Received: 23 January 2024 | Revised: 12 February 2024 | Accepted: 14 February 2024

DOI: 10.1111/dom.15528

ORIGINAL ARTICLE

WILEY

Associations of diabesity with all-cause and cardiovascular disease mortality: Findings from the Mexico City Prospective Study

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Funding information
Mexican Health Ministry; National Council of Science and Technology for Mexico; UK Medical Research Council to the MRC Population Health Research Unit at the University of Oxford

Abstract

Aim: To investigate the joint associations of diabetes and obesity with all-cause and cardiovascular disease (CVD) mortality in the Mexico City Prospective Study.

Materials and Methods: In total, 154 128 participants (67.2% women) were included in this prospective analysis. Diabetes was self-reported, while body mass index was used to calculate obesity. Using diabetes and obesity classifications, six groups were created: (a) normal (no diabetes and normal weight); (b) normal weight and diabetes; (c) overweight but not diabetes (overweight); (d) overweight and diabetes (prediabesity); (e) obesity but not diabetes (obesity); and (f) obesity and diabetes (diabesity). Associations between these categories and outcomes were investigated using Cox proportional hazard models adjusted for confounder factors.

Results: During 18.3 years of follow-up, 27 197 (17.6%) participants died (28.5% because of CV causes). In the maximally adjusted model, participants those with the

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highest risk {hazard ratio (HR): 2.37 [95% confidence interval (CI): 2.24-2.51]}, followed by those with diabesity [HR: 2.04 (95% CI: 1.94-2.15)]. Similar trends of associations were observed for CVD mortality. The highest CV mortality risk was observed in individuals with diabesity [HR: 1.80 (95% CI: 1.63-1.99)], followed by normal weight and diabetic individuals [HR: 1.78 (95% CI: 1.60-1.98)].

Conclusion: This large prospective study identified that diabetes was the main driver of all-cause and CVD mortality in all the categories studied, with diabesity being the riskiest. Given the high prevalence of both conditions in Mexico, our results reinforce the importance of initiating prevention strategies from an early age.

KEYWORDS
diabetes; mortality; obesity, cardiovascular diseases

1 | INTRODUCTION

The prevalence of obesity, a complex and multi-etiological condition, has tripled in the last 45 years worldwide, affecting both genders irrespective of socio-economic status.[1–3] In 2019, 52% of the global population was overweight or obese (approximately 1.9 billion and 650 million adults, respectively).[1] In the Americas region, the combined prevalence of overweight and obesity increased from 58.2% in 1980 to 92.5% in 2019. Mexico and the United States lead these prevalence rates, holding the highest figures in the region.[2]

Obesity is one of the major risk factors for the development of type 2 diabetes (hereafter: diabetes); both conditions have a severe impact on the lives of those affected. By 2017, a global prevalence of 6.3% was estimated, meaning about 462 million people had diabetes.[4] Obesity and diabetes share risk factors, such as unhealthy diets and low leisure time physical activity, as well as conditions and diseases, including cardiovascular diseases (CVD), dyslipidemia, hypertension, metabolic-associated fatty liver disease and metabolic syndrome, among others.[4,5] The factor that probably stands out in both conditions is insulin resistance, a consequence of abdominal adiposity.[6]

The term 'diabesity' describes a condition in which both diabetes and obesity coexist, referring to the close association in the pathophysiology of both conditions and how they exacerbate each other.[6,7] It represents the continuation of metabolic alterations that begin with resistance to the action of insulin in target cells and culminate in diabetes diagnosis. Although the etiology of diabetes may have genetic predispositions, its development is strongly influenced by environmental factors, dietary patterns and lifestyles.[8] The diabesity concept is emerging again as a powerful tool for reinforcing prevention and treatments in line with the high prevalence of obesity and diabetes across the globe. It is even more important now that drugs such as glucagon-like peptide-1 receptor agonists, initially developed for treating diabetes, have recently shown substantial weight loss.[9] Recent trials, in fact, showed that these drugs resulted in significant weight loss and CV protection for obese patients, irrespective of their diabetes status.[10]

Mexico is of particular interest since the obesity prevalence has reached a record level. In fact, according to the 2022 National Health and Nutrition Survey (ENSANUT 2022), the cumulative prevalence of overweight and obesity in the Mexican adult population was 75.2%, while abdominal obesity was 81.0%.[11] Furthermore, based on the same national data, the prevalence of diabetes was 18.3%.[12] Even if the individual association of obesity and diabetes with mortality has been widely investigated worldwide,[13–15] very few investigations have been conducted on the association of diabesity with adverse outcomes,[16] and, to the best of our knowledge, no large cohort studies have explored this association both in middle-aged and older adults in the Latin America Region. Therefore, considering that obesity and diabetes are known to be individually associated with mortality, this study aimed to investigate the joint associations of diabesity with all-cause and CVD mortality in the Mexico City Prospective Study.

2 | METHODS

The Mexico City Prospective Study is a population-based cohort study involving a follow-up of more than 150 000 adults (Figure S1). Briefly, between 1995 and 1997, door-to-door interviews were conducted to compile a record of all households in the neighbouring districts of Coyoacán and Iztapalapa in Mexico City.[17] Recruitment teams then visited households, and at least one adult aged ≥35 years was recruited from 94% of eligible households.[17] Trained nurses collected data in the participant's household, and the baseline survey took place from 1998 to 2004.[17] More information can be found elsewhere.[17]

2.1 | Ethics

The Mexican Ministry of Health approved the study as well a the Mexican National Council of Science and Technology (approval number 0595 P-M), and the Central Oxford Research Ethics Committee (C99.260). All participants provided written, informed consent. The data used in the current report were obtained through an open-access

data request made to the Mexico City Prospective Study principal investigators.

2.2 | Diabesity

Diabetes history was diagnosed as yes or no using self-reported information at baseline. Weight (kg) and height (m^2) were used to estimate obesity using body mass index (BMI), calculated as kg/m^2 and classified using the World Health Organization criteria for adults as follows: normal weight: 18.5-24.9 kg/m^2; overweight: 25.0-29.9 kg/m^2; obese: ≥30.0 kg/m^2. Underweight individuals (<18.5 kg/m^2) were removed from this analysis to avoid potential reverse causality.

Then, using diabetes and obesity classifications, six groups were created: (a) normal (no diabetes and normal weight); (b) normal-weight and diabetes; (c) overweight but not diabetes (hereafter: overweight); (d) overweight and diabetes (hereafter: prediabesity); (e) obesity but not diabetes (hereafter: obesity); and (f) obesity and diabetes (hereafter: diabesity).

As a sensitivity analysis, waist circumference was used instead of BMI as a measure of adiposity to classify obesity. Central obesity was classified as waist circumference ≥80 and ≥90 in women and men, following the Mexican classification.[11] Then, the following four categories were created for the sensitivity analysis: (a) normal (no diabetes nor central obesity); (b) diabetes (no central obesity); (c) central obesity (no diabetes); and (d) diabesity (central obesity and diabetes).

2.3 | Outcomes

The registration of deaths in Mexico is thorough, with almost all deaths certified medically and with few deaths attributed to unknown causes.[18] The outcomes included in this study were all-cause and CVD mortality. Mortality was tracked up to the 31 December 2020 through probabilistic linkage to the national death register based on the participant's name, age and sex. Diseases listed on the death certificates were coded according to the International Classification of Diseases, 10th Revision (ICD-10).[19]

2.4 | Covariates

Age at baseline was determined from the date of birth and baseline assessment. Sex was self-reported at baseline. Education level, civil status and occupation were self-reported. Educational level was classified using the following five categories: none; at least some elementary; at least some high school; at least some college; and at least some university. Civil status was classified as single, divorced or separated, married or living with a partner, and widowed. Occupation was classified as worker, student, housework, retired and unemployed.

Prevalent morbidity (morbidity count) was ascertained during a nurse-led interview at baseline, and participants were classified as having no prevalent morbidity or ≥1 prevalent morbidity based on 17 long-term conditions (emphysema, heart attack, angina, asthma, stroke, chronic kidney insufficiency, peptic ulcer, cirrhosis, hypertension, diabetes, some types of cancer and peripheral arterial disease).

Smoking [never, former (quit >3 years ago), current but not daily, daily (<10 cigarettes/day) and daily (≥10 cigarettes/day)], as well as alcohol intake (none, former use, ≤3 times/month, ≤2 times/week and ≥3 times/week), were self-reported. Diet quality was expressed as fruit and vegetable intake using the following groups: never, 1 or 2 days per week, 3 or 4 days per week, and ≥5 days per week, while physical activity was classified as <1 time/week, 1-2 times/week, and ≥3 times/week. Finally, participants were asked about their sleep duration, and the at-risk group was defined as sleeping <7 or >9 h per night. Further details on the Mexico City Prospective Study design and methodology are available elsewhere.[17]

2.5 | Statistical analyses

Descriptive baseline characteristics are presented as means with SD for quantitative variables and as frequencies and percentages for categorical variables according to the six diabesity categories.

Associations between diabesity categories and mortality outcomes were investigated using the Cox proportional hazard models, with the time of follow-up used as the timeline variable. Individuals in the normal category (no diabetes and normal weight) were used as the referent category. The results are reported as hazard ratios (HRs) with their 95% confidence intervals (95% CI).

Underweight participants (n = 826), those with missing data for one or more covariates (n = 2552), and those for whom it was unclear their vital status (n = 2011) were excluded from the all-cause and CVD mortality analyses (Figure S1). In addition, participants who already had or suffered from a heart attack, angina, stroke, or peripheral arterial disease at baseline were removed just from the CVD analyses (n = 12 423). The latter was carried out to account for the burden of diabesity categories in people without these major adverse CV conditions at baseline.

Analyses were adjusted using three incremental models: model 1 was adjusted for sociodemographic characteristics (age, sex, marital status, occupation and educational level); model 2 was additionally adjusted for morbidity count; and model 3 additionally included lifestyle factors (physical activity, smoking, alcohol intake, sleep categories and fruit and vegetable intake). In addition, further analyses were performed, including three landmark periods in model 3, to assess the impact of reverse causality. In these analyses, individuals who died during the first 2, 5 and 10 years of follow-up were removed from the analyses.

To investigate whether the associations between the diabesity categories and the outcomes differed by population groups, the analyses were stratified by age (≥65 years and <65 years) and sex (men and women). An interaction term among the subgroups, the diabesity categories, and the outcomes was fitted into the model to test for interaction.

As a sensitivity analysis, central obesity (waist circumference) was used instead of BMI to identify diabesity as a measure of adiposity. In

this case, participants without central obesity or diabetes were used as the referent group. Finally, a further sensitivity analysis was performed just for CVD mortality, where analyses were adjusted for statins and angiotensin-converting enzyme inhibitors at baseline. These drugs were included just as sensitivity covariates, considering people with major adverse CV outcomes at baseline (n = 12 423) were removed from the main analysis.

Stata 18 statistical software (StataCorp LP) was used to perform all analyses. Values for $p < .05$ were considered statistically significant. This study follows the STROBE reporting guidelines for cohort studies (see more details in the Supplementary material).[20]

3 | RESULTS

After removing participants with missing data and those whose vital status was unclear (n = 5389), 154 128 were finally included (Figure S1). The baseline characteristics of the total included population and the diabesity categories created are shown in Table 1. Overall, 67.2% of the total sample were women. Participants would probably be married or living with a partner, have a lower educational level, and be workers or houseworker. Regarding diabesity categories, a low proportion of the population had diabetes, irrespective of their nutritional status (13.3%). Among people with diabetes, the highest prevalence was observed in individuals with prediabesity. Compared with people without diabetes, irrespective of their nutritional status, diabetics were older (particularly those in the normal weight and diabetic category), would probably be houseworkers or unemployed, have lower educational levels, eat fruit and vegetables three to four times per week, and never smoke. More general characteristics are available in Table 1.

Over 18.3 (interquartile range: 17.5-19.6) years of follow-up, 27 197 (17.6%) participants died. Of them, 7743 (28.5%) died because of CV causes. Associations between diabesity categories and all-cause and CVD mortality are shown in Figure 1. In the minimally adjusted model, compared with normal weight and no diabetes, participants with diabetes had a higher mortality risk, being normal weight and diabetes participants those who had the highest risk [HR: 2.90 (95% CI: 2.76-3.06); $p < .001$], followed by those with diabesity [HR: 2.50 (95% CI: 2.38-2.62); $p < .001$]. In contrast, participants who were overweight had a lower mortality risk [HR: 0.96 (95% CI: 0.92-0.99); $p < .05$]. After further adjusting (models 2 and 3), the associations were attenuated but remained statistically significant for all the categories (Figure 1). When the landmark periods (2, 5 and 10 years) were included in model 3, associations were once again attenuated. Interestingly, after removing participants who died during the first 5 and 10 years of follow-up, the highest mortality risk was observed in individuals in the diabesity category [HR_{5years}: 2.33 (95% CI: 2.19-2.48); $p < .001$ and $HR_{10years}$: 2.65 (95% CI: 2.45-2.86); $p < .001$] while the previous protective association between overweight and all-cause mortality disappeared, with these individuals having a 5% and 16% higher risk compared with their counterparts (Figure 1).

Similar trends of associations were observed for CVD mortality. The highest CV mortality risk was observed in individuals with diabesity [$HR_{model\ 3}$: 1.80 (1.63-1.99); $p < .001$], followed by normal weight and diabetic individuals [$HR_{model\ 3}$: 1.78 (95% CI: 1.60-1.98); $p < .001$]. However, no significant association was identified for overweight individuals (model 3, Figure 1). Similar trends were observed for CV mortality in the landmark analyses as per all-cause mortality and when the statin and ACE inhibitors at baseline were included in the sensitivity analysis (Table S1). For instance, after removing the first 10 years of follow-up, all categories had a higher CVD mortality risk; however, the highest risk was observed in individuals who had diabesity [HR: 2.17 (95% CI: 1.88-2.51); $p < .001$], followed by prediabesity [HR: 1.95 (95% CI: 1.70-2.24); $p < .001$] and normal-weight diabetic individuals [HR: 1.73 (95% CI: 1.46-2.05); $p < .001$] (Figure 1).

The subgroup analyses by age and sex are shown in Table 2. Significant interactions were identified between all diabesity categories and age, both in all-cause and CVD mortality ($p < .05$). In all cases, the risk was higher in individuals <65 years than those >65 years. Regarding sex, only the categories with diabetes (i.e. normal-weight diabetes, prediabesity and diabesity) had a significant interaction for all-cause mortality. Yet, even if women had a higher all-cause mortality risk than men, men had a higher CVD mortality risk than women (Table 2).

Finally, when waist circumference was used to measure obesity instead of BMI, all categories were associated with a higher all-cause and CVD mortality risk, even after including the three different landmark periods (Table S2). As per BMI, the highest risk was observed in individuals with normal weight and diabetes, as well as those with diabesity, followed by those with central obesity. Interestingly, the risk in the diabesity category increased as long as the landmark periods were included [$HR_{2years\ diabesity}$: 2.31 (95% CI: 2.19-2.44); $p < .001$; $HR_{5years\ diabesity}$: 2.44 (95% CI: 2.30-2.59); $p < .001$; $HR_{10years\ diabesity}$: 2.59 (95% CI: 2.41-2.80); $p < .001$] (Table S2).

4 | DISCUSSION

Using data from the Mexico City Prospective Study, which is one of the largest and longest cohort studies in Latin America, we identified that diabetes was the main driver of all-cause and CVD mortality in all categories investigated. A previous Mexican study showed that rates of death were strongly associated with increased diabetes.[21] Interestingly, in the no-landmark analysis, individuals with normal weight and diabetes, as well as overweight individuals, showed the highest and lowest all-cause mortality risk, respectively. This may be associated with the obesity paradox effect, which has a critical role in the incidence of a disease but a protective effect on those with a severe condition.[22,23] Yet, the mechanism behind this association remains unknown. On the other hand, when the different landmark analyses were applied, individuals classified in the diabesity category had the highest overall mortality risk. Even if similar trends were identified when the waist circumference was used as an obesity criterion, no obesity paradox effect was observed in any of the models

TABLE 1 Baseline characteristics of the included population by the diabesity categories.

Variables	Overall	Normal	Normal weight diabetic	Overweight no diabetes	Prediabesity	Obesity	Diabesity
n (%)	154 128 (100)	26 467 (17.2)	4350 (2.8)	57 730 (37.5)	8635 (5.6)	49 334 (32.0)	7612 (4.9)
Age, years; mean (SD)	52.3 (13.0)	51.8 (14.8)	61.3 (12.2)	51.0 (12.9)	59.8 (11.5)	51.0 (11.8)	57.7 (11.0)
Sex, women; n (%)	103 550 (67.2)	16 348 (61.8)	2351 (58.2)	36 231 (62.8)	5378 (62.3)	37 136 (75.3)	5926 (77.8)
Marital status, n (%)							
Single	13 706 (8.9)	3339 (12.6)	294 (6.8)	5027 (8.7)	478 (5.5)	4067 (8.2)	501 (6.5)
Divorced/separated	10 829 (7.0)	2105 (8.0)	272 (6.2)	4022 (7.0)	493 (5.7)	3411 (6.9)	526 (6.9)
Living with a partner/married	110 492 (71.7)	17 756 (67.1)	2814 (64.7)	42 764 (74.1)	6008 (69.6)	36 046 (73.1)	5104 (67.1)
Widowed	19 101 (12.4)	3267 (12.3)	970 (22.3)	5917 (10.2)	1656 (19.2)	5810 (11.8)	1481 (19.5)
Occupation, n (%)							
Worker	65 498 (42.5)	12 742 (48.1)	1264 (29.1)	27 346 (47.4)	2772 (32.1)	19 226 (39.0)	2148 (28.2)
Student	106 (0.1)	47 (0.2)	1 (0.1)	34 (0.1)	1 (0.1)	23 (0.1)	0
Housework	72 174 (46.8)	10 349 (39.1)	2099 (48.2)	24 325 (42.1)	4327 (50.1)	26 446 (53.6)	4628 (60.8)
Retired	11 066 (7.2)	2094 (7.9)	616 (14.1)	4107 (7.1)	1046 (12.1)	2572 (5.2)	631 (8.3)
Unemployed	5284 (3.4)	1235 (4.7)	370 (8.5)	1918 (3.3)	489 (5.6)	1067 (2.1)	205 (2.7)
Education level, n (%)							
None	20 046 (13.0)	3241 (12.2)	979 (22.5)	6094 (10.6)	1800 (20.8)	6412 (13.0)	1520 (20.0)
Some elementary	72 460 (47.0)	10 039 (37.9)	2369 (54.5)	25 529 (44.2)	4867 (56.4)	25 197 (51.1)	4459 (58.6)
Some high school	37 701 (24.5)	7216 (27.3)	637 (14.6)	15 553 (27.0)	1304 (15.1)	11 871 (24.1)	1120 (14.7)
Some college	10 000 (6.5)	2274 (8.6)	140 (3.2)	4412 (7.6)	271 (3.1)	2697 (5.4)	206 (2.7)
Some university	13 921 (9.0)	3697 (14.0)	225 (5.2)	6142 (10.6)	393 (4.6)	3157 (6.4)	307 (4.0)
Prevalent morbidity (≥1), n (%)	56 660 (36.8)	5404 (20.4)	4350 (100)	14 201 (24.6)	8635 (100)	16 458 (33.4)	7612 (100)
Sleep (7-9 h/day), n (%)	104 027 (67.5)	17 738 (67.0)	2708 (62.2)	39 274 (68.0)	5512 (63.8)	33 923 (68.8)	4872 (64.0)
Number of days F&V are eaten, n (%)							
Never	26 044 (16.9)	4349 (16.4)	668 (15.4)	9679 (16.7)	1290 (14.9)	8833 (17.9)	1225 (16.1)
1-2 days/week	42 925 (27.8)	7072 (26.7)	1022 (23.5)	16 368 (28.4)	2150 (2.9)	14 359 (29.1)	1954 (25.7)
3-4 days/week	83 527 (54.2)	14 685 (55.5)	2617 (60.2)	31 104 (53.9)	5121 (59.3)	25 642 (52.0)	4368 (57.2)
≥5 days/week	1632 (1.1)	361 (1.4)	43 (0.9)	579 (1.0)	74 (0.9)	500 (1.0)	75 (1.0)
Smoking, n (%)							
Never	75 321 (48.9)	11 819 (44.7)	2075 (47.7)	27 023 (46.8)	4307 (49.9)	25 920 (52.5)	4177 (54.9)
Former, quit >3 years ago	30 665 (19.9)	4896 (18.5)	1007 (23.2)	11 538 (20.0)	2122 (24.6)	9374 (19.0)	1728 (22.7)
Current but not daily	16 957 (11.0)	2627 (9.9)	360 (8.3)	6898 (12.0)	709 (8.2)	5726 (11.6)	637 (8.4)
Daily, <10 cigarettes/day	21 366 (13.9)	4499 (17.0)	596 (13.7)	8485 (14.7)	1012 (11.7)	6011 (12.2)	763 (10.0)
Daily, ≥10 cigarettes/day	9819 (6.3)	2626 (9.9)	312 (7.1)	3786 (6.5)	485 (5.6)	2303 (4.7)	307 (4.0)
Alcohol intake, n (%)							
Never	30 583 (19.8)	5150 (19.5)	972 (22.3)	10 369 (18.0)	1913 (22.2)	10 223 (20.7)	1956 (25.7)
Former use	21 541 (14.0)	3491 (13.2)	976 (22.4)	7439 (12.9)	1809 (21.0)	6312 (12.8)	1514 (19.9)
Up to 3 times/month	92 250 (59.9)	15 459 (58.4)	2140 (49.2)	35 757 (61.9)	4473 (51.8)	30 476 (61.8)	3945 (51.8)
Up to 2 times/week	6975 (4.5)	1552 (5.9)	155 (3.6)	3050 (5.3)	312 (3.6)	1760 (3.6)	146 (1.9)
≥3 times/week	2779 (1.8)	815 (3.0)	107 (2.5)	1115 (1.9)	128 (1.4)	563 (1.1)	51 (0.7)

(Continues)

TABLE 1 (Continued)

Variables	Overall	Normal	Normal weight diabetic	Overweight no diabetes	Prediabesity	Obesity	Diabesity
Physical activity, n (%)							
None	119 705 (77.7)	19 451 (73.5)	3455 (79.4)	43 153 (74.8)	6672 (77.3)	40 750 (82.6)	6224 (81.8)
Up to 2 times/week	11 934 (7.7)	2389 (9.0)	253 (5.8)	5266 (9.1)	585 (6.7)	3034 (6.2)	407 (5.3)
≥3 times/week	22 489 (14.6)	4627 (17.5)	642 (14.8)	9311 (16.1)	1378 (16.0)	5550 (11.2)	981 (12.9)

Note: Descriptive characteristics by the obesity and diabetes categories are presented as means (SD) for quantitative variables and as frequencies and percentages for categorical variables.
Abbreviations: F&V, fruit and vegetable; n, number; SD, standard deviation.

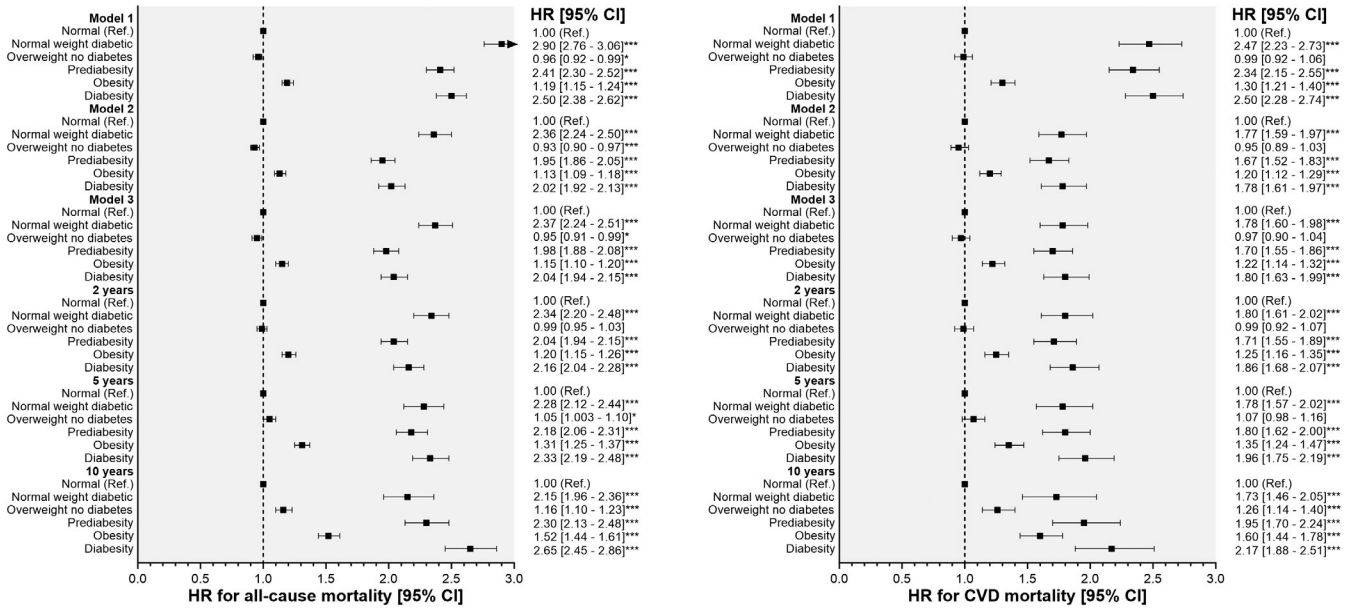

FIGURE 1 Associations between diabesity categories and all-cause and CVD mortality were investigated using Cox proportional hazard models. Individuals in the normal category were used as the referent. Model 1 was adjusted for sociodemographic characteristics (age, sex, marital status, occupation and educational level); model 2 was additionally adjusted for morbidity count; and model 3, additionally included lifestyle factors (physical activity, smoking, alcohol intake, sleep categories, and fruit and vegetable intake). In addition, further analyses were performed including three landmark periods in model 3. In these analyses, individuals who died during the first 2, 5 and 10 years of follow-up were removed from the analyses. ***$p < .001$; *$p < .05$. CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

investigated, and, once again, people classified in the diabesity category had one of the highest all-cause and CVD mortality risk.

The individual association of obesity and diabetes with all-cause[13,14] and CVD mortality[15] has been widely investigated in different populations across the globe. Nonetheless, very few prospective studies have explored their joint association with the occurrence of CVD and all-cause mortality over a long study period and in a large database. Over 11.25 years of follow-up of 5432 Iranians, diabesity (defined either using BMI or waist circumference) was associated with a higher incident CVD risk but not with CVD or all-cause mortality.[16] In Mexico, only one previous study in older adults explored this combination but focused mainly on cognitive impairment and mortality alone.[7] Using data from 7885 participants from the Mexican Health and Aging Study, Milani et al.[7] identified that diabesity was associated with a 1.70 higher risk of cognitive impairment relative risk: 1.70 (95% CI: 1.168-2.48) while for mortality, only diabetes was associated with a higher mortality risk. Even if the study by Milani et al.[7] also highlighted the superior role of diabetes in mortality compared with obesity, the study was conducted in a smaller population, without considering time to follow-up as a dependent variable and including only older adults, and, as we previously highlighted, <65-year-old individuals with diabesity are at higher risk of an adverse outcome.[7]

As it has just been underlined, the magnitude of associations identified in this study was stronger for both outcomes in individuals <65 years. A previous study also identified that younger people who had diabetes were more susceptible to higher all-cause and CVD mortality risk, probably because of the extra years with an excess risk of complications compared with people diagnosed at an advanced age.[24] Regarding sex, women showed stronger associations for all-cause mortality, while men for CVD mortality. This result is not surprising

TABLE 2 Association between diabesity and all-cause and CVD mortality by subgroups analyses.

		Normal	Normal weight diabetic	Overweight no diabetes	Prediabesity	Obesity	Diabesity
	Total/events	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All-cause mortality							
Age							
<65 years	124 270/13 604	1.00 (Ref.)	4.18 (3.84; 4.56)***	0.97 (0.92; 1.04)	3.01 (2.79; 3.25)***	1.34 (1.26; 1.42)***	2.87 (2.66; 3.11)***
≥65 years	29 858/13 593	1.00 (Ref.)	1.47 (1.37; 1.59)***	0.88 (0.84; 0.93)***	1.26 (1.18; 1.35)***	0.87 (0.83; 0.92)***	1.23 (1.15; 1.33)***
Interaction			***	*	***	***	***
Sex							
Women	103 550/15 595	1.00 (Ref.)	2.43 (2.25; 2.63)***	0.93 (0.88; 0.98)*	2.05 (1.92; 2.19)***	1.14 (1.08; 1.20)***	2.09 (1.95; 2.23)***
Men	50 578/11 602	1.00 (Ref.)	2.27 (2.09; 2.46)***	0.97 (0.92; 1.03)	1.86 (1.73; 2.01)***	1.17 (1.10; 1.24)***	1.86 (1.69; 2.03)***
Interaction			*	–	*	–	*
CVD mortality							
Age							
<65 years	115 887/3232	1.00 (Ref.)	3.23 (2.69; 3.88)***	1.08 (0.95; 1.23)	2.78 (2.37; 3.26)***	1.48 (1.30; 1.69)***	2.68 (2.27; 3.16)***
≥65 years	25 818/4511	1.00 (Ref.)	1.13 (0.98; 1.30)	0.82 (0.75; 0.89)***	1.01 (0.90; 1.13)	0.87 (0.79; 0.95)*	0.99 (0.87; 1.13)
Interaction			***	**	***	***	***
Sex							
Women	93 663/4405	1.00 (Ref.)	1.62 (1.40; 1.88)***	0.92 (0.83; 1.01)	1.66 (1.46; 1.88)***	1.18 (1.07; 1.30)**	1.68 (1.48; 1.90)***
Men	48 042/3338	1.00 (Ref.)	1.95 (1.66; 2.28)***	1.02 (0.92; 1.12)	1.71 (1.49; 1.97)***	1.26 (1.13; 1.42)***	1.96 (1.66; 2.32)***
Interaction			–	–	–	–	–

Note: Associations between diabesity categories and all-cause and CVD mortality by subgroups were investigated using Cox proportional hazard models. Individuals in the normal category were used as the referent. Analyses were adjusted for age, sex, marital status, occupation, educational level, morbidity count, physical activity, smoking, alcohol intake, sleep categories and fruit and vegetable intake when these were not used as moderator. ***$p < .001$; **$p < .01$; *$p < .05$; –, no interaction.

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

considering that previous studies have suggested sex differences in mortality rates associated with diabetes.[25,26] A systematic review and meta-analysis, which included 86 prospective cohorts,[25] highlighted that diabetes may be a stronger risk factor for CVD and all-cause mortality in women than men. Genetic and biological factors, as well as cultural and environmental conditions, may partially explain these differences.

Insulin resistance is postulated as the key element linking metabolic and CV alterations.[27] Preclinical, clinical and epidemiological studies have elucidated the relationship between obesity and insulin resistance and associated consequences such as diabetes and CVD.[28] It is suggested that elevated adipose deposits increase concentrations of free fatty acids. This increase is conditioned by insulin resistance, which contributes to excess circulating free fatty acids and ectopic lipid accumulation by not inhibiting hepatic lipogenesis. These processes elevate diacylglycerol and ceramide concentrations, reducing the insulin response, deregulating the leptin response, decreasing satiety, reducing adiponectin secretion, desensitizing the insulin receptor. These effects decrease the lipid-dependent metabolic rate and promote the release of proinflammatory cytokines by adipose tissue macrophages.[29] These cytokines induce mitochondrial dysfunction in muscle and adipose tissue, disrupting energy production and generating reactive oxygen species. This, in turn, further increases insulin desensitization through insulin receptor substrate phosphorylation, creating a vicious cycle between obesity, proinflammatory and oxidative stress, mitochondrial dysfunction, and systemic insulin resistance.[29] Furthermore, insulin resistance is associated with decreased nitric oxide production, affecting vascular contraction. These mechanisms position dysfunction in adipose tissue and associated macrophages as a crucial factor in systemic chronic inflammation, triggering damage in various organs and tissues. These metabolic, energetic, inflammatory and oxidative alterations in muscles and endothelia lead to CV dysfunction.[29] Western dietary patterns, characterized by excessive calorie intake with high concentrations of fats and carbohydrates, can trigger proinflammatory and oxidative stress and, therefore, predispose to the aforementioned scenario.[27]

The present study has important implications for policy and practice in Mexico. Given that the group of normal-weight individuals with diabetes is often associated with the highest risk of mortality, the present study suggests that the main determinant of mortality is not adiposity but diabetes. Metabolic alterations linked to insulin resistance and decreased muscle mass probably play a crucial role. For instance, Boonpor et al. have recently described this phenomenon in a prospective cohort that identified an increased risk of developing CVD in individuals with diabetes and sarcopenia.[30] Moreover, both in obesity and diabetes, dietary choices and lifestyles play a decisive role. In this context, the role of public policies becomes fundamentally important.[8] Since 2006, there have been increases in the prevalence of diabetes, hypertension and dyslipidaemia in Mexico, probably associated with the rise in obesity, poor-quality diet consumption and population aging.[31] The ENSANUTs do not report the prevalence of diabetes and other non-communicable diseases in individuals under 18 years; however, a Mexican study on schoolchildren and adolescents indicated the onset of diabetes at the early age of 11.17 years.[32] This scenario, which was characterized by high prevalences of overweight and obesity, is distressing in terms of quality of life, healthy life years, early mortality, impairment of the productive activity of the economically active population affected by illness, as well as the costs incurred by health care systems in the country.[33]

Our research question was investigated in a single, large, and well-characterized general population cohort. The analyses were adjusted for a comprehensive set of covariates. Also, we could assess whether the associations were consistent across population subgroups. A major driver of potential information bias, knowledge of disease status, was obviated entirely by ascertaining outcomes from routine administrative databases. However, this study also has limitations. First, although we included those confounding factors that were considered relevant and for which we had data, residual confounding because of unknown or unmeasured confounders is possible. Second, fruit and vegetables were used as a proxy of diet quality since no other diet variables in the cohort were available. Moreover, self-reported fruits and vegetables are subject to recall and misclassification bias and may change over time. Third, diabetes was self-reported at baseline. Even if previous studies have identified a high level of agreement between self-reported diabetes and medical records,[34] disease-differential recall or misclassification bias may exist. We tried to minimize potential reverse causation by including three landmark periods in our analyses (2, 5 and 10 years). Fourth, associations observed in an observational study cannot be assumed to infer causality. Finally, the Mexico City Prospective Study does not represent the Mexican population. Therefore, while risk estimates can be generalized, summary statistics such as prevalence and incidence should not be.

In conclusion, this large prospective study identified that diabetes was the main driver of all-cause and CVD mortality in all the categories studied, with diabesity being the riskiest, even after adjusting for a broad group of confounders, including different landmark periods and using waist circumference as a measure of obesity. Given the high prevalence of both conditions in Mexico, our results highlight the relevance of preventing both obesity and diabetes, particularly in younger ages, to decrease the risk of early mortality.

AUTHOR CONTRIBUTIONS

FP-R contributed to the conception and design of the study. GO'D and GF advised on all statistical aspects. FP-R and EA performed the literature search, the analyses and interpreted the data. All authors critically reviewed this and previous drafts. All authors approved the final draft for submission. FP-R and EA contributed equally to this work and are joint first authors. FP-R is the guarantor.

ACKNOWLEDGMENTS

We are grateful to Mexico City Prospective Study participants.

FUNDING INFORMATION

This research has been conducted using Mexico City Prospective Study (MCPS) Data under application number 2022-012. The MCPS

(https://www.ctsu.ox.ac.uk/research/mcps) is a long-standing scientific collaboration between researchers at the National Autonomous University of Mexico and the University of Oxford, and has received funding from the Mexican Health Ministry, the National Council of Science and Technology for Mexico, Wellcome, and core grants from the UK Medical Research Council to the MRC Population Health Research Unit at the University of Oxford.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15528.

DATA AVAILABILITY STATEMENT

Data from the Mexico City Prospective Study are available to bona fide researchers. The study's Data and Sample Sharing policy can be downloaded (in English or Spanish). Available study data can be examined in detail through the study's Data Showcase."

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REFERENCES

1. WHO. Obesity and overweight. 2021 https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight
2. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metabolism*. 2019;92:6-10.
3. Federation WO. The economic impact of overweight & obesity in 2020 and 2060. 2022 https://data.worldobesity.org/publications/WOF-Economic-Impacts-2-V2.pdf
4. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al KJ. Epidemiology of type 2 diabetes–global burden of disease and forecasted trends. *J Epidemiol Glob Health*. 2020;10(1):107-111.
5. García-Vega D, González-Juanatey JR, Eiras S. Diabesity in elderly cardiovascular disease patients: mechanisms and regulators. *Int J Mol Sci*. 2022;23(14):7886.
6. Michaelidou M, Pappachan JM, Jeeyavudeen MS. Management of diabesity: current concepts. *World J Diabetes*. 2023;14(4):396-411.
7. Milani SA, Lopez DS, Downer B, Samper-Ternent R, Wong R. Effects of diabetes and obesity on cognitive impairment and mortality in older mexicans. *Arch Gerontol Geriatr*. 2022;99:104581.
8. Cardoso S, Moreira PI. Diabesity and brain disturbances: a metabolic perspective. *Mol Aspects Med*. 2019;66:71-79.
9. Caruso I, Di Gioia L, Di Molfetta S, et al. Glucometabolic outcomes of GLP-1 receptor agonist-based therapies in patients with type 2 diabetes: a systematic review and network meta-analysis. *eClinicalMedicine*. 2023;64:102181.
10. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221-2232.
11. Campos-Nonato I, Galván-Valencia Ó, Hernández-Barrera L, Oviedo-Solís C, Barquera S. Prevalencia de obesidad y factores de riesgo asociados en adultos mexicanos: resultados de la Ensanut 2022. *Salud Publica Mex*. 2023;65:s238-s247.
12. Basto-Abreu A, López-Olmedo N, Rojas-Martínez R, et al. Prevalencia de prediabetes y diabetes en México: Ensanut 2022. *Salud Publica Mex*. 2023;65:s163-s168.
13. Abdi Dezfouli R, Mohammadian Khonsari N, Hosseinpour A, Asadi S, Ejtahed HS, Qorbani M. Waist to height ratio as a simple tool for predicting mortality: a systematic review and meta-analysis. *Int J Obes (Lond)*. 2023;47(12):1286-1301.
14. Yang JJ, Yu D, Wen W, et al. Association of diabetes with all-cause and cause-specific mortality in Asia: a pooled analysis of more than 1 million participants. *JAMA Netw Open*. 2019;2(4):e192696.
15. Zhong P, Tan S, Zhu Z, et al. Normal-weight central obesity and risk of cardiovascular and microvascular events in adults with prediabetes or diabetes: Chinese and British cohorts. *Diabetes Metab Res Rev*. 2023;39(8):e3707.
16. Mehrabani-Zeinabad K, Haghighatdoost F, Mohammadifard N, et al. Impact of diabesity phenotype on cardiovascular diseases, major cardiovascular events and all-cause mortality. *Sci Rep*. 2023;13(1):11266.
17. Tapia-Conyer R, Kuri-Morales P, Alegre-Diaz J, et al. Cohort profile: the Mexico City prospective study. *Int J Epidemiol*. 2006;35(2):243-249.
18. Mikkelsen L, Phillips DE, AbouZahr C, et al. A global assessment of civil registration and vital statistics systems: monitoring data quality and progress. *Lancet*. 2015;386(10001):1395-1406.
19. Alegre-Diaz J, Herrington W, Lopez-Cervantes M, et al. Diabetes and cause-specific mortality in Mexico City. *N Engl J Med*. 2016;375(20):1961-1971.
20. Network E. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Accessed November 4, 2021. https://www.equator-network.org/?post_type=eq_guidelines&eq_guidelines_study_design=observational-studies&eq_guidelines_clinical_specialty=0&eq_guidelines_report_section=0&s=+&eq_guidelines_study_design_sub_cat=0
21. Herrington WG, Alegre-Díaz J, Wade R, et al. Effect of diabetes duration and glycaemic control on 14-year cause-specific mortality in Mexican adults: a blood-based prospective cohort study. *Lancet Diabetes Endocrinol*. 2018;6(6):455-463.
22. Dramé M, Godaert L. The obesity paradox and mortality in older adults: a systematic review. *Nutrients*. 2023;15(7):1780.
23. Gnatiuc L, Alegre-Díaz J, Wade R, et al. General and abdominal adiposity and mortality in Mexico City: a prospective study of 150 000 adults. *Ann Intern Med*. 2019;171(6):397-405.
24. Sattar N, Rawshani A, Franzén S, et al. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. *Circulation*. 2019;139(19):2228-2237.
25. Wang Y, O'Neil A, Jiao Y, et al. Sex differences in the association between diabetes and risk of cardiovascular disease, cancer, and all-cause and cause-specific mortality: a systematic review and meta-analysis of 5,162,654 participants. *BMC Med*. 2019;17(1):136.
26. Lozano-Esparza S, López-Ridaura R, Ortiz-Panozo E, et al. Diabetes is associated with a higher risk of mortality among women in a middle-income country: results form the Mexican teacher's cohort study. *Diabetes Metab*. 2020;46(4):304-310.
27. Anderson EJ, Lustig ME, Boyle KE, et al. Mitochondrial H_2O_2 emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. *J Clin Invest*. 2009;119(3):573-581.
28. Xourafa G, Korbmacher M, Roden M. Inter-organ crosstalk during development and progression of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2023;20:27-49.
29. Hocking S, Samocha-Bonet D, Milner KL, Greenfield JR, Chisholm DJ. Adiposity and insulin resistance in humans: the role of the different tissue and cellular lipid depots. *Endocr Rev*. 2013;34(4):463-500.
30. Boonpor J, Pell JP, Ho FK, Celis-Morales C, Gray SR. In people with type 2 diabetes, sarcopenia is associated with the incidence of

cardiovascular disease: a prospective cohort study from the UK biobank. *Diabetes Obes Metab*. 2023;25:1900-1910.
31. Escamilla-Nuñez MC, Castro-Porras L, Romero-Martinez M, Zárate-Rojas E, Rojas-Martínez R. Detección, diagnóstico previo y tratamiento de enfermedades crónicas no transmisibles en adultos mexicanos. Ensanut 2022. *Salud Publica Mex*. 2023;65:s153-s162.
32. Evia-Viscarra ML, Guardado-Mendoza R, Rodea-Montero ER. Clinical and metabolic characteristics among Mexican children with different types of diabetes mellitus. *PLoS One*. 2016;11(12):e0168377.
33. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. *Nutr Rev*. 2012;70(1):3-21.
34. Jackson JM, DeFor TA, Crain AL, et al. Validity of diabetes self-reports in the Women's Health Initiative. *Menopause*. 2014;21(8):861-868.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Petermann-Rocha F, Apolinar E, Nazar G, et al. Associations of diabesity with all-cause and cardiovascular disease mortality: Findings from the Mexico City Prospective Study. *Diabetes Obes Metab*. 2024;1-10. doi:10.1111/dom.15528