

Changes in the diagnosis and management of diabetes in Mexico City between 1998-2004 and 2015-19

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ABSTRACT

Objective: To investigate the trends in diabetes prevalence, diagnosis, and management among Mexican adults who were participants in a long-term prospective study.

Research design and methods: In 1998-2004, 159,755 adults from Mexico City were recruited into a prospective study and in 2015-2019 10,144 survivors were resurveyed. Diabetes was defined as self-reported diagnosis, glucose-lowering medication use, or $HbA_{1c} \geq 6.5\%$. Controlled diabetes was defined as $HbA_{1c} < 7\%$. Prevalence estimates were uniformly standardised for age, sex and residential district. Cox models explored the relevance of controlled and inadequately controlled diabetes to cause-specific mortality.

Results: 99,623 participants in 1998-2004 and 8986 participants in 2015-2019 were aged 45-84 years. Diabetes prevalence increased from 26% in 1998-2004 to 35% by 2015-2019. Of those with diabetes, the proportion previously-diagnosed increased from 76% to 89%, and glucose-lowering medication use among them increased from 80% to 94%. Median HbA_{1c} among all with diabetes decreased from 8.2% to 7.3%, and the proportion of them with controlled diabetes increased from 16% to 37%. Use of blood pressure lowering medication among all with previously-diagnosed diabetes increased from 35% to 51% and their use of lipid-lowering therapy increased from 1% to 14%. The excess mortality risk associated with diabetes accounted for 34% of deaths at ages 35-74 years, of which 5% were attributable to controlled and 29% to inadequately controlled diabetes.

Conclusions: Inadequately controlled diabetes is a leading cause of premature adult death in Mexico. Improvements in diabetes management have increased diagnosis and control, but substantial opportunities remain to improve treatment, particularly with lipid-lowering therapy.

INTRODUCTION

The prevalence of diabetes in Mexico is among the highest in the world, causing about one-third of all premature deaths in adults¹ and much disability and expense.² In 2004, around half of all Mexican adults had no health insurance, but the subsequent introduction of *Seguro Popular*³ extended health insurance nationwide.⁴ The 2013 Mexican National Strategy for Overweight, Obesity and Diabetes aimed to improve health education and earlier identification and monitoring of major health risk factors.⁵ In 2016, diabetes was declared an epidemic and a national Mexican health emergency.⁶

The Mexico City Prospective Study (MCPS) is a blood-based prospective study of 150,000 Mexican adults who were originally recruited between 1998 and 2004. The prevalence of diagnosed diabetes at recruitment rose from 5% at age 40 to 20% at age 60, and diabetes at baseline was associated with a quadrupling of all-cause mortality at ages 35-74 years (more than double the proportional excess expected from studies of diabetes in high-income countries)^{1,7} with particularly high absolute excesses of mortality from cardiac disease, kidney disease and infection, and with the magnitude of the excess risk directly associated with the extent of glycemic control.⁸ National Mexican surveys done periodically from 2000 to 2018,⁹⁻¹² each involving about 45,000 people, found that the prevalence of diagnosed diabetes progressively rose over this period, but large surveys assessing temporal trends in undiagnosed diabetes, glycemic control or management of other risk factors are also needed.^{13,14}

The primary aim of this report is to use data from the MCPS to estimate how the prevalence of diabetes, its treatment, and its control in the population of Mexico City has changed between 1998-2004 and 2015-2019. A secondary aim is to put Mexican diabetes prevalence and control in perspective, by providing updated analyses of the MCPS data with respect to quantifying the relevance of controlled and uncontrolled diabetes (defined by a threshold HbA_{1c} level of 7%) to mortality in this population.

RESEARCH DESIGN AND METHODS

Study design and oversight

Study design, sampling methods and follow-up have been reported.⁸ Briefly, in 1998-2004, households from two neighbouring districts in Mexico City (Coyoacán and Iztapalapa) were visited systematically and all adults aged 35 years or more were invited to participate. Age, sex, socioeconomic status, smoking, and self-reported disease history (including diabetes and duration of diagnosis) and medication use were recorded. A question related to health services was added part way through recruitment and as a result was collected only in Iztapalapa. Trained nurses measured height, weight, hip and waist circumferences and sitting blood pressure and collected a 10 mL venous blood sample. In 2015-2019, a repeat survey was performed in a subset of surviving participants. For this resurvey, streets within the two study districts in which participants were previously recruited in 1998-2004 were selected at random, and then systematically revisited to identify participants who were still alive, living at the same address and willing to take part in a further survey. Resurvey information was collected electronically and included similar questions to those asked at the original survey in 1998-2004 (eg, on prior diseases and medications).

Blood samples at both the 1998-2004 and 2015-2019 surveys were separated and frozen in a central laboratory in Mexico City. Plasma and buffy coat samples were transported to Oxford, UK, for long-term storage. Buffy coat samples were analysed for HbA_{1c} in the ISO17025-accredited Wolfson laboratories, using validated high-performance liquid chromatography methods¹⁵ and calibrators traceable to International Federation of Clinical Chemistry standards.¹⁶

Approval was granted by ethics committees from the Mexican Ministry of Health, Mexican National Science and Technology Council, and University of Oxford, UK. At both surveys, study participants provided written informed consent.

Mortality follow-up

Mortality to 1 January 2018 was tracked through probabilistic linkage to the national death register, which ICD-10 codes all diseases mentioned on the death certificate. Study clinicians reviewed and, where necessary, recoded the underlying cause of death (in particular by accepting diabetes as the underlying cause only for deaths from an acute diabetic crisis).¹

Statistical Analysis

We defined diabetes as previously-diagnosed (self-reported medical diagnosis or use of any glucose-lowering medication) or undiagnosed (no previous diagnosis but $\text{HbA}_{1c} \geq 6.5\%$), and defined good control as $\text{HbA}_{1c} < 7\%$.¹⁷ The few with missing or implausible HbA_{1c} were excluded. To facilitate comparisons between the two surveys (1998-2004 vs 2015-2019) cross-sectional analyses of each survey were restricted to participants aged 45-84 years at the time of that survey (as few were aged >84 years in 1998-2004 or aged <45 in 2015-2019). Prevalence estimates for each of the four ten-year age ranges (from 45-54 years to 75-84 years) were uniformly standardised for sex and district of residence, and then averaged to calculate the overall uniformly age, sex and district-standardised prevalence at ages 45-84.

Cox regression was used to estimate the prospective relevance of controlled and inadequately controlled diabetes to all-cause mortality at ages 35-74 years (excluding mortality at ages 75-84 for consistency with our previous analyses of premature mortality).^{1,8} As before, these analyses excluded those with any other chronic disease at recruitment (vascular disease, chronic kidney disease, cancer, cirrhosis, or emphysema) and were adjusted for age-at-risk (5-year categories), residence (two districts), educational level (four groups), smoking status (never, former, light, moderate, or heavy), and anthropometric characteristics (height, weight, and waist and hip measurements). Excess mortality associated with controlled and inadequately controlled diabetes was then estimated using

previously-described methods.^{1,8} Analyses were performed with SAS, version 9.4, and R, version 3.5.1 (www.r-project.org/).

Role of funding sources

Funding sources had no role in study design, conduct, or analysis or the decision to submit for publication. JAD and JRE had full access to all study data and final responsibility for the decision to submit for publication.

RESULTS

Of 112,333 households with eligible participants visited from April 1998 to September 2004, 106,059 (94%) had at least one adult agreeing to participate and a total of 159,755 participants were recruited. Of these, 99,623 were aged 45-84 years and had complete data for the analyses in this report. From June 2015 to February 2019, 29,011 households of originally-recruited participants were randomly-selected and revisited, from which 8278 (29%) households provided a total of 10,144 participants who still lived at the same address, were home at the time of the revisit, and agreed to take part in the resurvey. Of these, 8986 were aged 45-84 years and had complete data. The characteristics of the 99,623 participants aged 45-84 years in the 1998-2004 survey and the 8986 participants aged 45-84 years in the 2015-2019 resurvey are shown in **Webtable 1**.

The uniformly age, sex and district standardized prevalence of diabetes (diagnosed or undiagnosed) at ages 45-84 years was 26% in the 1998-2004 baseline survey (midpoint 2002) but 35% by the 2015-2019 resurvey (midpoint 2017) (**Table 1**). In both surveys, the prevalence of diabetes was highest at ages 65-74 years (32% in 1998-2004 versus 41% in 2015-2019). Of those with diabetes, the proportion previously-diagnosed was 76% in 1998-2004 and 89% in 2015-2019, while of those with previously-diagnosed diabetes 80% in 1998-2004 and 94% in 2015-2019 were on at least one glucose lowering medication.

HbA_{1c} in those without diabetes was similar in 1998-2004 and 2015-2019 (**Webtable 1 and Figure 1**). In those with diabetes, however, median HbA_{1c} (unit = %) was about 0.9 units higher in 1998-2004 than in 2015-2019 (standardised median 8.2 versus 7.3 units). The prevalence of very poor control among those with diabetes (HbA_{1c} >10 units) fell from 28% in 1998-2004 to 18% in 2015-2019, while the proportion with good control (HbA_{1c} <7 units) rose from only 16% in 1998-2004 to 37% in 2015-2019 (**Table 1**). At both surveys HbA_{1c} levels were higher in younger than in older participants with diabetes (**Figure 1**), but within each age range the prevalence of good control improved between the two surveys (**Table 1**).

The age-specific (and sex and district standardised) prevalences of controlled diabetes, of treated but inadequately controlled diabetes, of diagnosed but untreated diabetes, and of undiagnosed diabetes are shown in **Figure 2**. The increase between 1998-2004 and 2015-2019 in the *proportion* of those with diabetes whose disease was being adequately controlled (**Table 1**) was counterbalanced by the increase in diabetes prevalence over this time period, so there was little net change in the prevalence of diagnosed but inadequately controlled diabetes (average across all ages: 16% in 1998-2004 and 18% in 2015-2019), or in the overall prevalence of inadequately controlled diabetes (average across all ages: 22% in 1998-2004 and 22% in 2015-2019).

The increased use of glucose-lowering medications between 1998-2004 and 2015-2019 reflected a large increase in biguanide use (mainly metformin) that exceeded the drop in sulfonylurea use (**Figure 3**). There was also a moderate increase in insulin use. The proportion of people with diabetes taking at least two glucose-lowering medications increased from 13% in 1998-2004 to 42% in 2015-2019 (**Webtable 2**). Insulin use was higher in those with than without self-reported CVD or CKD, but biguanide use was lower in those with CVD or CKD (perhaps reflecting metformin's relative contraindication with low kidney function).

Use of an anti-hypertensive medication (predominantly an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker), of aspirin or of a lipid-lowering drug (predominantly a statin) all increased between 1998-2004 and 2015-2019 (**Figure 3 and Webfigure 1**). Of those with previously-diagnosed diabetes, use of anti-hypertensive medication increased from 35% to 51%, use of aspirin increased from 3% to 12%, and use of a lipid-lowering drug increased from 1% to 14%. Among people with diabetes, use of these medications was higher in those with than without CVD or CKD, but even among those with CVD, only just over one-third were taking aspirin or a lipid-lowering drug.

During follow-up, which was for a median of 16 (IQR 15-17) years among survivors, there were 9465 deaths at ages 35-74 years. Among those who had at recruitment reported no chronic disease other than diabetes, the all-cause mortality rate ratio at these ages (RR) comparing those with versus those without diabetes at baseline was 2.3 (95% CI 2.1-2.5) for controlled and 3.9 (95% CI 3.8-4.1) for inadequately controlled diabetes (**Webtable 3**). Particularly for inadequately controlled diabetes, these RRs were larger at younger than at older ages, and the absolute excess risks associated with them accounted for 34% of all mortality at ages 35-74 (5% for controlled diabetes plus 29% for inadequately controlled diabetes). Deaths due to cardiac, renal and infectious diseases had the largest absolute excess risk associated with diabetes (**Webfigure 2**).

CONCLUSIONS

Diabetes and poor glycemic control are common in Mexico and carry a much worse prognosis than in high-income countries.¹ Comparing the baseline survey in 1998-2004 with the 2015-2019 resurvey, the age, sex and district-standardised prevalence of diabetes at ages 45-84 increased from about a quarter to about a third, the proportion of those with diabetes who were unaware of this decreased from about a quarter to about a tenth, and the use of at least one glucose-lowering medication (particularly metformin and insulin) increased from 80% to 94%, with about 40% now taking at least two glucose-lowering medications. Correspondingly, among those with diabetes the average HbA_{1c} decreased, and the proportion controlled (HbA_{1c} <7%) more than doubled. However, these improvements in diagnosis and treatment were counterbalanced by the increase in diabetes prevalence, so the prevalence of diagnosed but inadequately controlled diabetes has not changed much.

A limitation of our study is that it derives from just two districts of Mexico City, and so is not representative of the whole of Mexico. Despite this, our estimate of the prevalence of diabetes at ages 45-84 at recruitment is similar to the nationally-representative Encuesta Nacional de SALud y NUTricion (ENSANUT) study in 2006.¹⁴ Similarly, our estimate of the prevalence at resurvey is consistent with estimates for Mexico by the Global Burden of Disease investigators (**Webtable 4**)¹⁸ but somewhat higher than the ENSANUT 2016 estimate of 26% among 3700 adults aged 40 years or above.¹³ This could reflect differences in the age distribution between the two studies, as diabetes prevalence in ENSANUT at ages 60-69 years (average age of 65 years) was similar to the prevalence at ages 55-74 years in our resurvey. Our estimates of the proportion of those whose diabetes was controlled (16% in 1998-2004 and 37% in 2015-2019) are also somewhat higher than those reported in the ENSANUT studies (5% in ENSANUT 2006¹⁴ and 31% in ENSANUT 2016).¹³ The higher proportions with control of their diabetes in our study might reflect the higher mean age in our study, as we found control to be worse among younger adults. Taken together, the

proportion of those with diabetes who are controlled in Mexico is low compared with, for example, the average across all US populations between 2011 and 2016, in which 56% of those with diabetes were estimated to have their diabetes controlled.¹⁹

Our study reinforces the previous findings of the ENSANUT surveys but extends them in three important ways: first, by providing information on the use of diabetes drugs (and other drugs that reduce cardiovascular risk, such as lipid-lowering drugs), second by presenting key results separately at different ages, and third by relating diabetes control at recruitment directly to subsequent mortality. In our study, similar approaches to data collection were employed at both surveys and results were not fed back to participants (and so it is unlikely that the information recorded at resurvey would have been influenced by the fact that they had taken part in a similar survey more than a decade earlier). Although those involved in the 2015-2019 resurvey were (necessarily) study participants who had survived until 2015-2019, our uniform standardisation by age, sex and district ensure that the prevalence estimates for the 2015-2019 period provide a valid comparison with the equivalent estimates from the 1998-2004 period (and would also account for differences between the two surveys in factors correlated with age, such as duration of diabetes).

The characteristics of this study allowed reliable and detailed assessment of changes in diabetes management over the past ~15 years among adults in Mexico City. It draws data from a large study with high volunteer rates from two large municipalities which are home to about 2.5 million people representing a large spectrum of socio-economic statuses of the city. To enable like-with-like comparisons between recruitment and resurvey, our estimates were uniformly standardised for age (the largest determinant for prevalence of diabetes), sex and district. The observed increase in the standardized prevalence of diabetes between the 1998-2004 and 2015-2019 surveys is in close agreement with the country's diabetes projections²⁰ and is in concordance with the high incidence rate of diabetes²¹ in this population. The upsurge of diabetes in Mexico has been attributed to the underlying increase

of people with overweight and obesity in the country in the last 20 years.¹¹ Improving diet and increasing physical activity among the population could potentially help to control the epidemic of diabetes in the long-term, but it will also likely contribute to achieve better glycemic control among individuals with the disease.¹⁷ The improvements seen in diagnoses and treatment use between the two surveys will reflect a range of factors including, perhaps, secular changes in education (the standardised prevalence of having been educated to at least college level doubled between the two surveys).

An important finding from our study is the major opportunity to improve the use of other treatments proven to reduce CVD^{22,23} risk or CKD²⁴ progression. Although half of those with diabetes were on anti-hypertensive treatment and about 40% were on an ACEi or ARB by the 2015-2019 survey, the proportion using a statin was only 14%, and was only one-third in those who also had a history of CVD. Use of statins is also suboptimal in the US, but higher than in Mexico. In 2013, 58% of US people with recently diagnosed diabetes or with atherosclerotic CVD were treated with a statin.²⁵ Statin use in Mexico has been reported to be even lower than our results,²⁶ despite Mexican clinical guidelines beginning to recommend statin use in middle-aged adults with diabetes in 2004^{27,28} following the clear evidence of benefit from randomised trials.²⁹ Such extremely low statin uptake in Mexico may result from historical limited availability in public primary care, and a perception that results of a diagnostic blood lipid panel are necessary before initiating such therapy (with point of care testing reimbursed by *Seguro Popular* only introduced in 2017 to try to address this issue). A “fire and forget” approach (i.e. prescribing a generic moderately-intensive statin to people at high cardiovascular risk without further systematic lipid testing or dose adjustment) could be a simple strategy to address the challenge of supplying the millions of people with diabetes in Mexico with effective lipid lowering therapy and reducing vascular mortality.³⁰

Inadequately controlled diabetes was associated with a much greater excess mortality than controlled diabetes, accounting for about 30% of all premature deaths in this Mexican population, with the excess risk associated with controlled diabetes accounting for a further 5% of premature deaths. If anything, these may be underestimates because they are based on single baseline assessments of diabetes and HbA1c. The excess mortality risk associated with diabetes is likely to be mediated through a range of mechanisms, including non-glycemic risk factors related to the synergistic effects of adiposity, high blood pressure, CKD and dyslipidaemia,^{31,32} while some of the differences in mortality risk seen between those with controlled vs uncontrolled diabetes may be due to differential use of risk reducing treatments. Future analyses of these and other data (including genetic data) will explore such research questions. Until then, public health and fiscal interventions on the lifestyle drivers of adiposity would likely help reduce the rise in diabetes and help Mexico meet the global World Health Organization target to halt, by 2025, the rise in the age-standardised adult prevalence of diabetes from its 2010 level.³³ The challenge facing Mexico, and many other healthcare systems around the world, is how to deliver cost-effectively³⁰ and equitably to the growing millions of people who have diabetes simple glucose-lowering, anti-hypertensive and lipid lowering therapy.

CONTRIBUTORS

RC, RP, JA-D, PK-M and RT-C established the cohort. WGH, LG, RR-R, MH, JE, JA-D, PK-M and RT-C gathered the data. DA-R conducted the original analyses under the supervision of LG and JE; RW and WH contributed to the supervision of subsequent revisions of those analyses. DA-R and WGH wrote the first draft of the report. All authors contributed to revision of the report and agreed to its publication. JAD and JRE had full access to all the data in the study and take responsibility for data integrity and the accuracy of the analysis.

DECLARATIONS OF INTEREST

RC holds a British Heart Foundation Chair, and reports personal fees from UK Biobank and grants from Merck & Co, the Medicines Company (now Novartis) and Pfizer, outside the submitted work. RC has a patent for a statin-related myopathy genetic test licensed to University of Oxford from Boston Heart Diagnostics (but has waived any personal reward).

JRE and WGH report grants from Boehringer Ingelheim, outside the submitted work. All other authors declare no conflicts.

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FIGURES

Figure 1: Mean HbA_{1c} by age in those with versus without diabetes at recruitment (1998-2004) and at resurvey (2015-2019)

HbA_{1c} denotes glycosylated hemoglobin. Percentages adjusted for sex and district of residence. Diabetes defined as self-reported previous-medical diagnosis, use of glucose-lowering medication, or measured HbA_{1c} $\geq 6.5\%$.

Figure 2: Prevalence and control of diabetes at ages 45–84 years at recruitment (1998-2004) versus resurvey (2015-2019)

Prevalence estimates are standardised for sex and district of residence. Full bars represent the age-specific prevalence of diabetes, shown at the top of the bars in bold. Category-specific prevalences are shown in italics inside the relevant block within bars. Diabetes defined as previously-diagnosed diabetes (i.e. previous medical diagnosis or use of glucose-lowering medication) or undiagnosed diabetes (i.e. no previous diagnosis but HbA_{1c} $\geq 6.5\%$). Controlled diabetes defined as HbA_{1c} $< 7\%$.

Figure 3: Use of medications in participants aged 45-84 years with previously diagnosed diabetes at recruitment (1998-2004) and resurvey (2015-2019)

Estimates are uniformly standardised for age, sex, and district of residence. Previously-diagnosed diabetes defined as self-reported medical diagnosis or use of glucose-lowering medication. Any glucose-lowering includes insulin, biguanides, sulfonylureas, and others. Any anti-hypertensive includes alpha-blockers, ACEi, ARB, beta-blockers, calcium channel blockers, centrally acting anti-hypertensives, and diuretics. Any lipid-lowering therapy included statins, fibrates, resins, and others.

Table 1: Age-specific prevalence, diagnosis, treatment, and control of diabetes at recruitment and resurvey.

	Diabetes (diagnosed or undiagnosed)	Of these, percent previously- diagnosed	Of these, percent on glucose- lowering treatment	Controlled diabetes, all with diabetes	Controlled diabetes, those with previously- diagnosed diabetes	Controlled diabetes, those with previously diagnosed diabetes and on glucose-lowering treatment
Baseline survey (1998-2004)						
45-54 years	18%	70%	78%	10%	15%	19%
55-64 years	28%	77%	79%	14%	18%	23%
65-74 years	32%	81%	82%	18%	22%	28%
75-84 years	28%	77%	82%	22%	28%	35%
Overall, 45-84 yrs	26%	76%	80%	16%	21%	26%
Resurvey (2015-2019)						
45-54 years	25%	83%	92%	29%	35%	38%
55-64 years	35%	88%	94%	33%	38%	40%
65-74 years	41%	92%	95%	40%	44%	46%
75-84 years	38%	94%	94%	44%	47%	50%
Overall, 45-84 yrs	35%	89%	94%	37%	41%	44%

Controlled diabetes is defined as HbA1c <7.0%. Percentages within each ten-year age range are uniformly standardised for sex and district of residence. The four age-specific prevalences are then averaged to give the uniformly age, sex and district-standardised estimates at ages 45-84 years. Among participants aged 35-44 years at the baseline survey, percentage estimates were (following the order of the columns above): 7%, 60%, 72%, 9%, 15%, and 20%.

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