 % and 10.4% correspondingly (Organization, 2016). What's more as a lower-middle income country, diabetes prevalence in Uzbekistan is estimated at 8.7% for the total population with the prevalence at 9.1% for females and 8.3% for males (Organization, 2016). In Kyrgyzstan, a lower-middle income country, diabetes prevalence estimated to be 8.6% for the entire population with 9.3% and 7.8% prevalence rates for females and males, respectively (Organization, 2016e). Compared to the other Central Asian countries and despite being a lower-middle income country, Tajikistan has the lowest diabetes prevalence of 7.6% for the general population, females and males (Organization, 2016).

Known facts and risk factors of diabetes

As a metabolic disease, diabetes is characterized by either the pancreas' inability to produce insulin (Type 1) or when the body is unable to effectively use the insulin the pancreas produces (Type 2) (Organization, 2016c). Despite Type 2 diabetes being the most common globally, accounting for an estimated 90% of diabetes prevalence, other forms such as gestational diabetes (a temporary complication which occurs during pregnancy and has a long-term risk of Type 2 diabetes) along with impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) – both of which are known as pre-diabetes conditions – make the burden of diabetes equally more urgent in settings wherein risk factors such as co-occurring diseases are still a threat (Alisjahbana et al., 2007; Organization, 2016c). Research has also revealed that the majority of those living with diabetes experience difficulties in coping such as poor glucose and blood pressure control, depression and negative quality of life (D. Whiting, Unwin, & Roglic, 2010b).

Risk factors associated with the increase in diabetes prevalence include, but are not limited to: sedentary lifestyles or physical inactivity, unhealthy diets (e.g. high sugar intake), smoking, ageing populations, obesity, access to and type of health care, higher levels of urbanization and infectious diseases like TB and HIV (Federation, 2015; Supiyev et al., 2016; D. Whiting, Unwin, & Roglic, 2010a). More importantly, a meta-analysis and systematic review of 13 observational studies found that TB is three times more likely in individuals with diabetes regardless of study design and population (Jeon & Murray, 2008a). Based on their findings, Jeon & Murray (2008a) conclude that based on the current increase in global prevalence, diabetes will likely contribute significantly to current TB control and future burden, if efforts are not made to detect and treat diabetes. The increased morbidity and mortality associated with diabetes co-occurrence with infectious diseases like TB, warrants more research on how multilevel determinants affect the growing threat of diabetes on TB control.

Diabetes prevalence and control in Kazakhstan

Diabetes prevalence data in Kazakhstan is not only limited but often times differs by the entity that is reporting. For example, in 2011 the International Diabetes Federation (IDF) cited a prevalence rate of 7.5% among those aged 20-79 years-old while national data records reported that 1.3% of the population had diabetes (D. R. Whiting, Guariguata, Weil, & Shaw, 2011). Considering the previous discussion on Kazakhstan's health system development challenges, the inconsistences in diabetes prevalence estimates as noted here highlight the need for empirical studies that report diabetes estimates and thereby provide more support for ascertaining actual prevalence. Recent reports by the World Health Organization (WHO) estimates the national diabetes prevalence in Kazakhstan in 2016 to be 11.5% (Organization, 2016f), a proportion which is considerably higher than neighboring Kyrgyzstan which is estimated to have a diabetes prevalence of 8.6% within the general population (Organization, 2016e).

In their discussion of the sparse data on diabetes prevalence in Kazakhstan, Supiyev et al. (2016) use routine statistics to approximate the estimated current age-standardized prevalence of diabetes to be 12.5% among a sample of middle aged and older residents in urban (capital city of Astana) and rural (Akmol village) settings. This estimated diabetes prevalence in Kazakhstan is slightly higher than recent reports from the WHO (Organization, 2016f) and in comparison to estimates from Europe and the Russian Federation at 8.3% and 9%, respectively (Supiyev et al., 2016). The authors also find that diabetes prevalence is higher in the urban than in the rural area, at 16.3% and 8.5% respectively (Supiyev et al., 2016). Associated risk factors for diabetes prevalence among this Kazakhstani sample includes: older age, male gender, higher BMI and WHR (waist-to-hip ratio), Russian ethnicity and a family history of diabetes (Supiyev et al., 2016). Furthermore, Supiyev and colleagues (2016) state that age-standardized diabetes mortality in Kazakhstan is twice that of Russia – 10.1 vs. 4.5 per 100,000. A major limitation of the study is the fact the co-occurring diseases such as TB are not examined, despite Kazakhstan being one of the high TB burdened countries (Organization, 2016d) and the known associations between diabetes and TB (Murray, Oxlade, & Lin, 2011).

Due to the limited data on diabetes related empirical studies from Kazakhstan, there is a need to better understand the risk and protective factors associated with the co-occurrence of diabetes and TB in a country like Kazakhstan, where MDR-TB rates are on the rise (Davis et al., 2017; Zhussupov et al., 2016). Studies from neighboring Kyrgyzstan on diabetes prevalence offer some insight into the potential implication of diabetes on health outcomes, particularly as it relates to TB co-occurrence (Arnold et al., 2016; Skordis-Worrall et al., 2017). Briefly, these studies show that among the Kyrgyz population, individuals with diabetes and those co-affected with diabetes and TB were more likely to be older than those with only TB (Arnold et al., 2016). While the ensuing discussion will further detail these studies, it is worth noting that similar to Kazakhstan, Kyrgyzstan is experiencing an increasing prevalence in diabetes and is equally challenged by a weak health system response to this burden (Beran et al., 2013). Consequently, reporting on diabetes prevalence from evidence based studies provides a critical lens to examine the contribution of this chronic disease to other conditions such as TB, which like diabetes is also considered to be a 'tracer condition' (Beran et al., 2013).

Tuberculosis prevalence and incidence globally

Mycobacterium tuberculosis is a bacillus that causes TB and may affect the lungs (i.e. pulmonary TB) or other parts of the body (known as extra-pulmonary TB) (Organization, 2015b). A majority of TB infections are related to pulmonary TB as opposed to extra-pulmonary (Millet et al., 2013). The latest global TB report by the WHO estimates that there were 10.4 million new TB cases in 2015 (Organization, 2016d). Despite a global decrease in TB incidence since 2002, drug-resistant TB (e.g. multi-drug resistant, MDR-TB and extremely drug-resistant, XDR-TB) remains a major threat to public health systems. In recent years, an estimated 3.3% of new cases and 20% of previously treated cases were reported to have MDR-TB (Millet et al., 2013; Organization, 2015b).

Central Asian countries continue to have the highest levels of MDR-TB (i.e. resistance to two first line drugs, isoniazid and rifampicin) in the world with proportions remaining the same as in previous years (Organization, 2015b, 2016d). In particular, and despite efforts to scale up TB surveillance and control, the region persistently has the highest proportions of new and previously treated TB cases with MDR-TB (Organization, 2016d). According to the WHO (2015b), Kazakhstan (26%), Kyrgyzstan (26%) and Uzbekistan (23%) are among a short-list of countries with the highest proportions of MDR-TB among new cases. Furthermore, Kazakhstan, Kyrgyzstan, Tajikistan and Uzbekistan have the highest proportions of MDR-TB among previously treated TB cases with 58%, 55%, 52% and 62%, respectively in the world (Organization, 2015b).

For disadvantaged groups – including ethnic minorities, the poor and the hungry, immigrants, people who are drug dependent or incarcerated – TB remains a major health burden as most TB cases cluster among these groups (Hargreaves et al., 2011). In addition to comorbidities with chronic diseases such as diabetes and HIV/AIDS, risk factors strongly associated with developing TB include but are not limited to: age, alcohol abuse, tobacco use, body mass index (BMI) and severe malnutrition, poverty, overcrowding and social inequality (Millet et al., 2013). Since the collapse of the Soviet Union in 1991, the resurgence of TB in Central Asian countries like Kazakhstan has been linked to socioeconomic decline, gaps in TB control and other health services, and alcoholism (Lönnroth, Jaramillo, et al., 2010).

Tuberculosis incidence and control in Kazakhstan

As one of the 27 high MDR-TB burdened countries, Kazakhstan still faces major challenges in addressing the social, environmental and structural factors that negatively affect TB care and treatment (Terlikbayeva et al., 2012b). Using surveillance data from the National Tuberculosis Program (NTP) and the National Institute of Geography (NIG) in Kazakhstan, Terlikbayeva et al. (2012b) report that individual risk factors for MDR-TB transmission rates include but are not limited to diabetes diagnosis, migrant status, alcohol use, non-regular uptake of anti-tuberculosis medication and a registered contact of a TB or MDR-TB case. The authors also state that structural issues related to categorization and reporting practices may have negative implications on case notification rates within the country (Terlikbayeva et al., 2012b). Furthermore, Terlikbayeva et al. (2012a) find that case notification rates (CNR) of national MDR-TB incidence increased in 2007 to 2010 from 5.8 cases per 100,000 to 10.5 per 100,000 ($p = 0.12$). While these risk factors have been shown to be associated with TB, protective factors such as social support have been found to be associated with the reduction of MDR-TB treatment default rates in Kazakhstan (Kaliakbarova et al., 2013).

The historical inconvenience of the diabetes-TB convergence on current efforts of global disease prevention and management

Through a salient examination of clinical records and available literature on diabetes and tuberculosis in 1912, an American physician by name of Charles Montgomery raised critical points of considerations concerning the diabetes-TB relationship that are still relevant a century later. Most notably, Dr. Montgomery states that: 1) TB is more commonly associated with diabetes than other chronic diseases; and 2) the treatment of either disease in a patient with both diseases complicates the treatment of the other (Montgomery, 1912). In the time since Dr.

Montgomery's review, much has transpired in the singular treatment of both diabetes and TB (e.g. the discovery of insulin in the 1920 and the discovery of TB drug treatment in the 1940s to the 1960s) but the same cannot be said about the integrated treatment of both diseases (Restrepo, 2007). Over time the successes in the individual treatments of both diseases led to less consideration for the co-occurrence of both – a fact which is mainly due in part to a decrease of TB incidence in high income countries and the notion that diabetes was a 'high-income' country problem more so than in low income countries because of the access to unhealthy diet (A. Harries et al., 2013; Restrepo, 2007). However, with the current surge in diabetes prevalence and the slow decrease in TB incidence worldwide – particularly in low and middle income countries (LMICs) – researchers and policymakers are now realizing the need to better understand the emergent impact of diabetes prevalence on current TB incidence and treatment and vice versa (Mukhtar & Butt, 2016b; Organization, 2011).

In response to the resurgence of the diabetes-TB relationship, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease launched the Collaborative Framework for Care and Control of Tuberculosis and Diabetes, hereinafter "Collaborative Framework", in 2011 (Organization, 2011). At that time, the framework was developed as provisional pending better research and evidence on the co-occurrence of both diseases (A. Harries et al., 2013) and has yet to be standardized due primarily to the need for more robust research on this unique relationship. As noted in Table 1, the Collaborative Framework highlighted three core areas or objectives for the development of policy and research on both diseases: 1) to formulate the mechanisms of collaboration between diabetes and TB programs; 2) to enhance the detection and management of TB in patients with diabetes; and 3) to advance the detection and management of diabetes in patients with TB (A. Harries et al., 2013; Organization, 2011).

Harries et al. (2013) state that with these objectives and recommendations in mind, the framework also mentions several challenges for the care of this disease co-occurrence – namely the bi-directional screening of both diseases in routine settings, the treatment of patients with both diseases, and the prevention of TB in people with diabetes. It is with consideration of these objectives of the Collaborative Framework and the noted challenges of care for the co-occurrence of diabetes and TB that this study aims to provide empirical evidence for the associated risk and protective factors associated with both diseases – evidence that will serve to enhance efforts to standardize the integration of treatment for this dual epidemic.

Table 1. Recommended synergetic activities established by the Collaborative Framework*

Objectives:	Recommended activities:
Establish mechanisms for collaboration	Set up means of coordinating diabetes and TB activities.
	Conduct surveillance of TB disease prevalence among people with diabetes in medium and high-TB burden settings.
	Conduct surveillance of diabetes prevalence in TB patients in all countries.
	Conduct monitoring and evaluation of collaborative diabetes and TB activities.
Detect and manage TB in patients with diabetes	Intensify detection of TB among people with diabetes.
	Ensure TB infection control in health-care settings where diabetes is managed.

	Ensure high quality TB treatment and management in people with diabetes.
Detect and manage diabetes in patients with TB	Screen TB patients for diabetes.
	Ensure high-quality diabetes management among TB patients.
*** Adapted from the World Health Organization and International Union Against Tuberculosis and Lung Disease**	

Co-occurring diabetes and tuberculosis

Important considerations from the literature

Globally, the prevalence of diabetes among individuals with TB varies considerably by region and ranges from 12% to 44% (Ko et al., 2016). More importantly, of the estimated 9.6 million new cases of TB reported in 2014, 1 million of these cases were estimated to have co-occurring diabetes and TB (Lönnroth, Roglic, & Harries, 2014; Zheng et al., 2017). In the past two decades, a number of systematic reviews and clinical trials have studied the epidemiology of the association between diabetes and tuberculosis (Baker et al., 2011b; Jeon & Murray, 2008b; Lönnroth et al., 2014; C. R. Stevenson et al., 2007). Most notably, these studies have established that either disease is an important risk factor for the other although the specific mechanism(s) through which diabetes predisposes an individual to TB is still uncertain (Catherine R Stevenson et al., 2007). The findings from these studies have also noted a number of moderating risk and protective factors, including gender and age (Lönnroth et al., 2009), on the prevalence of co-occurring diabetes and TB. Additional risk and protective factors from the literature on co-occurring diabetes and TB include: a family history of TB or diabetes (Montgomery, 1912;

Viswanathan et al., 2012; Workneh, Bjune, & Yimer, 2016), ethnicity (Kamper-Jørgensen et al., 2015; Pablos-Mendez, Blustein, & Knirsch, 1997), substance abuse, e.g. smoking or alcohol (Delgado-Sánchez et al., 2015), BMI (Cai et al., 2017), occupation (Ko et al., 2016; Tahir, Akhtar, Yaqub, Mushtaq, & Javed, 2016), healthcare utilization (Workneh et al., 2016), migration (Girardi et al., 2017; Young, Critchley, Johnstone, & Unwin, 2009), and poverty (Delgado-Sánchez et al., 2015). In 2007, Stevenson and colleagues conducted one of the first studies to critically review the literature on the association between diabetes and TB (C. R. Stevenson et al., 2007). In particular, their review consistently found a statistically significant risk or odds of a diabetes and TB association varying between 1.5 fold to 7.8 fold increase, for the nine studies examined (C. R. Stevenson et al., 2007).

Following the work by Stevenson et al., Murray and her collaborators have conducted three notable systematic reviews on the relationship between diabetes and TB (Baker et al., 2011a; Jeon et al., 2010; Jeon & Murray, 2008a). The first of this collaboration was led by Jeon and Murray (2008a) and focuses on a systematic review and meta-analysis of thirteen observational studies. Based on the random effects analysis of cohort studies, Jeon and Murray (2008a) find that diabetes is associated with a 3-fold (RR = 3.11, 95% CI 2.27-4.26) increased risk of developing active TB. They also note that the risk of developing active TB for those with diabetes is higher among younger individuals, populations from high TB incident settings and those from non-North American populations (Jeon & Murray, 2008a). While biological plausibility in support of a causal relationship between diabetes and TB remains inconclusive, Jeon and Murray (2008a) hypothesize that based on animal and experimental studies of human plasma cells, diabetes potentially impairs the immune system's response to fight against TB infection.

The second installment of systematic reviews by Murray and colleagues examines the yield of screening for additional diabetes or TB cases among studies which implemented screening or preventative therapy for TB among individuals with diabetes and studies that screened for diabetes among individuals with active TB (Jeon et al., 2010). Based on their review, the authors contend that active screening in individuals with diabetes noted a high TB prevalence with a range between 1.7% and 36%; while screening for diabetes among individuals with TB also resulted in high diabetes prevalence with a range from 1.9% to 35% (Jeon et al., 2010). Given the previous finding of a 3.11 relative risk of developing TB among individuals with diabetes, the evidence from this systematic review consequently supports the need for research on this association in settings highly burdened by either diabetes or TB and with a growing burden of the other disease.

In addition to these studies, Murray and her team conducted a third systematic review this time focusing the impact of diabetes on tuberculosis treatment outcomes among thirty-three studies (Baker et al., 2011a). Here the researchers find that diabetes negatively affects TB treatment outcomes by increasing the risks of death, a combined outcome of failure and death, and relapse among individuals with TB (Baker et al., 2011a). Baker, Murray and their colleagues (2011a) suggest that the link between diabetes negative TB treatment outcomes (i.e. failure and death, death, and relapse) is most likely as a result of poor diabetes control which is worsened by TB infection. This speculation of the implication of poor diabetes control on TB treatment outcomes is notable given their previous systematic review of thirteen observational studies which suggests that diabetes impairs cell-mediated immunity (Jeon & Murray, 2008a) – suggesting that diabetes self-management may be an important area to intervene for not only diabetes care but TB control as well. In the case of diabetes, research shows that recurrent TB is highly possible for diabetes patients as a result of reduced immunity increasing an individual's vulnerability to prior TB infection reactivation (Jeon, Murray, & Baker, 2012).

Age and gender as potentially both risk and protective factors

Current research also suggests mixed or contradictory evidence for the role of age and gender as key moderating factors for the co-occurrence of both diseases. While some studies found older age to be more of a protective factor, in that risk reduced with age, this finding is not consistent across all studies as other empirical studies have not find any noticeable age trend for those with both diabetes and TB (Catherine R Stevenson et al., 2007). In the case of gender as a moderating factor, Stevenson et al. (2007) note inconsistencies in the literature as some studies describe a strong association with the male gender and other studies have found women to be at a higher risk for having co-occurring diabetes and TB. Similar to other studies, Stevenson and her colleagues (2007) find that there is some evidence to suggest that sex may vary by age for the association between both diseases in that one study noted a higher proportion of younger aged males having diabetes and TB, with females becoming more predominant with older age. Another study conducted by Restrepo and colleagues on the association between diabetes and TB on the Texas-Mexico border found that comorbid individuals were more likely to be Hispanic females and over 40 years old (Littleton & Park, 2009; Singer, Herring, Littleton, & Rock, 2011). In contrast, other studies have found that for individuals with TB being over 40 years in age, male and living in an urban environment were significantly associated with a higher risk of diabetes (A. Harries et al., 2015). These differences in associations with age and gender provide some support for the likelihood of both being a risk and protective factor for the co-occurrence of both diseases.

Additional risk and protective factors of note

Existing literature on the diabetes-TB relationship has shed more light on the potential risk factors associated with this co-occurrence. Through a systematic review of the literature, one study in particular examines existing evidence on the global and regional prevalence of this co-occurrence in addition to the factors that were either associated with or increase risk for concurrent diabetes and TB (Workneh, Bjune, & Yimer, 2017). While the previous systematic reviews on the diabetes-TB relationship have focused on the prevalence as it pertains to the risk of having both diseases concurrently (Jeon & Murray, 2008a; Catherine R Stevenson et al., 2007), bi-directional screening (Jeon et al., 2010), and the impact of diabetes on TB treatment outcomes (Baker et al., 2011a), Workneh, Bjune, and Yimer (2017) extend the current literature by including evidence on the risk or associated factors of co-occurring diabetes-TB from ninety-four studies which either reported on diabetes prevalence among TB patients or vice versa. Regarding current prevalence estimates of co-occurring diabetes-TB, the authors find that the burden of diabetes among individuals with TB is high at the global level (estimated global median at 16%, IQR between 9.0% and 25.3%) – with the highest prevalence observed in studies from Asia (estimated median prevalence of 17%, with IQR of 11.4% to 25.8%), Oceania (median prevalence at 23.2% with IQR of 12.8% to 39%) and North America (median prevalence of 23.6%, IQR between 17.3% and 35.4%) (Workneh et al., 2017). Interestingly, Workneh and colleagues (2017) also note that TB prevalence among individuals with diabetes is relatively higher in the Asia (median prevalence of 3.5%, IQR between 0.9% and 10.5%) and Africa (median prevalence at 5.6%, IQR of 3.5% to 5.8%) regions despite being low globally (median prevalence of 4.1%, IQR between 1.8% and 6.2%).

Using thematic descriptions such as socio-demographic and economic factors, behavioral factors, clinical factors, and other factors, Workneh and peers (2017) also find that the high global burden of concurrent diabetes-TB is sustained by heterogeneous risk or associated determinants. For socio-demographic and economic factors, *associated determinants* include male gender, older age, urban residence, education beyond primary schooling and family size; while *determinants which increased risk* include both male and female gender, older age, urban residence, place of birth, ethnicity, high-income status, and sedentary occupation (Workneh et al., 2017). Behavioral factors such as illicit drug use and sedentary lifestyle are reported to be *associated with* co-occurring diabetes-TB and others such as smoking and alcohol consumption *increase the risk* of having both concurrently (Workneh et al., 2017). For clinical factors, Workneh et al. (2017) mention *associated factors* found in the literature to include both lower and higher BMI, and being overweight or obese. The association of overweight or obese status with co-occurring diabetes-TB is important to note here as it is widely accepted that obesity increases diabetes risk; however, some findings show that overweight (with higher BMI of at least 30kg/m^2) sans diabetes is seemingly a protective factor against TB (Critchley et al., 2017). Clinical determinants mentioned by Workneh et al. (2017) *which increase the risk* of developing co-occurring diabetes-TB include lower and higher BMI, pre-existing and long duration of diabetes, poor glycemic control at TB diagnosis time, with factors such as HIV co-infection and malnutrition being round to be *low risk factors for having both diseases*. Other factors including family history of diabetes, type of TB treatment category and contact with a family member with TB were found to be associated with or increasing the risk of developing diabetes and TB concurrently (Workneh et al., 2017).

Similar findings from empirical studies have also been noted, with supplementary risk factors being raised. For example, a prospective study of the clinical characteristics of diabetes and TB patients in Peru, found that individuals with both diseases were significantly more likely to be older, married or partnered, and have less education but less likely to be undernourished when compared to individuals without diabetes (M. Magee et al., 2013). Noting that diabetes is the second most important risk factor for TB in higher income countries such as those in the Central Europe region, Caraffa and colleagues (2016) that among TB patients (including Italians and foreign-born participants) in a referral center in Rome, Italy, foreign-born individuals from countries *with national diabetes prevalence over 8%*, prevalence within the study sample was 12.7%. However, for foreign-born individuals from countries with national diabetes prevalence less than 8%, prevalence within the study sample was 4.7% and among Italian patients diabetes prevalence was 9.7% (Caraffa et al., 2016). The findings from this retrospective study of TB patients show that in addition to older age and being male, diabetes prevalence is independently associated with being foreign-born (Caraffa et al., 2016) – with this latter association highlighting the importance of international migration on the relationship between diabetes and TB. Moreover, a study conducted by Delgado-Sanchez et al. (2015) analyzed data from the National Tuberculosis Registry in Mexico from 2000 to 2012 and noted that individuals with diabetes who live in poverty more likely to be exposed to known risks for TB including but not limited to a higher probability of being in contact with individuals with active TB and having limited access to good-quality health care services.

In the case of TB treatment outcomes, diabetes status is a risk factor in that poorly controlled diabetes increases the risk of co-occurrence and may lead to poor TB treatment outcomes (Jeon et al., 2012; Zheng et al., 2017). In contrast, some studies have noted that diabetes is not associated with TB treatment outcomes (Cavanaugh et al., 2015; Singla et al., 2006), while others have found co-occurring diabetes-TB to be associated with successful TB treatment outcomes (Nissapatorn et al., 2005). Other studies have shown that the incidence of active TB is higher among insulin dependent individuals than non-insulin dependent (Dooley, Tang, Golub, Dorman, & Cronin, 2009).

Co-occurring diabetes and TB in Central Asia

Despite the increasing prevalence of diabetes and the burden of TB throughout the Central Asian region, only a few studies have examined the co-occurrence of both diseases and both studies are based in Kyrgyzstan (Arnold et al., 2016; Skordis-Worrall et al., 2017) and Uzbekistan (Yusupova et al., 2016). In their discussion of the economic burden of diabetes, TB and the co-occurrence of both diseases, Arnold and colleagues (2016) use cross sectional data from 309 diabetes and TB patients collected from patient survey in four health facilities in Bishkek, Kyrgyzstan. The survey includes information on patient health expenditure, socio-economic status (e.g. age, gender, educational level, employment status and household status) and financial coping strategies (e.g. support from social networks, social welfare and donations, income and savings etc.) (Arnold et al., 2016). Findings from the Kyrgyz study show that among individuals co-affected with both diabetes and TB associated risk factors include older age, male gender, lower socio-economic status, being less likely to receive social welfare support such as pensions and being more likely to experience catastrophic health spending (Arnold et al., 2016). In particular, the authors note that the financial burden experienced by individuals with both diabetes and TB is not only greater (in comparison with those with either disease) but is also caused by the structure of service provision – i.e. diabetes and TB services are siloed and not within the same health facilities (Arnold et al., 2016) – leading to a double burden of co-occurring disease management and the associated costs.

Another Kyrgyz study conducted by Skordis-Worrall et al. (2017) finds that individuals with both diabetes and TB have different experiences within the healthcare system in comparison to those with either diabetes or TB. Specifically, individuals with both diabetes and TB receive less care as result of the lack of training for allied health professionals and the siloed management of the each disease (Skordis-Worrall et al., 2017). This finding is most important as the authors mention that individuals with both diseases have significantly worse mental health outcomes as a result of their double burden but still receive less inpatient and outpatient care compared to those with either diabetes or TB (Skordis-Worrall et al., 2017). Furthermore, Skordis-Worrall and colleagues (2017) find that co-affected diabetes and TB patients are more likely to have more visits to health centers to receive medication than those with only diabetes or TB.

A recent study from the Samarkand region of Uzbekistan examines the characteristics and treatment outcomes of new pulmonary TB patients with comorbid conditions such as HIV or diabetes (Yusupova et al., 2016). Using a retrospective cohort study design, Yusupova and colleagues (2016) find that diabetes is the most common comorbidity accounting for roughly 60% of those individuals reporting a comorbidity and individuals with both diabetes and TB were older. In contrast to the Kyrgyz study that found co-occurring diabetes-TB to be less associated with receiving pensions (Arnold et al., 2016), the Uzbek study found over 70% of new pulmonary TB patients with comorbid diabetes to be either pensioners or invalids and as it pertains to TB treatment outcomes were more likely to have unfavorable or unsuccessful TB treatment outcomes (Yusupova et al., 2016). Taken all together, the findings from these studies point to the need to examine both the associated risk and potential protective factors in other Central Asian countries as it pertains to the co-occurrence of both diabetes and TB. Since countries in the Central Asian region are on the list of high TB-burdened countries and with the increasing prevalence of diabetes throughout the region, further consideration of these risks and potential protective factors at multiple levels of influence will provide key evidence for strengthening health systems response to this unique disease co-occurrence.

CHAPTER 3: THEORETICAL SUPPORT

Overview of the current chapter

In the following section, a discussion on the application of the ecological framework to the current study is provided. The use of the ecological framework is most applicable as it provides a systematic examination of the association between diabetes and TB – an approach that is currently missing in the literature as it pertains to the co-occurrence of both diseases in a population. An ecological framework provides a holistic approach to examining this co-occurring relationship while offering potential areas to intervene in regions, similar to Kazakhstan, which are highly burdened with TB and an increasing prevalence of diabetes. More pointedly, the original study design for the collected data utilizes the ecological framework as well. Hence, the pursuant discussion on the ecological framework includes the multiple levels of potential risk and protective factors concerning both diseases.

An Ecological Framework

As a well-established perspective, Bronfenbrenner's ecological systems paradigm uses a multi-tiered approach to assess individual, social and environmental factors – factors which may be either risk, protective or both – that influence human development and behavior

(Bronfenbrenner, 1977, 1989). Bronfenbrenner's model examines human development as one that is affecting and effected by multiple levels of influence (Bronfenbrenner, 1989; McLeroy, Bibeau, Steckler, & Glanz, 1988). In particular, the ecological approach focuses on how these levels of influence intersect and overlap to affect an individual's outcomes (Bronfenbrenner, 1977; Sallis, Owen, & Fisher, 2008). Each level or subsystem considers different aspects of an individual's environment beyond the single unit of the individual to consider the factors related to levels such as the interpersonal, neighborhood, cultural norms, community, institutional or structural levels (Kaufman, Cornish, Zimmerman, & Johnson, 2014).

In explaining the paradigm, Bronfenbrenner (Bronfenbrenner, 1977, 1989) delineated multiple levels of environmental influences on human development, nested within each other, as defined by the micro-, meso-, exo-, and macrosystem (McLeroy et al., 1988). The microsystem examines relational influences on the person-environment association with a particular focus on the immediate context or setting containing the person and comprises factors such as place, time, physical features, activity, individual characteristics as elements of a person's immediate setting (Bronfenbrenner, 1977, 1989). The mesosystem, often referred to as a system of microsystems (Bronfenbrenner, 1977), considers the interrelations or interactions among the various settings containing the individual – e.g. within peer groups, family, work etc. (Bronfenbrenner, 1989; McLeroy et al., 1988). The exosystem comprises of the larger social structures or systems, both formal and informal, that impact the individual, e.g. one's neighborhood (Bronfenbrenner, 1977, 1989). The macrosystem goes beyond the specific contexts directly affecting an individual's development as noted in the preceding levels and addresses the overarching structural and ideological influences of the culture or broader social context through institutions related to economic, social, educational (Bronfenbrenner, 1977) or health systems (McLeroy et al., 1988).

As noted by McLeroy and colleagues (1988) the ecological model essentially highlights the reciprocal nature between an individual and the environment as one that is transactional.

Sallis et al. (2008) describe ecological models as those which address the multiple levels of factors which influence health outcomes and that these factors *interact together* to affect health outcomes. The authors also contend that interventions focused solely on single-level factors are unlikely to have robust or continued population-wide effects (Sallis et al., 2008). Consequently, interventions that use the ecological systems approach as a conceptual framework focus on change at key points of intersection – including social and structural factors, as well as individual behavior (Schensul, 2009). Schensul (2009) further explains that these multilevel interventions are critical for addressing the risk conditions (i.e. structural and social factors) in addition to risk factors (individual factors) *concurrently* [emphasis added].

In order to assess the focal areas of intersection on the factors that may influence TB prevalence in Kazakhstan, the collected data for this dissertation used an ecological framework to conceptualize the study design and data collection of the environmental (e.g. healthcare access; service utilization; smoking norms), individual (e.g. sociodemographic characteristics; smoking status; alcohol use) and biological (e.g. BMI; diabetes status) factors associated with TB transmission and acquisition. In line with the application of the ecological framework used for the original study, this dissertation examines the multilevel nature of disease interaction and the factors associated with co-occurring tuberculosis and diabetes. An ecological model **(Figure 1)** has been constructed to demarcate this diabetes-tuberculosis association and the multilevel factors of interest that may contribute to the relationship.

Ecological systems model of the diabetes and TB relationship

For the purposes of this dissertation, these multi-level factors are explored at the individual (i.e. the microsystem), interpersonal networks (i.e. the mesosytem), community/ environmental (i.e. the exosystem), and macro-structural (i.e. the macrosystem) levels as it pertains to co-occurring diabetes and tuberculosis and in consideration of the available data analyzed as well as the current literature on this dual disease relationship. First, the individual level consists of modifiable and non-modifiable risk and protective factors that are commonly associated with both diabetes and tuberculosis. Second, the interpersonal networks level considers the informal and formal social networks that may impinge upon the relationship between the two diseases. Third, the community/ environmental level takes into consideration the social and environmental factors that may influence this co-occurrence in individuals and communities. Fourth, the macro-structural level encompasses the institutional practices or societal factors that further compound the relationship between diabetes and tuberculosis.

At the individual level, certain modifiable elements such as smoking, alcohol, diet or nutritional status, physical activity, BMI, marital status, education, occupation and non-modifiable sociodemographic determinants (e.g. age, gender, ethnicity) have been shown to have negative effects on the dynamic relationship between diabetes and tuberculosis (Dye, Trunz, Lönnroth, Roglic, & Williams, 2011; Lönnroth, Jaramillo, Williams, Dye, & Raviglione, 2009) and in addition to being potential buffers for the risk of the co-occurrence of both diseases (Workneh, Bjune, & Yimer, 2016). In general, several studies have noted that older age, higher BMI, higher education (i.e. secondary level and above), being married, sedentary occupations, and diabetes family history are associated with an increased prevalence of diabetes among those with TB (Critchley et al., 2017; Sarker et al., 2016).

Due to inconsistencies in the current literature, age and gender are potentially risk AND protective factors for concurrent diabetes and TB as some studies have found younger age to increase the risk of having both (Stevenson et al., 2007) but other studies have found the same with older age (Restrepo et al., 2007; Workneh, Bjune, & Yimer, 2017) while others find age not to be associated with co-occurring diabetes-TB (Pealing et al., 2015). It is plausible that older age is more of a risk factor for concurrent diabetes-TB as result of weak immune system which leaves older adults to be more susceptible to developing both diseases (Workneh et al., 2017). Conversely, healthy lifestyle behaviors including physical activity and healthy diet may act as a buffer or protective factor for both diseases (Cockerham, Hinote, Abbott, & Haerpfer, 2004; Workneh et al., 2017). Concerning the issue of physical activity (i.e. needed for diabetes but less likely to be physically active with TB), Harries et al. (2015) also note the conflicting lifestyle modifications associated with both diseases – the calorie restrictions associated with weight loss for diabetes versus the high protein, high calorie intake to gain weight for TB – may be a risk factor when both diseases are concurrent in an individual. Nonetheless, frequent outdoor physical activity is considered a protective factor against co-occurring diabetes-TB (Workneh et al., 2017).

At the interpersonal networks level, social support (Kaliakbarova et al., 2013) and smoking norms (Terlikbayeva et al., 2012) have been reported as key protective and risk factors of TB diagnosis in Kazakhstan. In their assessment of a psycho-social support (PSS) pilot program for patients considered to be at a high risk for TB treatment default, Kaliakbarova and colleagues (2013) find that the integration of the patient-oriented support program led to better management of MDR-TB patients during the outpatient, continuation phase of treatment and improved treatment adherence for participants. As the majority of MDR-TB patients in the East

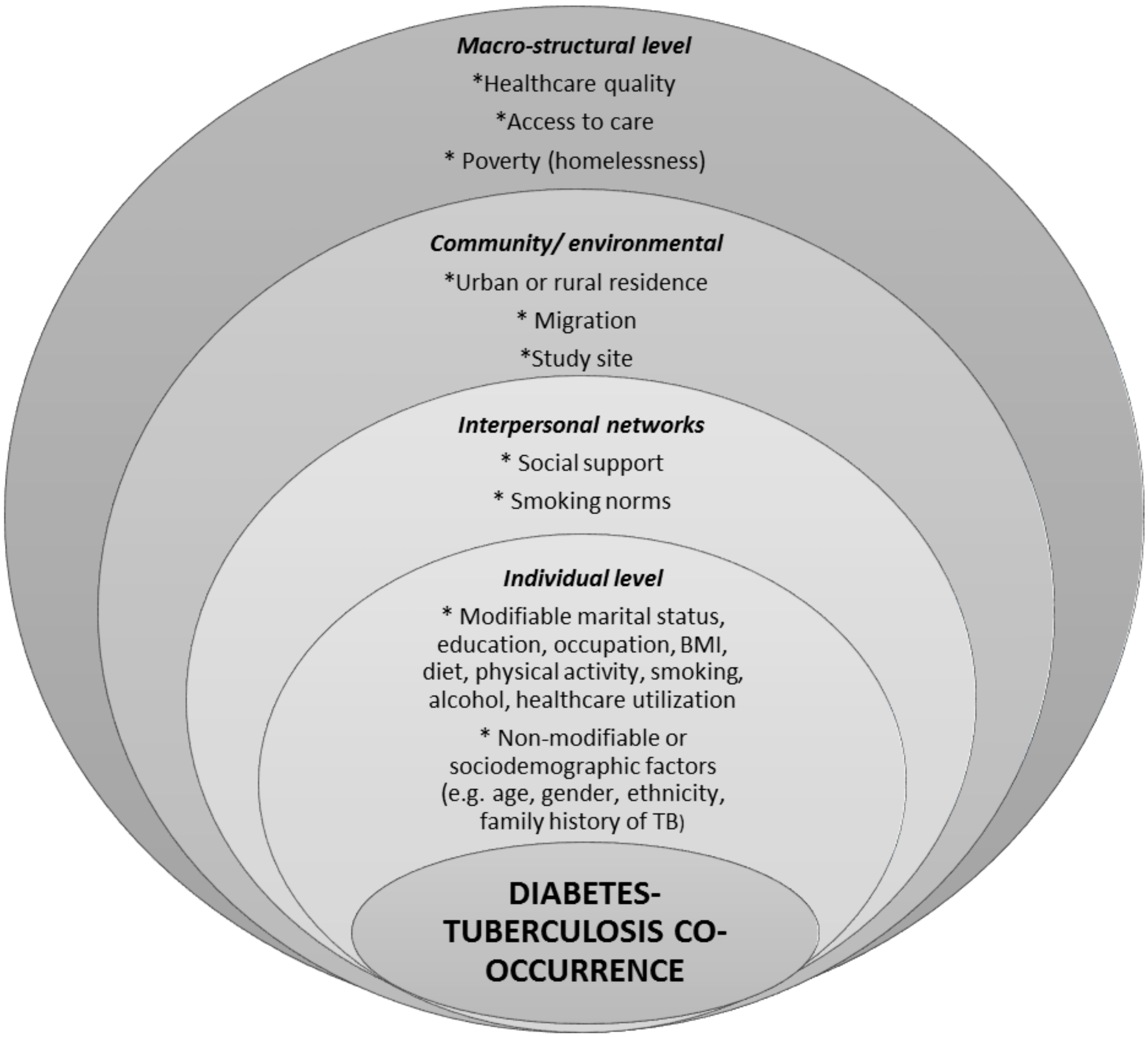
Kazakhstan region were considered vulnerable people (i.e. ex-prisoners, persons with HIV, the poor, the homeless, substance users and migrants), the authors state that these individuals suffered from a number of social and psychological problems such as alcoholism, unemployment, being low-income, lacking social support, homelessness and being undocumented migrants (Kaliakbarova et al., 2013). With a project team that included key service providers such as social workers and psychologists, the PSS program offered different forms of social support for these vulnerable MDR-TB patients including but not limited to temporary housing and food and clothing assistance (Kaliakbarova et al., 2013). Consequently, Kaliakbarova and colleagues (2013) find that social support, including those offered by state supported service providers, is a protective factor or a buffer for reducing rates of TB treatment default among MDR-TB patients. In the case of diabetes care and management, a systematic review of controlled intervention studies led by van Dam and colleagues (2005), notes that social support interventions such as peer social support groups and patient group consultations with diabetes care providers have positive effects on self-management and outcomes for persons with type 2 diabetes. Although empirical studies on the diabetes-TB relationship have yet to examine social support, recent literature review by Riza and colleagues (2014) advises that treatment services for individuals with concurrent diabetes and TB include social support services in the form of counseling and education which can have positive outcomes on lifestyle habits such as nutrition, weight loss, smoking cessation, and physical activity.

In addition to the factors previously mentioned that may impact the diabetes-TB relationship at both the individual and interpersonal networks levels, at the community/ environmental level the current study examines urban or rural residence, migration and the study sites for the collected data which included low and high TB burdened regions in Kazakhstan.

Urban or rural residence and migration have been noted to be associated with co-occurring diabetes and TB as potential risks (Caraffa et al., 2016; Harries et al., 2015). A number of studies have found urban residence to be associated with a higher prevalence of diabetes among TB patients (Delgado-Sánchez et al., 2015; Workneh et al., 2017); however, few studies mention rural residence as being associated with co-occurring diabetes-TB (Firănescu et al., 2017; Sarker et al., 2016). Despite the opposing views on residential type and the diabetes-TB relationship, it is clear that rural or urban residence may be a risk factor for this co-occurrence (Firănescu et al., 2017). Conversely, studies have noted that migration, particularly external migration, is a risk factor for TB (Huffman, Veen, Hennink, & McFarland, 2012) , diabetes (Misra & Ganda, 2007; Young, Critchley, Johnstone, & Unwin, 2009), and the co-occurrence of both diseases (Caraffa et al., 2016; Firănescu et al., 2017; Girardi et al., 2017). As the collected data analyzed for this dissertation was collected in four regions in Kazakhstan representing low and high TB burden, it is useful to assess study sites with higher TB burden as potential risk factors for the co-occurrence of both diseases. This assessment is useful based on the current literature which reports high TB burdened areas as being more likely to have higher diabetes-TB co-occurrence (Bloomgarden & Misra, 2017).

And finally, the macro-structural level considers the risk and protective determinants noted within the individual, interpersonal networks, and community/ environmental levels while including the role of determinants such as healthcare quality, healthcare access, and poverty on this dual disease interaction (de Colombani & Hovhannesyan, 2015; Ploubidis et al., 2012). Healthcare quality has been reported to be a protective factor for individuals with diabetes enrolled in an enhanced case management program offered through health centers, compared to those who were not enrolled, in that enrolled individuals were less likely to develop TB and more likely to have better TB treatment outcomes in the event that they developed TB (Lo et al., 2016). In addition, structural factors such as access to care have been shown to have negative outcomes on TB care and management in resource poor settings (Hudelson, 1996; Long, Johansson, Diwan, & Winkvist, 1999).

Figure 1: An Ecological Systems Model of the Diabetes-Tuberculosis Relationship



CHAPTER 4: STUDY DESIGN AND METHODOLOGY

Overview of the chapter

This section covers the design of the original including the recruitment and sampling plans. Additionally, the specific aims and hypotheses of the current study are discussed. And finally, the analytical procedures as well as the measures used are discussed.

Design, sampling, and recruitment

Consortium of partners

The Mapping of Social, Environmental and Genetic Factors Determining Susceptibility to Tuberculosis in Kazakhstan project (hereinafter 'TB Project') began in Kazakhstan in 2011 with data collection ending in 2014. Funded by Kazakhstan's Ministry of Education and Science (MES) to Nazarbayev University (NU) in Astana, Kazakhstan, the TB Project included a collaboration with Nazarbayev University's Center of Life Sciences (CLS), Columbia University's Global Health Research Center of Central Asia (GHRCCA), the National TB Center (NTBC), the National Association of TB Specialists (NATBS) and the National Geography Institute (NIG). As the lead organization for the project, GHRCCA maintained responsibility for the overall project management and implementation of the study. An integral partner for the TB Project and the coordinator of the National Tuberculosis Program (NTP) in Kazakhstan, the NTBC provided access to TB cases and their contacts as well as the infrastructure within TB clinics for research activities. One of four research centers at Nazarbayev University, the CLS analyzed the data, interpreted the results and provided a genomic laboratory for the collection and handling of the biological samples. While the NIG provided support to assess the geo-spatial distribution of TB and MDR-TB cases, the NATBS offered consultation on the study design and methods.

Study design

The design of the TB Project includes four components: 1) a case-control component which compares TB index cases with randomly selected community controls to estimate the impact of social and environment factors; 2) a prospective cohort component which aimed to examine and compare the multi-level social and environmental risk factors associated with the development of TB and MDR-TB among the TB index cases and community controls; 3) an integrated molecular epidemiology research component designed to identify different Mtb genotypes and examine the variability in the population and the roles of the different strain in the development of various TB clinical forms, disease severity, outcomes, epidemiology, and drug resistance and transmission of TB and MDR-TB among the new pulmonary TB index cases in four regions in Kazakhstan; and 4) a genetic component which examines genetic host susceptibility through candidate-gene research. As data is only available for the case-control component of the TB Project, the current dissertation focuses on this part only.

Along with methods such as laboratory testing, clinical examination and a thorough survey of participants, the matched case-control study design of the TB Project specifically investigates the multi-level social and environmental risk factors associated with the development of TB and MDR-TB among new pulmonary TB index cases and their household and community controls in four study sites or regions within Kazakhstan – Almaty (i.e. Almaty City and state), Kostanay and Kyzylorda. The random selection of the community controls provides a means to assess the estimated impact of the social and environmental factors through a comparison of the community controls with the TB index cases. The selection of the four study sites are based on epidemiological surveillance data disaggregated by region (or ‘oblast’ in Russian, an administrative territorial division in Kazakhstan consisting of a number of districts) and district (i.e. ‘rayon’ in Russian, a smaller territorial division) to represent low and high TB burdened regions (based on TB case notification rates) in Kazakhstan – Kyzylorda and Almaty city are high TB burdened regions while Almaty state and Kostanay are low TB burdened regions. In addition to their geographical differences (i.e. representing northern, southern and eastern parts of Kazakhstan), consideration is also given to the availability of research and lab infrastructure for each study site. The selected regions also represent the northern, southern and eastern parts of Kazakhstan i.e. covering the physical landscape of the country. **[See Appendix A for a map of Kazakhstan showing the four regions.]**

Study sampling

In an effort to certify that the study sample is representative of the general Kazakh population, the TB project employed a clustered sampling approach to randomly select 30 districts or rayons within each region for the recruitment of new TB incident cases and their controls. The sample includes 1,600 individuals, from the four regions, divided into three groups: TB index cases with newly detected pulmonary TB, household contacts (who are TB free) of the index participants, and external community or non-household controls who are TB free. TB index cases eligible for inclusion in the study had to be diagnosed within three months of the study starting and as is consistent with the World Health Organization’s (WHO) recommendations, had to either have a positive culture AND positive smear examination and confirmation by nucleic acid amplification testing; OR have clinical and x-ray presentation consistent with TB and response to treatment with anti-tuberculosis drug.

Matching of controls to a TB index case is done by nationality (i.e. both controls are the same nationality as the TB case) and a 10-year age range so that each index case has two matched controls who did not have a previous diagnosis of pulmonary TB. Information for eligible household contacts came from the pre-screening process of the TB index cases. In a situation in which several household contacts were available, the use of the Kish method[1] provided a means to randomly select the household contact study participant and this approach is a statistically rigorous technique previously employed in Kazakhstan. Moreover, eligible household and community controls had no previous diagnosis of pulmonary TB as defined by the study. Community controls are selected at random from the same neighborhood as the selected TB index case and assigned to the same primary care clinic.

Additional eligibility criteria were as follows: 1) all participants had to be 18 years or older at study screening; 2) all participants had to have a permanent residence address for three months or more; 3) each TB index cases had to have an availability of a household adult control; 4) Russian or Kazakh fluency for all participants; 5) all participants had to have no plans to relocate within twelve months of the studying screening; 6) all participants had to have an absence of any apparent severe mental disorders that may impede the consenting and questionnaire process; and 7) all participants could not have a physical illness expected to be terminal within a year of screening as determined by the research assistants during pre-screening and screening.

Power Analysis

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[1] Several studies describe the Kish method as the preferred approach for randomly selecting respondents within households in that all eligible individuals in the household are listed and sampled, therefore having equal probability of being selected (Oldendick, Bishop, & Tuchfarber, 1988; Rizzo, Brick, & Park, 2004).

For the collected data, it was calculated that the sample size of 1,600 participants (TB cases and controls) would allow 80% power to detect an odds ratio (OR) of 1.6 for any risk factor (including diabetes) with a prevalence between 10% and 85% in the controls and an odds ratio of 1.4 for any factor with a prevalence between 20% and 70%. Recruitment was aimed at 1,800 participants, 600 per each of the three groups (i.e. TB cases, family and community controls), to account for loss to follow-up.

Study recruitment

From June 2012 to May 2014, TB incident cases registered through the National Tuberculosis Program in the four sites with an invitation to participate in the study. TB doctors from the central oblast or regional-level TB dispensary recruited TB index cases, using a master list of new pulmonary TB cases identified in the cluster-sampled rayons of the oblast. In addition to his or her role as a physician at the TB clinic, GHRCCA hired, trained and supervised the TB doctor. Since he or she was the first point of contact for all new TB cases, the TB doctor's responsibility included introducing the study to all eligible new TB cases and referring them for prescreening by GHRCCA research personnel. Of those invited and pre-screened, 744 newly diagnosed TB cases were registered with 566 meeting the eligibility criteria and 562 agreeing to participate in the study (i.e. a participation rate of 76%). Interviews took place in separate rooms with research assistants available to help participants, if needed.

Recruitment of household controls began with the pre-screening of TB index cases when information on the availability of a potential eligible household contact was collected at that time. With that information from the TB index case pre-screening, a GHRCCA research staff then visited the address of the TB index case, introduced the study to an eligible adult and requested to pre-screen all potential adults available in the home. Upon confirmation of the availability of at least one household control potentially eligible for inclusion in the study, the research staff then scheduled a date for the screening and baseline interview. As previously mentioned, should more than one household member be eligible to participate the Kish method was employed to select the potential study participant. As in the case with TB index cases, all interviews for household controls took place in separate rooms with research assistants available to help participants, if needed.

For community controls, recruitment occurred after the identification of an eligible TB index case and household control. At this point, random selection of an individual community control took place in the same neighborhood as an index case. Upon the selection of a random house to visit, the study recruiters introduced the study to an adult member in the home and pre-screened any potentially eligible individual with availability. Similar to the household controls, the Kish method applied in situations wherein more than one member in the home is eligible. Should there be no response at the home visited, study recruiters than proceeded to the next randomly selected home. Interviews for community controls took place in separate rooms with research assistants available to help participants, if needed.

A construction of a participant flow diagram shows the 562 index cases included in the study as well as the 515 household controls and 523 community or external controls for a total of 1600 study participants. **[See Appendix B for the participant flow diagram.]**

Data collection procedures

Participant data was collected through an in-person 60-minute audio computer assisted self-interview (ACASI) conducted from June 2012 to May 2014. The advantages of using the ACASI technology included: 1) automated entry into a database which guaranteed data integrity; 2) the administration of survey questions in uniform fashion with skip patterns handled automatically; 3) audio and video enhancements assisted participants with limited or reduced literacy levels; and 4) a user-friendly video offered a guided tour through the survey. If needed, research assistants provided help to all participants with using ACASI and responded to any potential participant distress during the assessment. Programming of study instruments occurred in DatStat, a computer software package providing video presentations of question and response options in both Kazakh and Russian languages. All questionnaires were administered in private rooms with research assistants available, if necessary. Field staff in each of the four regions were trained in the ethics of human subjects' research, protocols, instruments, and data management, receiving a certification upon training completion.

The list of study data collected for each TB index case include: 1) a pre-screening survey; 2) a screening eligibility structured interview of routine demographic questions; 3) an assessment questionnaire inquiring about personal health data conducted through ACASI at baseline and for the six- and twelve-month follow-ups; and 4) an individual registration or medical extraction form provided by the NTBC within two weeks of the TB index case's enrollment in the study. The list of study data collected for both household and community controls include: 1) a pre-screening survey; 2) a screening eligibility structured interview; and 3) a baseline assessment questionnaire. Clinical data were collected for all TB index cases for the duration of the study included: clinical diagnosis, chest radiographic findings, smear status (whether positive or negative), type of primary detection, social and professional status, TB risk factors, duration of disease, presence of cavity decay, location, category and phase of TB treatment, side effects, TB treatment progress and outcomes, results of DST testing, and culturing. For the purpose of this dissertation, only final TB treatment outcomes collected from the medical extraction form are considered.

Human Subjects Protection

All identifying information were removed from the data before performing analysis. Ethical review was approved by Institutional Review Boards from Columbia University, the Center for Life Sciences of Nazarbayev University and the National TB Center of Kazakhstan. Informed consent were attained from all participants.

Specific aims and hypotheses

As mentioned before, this dissertation examines the multi-level risk and protective factors associated with co-occurring diabetes and TB among 1600 participants, of which 562 were new TB incident cases, in four TB burdened regions in Kazakhstan. More importantly, this study draws on the ecological framework to assess the multilevel associations of co-occurring diabetes-TB. The ecological framework supports the study design of the original data being used for this dissertation and assesses how disease co-occurrence may negatively impact TB treatment outcomes among individuals accessing TB care in regions with low and high TB burden in Kazakhstan. Since the co-occurrence of diabetes and TB has yet to be studied in Kazakhstan, the specific *aims of this dissertation* are:

<u>AIM 1:</u> To examine the prevalence of diabetes among those with TB (n=562) and those without TB (n=1,038) – controlling for age, education, ethnicity and gender – using self-reported cross-sectional baseline data among a sample of 1600 individuals in Kazakhstan.

Hypothesis$_1$: Diabetes prevalence is higher among individuals with tuberculosis than among those without TB.

<u>Data analysis for specific Aim 1</u>

In this aim, I examine the prevalence of diabetes among the entire sample of 1,600 participants and compare diabetes prevalence among those with TB (n=562) and those without TB (n=1,038) using self-reported baseline data. To test the hypothesis and since the data was collected using a matched case control design, a conditional logistic regression (CLR) model was applied to determine diabetes status among those with TB (i.e. cases) and those without TB (i.e. controls). CLR is applicable for this aim because matching has been done and this method always provides unbiased results (Connolly & Liang, 1988). First, Pearson's chi-square test was conducted to determine diabetes prevalence among the sample based on the variable *diabetesever* (i.e. Have you ever been diagnosed with diabetes?) which has a binary 'yes' or 'no' response. Second, a CLR model was analyzed where the variable group corresponded to "TB only" (=1) or "non-TB" (=0).

<u>Power analysis for Aim 1</u>

A logistic regression of a binary response variable (diabetic status) on a binary independent variable (group) with a sample size of 1600 observations achieves 90% power at a 0.05 significance level to detect a change in diabetic prevalence from 20.0% (in the non-TB group) to 27.3% (in the TB-group). This change corresponds to an odds ratio of 1.5. An adjustment was made since a multiple regression of the independent variable of interest on the other independent variables in the logistic regression obtained an R-Squared of 10%.

Aim 2: To identify multi-level risk and protective factors, guided by the ecological framework, of co-occurring diabetes-TB and TB, among individuals with both diseases and those with only TB using self-report data for the TB cases (n=562) collected at baseline.

Hypothesis $_1$: Selected multilevel risk and protective factors will be strongly associated with co-occurring diabetes-TB.

Data analysis for specific Aim 2

For this aim and based on previous research, I examine the multi-level risk and protective variables that are associated with TB as well as co-occurring diabetes and TB, among the TB cases (n=562). I use self-reported data collected at baseline to test the hypothesis. Multivariate logistic regression analyses were conducted to integrate the different levels of the ecological framework.

Power analysis for Aim 2

A logistic regression of a binary response variable (diabetes status) on a binary independent variable (group, i.e. diabetes-TB or TB only) with a sample size of 562 observations achieves 80% power at a 0.05 significance level to detect a change in diabetic prevalence from 20.0% (in the TB only group) to 27.3% (in the diabetes-TB group). This change corresponds to an odds ratio of 1.5. An adjustment was made since a multiple regression of the independent variable of interest on the other independent variables in the logistic regression obtained an R-Squared of 10%.

AIM 3: To examine clinical TB treatment outcomes (i.e. successful and unsuccessful) for individuals with co-occurring diabetes-TB and those with only TB using available clinical data for the TB cases (n=562).

Hypothesis $_1$: Individuals with co-occurring diabetes-TB are more likely to have higher percentage of unsuccessful TB treatment outcomes.

Data analysis for specific Aim 3

Using available clinical data, I examine the clinical TB treatment outcomes among the sample of 562 TB cases for those with TB only and those with co-occurring diabetes and TB for this aim. To test the hypothesis for this aim, I use Pearson's chi-square test with a cross-tab table to assess the levels of TB treatment (i.e. diabetes and TB vs. TB only) and levels of outcome (i.e. successful, unsuccessful and) for the sample of 562 TB cases.

AIM 4: To compare multi-level risk and protective factors, guided by ecological framework, of clinical TB treatment outcomes for individuals with both diseases and those with only TB using available clinical data for the TB cases (n=562).

Hypothesis $_1$: At each of the ecological levels, the selected multi-level risk and protective factors will be associated with unsuccessful TB treatment outcomes among those with co-occurring diabetes-TB.

Data analysis for specific Aim 4

In this aim, I compare the multi-level risk and protective factors of clinical TB treatment outcomes for those with TB only and those with diabetes and TB using baseline data. To examine this aim and for each grouping (i.e. TB only or diabetes-TB), a multiple logistic regression was conducted to model each of the two clinical TB treatment outcomes (i.e. successful or unsuccessful).

Power analysis for aim 4

A logistic regression of a binary response variable (treatment outcome) on a binary independent variable (group) with a sample size of 562 observations achieves 80% power at a 0.05 significance level to detect a change in diabetic prevalence from 20.0% (in the non-TB group) to 27.3% (in the TB-group). This change corresponds to an odds ratio of 1.5. An adjustment was made since a multiple regression of the independent variable of interest on the other independent variables in the logistic regression obtained an R-Squared of 10%.

Measurement

Questionnaire data collected included demographic variables, current health status, behavioral risk factors, substance usage, health services, migration history, HIV and Hepatitis C Status, HIV risk factors, mental health, physical activity, nutrition, social support, TB knowledge, healthcare discrimination and child sexual abuse history. Measures used included questions from: the Global Adult Tobacco Survey; Brief Symptom Inventory (BSI); Alcohol Use Disorder Identification Test (AUDIT); the CAGE, Alcohol Use Disorders Screening Test; Multidimensional Scale of Perceived Social Support (MSPSS); World Health Survey (WHS); International Physical Activity Questionnaire (IPAQ); Demographic Health Survey (DHS); and pilot studies conducted by the Global Health Research Center of Central Asia (GHRCCA). The GHRCCA pilot studies used were based on the Renaissance and Silk Road Health Project (SRHP) surveys, both of which were adapted, pilot tested and implemented in Kazakhstan. All other measures previously discussed were selected by the study team based on known high reliability and validity to the extent as possible. Additional criteria for these measures included prior usage of the instrument or scale in Kazakhstan, Central Asia or former Soviet Union countries. TB treatment outcome measures were collected from TB cases' medical cards and based on the WHO's International Classification of Diseases (ICD) 10.

Measures used for dissertation analysis

<u>Selected individual level variables:</u>

Non-modifiable variables include: age; gender; ethnicity (i.e. *Kazakh, Russian and Other*); and TB family history. Modifiable variables include education (i.e. *primary or secondary, high school, vocational, and currently a student or completed higher education*); marital status (i.e. *married or common-law, single or never married, divorced or separated, and* *separated*); employment or occupation (i.e. *employed, unemployed*), body mass index (BMI), daily consumption of vegetables and fruits, physical fitness self-rating, ever smoked tobacco, alcohol use (*ever*), and healthcare utilization (*Have you been to a doctor or another medical professional during the past 12 months?*).

Selected interpersonal networks level variables:

Measures relating to social support (i.e. total sum score based on the 12 questions of the MSPSS) and smoking norms (*Is smoking in your home allowed in all rooms?*) were used.

Selected community/ environmental level variables:

Macro level variables including urban or rural living, migration (*In which country, i.e. Kazakhstan, Russia or other country, were you born?*), and study site (i.e. *Almaty City, Almaty Area, Kostanay and Kyzylorda*) were examined**.**

Selected macro-structural level variables:

Structural level variables including poverty (*In the past 90 days, have you had a place to sleep?*), access to care (*Do you have a doctor or physician that you can see when you are sick or have a medical problem?*), and healthcare quality (*During any visit to a doctor or another medical professional during the past 12 months, were you advised to quit smoking tobacco?*) were assessed.

Selected treatment outcome measures:

Clinical TB treatment outcomes were categorized as: successful treatment outcome (i.e. *cured and treatment completed*) and unsuccessful treatment outcome (i.e. *died, failure, treatment interruption, continued care and MDR-TB*). TB treatment outcomes were collected and confirmed by chart data collected by health staff. **[Appendix C provides the definitions for each of the treatment outcome responses.]**

Data Analysis

The data were analyzed with Stata (Version 14). Self-reported data collected at baseline were assessed and based on validated measures on individual demographics and behaviors, health status and history, and environmental factors. It should be noted that for the analysis the full study sample size drops from 1600 to 1593 because of missing data. Likewise, for those with TB the available sample size for analysis is 555 instead of 562 as a result of missing data. Clinical TB treatment outcome data collected from TB incident cases were assessed and based on validated measures for TB treatment in Kazakhstan.

CHAPTER 5: RESULTS

Overview of chapter

This chapter presents the multi-level risk and protective factors associated with co-occurring diabetes and TB. Aims 1 and 2 presents the findings from the cross-sectional part of the study, while the results for Aims 3 and 4 include both the cross-sectional component as well as the available clinical data, primarily the final TB treatment outcome results.

Socio-demographic results

To begin with, I present the socio-demographic characteristics of the study sample with available data, n= 1593. The total sample size for the study was 1,600 participants and consists of those with TB only and those without TB. Due to missing data, the sample size for this dissertation analysis was 1,593 (n=7 missing). As shown in Table 2, the 555 individuals with TB accounts for 35% of the s sample. The average age for the sample is about 39 years old. The sample had relative parity between males (54%) and females (46%). But, there are variations in these characteristics by the groups. For example, the TB only group was slightly younger on average, the mean age was 35 years old (SD=13.1) compared to the non-TB group which had a mean age of 41 years old (SD=13.4). Similarly, males (55%) were more common in the TB only group, while females (59%) were more common in the non-TB group. These TB gender differences are consistent with previous studies reporting that generally males are more likely to be at a higher risk for TB (Ko et al., 2016). Finally, income is based on average monthly income, which is on average 40,894 Kazakh Tenge (equivalent to 273 US dollars in 2012).

For both TB and non-TB groups, individuals were more likely to be married or in a common-law relationship, at 62% and 73% respectively. Educational attainment was exactly the same in both groups, as 43% reported having a vocational degree. Unsurprisingly, the majority of respondents in both groups were Kazakh, 77% in the TB group and 75% in the non-TB group. There was not variation in urban or rural residence with the majority, 55% to 57% residing in an urban setting. Out of the four study sites, most of the individuals in both groups were either from Almaty Area (33% for the for both groups) or Kyzlorda (32% for both groups).

Table 2. Socio-demographic characteristics of the 1593 participants (i.e. those with TB and those without TB)

	TOTAL (N=1593)	**TB GROUP (N=555, 35% OF TOTAL SAMPLE)**	**NON- TB GROUP (N=1038, 65% OF TOTAL SAMPLE)**
DIABETES (DM) PREVALENCE			
(YES =1)	3.03% (48)	7.03% (39)	.87% (9)$^{+}$
AGE, MEAN (SD)	38.9 (13.5)	35.4 (13.1)	40.7 (13.4)
18-24	17.07% (272)	26.49% (147)	12.04% (125)
25-34	25.80% (411)	29.19% (162)	23.99% (249)
35-44	21.91% (349)	17.30% (96)	24.37% (253)
45 & OVER	35.21% (561)	27.03% (150)	39.6% (411)
SEX			
FEMALE	53.92% (859)	45.23% (251)	58.57% (608)
MALE	46.08% (734)	54.77% (304)	41.43% (430)
MONTHLY INCOME, MEAN (SD) $^{++}$	40894 (43870)	40987 (57256)	40845 (34668)
MARITAL STATUS			
MARRIED/COMMON LAW	68.74% (1095)	61.62% (342)	72.54% (753)
SINGLE, NEVER MARRIED	18.52% (295)	27.57% (153)	13.68% (142)
DIVORCED/SEPARATED	7.72% (123)	8.47% (47)	7.32% (76)
WIDOWED	5.02% (80)	2.34% (13)	6.45% (67)
EDUCATION			
PRIMARY/SECONDARY	7.66% (122)	7.39% (41)	7.80% (81)
HIGH SCHOOL	28% (446)	30.81% (171)	26.49% (275)
VOCATIONAL	43% (685)	43.06% (239)	42.97% (446)
CURRENT STUDENT/ COMPLETED HIGHER EDUCATION	21.34% (340)	18.74% (104)	22.74% (236)
EMPLOYED			
UNEMPLOYED	41.30% (658)	45.47% (252)	39.11% (406)
EMPLOYED	58.69% (935)	54.59% (303)	60.89% (632)
ETHNICITY			
KAZAKH	76.21% (1204)	76.94% (427)	74.86% (777)
RUSSIAN	15.38% (229)	13.87% (77)	14.64% (152)
OTHER	8.41% (160)	9.19% (51)	10.50% (109)
URBAN/ RURAL			
URBAN	44.35% (694)	45.47% (251)	43.73% (443)
RURAL	55.65% (871)	54.53% (301)	56.27% (570)

SITE			
ALMATY CITY	8.22% (131)	9.55% (53)	7.51% (78)
ALMATY AREA	32.89% (524)	33.33% (185)	32.66% (339)
KYZYLORDA	32.33% (515)	31.53% (175)	32.76% (340)
KOSTANAY	26.55% (423)	25.59% (142)	27.07% (281)

+ OUT OF 1031 RESPONDENTS INSTEAD OF 1,038 DUE TO MISSINGNESS.
++ 1 USD IS EQUIVALENT TO ABOUT 150 KAZAKHSTAN TENGE IN 2011 AND 2012.

AIM 1 FINDINGS: Prevalence of diabetes among those with TB and those without TB

Hypothesis: Diabetes prevalence is higher among individuals with TB than among those without TB.

As previously mentioned, Table 2 presents the socio-demographic characteristics for the study sample. Diabetes prevalence, or the percent of participants who had ever been diagnosed with diabetes, was on average 3.03% (N=48) for the total sample (n=1593). This aggregate statistic, however, masks striking differences in diabetes prevalence by TB status, i.e. TB only and non-TB. For the TB group, diabetes prevalence was about 7.03%, while less than 1% of individuals without TB (i.e. household and community controls) reported having been diagnosed with diabetes. The hypothesis was supported showing that participants with TB compared to those without TB, reported higher percentage of diabetes at 7% and 3%, respectively.

Socio-demographic characteristics of participants reporting diabetes status

For a more detailed assessment of the prevalence of diabetes, I restricted the sample to the participants that reported ‘yes’ to diabetes status (i.e. participants with and without TB who have diabetes) to examine the socio-demographic characteristics of this sub-group (n=48). Table 3 reports the characteristics for those with diabetes-TB and those with diabetes only. As expected the two groups differ on a number of characteristics and show different characteristics from the TB only and non-TB groups from Table 2. Eighty-one percent of the sample reporting diabetes diagnosis (n=48) had both diabetes and TB (n=39) while 19% had diabetes only (n=9). At a glance, there is little difference in average age between the two groups, yet there are more seniors in the diabetes only group with 66.7% (n=6). Gender differences are notable in the two groups as a higher percentage of those with diabetes and TB were male, 54% (n=21), while there are more females in the diabetes only group, 56% (n=5).

The average monthly income was slightly lower for the diabetes-TB group, 34,256 Tenge in comparison to the diabetes only group with an average of 36,089 Tenge. Forty-eight percent (n=19) of the diabetes-TB group had a vocational degree. The diabetes only group had similar percentages for educational level of 33% for high school, vocational and current student or completed higher education. More individuals in the diabetes-TB group reported being employed 54% (n=21), while 44% (n=4) reported the same in the diabetes only group. For rural or urban residence, the findings were the same for both diabetes reporting groups as the majority or 67% reported living in urban settings. Study site distribution showed that the majority of individuals in the diabetes-TB group were in the Almaty Area, 41% (n=16), while for the diabetes only group 33% were from the Almaty Area and Kyzylorda sites, respectively.

Table 3. Socio-demographic characteristics restricted to those who have diabetes (N=48)

	DM & TB (N=39)	DM only N= (9)
Age, mean (SD)	51.82 (11.41)	52.1 (12.75)
18-24	2.56% (1)	--
25-34	7.69% (3)	11.11% (1)
35-44	12.82% (5)	11.11% (1)
45 & over	76.92% (30)	77.78% (7)
Sex		
Female	46.15% (18)	55.56% (5)
Male	53.85% (21)	44.44% (4)
Marital Status		
Married/Common Law	82.05% (32)	88.89% (8)
Single, never married	5.13% (2)	--
Divorced/Separated	5.13% (2)	11.11% (1)
Widowed	7.69% (3)	--
Monthly income, mean (SD)	34256 (34133)	36089 (33585)
Education		
Primary/Secondary	7.69% (3)	--
High School	28.21% (11)	33.33% (3)
Vocational	48.72% (19)	33.33% (3)
Current Student/ Completed Higher Education	15.38% (6)	33.33% (3)
Employed		
Unemployed	46.15% (18)	55.56% (5)
Employed	53.85% (21)	44.44% (4)
Ethnicity		
Kazakh	71.79% (28)	55.56% (5)
Russian	17.95% (7)	22.22% (2)
Other	10.26% (4)	22.22% (2)
Urban/ Rural		
Urban	33.33% (13)	33.33% (3)
Rural	66.67% (26)	66.67% (6)
Site		
Almaty City	5.13% (2)	11.11% (1)
Almaty Area	41.03% (16)	33.33% (3)
Kyzylorda	28.21% (11)	33.33% (3)
Kostanay	25.64% (10)	22.22% (2)

Note: Total sample size for those reporting diabetes status is 48 out of the sample of 1593 individuals analyzed.

Logistic regression analysis to better estimate the diabetes-TB relationship for Aim1

To estimate the relationship between TB and diabetes, Table 4 presents results from regression analysis examining diabetes among those with TB and those without TB. My analysis starts with unconditional Model 1, which does not control for other factors which affect both the dependent variable (diabetes diagnosis) and independent variable (TB group). The odds ratio of TB in Model 1 is 8.6 (CI 4.13-17.85), which indicates that individuals with TB are roughly nine times more likely to have a history of diabetes than those without TB. This association is statistically significant (P-value = 0.000, 99% level). Model 2 adds important non-modifiable demographics (e.g. gender, age, and ethnicity) that can confound the relationship between diabetes and TB (Kamper-Jørgensen et al., 2015; Restrepo & Schlesinger, 2014). Controlling for these non-modifiable demographic characteristics increases the odds ratio to 16.58 (CI 7.50-36.66), which indicates that individuals with TB are roughly seventeen times more likely to report having diabetes than those without TB. Also, the results in Model 2 are in line with previous studies on the association between non-modifiable demographics such as increasing age and the diabetes-TB relationship (Ko et al., 2016). In this analysis, the elderly are more likely to have diabetes.

Finally, I include additional covariates in the fully-specified and preferred Model 3 to control for possible, modifiable covariates that may affect the diabetes and TB relationship. The additional covariates are marital status, employment status, homelessness, urban or rural residence, and study site. The odds ratio of 18.22 suggests that individuals with TB are eighteen times more likely to have diabetes than those without TB. From this analysis, it is noticeable that those who are older, 55 years and older, are more likely to report having diabetes. Also, other covariates are significantly correlated with diabetes. For example, education status becomes statistically significant when all of the covariates are included (as noted in Model 3). Individuals who have a vocational education are about four times (95% CI 1.09-17.37) more likely to report having diabetes; while those who are either students or have a higher educational degree are roughly five times (95% CI 1.13-24.78) more likely to report having diabetes. The association between diabetes and ethnicity is only notable when all covariates are included in the third model with the odds of being non-Kazakh or Russian being roughly two times more likely to be associated with both diseases. This finding however is not statistically significant. It should be noted that all the regression models were run with 1,586 observations, n=14 missing data.

Table 4. Logistic regression of the relationship of diabetes among those with TB and those without TB.

	Model (1)	Model (2)	Model (3)
Outcome variable: Diabetes ever (Yes =1)	OR (SE)	OR (SE)	OR (SE)
TB (TB diagnosis =1)	2.150*** (0.374)	2.808*** (0.405)	2.909*** (0.416)
Gender (Female=0)		-0.117 (0.328	-0.251 (0.352)
Age 18-24 years old		Ref.	Ref.
25-34 years old		1.202 (1.125)	1.113 (1.233)
35-44 years old		2.104* (1.090)	2.083* (1.216)
45-54 years old		2.791*** (1.054)	2.771** (1.223)
55 & over		4.458*** (1.037)	4.620*** (1.211)
Ethnicity Kazakh		Ref.	Ref.
Russian		0.447 (0.393)	0.247 (0.442)
Other		0.464 (0.469)	0.759 (0.501)
Education Primary/Secondary		Ref.	Ref.
High School		0.229 (0.657)	1.234* (0.721)
Vocational		0.365 (0.639)	1.382** (0.699)
Student/ Higher Education		0.271 (0.692)	1.548** (0.776)
Marital Status Married/ Common Law			Ref.
Single, never married			-0.277 (0.867)
Divorced/ Separated			-0.557 (0.667)
Widowed			-0.703 (0.704)
Employment Status			-0.113 (0.354)

Homelessness			-0.416 (0.741)
N^{+}	1586	1586	1586
+ Sample size drops from 1600 to 1586 because of missing data. ***** p<0.001, ** p<0.01, * p<0.05** **Notes: OR refers to odds ratio; SE stands for standard errors**			

AIM 2 FINDINGS: Multi-level factors associated with those with diabetes-TB and those with only TB

Hypothesis: The selected multilevel risk and protective factors (e.g. older age, higher body mass index (BMI), being male, being married or partnered, less education, low healthcare access and utilization, and living in an urban environment) will be strongly associated with co-occurring diabetes-TB.

Using the ecological framework, Table 5 presents the results of a multivariate logistic regression analysis examining the overlapping multilevel risk and protective factors associated with co-occurring diabetes and TB among the available sample of 555 respondents. The four models are based on an incremental inclusion of the ecological framework levels, i.e. individual, community, macro and structural. *The findings from this Aim do not fully support the hypothesis as older age, BMI, urban residence, low healthcare utilization and being born in another country other than Kazakhstan or Russia were the only statistically significant determinants associated with co-occurring diabetes-TB.*

Focusing on the individual level factors only Model 1, shows that age is only significant for individuals in the 45-54 years old (OR 14.29, 95% CI 1.10-185.69) as well as the 55 years and older (OR 80.57, 99% 6.14-1057.05) categories. Also in Model 2, individuals with TB who are obese are five times (95% CI 1.18-24.10) more likely to report having diabetes. This finding is statistically significant at the 95% CI level. Healthcare utilization, as determined by a “yes” response to having been to the doctor in the past 12 months, is 3 times more likely to be associated with higher odds of having diabetes-TB and is statistically significant at the 95% CI level (1.14-7.53). Alcohol use is associated with roughly two times odds of having both diseases;

however, this find is not statistically significant, (OR 2.20, P-value 0.104). Additionally, being male is associated with roughly 20% lower odds of having co-occurring diabetes-TB but this finding is also not statistically significant (OR 0.84, P-value 0.752).

In Model 2, individual and community level (i.e. social support and whether smoking is allowed in the home) factors are included and show that each of the statistically significant factors noted in Model 1 remain significant (i.e. older age, BMI and healthcare utilization). The inclusion of these variables does not change the model outcomes much with the exception that the odds for healthcare utilization increases and is four times more likely to be associated with co-occurring diabetes-TB. In addition to being obese, being overweight is also significant at the 95% CI level (OR 4.38, 1.12-17.17).

For Model 3, individual, community and macro level factors (i.e. urban or rural residence, study site, and migration as determined by country of birth) are examined. As previously noted in the preceding models, age, BMI (at the obese category only) and healthcare utilization remain statistically significant. Macro level variables for 'urban or rural residence' (OR 3.29, CI 1.20-9.06) and 'birth country' (OR 4.49, CI 1.16-17.47) were statistically significant at the 95% CI level. Country of birth being other than Russia or Kazakhstan (e.g. Uzbekistan, China) was about four times more likely to be associated with both diabetes and TB.

Model 4 includes the four levels (i.e. individual, community, macro and structural) and the findings remain the same as in Model 3 even with the inclusion of the poverty measure (homelessness in past 90 days), healthcare quality and 'access to care' variables. Specifically, being 45 years old and above, obese, having been to the doctor in the past 12 months, urban residence, and being born in a country other than Kazakhstan or Russia were associated with higher odds of having co-occurring diabetes-TB and were all statistically significant. Of note, in this final model being male having normal BMI, reporting ever smoking tobacco, being in either of the high or low burdened TB study sites, reporting homelessness in the past 90 days, being advised by a healthcare professional to quit smoking, and having a physician were not statistically significant and were all associated with lower odds of having both diseases. The findings of lower odds with co-occurring diabetes-TB with the male gender, family TB history, tobacco smoking history and homelessness is strikingly notable as previous studies have found that these are significant risk factors for having both diseases (Girardi et al., 2017; Lee et al., 2017; Martínez-Aguilar et al., 2015; Montgomery, 1912).

Table 5. Multivariate analysis of the associated risk and protective factors among those with diabetes-TB and those with only TB.

	Model 1 [Individual: non-modifiable factors]	Model 2 [Individual: non-modifiable + modifiable]	Model 3 [Individual + Community]	Model 4 [Individual + Community + Macro]	Model 5 [Individual + Community + Macro + Structural]
Outcome variable: Diabetes ever (yes = 1)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Gender (Female=0)	-0.331 (0.373)	-0.178 (0.562)	-0.282 (0.580)	-0.253 (0.606)	-0.269 (0.609)
Age					
18-24 years old	Ref.	Ref.	Ref.	Ref.	Ref.
25-34 years old	0.926 (1.165)	0.989 (1.324)	1.267 (1.371)	1.562 (1.389)	1.415 (1.423)
35-44 years old	2.035* (1.108)	1.991 (1.283)	2.309* (1.351)	2.501* (1.371)	2.384* (1.390)
45-54 years old	2.828*** (1.061)	2.659** (1.309)	3.011** (1.372)	3.419** (1.415)	3.454** (1.443)
55 years old & over	4.400*** (1.047)	4.389*** (1.313)	4.639*** (1.374)	4.889*** (1.419)	4.849*** (1.439)
Ethnicity					
Kazakh	Ref.	Ref.	Ref.	Ref.	Ref.
Russian	0.0600 (0.492)	-0.249 (0.618)	-0.232 (0.668)	0.284 (0.708)	0.339 (0.718)
Other	0.412 (0.608)	0.622 (0.672)	0.546 (0.705)	0.854 (0.747)	0.839 (0.766)
TB Family History (Yes=1)	-0.365 (0.543)	-0.674 (0.610)	-0.922 (0.647)	-1.206* (0.696)	-1.316* (0.725)
Marital Status					
Married/ Common Law		Ref.	Ref.	Ref.	Ref.
Single, never married		-0.0138 (0.940)	0.308 (0.982)	0.620 (1.004)	0.604 (1.026)
Divorced/ Separated		-0.481 (0.850)	-0.0395 (0.865)	0.126 (0.900)	0.297 (0.916)
Widowed		0.286 (0.910)	0.651 (0.923)	0.181 (0.951)	0.0308 (0.975)
Education					
Primary/Secondary		Ref.	Ref.	Ref.	Ref.
High School		0.639 (0.810)	0.473 (0.821)	0.560 (0.855)	0.438 (0.872)
Vocational		1.012 (0.776)	0.756 (0.803)	1.105 (0.857)	0.876 (0.884)

Student/ Higher Education		0.925 (0.927)	0.884 (0.940)	1.451 (1.020)	1.348 (1.030)
Employment Status		-0.195 (0.459)	-0.260 (0.479)	-0.00417 (0.509)	-0.0136 (0.518)
BMI **Underweight**		Ref.	Ref.	Ref.	Ref.
Normal		-0.150 (0.621)	-0.0679 (0.633)	-0.578 (0.671)	-0.545 (0.697)
Overweight		1.276* (0.679)	1.555** (0.705)	1.152 (0.733)	1.211 (0.749)
Obese		1.675** (0.769)	2.178*** (0.820)	2.309*** (0.859)	2.330*** (0.884)
Consume vegetable & fruits daily (Nutritional status)		0.294* (0.166)	0.263 (0.167)	0.245 (0.171)	0.228 (0.175)
Physical fitness self-rating		0.353 (0.316)	0.332 (0.333)	0.361 (0.358)	0.430 (0.381)
Ever Smoked Tobacco		-0.425 (0.580)	-0.321 (0.596)	-0.453 (0.645)	-0.334 (0.655)
Alcohol Use (Ever)		0.790 (0.485)	0.774 (0.501)	0.954* (0.538)	0.990* (0.543)
Been to doctor past 12 months (Healthcare utilization)		1.074** (0.482)	1.016* (0.564)	1.212** (0.612)	1.248** (0.618)
Social support (MSPSS) total score			0.561* (0.337)	0.502 (0.349)	0.610 (0.377)
Smoking allowed at home (Smoking norms)			1.348 (0.940)	1.627* (0.941)	1.711* (0.957)
Current residence type (Current living condition)			-0.377 (0.290)	-0.438 (0.365)	-0.370 (0.371)
Urban or rural residence				1.158** (0.559)	1.170** (0.566)
Study site **Almaty City (High TB burden)**				Ref.	Ref.
Almaty Area (Low TB burden)				0.160 (1.069)	0.0616 (1.083)
Kyzylorda (High TB burden)				0.0423 (1.178)	-0.297 (1.231)
Kostanay (Low TB burden)				-0.556 (1.080)	-0.450 (1.097)
Which country born (Migration)				0.738** (0.346)	0.710** (0.345)
Homeless within past 90 days					-0.373 (1.152)

Advised by doctor to quit smoking past 12 months (Healthcare quality)					-0.572 (0.624)
Have physician see when sick (Access to care)					-0.545 (0.690)
N+	**555**	**538**	**538**	**536**	**536**

+ Sample size differences due to missing data.
Standard errors in parentheses.
***** p<0.01, ** p<0.05, * p<0.1**

AIM 3 FINDINGS: Clinical TB treatment outcomes among the TB only and diabetes-TB group

Hypothesis: *Individuals with co-occurring diabetes-TB will more than likely have a higher percentage of unsuccessful TB treatment outcomes.*

Table 6 presents descriptive statistics of socio-demographic differences for TB treatment outcomes. Among those with unsuccessful TB treatment outcome, more individuals reported "no" to having been diagnosed with diabetes than those reporting "yes" to diabetes ever, 94% and 6% respectively. Likewise, the percentage of individuals reporting "yes" to diabetes diagnosis in the successful TB treatment outcome category was 93 % while those reporting "no" to diabetes diagnosis was 7%. *Thus, these null findings do not support the hypothesis that individuals with co-occurring diabetes-TB are more likely to have unsuccessful TB treatment outcomes*.

Table 6. Socio-demographic characteristics comparison of successful and unsuccessful TB treatment outcomes for those with TB

	Successful TB Treatment (N=454)	Unsuccessful TB Treatment (N=65)
Diabetes (DM) prevalence		
DM ever (Yes)	6.83% (31)	6.15% (4)
DM ever (No)	93.17 (423)	93.85% (61)
Age, mean (SD)	2.53 (1.33)	2.48 (1.13)
18-24 years old	27.53% (125)	24.62% (16)
25-34 years old	29.52% (134)	26.15% (17)
35-44 years old	15.64% (71)	29.23% (19)
45 years old & over	27.31% (124)	20% (13)
Sex		
Female	46.92% (213)	35.38% (23)
Male	53.08% (241)	64.62% (42)
Marital Status		
Married/Common Law	60.34% (274)	58.46% (38)
Single, never married	28.63% (130)	27.69% (18)
Divorced/Separated	8.37% (38)	12.31% (8)
Widowed	2.64% (12)	1.54% (1)
TB family history		
Yes	21.59% (98)	26.15% (17
No	78.41% (356)	73.85% (48)
Education		
Primary/Secondary	7.93% (36)	4.62% (3)
High School	33.04% (150)	23.08% (15)
Vocational	39.43% (179)	60% (39)
Current Student/ Completed Higher Education	19.60% (89)	12.31% (8)

Employed		
Unemployed	45.59% (207)	44.62% (29)
Employed	54.41% (247)	55.38% (36)
Ethnicity		
Kazakh	76.21% (346)	81.54% (53)
Russian	14.32% (65)	10.77% (7)
Other	9.47% (43)	7.69% (5)
Urban/ Rural		
Urban	44.57% (201)	55.38% (36)
Rural	55.43% (250)	44.62% (29)
Study site		
Almaty City	8.81% (40)	13.85% (9)
Almaty Area	36.78% (167)	12.31% (8)
Kyzylorda	29.74% (135)	40% (26)
Kostanay	24.67% (112)	33.85% (22)

Notes: Total sample for individuals with TB with clinical TB treatment outcomes is 519 from the total sample of 562 individuals with TB.

AIM 4 FINDINGS: Multi-level factors of TB treatment outcomes among the TB only and diabetes-TB groups

Hypothesis: At each of the ecological levels, the selected multi-level risk and protective factors (e.g. increased substance use, poor diet, low physical activity, being a migrant, living in an urban setting, poor healthcare quality, poor smoking norms, low healthcare access and utilization) will be associated with unsuccessful TB treatment outcomes among those with co-occurring diabetes-TB.

Table 7 presents the findings for the associated risk and protective factors among those with successful TB treatment outcome and those with unsuccessful TB treatment outcome when reported diabetes diagnosis is considered. Similar to Aim 2, the results are shown using an ecological framework approach, i.e. including specific variables incrementally. Model 1 shows only the individual level factors and similar to the findings from Aim 2, age is statistically significant at the 99% CI for individuals 55 years and older (OR 114.21, CI 7.85-1660.79). Likewise, being obese was nine times more likely to be associated with both diseases (CI 1.69-43.34 at the 99% level) and having successful treatment outcomes. Nutritional status was also significant at the 95% CI and had an odds ratio of 1.81 (CI 1.06-3.08) i.e. consuming vegetables and fruits on a daily basis (nutritional status) was almost 2 times more likely to be associated with having both diseases and successful treatment outcome. For Model 2, community level variables (e.g. social support and 'whether smoking is allowed in the home') are included in the model with individual level variables. For this model, older age (55 years and above), obese status, nutritional status and healthcare utilization remain statistically significant and have higher odds of being associated with reporting "yes" to diabetes and being successful in TB treatment outcome.

In Model 3, urban residence (OR 3.96, P-value 0.21) and migration status (OR 5.86, P-value 0.018) have higher odds of being associated with having diabetes and successful treatment outcome and are statistically significant in addition to the determinants from Models 1 and 2, which remained statistically significant yet again. With Model 4, the same trends for higher odds and statistical significance remain the same as with the findings from Aim 2. While TB treatment outcome does not have an effect on having both diseases, reporting a family history of TB, being normal weight, ever smoking tobacco, study site, healthcare quality, homelessness, and access to care are associated with lower odds of having co-occurring diabetes-TB.

Table 7. Multivariate analysis of associated risk and protective factors of the relationship of diabetes among those with successful and unsuccessful TB treatment outcomes.

	Model 1	Model 2	Model 3	Model 4	Model 5
	[Individual: non-modifiable factors]	[Individual: non-modifiable + modifiable]	[Individual + Community]	[Individual + Community + Macro]	[Individual + Community + Macro + Structural]
Outcome variable: Diabetes ever (Yes=1)	**OR (SE)**	**OR (SE)**	**OR (SE)**	**OR (SE)**	**OR (SE)**
Final TB treatment outcome (Unsuccessful = 0)	-0.372	0.363	0.399	0.105	0.162
	(0.612)	(0.745)	(0.764)	(0.814)	(0.838)
Gender (Female = 0)	-0.224	0.413	0.330	0.432	0.430
	(0.397)	(0.598)	(0.617)	(0.645)	(0.650)
Age					
18-24 years old	Ref.	Ref.	Ref.	Ref.	Ref.
25-34 years old	0.936	0.971	1.374	1.655	1.458
	(1.166)	(1.337)	(1.412)	(1.431)	(1.454)
35-44 years old	2.000*	1.986	2.384*	2.584*	2.386*
	(1.112)	(1.306)	(1.407)	(1.427)	(1.440)
45-54 years old	2.425**	2.322*	2.780*	3.294**	3.276**
	(1.083)	(1.352)	(1.448)	(1.488)	(1.497)
55 years old & over	4.428***	4.594***	4.896***	5.405***	5.333***
	(1.051)	(1.341)	(1.439)	(1.504)	(1.506)
Ethnicity					
Kazakh	Ref.	Ref.	Ref.	Ref.	Ref.
Russian	0.356	0.320	0.216	0.807	0.896
	(0.514)	(0.653)	(0.689)	(0.742)	(0.762)
Other	0.550	1.028	0.828	1.221	1.139
	(0.622)	(0.698)	(0.728)	(0.786)	(0.807)
TB family history (Yes=1)	-0.280	-0.445	-0.715	-1.070	-1.165
	(0.555)	(0.624)	(0.662)	(0.734)	(0.760)
Marital Status					
Married/Common Law		Ref.	Ref.	Ref.	Ref.

Single, never married		-0.0947	0.295	0.738	0.730
		(0.949)	(1.003)	(1.049)	(1.064)
Divorced/Separated		-0.205	0.167	0.464	0.665
		(0.868)	(0.887)	(0.926)	(0.946)
Widowed		0.351	0.708	0.106	0.00250
		(0.948)	(0.972)	(1.011)	(1.035)
Education					
Primary/Secondary		Ref.	Ref.	Ref.	Ref.
High School		0.456	0.299	0.396	0.320
		(0.839)	(0.849)	(0.910)	(0.935)
Vocational		0.919	0.690	1.153	0.987
		(0.815)	(0.841)	(0.937)	(0.977)
Current Student/ Completed Higher Education		0.914	0.805	1.565	1.513
		(0.990)	(1.007)	(1.142)	(1.158)
Employment		-0.0550	-0.124	0.0490	-0.0268
		(0.511)	(0.530)	(0.564)	(0.575)
BMI					
Underweight		Ref.	Ref.	Ref.	Ref.
Normal		-0.173	-0.0377	-0.639	-0.677
		(0.649)	(0.665)	(0.723)	(0.749)
Overweight		0.889	1.137	0.603	0.608
		(0.746)	(0.764)	(0.829)	(0.842)
Obese		2.133***	2.678***	2.968***	2.951***
		(0.826)	(0.881)	(0.968)	(0.987)
Consume vegetable & fruits daily (Nutritional status)		0.589**	0.532**	0.534**	0.526**
		(0.273)	(0.248)	(0.249)	(0.255)
Physical fitness self-rating		0.247	0.225	0.287	0.323
		(0.329)	(0.338)	(0.366)	(0.398)
Ever Smoked Tobacco		-0.768	-0.776	-1.022	-0.919
		(0.616)	(0.631)	(0.710)	(0.727)
Alcohol Use (Ever)		0.564	0.583	0.889	0.944
		(0.537)	(0.558)	(0.615)	(0.626)

Been to doctor past 12 months (Healthcare utilization)		1.123**	0.910	1.219*	1.282*
		(0.545)	(0.629)	(0.701)	(0.722)
Social support (MSPSS) total score			0.479	0.458	0.584
			(0.367)	(0.389)	(0.424)
Smoking allowed at home (Smoking norms)			1.344	1.832*	1.929*
			(0.966)	(0.992)	(1.010)
Current residence type (Current living condition)			-0.490	-0.487	-0.418
			(0.325)	(0.401)	(0.410)
Urban or rural residence				1.339**	1.362**
				(0.647)	(0.656)
Which country born (Migration)				0.845**	0.806**
				(0.374)	(0.376)
Study site					
Almaty City (High TB burden)				Ref.	Ref.
Almaty Area (Low TB burden)				0.104	0.0282
				(1.214)	(1.230)
Kyzylorda (High TB burden)				-0.397	-0.637
				(1.269)	(1.322)
Kostanay (Low TB burden)				-0.917	-0.878
				(1.221)	(1.261)
Homeless within past 90 days					-0.0960
					(1.170)
Advised by doctor to quit smoking past 12 months (Healthcare quality)					-0.373
					(0.676)

Have physician see when sick (Access to care)					-0.734
					(0.736)
N+	519	504	504	502	502
+ Sample size differences due to missing data. Standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1					

CHAPTER 6: DISCUSSION & CONCLUSION

Overview of the chapter

This the first study to examine the multi-level risk and protective factors associated with diabetes prevalence among newly diagnosed TB cases in Kazakhstan. In general, the study findings support previous research conducted in Kazakhstan which indicate that diabetes is an important and significant, independent risk factor for individuals with TB among the current study sample as 7% of participants reported having diabetes (Davis et al., 2017; Hermosilla et al., 2017). Crude analysis showed that individuals with TB had roughly nine times higher odds of having diabetes than those without TB. This association supported the hypothesis of the current study that diabetes prevalence would be higher among those with TB than those without.

The findings also show that diabetes prevalence is not associated with unsuccessful TB treatment outcomes. Although this finding is contrary to the hypothesis that individuals with co-occurring diabetes-TB will more likely have unsuccessful TB treatment outcome, this 'no association' is consistent with other studies (Cavanaugh et al., 2015). In the following sections of this chapter, a more focused discussion on the multilevel risk and protective factors associated with both diseases is provided.

Multilevel risk and protective factors associated with co-occurring diabetes and TB

*Individual and interpersonal level factor*s

Study findings support previous research noting that age as a non-modifiable risk factor is significantly associated with co-occurring diabetes and TB. In this study, being 45 years old and above was significantly associated with having both diseases, with the odds increasing for those with diabetes-TB and as age increased. This association was significant even as additional covariates were included for each ecological level. While other studies have found that increasing rates of diabetes among TB patients was more pronounced among individuals 40 years and younger (Zheng et al., 2017), the current study's finding of older age having a stronger association with diabetes-TB has also been observed in previous studies (M. Magee et al., 2013; Manjareeka, Palo, Swain, Pati, & Pati, 2016; Workneh et al., 2016). Using a nationwide population-based study, Ko et al. (2016) noted that the stronger association of older age with co-occurring diabetes-TB may be as result of the higher risk of developing diabetes with older age.

In addition to older age, being obese and reporting 'yes' to seeing a doctor in the past 12 months (used here as a marker for healthcare utilization) were statistically significant across all models and levels and had higher odds of being associated with both diabetes and TB. These findings are consistent with other studies that found the same regarding higher BMI (e.g. being obese) (Alisjahbana et al., 2007) and being older (Anthonia Okeoghene Ogbera et al., 2015; Ruslami, Aarnoutse, Alisjahbana, Van Der Ven, & Van Crevel, 2010). It is notable that although other studies have found a significant association with co-occurring diabetes-TB and several individual level factors such as gender, ethnicity, family history of TB, marital status, education level, employment status, physical fitness rating, smoking ever and alcohol use (ever), in this sample none of these factors were found to be significantly associated with both diseases. The finding of no statistical significance and lower odds of having both diseases as a male is particularly striking as some studies have found being female to be associated with both diseases (Perez, Brown, & Restrepo, 2006) while other studies have found that being male was strongly associated with diabetes-TB (Lee et al., 2017; Tahir et al., 2016). Unlike the current study, previous studies have found that among those with newly diagnosed pulmonary TB no significant association between gender and having diabetes existed (Manjareeka et al., 2016). Tahir et al. (2016) found that although gender, occupation and smoking were not associated with diabetes-TB, age and education were significantly associated with the co-occurrence of both diseases. Despite other studies highlighting nutritional status as a risk for diabetes and potential risk for TB (Dye et al., 2011), in the current study reported nutritional status was not statistically significant nor was it associated with both diseases.

Community/ environmental and macro-structural level factors

When macro (e.g. urban or rural residence, migration and study site) and structural (e.g. poverty, healthcare quality and access to care) level factors were included in the model, urban residence and being born in another country (migration status) were shown to be statistically significant. Urban residence was found to be associated with diabetes diagnosis among those with TB with the odds being about 3 times more likely; while being born in another country (e.g. Uzbekistan, China) was roughly 4 times more likely to be associated with both diseases. This finding of an association between migration status and diabetes-TB co-occurrence is noteworthy as several studies have found migrant or foreign-born status to be significantly associated with both diseases (Caraffa et al., 2016; Girardi et al., 2017). In the current study, a small population (n=41 or 7% of the 555 participants analyzed) reported being born in another country. Given the increasing prevalence of migrants in upper middle-income countries like Kazakhstan (Ismayilova et al., 2014; Kumparatana, Cournos, Terlikbayeva, Rozental, & Gilbert, 2017), more research is needed on the co-occurrence of diabetes and TB in this vulnerable population.

Diabetes and TB treatment outcome

It is noteworthy that for this study roughly 89% of those with reported treatment outcomes were successful. This finding is similar to current estimates from Kazakhstan which shows that out of a cohort of 12,473 new and relapse TB cases, 90% had successful treatment outcomes in 2014 (Organization, 2016d). The findings for the multi-level risk and protective factors associated with TB treatment outcome and reporting diabetes diagnosis remained the same as those mentioned for TB status. Specifically, individuals with successful TB treatment outcome who reported having diabetes were more likely to be older, be obese, consume fruits and vegetables daily, report healthcare utilization in the past 12 months, live in an urban environment and have been in a country other than Kazakhstan or Russia. Interestingly enough, *the results show that TB treatment outcome is not associated with diabetes diagnosis in this sample*.

This finding of no association or significance regarding diabetes diagnosis on TB treatment outcome is similar to previous studies (Baghaei, Marjani, Javanmard, Tabarsi, & Masjedi, 2013; Cavanaugh et al., 2015; Dooley et al., 2009). However, inconsistencies remain in the literature surrounding the impact of diabetes on TB treatment outcome as other studies have found that diabetes diagnosis was associated with unsuccessful TB treatment outcome (Lee et al., 2017; Mukhtar & Butt, 2016a; Perez-Navarro et al., 2017; Zheng et al., 2017). More research is critically needed in settings with high TB burden to better understanding this potential association. Factors such as age (55 years and above) and being obese were strongly associated and statistically significant for those that reported diabetes diagnosis and had successful treatment outcome. A noticeable difference with the TB treatment outcome findings is that consuming vegetables and fruits daily was statistically significant and had roughly two times the odds of being associated with reported diabetes diagnosis and successful TB treatment outcome.

Conclusion

Study findings support previous studies in that the prevalence of diabetes is noticeably higher for those with TB than individuals without TB. More importantly, diabetes was found to be associated with nine times the odds of having TB. Considering the three main objectives outlined by the Collaborative Framework, these findings suggests that more research on the co-occurrence of this relationship in high TB burdened regions similar to Kazakhstan are urgently needed. Of particular note, objective three of the Collaborative Framework (2011), i.e. “to detect and manage diabetes in patients with TB”, highlights the significance of the high prevalence of diabetes among those with TB within this sample and the need to screen TB patients for diabetes in settings like Kazakhstan which have a higher burden of MDR-TB. The need to further study the potential association between diabetes and MDR-TB Kazakhstan is especially important given the fact that diabetes has been noted as a risk for developing MDR-TB (Fisher-Hoch et al., 2008).

For individuals with both diseases, it is notable that being older (45 years and above), obese and healthcare utilization with a 12-month period are significantly associated with co-occurring diabetes in this study. These results point to the need to conduct robust, longitudinal studies that focus on the overlapping risk and protective determinants associated with both diseases in order to better understand whether these factors are specific to certain settings or generalizable to all settings with high TB burdens. Moreover, the finding of no association between diabetes status and unsuccessful TB treatment is of particular significance as a number of findings have found that diabetes is associated with unsuccessful treatment outcomes (Jeon et al., 2012; Jiménez-Corona et al., 2012; Perez-Navarro et al., 2017) and only a limited number (this study included) have found no association between diabetes and TB treatment outcome (Cavanaugh et al., 2015; M. Magee et al., 2013).

Finally, the findings from the current study show the importance of establishing better healthcare systems which address the dual burden of diseases. As previously mentioned, Kazakhstan, despite being an upper-middle income country, has a health care system that is not well-equipped to address the burden of co-occurring diseases (Adambekov et al., 2015). In their discussion of the health challenges in Kazakhstan and throughout Central Asia, Adambekov and colleagues (2015) mention the double burden of chronic and infectious diseases as one of the major health systems' challenges within the region. Hence, the results of the current study point to a number of areas of intersection for addressing this dual burden (e.g. focusing on individual level factors as well as macro level factors such as urban residence and migration history) – all of which are important for future research on the co-occurrence of both diseases globally.

Study limitations and strengths

Although this study is the first to critically examine the relationship of diabetes and TB in Kazakhstan, there are some recognizable limitations which must be addressed in future research. Due to the cross-sectional design of the collected data, temporality and causal associations between diabetes and TB cannot be determined. This limitation suggests the need for developing longitudinal studies focused on the co-occurrence of both diseases and with consideration for the assessment of multilevel risk and protective determinants at each time period. One such study that included a longitudinal study design discovered that TB risk is higher during the first two years after the diagnosis of diabetes; while no significant effect was noted subsequently (Kamper-Jørgensen et al., 2015; Sotgiu et al., 2015). Another weakness of the current study is that the small sample for those with co-occurring diabetes may bias the results, leading to an overestimation of the findings. Moreover, clinical confirmation of diabetes history, including blood glucose control was not collected as diagnosis was based on self-reported data. This may lead to an underestimation of the actual frequency of diabetes prevalence (Delgado-Sánchez et al., 2015). Survey measures are based on self-reported data and may result in response bias. Finally, TB incidence cases were limited to those with access to Kazakhstan's National

Tuberculosis Program and who met the study eligibility criteria, thus excluding all incident TB-positive patients living alone or without access to TB care.

Withstanding these limitations there are several strengths of the current study. This study is the first to examine the relationship between diabetes and TB in Kazakhstan and the only such study that focuses on the multilevel risk AND protective factors of this disease interaction. The inclusion of additional variables into the multivariate models strengthens the findings as omitted variable bias is reduced as a result. Study findings showing a high risk of diabetes among those with TB is critical for the control and management of TB in settings like Kazakhstan which have a high TB burden and increasing prevalence of diabetes. Additionally, the finding that diabetes diagnosis is not associated with unsuccessful TB treatment outcome is highly relevant for further research as this finding may indicate particular factors that could lead to successful TB treatment outcomes for those with co-occurring diabetes and TB.

CHAPTER 7: STUDY IMPLICATIONS

Social Work Practice and Policy

The findings from the current study places more emphasis on the need for multidisciplinary teams, including social work practitioners and researchers, to address the multilevel determinants associated with co-occurring diabetes and TB. More importantly, the findings will inform interventions on the multilevel risk and protective factors associated with disease co-occurrence. As noted by Sallis et al. (2008), interventions that address multilevel risk and protective determinants of health outcomes are more robust in that they tend to have more long-term, population wide effects. Social work researchers and practitioners are well-equipped to not only address the risks associated with negative health outcomes but to also include the protective factors that contribute to positive health outcomes. The findings also point to the need for more research and policies on how to best integrate diabetes-TB into healthcare systems in low-resourced settings or regions wherein either disease is more common and the other is increasing in prevalence. As such, the findings from this study support public health policies to address co-occurring disease issues and encourages multidisciplinary collaborations in research, policy and practice with emphasis on prevention and intervention outcomes for individuals and populations burdened by both diseases.

Global health policy and research

Study findings from this dissertation will have implications on a number of areas of concern regarding the global burden co-occurrence of diabetes and TB such as: 1) the actual prevalence of diabetes co-occurrence in a high TB burdened setting and 2) multilevel multi-level risk and protective factors that may contribute to co-occurring diabetes and tuberculosis. Co-occurring diseases like diabetes and TB are steadily on the rise and more studies like the current study are warranted to advance health policy regarding integrated intervention and prevention care and management. Globally, national programs addressing the joint burden are in dire need in settings with higher or increasing burdens of either disease (Kapur, 2016; Odone, Houben, White, & Lönnroth, 2014) and empirical studies like the current study provide more evidence for the need to integrate bi-directional screenings programs within healthcare systems. Such a program has been implemented in India – a country which has the highest burden of TB and the second highest burden of diabetes worldwide – to focus on screening TB patients for diabetes and has been successful (Kumar et al., 2014). More importantly, the findings underscore several of the recommendations provided by the World Health Organization (WHO) and the International Union Against Tuberculosis & Lung Disease's joint framework on diabetes and TB. For example, the need to increase awareness of and knowledge about the interactions between diabetes and TB, i.e. the joint risk factors, and the promotion of the management of diabetes in TB patients. This study also gives priority to the key determinants that global health practitioners can systematically intervene on, thereby helping to establish better standards of integrated care for both diseases.

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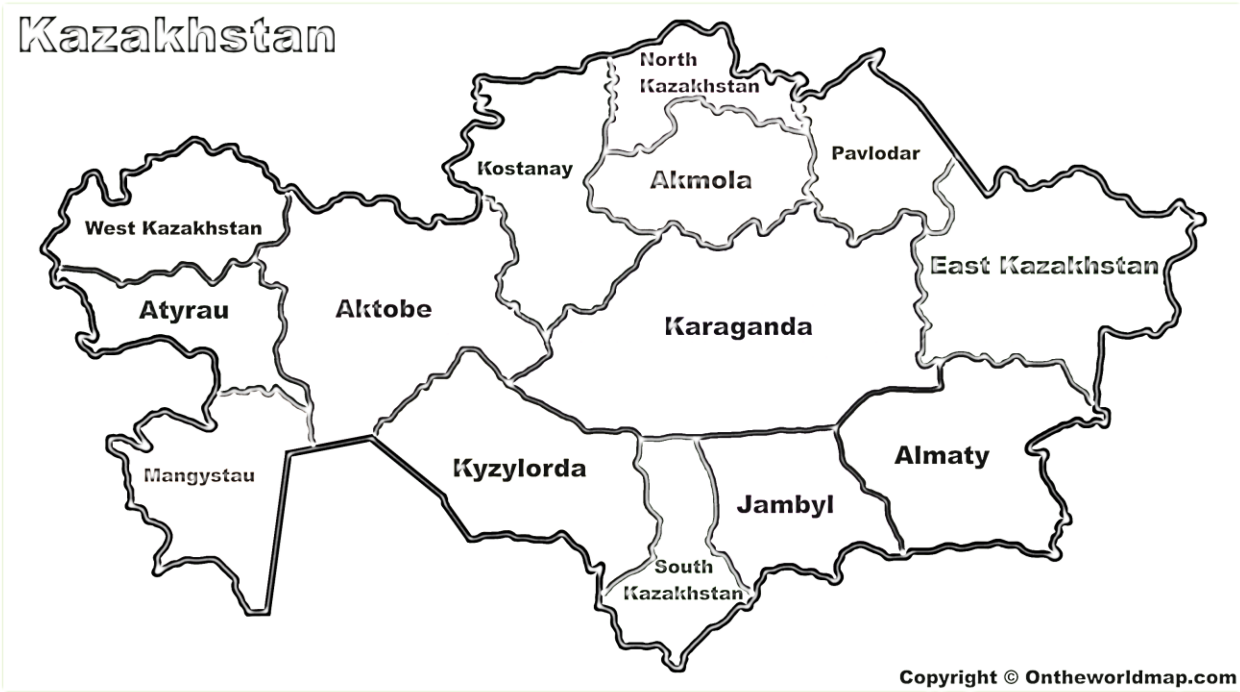
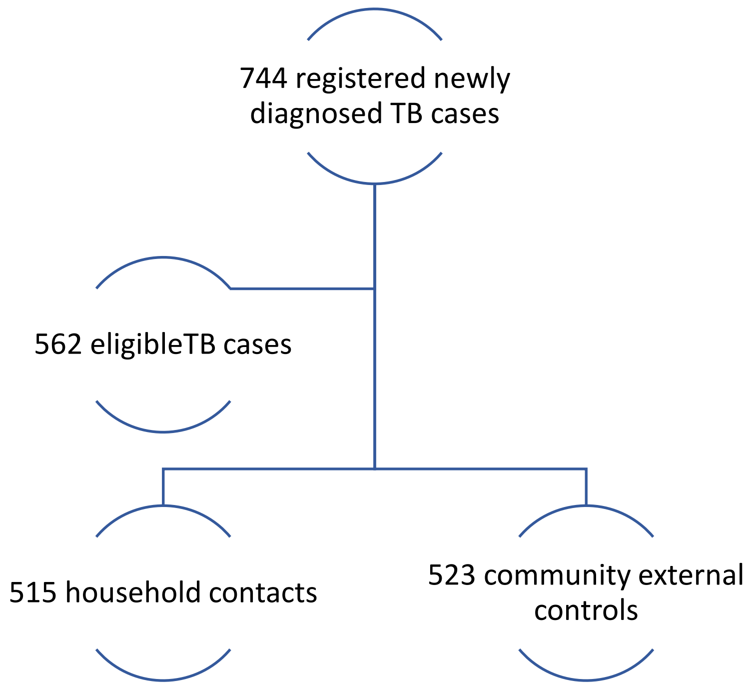
Appendix A. Map of Kazakhstan showing the four study regions



Appendix B. TB Project participant flow diagram (total sample of 1600).



Appendix C. Definitions for each of the treatment outcome responses

Treatment outcome	Definition
Cured	Bacterioscopy result was negative at the end of treatment and in two previous tests
Treatment completed	A patient has received all prescribed dozes of TB drugs within the fixed time period, but does not meet "cured" or "failed treatment" criteria
Failed treatment	A patient is still smear positive at the 5th month of treatment and later, or initially negative microscopy result became positive after intensive treatment phase
Regimen violation	A patient interrupted treatment for 2 and more moths
Died	A patient has died in the course of treatment irrespectively of the cause of death
Transferred	A patient has dropped out of treatment facility's observation and is now under observation of another facility, and his/her treatment outcome is unknown. ***Note***: treatment outcome must be reported to the region where a patient came from (where the treatment was initiated)
Transferred to Category IV	A participant has multidrug resistant form of TB (minimum to HR)
Note: Combination of "treatment completed" and "cured" is considered to be an indicator of successful treatment and all others are considered unsuccessful treatment.	