

Analysis on Cause-Specific Atherothrombotic Cardiovascular Disease Mortality in Mexico: 2011-2015

Keywords

stroke, infarction, cerebrovascular disease, peripheral artery disease, Keywords: Cardiovascular disease

Abstract

Introduction

In Mexico, cardiovascular disease (CVD) represents the most important cause of mortality and disability. We aimed to analyze the mortality rate due to specific causes of atherothrombotic CVD from 2011 to 2015.

Material and methods

We analyzed 3,105,975 death certificates issued from January 2011 through December 2015. The 10th version of the International Classification of Diseases (ICD) codes was used to select CVD death records for ischemic heart disease, heart failure, cerebrovascular disease, and peripheral artery disease. Regional analyses from the different federal states were also performed.

Results

We analyzed 594,370 (19.1%) death certificates. Age-standardized CVD mortality showed a more stable pattern, from 96.7 per 100,000 people in 2011, to 111.7 per 100,000 in 2015. Cause-specific mortality rates increased more during the period for ischemic heart disease (63.8 vs. 74.8 per 100,000 people, in 2011 vs. 2015, respectively), as compared to heart failure (6.9 vs. 8.1 per 100,000 people), cerebrovascular disease (28.4 vs. 30.2 per 100,000 people), or peripheral artery disease (0.52 vs. 0.55 per 100,000 people). Overall, the survival age was significantly shorter in men (mean age at death 72.04 ± 16.23 years) than in women (77.73 ± 14.77). Ischemic heart disease and cerebrovascular disease showed the shortest survivals. The number of deaths increased steadily among the older population, with the steepest increase for overall ischemic heart disease over time.

Conclusions

Atherothrombotic CVD mortality in Mexico increased during the study period due to ischemic heart disease. Compared to their counterparts, survival age was shorter in men and in patients with ischemic heart disease and stroke.

Explanation letter

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First, we want to apologize the delay in manuscript revision, but the health status of one of the authors during this pandemic avoided prompt answer.

We have updated the reference list to the current status. We have also analyzed the reviewers' suggestions and comments to our previous paper. Changes in this revised version are highlighted, as suggested by the reviewers.

We appreciate the kind attention that the reviewers and the editorial team have given to our manuscript.

Response to reviewers

Reviewer 1

The recently added funding/acknowledgement section appears to be incomplete and contains generic text "This analysis received restricted funds from Boehringer-Ingelheim, Paracelsus and ANLTYK. These companies did not propose the study or participate in data capture; however, they were involved in the data analysis, manuscript draft and the decision to submit for publication. Writer name, degree of Paracelsus provided editorial support which was contracted and funded by "company name". Please fully complete this section with all details

Response: Thank you for this comment. We have now corrected this text.

Reviewer 2

The authors of reviewed article present their analysis of cardiovascular disease (CVD) mortality development in Mexico in 2011-2015 period. They concluded that CVD mortality in studied period is increasing, particularly due to ischemic heart disease among the population aged >65 years. It is interesting paper with respectable amount of data. It confirms different mortality tendencies in different regions of the world.

My points

1) □ The authors analyzed 3.105.975 death certificates between 2011 and 2015 but they identified only 594.370 death certificates with CVD which is 19.1%. In my opinion, it is much lower number of CVD mortality than I would expect in middle-income country as Mexico. It should be explained, the risk of selection bias could significantly influence presented results.

Response: We agree. We also believe there is a selection bias towards identifying as the basic (not contributing) cause of death to diabetes mellitus, since this comorbid condition is very common. We have now included a Discussion on this factor. Moreover, a further paper is in revision status addressing this phenomenon of miscoding and veiled death causes.

2) □ In the discussion (line 136) the authors stated that „In the present analysis, we observed the historical inflection point of the progressive decrease of CVD mortality in Mexico.“ It should be clarified because it is in contrary with author’s conclusion that „mortality in studied period is increasing“(line 197). Moreover, it would be important to discuss the presented results with some older data (if they are available) in order to ascertain if presented results reflect continuation of unfavourable mortality development or if presented data (although in studied period mortality is increasing) are not even better in comparison with CVD mortality in the past.

Response: We completely agree and have changed the text: “Compared to previous reports about the speed of growth of atherothrombotic mortality in Mexico [13], in the present analysis, we have potentially observed the historical inflection point of a progressive slowing of CVD mortality growth in Mexico.”

3) □ The conclusion of increased mortality in studied period deserves some author’s comment, because they stated in the discussion (line 137) „... a more widespread awareness among the Mexican population about the risk factors and clinical features of diseases...“. What are potential reasons for mortality increase in Mexico in the author’s opinion? Such consideration would be interesting for readers unfamiliar with situation in Mexico.

Response: We agree. We have amended the Conclusion considering this important comment.

4) □ Line 21 of the abstract: “The number of deaths increased steadily among the older population, with the steepest decline for overall ischemic heart disease over time” and line 118 of the results „The decline was steeper for ischemic heart disease in the older population, while essentially stable for heart failure or peripheral artery disease“. It seems to me that the authors mean „increase“ instead of „decline“.

Response: Thank you for this observation. We have corrected these to words to “increase” (instead of “decline”).

[AUTHOR'S REVISION LETTER.doc](#)

[ABSTRACT]

Introduction: In Mexico, cardiovascular diseases (CVD) represent the most important cause of mortality, disability, and premature death. We aimed to analyze the mortality rate due to specific causes of atherothrombotic CVD, from 2011 to 2015.

Material and methods: We analyzed 3,105,975 death certificates issued from January 2011 through December 2015. The 10th version of the codes published by the International Classification of Diseases (ICD) was used to select CVD death records for ischemic heart disease, heart failure, cerebrovascular disease, and peripheral artery disease. Regional analyses from the different federal states were also performed to provide inferences on the economic regions of the country.

Results: We analyzed 594,370 (19.1%) death certificates with CVD as the basic cause of death occurring in Mexico during 2011–2015. Age-standardized CVD mortality showed a more stable pattern, from 96.7 per 100,000 people in 2011, to 111.7 per 100,000 in 2015. Cause-specific mortality rates increased more during the period for ischemic heart disease (63.8 vs. 74.8 per 100,000 people, in 2011 vs. 2015, respectively), as compared to heart failure (6.9 vs. 8.1 per 100,000 people), cerebrovascular disease (28.4 vs. 30.2 per 100,000 people), or peripheral artery disease (0.52 vs. 0.55 per 100,000 people). Overall, the survival age was significantly shorter in men (mean age at death 72.04 ± 16.23 years) than in women (77.73 ± 14.77). Ischemic heart disease and cerebrovascular disease showed the shortest survivals. The number of deaths increased steadily among the older population, with the steepest **increase** for overall ischemic heart disease over time.

Conclusions: Atherothrombotic CVD mortality in Mexico increased during the study period particularly at the expense of ischemic heart disease. Compared to their counterparts, survival age was shorter in men and in patients with ischemic heart disease and stroke.

Keywords: Cardiovascular disease, cerebrovascular disease, infarction, peripheral artery disease, stroke.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the world with more than 17.9 million persons affected per year. It accounts for approximately 30% of all deaths, out of which 80% occur in low- to middle-income countries [1-6]. It is estimated that by 2020, about 23.6 million people will die from CVD, alarmingly maintaining the first rank in mortality worldwide [4,5]. CVD encompasses a group of disorders that affect the heart and blood vessels, including ischemic heart disease, cerebrovascular disease, peripheral artery disease (PAD), heart failure, and sudden death, among other atherothrombotic and non-atherothrombotic diseases. It is estimated that 92.1 million adults in the United States have at least one type of CVD. Among these patients, 46.7 million are people aged > 60 years [3,4,6].

In Mexico, CVD represents one of the most significant causes of disability and premature death, leading to a considerable increase in the cost of health care [5-7]. In 2008, CVD mortality accounted for more than 17% of all deaths in the country and by 2012 approximately 109,000 people died from heart disease [7,8]. Currently, CVD is the leading cause of death in the Mexican population. However, a small but constant decrease has been recently observed due to the implementation of programs such as the "Infarction Code" [6,8]. Along with diabetes mellitus, the National Health System considers CVD as the main non-communicable health problem in the country [4]. We aimed to analyze the population mortality due to specific CVD causes of death during the period 2011-2015. Our hypothesis was that CVD mortality in Mexico is beginning to reach a plateau in annual population-adjusted mortality rates. These results are part of a comprehensive analysis that includes recent periods and non-communicable causes of death within the country.

Methods

In this descriptive observational study, a total database of 3,105,975 death certificates provided by SINAIS/DGIS was consulted during the period from January 2011 through December 2015. This database is made of all death certificates issued during the 2011–2015 period in the whole country (a total of 32 Federal States) [9]. Briefly, in Mexico death certificates are registered locally in the informatics department of each healthcare institution, public ministry, and other legal entities of the respective municipality. These death records are consolidated by the SINAIS/DGIS in a comprehensive electronic database by using the global WHO format. A database is freely available for each year with the basic cause of death, excluding contributing causes and comorbidities [9]. Records of diseases associated to death due to atherothrombotic CVD were identified (as defined by the American Heart Association [AHA]), with the codes of the International Classification of Diseases tenth revision (ICD-10). We selected and analyzed ICD-10 classification codes of ischemic heart disease (I25.0, I25.1, I25.2, I25.3, I25.4, I25.5, I25.6, I25.8, I25.9), heart failure (I50.0, I50.1, I50.9), cerebrovascular disease (I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9, I67.0, I69.0, I69.1), and peripheral artery disease, (I73.1, I73.9, I74.0, I74.1, I74.2, I74.3, I744, I74.5, I748, I74.9). These ICD-10 codes were used to put together a separate database to analyze established atherothrombotic CVD, excluding hypertension, heart arrhythmias, and thrombotic venous diseases. In this new electronic database we identified the proportion of deaths associated with the specific causes of atherothrombotic CVD that were selected for the present analysis, taking into account the corresponding ICD-10 codes. Thence, a database of death certificates was extracted (i.e., 132,148 deaths from atherothrombotic CVD as a basic cause of death), taking into account the basic causes of death reported by the Mexican Ministry of Health during the aforementioned period. These databases were analyzed without patient identification, social security numbers, hospital record numbers, or any personal contact details. A consent disclaimer was obtained for the present analysis of public raw data [9]. No risk expositions

were derived from the present retrospective official database analysis.

Mortality rates were assessed by using the frequencies of ICD-10 usage (indicating that an individual died from CVD) and computed per 100,000 inhabitants of Mexico according to the population size of each year reported by the National Census of Population and Housing [10]. Age-standardized mortality rates were calculated by using the World Health Organization (WHO) population model. For this calculation, the following data were used: Mexican national population at mid-year in the period of the prefixed analysis (2011–2015) and the number of deaths recorded in death certificates within each year of the period, for the selected specific causes of death and for CVD as the sum of the specific cases (ICD-10 codes). Demographic data are presented as relative frequencies. The Pearson chi-squared test (or Fisher's exact test, as appropriate) was used to compare the frequencies of qualitative nominal variables between two groups. All *P* values for comparisons were two-tailed and considering statistical significance when $P < 0.05$. Economically active age groups were analyzed according to the definitions of the National Institute of Statistics, Geography and Informatics (INEGI) for this population sector [10].

Results

A total of 3,105,975 death certificates issued in Mexico were identified for the study period running from January 2011 to December 2015. After applying the selection criteria for individual certificates records, a unified database was obtained with a total of 594,370 records corresponding to CVD as the basic cause of death. During 2011, a total of 107,227 death certificates accounted for CVD, which rose to 130,279 death certificates in 2015 (53.2% deaths corresponded to men in 2015) (Table 1). The age-standardized mortality rate for CVD as the basic cause of death exhibited a trend that steadily increased during the period, from 92.7 per 100,000 in 2011, to 107.7 per 100,000 in 2015 (Table 2).

The survival age was significantly shorter ($P < 0.001$) in men (mean age at death

72.04±16.23 years) than in women (mean age at death 77.73±14.77 years) (Figure 1A). Such gender-related discrepancies in the age at death according to sex were maintained for ischemic heart disease (71.97±15.88 vs. 78.65±14.02 years, $P < 0.001$), heart failure (75.69±17.84 vs. 78.80±16.05 years, $P < 0.001$), cerebrovascular disease (71.71±16.72 vs. 75.55±15.71 years, $P < 0.001$), and peripheral artery disease (75.02±16.59 vs. 79.83±14.68 years, $P < 0.001$). In general, ischemic heart disease and cerebrovascular disease had the shortest survival compared to heart failure or peripheral artery disease (Figure 1B).

The crude number of deaths increased steadily among the population aged >65 years, with a slope that was disproportional to the population growth in that particular age group (Figure 2). The increase was steeper for ischemic heart disease in the older population, while essentially stable for heart failure or peripheral artery disease (Figure 3).

The Mexican federal states contributed differently to CVD mortality during the period (Figure 4), without differences according to year of registry, age or sex.

Discussion

In this study we observed that CVD mortality is showing a growing pattern, essentially at the expense of ischemic heart disease. Compared to women, men showed a younger age at death (i.e., survival age), which is an epidemiological concept that differs from “life expectancy” (i.e., the statistical measure of the mean time a human is expected to live, based on the year of birth). Moreover, cause-specific analysis showed that the shortest survival we observed in ischemic heart disease and cerebrovascular disease, which are the causes of CVD death with the highest death tolls. These findings are relevant in general terms, since it has been estimated that approximately 80% of deaths due to CVD occur in low- to middle-income countries, affecting both sexes equally [1-6]. Moreover, the global CVD burden has increased over recent decades, in high- and low-to-middle-income nations. In Mexico, these diseases still represent a serious public health problem that entail significant burden in terms of prevalence and medical care costs [1,5,6,8-12].

Compared to previous reports about the speed of growth of atherothrombotic mortality in Mexico [13], in the present analysis, we have potentially observed the historical inflection point of a progressive slowing of CVD mortality growth in Mexico. This phenomenon can be explained by a more widespread awareness among the Mexican population about the risk factors and clinical features of diseases that occur as a consequence of artery occlusions, as well as the implementation of programs such as "Infarction Code" to control atherothrombotic diseases through the development of high-impact strategies aimed to raise the awareness of the main causes of CVD morbidity and mortality [6,8]. Nonetheless, in order to determine that such epidemiological pattern change is sustained, an extended analysis on recent years should be performed and it is currently in preparation.

The economically active population is made of people who provide labor for the production of goods and services. Among the most important causes of death within this sector of the population are diabetes mellitus and CVD, especially in people aged 45 to 64 years [9]. In the present study we observed that CVD deaths occurred in high numbers among the economically active population, an alarming finding considering the loss of the productive force of the nation. Furthermore, CVD mortality is higher in the most important Federal States of Mexico, ranked by gross domestic product (GDP) and population size, such as Mexico City (a new Federal State in Mexico), Jalisco, State of Mexico, Veracruz, Puebla, and Nuevo León [10-12]. The explanation to this phenomenon could be related to the exposure to risk factors prevailing in big urban areas, although with the current methodology we cannot discard underdiagnosis of CVD entities in the small or underdeveloped regions of Mexico. The present study provides paramount hypotheses currently being tested by our group and by other researchers.

Mexico is an upper middle-income country that has one of the highest prevalence rates for diabetes mellitus in the world [10,13], in addition to the fact that glycemic control in people with this disease is often deficient and relates to frequent concomitant pathologies (e.g., CVD, dyslipidemia, hypertension, and end-stage renal impairment, among several

others) that increase morbidity and mortality [14-16]. The WHO has estimated that there are problems in reporting mortality associated with diabetes mellitus as the basic cause of death, because diabetes mellitus can in turn lead to CVD and other chronic micro and macrovascular complications, so when mutually-exclusive basic causes of death are considered, CVD-related death in patients with diabetes mellitus may be assigned to the later instead of atherothrombotic CVD [14,17-21].

Our results are comparable to those recently observed in the Brazilian population [22], specifically with respect to the overall trends of CVD deaths. A remarkable difference versus the Brazilian report is that we limited the analysis of ICD-10 classification codes to specific atherothrombotic diagnoses, excluding the unspecific codes related to “diseases of the circulatory system” (ICD-10 codes I00–I99) and other unspecific codes to avoid the inclusion of garbage codes. This methodology, of course, might underestimate the CVD burden in Mexico, which will feature in a future analysis by our research team. **Moreover, there exist a great possibility of misclassification of the basic cause of death biased towards general diagnoses such as diabetes mellitus and hypertension, which represent very common comorbid conditions. This paper calls to attention about what is considered a basic cause of death and how the death analyses are performed. Future studies need to address this issue.** This fact can also be deduced from a comparison with CVD mortality in Argentina [23], which, globally, is higher than that reported in the present analysis [24]. Nevertheless, our study aimed to analyze the population mortality of specific atherothrombotic diseases, which may be important when discussing specific etiologies that conform the cardiovascular burden of disease.

The present study has limitations that must be addressed for an accurate interpretation of data. It is worth to mention that this analysis is on a relatively short period of time and that the last year is 2015, therefore, recent changes in epidemiological patterns cannot be detected. Another topic of discussion is that only the basic cause of death in the certificates was studied, as this is the only cause of death available in the public SINAIS/DGIS databases, and therefore, it is not known how many people who died from

CVD was related with other diagnoses, such as diabetes mellitus. It is also possible that heart failure has been either underdiagnosed or misclassified with other related causes of death, such as diabetes or hypertension [25]. Moreover, since a death certificate usually does not give account of any previous atherothrombotic events, we were not able to analyze the possible influence of recurrent (versus first-ever) events explaining the differences in the causes of death analyzed. Another limitation is the lack of data on comorbidities and risk factors that may indirectly contribute to CVD deaths. Nevertheless, the results from this study are based on official death certificates pertaining to the Mexican public health system, which is the source of information for other estimations about disease burden [26].

Conclusion

In conclusion, although CVD mortality in Mexico is still increasing (particularly associated with ischemic heart disease among the population aged >65 years), compared with other reports we have observed a progressive slowing of CVD mortality growth. Moreover, compared to other clinical forms of CVD, patients with ischemic heart disease and cerebrovascular disease have the shortest survival. Male sex is also associated to a reduced survival age. These findings set the basis for new research hypotheses aimed to better explain the sex and regional disparities observed in our emerging economy.

Acknowledgments

The authors appreciate the collaboration of Dr. Carlos Fernandez Barros in the revision of the final manuscript. This analysis received restricted funds from Boehringer-Ingelheim, Paracelsus, and ANLTYK. These companies did not propose the study or were involved in data capture. Nonetheless, these companies were participated in data analysis, manuscript draft and the decision to submit for publication. Paracelsus provided editorial support, which was contracted and funded by Boehringer-Ingelheim.

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Table 1. Cardiovascular disease analyzed through death certificates during the period 2011-2015, according to sex. The numbers in parentheses represent the proportion that each year accounts for over the five-year period.

Number of deaths (% over the 5-year period)	Year of registry					Total
	2011	2012	2013	2014	2015	
Total cardiovascular disease						
Men	56693 (17.9)	60176 (19.0)	63944 (20.2)	65728 (20.8)	69647 (22.0)	316188 (100)
Women	50529 (18.2)	53315 (19.2)	56359 (20.3)	57312 (20.6)	60626 (21.8)	278141 (100)
Ischemic heart disease						
Men	38786 (17.6)	41279 (18.8)	44508 (20.2)	46176 (21.0)	49256 (22.4)	220005 (100)
Women	30479 (17.6)	32767 (18.9)	35067 (20.2)	36157 (20.9)	38882 (22.4)	173352 (100)
Heart failure						
Men	3097 (18.8)	3125 (19.0)	3395 (20.6)	3273 (19.9)	3593 (21.8)	16483 (100)
Women	3765 (19.7)	3866 (20.2)	3959 (20.7)	3723 (19.5)	3828 (20.0)	19141 (100)
Cerebrovascular disease						
Men	14557 (18.6)	15531 (19.8)	15763 (20.1)	16036 (20.5)	16511 (21.1)	78398 (100)
Women	15982 (19.0)	16371 (19.5)	16997 (20.2)	17128 (20.4)	17595 (20.9)	84073 (100)
Peripheral artery disease						
Men	253 (19.4)	241 (18.5)	278 (21.4)	243 (18.7)	287 (22.0)	1302 (100)
Women	303 (19.2)	311 (19.7)	336 (21.3)	304 (19.3)	321 (20.4)	1575 (100)

Table 2. Number of deaths and age-standardized mortality rates per specific cardiovascular disease, 2011-2015.

	Year of registry				
	2011	2012	2013	2014	2015
Ischemic heart disease					
Number of deaths	69268	74057	79586	82334	88144
Mortality rate per 100000	63.88	66.27	70.22	70.78	74.84
Heart failure					
Number of deaths	6862	6991	7354	6996	7421
Mortality rate per 100000	6.93	6.97	7.21	7.84	8.13
Cerebrovascular disease					
Number of deaths	30541	31905	32762	33165	34106
Mortality rate per 100000	28.40	29.26	29.67	29.70	30.18
Peripheral artery disease					
Number of deaths	556	553	614	547	608
Mortality rate per 100000	0.52	0.51	0.56	0.50	0.55
Overall cardiovascular disease					
Number of deaths	107227	113506	120316	123042	130279
Mortality rate per 100000	96.69	100.96	105.62	106.78	111.66

[Figure legends]

Figure 1. *A:* Kaplan-Meier plot showing the survival curves according to sex in the overall atherothrombotic cardiovascular disease death certificates database, 2011–2015. *B:* Kaplan-Meier plot showing survival curves according to specific causes of atherothrombotic cardiovascular diseases analyzed in this study, 2011–2015.

Figure 2. Crude number of deaths due to total atherothrombotic cardiovascular disease, according to age and year of record.

Numbers followed by “+” or “–” express the percentage increase or decrease, respectively, between the first and last year analyzed.

Figure 3. Crude number of deaths due to specific causes of atherothrombotic cardiovascular disease, according to age and year of registry.

Numbers followed by “+” or “–” express the percentage increase or decrease, respectively, between the first and last year analyzed.

Figure 4. Number of deaths due to atherothrombotic cardiovascular disease from the different Mexican federal states, from 2011 to 2015. The numbers represent the contribution of each federal state to the entire atherothrombotic cardiovascular disease mortality rate in Mexico.

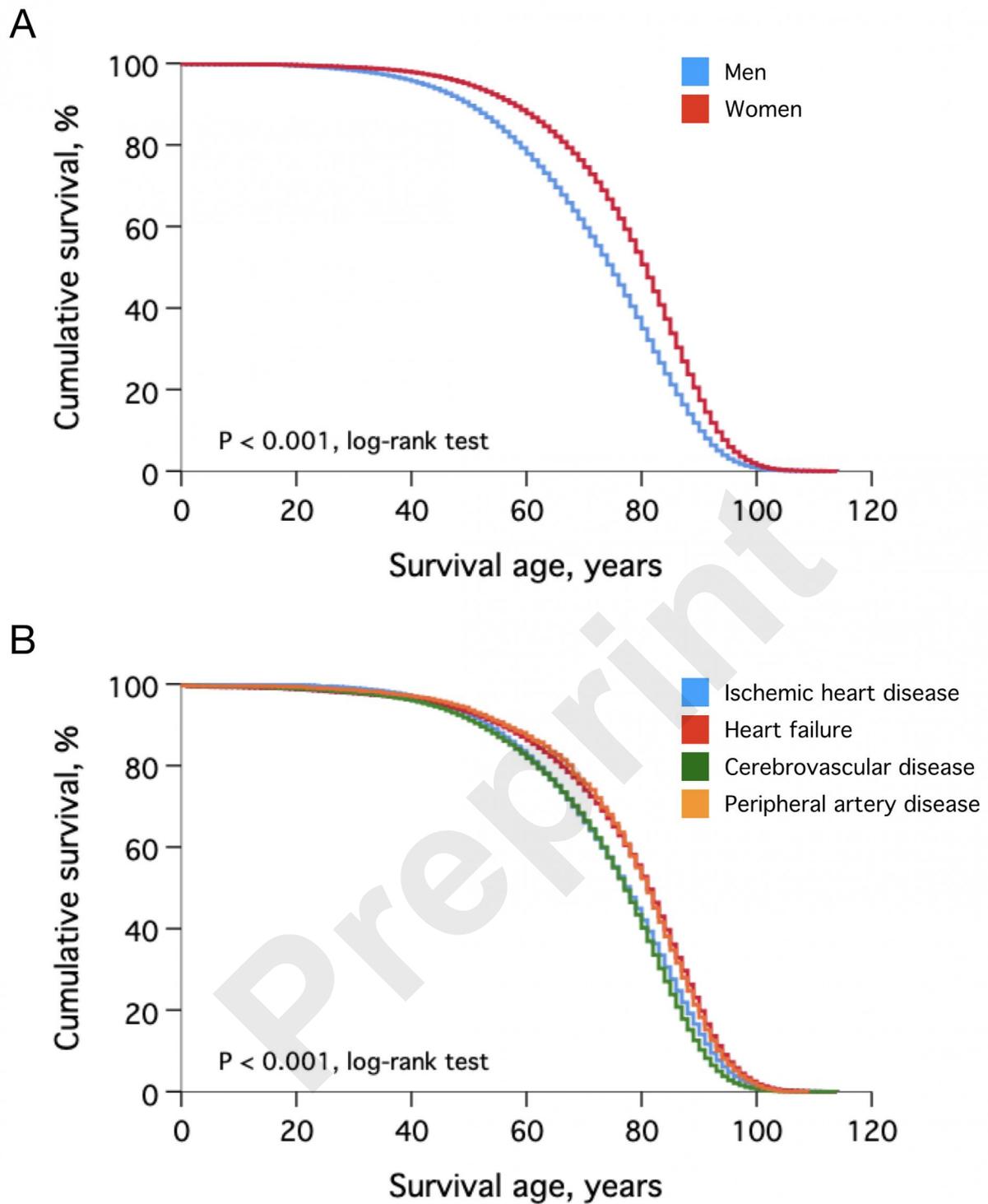


Figure 1. A: Kaplan-Meier plot showing the survival curves according to sex in the overall atherothrombotic cardiovascular disease death certificates database, 2011–2015. B: Kaplan-Meier plot showing survival curves according to specific causes of atherothrombotic cardiovascular diseases analyzed in this study, 2011–2015.

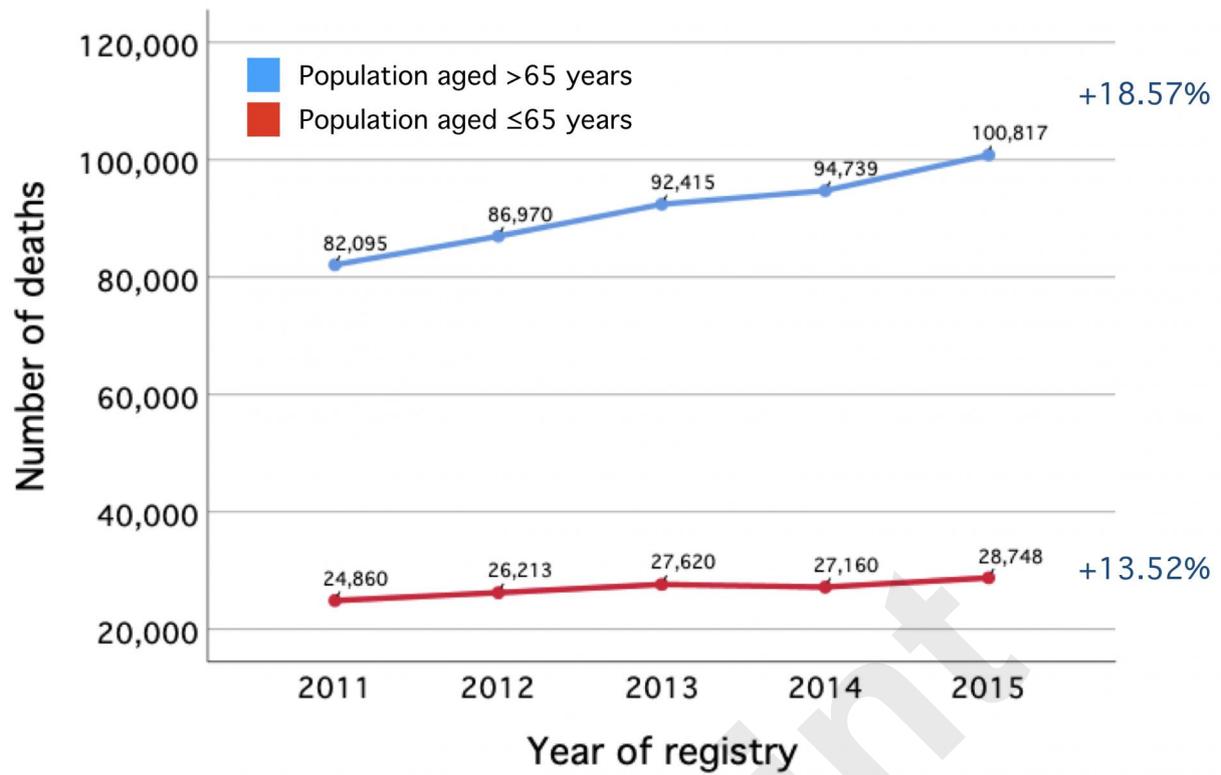


Figure 2. Crude number of deaths due to total atherothrombotic cardiovascular disease, according to age and year of record. Numbers followed by “+” or “-” express the percentage increase or decrease, respectively, between the first and last year analyzed.

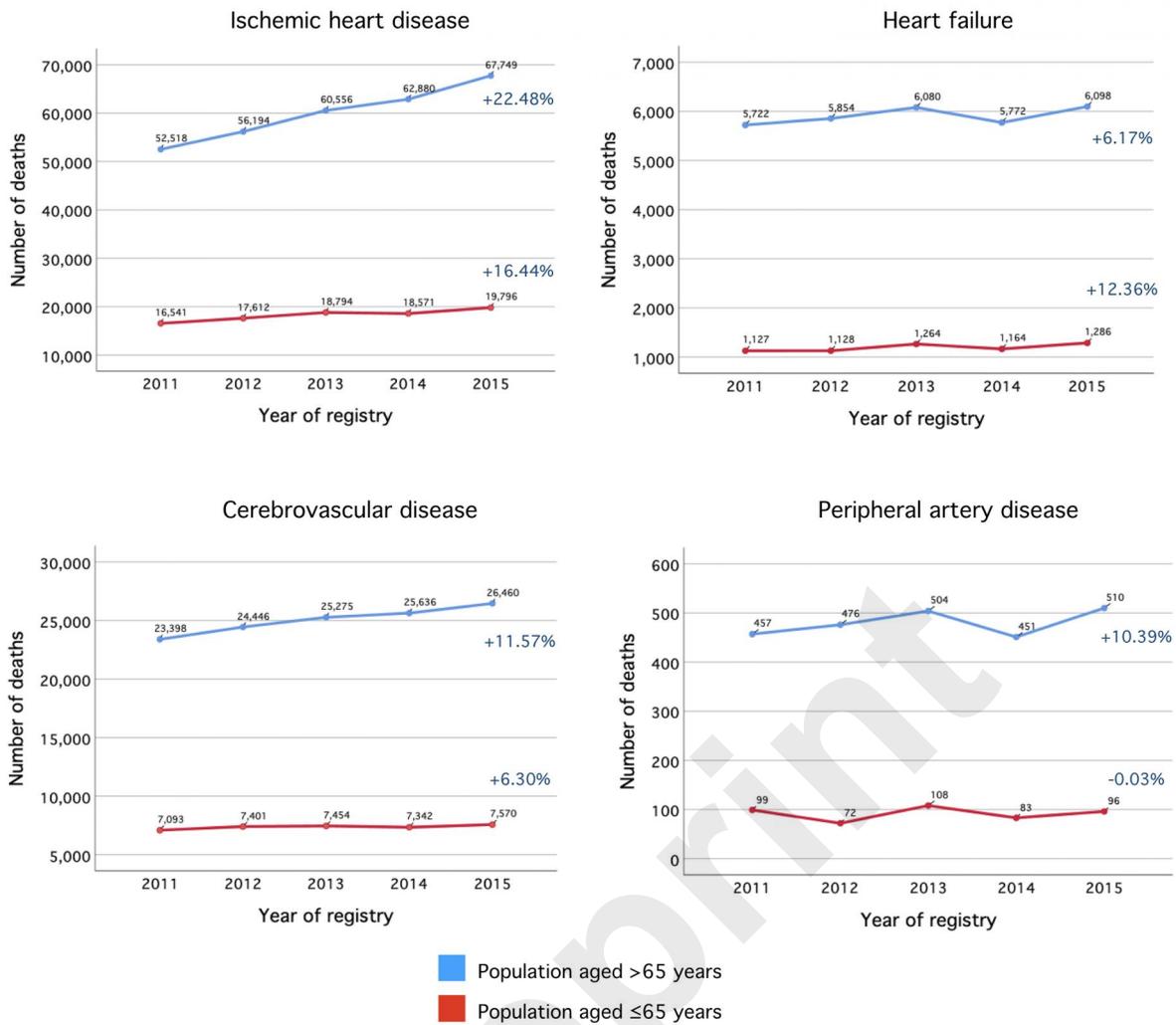


Figure 3. Crude number of deaths due to specific causes of atherothrombotic cardiovascular disease, according to age and year of registry. Numbers followed by “+” or “-” express the percentage increase or decrease, respectively, between the first and last year analyzed.

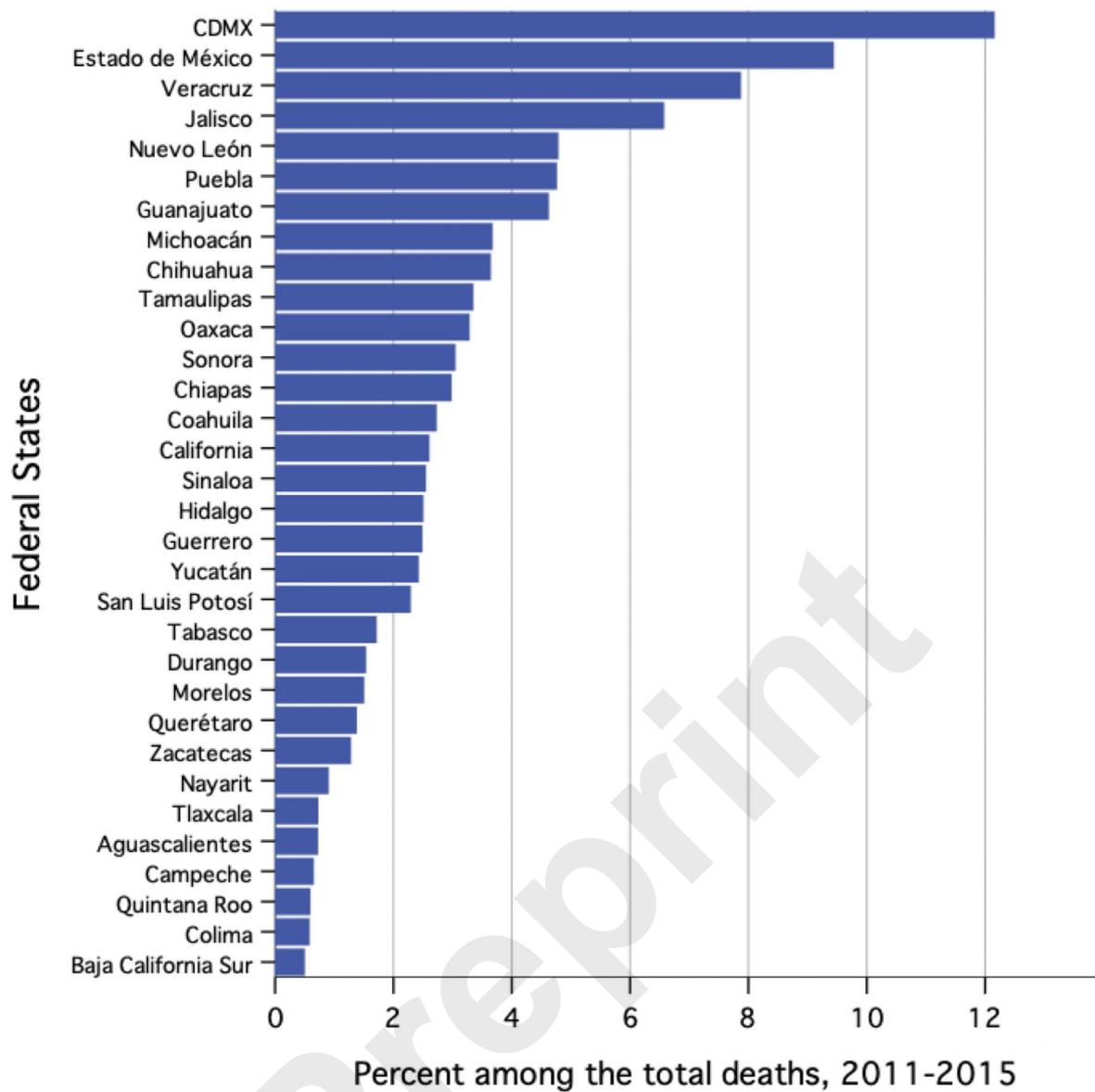


Figure 4. Number of deaths due to atherothrombotic cardiovascular disease from the different Mexican federal states, from 2011 to 2015. The numbers represent the contribution of each federal state to the entire atherothrombotic cardiovascular disease mortality rate in Mexico.