Diabetes subgroups and sociodemographic inequalities in Mexico: a cross-sectional analysis of nationally representative surveys from 2016 to 2022

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Summary

Background Differences in the prevalence of four diabetes subgroups have been reported in Mexico compared to other populations, but factors that may contribute to these differences are poorly understood. Here, we estimate the prevalence of diabetes subgroups in Mexico and evaluate their correlates with indicators of social disadvantage using data from national representative surveys.

Methods We analyzed serial, cross-sectional Mexican National Health and Nutrition Surveys spanning 2016, 2018, 2020, 2021, and 2022, including 23,354 adults (>20 years). Diabetes subgroups (obesity-related [MOD], severe insulin-deficient [SIDD], severe insulin-resistant [SIRD], and age-related [MARD]) were classified using self-normalizing neural networks based on a previously validated algorithm. We used the density-independent social lag index (DISLI) as a proxy of state-level social disadvantage.

Findings We identified 4204 adults (median age: 57, IQR: 47–66, women: 64%) living with diabetes, yielding a pooled prevalence of 16.04% [95% CI: 14.92–17.17]. When stratified by diabetes subgroup, prevalence was 6.62% (5.69–7.55) for SIDD, 5.25% (4.52–5.97) for MOD, 2.39% (1.95–2.83) for MARD, and 1.27% (1.00–1.54) for SIRD. SIDD and MOD clustered in Southern Mexico, whereas MARD and SIRD clustered in Northern Mexico and Mexico City. Each standard deviation increase in DISLI was associated with higher odds of SIDD (OR: 1.12, 95% CI: 1.06–1.12) and lower odds of MOD (OR: 0.93, 0.88–0.99). Speaking an indigenous language was associated with higher odds of SIDD (OR: 1.35, 1.16–1.57) and lower odds of MARD (OR 0.58, 0.45–0.74).

Interpretation Diabetes prevalence in Mexico is rising in the context of regional and sociodemographic inequalities across distinct diabetes subgroups. SIDD is a subgroup of concern that may be associated with inadequate diabetes management, mainly in marginalized states.

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Keywords: Diabetes subgroups; Mexico; Inequalities; Insulin deficiency; Prevalence

Research in context

Evidence before this study

A novel data-driven clustering approach introduced in recent years led to the identification of distinct diabetes subgroups, including mild obesity-related diabetes (MOD), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild age-related diabetes (MARD), and severe-autoimmune diabetes (SAID). MARD has generally been reported as the most prevalent subgroup across high-income countries, whereas SIDD has been reported as the most prevalent subgroup in India and Mexico. To date, these differences in prevalence across populations are not well understood. We conducted a PubMed database search without language restriction for studies evaluating the prevalence of diabetes subgroups in Latin America and low- and middle-income countries published between September 1, 2017, and January 1, 2024. The search terms were "diabetes subgroups" AND "diabetes clusters" AND "diabetes phenotypes". We identified a number of studies on the topic, most of which were conducted in North America, Europe, and Asia. However, no studies to date have explored factors that could explain differences in diabetes subgroup prevalence, particularly as it relates to sociodemographic inequalities in Latin America.

Added value of this study

This study adds to the existing literature by providing new insights into the prevalence of diabetes subgroups in Mexico. We report important heterogeneity in the epidemiological distribution of four diabetes subgroups over time, across geographic regions, and across different social disadvantage levels. Specifically, we show a distinct regionalization of diabetes subgroups, whereby MARD and SIRD were more prevalent in Northern Mexico, and SIDD and MOD were most prevalent in southern Mexico. Notably, SIDD was the most prevalent phenotype (4 in every 10 cases), and our pooled estimates showed that a higher level of social disadvantage and speaking an indigenous language was associated with higher odds of having the SIDD phenotype.

Implications of all the available evidence

The high prevalence of SIDD in Mexico is a major public health concern, particularly given a regionalization of this subgroup in areas of Mexico with higher levels of social disadvantage. These findings suggest that tailored approaches that consider diabetes heterogeneity may be warranted in Mexico and in similar contexts to reduce disparities in diabetes care.

Introduction

Diabetes mellitus, largely type 2 diabetes, affects an estimated 537 million adults globally and is a rapidly growing cause of morbidity and premature mortality.[1] Although the biochemical definition of type 2 diabetes is well-established, there is increasing recognition of heterogeneity in the clinical presentation, disease course, and associated complications of this condition.[2,3] In Mexico, where one in every six adults has diabetes (87.3 million), type 2 diabetes has been long considered a heterogeneous disease given the admixed ancestry of subsets of the population and heightened genetic susceptibility to metabolic disease.[1,4–7] A more nuanced characterisation of distinct diabetes subgroups, however, was made possible in recent years through the adaptation of the novel data-driven clustering approach proposed by Ahlqvist et al.[5,6] Using metabolic surrogates, our group was able to reproduce four of the originally proposed diabetes subgroups in the Mexican population according to phenotypic similarity: mild obesity-related diabetes (MOD), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), and mild age-related diabetes (MARD).[8] Importantly, in previous research we have documented key differences in the overall prevalence of these subgroups compared to other populations, but mechanisms underlying these differences remain elusive.[9] Since diabetes subgroups may have different rates of glycaemic progression and complications, understanding factors that may explain differences in their regional distribution could have important implications for epidemiologic surveillance of diabetes in Mexico and in other middle-income countries.[4]

Although MARD has been the most common subgroup reported in European, U.S., and Chinese populations, we found a high prevalence of insulin deficiency in Mexico, with an astounding 41.5% of cases corresponding to the SIDD subgroup.[6,8–10] We also observed that SIDD incidence could be substantially reduced following an intensive 3-month multidisciplinary intervention, which suggests that subgroups are not static and can transition to more favourable clinical profiles with intensive glucose-lowering therapy. We hypothesized that the higher prevalence of SIDD in Mexico could be attributed to glucotoxicity and beta-cell dysfunction resulting from chronic suboptimal glycaemic management, which may be more common in areas with higher social disadvantage.[11] However, the association between diabetes subgroups in Mexico and sociodemographic factors has not yet been examined.

As in other middle-income countries, the alarming rise in diabetes prevalence observed in Mexico over the

past three decades has been largely attributed to a rise in the burden of metabolic disease in the setting of epidemiologic and nutrition transitions.[12] As economic development increases, the burden of metabolic disease is predicted to shift from affluent individuals to groups of low socioeconomic status.[13,14] This shift has been reported in other parts of Latin America and is currently being observed in Mexico, where diabetes prevalence is increasingly more common among individuals of lower socioeconomic status.[14,15] Moreover, there is substantial regional and state-level variation in diabetes prevalence in Mexico and large differences in state-level health system capacity.[16,17] Thus, understanding the diabetes subgroup framework in the context of sociodemographic and geographic differences in Mexico could help trace health disparities in diabetes care and inform tailored approaches to diabetes management. In this study, we examine diabetes heterogeneity in Mexico through two objectives: 1) we estimated diabetes subgroup prevalence using nationally representative surveys spanning 2016, 2018, 2020, 2021, and 2022, stratified by key demographic variables; and 2) we assessed the geographic distribution of diabetes subgroups as well as the association between diabetes subgroups and correlates of social disadvantage.

Methods

Study design

We conducted a serial, cross-sectional analysis of adults (>20 years) from the Mexican National Health and Nutrition Survey (ENSANUT) for the years 2016, 2018, 2020, 2021, and 2022. Complete sampling methods, survey instruments and response rates for each cycle have been published elsewhere.[18–22] The ENSANUT is a population-based survey that aims to evaluate Mexican adults' health and nutritional status and is representative at the national, regional, and rural/urban levels. ENSANUT uses a two-stage probabilistic cluster stratified sampling based on households and individuals and has been conducted in 2006, 2012, 2016, 2018, 2020, 2021, and 2022. For this study, ENSANUT 2006 and 2012 were not included because of insufficient biomarkers to perform data-driven diabetes subgroup analyses. A random subsample of each individual ENSANUT cycle had an additional biochemical evaluation with serum samples for glycated haemoglobin (HbA1c), fasting insulin and glucose, and a fasting lipid profile; these biomarkers were used to estimate the classification of data-driven diabetes subgroups. Further methodology and a complete flowchart of the selection of study participants are outlined in Supplementary Methods. This work adheres to the STROBE guidelines for reporting of retrospective cohort studies (Supplementary Table S1). This project was registered and approved by the Research Committee at Instituto Nacional de Geriatría, project number DI-PI-006/2020.

Diabetes definition

Diabetes was defined by self-report among individuals who answered "yes" to the question "Has a doctor ever told you that you have diabetes (or high blood sugar)?" or by either a fasting blood glucose level of ≥126 mg/dL or a HbA1c ≥6.5%. Individuals who met the biochemical definition of diabetes but who responded "no" to a prior diagnosis of diabetes were categorized as having undiagnosed diabetes.

Diabetes subgroup classification

Among participants living with diabetes, the prediction of data-driven diabetes subgroups was performed using the algorithms previously developed by our team and successfully applied to U.S. populations.[8,9] This diabetes subgroup classification is based on a supervised machine learning algorithm that uses self-normalizing artificial neural networks (SNNNs) trained with surrogate metabolic measures to estimate insulin action from population-based studies. The SNNN approach has the advantage of overcoming the limited availability of C-peptide measurements by implementing insulin measurements to evaluate insulin sensitivity and β-cell function with the Homeostasis Model Assessment (HOMA) model. SNNN models were originally trained using NHANES-III data and were compared with k-means clustering results using the original variables proposed by Ahlqvist et al., leading to consistent definitions in ENSANUT 2016 for the original study.[6] Further methodology of our classification algorithm is presented in Supplementary Methods. For the current analyses, the classification considered the original clustering variables, namely age at diabetes diagnosis (among previously diagnosed diabetes), BMI, and HbA1c, along with HOMA2 metrics estimated using fasting glucose and insulin measurements instead of C-peptide to obtain HOMA2-IR and HOMA2-β. For subgroup estimation, we used an electronic-based application previously developed by our group, available at https://uiem.shinyapps.io/diabetes_clusters_app/. Four subgroups were considered in this analysis, as previously defined in the introduction: MARD, MOD, SIDD, and SIRD. The SNNN algorithm does not explicitly consider severe autoimmune diabetes (SAID) as it was conceived as a subgroup of autoimmune diabetes that requires positive anti-glutamic acid decarboxylase antibodies. Due to the unavailability of these measurements in ENSANUT, estimates for SAID prevalence were not considered for this study. In the 2020 survey, which did not include age at diabetes diagnosis, calendar age was used instead as the classification variable.

Density-independent social lag index

To quantify the impact of sociodemographic inequalities on the distribution of data-driven diabetes subgroups, we used the social lag index (SLI) developed by the National Council for the Evaluation of Social

Development Policy (CONEVAL) from years 2015 and 2020. The SLI is a metric obtained from a principal component analysis of 10 indicators that quantify social deprivation in education, healthcare access, housing services, quality, space, and household assets, highlighting four key areas of social deficiency.[23] Nevertheless, previous research from our team identified that SLI correlates with population density ($r = 0.734$, $p < 0.001$), which could bias the estimations of diseases.[24] Therefore, to evaluate social inequalities independent of population density, we used residuals of linearly regressed population density onto SLI values to approximate a density independent SLI (DISLI). We then categorised states into five SLI categories (Very Low-SLI, Low-SLI, Moderate-SLI, High-SLI, and Very-High SLI) based on the Dalenius & Hodges method. Further methods of DISLI estimation are available in Supplementary Methods. The population density was calculated as proposed by the National Institute of Geography and Statistics (INEGI) for all states. DISLI is a proxy of social disadvantage validated for Mexico City and used in previous research by our group.[24,25] Higher values of DISLI indicate a higher degree of social inequalities. DISLI from 2015 was implemented for ENSANUT cycles 2016 and 2018, while the definition from 2020 was implemented for the 2020, 2021, and 2022 cycles. Finally, we also considered speaking an indigenous language as a proxy of the individual-level social disadvantages experienced by this population. This was considered when a participant self-reported speaking a native language according to the ENSANUT sociodemographic questionnaire for each cycle.

Statistical analyses

Weighted prevalence estimations

The prevalence of diabetes was estimated using sample weights from ENSANUT for participants with available insulin measures; all estimations were conducted using the *survey* R package (Version 4.2).[26] We performed descriptive estimations of weighted prevalence at national, regional, and state levels. Furthermore, we performed subgroup analyses, and trends were stratified by sex, age (<60 vs ≥ 60 years), levels of DISLI (grouped into very low, low, and moderate against high and very high), and urban/rural context.

Changes in prevalence of diabetes subgroups

To assess changes in prevalence over time, we estimated yearly changes (YC) by fitting mixed effects linear regression models using the number of years between ENSANUT cycles as a continuous variable. To increase the statistical power and consider region-level dynamics which may influence changes in diabetes subgroup prevalence over time, we fitted the linear models using state-level prevalence estimates and pooled estimates as our dependent variable with a random intercept for each state. Where linearity assumptions were not met, mixed effects quantile median regression models were fitted with the *lqmm* R package (Version 1.5.8),[27] estimating confidence intervals with 1000 bootstrapped samples.

Correlates of diabetes subgroup spatial distribution

To visualise the geographical distribution of pooled estimates of regional-level diabetes subgroup prevalence in the studied period in Mexico, we used choropleth maps with the *ggmap* R package (Version 3.0.2) plotting predicted regional-level diabetes subgroup prevalence obtained from mixed effect linear regression models.[28] To evaluate the spatial dependence in the distribution of diabetes subgroup prevalence, we used Moran's I statistic, which was obtained as an indicator of global spatial autocorrelation, and its significance was assessed through an inference technique based on randomly permuting the observed values over the spatial units. Bivariate correlations between potential determinants of diabetes subgroup prevalence (DISLI, undiagnosed, and untreated diabetes prevalence) were evaluated with Lee's L test for spatial autocorrelation using a spatial weights matrix with the *spdep* R package (Version 1.2.8) for each diabetes subgroup per ENSANUT cycle separately.[29]

Association of diabetes prevalence and diabetes subgroups with social-lag index

Finally, to evaluate the association of diabetes subgroup distribution with DISLI, we fitted mixed effects logistic regression models at the individual level amongst individuals with diabetes, using a random intercept for each state and weighting all estimates using sampling weights for each ENSANUT cycle and diabetes subgroups codified indicator variables as the dependent variables. Next, we pooled these results using random effects linear models to obtain an overall metric for the association of each diabetes subgroup per ENSANUT cycle with the continuous and categorized DISLI metrics. Finally, we fitted an interaction model using the variable of speaking an indigenous language with DISLI with the diabetes subgroups and having diagnosed or undiagnosed diabetes. We used the Bayesian Information Criteria to evaluate the added value of the interaction model. Further methods of our fitted mixed-effects logistic regression model are presented in Supplementary Methods. All statistical analyses were conducted using R version 4.1.2, and a p-value = 0.05 was considered our statistical significance threshold.

Role of the funding source

This research was supported by Instituto Nacional de Geriatría in Mexico. The funding bodies had no involvement in study design, collection, management, analysis, and interpretation of data or the decision to submit for publication.

Results

Study population

We identified 148,714 individuals surveyed on the 2016, 2018, 2020, 2021, and 2022 ENSANUT cycles, of whom 78,553 were 20 years or older. Our final study sample included 23,354 subjects 20 years or older with complete data to estimate venous blood weights; 4204 participants had diabetes (Supplementary Figure S1). A STROBE flow diagram of participant inclusion by the ENSANUT cycle is presented in Supplementary Figure S2. The characteristics of the included sample by sex and by ENSANUT cycles are presented in Supplementary Table S2 and Supplementary Table S3, respectively. In Table 1, we summarise the characteristics of the complete study sample of participants living with diabetes overall, and stratified according to each of the four diabetes subgroups. Overall, the median age was 57 years (IQR: 47–66), 64% (n = 2698) of the sample were women, 8.8% (n = 370) spoke an indigenous language, and 27% (n = 1150) were categorized as having high social lag. In terms of diabetes characteristics, 70% (n = 2929) of participants were categorized as having diagnosed diabetes. The median age at diabetes diagnosis was 49 years (IQR: 40–59), and 64% (n = 2616) of individuals reported taking some glucose-lowering treatment, with oral glucose-lowering monotherapy being the most commonly reported treatment (43% of participants). Median HbA1c was 7.40% (IQR: 6.20–9.50); 38% (n = 1581) of participants had an HbA1c between 7 and 10%, and 20% (n = 807) of participants had an HbA1c >10%.

Descriptive characteristics of diabetes subgroups in Mexico

When stratified according to each diabetes subgroup, individuals in the SIDD subgroup had a median HbA1c of 9.80% (IQR: 8.70–11.00), whereas lower median HbA1c levels were observed in the MOD (6.50% [IQR: 5.80–7.10]), MARD (6.40% [IQR: 5.70–7.10]), and SIRD (6.20% [IQR: 5.60–6.90]) subgroups. When HbA1c was stratified into categories, 53% (n = 924 of 1773) of participants in the SIDD subgroup had an HbA1c level between 7% and 10%, and 44% (n = 764 of 1773) had an HbA1c level greater than 10%, whereas most participants in the other subgroups had an HbA1c level of less than 7%. Participants in the SIDD subgroup had the highest proportion of diagnosed diabetes cases (74%, n = 1316 of 1773), compared to MARD (67%, n = 456 of 676), MOD (66%, n = 912 of 1376), and SIRD (64%, n = 244 of 379). Participants in the SIDD subgroup also had the lowest proportion of untreated diabetes (30%, n = 527 of 1773), compared to the MARD (39%, n = 267 of 676), MOD (40%, n = 557 of 1376), and SIRD (38%, n = 143 of 379) subgroups. In terms of cardiovascular risk factors, arterial hypertension was most prevalent among people in the SIRD subgroup, whereas hypercholesterolemia and hypertriglyceridemia were most prevalent in the SIDD subgroup.

Pooled prevalence of diabetes subgroup in Mexico

During the studied periods, we estimated a pooled prevalence (PP) of diabetes of 16.04% (95% CI: 14.92–17.17). When stratified according to each diabetes subgroup, SIDD was the most prevalent subgroup (PP: 6.62%, 95% CI: 5.69–7.55; n = 1773), followed by MOD (PP: 5.25%, 95% CI: 4.52–5.97; n = 1376), MARD (PP 2.39%, 95% CI: 1.95–2.83; n = 676), and SIRD (PP%: 1.27, 95% CI: 1.00–1.54, n = 379). The yearly prevalence trends of diabetes subgroups were consistent across the studied period, whereby SIDD remained as the most prevalent subgroup over time, followed by MOD, MARD, and SIRD (Fig. 1).

Trends in diabetes subgroup prevalence in the studied period

The overall prevalence of diabetes in Mexico increased from 13.4% (95% CI: 11.6–15.3) in 2016 to 18.2% (95% CI: 15.7–20.7) in 2022, with a significant increase over time (YC: 0.54%, 95% CI: 0.11–0.96, $p = 0.013$). Diagnosed diabetes increased steadily in Mexico over the study period, from 9.2% (95% CI: 7.8–10.6, in 2016 to 12.3%, 95% CI: 10.11–14.49) in 2022 (YC: 0.30%, 95% CI: 0.02–0.57, $p = 0.036$), while prevalence of undiagnosed diabetes varied significantly during the study period, with a maximum of 6.5% (95% CI: 5.8–7.4) in 2018 and a minimum of 4.1% (95% CI: 3.0–5.2) in 2016, and no significant changes over time (YC: 0.23%, 95% CI: −0.05 to 0.52, $p = 0.114$). Regarding diabetes subgroups, we identified only a significant increase over time for the SIRD subgroup (YC: 0.29%, 95% CI: 0.13–0.45, $p < 0.001$). Trends for the rest of the subgroups pointed towards increases, without reaching statistical significance. Regarding trends in overall diabetes and diabetes subgroups over time, we identified a higher prevalence of SIDD for women and for individuals living in states with high and very-high social lag and in urban contexts. For adults ≥60 years, the prevalence of diabetes, MARD, and SIRD were higher compared to younger adults (Supplementary Figure S3).

Region and state-level distribution of diabetes subgroups

At the regional level, the highest pooled prevalence of diabetes in the studied period was observed in Central Mexico and Mexico City, with the highest prevalence recorded in the state of Veracruz in the Gulf of Mexico (Fig. 2A). When stratified by diabetes subgroup, the highest pooled prevalence for MARD during the studied period was observed for states in the U.S. Border region and in Mexico City, whereas the pooled prevalence for MOD was highest in the Gulf of Mexico and in the state of Veracruz (Fig. 2B and C). For severe subgroups, states with the highest pooled prevalence for SIDD were in Southern Mexico, specifically in the Southern Pacific and Peninsula region, whereas SIRD had the highest pooled prevalence in Mexico City and

Characteristic	Overall, N = 4204	MARD, N = 676	MOD, N = 1376	SIRD, N = 379	SIDD, N = 1773
Age, (Years)	57 (47, 66)	69 (63, 75)	50 (41, 59)	65 (59, 71)	55 (46, 63)
Sex, (%)					
Men	1506 (36%)	309 (46%)	432 (31%)	131 (35%)	634 (36%)
Women	2698 (64%)	367 (54%)	944 (69%)	248 (65%)	1139 (64%)
Indigenous language, (%)	370 (8.8%)	61 (9.0%)	108 (7.8%)	30 (7.9%)	171 (9.6%)
Social lag category, (%)					
Very low	571 (14%)	96 (14%)	197 (14%)	50 (13%)	228 (13%)
Low	1729 (41%)	299 (44%)	582 (42%)	191 (50%)	657 (37%)
Moderate	754 (18%)	115 (17%)	257 (19%)	66 (17%)	316 (18%)
High	520 (12%)	91 (13%)	148 (11%)	24 (6.3%)	257 (14%)
Very high	630 (15%)	75 (11%)	192 (14%)	48 (13%)	315 (18%)
Area of residence, (%)					
Rural	1380 (33%)	225 (33%)	440 (32%)	115 (30%)	600 (34%)
Urban	2824 (67%)	451 (67%)	936 (68%)	264 (70%)	1173 (66%)
BMI, (kg/m2)	29.6 (26.5, 33.4)	27.3 (24.7, 29.9)	31.2 (27.9, 35.1)	31.7 (28.3, 35.3)	29.0 (26.1, 32.7)
Waist, (cm)	100 (93, 109)	98 (91, 105)	102 (95, 111)	105 (98, 115)	99 (92, 108)
HbA1c, (%)	7.40 (6.20, 9.50)	6.40 (5.70, 7.10)	6.50 (5.80, 7.10)	6.20 (5.60, 6.90)	9.80 (8.70, 11.00)
A1c categories, (%)					
<7	1737 (42%)	469 (71%)	927 (69%)	284 (76%)	57 (3.3%)
7–10	1581 (38%)	182 (28%)	393 (29%)	82 (22%)	924 (53%)
>10	807 (20%)	10 (1.5%)	26 (1.9%)	7 (1.9%)	764 (44%)
Diagnosed diabetes, (%)	2928 (70%)	456 (67%)	912 (66%)	244 (64%)	1316 (74%)
Untreated, (%)	1494 (36%)	267 (39%)	557 (40%)	143 (38%)	527 (30%)
Undiagnosed diabetes, (%)	1276 (30%)	220 (33%)	464 (34%)	135 (36%)	457 (26%)
Age at diabetes diagnosis, (Years)	49 (40, 59)	64 (58, 70)	43 (36, 50)	60 (53, 65)	47 (39, 55)
Glucose-lowering medications					
Insulin only	200 (4.8%)	10 (1.5%)	53 (3.9%)	19 (5.0%)	118 (6.7%)
Oral-Agents only	1793 (43%)	300 (44%)	576 (42%)	131 (35%)	786 (44%)
Both	308 (7.3%)	16 (2.4%)	101 (7.3%)	44 (12%)	147 (8.3%)
Any	315 (7.5%)	59 (8.7%)	121 (8.8%)	19 (5.0%)	116 (6.5%)
Unknown	1588 (38%)	291 (43%)	525 (38%)	166 (44%)	606 (34%)
HOMA2-IR	1.43 (0.87, 2.53)	0.96 (0.60, 1.54)	1.54 (0.93, 2.66)	2.72 (1.49, 5.60)	1.43 (0.88, 2.42)
HOMA2-B	42 (18, 78)	45 (30, 66)	61 (41, 90)	129 (93, 182)	17 (9, 33)
Arterial hypertension, (%)	2371 (57%)	423 (64%)	759 (55%)	253 (68%)	936 (53%)
Hypercholesterolemia, (%)	1653 (40%)	253 (38%)	479 (36%)	124 (34%)	797 (46%)
Hypertriglyceridemia, (%)	2869 (70%)	392 (59%)	921 (69%)	246 (68%)	1310 (76%)
Previous CVD, (%)	202 (4.8%)	42 (6.2%)	57 (4.1%)	23 (6.1%)	80 (4.5%)
Smoking status, (%)					
Never smoker	2383 (63%)	331 (56%)	822 (64%)	228 (68%)	1002 (64%)
Previous smoker	507 (13%)	88 (15%)	172 (13%)	43 (13%)	204 (13%)
Current smoker	888 (24%)	171 (29%)	290 (23%)	63 (19%)	364 (23%)

Data is presented as median (with interquartile range) or absolute frequency (with percentage). Abbreviations. BMI, Body mass index; WC, Waist circumference; FPG, Fasting plasma glucose; HOMA2-IR, Homeostatic model assessment for insulin resistance; MARD, Mild-age related diabetes; MOD, Mild-obesity diabetes; SIDD, Severe-insulin deficient diabetes; SIRD, Severe-insulin resistant diabetes.

Table 1: **Population characteristics, overall and according to diabetes subgroups across ENSANUT cycles (2016–2022).**

Central Northern Mexico (Fig. 2D and E). Evaluation of the changes in trends of diabetes at the region level revealed that the largest increases in overall diabetes prevalence over the studied periods were recorded in Central Mexico (YC: 0.89%, 95% CI: 0.16–1.61, $p = 0.022$), from 10.7 (95% CI: 7.87–13.53) in 2016, to 17.0% (95% CI: 12.22–21.78) in 2022; no significant change was observed over time in Southern or Northern Mexico or in the Metropolitan Area. However, we identified significant heterogeneity in the changes in diabetes subgroups over time across Mexican regions, primarily for severe diabetes subgroups. SIRD increased significantly over time in Northern Mexico (YC: 0.32%, 95% CI: 0.07–0.56, $p = 0.016$), while MOD decreased over time only in Southern Mexico (YC: –0.49, 95% CI: –0.93 to –0.05, $p = 0.036$). No significant changes over time were observed for SIDD or MARD (Supplementary Table S4).

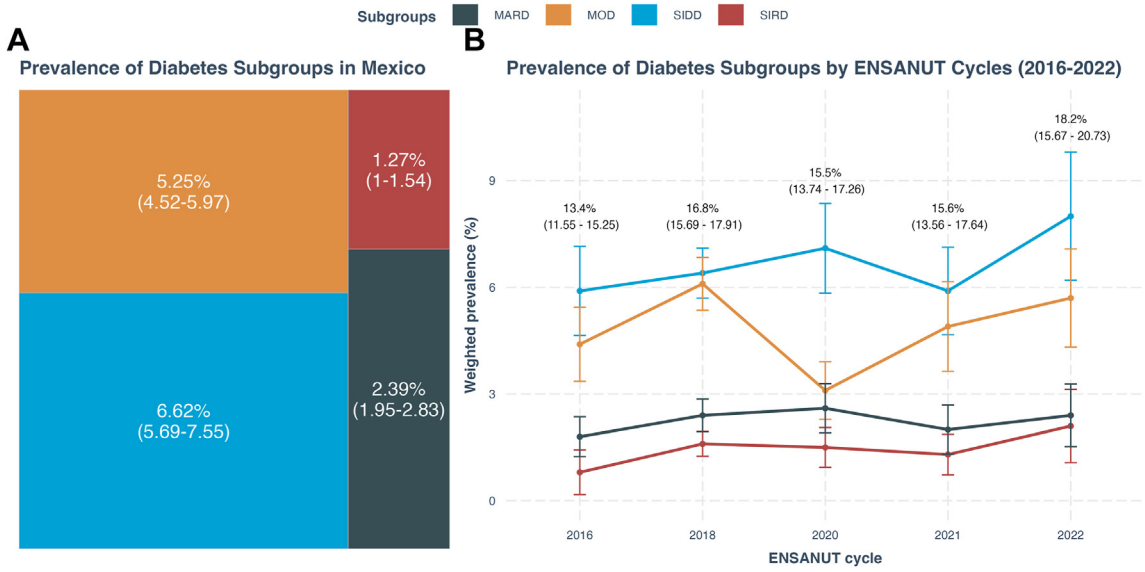

Fig. 1: Pooled prevalence with 95% confidence intervals of diabetes subgroups in Mexico during the 2016, 2018, 2020, 2021, and 2022 period (**A**), along with the trends of diabetes subgroups per each ENSANUT Cycle (**B**). **Abbreviations**: MARD, Mild Age-Related Diabetes; MOD, Mild Obesity-Related Diabetes; SIDD, Severe Insulin-Deficient Diabetes; SIRD, Severe Insulin Resistant Diabetes. *Annotations*: Error bars represent 95% confidence intervals.

Correlates of the spatial distribution of diabetes subgroups

Using Moran's I-statistic, we detected significant spatial autocorrelation only for severe diabetes subgroups, particularly for SIDD in 2016 (Moran's I = 0.327, $p = 0.002$) and 2018 (Moran's I = 0.221, $p = 0.021$), and SIRD in 2016 (Moran's I = 0.240, $p = 0.016$) (Supplementary Table S5). We then evaluated whether the distribution of diabetes subgroup prevalence correlated with additional factors, including DISLI and prevalence of untreated or undiagnosed diabetes, using spatial correlation analyses. We found that the prevalence of SIDD in 2020 (Lee's L = 0.334, $p = 0.001$) and in 2021 (Lee's L = 0.235, $p = 0.037$) spatially correlated with

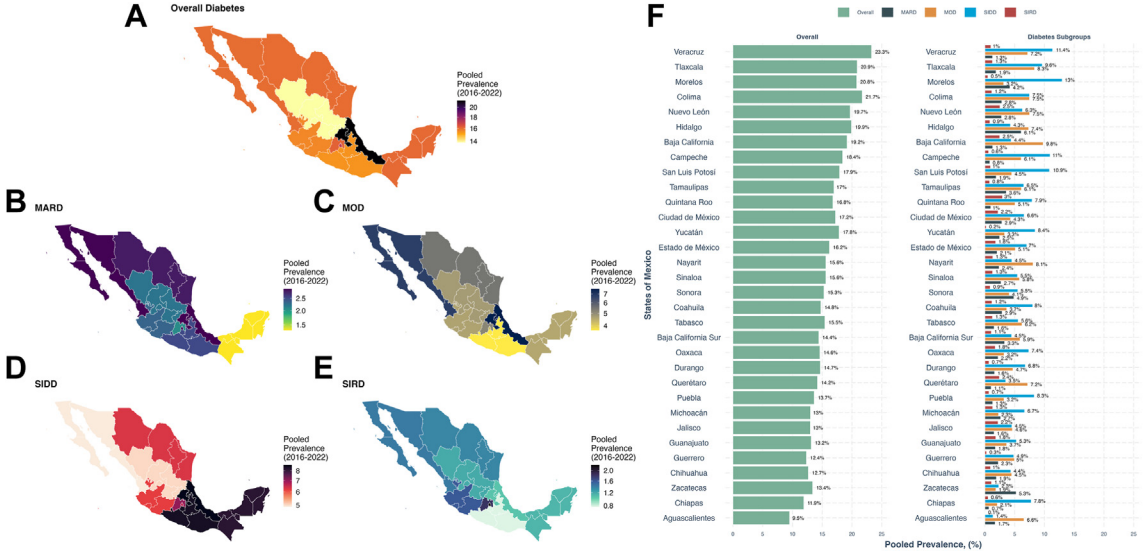

Fig. 2: Predicted pooled prevalence from 2016, 2018, 2020, 2021, and 2022 per region for overall diabetes (**A**), MARD (Mild Age-Related Diabetes, **B**), MOD (Mild Obesity-Related diabetes, **C**), SIDD (Severe Insulin-Deficient Diabetes, **D**), and SIRD (Severe Insulin Resistant Diabetes, **E**), as well as prevalence of diabetes and diabetes subgroups per state in Mexico (**F**).

DISLI, with a clustering of states with high SIDD prevalence and high social lag in Southern Mexico. Similarly, social lag was spatially correlated with MOD prevalence in 2016 (Lee's L = 0.161, p = 0.022) and in 2018 (Lee's L = 0.140, p = 0.138), particularly in the Southern Gulf of Mexico (Supplementary Table S5). We then evaluated the spatial correlation between SIDD and MOD subgroups with the prevalence of untreated and undiagnosed diabetes. We found that SIDD prevalence was spatially correlated in states with a high prevalence of untreated (Lee's L = 0.264, p = 0.007), and undiagnosed diabetes in 2016 (Lee's L = 0.283, p = 0.004); conversely, the MOD subgroup was spatially correlated in states with a high prevalence of untreated diabetes in 2018 (Lee's L = 0.497, p < 0.001), and in 2021 (Lee's L = 0.436, p = 0.008), and with a high prevalence of undiagnosed diabetes in 2018 (Lee's L = 0.379, p = 0.010) and in 2021 (Lee's L = 0.471, p = 0.006).

Influence of social lag on diabetes subgroup prevalence

To confirm the influence of social lag on the prevalence of diabetes and its subgroups in different ENSANUT cycles at the individual level, we fitted mixed-effects individual-level logistic regression models with a random intercept per state, considering sampling weights amongst individuals with diabetes. Notably, higher DISLI was associated with higher odds of the SIDD subgroup for the studied cycles, while a negative association was observed for MARD in 2016 and MOD in 2022 (Fig. 3). Pooling all ENSANUT cycles (2016, 2018, 2020, 2021, and 2022), we identified higher odds of the SIDD subgroup associated with each standard deviation increase in DISLI (OR: 1.12, 95% CI: 1.06–1.12, p < 0.001) and lower odds of the MOD subgroup with each standard deviation increase in DISLI (OR: 0.93, 95% CI: 0.88–0.99, p = 0.019). Finally, compared to individuals living in states with very low social lag, individuals living in states with high (OR: 1.39, 95% CI: 1.14–1.69, p < 0.001) and very high social lag (OR: 1.35, 95% CI: 1.11–1.65, p < 0.001) had higher odds of belonging to the SIDD subgroup. When adjusting for indigenous language, DISLI was not associated with higher odds of SIDD, but speaking an indigenous language was associated with higher odds of SIDD (OR 1.35, 95% CI: 1.16–1.57, p < 0.001). Furthermore, speaking an indigenous language was associated with lower odds of the MARD subgroup after adjustment by DISLI (OR 0.58, 95% CI: 0.45–0.74, p = 0.02). Notably, we identified an interaction between speaking an indigenous language and higher DISLI with having higher odds of either undiagnosed (OR 1.42, 95% CI: 1.11–1.83, p < 0.001) or untreated diabetes (OR 1.48, 95% CI: 1.16–1.89, p < 0.001), indicating that the risk of indigenous identity associated with SIDD may be linked to lower diabetes screening or inadequate diabetes management in this population.

Discussion

In this study, we provide a comprehensive characterisation of the prevalence, trends, and regional distribution of diabetes subgroups in Mexico using nationally representative surveys spanning 2016 to 2022. We show important heterogeneity in the epidemiological distribution of four diabetes subgroups over time, across geographic regions, and across different social disadvantage levels. Specifically, we demonstrate a distinct regionalization of diabetes subgroups, whereby MARD and SIRD were more prevalent in Northern Mexico, and SIDD and MOD were most prevalent in southern Mexico. Notably, SIDD was the most prevalent subgroup (4 in every 10 cases), and our pooled estimates showed that a higher level of social disadvantage and speaking an indigenous language was associated with higher odds of SIDD. In contrast, a higher level of social disadvantage was associated with lower odds of MOD, and speaking an indigenous language was associated with lower odds of MARD. These findings suggest that although the prevalence of diabetes is rising rapidly in Mexico, there may be distinct diabetes subgroups driving this increase, which could have important implications for epidemiologic surveillance and diabetes management.

We also found important differences in diabetes-specific parameters across the four diabetes subgroups. SIDD was characterized by the highest median HbA1c (9.70%; IQR [8.60, 11.00]), compared to all other subgroups (median HbA1c < 6.5%), with over 40% of people in the SIDD subgroup having an HbA1c of 10% or greater. These findings support our hypothesis that the SIDD subgroup's insulin deficiency may reflect glucotoxicity and beta cell dysfunction. However, while some of our spatial analysis suggests that part of this glucotoxicity could be occurring in the setting of untreated and undiagnosed diabetes, individuals in the SIDD subgroup had the highest proportion of diagnosed and the lowest proportion of untreated cases. Thus, it is also possible that people within the SIDD subgroup in Mexico may not be optimally managed, in part due to insufficient health resources, suboptimal treatment allocation, and limited access to novel glucose-lowering pharmacotherapies and multidisciplinary care strategies. Given that SIDD could transition to milder subgroups with intensive glucose-lowering treatment, our findings could help guide tailored approaches to identify individuals at risk of insulin deficiency and optimally manage glucose control.[8]

Our finding of SIDD being the most prevalent subgroup in Mexico diverges from other epidemiological reports, in which MOD and MARD subgroups are predominant in populations of European descent.[6,9,30,31] Interestingly, in contrast to studies from high-income countries, where the predominant diabetes subgroups were milder and related to obesity and aging, studies from low- and middle-income countries have shown a

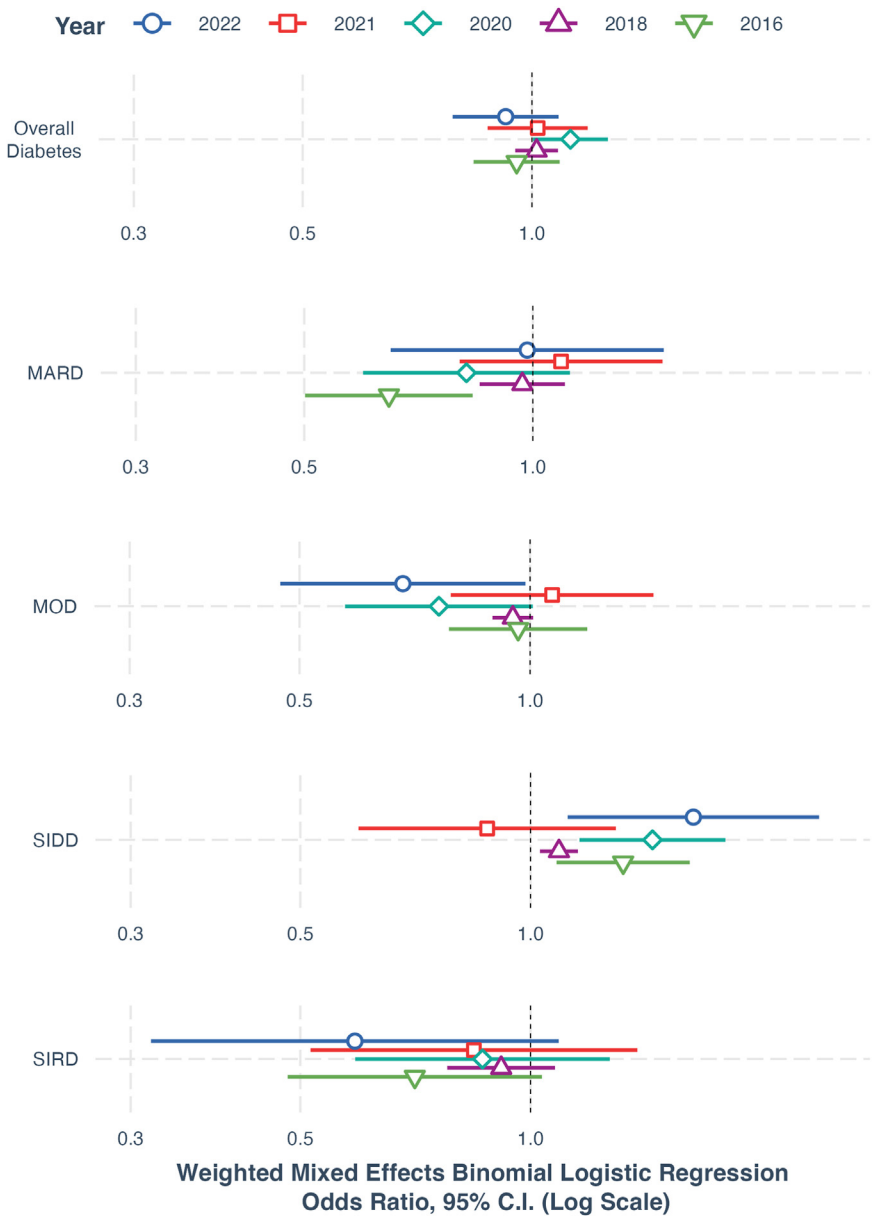

Fig. 3: Weighted Mixed Effects Logistic Regression Model at the individual-level to assess the association of the density-independent social lag index (DISLI) with diabetes and diabetes subgroups in each ENSANUT cycle during the 2016, 2018, 2020, 2021, and 2022 period. **Abbreviations**: MARD, Mild Age-Related Diabetes; MOD, Mild Obesity-Related Diabetes; SIDD, Severe Insulin-Deficient Diabetes; SIRD, Severe Insulin Resistant Diabetes.

predominance of severe diabetes subgroups. Prasad Rashmi et al. recently reported that the predominant variant of two geographically distinct Indian cohorts of adults living with young-onset type 2 diabetes were the SIDD and MOD subgroups.[32] These findings were attributed to malnutrition occurring early in life, which may be associated with a concomitant decrease in beta-cell function. Another study in India also showed that diabetes emerged in regions with adverse socioeconomic and environmental factors, which could be potentially related to SIDD subgroups.[33] Since the introduction of the diabetes subgroup framework to better characterize diabetes heterogeneity by Ahlqvist et al., the predominance of obesity and age-related subgroups has been explained by population aging and higher accumulations of adiposity.[4] Our study suggests that sociodemographic inequalities at the individual and regional level, along with the high prevalence of

undiagnosed and sub-optimally managed diabetes in Mexico, could help explain the increased prevalence of severe diabetes subgroups in recent years.

The high burden of diabetes in Mexico has been attributed to an intersection of several social, biological, and environmental factors previously described for this population.[8,34] Specific genetic variants have also been implicated in the increased risk for diabetes and its related complications in the Mexican population.[35,36] Moreover, these genetic variants affect metabolic traits that interact with other factors, such as high-calorie diets, sedentary lifestyle, and psychosocial stressors, which are associated with increased risk of metabolic syndrome, obesity, and dyslipidaemia.[7] There is a complex interplay between individual-level risk factors and sociodemographic factors involving local aspects of healthcare provision and diabetes care in Mexico, which likely influence diabetes prevalence and long-term glycaemic management and prevention of macrovascular complications. These include insufficient primary-care coverage for early disease detection, lack of unified strategies to diminish the burden of cardiometabolic risk factors, inadequate deployment of prevention strategies, and sparse healthcare personnel to cover the healthcare needs of patients living with diabetes; notably, these challenges to diabetes monitoring and screening have been more evident in rural settings and in Southern Mexico in recent years.[16,37,38] Consistent with those observations, our results suggest that the prevalence of diabetes subgroups may be associated with quality of diabetes care in Mexico. Overall, our results could be interpreted as a call to action to implement cost-effective strategies and healthcare policies that prioritize early screening, monitoring, and targeted treatment based on individualized management in order to mitigate the onset of severe diabetes subgroups or at least shift the drivers of this increase from severe to milder diabetes phenotypes. In turn, this could reduce the risk of adverse long-term outcomes and improve diabetes care in Mexico.[30,31]

Strengths and limitations

Our study provides the first comprehensive insight into the distribution of diabetes subgroups in Mexico and the potential sociodemographic contributors to the regionalization of these subgroups in Mexico. To this end, we implemented serial cross-sectional evaluations of nationally representative surveys with a wide array of biomarkers useful to evaluate diabetes subgroups over time. We were also able to evaluate trends of diabetes subgroups at the regional level to explore both region and time-dependent dynamics in diabetes prevalence across relevant risk groups over the 2016, 2018, 2020, 2021, and 2022 periods. Given the inherent limitations posed by the algorithm proposed by Ahlqvist et al. for its implementation in low- and middle-income countries, we were able to reproduce the features of their proposed classification using surrogate insulin-based measures with our machine learning algorithm, which has previously been successfully applied for characterizing trends of diabetes subgroups over time in U.S. populations.[9] This overcomes limitations shown in previous diabetes subgroup studies using insulin-based measures for the HOMA model, which have otherwise led to inconsistent classifications.[39] Despite these strengths, we acknowledge some limitations. First, to increase statistical power, we estimated state-level prevalence of diabetes and its subgroups to evaluate trends over time; however, ENSANUT is primarily designed to provide estimates at the regional level, which may lead to imprecise estimates for trend analyses. Furthermore, our results may not capture the prevalence of diabetes subgroups at a smaller grouping level (e.g., such as municipal or by city). Additionally, we acknowledge that our analyses were not adjusted for multiplicity, which could result in some statistically significant results occurring due to chance. To overcome this, we replicated all analyses at the regional level to confirm the direction of the trends and observed associations, obtaining similar results. Second, we evaluated correlates for the regionalization of diabetes subgroups and prevalence of undiagnosed and untreated diabetes with a social lag index, primarily at the state and regional level, which does not allow us to make inferences on the influence of these factors at the individual level. We addressed this limitation by fitting a mixed effects hierarchical model at the individual level and replicated the association between social lag and the SIDD subgroup. However, our study should be primarily interpreted as an ecological design, which means that it cannot draw conclusions about the management of diabetes at an individual level. Therefore, further studies are necessary to provide evidence on which socioeconomic and clinical factors might directly influence the distribution of diabetes subgroups. Third, three surveys were conducted (2020-2021-2022) during the COVID-19 pandemic. We reported diabetes-related excess mortality during these periods, especially deaths related to hyperosmolar states and diabetic ketoacidosis.[11] Thus, subgroups with a tendency to develop these complications (e.g., SIDD) may have had higher mortality rates, and therefore, their prevalence may have been modified during these periods. Fourth, the 2020 survey did not inquire about the age of diabetes diagnosis. Instead, our algorithm used calendar age as a classification variable, potentially introducing bias within this parameter. Finally, although genetic ancestry and indigenous ethnicity have been shown to influence diabetes prevalence in Mexico,[40,41] we were unable to reliably estimate the prevalence of diabetes subgroups for indigenous participants in ENSANUT, given that the inclusion of these individuals in biomarker subsamples has been limited. Future studies should investigate the influence of genetic ancestry on diabetes subgroups in Mexico, an approach that has shed light on the

pathophysiology of type 2 diabetes in populations of European and Asian descent.[42]

Conclusion

Our study shows heterogeneity in the prevalence of diabetes subgroups in Mexico across different geographic regions, sociodemographic characteristics, and metrics of glycaemic control. Our findings suggest that the growing burden of diabetes, particularly of the SIDD subgroup, may be related to social disadvantage. In Mexico, tailored strategies should be considered to improve early diagnosis, optimize glycaemic management, and to implement effective preventive strategies that address sociodemographic and structural factors that may be contributing to the prevalence of severe diabetes subgroups.

Contributors

Research idea and study design: NEAV, OYBC, JAS; data acquisition: OYBC, NEAV, CAFM; analysis/interpretation: NEAV, OYBC, CAFM, DRG, AVV, MRBA, ASN, PSC, LFC, JPDS, GDL, RPS, GVA, JAS; statistical analysis: NEAV, OYBC; manuscript drafting: NEAV, OYBC, CAFM, DRG, AVV, MRBA, ASN, PSC, LFC, JPDS, GDL, RPS, GVA, EC, JCF, JAS; supervision or mentorship: NEAV, OYBC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. NEAV, OYBC, and CAFM had full access to the raw data and verified it prior to and after statistical analyses. NEAV, OYBC and CAFM took full responsibility for the decision to submit for publication.

Data sharing statement

All code, datasets, and materials are available for the reproducibility of results at https://github.com/oyaxbell/diabetes_clusters_ensanut/

Editor note

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Declaration of interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100732.

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