Aus dem Koordinierungszentrum für klinische Studien

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Geography of diabetes complications and quality of diabetes care in Mexico, a cross-sectional analysis of the Health and Nutrition Survey ENSANUT 2012

Inaugural-Dissertation

zur Erlangung des Doktorgrades der gesamten Humanmedizin

dem Fachbereich Medizin der Philipps-Universität Marburg

vorgelegt von

Fauve Linssen aus Worms,

Marburg, 2019

Angenommen vom Fachbereich Humanmedizin der Philipps-Universität

Marburg am: 16.08.2019

Gedruckt mit Genehmigung des Fachbereichs

Dekan: Prof. Dr. Helmut Schäfer

Referent: Herr PD Dr. J.-P. Reese

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"It is unreasonable to expect that people will change their behavior easily when so many forces in the social, cultural, and physical environment conspire against such change. If successful programs are to be developed to prevent disease and improve health, attention must be given not only to the behavior of individuals, but also to the environmental context within which people live" (Institute of Medicine, 2000)[1].

[1] Smedley BD and Syme LS. Promoting Health. Intervention Strategies from Social and Behavioral Research. Washington: Institute of Medicine; 2000: 5

Abbreviations

DALY	Disability Adjusted Life Years
DF	Diabetic Foot
DKD	Diabetic Kidney Disease
DN	Diabetic Neuropathy
DPN	Distal Polyneuropathy
DR	Diabetic Retinopathy
ENSANUT	ENcuesta NAcional de SAlud y NUTrición
ESRD	End-Stage Renal Disease
et al.	et alia
Etc.	Et Cetera
HCR	states with High Complication Rates
i.a.	inter alia
ICR	states with Intermediate Complication Rates
IMSS	Instituto Mexicano de Salud Social
ISSSTE	Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado
KDOQI	Kidney Disease Outcome Quality Initiative
KEEP	Kidney Early Evaluation Program
LCR	states with light complication rates
LEA	Lower Extremity Amputation
LMIC	Low- and Middle Income Country
MA	Macroalbuminuria
MiA	Microalbuminuria
n.a.	not available
PDR	Proliferative Diabetic Retinopathy
PVD	Peripheral Vascular Disease
resp.	respectively
SES	socioeconomic status
SP	Seguro Popular (Public health care)
T2DM	Type 2 Diabetes Mellitus

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Zusammenfassung (deutsche Version)

Der größer werdende Anteil mikrovaskulärer Diabeteskomplikationen ist ein zunehmendes Problem in der mexikanischen Bevölkerung. Dabei sind Menschen in einkommensschwachen- und strukturell benachteiligten Regionen einem höheren Risiko ausgesetzt, früher an Diabeteskomplikationen zu erkranken. Um die Rate neu aufgetretener Diabeteskomplikationen effektiv zu reduzieren, ist eine frühzeitige Diagnosestellung und medizinische Betreuung notwendig. Jedoch konnte eine umfassende Diabetesversorgung in einkommensschwachen und abgelegenen Regionen Mexiko's bisher nicht umgesetzt werden.

Das Ziel dieser Studie ist, herauszufinden, inwiefern soziale- und geopolitische Faktoren die Inanspruchnahme präventiver Maßnahmen und damit die Entwicklung diabetischer Komplikationen beeinflussen.
Zu diesem Zwecke werden im Folgenden die Punkte i-iii untersucht:
i) Sozioökonomische Unterschiede zwischen Diabetikern mit und ohne Diabeteskomplikationen.
ii) Einflussfaktoren auf das Vorhandensein von Diabeteskomplikationen auf regionaler- und Bundeslandebene.
iii) Einfluss ländlicher Herkunft auf die Inanspruchnahme präventiver Maßnahmen und das Vorhandensein von Diabeteskomplikationen.

Dafür benutzten wir Querschnittsdaten der mexikanischen Gesundheits- und Ernährungsumfrage (ENSANUT) 2012. Mittels einer systematischen Literaturrecherche wurde die Verfügbarkeit epidemiologischer Studien in Bezug auf mikrovaskuläre Diabeteskomplikationen untersucht und die Ergebnisse der ENSANUT 2012 mit Ergebnissen vorhergehender Studien aus Mexiko verglichen.
Für die weitere Datenanalyse wurden 4,261 befragte Studienteilnehmer im Alter von 20 Jahren und älter mit bekannter Diabetesdiagnose eingeschlossen. Univariate Analyse, Datenvisualisierung und multiple logistische Regressionsmodelle kamen zur Anwendung um Zusammenhänge zwischen sozioökonomischer Determinanten, Inanspruchnahme von Präventivmaßnahmen und Vorhandensein von Diabeteskomplikationen im ländlichen- und städtischen Raum, sowie zwischen den 32 Staaten Mexiko's zu untersuchen.

Aus den Ergebnissen geht hervor, dass selbst-berichtete Daten in Bezug auf die Prävalenz mikrovaskulärer Diabeteskomplikationen von 44.7% bis zu 77.1% variieren. Höchste Prävalenzen traten gruppiert im Zentrum der West und Ostküste und entlang des Golfs von Mexiko auf. Sozioökonomische Faktoren (niedriger soziökonomischer Status und Bildungsstandard, Marginalisierung und fehlende Krankenversicherung) waren positiv mit dem Auftreten von Diabeteskomplikationen assoziiert. Jedoch konnte bei der visuellen Inspektion der Prävalenzdaten, kein Zusammenhang zwischen geographischer Häufung von Diabeteskomplikationen und sozioökonomischer Entwicklung der zugehörigen Region gefunden werden.
Die weitere Analyse ergab, dass ländlicher Wohnsitz signifikant mit dem Auftreten von Diabeteskomplikationen assoziiert war (OR = 1.31; 95%CI = 1.02 – 1.69). Ebenso gaben 71% der befragten Studienteilnehmer aus ländlichen Regionen an, in den letzten 12 Monaten an keiner Diabetesvorsorge teilgenommen zu haben, im Vergleich zu 60% der Studienteilnehmer aus urbanen Regionen ($p < 0.001$).

Daraus ergibt sich, dass weitere Interventionen auf gesundheitspolitischer Ebene notwendig sind, um die Inanspruchnahme und Compliance von Präventivmaßnahmen unter Diabetikern zu fördern und damit die Krankheitslast im ländlichen Mexiko zu senken. Es besteht weiterhin Unklarheit, ob eine kausale Beziehung zwischen sozioökonomischem Status und geographischer Gruppierung von Diabeteskomplikationen zwischen Mexiko’s Staaten besteht.

Summary

The increasing number of people with microvascular diabetes complications is an emerging problem in Mexico. People with less financial resources and those living in deprived areas in terms of infrastructure are at an elevated risk of developing diabetes complications earlier in their lifetime. Early detection and care of diabetes is necessary in order to effectively control and reduce the rate of complications. However, providing comprehensive diabetes care in low-income settings and remote areas of Mexico has not yet been achieved (Tapia-Conyer, Gallardo-Rincón, & Saucedo-Martinez, 2013).

The aim of this study is to determine how social and geopolitical determinants influence the utilisation of preventive measures and with that the development of diabetes complications. In order to do this, we explore the following points:
i) Socioeconomic differences between people with and without diabetes complications.
ii) The impact of the area of residency in Mexico's socio-economical diverse regions on the prevalence of microvascular diabetes complications
iii) How rural residency affects utilisation of preventive measures and the presence of diabetes complications

We used cross-sectional data from the Mexican Health and Nutrition Survey (ENSANUT) 2012. A systematic literature review was conducted to assess the availability of epidemiological studies on microvascular diabetes complications and compare self-reported data from the ENSANUT 2012 with evidence from prior research conducted in Mexico.
For further data analysis, 4,261 respondents aged 20 years and older with diabetes were included in the study. Univariate analysis, data visualization and multiple logistic regression models were performed to test associations between social determinants, the utilisation of preventive measures and the presence of diabetes complications in rural and urban areas as well as between Mexico's 32 federal states.

The results demonstrate that self-reported presence of microvascular diabetes complications varies from 44.7% to 77.1%. The highest prevalence is clustered in the centre of the West and the East coast and along the Gulf of Mexico. Socioeconomic factors (lower socioeconomic and educational status, marginalisation and absence of health insurance) are positively associated with the presence of diabetes complications.

However, upon visual inspection, the geographical clustering of diabetes complications was not associated with the socioeconomic development of the area.
Further analysis revealed that rural residency is significantly associated with the presence of diabetes complications (OR = 1.31; 95%CI = 1.02 – 1.69), and 71% of rural residents had not performed any preventive measure in the past 12 months compared to 60% in urban areas ($p < 0.001$).

Based on these results, health political efforts to improve the feasibility and compliance of preventive diabetes care in rural areas should be undertaken to decrease the burden of disease. If a causal relationship between socioeconomic status and the geographical clustering of diabetes complications across Mexico's states exists, needs to be further evaluated.

1 PART I: Epidemiology of diabetes complications in Mexico and Central America – A systematic literature review

1.1 Introduction

1.1.1 Diabetes in low- and middle-income countries

Diabetes is known to be an emerging problem all over the globe. Approximately 8.3% of the world population suffers from diabetes(Kwak & Park, 2015). With regard to Latin America, it is estimated that around 26 million people and 9 million people in Mexico suffer from diabetes (International Diabetes Federation, 2013).

The prevalence of type 2 diabetes mellitus (T2DM) is steadily increasing, with a great increase observed in low- and middle-income countries (LMIC). Specifically, it was predicted that between 1995 and 2025 the number of individuals with diabetes would increase by 170% in LMICs compared to a 42% increase in nations with high income(Esterson, Carey, Piette, Thomas, & Hawkins, 2014). At present, approximately 80% of the people with diabetes live in LMICs, which are more affected by the consequences of T2DM compared to high-income nations (Seuring, Archangelidi, & Suhrcke, 2015).

The Central American region is located between the isthmus of Tehuantepec (at the Guatemalan-Mexican border) and Panama. Mexico does not strictly belong to the Central American region, but it shares a great part of its cultural and historical heritage. As for the whole Latin American region, diabetes is an emerging problem, which requires more health care facilities and health care workers to serve the ever-increasing demand for diabetes care. However, four of the eight countries in Central America and Mexico have fewer than 23 health care workers per 10.000 people, which is the number of workers necessary to cover the primary health care needs of a population according to the World Health Organization (World Health Organization, 2009). Greater disparities in health care supply exist between rural and urban regions, with shortages of rural physicians and specialists in the Latin American region (Centers for Disease Control and Prevention, 2017; Colon-Gonzalez, El Rayess, Guevara, & Anandarajah, 2015). With regard to diabetes, less access to health care, misperceptions of the concept of chronic diseases and the high costs of medication compared to wages have made adherence to treatment increasingly difficult in the past. The consequences have included the late detection of diabetes, insufficient controlled risk factors and lack of prevention that resulted in micro/macrovascular complications with stronger impacts on poor and disadvantaged population groups. Diabetes complications disable people at economically productive ages, and an increase in early onset diabetes (before the age of 40) has been observed in recent years, which has increased the demand for and necessity of fostering awareness for the prevention of diabetes complications (Wilmot & Idris, 2014).

1.1.2 Why diabetes complications are a major problem in Central America and Mexico

Some of the reasons for the accelerated increase in diabetes over the past decades include epidemiological transition, globalisation and urbanisation, which has led to changing dietary patterns and a shift from manual labour to sedentary lifestyles(Islam et al., 2015). The epidemiological transition is based on the theory that profiles of countries change in accordance to their state of development. This change is reflected in higher life expectancies, decreased fertility rates and changing patterns in disease risk and mortality, with higher counts of chronic and non-communicable diseases and lower proportions of communicable and infectious diseases(McKeown, 2009). More developed countries in Latin America (e.g. Uruguay) have completed epidemiological transitions and are characterised by a high number of non-communicable diseases and lower mortality rates due to infectious diseases. Mexico and Costa Rica are at late stages of the epidemiological transition and experienced the highest increase in non-communicable diseases between 1980 and 1990(Stevens et al., 2008). Developing countries in Central America, particularly Guatemala, Honduras, Nicaragua and El Salvador, are facing a delayed transition with high numbers of deaths due to communicable diseases, undernutrition, maternal and perinatal causes and increasing rates of non-communicable diseases(Marinho, Soliz, Gawryszewski, & Gerger, 2013). Similar observations have been made across different areas in Mexico(Stevens et al., 2008). Countries and areas at earlier stages of the transition could face a double burden with high numbers of communicable and non-communicable diseases. With regard to diabetes, the epidemiological transition produces increased numbers of people that develop diabetes complications, especially in pre-transitional areas where the focus remains on treatment of communicable diseases rather than on the prevention of the development and progression of chronic conditions. Furthermore, the disability caused by diabetes complications and other non-communicable diseases can lead to a decrease in working hours, increased risk of hospitalisations and health expenditures that exceed the financial capacities of poor populations, resulting in a circle of impoverishment due to illness (Daivadanam, 2012).

1.1.3 Problem outline – Availability of epidemiological data on diabetes

Estimating the prevalence of diabetes complications is essential in order to evaluate the impact and future burden of diabetes. However, accurate estimations of the prevalence of diabetes and diabetes complications are difficult to assess due to large numbers of undiagnosed people, diagnostic differences and inconsistent registration and documentation of diabetes complications. Approximately 24% to 50% of the adult population in the South and Central American region are undiagnosed(Aschner et al., 2014). Increased numbers of undiagnosed cases are mainly a result of lack of knowledge and education, barriers to health care and insufficient data management among different health care providers. People living in rural and remote areas, ethnic minorities and people with low financial capacities are especially at risk of remaining undiagnosed and developing diabetes complications at earlier ages. The International Diabetes Federation (IDF) regularly publishes estimations on the prevalence and burden of diabetes across the adult population for most countries in the world. Despite its reputation of producing reliable and high-quality information, the publications for some countries lack sufficient data for one to make correct estimations. For example, the information on Panama and El Salvador is based on extrapolation using countries with similar demographic and geographic characteristics(Aschner et al., 2014) and epidemiological diabetes surveillance has not been applied in most Latin American countries (Barcelo & Rajpathak, 2001).

In the following section, we provide a brief description of clinical symptoms, diagnostic measures, therapy and preventive measures of the most common microvascular diabetes complications. The first section of this analysis comprises systematic literature research with the intention of clarifying the availability of epidemiological data of diabetes complications in Central America and Mexico. We further discuss the results and critically review methodological approaches to make estimations about diabetes complications.

The second section provides a detailed analysis of microvascular diabetes complications in Mexico with the intention of exploring demographic, socioeconomic and health access factors that contribute to the presence of diabetes complications and consequently impact the distribution of diabetes complications across Mexican states and across rural/urban areas of Mexico. The third and last section further analyses rural and urban people with diabetes complications and their participation in preventive screenings in Mexico.

1.1.4 Diabetes complications – Aetiology, diagnosis, treatment and prevention

Diabetic vascular complications have reasonable impacts on quality of life given that they are a major cause of various disabilities like acquired blindness, End Stage Renal Disease (ESRD), Lower Extremity Amputations (LEA), diabetic neuropathy (DN) and cardiovascular disease, which account for higher mortality rates in patients with diabetes. Although a greater focus in literature lies on macrovascular complications, due to the increased epidemiological importance of cardiovascular diseases in recent years, microvascular complications are highly disabling conditions. Additionally, microvascular complications have been demonstrated as targetable by prevention and are therefore indicators of the quality and quantity of diabetes care(Sharma, Sharma, Maheshwari, Sharma, & Gupta). However, the development of diabetes complications also depends on environmental factors and genetic dispositions, including familial aggregation and racial differences, which are not modifiable(Kwak & Park, 2015). Environmental factors including duration of diabetes, degree of hyperglycaemia, blood pressure and dyslipidaemia are modifiable risk factors, and effective control decreases the morbidity and mortality of patients with diabetes. International guidelines define the type and amount of preventive screenings (HbA1c tests, foot and eye revision, renal impairment testing, etc.) necessary to achieve adequate blood glucose control and reduce risk factors. According to international and Mexican guidelines, preventive screenings should be assessed at least annually, and other comorbidities such as hyperlipidaemia and arterial hypertension should be treated and controlled regularly(Secretaria de Salud, 2010) (American Diabetes Association, 2012).

Diabetic vascular complications are divided into two main groups:
1) Microvascular complications
2) Macrovascular complications
Microvascular complications affect the capillary bed of organs, mainly causing diabetic retinopathy, nephropathy, neuropathy, diabetic foot ulcers (DF) and lower extremity amputations. Macrovascular complications are associated with cardiovascular diseases like the manifestations of coronary heart disease, strokes and peripheral vascular diseases. In the following section, microvascular diabetes complications that are included in this analysis are further described.

1.1.4.1 Diabetic neuropathy, diabetic foot ulcers and lower extremity amputations

The most common form of DN ('chronic sensorimotor distal symmetric polyneuropathy (DPN)') was estimated to be present in about 20% to 50% of adult diabetic patients living in the US in 2005 (Boulton et al., 2005). Diabetic neuropathy is characterised by a progressive loss of distal sensation, leading in some cases to motor weakness through axonal loss(Feldmann, Shefner, & Dashe, 2015). Other forms of DN include diabetic autonomic neuropathy and focal neuropathy, with gastroparesis, constipation, diarrhea, anhidrosis, bladder dysfunction, erectile dysfunction, exercise intolerance, resting tachycardia, silent ischemia and sudden cardiac death(Edwards, Vincent, Cheng, & Feldman, 2008).

Patients with DPN report numbness, burning or 'electrical' pain, which gets worse at night, and loss of the sensation of light touch, vibration and temperature during physical examination(Fowler, 2008). Distal symmetric polyneuropathy increases the risk of developing painless foot ulcers that can remain undetected(Millan-Guerrero et al., 2012). This, in turn, predestines for ulcer infections and increased risk of LEA. People with diabetes experience LEA 17 to 40 times more often compared to people without diabetes, and about 85% of all people with LEA have had a previous foot ulcer(Boulton, 2004; Fard, Esmaelzadeh, & Larijani, 2007). Subsequent amputations are common. About 50% of people with one LEA undergo another LEA within five years (Monteiro-Soares, Boyko, Ribeiro, Ribeiro, & Dinis-Ribeiro, 2011). Furthermore, the mortality rate after LEA increases to 70% in the fifth year after amputation(Larsson, D Agardh, Apelqvist, & Stenström, 1998).

According to guidelines from the American Diabetes Association (ADA), a physician should perform a comprehensive foot exam at the onset of diabetes and at least once annually afterwards. This foot exam should include an assessment of risk factors, history of previous foot ulcers, a vascular and dermatological assessment with a focus on skin lesions and musculoskeletal deformities. Furthermore, any of the five neurological exams are recommended to detect DPN or any progression. These include the use of a 10-gram monofilament, a pinprick sensation test, a vibration test using a 128-Hz tuning fork or biothesiometer and/or ankle reflex assessment (American Diabetes Association, 2015).

Apart from tight glycemic control, which demonstrated modest effects on progression, no specific treatment for DN is available. However, blood glucose, blood pressure control, avoidance of nerve and vasculotoxic agents and simple routine procedures have reduced patient's risk for amputation. These simple routine check-ups include daily inspection of the foot, wearing adequate footwear, extensive ulcer management and patient education(Apelqvist, Bakker, van Houtum, & Schaper, 2008). According to a previous report, effective preventive programs aiming at early detection and control of risk factors for foot ulceration and treatment with a multidisciplinary approach have reduced the rate for LEA by 49-85% (Apelqvist, Bakker, van Houtum, Nabuurs-Franssen, & Schaper, 2000).

1.1.4.2 Diabetic retinopathy

Diabetic retinopathy (DR) is a characteristic complication of diabetes mellitus, marked by the degeneration of retinal vessels through inflammatory processes, neovascularisations and neurodegeneration(Xu et al., 2014). The risk of developing this manifestation increases with the duration of diabetes. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 30 years after diagnosis, nearly all patients had some degree of retinopathy, and the prevalence of proliferative retinopathy (last and sight-threatening stage) was about 60%(Klein, Knudtson, Lee, Gangnon, & Klein, 2008). Retinal changes can be detected through ophthalmologic examinations and are classified as follows:

a) background retinopathy
b) preproliferative retinopathy and
c) proliferative retinopathy

Background retinopathy appears as 'dots' representing small haemorrhages in the retina. Haemorrhages together with microaneurysms indicate early stages of DR. 'Hard exudates' result from lipid depositions around the haemorrhages as signs of microvascular leakage. Hard exudates can endanger one's vision if they get close to the macula. Microaneurysms (dilated retinal vessels) appear as red dots in funduscopy. Retinal oedema can appear at this stage through microvascular leakage and often needs treatment as it can cause visual impairment. Proliferative retinopathy clinically results in so-called 'cotton wool spots', indicating the formation of new vessels on the surface of the retina induced by elevated vascular endothelial growth factor (VEGF) expression as a response to vascular hypoxia. These new vessels are likely to be damaged, causing vitreous haemorrhages. The corresponding symptom is called 'mouche volantes'. Repair mechanisms cause traction and consequently lead to the detachment of the vitreous body from the retina, resulting in one's irreversible visual loss(Fowler, 2008). Diabetic retinopathy is the primary cause of blindness among adults between 20 and 74 years of age. Optimising glycaemic- (HbA1c $\leq$ 7 %) and blood pressure control ($\leq$ 130 mmHg / $\leq$

80 mmHg) has been demonstrated to decrease the progression and person's risk for DR(Chew et al., 2010; 'Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38', 1998). An ophthalmologist or optometrist should perform a comprehensive dilated eye examination initially; follow-ups to detect any progress should be repeated annually. The rationale behind that is the option for laser photocoagulation surgery, which reduces the neovascularization induced by the hypoxia of damaged vessels. Neovascularization processes occurring at the retinal disc especially cause vision impairment and blindness and can be effectively prevented by laser photocoagulation surgery or pharmacological intervention with VEGF inhibitors('Preliminary report on effects of photocoagulation therapy. The Diabetic Retinopathy Study Research Group.', 1976).

1.1.4.3 Diabetic kidney disease

Glomerulosclerosis, progressive albuminuria and declining glomerular filtration rate (GFR) are the histopathological and clinical correlates of diabetic kidney disease (DKD). Diabetic kidney disease is one of the leading causes of ESRD, which eventually requires renal replacement therapy. It is associated with high morbidity and mortality rates; according to the United States Renal Data System (2013), only 34% of patients receiving haemodialysis have survived the subsequent five years(Collins et al., 2014). The United Kingdom Prospective Diabetes Study (UKPDS) found that 10 years after diabetes onset, 25% of patients had microalbuminuria (MiA). Of those patients with MiA, 30 to 45% progressed to MA over a 10-year period, and some of them reported progression despite stable glucose control(Caramori, Fioretto, & Mauer, 2000; Gross et al., 2005). Screening for diabetic nephropathy should start at the time of diagnosis, since approximately 7% of all patients with diabetes present symptoms of MiA at that time. Albumin excretion rates in a spot urine sample should be performed, as suggested by ADA guidelines, and re-confirmed after three and six months if abnormal results are found. Furthermore, other causes of albuminuria need to be considered, and renal biopsy is the only measurement that can confirm DKD with certainty(Gross et al., 2005). However, the absence of clinical symptoms at early stages of DKD makes the condition more detectable at advanced stages. As a consequence, frequent screenings for renal impairment and control of risk factors are needed to prevent chronic kidney failure. Annual exams measuring urine albumin excretion rates and serum-creatinine levels are recommended in order to detect any decline in renal function. Additionally, risk factors for the progression of DKD include hyperglycaemia, increased blood pressure levels, elevated serum lipid levels and tobacco consumption, all of which need to be reduced and controlled during each physician visit.

1.2 Objectives - Systematic literature review

Systematic literature research was conducted in order to determine the availability of epidemiological data on diabetes complications in Mexico and Central America. This served as a foundation for the subsequent analysis of Mexico. The aims of this systematic literature research were i) to review if population-based data exist for Central American countries; ii) to determine if these data were comparable to data from the Mexican Health and Nutrition Survey ENSANUT 2012); and iii) to compare the prevalence of diabetes complications in Mexico based on previous research that used data from the Mexican Health and Nutrition Survey 2012 (Encuesta Nacional de Salud y Nutrición, ENSANUT 2012).

To reach these aims, articles that contained information on the prevalence of diabetes complications in Mexico and Central America were retrieved, and diabetes complication prevalence was compared to results from Mexico.

1.3 Search methods

The database PubMed was systematically screened using mesh and search terms to match published documents with relevant information on diabetes complications. A reproducible stepwise approach was used to find relevant literature. During the first attempt, the mesh term search engine of the database PubMed helped us find synonyms for ‘diabetes complications’, ‘Central America’ and ‘Mexico’ to broaden the number of results. Each mesh term was numbered and systematically connected with the operators ‘AND’ or ‘OR’, resulting in a smaller selection of search results. The mesh term ‘diabetes complication’ in particular was connected with the mesh term of each country. For Central American countries, the search was restricted to population-based data only. Thus, clinical data were not considered. A more detailed literature review was performed for Mexico in order to guarantee uniqueness with regard to the topic for Mexico and gain an idea of the extent to which diabetes complication rates from clinical studies differed from observations of self-reported data from the ENSANUT 2012. We further reviewed the reference list of documents that found inclusion, which resulted in four additional references.

The search was restricted to the years between 2000 and 2016, ensuring comparable data. For the same reason, documents created in the US were not considered, as migration and acculturation have diverse effects on health behaviour and outcome(Afable-Munsuz, Mayeda, Pérez-Stable, & Haan, 2013; Antecol & Bedard, 2006). Documents that provided epidemiological information on the following diabetes complications were included in our analysis: visual impairment caused by diabetes, DR and blindness, LEA, DKD/DN and ESRD requiring dialysis.

Details concerning inclusion and exclusion criteria are displayed below. Table 1 and Table 2 present a detailed description of the search strategy. Due to the heterogeneity of populations and study designs, we did not conduct further statistic analyses of the results but limited the analysis to a descriptive comparison across retrieved documents.

Inclusion criteria:

1. Studies with data on diabetes complications of at least one complication caused by T2DM or where there was no distinction made between T2DM and T1DM
2. Period: 2000 to 2015
3. Studies with epidemiological data from Mexico or Central American (Guatemala, Nicaragua, El Salvador, Honduras, Belize, Costa Rica, Panama)
4. English or Spanish language
5. Full-text articles available

Exclusion criteria:

1. Mexican/Central-American emigrants residing in the US or in other countries.
2. Studies that were conducted in the US or any country other than Mexico
3. Diabetes mellitus due to secondary causes or aetiologies other than T2DM (gestational, early onset diabetes mellitus, etc.)
4. Studies exclusively including patients with type 1 diabetes mellitus
5. Patient cohorts where the diabetes prevalence was unclear
6. Documents reporting the prevalence of a diabetes complication in patient cohorts referred from primary care units to specialised hospitals for screening (These documents were excluded because the selected cohorts had a complication prevalence of ideally nearly 100%. However, documents that were conducted in specialist centres with no prior selection through other health care practitioners were not excluded.)

Table 1. PubMed Mesh Term Search

No.	Component [Mesh]	Search term	Hits	First se-lection	Final se-lection
#1	Diabetes complication	"Diabetes Complications"[Mesh]	104,868		
#2	Mexican Americans	Mexican American [MeSH Terms]	3,361		
#3	Central Americans	American Indians, Central [MeSH Terms]	440		
#4	Central America	Central America [MeSH Terms]	11,915		
#5	Mexico	Mexico [MeSH Terms]	27,762		
#1 AND #2		("Diabetes Complications"[Mesh]) AND Mexican American [MeSH Terms]	72	8	1
#1 AND #3		"Diabetes Complications"[Mesh]) AND American Indians, Central [MeSH Terms]	1	0	0
#1 AND #4		("Diabetes Complications"[Mesh]) AND Central America [MeSH Terms]	15	5	0
#1 AND #5		("Diabetes Complications"[Mesh]) AND Mexico [MeSH Terms]	135	18	10

Table 2. PubMed Manual Search on diabetes complications in Mexico

No.	Search term	Hits	First Selection	Final Selection	Additional documents[1]
#1	Diabet* retinopathy AND Mexic*	218	25	7	1
#2	Diabetic neuropathy AND Mexic*	148			
#3	Diabet* foot AND Mexic*	105			
#4	Diabet* amputation AND Mexic*	59			
#5	Diabet* nephropathy AND Mexic*	516			
#6	Diabet* kidney AND Mexic*	462			
#7	#2 OR #3 OR #4	224	16	5	2
#8	#5 OR #6	516	39	6	1

[1] Additional documents that were found through screening of reference list of other documents

1.4 Results of the systematic literature review on diabetes complication in Mexico and Central America

The search yielded 1,182 articles. A total of 16 documents were retrieved and are presented in Tables 3 through 6. A flowchart of the selection procedure of relevant articles is provided below (see Figure 1). No epidemiological information with national representative data for diabetes complications was found for Central America. Results for each analysed microvascular complication found for Mexico are presented below.

Diabetic retinopathy

The prevalence of DR ranged from 31.7% to 73.0% (see Table 3). The presentation of advanced stages of DR (Proliferative Diabetic Retinopathy, PDR) varied from 8% to 81.4% among people with DR. Higher prevalence was found in studies that were conducted in specialised ophthalmologic clinics (73%(Cervantes-Castañeda, Menchaca-Díaz, Alfaro-Trujillo, Guerrero-Gutiérrez, & Chayet-Berdowsky) and 51%(Rodríguez-Saldana et al., 2010)) and in a study conducted in public hospital, where patients who have had diabetes for more than 10 years and whose median age was 60 years were included (68% (Cepeda-Nieto et al., 2015)).

Lower prevalence was found in studies that were conducted in primary health care clinics or family medicine units of hospitals, where the data was collected by general physicians (27.5%(Sabag-Ruiz, Alvarez-Félix, Celiz-Zepeda, & Gómez-Alcalá, 2006), 33.3%(Carrillo-Alarcón, López-López, Hernández-Aguilar, & Martínez-Cervantes, 2011) and 42.5% (Lavalle-Gonzalez et al., 2012)). In this analysis, DR was diagnosed either through (non-) dilated funduscopy, retrospective analysis of clinical charts or, as mentioned one document, based on self-report. A study by Polack et al. tested a screening tool for DR in a household survey setting using a probabilistic population-based study design. The study personnel visited households and assessed the presence of DR and blindness among patients with diabetes using fundus photography. They reported a prevalence of 38.9% for DR and 4.5% for blindness (Polack et al., 2012). Another study found that the prevalence of DR was about 10.4% among nine Latin American countries, including Mexico and Guatemala. In this study, general practitioners of each country were asked to fill out study questionnaires with information on patients with T2DM, including the presence of microvascular and macrovascular diabetes complications(Lopez Stewart et al., 2007). The proportion of self-reported DR in the ENSANUT 2012 was

13.9% of survey participants. Visual impairment was reported by 47.6% of participants and blindness by 6.6%.

Diabetic neuropathy, diabetic foot ulcer and lower extremity amputation

Six studies reported on the prevalence of DN, DF and LEA, see Table 4 Diabetic neuropathy, foot ulcer and lower extremity amputation in Mexico Three studies that were conducted in an outpatient family medicine unit belonging to IMSS/ISSSTE hospitals (tax-funded social security hospitals) found that the prevalence of DN was about 42.6% (Sabag-Ruiz et al., 2006), 54.5%(Camacho López, 2011) and 69%(Ibarra R, Rocha L, Hernández O, Nieves R, & Leyva J, 2012). One document from a primary care centre in Colima reported a prevalence of 27.1% for DN(Bañuelos-Barrera, Arias-Merino, & Banuelos-Barrera, 2013). The multicentre study conducted by Lavalle-Gonzalez et al. in 2012 found a prevalence of DN of 62.8% (Lavalle-Gonzalez et al., 2012), and another study by Rodriguez-Saldana et al. (2010) assessed the prevalence of DN, DF and LEA by self-report of patients that attended specialised ophthalmologic clinics and found a prevalence of 25.8%, 10.5% and 3.8%, respectively (Rodríguez-Saldana et al., 2010). All documents provided data on the prevalence of DN (25.8%, 27.1%, 42.6%, 54.5%, 62.8 and 69.0%), yet prevalence of DF was reported in only three out of six documents (2.4%, 10.8% and 10.5%), and LEA rates were extracted from one document (3.8%). The prevalence of DN reported in the ENSANUT 2012 was about 42.6% across people with diabetes. Rates for DF and LEA were 7.2% and 2.0%, respectively.

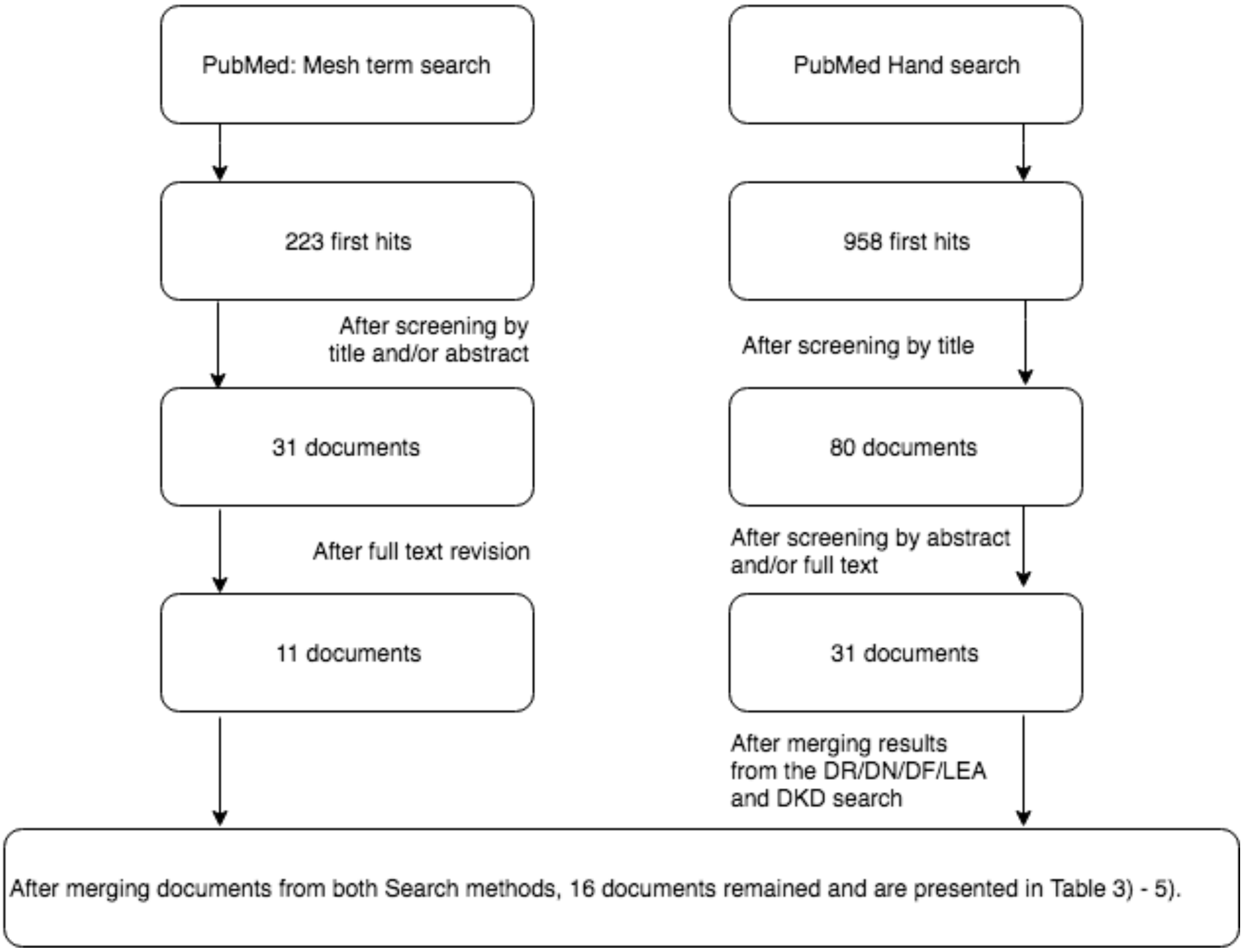
Diabetic kidney disease

Diabetic kidney disease (also termed 'diabetic nephropathy') was common among patients with diabetes in all documents. Prevalence of DN ranged from 16% to 38%. Early nephropathy was reported in 40% to 85% of patients. Overt nephropathy was reported in one document at 29%. Different diagnostic measures were used. Two studies used the definition of the Kidney Disease Outcomes Quality Initiative (KDOQI), which defines 'early nephropathy' as MiA (urine albumin excretion rate = 30-300 mg/day) with normal GFR or absence of MiA and mildly decreased GFR (60-89 ml/min/1.73 m^2). Macroalbuminuria (MA: urine albumin excretion >300mg/ day) and/or a GFR<60 ml/min/1.73 m^2) was defined as 'overt nephropathy'. One study used information from self-reports, two from the attending specialist/physician, two from clinical trials and one was a community-screening program.

Three studies were conducted in IMSS hospitals: one was conducted in Coahuila using data from retrospective analysis of clinical charts (DKD=20.5%)(Sabag-Ruiz et al., 2006), and two were clinical trials conducted in Sonora and Jalisco using dipstick urine to measure the presence of albuminuria and blood tests to asses creatinine levels for GFR calculations. These two latter documents reported a prevalence of 40% for early nephropathy, 29% for overt nephropathy and 20% for any kind of DKD as assessed by the attending physician (Cueto-Manzano et al., 2005; Leza-Torres, Briones-Lara, Gonzalez-Madrazo, De la Cruz-Martinez, & Ramos-Davila, 2005). One prospective study collected data from three major ophthalmologic hospitals in Mexico, and patients were asked to fill out forms that contained information on their history of DKD. This document reported the lowest prevalence for DKD with a rate of 15.9%(Rodríguez-Saldana et al., 2010)One study was conducted as part of a community-screening program (Kidney Early Evaluation Program, KEEP) in Jalisco and Mexico City, where urine and blood samples were taken on-site. The level of urine-albuminuria as well as serum-creatinine was assessed to estimate GFR. Among people with diabetes, CKD was 38% in Jalisco and was three percentage points lower in Mexico City (Obrador et al., 2010). Similar results were found by the multicentre study by Lavalle-Gonzalez et al. (2012), with a prevalence of 37% (Lavalle-Gonzalez et al., 2012). Data from two rural primary health care centre reported lower rates of 23.8% (Zenteno-Castillo et al., 2015).

Among ENSANUT 2012 participants, 1.4% of all individuals with diabetes suffered from ESRD and required renal replacement therapy. The ENSANUT 2012 data did not provide information on earlier stages of renal dysfunction and rates of MiA or MA.

Figure 1. Flowchart - Systematic literature research



*DR = Diabetic Retinopathy, DN = Diabetic Neuropathy, DF = Diabetic Foot, LEA = Lower Extremity Amputation, DKD = Diabetic kidney disease

Table 3. Prevalence of diabetic Retinopathy in Mexico

Author	Study period	Study place	Study characteristics (N= counts; Age in years)	Diagnostic measure	DR prevalence*
Mendoza-Herrera et al. (2017)	2014 - 2016	Morelos, mobile unit screening in 3 low income municipalities	N(total) = 11468, ≥ 20 years N(DM) = 1768 Mean age = 57.2 (SD = 11y) Female = 73%	(Non-) dilated funduscopy	Overall: 31.7% NPDR = 59.6% PPR = 17.9% PDR= 22.5%
Cepeda-Nieto et al. (2015)	n.a.	IMSS hospital Saltillo,	N(DM) = 177, patients with a previous diagnosis > 10 years Median age = 60 Female = 39%	Non-dilated funduscopy	Overall: 68% NPDR = 41.3% PDR = 58.7%
Jimenez-Baez et al. (2015)	n.a.	Quintana Roo, eight IMSS primary-care units	N(DM) = 105 Women = 55% Mean age = 48 (SD=11.1)	Dilated funduscopy	Overall: 23.8% NPDR = 92.0% PDR = 8%
Cervantes-Castaneda et al. (2014)	2006 - 2010	Baja California, Ophthalmology Centre Tijuana, retrospective analysis	N(DM) = 500 Mean age = 57.7 (SD=11.0)	Information from clinical charts	Overall= 73.0% NPDR = 18.6% PDR = 81.4%
Polack et al. (2012)	2010	Chiapas, population representative study	N = 1974 N(DM) = 347	Dilated fundus photographs	Overall= 38.9% Severe DR= 21.0% Blindness = 4.5%

Rodrígue z-Saldana et al. (2010)	2001-2007	Mexico City, three ophthalmology hospitals	N(T2DM) = 1000 Mean age= 60.5 Female = 61.1%	Self-report	Overall= 51.1% Blindness = 16.3%
Sabag-Ruiz et al. 2006	2001 - 2002	Sonora, family unit in Obregón City, retrospective analysis	N(DM) = 250 Mean age = 59.3 (30-87 years)	Clinical charts, diagnosed by an Ophthalmologist	Overall: 27.5% PPR = 14.3% PDR = 85.7%
Carillo-Alarcón (2011)	2010	Hidalgo, five primary health care centre	N(DM) = 117 Mean age = 58.1 (SD=11.1) Female=77.8%	Dilated funduscopy	Overall 33.3% NPDR = 89.8% PDR = 10.2%
Lavalle-Gonzalez et al. 2012	2007	Mexico, physicians from 32 states, prospective, multicentre study	N(T2DM) = 2439 N(T1DM) = 203 Female = 60% Mean: 56.7%	Ophthalmologists diagnosed presence of DR	Overall: 42.5%

DR = Diabetic Retinopathy
Overall = Prevalence of any severity level of diabetic retinopathy
NPDR = Non-proliferative Diabetic Retinopathy
PPDR = Pre-Proliferative Diabetic Retinopathy
PDR = Proliferative Diabetic Retinopathy
IMSS = Instituto Mexicano del Seguro Social (Social Security, tax-funded health care)
T2DM = Type 2 Diabetes Mellitus
T1DM = Type 1 Diabetes Mellitus
SD = Standard Deviation
n.a. = not available
*Prevalence of DR stages (NPDR/PDR) was reported as % of the total DR prevalence

Table 4 Diabetic neuropathy, foot ulcer and lower extremity amputation in Mexico

Author	*Study period*	*Study place*	*Study characteristics (Age in years)*	*Diagnostic measure*	*Prevalence DN/DF/LEA**
Banuelos-Barrera et al. 2013	2012	Colima, Primary care centre	N(T2DM) = 87 Mean age: 58.8 >30 years (SD=12.2) Female = 70.1%	Semmes-Weinstein monofilament test	DF ulcer: 2.4% DN: 27.1% PVD[#]: 52.4%
Ibarra R et al. 2012	n.a.	Guanajuato, Outpatient Family medicine unit (IMSS institute **)	N(T2DM)=348 Mean age: 58 Diabetes duration: 5-15y Female: 60%	Michigan Neuropathy Screening Instrument	DN: 69%
Camacho López 2011	n.a.	Sinaloa, Outpatient Family medicine unit (ISSSTE institute**)	N(T2DM) = 207 Female: 59% Mean age: 59 (SD=12.5)	Neuropathy Symptoms Score	DN: 54.5%
Sabag-Ruiz et al. 2006	2001-2002	Sonora, Family medicine unit (IMSS institute)	N(T2DM) = 168 Female: 64.9%	Physician diagnosis, no further information available	DN = 42.6% DF: 10.8%
Lavalle-Gonzalez et al. 2012	2007	Mexico, physicians from 32 states, prospective, multicentre study	N(T2DM) = 2439 N(T1DM) = 203 Female = 60%	Neurologists diagnosed presence of DN/PVD	DN = 62.8
Rodríguez-Saldana et al. (2010)	2001-2007	Mexico City, 3 ophthalmologic hospitals	N(T2DM) = 1000 Mean age= 60.5 Female = 61.1%	Data obtained from self-report	DF = 10.5% DN = 25.8 LEA = 3.8%

* DN = Diabetic neuropathy; DF = Diabetic Foot; LEA = Lower Extremity Amputation

**IMSS and ISSSTE = Social Security, tax-funded health care

[#] PVD = Peripheral Vascular Disease

SD = Standard deviation, T2DM: Type 2 diabetes mellitus

no

Table 5. Prevalence of diabetic kidney disease (DKD) in Mexicans with diabetes

Author	Study period	Study place	Study characteristics (Age in years)	Diagnostic measure	Prevalence of DKD
Zenteno-Castillo et al. 2015	2010-2011	Guanajuato, data from 2 rural primary health care centres	N(T2DM) = 335 Female Mean age = 69.3 (SD=11)	Kidney Disease Outcomes Quality Initiative	23.8%
Lavalle-Gonzalez et al. 2012	2007	Mexico, physicians from 32 states, prospective, multicentre study	N(T2DM) = 2439 N(T1DM) = 203 Female = 60%	Nephrologists diagnosed presence of diabetic nephropathy	37.3%
Rodríguez-Saldana et al. (2010)	2001-2007	Mexico City, 3 specialised ophthalmologic hospitals	N(T2DM) = 1000 Mean age= 60.5 Female = 61.1%	Self-reported history of diabetic nephropathy	15.9%
Obrador et al. 2010	2008 - 2009	Mexico and Jalisco; Community screening program	N(DM) Mexico = 425 (28%) N(DM) Jalisco = 808 (44%)	On-site urine and blood sample tests	Mexico = 35% Jalisco = 38%
Sabag-Ruiz et al. 2006	n.a.	Sonora, Family medicine unit (IMSS institute*)	N(DM) = 252 Female = 64.9% Mean age = 59.3 (30 - 87yrs)	Retrospective analysis, Information from clinical charts	20.5%

Leza-Torres 2005	2004	Coahuila, IMSS hospital	N(T2DM) = 301 female = 59.0% mean age = 57.2 (SD = 10.9)	Urine and blood sample	MiA** = 85.3% MA = 11.5%
Cueto-Manzano et al. 2005	n.a.	Jalisco, 3 primary care medical units	N(T2DM) = 756 Mean age: 54 (SD=10) female = 65% Urine and blood sample DKD definition: Kidney Disease Outcomes Quality Initiative (KDOQI)		MiA** / GFR 60-89 ml/min = 40% MA / GFR<60ml/min) = 29%

*IMSS = Instituto Mexican de Salud Social (Social Security, tax-funded health care)

**MiA = Microalbuminuria; MA = Macroalbuminuria; GFR= Glomerular Filtration Rates

T2DM = Type 2 Diabets mellitus, DM = Diabetes Mellitus

1.4.1 Discussion

The rising incidence and prevalence of diabetes complications are economically challenging health systems in Latin America(van Dieren, Beulens, van der Schouw, Grobbee, & Neal, 2010). This trend has been observed over a long period of time; however, we could not find epidemiological and nationally representative data on the prevalence of diabetes complications in Central America. We found epidemiological data on microvascular complications that were representative of the entire population exclusively for Mexico. Although Costa Rica and Panama regularly conduct national health and nutrition surveys, no reports on diabetes complications were available. Similar to prior epidemiologic investigations into microvascular complications, we found limitations with respect to a lack of consensus on the classification of microvascular complications, severity levels and the definition of the surveyed population (population with T1DM or T2DM and those with risk factors versus the general population with diabetes)(Kvitkina et al., 2015). The following section intends to critically review these differences with regard to the level of comparability of information obtained from the ENSANUT 2012 (Gutierrez et al., 2012).

Diabetic retinopathy in Mexico:

We compared documents with information on the prevalence of microvascular diabetes complications that were conducted in households or at the community level, in primary health care clinics, in general and specialised clinics with data from the ENSANUT 2012 survey.

The prevalence of DR was substantially lower in the ENSANUT 2012 compared to other studies (13.9% vs. 31.7%-73.0%,). The most comparable document was a population-based study by Polack et al. conducted in 2010 in the state of Chiapas(Polack et al., 2012). Similar to the ENSANUT 2012, a clustered household survey design was applied. The prevalence of DR was assessed through fundus photography conducted in the households of survey participants. The authors found that DR was prevalent in 38.9% of all participants, which was more than twice as high compared to the prevalence of DR in ENSANUT 2012. The prevalence of blindness caused by diabetes was higher in ENSANUT, at 6.6% compared to 4.5% in Polack et al., which is surprising because Chiapas is the state with the lowest socioeconomic and developmental profile among the Mexican states(Instituto Nacional de Estadistica y

Geografía, 2014). People from lower socioeconomic levels are more likely to present advanced stages of microvascular diabetes complications, particularly diabetes-acquired blindness caused by delayed surgical and pharmacological intervention(Funakoshi et al., 2017).

Other documents presented higher rates for DR; however, the study design and the population differed substantially from ENSANUT 2012. For example, a multicentre study conducted in all 32 states of Mexico by Lavalle-Gonzalez et al. (2012) reported a prevalence of 42.5%(Lavalle-Gonzalez et al., 2012). The data for this study were collected by general practitioners using case report forms. However, the higher prevalence of diabetes complications in this study could be due to selection bias. Similarly, the significantly high prevalence of 68% found by Cepeda-Nieto et al. (2015) might be explainable by the older age and selection criteria of patients who had diabetes for at least 10 years or more. In the US, approximately 29% of survey participants with diabetes from the American Health and Nutrition Examination (NHANES) presented any degree of DR, which is still about 15% higher than in the ENSANUT 2012 (Zhang et al., 2010). In summary, specialised ophthalmologic clinics found the highest prevalence of DR, followed by multicentre studies, the population-based study by Polack et al. and data that were retrieved from family medicine units. Considering the high discrepancy in the prevalence of DR in Mexico, we can assume that DR in the ENSANUT cohort is fairly underestimated. We expect that many respondents with DR did not know about their diagnosis, either because they were not diagnosed or were not familiar with the medical term. These respondents could be found in the ‘vision impairment group’, which was prevalent in 47.6% of all people with diabetes. However, whether the cause of the vision impairment was DR or any other sight affecting condition (e.g. diabetic maculopathy) is uncertain. Consequently, the actual prevalence of DR is assumed to be between 14% and 40%, as results from the systematic literature research suggest. These findings point out the difficulty of estimating the prevalence of diabetes complications based on self-reported data. In order to increase the quality and reliability of the complication prevalence it would be necessary to use diagnostic tests (such as blood- or ophthalmologic tests). However these are expensive in large population based surveys, which limits the feasibility of such tests in population based surveys(Mendoza-Herrera et al., 2017).

Diabetic neuropathy, diabetic foot ulcer and lower extremity amputation:

Studies that were included in this systematic literature review reported a prevalence of DN between 25.8% and 69.0% The diagnostic measures used included the Semmes-Weinstein monofilament test, the Michigan Neuropathy Screening instrument, the Neuropathy Symptom score, self-reported data or a specialist opinion that diagnosed the presence of DN. For comparison, 42.6% of respondents with diabetes from ENSANUT 2012 reported a history of numbness or burning in the soles of the feet, indicative of DN. Aside from the report by Sabag-Ruiz et al. (DN = 42.8%) and Rodriguez-Saldana et al. (DN = 25.8%), results of the systematic literature research suggest higher rates of DR compared to the ENSANUT data for DN. The low prevalence in Rodriguez-Saldana et al. might be a result of the patient cohort and setting. In this case, DN was observed to be comorbid in patients who initially attended an ophthalmologic centre because of vision impairment. Although Sabag-Ruiz et al. reported similar rates for DN compared to ENSANUT 2012, it is likely that the prevalence of DN is actually higher than reported because patients might actually have DN without presenting the typical burning or sensation of pain in the foot or soles. However, it is noteworthy that almost half of all patients with diabetes in ENSANUT reported this symptom and were thereby at higher risk of developing foot ulcerations. Compared to the prevalence found in the Latin American region (DN = 15.5%), the high rate in Mexico gave reason for concern. However, this prevalence found in the Latin American region must be considered with caution as general practitioners in several Latin American countries reviewed patient charts over a two-week period and collected data from the first 8 to 12 patients with T2DM who sought consultation. The history of diabetes complications in patient charts might be incomplete, and it is not certain whether the participating physicians completed a full screening to detect any complication in those 8 to 12 patients. This may explain the overall lower prevalence of diabetes complications in this document. According to estimations from a landmark study with 4.400 patients evaluated over 25 years, about 50% of all people developed some form of DN(Pirart, 1978).

With regard to DF, only few a few reviews provided epidemiological information. One of the reasons is that DF is usually measured through hospital discharge letters for cost estimations and not for prevalence rates. However, these few documents reported that the prevalence of foot ulcers ranged from 2.4% to 10.8%, compared to 7.2% of patients with diabetes in ENSANUT 2012. The yearly prevalence of DF in the US was consistent with ENSANUT 2012 findings: in 2008, 8% of Medicare beneficiaries with diabetes had a history of a DF and 1.8% had LEA(Margolis et al., 2011). Lower extremity amputation in ENSANUT 2012 was reported in 2.0% of all cases of diabetes and was lower in the Latin American Region (0.9% of all survey participants). It is noteworthy that the prevalence of DF in self-reported data has likely been underestimated. In the National Health Interview survey conducted in the US, self-reported data on DF were considered to underestimate the actual prevalence by one third(Margolis et al., 2011). Similar or even higher estimations can be expected for the cohort surveyed in ENSANUT 2012.

Diabetic kidney disease:

Diabetic kidney disease (DKD), also termed diabetic nephropathy (DN) is glomerulopathy caused by metabolic and hemodynamic alterations. Diabetic kidney disease is the leading cause of renal failure in most populations(Reutens, 2013), and approximately one third to one half of patients with diabetes develop DKD of any stage (De Boer, 2014). However, estimating the prevalence of DKD is difficult. First, a definite diagnosis can solely be confirmed by renal biopsy, which is performed only if the diagnosis remains unclear. Second, while diabetes might be the underlying cause for most cases of DKD, other comorbid diseases potentially confound the prevalence. For example, non-diabetic renal disease in patients with diabetes was reported in 27% to 79% of patients(Park, 2014). Furthermore, no uniform diagnosis criteria and screening method for DKD exists because established methods have shortfalls when it comes to confirming DKD. In most epidemiological studies, screening for DKD uses urine albumin excretion rates from 24-hour urine collections, albumin-creatinine ratios and/or estimated glomerular filtration rates (GFR)(De Boer, 2014). However, GFRs naturally decrease with increasing age without causing any abnormality in albumin excretion rates(Stanton, 2014). Even so, the use of MiA screening with urine dipsticks has recently been questioned due to the process' low sensitivity and specificity in predicting kidney outcomes. In this regard, the paradigm of irreversible progress from MiA to MA and then chronic renal failure has been disproved, and spontaneous remission to normal kidney function has been observed at any stage at the occurrence of proteinuria(Maclsaac, Ekinci, & Jerums, 2014). This has led to differences in the definitions of DKD and has had implications on screening methods for DKD. The Kidney Disease Outcomes Quality Initiative (KDOQI) guideline suggests that DKD is likely if persisting albuminuria in combination with arterial hypertension and declining

GFRs exist in patients with diabetes(Parving, Persson, & Rossing, 2015). As for this research, DKD was considered based on self-report, clinical diagnosis or the presence of MiA or MA. The diagnosis was highly variable and ranged from 15.9% to 38.0%. Self-reported data reported a lower prevalence of 15.9% (Rodriguez-Saldana et al. 2010), whereas nephrologists in the multi-centre study conducted by Lavalle-Gonzalez et al. (2012) found a prevalence more than twice as high (37.3%). Similar results were found in the community screening program: 35% of diabetes patients from Mexico City and 38% from Jalisco presenting chronic kidney disease(Obrador et al., 2010). The ENSANUT 2012 only reported the necessity for renal replacement therapy among people with diabetes. Accordingly, the prevalence of DKD in the ENSANUT 2012 was lowest due to the exclusion of earlier stages of DKD and accounted for only 1.4% of people with diabetes. One of the reasons for this exclusion might be that self-reporting of earlier stages of DKD is an inadequate measure, as decreased kidney function can be compensated for by other organs and can remain symptomatically silent over a long period of time. Additionally, screening for MiA or MA is infrequently performed for patients with T2DM, resulting in a large number of unreported cases. For example the Kidney Early Evaluation Program (KEEP), a free community screening program conducted in Jalisco and Mexico City observed concerning results: 35% to 38% of the screened participants with diabetes were diagnosed with DKD, 1% of the participants in Mexico City were aware of the diagnosis although 71% of them reported they had been seen by a physician in the previous year. In Jalisco, none of the study participants with DKD knew about their diagnoses(Obrador et al., 2010).

Certainly, ESRD is the most expensive consequence of diabetes, leading to more disabilities and death compared to other diabetes complications(Barquera et al., 2013). Although it is also the least prevalent diabetes complication, it is estimated that end stage renal disease will become an increasing trend in the future. It is likely that the demand for renal replacement therapy will rise(Alegre-Diaz et al., 2016). As opposed to other Latin American countries, Mexico does not provide universal access to dialysis, and renal replacement therapy was not equally available throughout the country. According to García-García et al. (2005), renal replacement therapy was at the time of the study only accessible to the insured population. However, the poor population was severely underserved. In this study conducted shortly after the implementation of universal public health care ('Seguro Popular'), half of the studied population with chronic kidney disease was uninsured and had access to eight haemodialysis stations, in comparison to the insured population, which had access to 34 stations. Furthermore, poor people were found to be receiving dialysis therapy at a later point compared to those with better socioeconomic backgrounds(Garcia-Garcia et al., 2005). This shortfall may have been improved since the implementation of universal public health care ('Seguro popular'); however, the exact number of people with diabetes suffering from DKD remains unclear, and it is conceivable that renal failure is the cause of premature death in many underserved communities. Furthermore, microvascular diabetes complications, DKD and other similar complications are preventable. Increased prevalence of complications is indicative of delayed diagnoses, treatment and insufficient prevention and provision of diabetes care.

In conclusion, we found no existing information on microvascular diabetes complications representative of the Central American countries. Only Mexico was found to have assessed diabetes complication rates in the form of the National Health and Nutrition Surveys, which provide high-quality data and provide a valuable tool for estimating the burden of diabetes complications in a nationally representative sample (Barquera et al., 2013). However, these data rely on self-reporting, which leads to uncertainty in terms of the accuracy and validity of the underlying medical diagnosis(Short et al., 2009). Documents that were obtained to compare clinical data on complication prevalence in Mexico to ENSANUT 2012 data were heterogeneous in terms of study design and studied population. The prevalence of diabetes complications was high for Mexicans, and clinical data reported higher prevalence of DR and partially for the prevalence of DKD and DF compared to the data provided by ENSANUT 2012. The most comparable element was DR. Although the populations differed, the diagnostic measure was similar between all documents, except for the document by Rodriguez-Saldana et al. who assessed DR based on self-reports. Diagnostic comparability is expected even for information from clinical charts because dilated or non-dilated funduscopy was the established method for assessing DR at the time. Clearly defined diagnosis criteria were available for DR and were identical across the studies. The document provided by Polack et al. was especially valuable for estimating the discrepancy between self-reported data from ENSANUT 2012 and information obtained through funduscopy with a comparable study setting. The comparison suggests that the prevalence of DR was 2.8 times higher in information obtained through funduscopy compared to self-reported data. Therefore, it is likely that other complications in the ENSANUT were similarly underestimated. However, the lack of comparability between documents only allows for approximations, and comparisons should be made with caution. The implementation of a central diabetes register, where medical records on the history of diabetes, comorbidities, complications, treatments, physician follow-ups, and other documents are filed, and similar studies to the one by Polack et al. could markedly improve data availability and validity. Finally, it is important to mention that the results presented in this dissertation are not exhaustive and rather serve to provide a general impression of the availability and quality of data in Mexico and Central America.

In the following section, we conduct a detailed analysis of the epidemiology, risk factors and spatial distribution of diabetes complications, as well as describe the utilisation of preventive measures in rural and urban areas of Mexico using the Mexican National Health and Nutrition Survey (ENSANUT 2012).

2 PART II: Diabetes complications in Mexico

2.1 Introduction

2.1.1 Epidemiology of Type 2 Diabetes Mellitus in Mexico

Mexico has experienced a fast epidemiological transition in the past decade. In comparison to all OECD nations, Mexico has demonstrated the strongest development in recent years. With this improvement, a shift in the high prevalence of infectious diseases and undernutrition to a high prevalence of non-communicable diseases took place. Along with urbanisation and development came changes in dietary and physical activity patterns, leading Mexico to experience the largest increase in obesity and diabetes ever recorded worldwide(Barquera et al., 2008). Nationally, non-communicable diseases caused 75% of total deaths and 68% of total Disability Adjusted Life Years (DALY), and 9.7% of deaths were attributable to diabetes(Stevens et al., 2008). The results of National Health and Nutrition Surveys in Mexico suggested a rise in the prevalence of diabetes over the past several decades. In the first national health survey, conducted in 2000, the prevalence of previously diagnosed diabetes was about 5.8%. This increased to 7.3% in 2006, along with an additional 7.1% of people with undiagnosed diabetes that were screened during the survey, making the total prevalence 14.4%(Villalpando et al., 2010). Results from ENSANUT 2012 suggested that the prevalence of diabetes was 9.2%, without taking undiagnosed cases into account(Hernández-Ávila, Gutiérrez, & Reynoso-Noverón, 2013). No national incidence rates for diabetes in Mexico have been published. However, Meza et al. (2015) estimated an exponential increase during 1960 and 2012, with rates doubling every 10 years(Meza et al., 2015). With regard to the age of onset of diabetes, people in developing countries are diagnosed with diabetes between 45 and 64 years of age, while a majority of people from developed countries are diagnosed with diabetes over the age of 64 (Wild, Roglic, Green, Sicree, & King, 2004). This predicts the development of diabetic complications, with diabetes duration and glycaemic control being the most relevant risk factors(Knuiman, Welborn, McCann, Stanton, & Constable, 1986). As outlined beforehand, diabetes complications are frequently found in patients with diabetes in Mexico (Results from the systematic literature research: DR: 32 – 73%; DN: 26 - 69%; DF: 2 – 11%; DKD: 16 -38%), and social determinants have relevant effects on the utilisation of preventive measures(Walker, Smalls, Campbell, Strom Williams, & Egede, 2014). Certain factors, such as socioeconomic disadvantage, health care access and demographic characteristic, predispose people to lower treatment adherence and glycaemic control. Additionally, people from low- and middle- income countries are often referred to specialised centres when diabetes complications reach irreversibly advanced stages, leading to financial impacts on individuals and health systems(Barquera et al., 2013; Cervantes-Castañeda et al.).

2.1.2 The economic burden of diabetes complications in Mexico

In 2010, diabetes ranked 11th among the main reasons for hospitalisations and was increasing hospital stays by 2.6 days compared to other diseases(Rull et al., 2005). Arredondo and Reyes (2013) calculated the direct and indirect costs of diabetes in 2011 in Mexico. The direct costs of diabetes were primarily due to prescribed anti-diabetic medication, followed by outpatient care (consultations) and hospitalisation. Twenty-four percent of all direct costs were spent on DKD, 3% on DR, 0.8% on DN and 0.5% on peripheral vascular disease. Indirect costs represented 56 % of the total cost of diabetes mellitus in Mexico in 2011, and costs arising due to permanent handicap made up for 93% of all indirect costs followed by premature mortality (5%) and temporary handicap (2%)(Arredondo & Reyes, 2013). Once diabetes complications appeared, the annual average diabetes cost increased by 75% for DN, 13% for vascular complications, 8% for retinopathy and 3% for neuropathy(Barquera et al., 2013). Arredondo and Reyes pointed out that the majority of all costs arose from the indirect costs, with permanent handicap and chronic renal failure in particular being the most expensive factors of all arising costs. This is particularly problematic considering that an increasing trend towards early onset diabetes has been observed in recent years in Mexico. In 1993, 1.8% of the population at or above 40 years of age had diabetes. This prevalence reached 2.3% in 2000(Olaiz-Fernández, Rojas, Aguilar-Salinas, Rauda, & Villalpando, 2007) and 5.7% in 2006(Jimenez-Corona, Rojas, Gomez-Perez, & Aguilar-Salinas, 2010). Economically, patients with early onset diabetes have an increased risk of developing disabling diabetes complications at a younger age, which reduces productivity and employment chances compared to those who experience complications at an older age(Seuring, Goryakin, & Suhrcke, 2015). Also people that work in the informal sector (approximately 58% in 2005) rely on their income even at older age due to the lack of financial security and health care coverage. (Aguila, Diaz, Fu, Kapteyn, & Pierson, 2011).

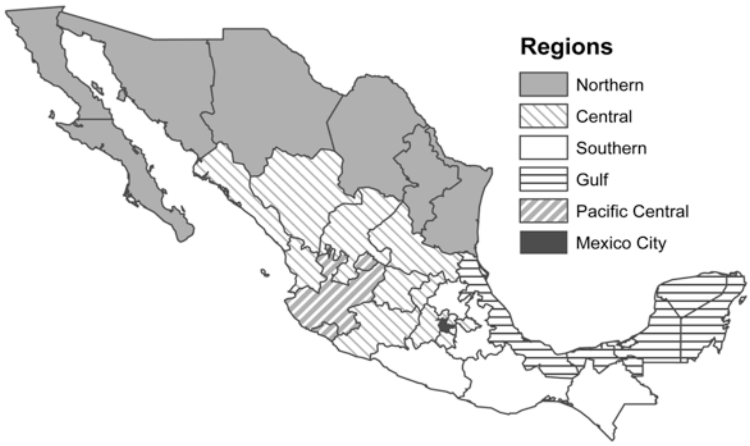
Although out-of-pocket-payments in Mexico have been reduced by 12.6% since 2009, they remain high, making up 41% of all health spending in 2016, and are twice as high compared to the OECD average(OECD Organisation for Economic Coooperation and Development, 2017). Accordingly, Mexican households can afford approximately 50% of all costs, and only 45% of the medical expenses required to manage diabetes are covered by the government(Arredondo & Reyes, 2013). Taking all these factors into account, preventive medicine in patients with diabetes has gained importance in Mexican health policy and should be cost-effective at all stages of diabetes. According to Castro-Ríos et al. (2010), each US dollar spent on prevention would save $84 to $323 over a 20-year period(Castro-Rios, Doubova, Martinez-Valverde, Coria-Soto, & Perez-Cuevas, 2010).

Public health care, ‘Seguro Popular’ (SP), covers a large part of the needs of the Mexican population with diabetes and those with diabetes complications. People that are insured by SP largely represent the formerly uninsured population, the unemployed population and people working in the informal sector with lower economic resources. Prior to the implementation of SP in 2003, almost half of the population did not have any health insurance(Sosa-Rubí, Galárraga, & López-Ridaura, 2009). While Social Security (SS) is equally funded by the employee, the employer and the government, SP (public health care) is fully or partially subsidised by the government depending on a person's employment status(Dantés et al., 2011). Consequently, states and areas where there are high prevalence of diabetes and high complications rates and where large proportions of SP affiliates or uninsured patients live rely more on public funding to cover the health care needs of the population (Davidson, Andersen, Wyn, & Brown, 2004; OECD Organisation for Economic Coooperation and Development, 2016b).

2.1.3 Geographical differences of diabetes outcome

Geographic analysis of illness patterns helps to establish public health interventions aimed at monitoring and controlling communicable diseases where these are most required. Geographic disparities in diabetes outcomes have been observed in prior studies. In the US, DF and amputation is clustered in neighbouring areas. Areas with high rates of LEA were associated with lower socioeconomic statuses, African American ancestry and higher mortality from DF(Margolis et al., 2011). Observations in Mexico suggest that diabetes mortality differs across regions. In a document from 1995, Escobedo and Santos found that states situated in the north and the federal district of Mexico had higher diabetes mortality rates compared to southern states(Escobedo-de la Pena & Santos-Burgoa, 1995). However, diabetes mortality in southern states increased by 128% from 1980 to 2000, compared to the northern region where mortality rates only increased by 32.5%(Barquera et al., 2013). Stevens et al. (2010) explain mortality disparities with regional differences in regard to the current epidemiological transition stage. According to their results with data from 2010, the southern region was the least developed region and, at the earliest transitional stage, was facing a double burden of pre-transitional diseases (e.g. infectious disease, malnutrition, etc.). This region simultaneously had the highest burden of chronic non-communicable disease (Diabetes mellitus, Cardiovascular disease, etc.) per capita. In comparison, the northern and the Pacific Central region reflected the highest level of social and economic development with an epidemiological transition profile of high-income nations(Stevens et al., 2008). The southern region and the Yucatán peninsula have the highest proportion of indigenous communities. While the Yucatán peninsula has largely benefitted from tourism in recent years, the states to the south have not benefited from equivalent economic resources and lag behind in structural development. All of these factors contribute to the heterogeneous socioeconomic patterns associated with differences in diabetes outcomes. The description of regions in this analysis refers to the regions established by Stevens et al. in 2010 (see Figure 2 below).

Figure 2. Regions of Mexico



Mexican regions based on geographic proximity and similarity over several indicators, including a deprivation index, per capita GDP, and overall mortality levels (from Stevens et al., 2010 (Stevens et al., 2008))

2.1.4 Diabetes in rural and urban areas

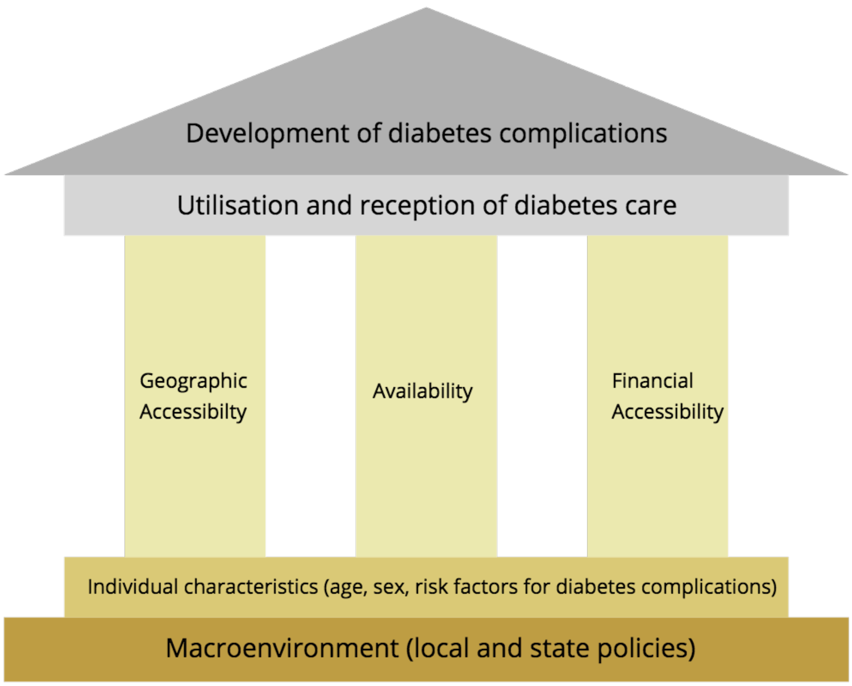
Similar to interstate disparities with regard to diabetes outcomes, urban and rural localities differ concerning the prevalence of diabetes and diabetes complications. However, inconsistent results from prior research indicate that rural-urban differences regarding the prevalence of diabetes and diabetes-related complications are bound to context. For example in Mexico, the prevalence of diabetes was higher in urban areas compared to rural areas in 2000 (10.4% vs. 5.6%, resp.) and in 2006 (15.5% vs. 8.2%, resp.) (Barquera et al., 2008). Yet, in a cross-sectional study in the US using data from the Behavioral Risk Factor Surveillance system (BRFSS), the prevalence of diabetes was 8.6% higher among rural respondents due to increased rates of poverty, obesity and tobacco use among the rural population living in the US(O'Connor & Wellenius, 2012). Likewise, rural residents in the US reported higher rates of DR compared to urban residents (25.8% vs. 22.0%, p=0.007) in the BRFSS 2006(Hale, Bennett, & Probst, 2010). Additionally, in China, DR was more prevalent across rural regions (29.1–43.1 %) compared to urban areas (18.1%), most likely because of inadequate screening techniques and care for diabetes in rural areas. Conversely, the prevalence of DR in

India was higher in urban areas (18.0% in urban vs. 10.8% in rural areas), potentially due to selective mortality of people with diabetes complications in rural India(Lee, Wong, & Sabanayagam, 2015). In rural areas of Mexico, access to and quality of diabetes care was reported to be considerably lower. According to Salinas et al., in 2011, older Mexicans living in rural areas were less likely to have health care coverage and health care services were difficult to access(Salinas, Al Snih, Markides, Ray, & Angel, 2010). Lower physician and specialist densities, resulting in larger travel distances for patients, also limited access to health care. For example, in the federal district in Mexico, the physician density was 3.9 per 1000 inhabitants, whereas Chiapas and Puebla, states with large rural areas, had a physician density of 1.3 per 1000 inhabitants in 2013(OECD Organisation for Economic Coooperation and Development, 2016a). Furthermore, socioeconomic differences between rural and urban areas resulted in catastrophic health expenditures that were 3.5 times higher in rural Mexico compared to urban households(Knaul et al., 2011). In order to explore the effects of locality on the development and progression of diabetes complications, we established a framework to structure the subsequent analysis.

2.2 Analytical framework – Access to diabetes care

As suggested by previous research, we viewed geographical differences considering the development of diabetes complications as resulting from the decreased participation of individuals in diabetes complication screenings and subsequent insufficient blood glucose control. Access to health care or, in this case, diabetes care, has been previously defined based on the need for services. This concept relies on the availability and affordability of services as well the ability to receive health services and to receive health care that is appropriate to the needs of the patient. This also further implies that patients understand the advantage of preventive measurements(Levesque, Harris, & Russell, 2013). We adapted the previously established framework of Peters et al. (2008) in '*Poverty and Access to Health Care in Developing Countries*' to fit univariate and multivariate models for the use of the ENSANUT 2012 data(Newman et al., 2015). This approach simplifies the complex set of interactions among patients and providers and explores factors that lead to geographical disparities in diabetes outcomes (see Figure 3). In our model, performance of diabetes screening and follow-ups was used as a parameter to measure access to diabetes care. The model is based on three main dimensions of access: i) geographic accessibility; ii) availability; and iii) financial accessibility. In this model, geographic accessibility depends on the user and service's location, with differences between rural and urban residents and differences between states. The concept of 'availability' means that health care demands are covered by the health care provider, including operation and travel times and to ensure sufficient staff and equipment in health facilities to meet the health demands of a person seeking health care. Financial accessibility consists of two elements: the cost of the services and the user's resources and willingness to pay for these services that are in direct relation to the health care and socioeconomic status of the user. These factors are the individual's characteristics (including age, sex, and risk factors for the development of diabetes complications: diabetes duration, comorbidities, smoking, diabetes treatment) and policies at 'macroenvironmental level'(Peters et al., 2008). The three main columns in the conceptual framework (geographic accessibility, availability and financial accessibility) are considered to interact with health policies and with the individual's characteristics. The result defines the probability and opportunity for patients with diabetes to seek on-going medical care, which influences the development and presence of diabetes complications.

Figure 3. Conceptual framework



* Conceptual framework adapted from Peters et al. (2008)(Peters et al., 2008)

2.3 Objectives of the quantitative analysis

The aim of this analysis is to assess factors that are associated with presence of microvascular diabetes complications in different environmental settings. According to prior findings, we assumed that Mexico's geographically, politically and socioeconomically heterogeneous landscape has influenced people's access to and utilisation of preventive diabetes complication screenings, consequently affecting the development of diabetes complications.

Therefore, we analysed whether Mexican people with microvascular complications were clustered in certain areas. Using data-mapping techniques, we explored whether the geographical pattern of diabetes complications visually matched the distribution of areas with lower developmental statuses. We also explored whether a type of health care (public health care or no health care versus social health care) and other socioeconomic factors at the individual level were associated with the clustering of diabetes complications.

The next step was to analyse whether adherence to follow-up screenings across people with diabetes complications depended on their areas of residency (urban or rural), type of health care and socioeconomic factors. Descriptive statistics and logistic regression analysis were used, with performance of follow-up screenings and the number of consultations over the past 12 months as independent variables.

Spatial patterns of diabetes mortality and burden have been previously described. However, to our knowledge, this dissertation's investigation into the spatial disparities of microvascular diabetes complications across Mexico's states and rural areas is unique and aims to support further interventions in less developed areas of Mexico.

2.4 Material and Methods

2.4.1 The National Health and Nutrition Survey (ENSANUT 2012)

The data for this study were obtained from the National Health and Nutrition Survey (Encuesta Nacional de Salud y Nutrición, Ensanut 2012), a probabilistic, multistage and clustered household survey representative of the entire Mexican population (approximately 115 million inhabitants in 2012), according to estimates by the population register in 2012. For each federal state, urban and rural area distributions were sampled in proportion to their real size, while areas with the highest deprivation were oversampled in order to achieve a considerable sample size even for minorities living in these areas. Whether an area was highly deprived or not was decided based on an index that was created in 2005 by the Consejo Nacional de Evaluación de la Politica de Desarollo Social (CONEVAL). The application of weighting factors for oversampled areas were considered to achieve the appropriate weight and ensure correct observations. More information on the survey design can be found elsewhere(Romero-Martínez et al., 2013). Information on the socio-demographic and health-related factors of all participants was obtained. Respondents with a previous self-reported diagnosis of diabetes were asked further questions regarding diabetes complications, duration, care, treatment, among other things. The presence of diabetes complications was assessed based on questions asked to individuals about the presence of leg or foot ulcers, limb amputation, visual impairment, retinal damage, loss of sight, ESRD requiring dialysis and foot pain or burning indicating DN. Blood samples were drawn from 751 individuals. However, after exclusion of patients with missing information, only 712 of those with HbA1c measurements remained. Participants were instructed to fast for 12 hours, and the time of the last meal was registered. No distinction between type 1 and type 2 diabetes mellitus was made.

The datasets containing information on the survey participants were split into several datasets. Dataset merging to attain all outcome variables in one dataset was achieved using the two key variables, ‘folio’ and ‘intp’, which assign a number to each household and to each inhabitant. Depending on the survey group, each dataset contained different weighting factors. In this statistical analysis, the weighting factor ‘pondef’ (≥ 20 years old) was used for adults.

The socioeconomic indicator used in the ENSANUT 2012 was based on the National Income and Expenditure Survey conducted in 2010 (INEGI 2010). Briefly, cut-off-values for each decile were set up[2], which assigned each household depending on its highest probability to one of the deciles. Variables used for the prediction of the income decile were demographic structure of the household, such as years of education, employment and sex of the head of family; sociodemographic characteristics, like the number of people living in the household or number of children; apartment characteristics and goods that resemble a certain level of prosperity; patterns of consumption and expenses of the household; and characteristics of the region of residency. A detailed description of the assessment of the indicator is described elsewhere(Gutiérrez, 2013). In this analysis, we used quintiles, hence each two neighbouring deciles were grouped into one, resulting in five quintiles.

2.4.2 Access to ENSANUT data

Access to data was permitted by online registration at *http://ensanut.insp.mx/forma_registro.php#.Vg2LQXi4k0o*. The name and email address of the submitter, name of a responsible person, institution, investigator's role and a brief description of the investigator's topic was requested for the registration. Once registration was completed, access to data download was permitted with a username and password.

[2] Income decile: 'The total income deciles divide the population aged 15 years and over into 10 equal-sized groups according to the rank of the total income. Those in the bottom decile group are the ones who fall in the lower 10 percent of the total income distribution. Those in the top decile group are the ones who fall in the highest ten percent of the total income distribution' (Statistics Canada, 2016).

2.4.3 Statistical Methods

Figure 4 outlines the analytical procedure of this analysis. In summary, this analysis was divided into three main chapters, exploring differences among individuals, states and rural/urban areas.

At first, individuals with and without diabetes complications were described using univariate analysis. We included variables that were positively associated with the presence of diabetes complications in previous publications. Variables that were significantly associated with the presence of diabetes complications in the univariate analysis or variables of particular interest were subsequently used as covariates in the logistic regression analysis.

Second, a descriptive analysis was performed to explore the prevalence of diabetes complications across the 32 federal states of Mexico. States with high, intermediate and low rates of diabetes complications were grouped, and univariate analysis was performed in accordance with the results of the logistic regression in order to explore socioeconomic differences among the states with different complication rates.

Lastly, a descriptive and multivariate logistic regression analysis explored differences between residents with diabetes complications from rural and urban areas with regard to guideline adherence of preventive measures.

To estimate the distribution of the groups that we compared, we calculated percentages for categorical variables and measures of central tendency for numerical variables. The Rao-Scott chi-square test as an adjusted version of the Pearson chi-square test was used to estimate univariate associations(Rao & Scott, 1987). A significance threshold was set at .05, and p-values were provided for the descriptive analysis. All calculations were performed using the Complex Sample Function of SPSS 22.0. A comprehensive guide for statistical analysis of the ENSANUT data can be found elsewhere(Romero Martínez, 2012). For the univariate analysis, we provided the weighted and un-weighted counts of each subgroup to provide information on the actual number of surveyed people and the corresponding people represented. In the logistic regression analysis and in the subgroup analysis with small case samples, we preferred to report the actual number of surveyed people in order to provide a better idea of the statistical relevance and ability to generalise the results for the Mexican population. However, the percentages refer to the weighted population, meaning that the counts presented cannot be used to calculate the presented proportions.

Results of the logistic regression models were presented with estimated Odds Ratios (OR) and corresponding 95% confidence intervals. Bonferroni correction was considered to reduce the likelihood of finding an erroneous significant effect caused by multiple testing. To detect extensive multicollinearity among variables, we calculated variance inflation factors (VIF) for each variable. A variance inflation factor greater than 10 indicated multicollinearity and such variables were not included to our model, as suggested by prior studies (Vatcheva, Lee, McCormick, & Rahbar, 2016).

Figure 4. Analytical procedure

I. Exploratory analysis of factors for presence of diabetes complications

Descriptive analysis of the study sample
(Individuals with versus individuals without diabetes complications)
and
Multivariate logistic regression analysis to identify independent factors of the presence of diabetes complications

II. Prevalence of diabetic complications – Interstate disparities

Exploration of spatial patterns of diabetes and diabetes complications and associated risk factors among Mexico's 32 states

III. Diabetes care in urban and rural areas

Descriptive analysis of people with diabetes complications in rural and urban areas
and
Multivariate logistic regression analysis on preventive measures performed in urban versus rural areas among people with diabetes complications

I. Exploratory data analysis of factors contributing to the presence of diabetes complications

In order to explore the influence of demographic and socioeconomic factors as well as the influence of access to health care on the presence of diabetes complications, we used contingency tables and OR to measure the association between the two variables. Further logistic regression analyses served to identify independent factors of the presence of diabetes complications. In order to avoid multicollinearity in the logistic regression analysis, we did not include each preventive item. Instead, we selected 'any preventive measure' and 'frequency of diabetes control in the past 12 months' for the logistic regression model. 'Any preventive measure' was computed through a simple inversion of the values of 'no preventive measure performed in the past 12 months'. Other variables that were not significantly associated with diabetes complications in the univariate analysis but were still included in the logistic regression model were ethnicity and insurance status, as these variables were of special interest for the subsequent analysis. The model included the following variables (* marks the reference category):

Dependant variable

Presence of diabetes complications versus no presence of diabetes complications*.

Independent factors

Gender	Female versus male gender*
Ethnicity	Indigenous versus non-indigenous origin*
Education	Less than primary school, less than secondary school versus secondary school or more*
Employment	Unemployed, retiree, housekeeper and 'other' versus being employed*
SES	Belonging to the 1st, 2nd 3rd, 4th versus 5th quintile*
Marginality Index	High marginality versus low marginality index*
Antidiabetic treatment	Insulin or oral antidiabetic medication (e.g. Metformin) or the combination of both versus no pharmaceutical diabetes treatment*
Use of alternative medicine	Using alternative medicine (e.g. herbs or traditional healing methods) alone versus non-utilisation of alternative medicine*

Physical exercise	Performance of physical exercise to prevent or delay diabetes progression versus no exercising*
Preventive actions performed	Any preventive measure performed in the past 12 months versus no preventive measure performed*
Annual diabetes controls	Less than four diabetes controls performed by a physician versus four or more diabetes controls*

Potential confounders for presence of diabetes complications were used as covariates:

Diabetes duration	Respondents were asked how long ago they were first diagnosed with diabetes, measured in years with five-year steps
Age	Age of the respondent was measured in years with 10-year steps

II. Geographical disparities of diabetes complications across Mexico's states

Contingency tables were used to calculate the rates of diabetes complications for each federal state. States were combined into three groups, with approximately equal distributions, of low, intermediate and high rates of diabetes complications. States were grouped as follows:

1) States with low diabetes complication rates (LCR: ≤ 55.0% of people with diabetes)
2) States with intermediate diabetes complication rates (ICR: 55.1% - 65.0%)
3) States with high diabetes complication rates (HCR: ≥65.0%)

The assumption of normality was based on each combination of age, gender and state of HCR, LCR and ICR as assessed by visual inspection of Normal Q-Q Plots and Histograms for each group and combination of age and sex. Previous results from the logistic regression (factors that contributed to the presence of diabetes complication) were used to determine whether individual characteristics, socioeconomic factors and access to diabetes care differed among the three groups. Again, contingency tables and tests for equal cell distributions across the three groups were calculated.

We further inspected and compared the prevalence of diabetes and diabetes complications using choropleth maps. A low prevalence of diabetes served as a potential predictor of undiagnosed diabetes across areas with high complication rates similar to previous studies(Zhou et al., 2015). For this reason, we used Tableau Desktop Professional 10.3 and created choropleth maps of the prevalence of diabetes and diabetes complications. We further inspected geographical patterns of rural residency, health insurance status and preventive care utilisation among people with diabetes and compared these patterns to the spatial distribution of rates of diabetes complications. The outlines of the maps were downloaded from the 'ArcGIS' homepage: *http://www.arcgis.com/home/item.html?id=ac9041c51b5c49c683fbfec61dc03ba8,* (last accessed 02-02-2018*)*. The shapefile was provided by mhoel@uss.on.ca, with no special restrictions or limitations on using and publishing the outline of the map.

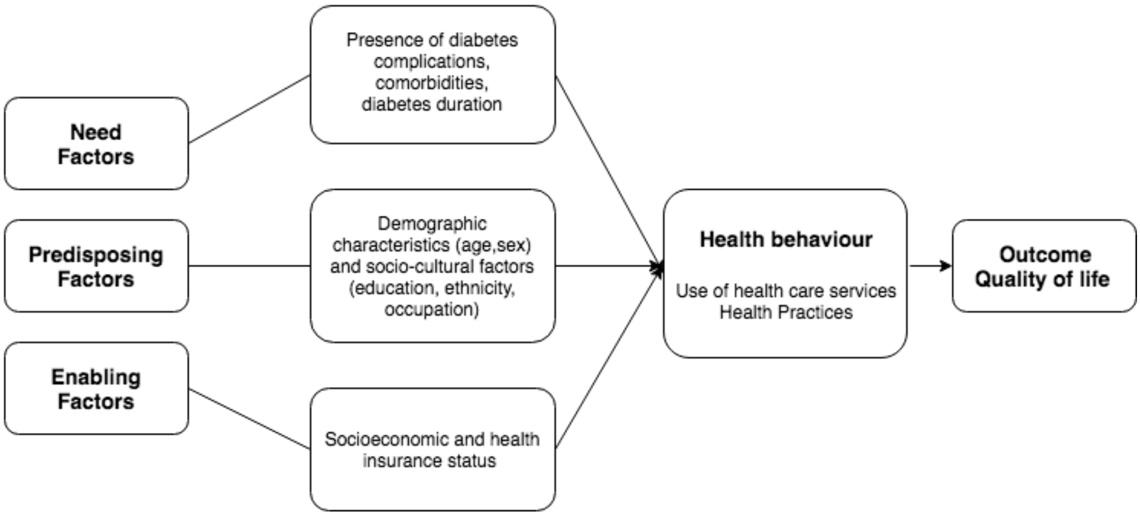
Data Visualization using Tableau Desktop Software.

Data Visualization was executed using Tableau 2017 Professional edition, Tableau Software Inc., Seattle Washington, United States. Prior registration was requested during the installation process of the Tableau Desktop Software. Tableau Desktop is an open-source service that allows anyone to publish interactive visualisations of data on the web. Visualisations can be embedded in webpages and blogs, they can be shared via social media or email, and they can be made available for download to other users. Tableau Desktop Software does not claim copyrights and ownership of self-compiled maps.

III. The rural-urban divide

We conducted a further analysis to test the association of diabetes care utilisation among rural and urban residents with diabetes complications. The model we established to explore rural-urban differences in diabetes care was based on the analytical framework from Andersen's 'Behavioral Model of Health Services Use' (Babitsch, Gohl, & von Lengerke, 2012). Andersen's Model used need, predisposing and enabling factors to explain differences in health care utilisation. The presence of diabetes complications, comorbidities and diabetes duration defined the need for diabetes care. Predisposing factors include demographic characteristics (age and sex) and social factors (occupational status and ethnicity) that 'biologically' and 'culturally' predispose individuals to use health care services. Enabling factors include financial and organisational factors, such as the socioeconomic and health insurance status of individuals, which affect one's ability to afford health care (See Figure 5).

Figure 5. Conceptional framework for assessing health service use and diabetes outcome.



First, the univariate analysis was used to test for demographic and socioeconomic differences, modelled after the elaborated conceptual framework. We further analysed how many people in rural and urban areas received comprehensive diabetes care with annual eye and foot revision, Hba1c and MiA tests ('Comprehensive diabetes care'). This variable was determined based on the sum of all the preventive measures carried out over the past 12 months. The values of the variable ranged from a minimum of zero simultaneous preventive actions to a maximum of four simultaneous preventive measures performed in the past 12 months.

Separate logistic regressions were performed to test the adjusted association of diabetes care between rural and urban areas. The dependent variable in each logistic regression model contained one of the recommended screenings/diabetes follow-ups that were carried out (eye revision, foot revision, HbA1c-, MiA test, venous blood glucose tests and four or more diabetes controls with a physician and report of any/no preventive measure). An individual's area of residency (rural vs. urban) served as an independent variable. Variables that were expected to interact with the variable of diabetes care utilisation were used as covariates (*marks the reference group):

Dependant variable

Performance of one annual eye revision, foot revision, HbA1c test, MiA test, venous blood glucose tests and four or more diabetes controls with a physician).

Independent factors

Rural versus urban residency

Model covariates

1. **<u>Predisposing factors</u>:** age, female gender, self-reported indigenous origin and employment (0 = 'unemployed', 1 = 'employed', 2 = 'retiree', 3 = 'housekeeper' and 4 = 'other')
2. **<u>Enabling factors:</u>** ENSANUT generated a socioeconomic indicator using demographic and socioeconomic data based on the National Income and Expenditure Survey 2010. The indicator divided Mexican households into quintiles, with '1' representing the least favourable and '5' representing the most favourable living conditions. More information on the indicator can be found elsewhere (Gutiérrez, 2013). Health insurance was recoded if the respondent had '0' for no health insurance, '1' for 'Seguro Popular', a social health care provider introduced in 2003 by the government to cover the formerly uninsured population, and '2' for all other health care provider (e.g. private or institutional health care provider).
3. **<u>Need factors</u>:** Respondents were asked how many years ago they were first diagnosed with diabetes. Furthermore, the presence of comorbidities was computed as a composite variable, coded '1' at presence of cardiovascular disease (history of myocardial infarction, angina pectoris or cardiac insufficiency), previous diagnosis of arterial hypertension and/or previous diagnosis of hypercholesterolemia and '0' if none of the mentioned comorbidities were present.

2.5 Results

2.5.1 Data quality

Out of 46,277 adults (people aged 20 years or older), 4,490 people with a previous diagnosis of diabetes (representative for approximately 6.4 Million people) were surveyed in ENSANUT 2012. We further excluded cases with missing entries. This resulted in a final case count of N=4254, with N=236 excluded cases (see Figure 6). The distribution of missing entries by variable is depicted below (see Table 6).

Figure 6. Flowchart of inclusion and exclusion criteria of survey participants

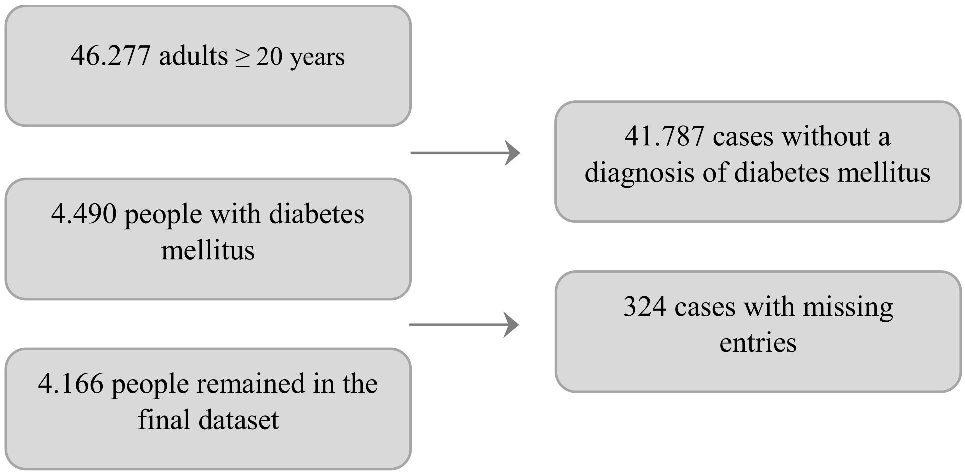


Table 6. Distribution of variables with missing values*

Variable description	*Variable No.*	*Valid (N)*	*Valid (%)*	*Missing (N)*	*Missing (%)*
Diabetes duration	a302b	4454	99.2%	36	0.8%
Freq. DM controls	a305	4472	99.6%	18	0.4%
Cholesterol test	a601	4432	98.7%	58	1.3%
Triglyceride test	a603	4406	98.1%	84	1.9%
Chol/Trig screening	a1001c	4470	99.5%	20	0.5%
Smoking freq.	a1303a	4489	100%	1	0.0%
Health insurance	afilia_1ra	4487	99.9%	3	0.1%

** no missing values were found for all other variables that are not mentioned*

Except for age and duration of diabetes, included survey participants did not differ significantly from participants that were excluded due to missing entries. The 324 excluded people were approximately 15 years older (p < 0.001), and had a mean diabetes duration of 16 years compared to nine years in the work file (p < 0.001). They were less likely to be of indigenous origin (20% vs. 23%), lived in rural areas rather than in urban or metropolitan areas (16% vs. 15%), reflected a higher prevalence of microvascular diabetes complications by 8% and were more likely to have a lower socioeconomic background (see Table 7).

Table 7. Description and comparison of ex- vs. included cases

			Excluded cases (N = 324)		***Included cases (N = 4166)***		
Variable description	*Variable name*	*Value*	*N**	*% / Mean(SE)*	*N**	*% / Mean(SE)*	*p-value≠*
Age	edad	years	324	**71(1.3)**	4166	**56 (0.4)**	<0.001
Sex	sexo	female	198	**51.0**	2569	**56.0**	0.371
		male	126	**49.0**	1597	**44.0**	
Ethnicity	h215	non-indig.	236	**80.6**	3117	**76.9**	0.342
		indigenous	88	**19.4**	1049	**23.1**	
Residency	est_urb	urban/metr.	221	**85.1**	3012	**76.9**	0.592
		rural	1154	**16.3**	103	**14.9**	
SES	quintiles	1st	106	**24.1**	890	**18.8**	0.101
		2nd	71	**24.3**	791	**19.1**	
		3rd	56	**21.8**	757	**17.9**	
		4th	58	**18.1**	963	**24.7**	
		5th	33	**11.7**	765	**19.5**	
Diabetes duration	a302b	years	324	**16(1.4))**	4166	**9(0.2)**	<0.001
Complication prevalence	kom_ges		236	**68.7**	25	**61.4**	0.172

* N(total) =counts refer to the un-weighted number

≠Significance is based on the adjusted second-order Rao-Scott Chi Square statistic.

2.5.2 Diabetes complications – Risk factors

Descriptive analysis of people with and without diabetes complications

Representative of approximately 5.9 million Mexicans with diabetes, 4,166 people were included in the analysis. This resulted in a prevalence of diabetes of 8.1%. Additionally, 2.3 million people were diagnosed with diabetes but had no diabetes complications (38.6% of all people with diabetes). About 3.6 million people with diabetes reported having any of the analysed diabetes complications, resulting in a prevalence of complications of 61.4% (N=2546). Vision impairment and DN were reported with the highest frequencies compared to all analysed complications. Lower extremity amputations and renal replacement therapy were reported with the lowest frequencies.

Figure 7. Diabetes complication prevalence in % of people with diabetes in Mexico

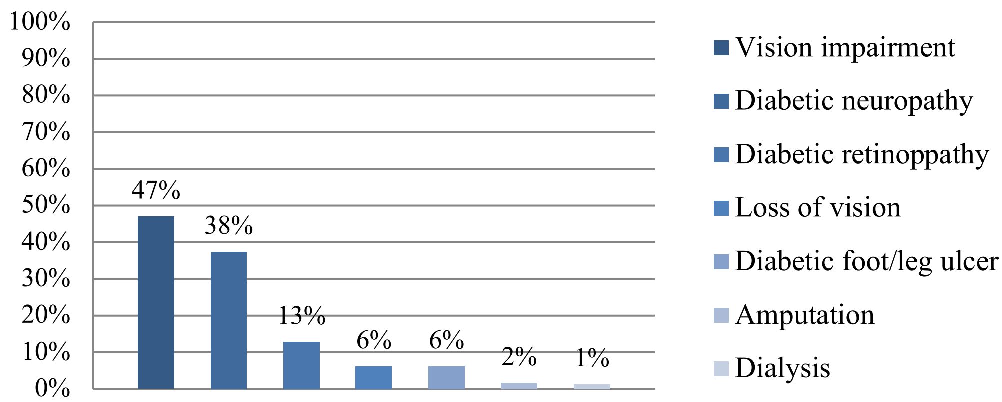


Figure 9 shows the proportion of people with diabetes complications among people with diabetes in Mexico. According to ENSANUT 2012 data, almost half of the population reported any kind of vision impairment, while 13% reported diagnosed diabetic retinopathy. Diabetic neuropathy was highly prevalent as well with a prevalence rate of 38% of the diabetic population. More advanced complications such as blindness, diabetic foot/eg ulcer, and dialysis were less prevalent.

A detailed description of survey participants with and without diabetes complications is displayed in Table 8. On an individual level, the female gender (p=0.018) and comorbidities (p=0.001), such as arterial hypertension, cardiovascular disease and hypercholesterolemia were positively associated with the self-reported presence of diabetes complications. Infrastructure in terms of living in rural and highly marginalised areas had a significant effect on the presence of diabetes complications. Eighteen percent of the respondents with complications lived in rural areas versus 13% in the non-complication group (p<0.001), and 20% versus 16%, respectively, lived in highly marginalised areas (p=0.009). Similar to this observation, respondents with complications were more likely to have a lower socioeconomic background (40% in the complication-group belonged to the lowest two lowest socioeconomic quintiles vs. 34% in the non-complication group) and more likely to have a higher school degree; 13% of the respondents with complications versus 9% in the non-complication group had not obtained more than a primary school degree. Correspondingly, unemployment rates were higher for those with complications (12% vs. 8%). With regard to the utilisation of preventive diabetes care among people with and without diabetes complications, 70% of those with complications reported to be seen by a doctor for diabetes control purposes. Specific care, such as eye or foot revision, HbA1c tests and tests to check for MiA were realised in 7% to 17% of all patients with complications in the previous year and was higher among individuals with diabetes complications. Adequate blood glucose control with HbA1c levels equal or below 7% was achieved by a minority in both groups and was lower in the complication group (22% versus. 24%, respectively). However, the difference between both groups was not statistically significant (p=0.668).

Table 8. Description of participants with and without diabetes complications

Variable	Value	Respondents without diabetes complications N (weighted in 10.000) = 227.3	N (raw) = 1620	**% / Mean (SE)**	Respondents with diabetes complications N (weighted in 10.000) = 361.5	N (raw) = 2546	**% / Mean (SE)**	p-Value ≠
Individual level								
Gender	Female	124.7	1017	**50.8**	2.32	1750	**58.6**	**0.018**
Age, yrs		227.3	1620	**54 (0.6)**	361.4	2546	**57 (0.4)**	n.a.
Ethnicity	Indigenous origin	55.1	432	**22.6**	91.1	705	**22.9**	0.987
Diabetes duration, yrs		227.3	1620	**7 (0.3)**	361.4	2546	**10 (0.3)**	n.a.
Smoking	yes	80.8	534	**35.5**	137.5	883	**38.0**	0.335
Comorbidities		129.6	885	**57.0**	237.2	1663	**65.6**	**0.001**
Health care access								
Insurance	Uninsured	34.1	225	**15.0**	60.9	313	**16.9**	0.176
	Public	65.7	577	**28.9**	11.6	988	**32.0**	
	Other	12.7	818	**56.1**	18.5	1245	**51.2**	
Infrastructure	rural residency	30.6	438	**12.6**	72.8	819	**18.3**	**<0.001**
	high marginalization	36.1	490	**15.9**	72.1	857	**19.9**	**0.011**
Socioeconomic factors								
Socio-economic household	1st quintile	39.6	332	**17.4**	70.8	558	**19.6**	**<0.001**

level	2nd quintile	38.6	287	**17.0**	73.9	504	**20.4**	
	3rd quintile	36.3	273	**16.0**	69.0	484	**19.1**	
	4th quintile	54.2	368	**23.8**	91.3	595	**25.3**	
	5th quintile	58.5	360	**25.8**	56.3	405	**15.6**	
Education	none/less than primary	21.34	211	**9.4**	48.5	368	**13.4**	**<0.001**
	less than secondary	147.2	1094	**64.8**	267.6	1892	**74.0**	
	secondary or more	5.9	315	**25.8**	45.3	286	**12.5**	
Employment	unemployed	12.2	73	**5.4**	27.7	191	**7.7**	**0.001**
	employed	114.5	719	**49.9**	136.0	906	**37.6**	
	retiree	21.8	146	**9.6**	34.7	237	**9.6**	
	housekeeper	70.3	624	**30.9**	148.5	1127	**41.1**	
	other	9.5	58	**4.2**	14.4	85	**4.0**	
Diabetes care/Treatment adherence								
Treatment	Insulin and/or oral agent	177.5	1322	**78.1**	326	2322	**90.2**	
	Nothing	49.8	298	**21.9**	35.4	224	**9.8**	**<0.001**
	Alternative medicine	14.4	125	**6.3**	43.4	271	**12.0**	**<0.001**
Prevention	≥ 4 doctor visits	126.9	1025	**55.8**	252.2	1860	**69.8**	**<0.001**
	HbA1c controls	19.4	119	**8.5**	35.33	244	**9.7**	0.420
	Venous blood glucose control	104.7	708	**46.1**	208.0	1392	**57.6**	**<0.001**

	Foot revision	22.8	157	**10.0**	60.0	385	**16.6**	**<0.001**
	Eye revision	15.7	121	**6.9**	34.8	236	**9.6**	**0.041**
	Microalbuminuria test	14.9	90	**6.6**	35.8	218	**9.9**	0.064
	No prevention	159.7	1196	**70.3**	223.2	1670	**61.7**	**0.001**
Glycaemic control	HbA1c ≤ 7%	7.7	58	**23.9**	12.8	91	**21.6**	**0.668**
	HbA1c > 7%	24-4	187	**76.1**	46.6	365	**78.4**	

People with diabetes: N (total)= 4166

All calculations (%/SE) refer to the weighted counts (N weighted) and cannot be calculated using N(raw)

[1]*N(glycemic control, un-weighted) = 701*

[≠]*p- Values were calculated using adjusted Rao-Scott Pearson Chi- Square statisticS.*

Logistic regression analysis of contributing factors to the presence of diabetes complications

We analysed the association between the presence of diabetes complications and demographic, socioeconomic and diabetes-related factors using logistic regression analysis, with the presence of diabetes complications as the outcome/dependent variable. Results are presented in Table 9. Individuals with diabetes complications were more likely to have less than secondary or primary school education (OR = 1.46; p=0.004) and were more likely to live in rural areas (OR = 1.31; p=0.034). The socioeconomic household level of Mexicans with diabetes was significantly associated with the presence of diabetes complications; compared to the 5th quintile, residents from lower quintiles were approximately 1.5 times more likely to present diabetes complications, except for the lowest quintile, which missed the significance threshold. Similarly, adults enrolled in 'Seguro Popular' did not have significantly higher odds of reporting a previous diagnosis of one of the complications. However, those without health insurance, compared to people that were affiliated with institutional health care, were 1.6 times more likely to have diabetes complications (p=0.01). In terms of antidiabetic treatment, one's likelihood of presenting diabetes complications and using alternative medicine was twofold compared to respondents who did not use alternative medicine (homeopathy, herbal medicine and other alternative medicine). Ongoing treatment with insulin and/or oral antidiabetic agents increased a person's OR of reporting diabetes complications by 1.81 times compared to respondents with no pharmaceutical treatment (95%CI = 1.27 – 1.59). People who exercised regularly were more likely to belong to the non-complication group (OR = 0.62; 95%CI = 0.45 – 0.82). Prevention was significantly more common among those with diabetes complications. Any preventive screening and more than four annual diabetes controls were more likely provided to people with complications (OR = 1.56; 95%CI = 1.22 – 1.99). However, more than four annual diabetes controls missed the significant level with borderline 95-CI intervals (OR = 1.30; 95%CI = 0,99 - 1.69), but was greater among people with diabetes complications. Diabetes duration increased the likelihood of having diabetes complications by 1.18 for every five years, but age did not increase the risk of experiencing diabetes complications significantly.

Table 9. Multivariate logistic regression analysis of independent factors predicting the presence of diabetes complications

Variables	OR	95% CI Lower	95% CI Upper
Age	1.01	0.89	1.13
Female gender	0.96	0.71	1.29
Ethnicity			
Indigenous origin	0.96	0.73	1.20
Non-indigenous origin	.	.	.
Education			
Less than primary school	**1.46**	**1.00**	**2.15**
Less than secondary school	**1.48**	**1.16**	**1.90**
Secondary school or more	.	.	.
Employment			
Unemployed	1.39	0.75	2.59
Retiree	1.06	0.68	1.66
Housekeeper	1.31	0.96	1.79
Other	0.98	0.51	1.88
Employed	.	.	.
Socioeconomic level			
1st quintile	1.32	0.93	1.88
2nd quintile	**1.48**	**1.04**	**2.11**
3rd quintile	**1.59**	**1.11**	**2.28**
4th quintile	**1.50**	**1.06**	**2.12**
5th quintile	**.**	**.**	**.**
Marginality Index			
High	1.09	0.87	1.37
Low	.	.	.
Residency			
Rural	**1.31**	**1.02**	**1.69**
Urban/Metropolitan	.	.	.
Health insurance			
None	**1.62**	**1.15**	**2.27**
Seguro popular	1.10	0.83	1.46
Else	.	.	.

Antidiabetic treatment			
Insulin and/or oral agent	**1.81**	**1.27**	**2.59**
None	**.**	**.**	**.**
Use of alternative medicine			
Yes	**2.03**	**1.42**	**2.88**
No	**.**	**.**	**.**
Physical exercise			
Yes	**0.62**	**0.45**	**0.82**
No	**.**	**.**	**.**
Diabetes duration (per 5 years)	**1.18**	**1.08**	**1.29**
Presence of comorbidities			
Yes	**1.42**	**1.15**	**1.75**
No	**.**	**.**	**.**
Preventive actions performed			
Yes	**1.56**	**1.22**	**1.99**
No	**.**	**.**	**.**
Annual diabetes controls			
< 4	0.77	0.59	1.01
≥ 4	.	.	.

Population sample: Mexican residents with a previous diagnosis of diabetes (N = 4166)

* Pseudo R^2 Nagelkerke: 0.144

** Reference category: individuals without diabetes complication

2.5.3 Regional disparities with regard to the presence of diabetes complications

The geographic pattern of rates of diabetes and diabetes complications differed across Mexico's federal states. Diabetes prevalence ranged from 5.3% in Chiapas to 11.3% in Mexico City, resulting in a mean of 8.5%. Prevalence of any microvascular diabetes complications as a percentage of the population with diabetes varied from 42% in Quintana Roo to 77% in Guanajuato and Tamaulipas, resulting in a mean of 61.4%. Figure 8 and Figure 9 display the heterogeneous distribution of diabetes and its complications. Diabetes prevalence was highest along the Gulf of Mexico, in the state of Mexico and in Mexico City and was lowest in the southwest and parts of northern Mexico (Figure 8). Increased diabetes complication rates were observed mostly in states located in the centre and east central part of Mexico (Figure 9). The state with the strongest discrepancy, demonstrating a low prevalence of diabetes and a high prevalence of diabetes complications, was Chiapas. Chiapas had the lowest prevalence of diabetes of the 32 states (5.3%), but ranked 24th of 32 states in regard to the prevalence of diabetes complications (approximately 68%). Michoacán and Guanajuato followed this trend with rates of diabetes of 7.1% and 7.6%, respectively,, and a diabetes complication rate of 73% and 77%, respectively.

Three groups of states were established in accordance with their respective diabetes complication rates. States with HCR (≥ 65.0% of the population with diabetes) included Chiapas (67.9%), Tlaxcala (68.4%), Durango (68.9%), Jalisco (68.9%), Chihuahua (70.0%), Michoacán (71.8%), Veracruz (72.2%), San Luis Potosi (74.7%), Tamaulipas (76.5%) and Guanajuato (76.5%).

States with ICR (55.0% - <65.0%) were Colima (57.3%), Tabasco (58.5%), Federal District (=Mexico City) (58.7%), Aguascalientes (58.9%), Queretaro (60.8%), Zacatecas (62.5%), Puebla (63.6%), Nuevo León (63.2%), Coahuila (64.0%), and Oaxaca (63.1%).

The lowest complication rates (LCR < 55.0%) were observed in Quintana Roo (41.7%), Baja California North (44.5%), Yucatán (45.2%), Nayarit (45.5%), Sonora (46.0%), Sinaloa (48.7%), Morelos (49.8%), Baja California South (50.4%), Campeche (51.4%), Guerrero (53.6%), Mexico (53.9%) and Hidalgo (54.4).

Figure 8. Distribution of diabetes prevalence in Mexican states, in % of the general population

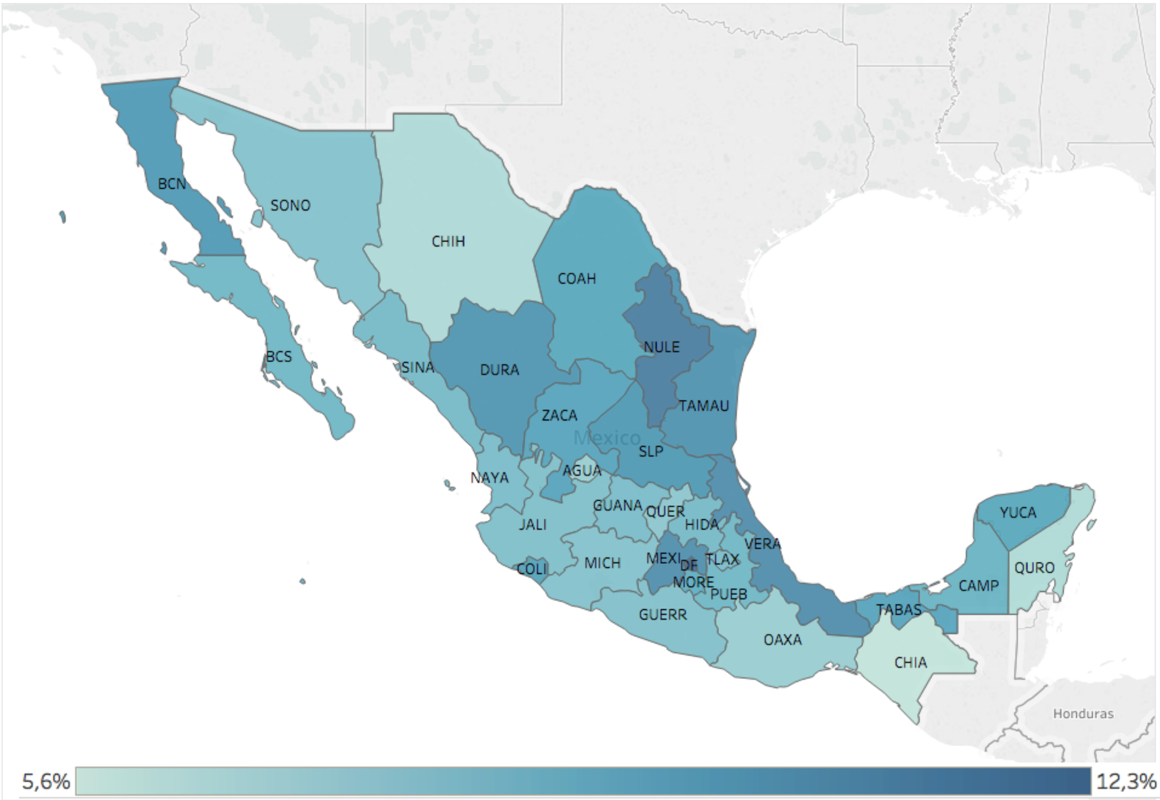


Figure 8 shows the rate of people that reported a previous diabetes diagnosis across all citizens from the 32 Mexican states. Chihuahua and the southern coast as well as states bordering with Central America in the south show low rates beginning from 5.6% in Chiapas. In some states along the gulf of Mexico as well as in Baja California Norte we observed more than twice as many people with diabetes compared to the north of Mexico and the south- and west coast of Mexico.

Abbreviations of states: AGUA = Aguascalientes, BCN = Baja California North, BCS = Baja California South, CAMP = Campeche, CHIA = Chiapas, CHIH = Chihuahua, COAH = Coahuila, COLI = Colima, DF = Federal district, DURA = Durango, GUANA = Guanajuato, GUERR = Guerrero, HIDA = Hidalgo, JALI = Jalisco, MEXI = Mexico, MICH = Michoacán, MORE = Morelos, NAYA = Nayarit, NULE = Nuevo León, OAXA = Oaxaca, PUEB = Puebla, QUER = Queretaro, QURO = Quintana Roo, SLP = San Luis Potosi, SINA = Sinaloa, SONO = Sonora, TABAS = Tabasco, TAMAU= Tamaulipas, TLAX= Tlaxcala, VERA= Veracruz, YUCA = Yucatán, Zaca = Zacatecas

Figure 9. Diabetes complications in % of people with diabetes

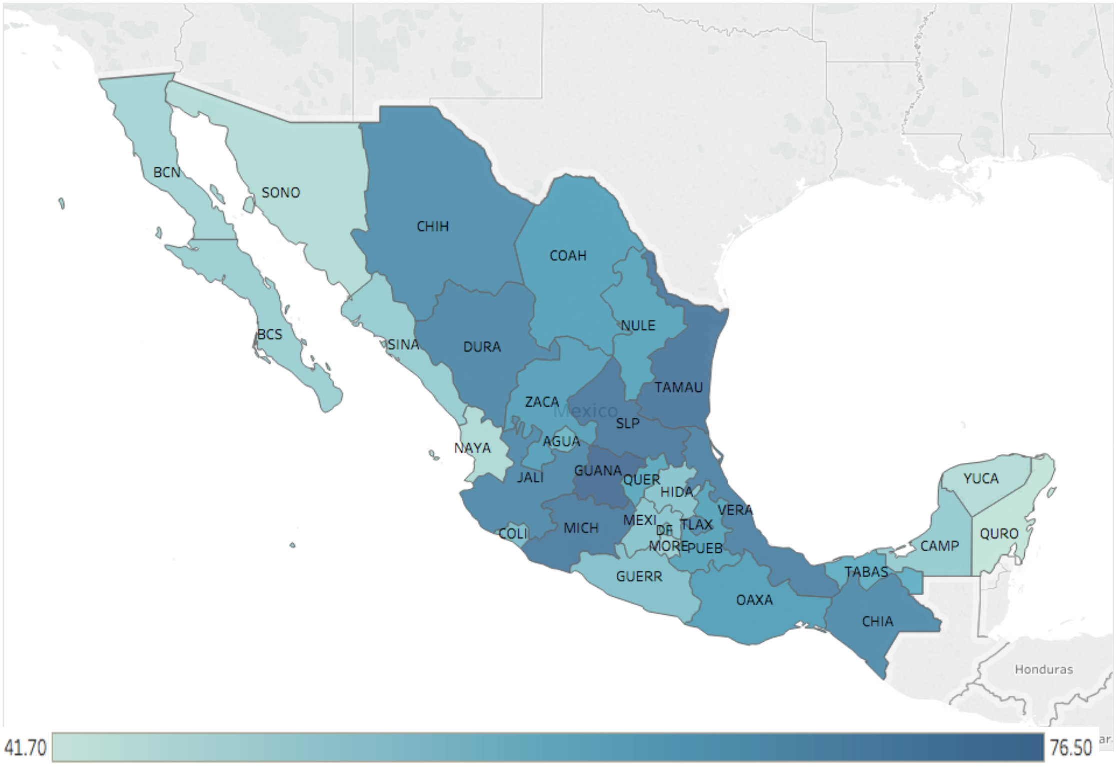


Figure 9 shows the rate and distribution of people with diabetes complications across all people with diabetes and across all states. The highest rate of complications by state was found in Guanajuato with 76.5%. States with a high rate of diabetes complications (≥ 65% of all people with diabetes) included: Chiapas (67.9%), Tlaxcala (68.4%), Durango (68.9%), Jalisco (68.9%), Chihuahua (70.0%), Michoacán (71.8%), Veracruz (72.2%), San Luis Potosi (74.7%), Tamaulipas (76.5%). The lowest rates were found in the northwest in Sonora Baja California, Nayarit, Sinaloa and on the Yucatan Peninsula starting at 41.7%.

Abbreviations of states : AGUA = Aguascalientes, BCN = Baja California North, BCS = Baja California South, CAMP = Campeche, CHIA = Chiapas, CHIH = Chihuahua, COAH = Coahuila, COLI = Colima, DF = Federal district, DURA = Durango, GUANA = Guanajuato, GUERR = Guerrero, HIDA = Hidalgo, JALI = Jalisco, MEXI = Mexico, MICH = Michoacán, MORE = Morelos, NAYA = Nayarit, NULE = Nuevo León, OAXA = Oaxaca, PUEB = Puebla, QUER = Queretaro, QURO = Quintana Roo, SLP = San Luis Potosi, SINA = Sinaloa, SONO = Sonora, TABAS =

For further comparison across the three groups, we checked the assumption of normality, which was satisfied for age and all group combinations of gender and classification as a state with high, intermediate and low complications. Furthermore, we used contingency tables to analyse the relationship between socioeconomic levels, health care status, rural residency and received diabetes care for those living in areas with high rates of diabetes complications versus those in states with lower complication rates. Results are presented in Table 10. Only ethnicity, indigenous versus non-indigenous origin, was not significantly associated with residency in HCR states. Comparison of the socioeconomic statuses between HCR and LCR/ICR states revealed that HCR states had a higher number of households belonging to lower quintiles (1^{st} and 2^{nd}) compared to ICR/LCR states (HCR=43.0% vs. 35.2%, p=0.033) according to ENSANUT data.

In terms of rural residency, there was a large difference between the groups: approximately 23% of people with diabetes living in HCR states came from rural areas compared to 13% in ICR and LCR states ($p \leq 0.001$). A significant difference with regard to the type of health insurance was observable. A majority of those in the ICR/LCR group received tax-funded institutional health care (55.0%), whereas individuals from states with a prevalence of high complications were rather affiliated with 'Seguro Popular' or had no health insurance (50.8%), (p= 0.033).

There were significant differences with regard to the utilisation of preventive measures across the three groups. Less people in HCR states performed any preventive measures (p=0,004) and received annual HbA1c tests (p<0.004). However, higher rates of frequent physician visits for diabetes care (≤4 annual visits) and determination of venous blood glucose were reported among residents from HCR states. No significant difference was observed with regard to eye revisions and screenings for MiA (see Table 10).

Table 10. Descriptive analysis of individuals with diabetes living in states with a high prevalence of diabetes complications

	HCR* N (raw = 2941)	**LCR/ICR*** N (raw = 1320)	**p-Value**$^{\neq}$
Socioeconomic quintile			**0.033**
1st (lowest)	20,6%	17,8%	
2nd	22.4%	17.4%	
3rd	16.6%	18.5%	
4th	22.2%	26.0%	
5th (highest)	18.1%	20.2%	
Ethnicity			0.288
indigenous	21.5%	24.0%	
non-indigenous	78.5%	76.0%	
Health insurance			**0.033**
None	15.7%	16.3%	
Public health care	35.1%	28.6%	
Institutional/Private health care	49.2%	55.0%	
Any preventive measure			**0.004**
yes	29.3	37.6%	
no	70.3%	62.4%	
Frequency of physician visits			**0.030**
≥ 4	68.1%	62.5%	
<4	31.9%	37.5%	
Residency			**<0.001**
rural	22.5%	13.1%	
urban/metropolitan	77.5%	86.9%	

*HCR = high complication rate; states with a diabetes complication prevalence ≥ 65.0%, LCR/ICR = low/intermediate complication rates; states with a diabetes complication prevalence <65.0%

$^{\neq}$p-values were calculated using Rao-Scott adjusted Chi-Square statistics

Figure 10. Use of preventive diabetes care among states with low-intermediate and high rates of diabetes complications

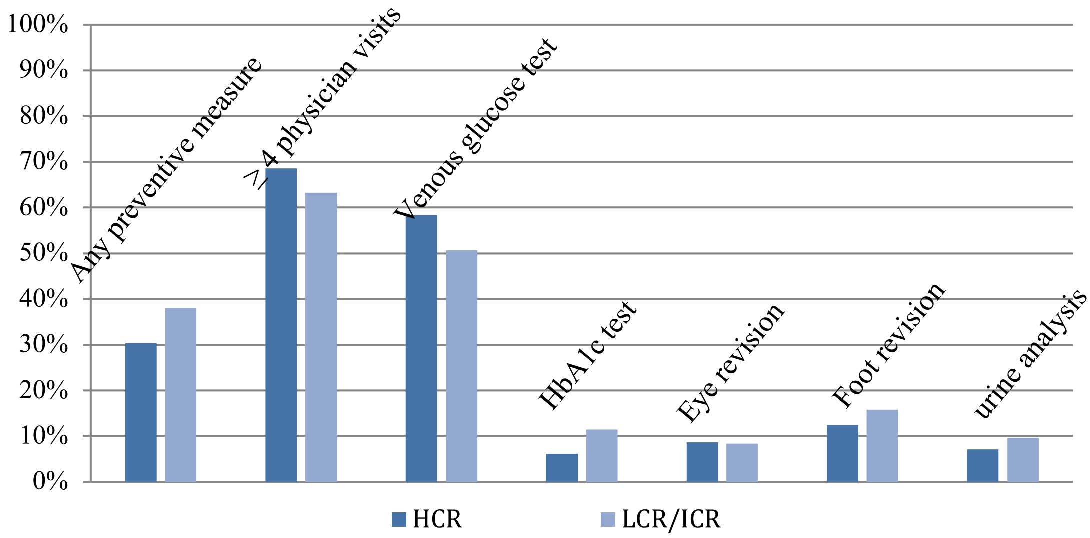


Figure 9 shows thata any preventive measure was performed by only 30% and 38% of people in LCR/ICR and HCR states, respectively.
Specific preventive measures (HbA1c, foot revision, microalbuminuria test) were performed more often in states with low/intermediate complication rates.
Conversely, frequent physician visits and venous blood glucse tests were performed more often in states with high complication rates (≥65% with diabetes complications = HCR states).

Spatial distribution of individuals by health insurance status, rural residency and utilisation of diabetes care

Across people with diabetes, frequencies of public health care ('Seguro Popular, SP') or lack of health insurance were higher in southern states and lower in the centre and the north. Affiliation with public health care among people with diabetes ranged from 8.7% in Coahuila in the north to 57.4% in Chiapas in the south. Lack of health insurance was lowest in Aguascalientes (Central Mexico) at 3.4% and highest in southern states in Guerrero and Michoacán (27.0% and 26.6%, respectively). In Figure 12 we mapped the distribution of people that are either uninsured or receiving public health care and observed increasing rates from the north to the south. The distribution of uninsured/SP affiliates matched the development pattern of states (using Mexico's rankings on the Human Development Index with data provided by development data reports of the UN) as displayed in Figure 11. Chiapas, Guerrero, Oaxaca and Michoacán had the lowest ranking on the Human Development Index (0.667 – 0.700) and reflected high frequencies of non-utilisation of preventive measures (72.6% in Michoacán to 82.3% in Guerrero). The highest rates of non-utilisation were observed in Quintana Roo, Guerrero and Chihuahua, with more than 80% of people reporting that no preventive measure had been taken in the past year, compared to approximately 50% non-utilisation in Queretaro and Mexico City (Figure 13). Furthermore, the proportion of people with diabetes living in rural areas was high among states with low developmental profiles and lack of health insurance or SP affiliation (28.2% in Chiapas, 26.1% in Guerrero, 28.0% in Oaxaca and 29.2% in Michoacán), compared to the average of 15.9%. However, the states with largest rural areas were located in the centre (Zacatecas = 46.8% and Hidalgo= 41.1%) and to the south (Tabasco = 36.8% and Veracruz = 33.9%) (Figure 14).

The spatial distribution of rates of diabetes complications visually matched neither the pattern of health insurance and development status nor the rates of non-utilisation of preventive measures despite statistical associations in the logistic regression analysis.

Figure 11. Human development index by state, general population in Mexico*

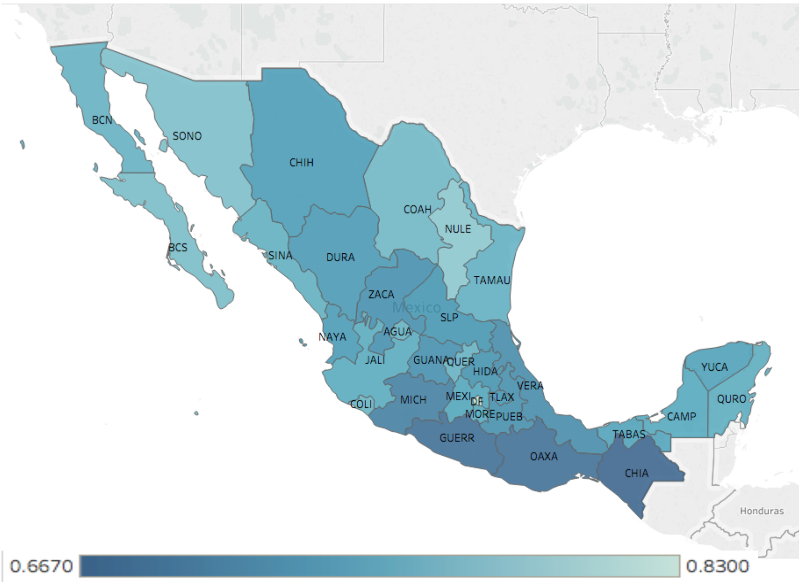


Fig .11 shows the HDI for each state in Mexico. From north to south the HDI shows a decreasing trend according to data from the United Nation Development Program§. It is highest in Nuevo Leon (north-east) with 0.83, equivalent to the HDI of developed countries (HDI>0.732), and lowest in Chiapas, Oaxaca and Guerrero with 0.667 (equivalent to the HDI of developing countries).

Figure 12. Rates of individuals with public health care (Seguro Popular) or no health insurance, in % of people with diabetes*§

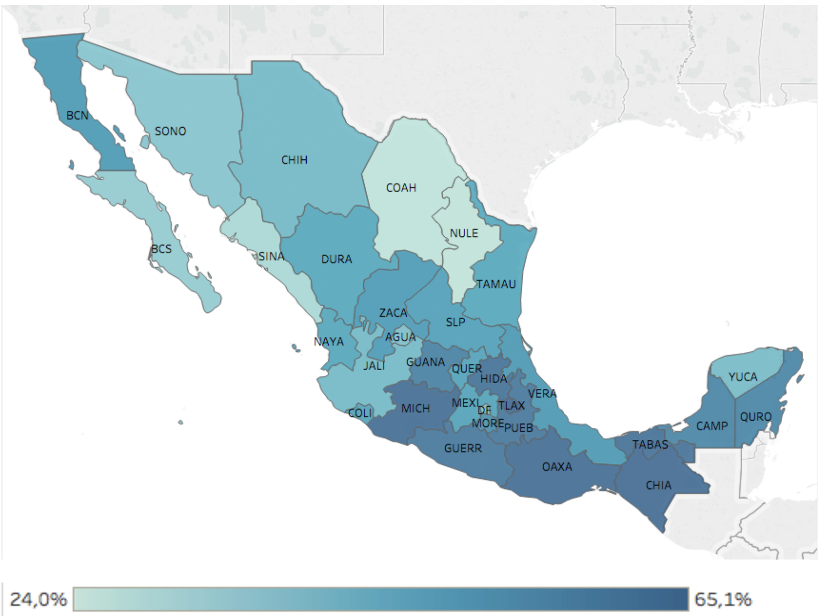


Fig. 12. Analogue to Fig. 11 an increase from the north to the south can be observed considering the health care status among people with diabetes. More people with diabetes that were formerly uninsured and are insured with public health care or remain uninsured can live in southern Mexico and on the Yucatán.

State abbreviations for Fig 11 and 12: AGUA = Aguascalientes, BCN = Baja California North, BCS = Baja California South, CAMP = Campeche, CHIA = Chiapas, CHIH = Chihuahua, COAH = Coahuila, COLI = Colima, DF = Federal district, DURA = Durango, GUANA = Guanajuato, GUERR = Guerrero, HIDA = Hidalgo, JALI = Jalisco, MEXI = Mexico, MICH = Michoacán, MORE = Morelos, NAYA = Nayarit, NULE = Nuevo León, OAXA = Oaxaca, PUEB = Puebla, QUER = Queretaro, QURO = Quintana Roo, SLP = San Luis Potosi, SINA = Sinaloa, SONO = Sonora, TABAS = Tabasco, TAMAU= Tamaulipas, TLAX= Tlaxcala, VERA= Veracruz, YUCA = Yucatán, Zaca = Zacatecas

§HDI data were retrieved from the Human Development Data Reports established by the UN; the score consider three dimensions: the life expectancy index, Education index and GNI index and explains how two countries or states with similar GNI per capita score different human development index (De la Torre García, 2015).

Figure 13. Rates of non-utilisation of preventive measures % of people with diabetes

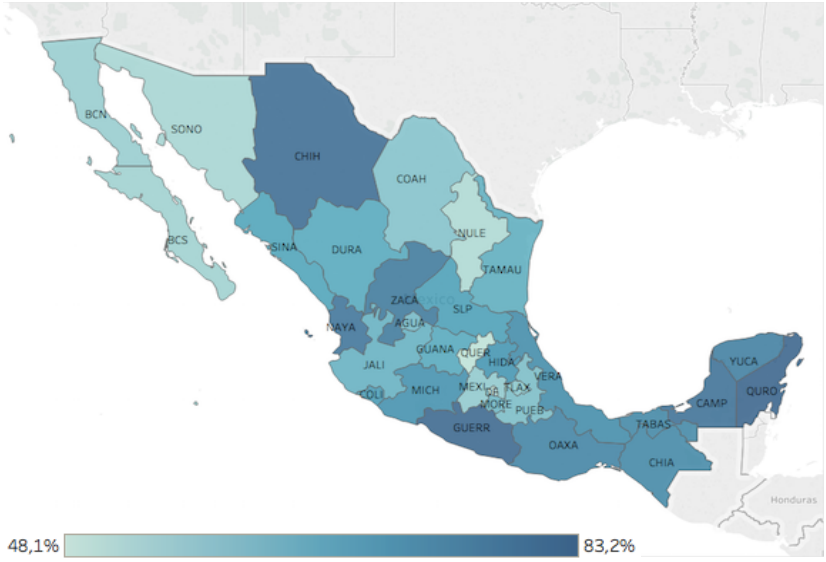


Figure 12 shows the non-utilisation of preventive measures across the population with diabetes, except for Chihuahua southern states and Yucatán have lower proportions for diabetes care participation compared to southern states except for Chihuahua

Figure 14. Rates of rural residency, % of people with diabetes*

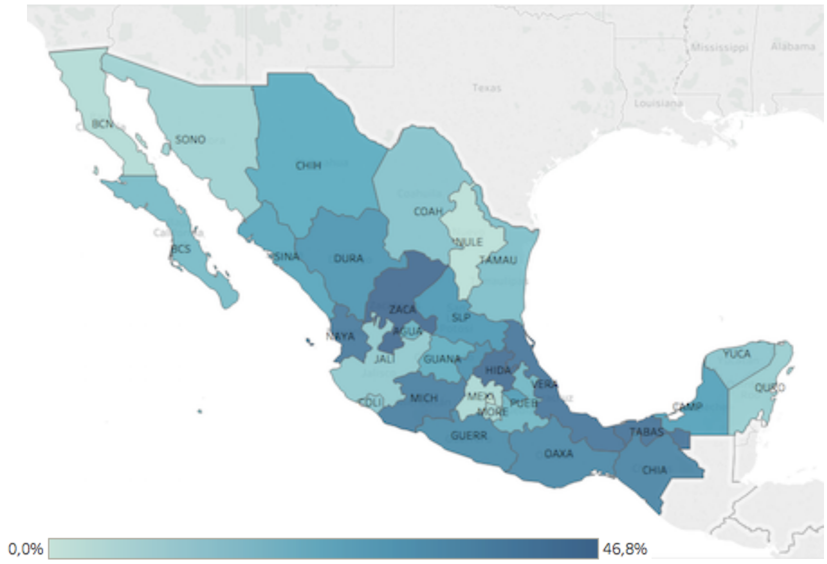


Figure 13 demonstrates the proportion of people with diabetes living in rural areas. Comparing Figure 12 and 13 rural residency and non-utilisation of preventive measures matches for southern states, Zacatecas and Nayarit on visual inspection.

*State abbreviations for Fig 13 and 14: AGUA = Aguascalientes, BCN = Baja California North, BCS = Baja California South, CAMP = Campeche, CHIA = Chiapas, CHIH = Chihuahua, COAH = Coahuila, COLI = Colima, DF = Federal district, DURA = Durango, GUANA = Guanajuato, GUERR = Guerrero, HIDA = Hidalgo, JALI = Jalisco, MEXI = Mexico, MICH = Michoacán, MORE = Morelos, NAYA = Nayarit, NULE = Nuevo León, OAXA = Oaxaca, PUEB = Puebla, QUER = Queretaro, QURO = Quintana Roo, SLP = San Luis Potosi, SINA = Sinaloa, SONO = Sonora, TABAS = Tabasco, TAMAU= Tamaulipas, TLAX= Tlaxcala, VERA= Veracruz, YUCA = Yucatán, Zaca = Zacatecas

2.5.4 The rural-urban divide of diabetes care and diabetes complications

Descriptive analysis of people with diabetes complications in rural and urban areas of Mexico

As expected, diabetes rates were higher in urban areas of Mexico (urban: 9.0% versus rural: 6.5%), whereas the rate for diabetes complications was higher for rural areas – approximately 70% in rural areas and 60% in urban areas. See Figure 15. [3]

From a socioeconomic perspective, a greater part of the rural population with diabetes complications belonged to the 1st and 2nd quintiles (34.8% and 23.2%). Additionally, 21.1% of the rural versus 12.1% of the urban participants did not have any school degree. Affiliation with public health care ('Seguro Popular') was more common among rural residents (rural = 57% vs. urban = 26%), while urban residents preferred affiliation with institutional and private health care (rural = 27% vs. urban= 57%). Similar distributions for absence of health care coverage were observed in both groups (16% in urban areas and 17% in rural areas). In terms of comorbidities and cardiovascular risk factors, we observed lower risk profiles for the rural population. Hypercholesterolemia and cardiovascular disease were more common among urban residents. In addition, in terms of preventive measures, rural residents were significantly less likely to have had one annual foot revision (p=0.002), MiA testing (p=0.010) and venous blood glucose testing (p=0.017) (see Table 11).

Comprehensive diabetes care

The number of preventive measures performed in the past 12 months differed between the two groups. No prevention measures were reported by 71% of people (n= 527) in rural areas, compared to 60% (n=1143) in urban areas. This subgroup was more likely to have a lower school degree, belong to a lower socioeconomic level, was either affiliated to public health care (Seguro Popular) or had no health insurance, lived in a rural area and was less likely to report cardiovascular comorbidities (not displayed). However, the majority of rural and urban participants stated they had seen their physician for regular and frequent (four or more times) diabetes controls in the previous 12 months with no difference between the two groups (70% in urban and

[3] The following description refers to Mexicans with diabetes complications.

70% in rural areas).

Venous blood glucose testing compared to other more specific tests was relatively common. Half of the rural population versus approximately 60% of the urban population stated that their venous blood glucose was tested in the past 12 months, whereas all other screening tests (eye and foot revision, MiA and HbA1c testing) were performed less frequently. On average, 7.5% of rural residents and 12.9% of urban residents had performed one of these specific screening tests. Less than 10% of all respondents reported more than two simultaneous tests in 12 months, and approximately 1% of the respondents received more comprehensive diabetes care, with all four preventive measurements performed in the past 12 months.

Figure 15. Urban versus rural areas: Diabetes and diabetes complication rates

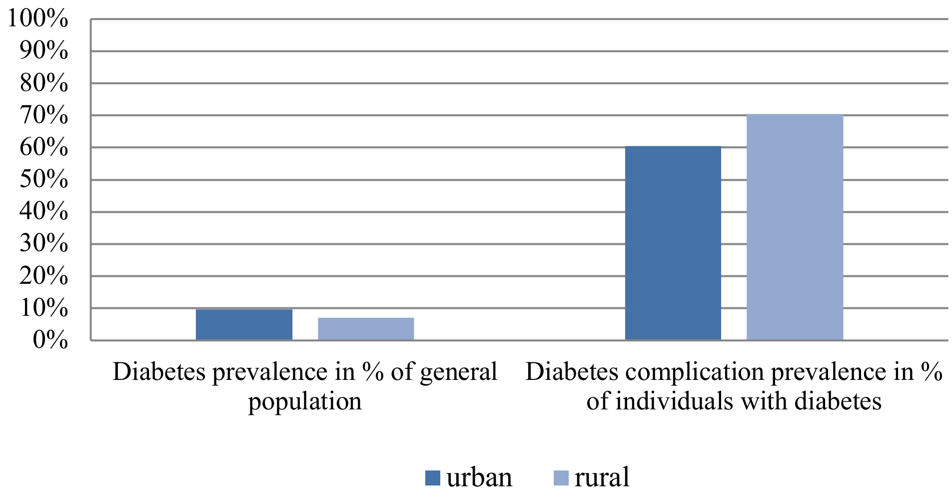


Table 11. Descriptive analysis - diabetes care in rural and urban areas

Diabetes care in the past 12 months	Rural residency ≤ 2500 inhabitants N=743[1] (29.2%)	Urban/ metropolitan residency > 2500 inhabitants N=1803 (70.8%)	P-Value[2]
Eye revision			
Yes	48 (5.6)	188 (10.5)	0.006
No	695 (94.4)	1615 (89.5)	
Foot revision			
Yes	84 (10.8)	301 (17.9)	0.002
No	659 (89.2)	1502 (82.1)	
Microalbuminuria test			
Yes	50 (6.2)	168 (10.6)	0.074
No	693 (93.8)	1653 (89.4)	
HbA1c monitoring			
Yes	53 (6.5)	191 (10.5)	0.037
No	690 (93.5)	1612 (89.5)	
Venous blood glucose testing			0.017
Yes	354(50.0)	1038 (59.3)	
No	389 (50.0)	765 (40.7)	
Physician visit			
≥ 4	551 (69.7)	1309 (69.8)	0.971
< 4	192 (30.3)	494 (30.2)	
No preventive action			
Yes	527 (71.0)	1143 (59.7)	0.001
No	219 (29.0)	660 (40.3)	

[1] Counts refer to the un-weighted number of individuals (number of individuals that were actually interviewed), percentages refer to the weighted number of individuals representative to Mexico's entire population).

[2] Results and p-value were calculated using Pearson's Chi Square statistics

Logistic regression results for adjusted associations between residency and diabetes care utilisation.

Table 12 summarises the findings of the logistic regression models, displaying the association between residency and diabetes care among Mexicans with diabetes complications after adjusting for age, sex, ethnicity, employment status, socioeconomic level, health insurance status, diabetes duration and comorbidities. No prevention was reported significantly more often among individuals living in rural areas (OR = 1.39, 95%CI = 1.02-1.90). Rural residency was also associated with lower odds of performance of foot examinations (OR= 0.64, 95%CI = 0.42 – 0.97). Except for frequency of doctor visits, other preventive methods displayed the same trend but did not reach a significant level. Significance was maintained even after Bonferroni adjustment. Lower socioeconomic status was significantly associated with people that reported non-utilisation of any preventive measures in the past 12 months. The first, second and third quintile had approximately two to three times higher OR for reporting lack of any performed preventive measures (1^{st} quintile: OR = 2.48; 95%CI 1.59 – 3.88; 2^{nd} quintile: OR = 2.46; 95%CI = 1.61 – 3.77; 3^{rd} quintile: OR = 2.10; 95%CI = 1.36 – 3.25 versus 5^{th} quintile). The lowest socioeconomic quintile also had significantly lower OR for reporting HbA1c testing in the previous year, compared to the highest quintile (OR= 0.40; 95%CI = 0.21 – 0.76). On the other hand, lower socioeconomic status was not significantly associated with the reception of any other preventive screening.

In addition, health insurance status was not significantly associated with the utilisation of specific diabetes care among people with diabetes complications. However, health care provider and frequency of physician visits were significantly associated. Respondents with Social Security (IMSS, ISSSTE) were four times more likely to reach the recommended standard of four physician visits per year, compared to those without health care (OR = 4.35; 95%CI = 2.78 – 6.67). Correspondingly, respondents with no health insurance were significantly less likely to receive a venous blood glucose test in the past 12 months (OR= 0.44; 95%CI: 0.30 – 0.67)

Table 12. Logistic regression results for associations between diabetes care and rural versus urban residency among Mexican adults with diabetes complications

	No preventive action (N=2546)		***HbA1c test*** *(N=2546)*	
	OR	95% CI	OR	95%CI
Residency				
Rural	**1.39**[1]	**(1.02 – 1.90)**	0.62	(0.36 – 1.06)
Urban	.	.	.	.
Age				
≤ 40	.	.	.	.
41 – 60	1.23	(0.78 – 1.94)	0.74	(0.38 – 1.44)
61 – 80	1.38	(0.87 – 2.20)	0.73	(0.34 – 1.58)
> 80	2.10	(0.84 – 5.22)	**0.13**	**(0.03 – 0.53)**
Female gender	0.97	(0.69 – 1.37)	1.63	(0.93 – 2.88)
Ethnicity				
Indigenous	1.03	(0.76 – 1.41)	0.98	(0.64 – 1.51)
Non – indigenous	.	.	.	.
Socioeconomic level				
1st quintile	**2.48**	**(1.59 – 3.88)**	**0.40**	**(0.21 – 0.76)**
2nd quintile	**2.46**	**(1.61 – 3.77)**	0.74	(0.40 – 1.38)
3rd quintile	**2.10**	**(1.36 – 3.25)**	0.66	(0.36 – 1.24)
4th quintile	1.35	(0.90 – 2.03)	0.64	(0.36 – 1.16)
5th quintile	.	.	.	.
Employment				
Unemployed	1.29	(0.72 – 2.31)	1.79	(0.73 – 4.34)
Retiree	0.79	(0.49 – 1.28)	1.19	(0.56 – 2.53)
Housekeeper	1.03	(0.71 – 1.50)	0.75	(0.47 – 1.22)
Employed	.	.	.	.
Health insurance				
None	1.40	(0.92 – 2.12)	1.39	(0.81 – 2.40)
Seguro Popular	1.10	(0.79 – 1.51)	1.30	(0.83 – 2.04)
Else	.	.	.	.
Diabetes duration				
(per 5 years)	0.94	(0.87 – 1.01)	0.95	(0.86 – 1.05)
Comorbidities				
Yes	0.76	(0.57 – 1.02)	1.26	(0.78 – 2.05)
No	.	.	.	.

Continuation Table 12

	Eye revision (N=2546)		*Foot revision (N=2546)*	
	OR	95% CI	OR	95%CI
Residency				
Rural	0.64	(0.39 – 1.04)	**0.64**	**(0.42 – 0.97)**
Urban	.	.	.	.
Age				
≤ 40	.	.	.	.
41 – 60	0.77	(0.41 – 1.44)	1.32	(0.39 – 4.44)
61 – 80	0.97	(0.48 – 2.00)	1.15	(0.39 – 3.38)
> 80	0.59	(0.14 – 2.50)	0.97	(0.34 – 2.81)
Female gender	1.13	(0.69 – 1.83)	1.51	(0.98 – 2.33)
Ethnicity				
Indigenous	1.49	(0.91 – 2.46)	0.91	(0.62 – 1.35)
Non – indigenous	.	.		
Socioeconomic level				
1st quintile	0.53	(0.27 – 1.05)	0.70	(0.40 – 1.24)
2nd quintile	0.53	(0.26 – 1.10)	0.64	(0.37 – 1.09)
3rd quintile	**0.35**	**(0.16 – 0.78)**	0.53	(0.30 – 0.95)
4th quintile	0.69	(0.35 – 1.36)	0.97	(0.58 – 1.62)
5th quintile	.	.	.	.
Employment				
Unemployed	1.08	(0.40 – 2.93)	1.15	(0.55 – 2.41)
Retiree	1.25	(0.61 – 2.57)	1.24	(0.68 – 2.26)
Housekeeper	0.79	(0.45 – 1.39)	0.81	(0.52 – 1.27)
Employed	.	.	.	.
Health insurance				
None	0.64	(0.27 – 1.51)	1.07	(0.62 – 1.83)
Seguro Popular	**0.61**	**(0.39 – 0.97)**	0.98	(0.63 – 1.52)
Else	.	.	.	.
Diabetes duration (per 5 years)	**1.19**	**(1.05 – 1.34)**	**1.15**	**(1.04 – 1.27)**
Comorbidities				
Yes	1.39	(0.94 – 2.05)	1.14	(0.78 – 1.66)
No	.	.	.	.

Continuation Table 12.

	Microalbuminuria test (n = 2546)		*Venous blood glucose test (n = 2546)*	
	OR	95% CI	OR	95% CI
Residency				
Rural	0.82	(0.47 -1.44)	1.21	0.89 – 1.66
Urban	.	.	.	.
Age				
≤ 40	.	.	.	.
41 – 60	0.59	(0.31 – 1.13)	0.96	(0.60 – 1.52)
61 – 80	0.52	(0.24 – 1.14)	0.77	(0.48 – 1.24)
> 80	0.41	(0.11 – 1.54)	0.84	(0.29 – 2.48)
Female gender	1.23	(0.69 – 2.18)	1.15	(0.81 – 1.64)
Ethnicity				
Indigenous	0.62	(0.35 – 1.10)	0.80	(0.60 – 1.07)
Non – indigenous	.	.	.	.
Socioeconomic level				
1st quintile	0.56	(0.27 - 1.20)	0.63	(0.39 – 1.01)
2nd quintile	0.77	(0.39 – 1.50)	0.78	(0.48 – 1.27)
3rd quintile	0.83	(0.40 – 1.75)	0.84	(0.53 – 1.33)
4th quintile	0.79	(0.44 – 1.42)	1.00	(0.63 – 1.58)
5th quintile	.	.	.	.
Employment				
Unemployed	1.72	(0.72 – 4.13)	1.06	(0.65 – 1.73)
Retiree	1.53	(0.73 - 3.20)	1.44	(0.87 – 2.38)
Housekeeper	1.20	(0.68 – 2.10)	1.09	(0.75 – 1.57)
Employed	.	.	.	.
Health insurance				
None	0.47	(0.18 – 1.19)	**0.44**	**(0.30 – 0.67)**
Seguro Popular	0.73	(0.39 – 1.37)	0.82	(0.60 – 1.13)
Else*	.	.	.	.
Diabetes duration (per 5 years)	1.14	(0.99 – 1.30)	1.02	(0.94 – 1.11)
Comorbidities				
Yes	1.07	(0.61 – 1.87)	**1.51**	**(1.15 – 1.96)**
No	.	.	**.**	**.**

Continuation Table 12.

	≥ 4 Annual physician visits (n = 2546)	
	OR	95% CI
Residency		
Rural	1.20	(0.87 – 1.65)
Urban	.	.
Age		
≤ 40	.	.
41 – 60	0.49	(0.16 – 1.44)
61 – 80	0.54	(0.20 – 1.52)
> 80	0.58	(0.20 – 1.67)
Female gender	1.43	(0.93 – 2.20)
Ethnicity		
Indigenous	0.89	(0.65 – 1.23)
Non – indigenous	.	.
Socioeconomic level		
1st quintile	1.05	(0.61 – 1.78)
2nd quintile	0.91	(0.52 – 1.60)
3rd quintile	0.90	(0.53 – 1.54)
4th quintile	1.09	(0.63 – 1.89)
5th quintile	.	.
Employment		
Unemployed	1.27	(0.70 – 2.30)
Retiree	1.25	(0.73 – 2.10)
Housekeeper	1.45	(0.95 – 2.22)
Employed	.	.
Health insurance		
None	**0.23**	**(0.15 – 0.36)**
Seguro Popular	0.70	(0.49 – 1.01)
Else	.	.
Diabetes duration (per 5 years)	1.22	(1.10 – 1.34)
Comorbidities		
Yes	1.14	(0.85 – 1.52)
No		

*Else = Private or institutional health insurance (IMSS/ISSSTE, Pemex, Defensa/Marina

[1]Bold numbers indicate significant test result.

2.6 Discussion

2.6.1 Major Findings

Rates for diabetes and diabetes complications were distributed unequally across Mexico's 32 federal states and among rural and urban areas. Across states, the prevalence of diabetes ranged from 5% to 11% of whom 42% to 77% reported diabetes complications (Chapter 2.1.3, Figure 8). Diabetes prevalence was higher in urban areas, at 9%, versus 7% in rural areas. However, the distribution was inversed for diabetes complications: approximately 70% of residents from rural areas reported microvascular diabetes complications versus 60% in urban areas.

Results suggest that diabetes outcomes are associated with social determinants, in particular lack of health insurance (OR = 1.62; 95%CI = 1.15 – 2.27) and lower educational status (less than primary school compared to secondary school or more: OR = 1.46; 95%CI = 1.00 – 2.15) (Table 9). However, this association was not consistent with other socioeconomic factors, such as a high level of marginality, which did not increase someone's odds of having diabetes complications.

Socioeconomic differences were partially reflected in the geographical disparities of diabetes complication rates. Areas with high complication rates were observed to conglomerate in the centre and along the Gulf Coast and were lowest in the northwest (along the US-Mexican border) and southeast (on the peninsula of Yucatán) region of Mexico. Those areas with high rates of self-reported diabetes complications (= HCR states: ≥65% of all people with diabetes complications) had higher proportions of rural residents (23% versus 13%, $p<0.001$) and more individuals receiving public health care (35% versus 29%), $p = 0.033$ (Chapter 2.5.3).

It is noteworthy that individuals from states with high complication rates reported a lower frequency of diabetes care participation; 38% in states with intermediate-/low complication rates versus 32% in states with high complication rates received the recommended quarterly diabetes controls with a physician ($p=0.004$).

Similarly, residents from rural areas with diabetes complications received recommended diabetes care to a lesser extent compared to their urban counterparts. For example, no preventive measures were reported from 29% of urban residents versus 40% from rural residents, resulting in 0.7 times lower likelihoods for reported reception of diabetes care (95%CI = 1.02 – 1.90) among rural residents. Surprisingly, neither indigenous origin nor lack of health insurance had a significant impact on the self-reported reception of diabetes care screenings.

The observed differences may provide supplementary information for the implementation of local prevention policies to improve diabetes care, especially in rural areas and socioeconomically deprived areas.

2.6.2 Social and ethnic determinants of diabetes outcome and care

We assumed that socioeconomic factors mediate the use of preventive measures and presence of diabetes complications, reflected by geographical clustering of areas that show high diabetes complication rates and lower socioeconomic or developmental profiles and infrastructural resources compared to areas with lower diabetes complications rates. As a prerequisite, we examined if socioeconomic status (SES) was associated with diabetes complications among ENSANUT survey participants and found that SES was significantly associated with increased self-reported presence of microvascular complications in the descriptive analysis. Approximately 60% of the people with diabetes complications belonged to the lowest three socioeconomic quintiles. Among people without diabetes complications in the same socioeconomic groups only 51% belonged to the lowest three quintiles ($p<0.001$) (Table 8). After adjustment for other variables that have been associated with the presence of diabetes complications in former publications (age, diabetes durations, diabetes treatment, presence of comorbidities and type of health insurance), the likelihoods for presence of diabetes complications were still about 1.3 to 1.5 times higher for households with lower socioeconomic status (Table 9).

These findings, which were extracted from a national representative survey, support the argument that the presence and development of diabetes complications are associated with the socioeconomic situation of Mexican individuals with diabetes. Despite numerous economic improvements in recent years, including the introduction of public health care for formerly uninsured people, the use of preventive diabetes care may still be limited by area of residency and the associated socioeconomic differences among Mexico’s regions. According to our results, residents from lower socioeconomic households encountered more barriers to diabetes care consultations. For example, those with a reported lack of diabetes care interventions had lower school degrees, received more often funding from public health care or had no health care insurance and a higher proportion lived in rural areas. Residency in rural areas provided consistent results and was associated with more diabetes complications and inconsistent utilisation of preventive diabetes care.

These results were conform with previous findings, in which lower education, low or middle income, receipt of public assistance and irregular employment were positively associated with the presence of nephropathy or retinopathy(Funakoshi et al., 2017). Additionally, Delmerico (2013) reported that social determinants, e.g., educational achievement and higher poverty rates, were major factors that led to hospitalisations for diabetes-related complications(Delmerico, 2013).

Another study from the UK found that OR increased for sight-threatening DR and decreased by 11% for ophthalmologic screenings with each increasing quintile of deprivation(Scanlon et al., 2008). However, results for the association between socioeconomic status and utilisation of preventive measures seemed to be less consistent. One study conducted in Canada found that referral rates to a diabetes centre did not differ across all income quintiles(Rabi et al., 2006).

In this analysis, we found high associations between socioeconomic status and receipt of ophthalmologic exams across people with diabetes complications. However, these results missed the 95% significance threshold, except for the third quintile when compared to people from the highest socioeconomic quintile (5^{th} quintile), (OR (3^{rd}-quintile)=0.35; 95%CI = 0.16-0.78)). Likewise, HbA1c determination was less common among people from the lowest socioeconomic quintile compared to those in the highest quintile (OR= 0.40; 95%CI = 0.21 – 0.76) (Table 12). Other screenings or physician visits did not demonstrate significant associations with SES, although all reflected the same trend with lower OR for lower quintiles compared to the highest quintile.

We also assumed that indigenous people were less likely to receive diabetes care due to multiple socioeconomic and cultural barriers and would have higher odds of reporting microvascular complications. However, contrary to previous reports concerning diabetes management and outcomes among ethnic minorities (Karter et al., 2002; Mainous, Diaz, Koopman, & Everett, 2007; Nwasuruba, Osuagwu, Bae, Singh, & Egede, 2009) Mexico’s indigenous population did not differ significantly from the non-indigenous population. People of indigenous origin in this study had comparable likelihoods for the presentation of diabetes complications to non-indigenous groups (OR =0.96, 95%CI = 0.73 – 1.20) (see Table 9). Similarly, diabetes follow-ups with screenings for end-organ damage were provided equally to indigenous and non-indigenous people. Analogue results from the ENSA 2000 (the first national health and nutrition survey in Mexico) demonstrated that health care utilisation was not significantly lower for indigenous groups. In contrary, Handa (2007) found that the indigenous population had significantly higher rates of curative care utilisation(Handa, 2007). This apparent protective trend among those of indigenous origin and those presenting diabetes complications was surprising, as ethnic minorities in Mexico and other countries experience higher systems-level barriers to receiving adequate health care(Golden et al., 2012; Spanakis & Golden, 2014). For example household incomes of ethnic minorities in rural areas were 40% to 50% lower than those of rural non-indigenous households, and 44.2% of people residing in indigenous municipalities were suffering from extreme poverty in 2010 (Hale et al., 2010; Leyva-Flores, Servan-Mori, Infante-Xibille, Pelcastre-Villafuerte, & Gonzalez, 2014). Non-indigenous groups in Mexico were also more likely to have received medical care due to a problem that occurred in the previous two weeks compared to indigenous groups (58% versus 53%, respectively). Lack of receipt of medical assistance was mainly attributed to a lack of money or lack of service supply (lack of confidence, ill-treatment, unavailability and remoteness). However, significant differences disappeared after adjustment for socioeconomic factors among indigenous and non-indigenous groups. Thus, the authors concluded that socioeconomic conditions and the type of health care provider rather than ethnic differences determined people's utilisation of primary health care(Leyva-Flores et al., 2014). Similar reports support the conclusion that socioeconomic determinants have stronger effects on diabetes outcomes than ethnicity itself (Link & McKinlay, 2009; Osborn, de Groot, & Wagner, 2013). For example, one study found that lack of seeking health care among indigenous groups was related to linguistic, geographic, economic and cultural aspects(Ibáñez-Cuevas, Heredia-Pi, Meneses-Navarro, Pelcastre-Villafuerte, & González-Block, 2015). In this context, it is conceivable that intra-ethnic effects are levelled out when we compare all indigenous groups to non-indigenous groups. For example in the ENSANUT 2012, 23.0% (N=158) of people living in Chiapas did not speak Spanish compared to 6.7% (N=58) in Yucatán. Additionally, the southern region is geographically divided by three major mountain ranges (Sierra Madre del Sur, Sierra Madre de Oaxaca and Sierra Madre de Chiapas) that disperse and isolate indigenous communities in this region, leading to the lower accessibility of health care. However this situation may be different for indigenous communities in the northern area and access to diabetes care might be similar to non-indigenous groups. Therefore, a state- or community-level analysis of diabetes outcomes and health care utilisation among indigenous people could provide further information and validate the possible effects of intra- and inter-ethnic differences (Bello-Chavolla, Rojas-Martinez, Aguilar-Salinas, & Hernandez-Avila, 2017).

2.6.3 Effective access to diabetes care

Previous reports have clearly demonstrated that the implementation of public health care and other specific programs targeting the poorer population were successful in improving health care access in general and diabetes care in particular (Consejo Nacional de Evaluación de la Politíca de Desarollo Social (CONEVAL), 2014; Sosa-Rubí et al., 2009; Tapia-Conyer et al., 2013; Thoumi, Udayakumar, Drobnick, Taylor, & McClellan, 2015). People enrolled in public health care ('Seguro Popular') compared to the uninsured population received on average 3.13 more insulin injections per week, had lower proportions of poor blood glucose control (37.6% versus 46.2%) and had greater access to blood glucose tests (Sosa-Rubí et al., 2009). Flores-Hernandez et al. (2015) demonstrated improvements with regard to diabetes care over a six-year period in Mexico, comparing data from ENSANUT 2006 and 2012. There were relative improvements with regard to Urine MiA-, HbA1c testing and foot revision of 6.4%, 4.2% and 5.8%, respectively. The author concluded that many of the improvements were due to increasing public health care affiliations(Flores-Hernandez et al., 2015).

However, some areas of Mexico seemed to have difficulties providing effective access to health care. According to our results, 16% of the diabetic population did not have any health insurance, 31% received public health care ('Seguro popular') and 53% were affiliated with social security (IMSS, ISSSTE, Pemex, etc.). The population without health insurance represented the group with the greatest vulnerability to poor diabetes outcomes among all health care types. The likelihood of this group presenting diabetes complications was 1.62 times higher compared to people receiving tax-funded social security (IMSS, ISSSTE, and other, Social Security services) (OR = 1.62; 95%CI = 1.15 – 2.27) even after adjustment for other socioeconomic factors. Although this did not reach the significance threshold, we considered it noteworthy that SP affiliates had higher odds of presenting diabetes complications (OR =1.10, 95%CI = 0.83-1.46) and had lower odds for regular diabetes follow-ups with their physicians (OR = 0.70, 95%CI: 0.49-1.01) compared to people receiving tax-funded social security (see Table 9). In accordance with these findings, another document confirmed that close to 35% of the population with SP affiliation in 2010 did not receive medical attention despite having a health problem because it was 'too expensive', they 'had to wait too long' or they 'did not receive treatment'(Consejo Nacional de Evaluación de la Politíca de Desarollo Social (CONEVAL), 2014). This is problematic in terms of treatment adherence of chronic conditions. A report from CONEVAL explains the underutilisation of health services among public health care users by a relative decrease in health care providers compared to the fast increase of health demands in the population, which led to long waiting hours and shortfalls in equipment and quality of care(Consejo Nacional de Evaluación de la Politíca de Desarollo Social (CONEVAL), 2014). In patients with chronic conditions, treatment adherence depends on regular follow-ups and diabetes controls. However, the quest for universal health care in Mexico needs further improvements to facilitate the utilisation of these preventive measures and increase efforts to provide effective access to diabetes care.

2.6.4 Diabetes care in rural areas

Previous research has demonstrated that barriers to receive health care were substantially higher in rural areas compared to urban areas(Brems, Johnson, Warner, & Roberts, 2006). Residents from small communities with only one health care centre frequently experienced lack of access to medications, poor health care quality and a small timeframe for possible consultations. For example, rural primary health care centres had difficulties providing drugs, resulting in only 56% of patients receiving the prescribed medicine(Tapia-Conyer et al., 2013). Accordingly, results of self-reported data from the ENSANUT 2012 indicate that the majority of Mexicans with diabetes complications did not receive ADA-recommended standards of diabetes care, with greater effects for rural communities. In the descriptive analysis, obtaining specific screenings for the detection and prevention of diabetes complications (HbA1c tests, ophthalmologic exams, foot/leg and urine screenings) were significantly less common among rural residents (rural vs urban: eye revision: 5.6% vs. 10.5%, p=0.006; foot revision: 10.8% vs. 17.9%, p=0.002; urine screening: 6.2.0% vs. 10.6%, p=0.074; Hba1c monitoring: 6.5% vs. 10.5%, p=0.037, Table 11). A minority in both groups received comprehensive care with all three and all four preventive measurements that were performed in the past year (0.9%, n=24 and 0.3%, n=3, respectively). Yet the frequency of doctor visits did not differ between the two groups in descriptive analysis (the rate of four or more annual physician visits was about 70% among individuals with diabetes complications in urban as well as in rural areas). Surprisingly in logistic regression analysis, where we controlled for age, sex, socioeconomic differences and ethnic differences, individuals from rural areas had higher odds to receive four or more diabetes controls per year, however the confidence interval was very large so that the level of uncertainty of this effect was considered too high to draw any conclusion from it (OR = 1.20; 95%CI = 0.87 – 1.65; Table 12).

Also venous blood glucose determination was widely used in rural as well as in urban areas (49% and 59% of patients with diabetes in rural and urban areas respectively). This might result from the widely available and accepted venous blood glucose tests that seem to replace the application of the other specific (time- and cost intensive) methods such as foot-, eye-, urine- revision and HbA1c analysis.

The rate for not receiving any specific preventive measure was high across both groups and even higher for rural residents; 71% of the respondents living in rural areas compared to 59% in urban areas (p=0.001) reported that they did not receive diabetes care. In conclusion, a majority of respondents with diabetes complications (approximately 70% in rural and urban areas) reported to see their doctor for diabetes controls on a regular and frequent basis (four times or more per year). However diabetes follow-ups that covered all screening tests were carried out only for a small percentage of attending patients according to patients' self-reports.

A previous study, conducted by Nathan et al. (2010), demonstrated higher rates for DR and DF among rural residents compared to urban residents in the US. Correspondingly, they observed that rural residents were less likely to engage in foot and eye revision. However, the overall frequency for diabetes care consultation, independent of area of residency, was significantly higher in the US. For example, foot and eye exams were carried out in more than 70% of all cases, while this was true in 5% to 18% of cases in Mexico(Hale et al., 2010).

2.6.5 Regional disparities in diabetes outcome

High diabetes complications were primarily clustered in the centre, from the Pacific region to the Gulf Coast. Lowest complication rates were observed in the northwest, in three states bordering the state of Mexico and on the peninsula of Yucatán (Figure 8). Diabetes complication prevalence largely differed between the states, ranging from 42% to 77% (Figure 9). In descriptive analysis, distinguishing characteristics of people living in states with high diabetes complication rates were affiliation with public health care or lack of health insurance, rural residency and lower proportions of people receiving preventive diabetes care. An interesting observation was that some states substantially differed regarding the prevalence of diabetes and diabetes complications. We observed that three states (Chiapas, Michoacán (southern Mexico) and Guanajuato (central Mexico)) had very low rates of diabetes in the general population and very high rates of diabetes complications among people with diabetes. It is plausible that individuals from these states remained undiagnosed until symptoms of diabetes-related complications occurred. Thus, the inverse patterns of 'below-average diabetes prevalence' and 'above-average-complication rate' could be used as a surrogate parameter to indicate late diabetes detection and higher measures of people with undiagnosed diabetes. However this remains a theory and needs to be evaluated.

We also compared the visual distribution of rural residency, health insurance status and health care utilisation among people with diabetes with the distribution of diabetes complication across Mexican states in order to determine states with the greatest need for improvement of access to diabetes care.

Since previous results suggested that rural residency, diabetes care utilisation, socioeconomic status and partially health care status impact diabetes outcomes, we considered three possible barriers to effective accessibility of diabetes care:

1. Residency in areas with low developmental profiles and large rural areas
2. Lack of health insurance or large proportions of public health care affiliates
3. Low diabetes care participation.

With our results we raise the hypothesis that the south and partially the central regions met the greatest challenges to providing adequate diabetes care and improving diabetes outcome. First, because people from the south were more likely to be covered by public health care or did not have any health insurance (see Figure 12).

As outlined before, a report by CONEVAL found that effective access to public health care decreased in recent years due to the large increase of public health care affiliates, and a serious relative decrease of hospital beds per 1,000 public health care-affiliates was noted in a two-year span (from 2008 to 2010), especially in the southern and central states bordering the south of Mexico(Consejo Nacional de Evaluación de la Politíca de Desarollo Social (CONEVAL), 2012). Second, we found that the proportion of those living in rural areas among people with diabetes was larger in the south compared to the north (17% - 41% in the south versus 4.9% - 18% along the border US-Mexican border) (Figure 14).

Third, the developmental profile of southern states (using the HDI Index as surrogate parameter for development) was lower (see Figure 11), similar to previous findings about the socioeconomic south-north divide of Mexico and the increased diabetes burden of southern states(Barquera, Tovar-Guzmán, Campos-Nonato, González-Villalpando, & Rivera-Dommarco, 2003; Stevens et al., 2008; Villalpando et al., 2010). However, this hypothesis relies on the visual inspection of choropleth maps and we suggest that this theory needs further verification using multilevel logistic regression analysis, as described and applied in other countries for similar purposes(Khan & Shaw, 2011; Zhou et al., 2015).

2.6.6 Limitations

We visually compared the distribution of diabetes complications across Mexican states with the distribution of people with diabetes living in rural areas. Despite significant associations among rural residency and diabetes complications in former analysis, we could not find a visual association. The same situation was observed for affiliation to public health car or absence of any health insurance.

A possible explanation is that the explanatory power of our logistic regression models is overall low. It is likely that statistical significance cannot be observed visually because associations were rather small. Also other factors that were not included in the analysis may have had larger impacts on the presence of diabetes complications. One of those unmeasured variables could be the different expansion pattern of public health care across Mexico's states. Access to public health care did not unfold equally across the country, and areas with lower socioeconomic profiles and poor infrastructure lagged behind in achieving effective health care coverage by public health care (Seguro Popular)(Beltran-Sanchez, Drumond-Andrade, & Riosmena, 2015). As a result, areas where effective access to health care enabled formerly uninsured people to seek medical care might have better diabetes outcomes than areas that lagged behind in the integration process of Seguro Popular. However, this effect on diabetes outcomes remains unknown, as we did not include the year of affiliation with Seguro Popular in this analysis.

Undetected diabetes is one of the most important limitations of this study and is known to be a major problem in population-based surveys. In the Mexican Health and Aging study, undiagnosed diabetes in Mexico among people older 50 years was about 18%(Kumar, Wong, Ottenbacher, & Al Snih, 2016). The IDF reported undiagnosed diabetes rates in North America and the Caribbean of 25% to 29.4% among people aged 20 to 79 years old in 2012. In the ENSANUT 2006, a diabetes prevalence of 7.1% was reported with an expected overall prevalence of around 14%(Sosa-Rubí et al., 2009), and only 23.7% of the adult population was screened for T2DM(Gutierrez et al., 2012). However, we could not find state-level information on the rates of undiagnosed diabetes.

Biases in population data

It was noteworthy that the excluded survey participants were significantly older (Mean(excluded) = 71 years versus Mean(included) = 56 years, $p<0.001$)) and had a significantly longer diabetes duration ((Mean (excluded) = 16 years versus Mean(included) = 9 years, $p<0.001$; Table 7)). Although not significantly different, excluded participants were also more likely to be of indigenous origin, lived in rural areas and had lower socioeconomic backgrounds. This raises the hypothesis that the target population of this analysis (the rural, remote and poor population) are not represented very well and that very comorbid and old patients with diabetes complications are not included because they are not able to participate in surveys, resulting in a selection bias. In general undiagnosed diabetes in self-reported data needs to be taken into consideration when interpreting results. Just alike old and comorbid survey participants, those with poor access to health care due to financial incapacities or infrastructural reasons, such as residency in remote areas, might remain undetected despite the presence of diabetes complications. In another publication, people living in rural areas had the lowest detection rates of diabetes(Zhou et al., 2015). This in turn suggests that no differences exist in diabetes outcomes and care among minorities or underserved populations in comparison to the general population. This effect could explain why there was no difference between indigenous and non-indigenous populations, neither in diabetes care utilisation nor in diabetes outcome because those with poor outcomes due to marginality were not included to this analysis.

Further limitations could have resulted from survival bias in remote areas and unfavourable living conditions. In other words, these people have a higher chance of dying from diabetes complications before diabetes is detected, similar to previous findings from India, which demonstrated that urban areas had higher rates of diabetes complications. This was explained by the 'selective mortality' of people with diabetes living in rural areas(Lee et al., 2015). However, this question is left to speculation, and we suggest that further research on diabetes, its outcome and health care utilisation needs to be carried out, as mentioned before.

We further recognise that we did not countercheck the plausibility of responses. In this regard, recall bias, resulting from people's capabilities of providing precise health status reports, might be present. This depends on several factors like age, morbidity and individual health perceptions. For example, old and multi-morbid people may find it difficult to recall a diagnosis of a doctor. However, we tried to evaluate the concordance of self-reported data and clinical trials with the systematic literature review, and we suggest that all presented results need to be read with care in terms of making generalisations. Also desirability bias can often be observed in population data, since survey participants might be aware that preventive diabetes care is necessary and recommended by the doctor. Therefore the proportion of people with four or more diabetes consultation might be higher than it actually is because people know they should have seen the doctor at least four times per year. On the other hand, some people may not know what a preventive measure is or cannot name the preventive exam, which lead to the erroneous assumption that more people did not receive the recommended preventive diabetes exam.

Not all factors that theoretically contribute to poor treatment adherence, as described in the introduction, and that were identified in other publications were available for data analysis. Therefore, it is likely that residual confounding due to unmeasured characteristics exist. For example, our models did not account for geographical differences caused by transportation issues and distance to primary health care centres/clinics as well as for the physician density between states and areas, since these variables were not measured in ENSANUT 2012 data. In a previous study conducted in Mexico in 1998, lower utilisation rates for preventive measures were partially explained by infrastructural issues, in particular the distance to the main road and to health clinics(Handa, 2007). Identification of areas where the infrastructure limits treatment adherence is important for strategic health care intervention. For example, public health care enrolees living in areas with an above-median number of physicians and more health units per population of 1,000 had higher odds of receiving blood glucose tests (OR= 15.85) and lower odds of displaying poor blood glucose control (OR= 0.20)(Sosa-Rubí et al., 2009). This is possibly even reflected in the low measures of fit for the logistic regression models in this analysis. Area of residency and socioeconomic and individual factors were responsible for only a small portion of increased diabetes-complication rates and the lack of compliance with treatment follow-ups.

Furthermore, the established conceptual framework did not account for differences concerning genetic susceptibility and family history of diabetes complications. This might further limit the explanatory power of this work. However, we did not intend to explore all possible risk factors for diabetes complications but rather tried to evaluate the impact of socioeconomic and associated geographic determinants that contributed to the development of diabetes complications.

With regard to the results of diabetes outcomes across Mexico's 32 federal states, we were not able to perform a detailed analysis of contributors for each complication based on the limited numbers of cases. It is difficult to generalise results, particularly for low prevalent complications like diabetes kidney disease. For this reason, we only distinguished between the presence and absence of any of the mentioned complications. However, this analysis refers to selected diabetes complications, and the pattern or distribution of diabetes complications across states may change depending on investigated diabetes complications. More cases with diabetes complications could contribute to a more detailed picture of the development of complications, enabling investigations for each complication on a state or even community level. We suggest that state-level observations on prevalence of diabetes complications and socioeconomic indicators need to be further analysed using multilevel analysis. Multilevel logistic regression has been demonstrated as a positive approach to linking the socioeconomic characteristics of areas (e.g. states, municipalities, neighbourhoods, etc.) with individual health(Merlo et al., 2006; Zhou et al., 2015).

Furthermore, we cannot make a statement on the quality of care from a provider perspective. Our results suggest that patients do not receive diabetes care as recommended and that physicians do not provide adequate diabetes care because few patients recalled receiving preventive screenings in the past year. Rodriguez-Saldana et al. (2010) claimed that quality of diabetes care in Mexico was still deficient as a result of scarce resources at the primary health care level, guideline non-adherence of physicians and persisting acute disease approaches instead of application of a multidisciplinary strategy focused on the prevention of long-term complications(Rodríguez-Saldana et al., 2010). In high demand–low resource settings where physicians do not have the time and means to carry out comprehensive diabetes care and screenings because of high patient emergence, the quality of diabetes care might be particularly lower than in urban and metropolitan areas where physician density is higher. However, information on the quality of health in remote areas is scarce, and the high rate of microvascular diabetes complications in some areas might reflect deficiencies in diabetes care, which need to be verified and addressed by further research.

2.7 Conclusion

In summary, the results presented here demonstrate that rates of diabetes complications vary in Mexico depending on residency, federal state and on inter-individual factors indicating inequalities in access to health care and differences in the quality of health care and prevention. We could not find a direct relationship between the geographical pattern of diabetes complications and socioeconomic or health care characteristics of states. Only some states in the south showed the tendency to be more affected by socioeconomic- and health care status and diabetes care participation in terms of diabetes outcome. Though we found that comprehensive diabetes care was overall low in Mexico. Individuals living in rural and lower socioeconomic settings had higher likelihoods of presenting diabetes complications and were less likely to receive diabetes care. Assuming that the southern region is still undergoing transformation, as suggested by Stevens et al. (2008), life expectancy will further increase with augmenting proportions of older people, resulting in a greater incidence and prevalence of DM (Stevens et al., 2008). Diabetes complications are associated with increasing age and diabetes duration. Therefore, we expect that states at pre-transitional stages will experience larger economic impacts caused by DM and that they will have less time to react to the consequences of DM compared to states that have higher developmental profiles(Corriere, Rooparinesingh, & Kalyani, 2013). States with high diabetes complication rates need to improve treatment adherence and intensify current programs that support the utilisation of preventive measures and screenings. Furthermore, states at earlier transitional stages and with high diabetes complication rates require more financial support by the government. Allocation of financial resources from higher developed to lower developed states could support the implementation of preventive programs.

An approach that has shown promising effects on diabetes outcome is the implementation of community health workers (CHWs). A growing body of evidence suggests that knowledge about diabetes, self-monitoring and self-care as well as lifestyle changes improve with the intervention of CHWs(Shah, Kaselitz, & Heisler, 2013). Another document found that even CHWs without formal professional medical training were successful in providing screenings and identifying high-risk patients(Gaziano et al., 2015). These types of CHW programs could gain more importance in the future, especially in low-resource settings, in order to effectively provide diabetes care and screening at low costs. In rural Chiapas, a non-governmental organisation introduced a CHW program with visits at three-month intervals in addition to routine physician visits. First results demonstrated that blood pressure levels were significantly lower for those that reported treatment adherence. However, further evidence on the cost effectiveness and feasibility of CHW programs is needed(Newman et al., 2015).

Multifaceted approaches that intervene at different levels are necessary; e.g. on health care provider level to improve the implementation of diabetes care, on patient level to improve understanding and compliance for preventive measures and from health policy makers in order to decrease barriers for diabetes care by assuring that costs for diabetes care are covered. Otherwise the rising prevalence of diabetes and associated complications have the potential to enlarge the gap between the rich and the poor population and decelerate developmental changes.

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Appendix

Description of Variables

Presence of diabetes complications was defined as reporting at least one previous diagnosis of diabetic foot or leg ulcer, amputation, visual impairment, diabetic retinopathy, blindness, diabetic neuropathy and/or diabetic nephropathy requiring dialysis. This variable was composed using the following command: A313a-h represent the variables defining each complication that were included into our analysis. describes all variables that were used for univariate and multiple logistic regression analysis.

```
COMPUTE kom_ges = 0.
IF a313a = 1 kom_ges = 1.
IF a313b = 1 kom_ges = 1.
IF a313d = 1 kom_ges = 1.
IF a313e = 1 kom_ges = 1.
IF a313h = 1 kom_ges = 1.
EXECUTE.
```

Table 13. Variables used for univariate and multiple logistic regression analysis

Variable name	**Description**	**Measure**	**Values**
SOCIODEMOGRAPHIC VARIABLES /RESIDENCY			
Edad	Age in years	Scale	20 – 114 years
Age_binned	Age in years	Categorical	1 = ≤ 40years 2 = 41-60 years 3 = 61-80 years 4 = > 80 years
Sexo	Gender	Nominal	0 = Male 1 = Female
Entidad	Federal states	String	01 = Aguascalientes 02 = Baja California North 03 = Baja California South

			04 = Campeche 05 = Coahuila 06 = Colima 07 = Chiapas 08 = Chihuahua 09 = Federal district 10 = Durango 11 = Guanajuato 12 = Guerrero 13 = Hidalgo 14 = Jalisco 15 = Mexico 16 = Michoacán 17 = Morelos 18 = Nayarit 19 = Nuevo Leon 20 = Oaxaca 21 = Puebla 22 = Queretaro 23 = Quintana Roo 24 = San Luis Potosi 25 = Sinaloa 26 = Sonora 27 = Tabasco 28 = Tamaulipas 29 = Tlaxcala 30 = Veracruz 31 = Yucatán 32 = Zacatecas
state_prevalence_kom_ges	states with high-, intermediate- and low rates of diabetes complications (HCR-,ICR-, LCR states)	Ordinal	1 = ≤ 55.0% (LCR) 2 = 55.1 – 65.0% (ICR) 3 = > 65.0% (HCR) of residents with complications of all people with diabetes
stategroups_HCRvsILCR	states with high	Nominal	1= HCR states

(state_prevalence_ kom_ges recoded)	complication rates versus all other		2 = ICR/LCR states
Rural_residency (est_urb recoded)	Area of residency	Nominal	0 = Urban 1 = Rural
h215	Indigenous origin	Nominal	0 = Non- indigenous 1 = Indigenous
quintiles	Socioeconomic household level in quintiles	Ordinal	1 = 1st quintile 2 = 2nd quintile 3 = 3rd quintile 4 = 4th quintile 5 = 5th quintile
education (H218a recoded)	Education, highest achieved school degree	Ordinal	0 = None, Preparatory school, Kindergarden 1 = less than Secondary 2 = Secondary or more
employment (H221 recoded)	Employment	Nominal	0 = unemployed 1 = employed 2 = Retiree 3 = housekeeper 4 = other
health_insurance1 (afilia_1era recoded)	Health care provider	Nominal	0 = None 1 = Seguro popular (public) 2 = Other (Institutional/private)
health insurance2 (health_insurance1 recoded)	Health care provider	Nominal	0 = None or Seguro Popular 1 = Other
DIABETES-RELATED VARIABLES			
A301	Previous diagnosis of diabetes	Nominal	0 = no 1 = yes
A313a	Diabetic foot/leg ulcer	Nominal	0 = no 1 = yes
A313b	Limb amputation	Nominal	0 = no

	as a cause of diabetes		1 = yes
A313c	Visual impairment caused by diabetes	Nominal	0 = no 1 = yes
A313d	Diabetic Retinopathy	Nominal	0 = no 1 = yes
A313e	Blindness caused by diabetes	Nominal	0 = no 1 = yes
A313f	Requiring dialysis as a cause of diabetes	Nominal	0 = no 1 = yes
A313i	Diabetic neuropathy	Nominal	0 = no 1 = yes
A313a,b,c,d,e,f,i	Kom_ges = Composite variable; presence of any diabetic complication	Nominal	0 = no 1 = yes
A302b	Diabetes duration in years	Scale	0 – 79 years
A307	Pharmacological diabetes treatment	Nominal	0 = None 1 = Insulin and/or antidiabetic agent
A309a	Diet to control diabetes	Nominal	0 = no 1 = yes
A309b	Exercise to control diabetes	Nominal	0 = no 1 = yes
A309c, A309d, A309e	Composite variable; other diabetes treatment with herbs or alternative	Nominal	0 = no 1 = yes

	medicine		

DIABETES COMORBIDITIES			
A401	Previous diagnosis of arterial hypertension	Nominal	0 = no 1=yes
A601	Previous diagnosis of Hypercholesteremia	Nominal	0 = no 1 = yes 2 = not tested
A502a	Previous history of Myocardial infarction	Nominal	0 = no 1 = yes
A502b	Previous history of Angina pectoris	Nominal	0 = no 1 = yes
A502c	Previous history of coronary insufficiency	Nominal	0 = no 1 = yes
Cardiovascular_ disease	Composite variable of A502a, A502b, A502c	Nominal	0 = no 1 = yes
Comorbidities	Composite variable of A401, A601, cardiovascular disease	Nominal	0 = no 1 = yes
DIABETES CARE			
Hba1c2 (scale)	HbA1c binned	Ordinal	0 = ≤ 7% 1 = > 7%
A310d	Venous blood glucose test (past 12 months)	Nominal	0 = No 1 = Yes
A310e	HbA1c controls (past 12 months)	Nominal	0 = No 1 = Yes
A312a	Foot revision (past 12 months)	Nominal	0 = No 1 = Yes
A312c	Eye revision)past 12 months	Nominal	0 = No 1 = Yes
A312d	Microalbuminuria test (past 12 months)	Nominal	0 = No 1 = Yes
A312e	No preventive measure (past 12 months)	Nominal	0 = Yes 1 = No
a312e_rec	Any preventive		1 = Yes

	measure		2 = No
doctor_visits (A305 recoded)	Number of physician visits to monitor diabetes control (past 12 months)	Ordinal	0 = < 4 times 1 = ≥ 4 times
A310d, A310e, A312a, A312c, A312d	Comprehensive health care, Sum of preventive measures (PM)	Ordinal	0 = no PM 1 = one PM 2 = two simultaneous PM 3 = Three simultaneous PM 4 = four simultaneous PM 5 = five simultaneous PM

Verzeichnis meiner akademischen Lehrer

Adamkiewicz , Arabin, Arndt, Arneth, Baranovski, Bartsch, Barth, Bauer, Baum, Becker, Berger, Best, Bette, Beyer, Bliemel, Bösner, Bonaterra, Braun, Brehm, Bücking, Buerke, Burchert, Busch, Carl, Cetin, Czubayko, Dannlowski, Daut, Decher, del Rey, Denzer, Depboylu, Dodel, Dolnik, Donner-Banzhoff, Eberhart, Efe, Eggers, Eggert, Eikmann, Engenhardt-Cabillic, Fendrich, Feuser, Fischer, Fisseni, Franz, Friedrichs, Friebertshäuser, Friedberg, Frink, Fritz, Fröbius, Fuchs-Winkelmann, Gallmeier, Gebhardt, Gerstner, Görg, Graumann, Gress, Greulich, Grgic, Grimm, Grote, Grundmann, Hammerich, Hegele, Heinis, Hering, Hertl, Herz, Heyse, Hildeb- randt, Hoch, Höffken, Hoffmann, Hofman, Holland, Hoyer, Hundt, Jansen, Jerrentrup, Kalder, Kalmus, Kampmann, Kann, Karger, Keller, Kill, Kim-Berger, Kinscherf, Kircher, Kirschbaum, Klaus, Kluge, Knake, Knöppel, Knorrenschild, Koehler, Köhler, König, Kolb- Niemann, Koolmann, Kortus-Götze, Krüger, Kruse, Kühnert, Kuhlmann, Lauterjung, Lechler, Lehnhardt, Leinweber, Leonhardt, Librizzi, Lill, Lohoff, Lüsebrink, Luster, Mahnken, Maisner, Maier, Melekian, Menzler, Merte, Metzelder, Mirow, Moll, Moosdorf, Naumann, Neff, Neubauer, Neumüller, Nedadic, Nikolaizik, Nimsky, Oberkircher, Obermayr, Oberwinkler, Oertel, Oliver, Opitz, Ossendorf, Overmann, Pagenstecher, Pankuweit, Peterlein, Plant, Politi, Preisig-Müller, Prestroff, Printz, Quint, Reese, Reiter, Renz, Richter, Rief, Ries, Röttgers, Rost, Ruchholtz, Rüsch, Schäfer, Schales, Schieffer, Schofer. Schratt, Schütz, Schuh, Schulze, Schwella, Schymalla, Sekundo, Seipelt, Seitz, Sesterhenn, Sevinc, Shams-Eldin, Sommer, Sprenger, Steiniger, Strecker, Strick, Strik, Tackenberg. Timmermann, Timmesfeld, Thieme, Thiemer, Vahdad, Visciani, Verburg, Völlger, Vojnar, Vogelmeier, Vogt, Vorwerk, Wagner, Wahl, Waldmann, Weihe, Weisser, Westermann, Wiater, Wilhelm, Willeke, Wißniowski, Wittig, Wollmer, Wrocklage, Wündisch, Wulf, Zavorotnyy, Zemlin, Ziebart, Ziller, Zovko

Danksagung

Mein außerordentlicher Dank gilt Herrn PD Dr. Reese, stellvertretender Leiter des Koordinierungszentrums für klinische Studien der Philipps Universität Marburg. Ich möchte mich ganz herzlich bedanken für die außerordentlich gute Betreuung und für die Unterstützung bei der Konzeption und Beratung während des gesamten Arbeits- und Schreibprozesses. Außerdem möchte ich mich für die vielen gestalterischen Freiräume und das Vertrauen bedanken.

Ich möchte mich bei Herrn Rodrigo Espinosa de la Peña vom „Centro de Investigacion en Evaluación y Encuestas de Mexico“ bedanken, der mir bei Fragen zur Encuesta Nacional de Salud y Nutricion eine große Hilfe war und mir viele nützliche Informationen über das Gesundheitswesens in Mexiko zukommen ließ.

Ich möchte mich auch bei Herrn Dr. Galindo und der Familie Lopez bedanken, denen ich viele interessante Gespräche und Einblicke in die lateinamerikanische Kultur, Lebens- und Denkweise verdanke.

Zuletzt gilt mein großer Dank meinen Eltern, für die liebevolle Unterstützung während des gesamten Studiums. Weiterhin danke ich meinen Freunden, die immer ein offenes Ohr für mich hatten und mir während der gesamten Dissertation zur Seite standen und mich immer wieder motivierten.