Coronavirus Pandemic

Association between obesity and diabetes prevalence and COVID-19 mortality in Mexico: an ecological study

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Abstract
Introduction: Mortality rates associated with COVID-19 vary widely between countries and, within countries, between regions. These differences might be explained by population susceptibility, environmental factors, transmission dynamics, containment strategies, and diagnostic approaches. We aimed to analyze if obesity and diabetes prevalence are associated with higher COVID-19 mortality rates in Mexico.
Methodology: We analyzed the mortality rate for each of the 2,457 municipalities in Mexico, one of the countries with highest COVID-19 mortality rate, during the first seven months of the pandemic to identify factors associated with higher mortality, including demographic, health-related characteristics (prevalence of obesity, diabetes, and hypertension in adults older than 20 years old), and altitude.
Results: During the first seven months of the COVID-19 pandemic there were 85,666 deaths reported in Mexico, with a cumulative mortality rate of 67 per 100,000 population. The mean mortality rate for the 2,457 municipalities in Mexico was 33.9 per 100,000 population. At a municipal level, the prevalence of diabetes and obesity, as well as high human development index, and location at < 500 or > 2000 above sea level were associated with higher mortality rate.
Conclusions: Elevated obesity and diabetes prevalence explain, in part, high COVID-19 mortality rates registered in certain municipalities in Mexico. These results suggest that a regionalized approach should be considered to successfully limit the impact of SARS-CoV-2.

Key words: COVID-19; SARS-CoV-2; pandemic; mortality; diabetes; obesity; respiratory viruses.

Introduction

On December 31, 2019 a cluster of patients with pneumonia was reported in Wuhan, China, subsequently determined to be caused by a novel coronavirus (SARS-CoV-2), and on March 11, 2020, COVID-19 was declared a pandemic by the World Health Organization [1]. The majority of SARS-CoV-2 infections are mild or asymptomatic. However, a large number of patients develop pneumonia which might be severe and lead to death; older age and comorbidities are associated with higher mortality risk [2].

Underlying conditions associated with poor COVID-19 outcome include hypertension, diabetes, chronic lung disease, cardiac disorders, and chronic kidney disease[3-5]. Of relevance, multiple reports have identified obesity as an important risk factor for severe COVID-19 [6,7]. The association of obesity with severe COVID-19 is a concern in Mexico because of the high prevalence of this disorder: obesity was reported to be present in 36.1% of Mexican adults older than 20 years of age in 2018 [8].

Another notable aspect of the current pandemic is that countries throughout the world have reported very different COVID-19 mortality rates [9,10]. In addition to viral and host characteristics, environmental and social factors may be responsible for these differences [11]. Also, differences in virological testing practices and transmission containment strategies between countries might also explain some of these differences. However, this also may affect the ability to identify population factors associated with worse outcomes. Previous studies have reported that COVID-19 mortality rate is associated with obesity prevalence [12]. These observations are consistent with the high prevalence of this disorder among severe COVID-19 patients and highlights the relevance of this comorbidity during the pandemic. In order to further assess the role of obesity on the impact of COVID-19 in a population, we analyzed the association between the prevalence of this condition and COVID-19 mortality rate in all municipalities in Mexico.

Methodology

Data sources

In this study, we used COVID-19 public data provided by the Mexican Ministry of Health. Daily data for SARS-CoV-2 confirmed infections notified by the Health Ministry of Health for every municipality in each of the 32 states in Mexico were obtained from the National Science and Technology Council (Consejo Nacional de Ciencia y Tecnología, CONACYT) COVID-19 website on December 22, 2020. The characteristics of each municipality were obtained from public databases provided by the Mexican National Institute for Federalism and Municipal Development (Instituto Nacional para el Federalismo y el Desarrollo Municipal, INAFED) and the United Nations Development Programme [13]. Data on human development index (HDI) for 2015 was not available for eleven municipalities; in these cases, HDI reported in 2010 was used. Obesity, hypertension, and diabetes prevalence for each municipality were obtained from the 2018 National Health and Nutrition Survey [8].

Time period

To define the time period to include in the analysis, we analyzed the daily number of COVID-19 cases reported nationally in Mexico from January 1, 2020 through December 20, 2020. The epidemiological curve showed an initial wave, which peaked in August, followed by a second wave which is still ongoing. We limited the analysis to the first wave, since the second epidemic wave is still ongoing. The decline in cases after the first wave stopped in mid-September, and an increase in cases was recorded starting in October (Figure 1). Therefore, the time-period included in the
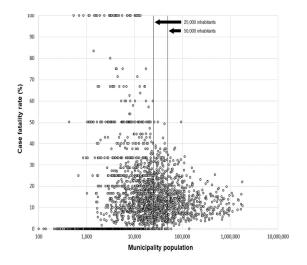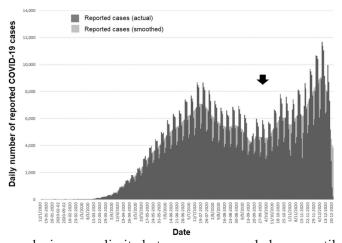

Figure 1. Daily number of COVID-19 cases reported in Mexico. Dark gray bars indicate the number of cases reported for a specific date; weekly fluctuations are observed as a result of reporting and testing practices. Light gray bars show smoothing of the curve. The arrow indicates September 30, 2020.

analysis was limited to cases recorded up until September 30, 2020. Taking into account that the first COVID-19 case in Mexico was reported on February 27th, this analysis includes the first seven months of the pandemic. During this period, there were 799,497 confirmed cases and 85,666 deaths. The overall case fatality rate (CFR) was 10.71%. This high fatality rate likely reflects selection criteria for testing in Mexico, which prioritize severe cases (100% of hospitalized patients are required to be tested by PCR), while testing of mild cases is limited to selected medical care facilities (only a small proportion of cases fulfilling the surveillance case definition for suspected COVID-19 are eligible for testing).

Selection of municipalities

There are 32 states in Mexico and each of them is divided in a varied number of municipalities. In total, there are 2,457 municipalities in the country. SARS-CoV-2 testing is not available in all municipalities; to assess the potential impact of this on COVID-19 mortality registries, we analyzed the cumulative number of COVID-19 cases and deaths for each municipality, and estimated the CFR. For municipalities with no COVID-19 cases reported (n = 231), the CFR was considered as zero. The mean municipal CFR was 14.57%, ranging from 0 to 100%. We assessed the effect of population size on CFR, because small communities may not have access to testing resulting in non-recording of cases in some municipalities, or testing might be limited to severe or fatal cases resulting in falsely elevated CFR (such as those municipalities reporting 100% CFR). The

Figure 2. COVID-19 CFR for each of the 2,457 municipalities in Mexico according to population size.

proportion of municipalities with 0% or 100% CFR increased as the population size decreased (Figure 2). A large proportion of municipalities with populations under 1,000 inhabitants had CFR of 0% or 100%.
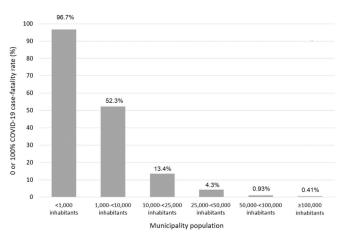
To define the municipal population size that may provide reliable mortality estimates, we analyzed the proportion of municipalities with 0% or 100% CFR based on population size (Figure 3). The CFR was either 0% or 100% in almost all municipalities under 1,000 population. In contrast, less than 1% of municipalities with populations over 50,000 reported CFR of 0% or 100%. Municipalities with population size less than 25,000 were considered as unreliable to assess mortality, while municipalities with populations over 50,000 were considered highly reliable. Based on this, the main analysis was carried out for municipalities over 50,000 inhabitants (n = 457); secondary analyses were carried out including all municipalities with 25,000 or more inhabitants (n=830), and all municipalities in the country (n = 2,457). The aforementioned municipality groups account for 78.4% (100,157,095 / 127,792,286), 88.8% (113,437,174 / 127,792,286), and 100% of Mexico's population, respectively.

Data analysis

We determined the association between COVID-19 incidence and mortality rates for each municipality and demographic, health-related characteristics (including the prevalence of obesity, diabetes, and hypertension in adults older than 20 years old), and altitude. Bivariate analysis was carried out using Pearson's correlation coefficient and Student's t test or Mann Whitney U test. Multivariate linear regression analysis was carried out to determine the independent association between each variable and COVID-19 mortality. A *p* value < 0.05 was considered as statistically significant. Analysis was performed using SPSS for Windows (IBM SPSS Statistics 25.0).

Figure 3. Proportion of municipalities with CFR of 0% or 100% according to population size.

Results

There are 32 federal entities in Mexico, each of them divided in municipalities (except Mexico City, where municipalities are identified as townships). Municipal populations vary widely between 95 and 1,815,551 inhabitants (mean 52,011). The mean population of the 457 municipalities with more than 50,000 inhabitants was 219,162. The main characteristics of Mexican municipalities are shown in Table 1.

During the first seven months of the COVID-19 pandemic in Mexico (cases occurring until September 30, 2020) there were 799,497 cases and 85,666 deaths reported nationwide. The cumulative COVID-19 incidence and mortality rates were 625.6 and 67 per 100,000 population, respectively. COVID-19 incidence and mortality rates were calculated for each municipality. The mean incidence per municipality was 289.4 per 100,000 population and the mean mortality rate was 33.9 per 100,000 population (Table 2). Municipalities with larger population showed higher incidence and mortality rates.

Table 1. Characteristics of 2,457 municipalities in Mexico.

Characteristics	Municipalities with population > 50,000 (n = 457)	Municipalities with population > 25,000 (n = 830)	All municipalities (n = 2,457)
Population density (inhabitants/km^2)	208.1 (84.1- 597.3) *	131.6 (53.1-345.5)	56.4 (20.0-150.5)
Male population (%)	48.6 (48.0- 49.2)	48.7 (48.0-49.4)	48.7 (47.8-49.6)
Population 60 years of age and older (%)	8.4 (7.0- 9.9)	8.9 (7.4-10.7)	10.7 (8.6-14.0)
Population speaking native languages (%)	0.6 (0.2- 2.7)	0.7 (0.2-5.1)	1.1 (0.2-22.3)
Adult population with obesity (%)	35.5 (31.8- 40.7)	34.7 (30.8-39.5)	32.2 (26.5-38.0)
Adult population with hypertension (%)	18.1 (15.7- 20.8)	18.1 (15.7-20.7)	18.6 (16.1-21.6)
Adult population with diabetes (%)	10.1 (8.8- 11.7)	10.1 (8.8-11.7)	10.0 (8.7-11.6)
Human development index	0.75 (0.71-0.79)	0.72 (0.67-0.76)	0.67 (0.62-0.73)

*Median (interquartile range).

Table 2. COVID-19 incidence, mortality rate and CFR based on municipality population size.

Municipality population	COVID-19 incidence (per 100,000)	COVID-19 mortality rate (per 100,000)	COVID-19 CFR (%)
< 25,000 (n = 1627)	207.7	26.2	14.9
25,000-50,000 (n = 373)	310.1	37.7	14.9
> 50,000 (n = 457)	556.1	58.5	13.3
All municipalities (n = 2,457)	289.4	33.9	14.6

Table 3. Characteristics associated with COVID-19 incidence for municipalities with >50,000 inhabitants in Mexico.

Characteristic	Univariate (ρ)	*p* value	Multivariate (B)	Multivariate (beta)	*p* value
Population density (inhabitants/km^2)	0.31*	< 0.001	0.008	0.048	0.29
Male population (%)	-0.09	0.042	-27.89	-0.065	0.18
Population 60 years of age and older (%)	0.11	0.015	-9.69	-0.050	0.33
Population speaking native languages (%)	-0.2	< 0.001	2.16	0.070	0.10
Adult population with obesity (%)	0.33	< 0.001	0.36	0.005	0.93
Adult population with hypertension (%)	0.26	< 0.001	1.71	0.017	0.73
Adult population with diabetes (%)	0.39	< 0.001	42.1	0.203	< 0.001
Human development index	0.59	<0 .001	3517	0.507	< 0.001
Altitude < 500 m	NA	< 0.001	147.9	0.159	0.002
Altitude > 2,000 m	NA	0.133	118.0	0.123	0.006

*Correlation coefficient (ρ).

Table 4. Characteristics associated with COVID-19 mortality for municipalities with >50,000 inhabitants in Mexico.

Characteristic	Univariate (ρ)	*p* value	Multivariate (B)	Multivariate (beta)	Adjusted *p* value
Population density (inhabitants/km^2)	0.37*	< 0.001	0.001	0.105	0.008
Male population (%)	-0.10	0.032	-5.621	-0.159	< 0.001
Population 60 years of age and older (%)	0.08	0.096	-1.449	-0.089	0.043
Population speaking native languages (%)	-0.25	< 0.001	0.033	0.013	0.726
Adult population with obesity (%)	0.43	< 0.001	0.726	0.134	0.013
Adult population with hypertension (%)	0.23	< 0.001	-0.709	-0.083	0.046
Adult population with diabetes (%)	0.44	< 0.001	4.552	0.264	< 0.001
Human development index	0.62	< 0.001	245.809	0.427	< 0.001
Altitude < 500 m	NA	< 0.001	21.008	0.272	< 0.001
Altitude > 2000 m	NA	0.005	15.874	0.199	< 0.001

*Correlation coefficient (ρ).

Table 5. Characteristics associated with COVID-19 mortality (deaths per 100,000 population) for municipalities with > 25,000 inhabitants and all municipalities in Mexico.

Characteristics	Municipalities with population > 25,000 (n = 830)			All municipalities (n = 2,457)		
	Multivariate (B)	Multivariate (beta)	Adjusted *p* value	Multivariate (B)	Multivariate (beta)	Adjusted *p* value
Population density (inhabitants/km^2)	0.002	0.089	0.002	0.003	0.097	< 0.001
Male population (%)	-4.778	-0.139	< 0.001	-3.330	-0.135	< 0.001
Population 60 years of age and older (%)	-0.888	-0.061	0.063	-0.280	-0.035	0.175
Population speaking native languages (%)	0.082	0.043	0.154	0.050	0.037	0.093
Adult population with obesity (%)	0.767	0.146	< 0.001	0.505	0.121	< 0.001
Adult population with hypertension (%)	-0.650	-0.077	0.018	-0.999	-0.112	< 0.001
Adult population with diabetes (%)	3.147	0.199	< 0.001	1.709	0.101	< 0.001
Human development index	260.190	0.501	< 0.001	226.147	0.435	< 0.001
Altitude <500 m	15.399	0.202	< 0.001	9.354	0.106	< 0.001
Altitude >2000 m	15.332	0.187	< 0.001	7.145	0.077	< 0.001

The mean CFR was slightly lower in municipalities with populations > 50,000 (13.3%) than in those with population under 50,000 (14.9%), suggesting that the higher mortality rate (per municipality) was not the result of greater severity of registered cases.

The primary analysis focused on municipalities with > 50,000 population. We analyzed the association between demographic (population density, proportion of male population, proportion of population 60 years of age and older, proportion of population speaking native languages), underlying conditions (proportion of population with obesity, hypertension, and diabetes), socio-economic factors (HDI), and altitude and COVID-19 incidence and mortality rates.

There was a significant association between all the analyzed factors and COVID-19 incidence (por 100,000 population) (Table 3). Multivariate analysis showed that independent variables associated with higher disease incidence included the prevalence of diabetes in the population (adjusted beta 0.2; $p < 0.001$), HDI (adjusted beta 0.51; $p < 0.001$), altitude of municipality under 500 m (adjusted beta 0.16; $p = 0.002$), or above 2,000 m (adjusted beta 0.12; $p = 0.006$).

A significant association was also observed between all analyzed factors and COVID-19 mortality rate, except the percentage of population 60 years of age or older (Table 4). Multivariate analysis confirmed a significant independent association between most variables and mortality rate. A higher proportion of adult population with obesity and diabetes were associated with increased mortality rates ($p = 0.013$ and $p < 0.001$, respectively). Also, increased population density and HDI were associated with higher mortality. In contrast, the proportion of adults 60 years and older and the proportion of male population were inversely correlated with mortality.

Inclusion of COVID-19 incidence rate as a covariate did not have a major effect on the statistical significance of most associations. As for the association between obesity and COVID-19 mortality, inclusion of COVID-19 incidence had no significant effect in the unstandardized (0.715) and standardized (0.132) coefficients, while the statistical significance (adjusted p value) remained highly significant $p = 0.006$.

Additional analyses were carried out including municipalities with 25,000 inhabitants or more, as well as including all 2,457 municipalities. Results of these analyses showed similar results to those observed on the primary analysis (Table 5): a significant association between population density, proportion of female population, proportion of the population with obesity, hypertension, and diabetes, HDI, and municipality altitude under 500 m or over 2000 m above sea level and COVID-19 mortality rate was observed.

Discussion

In this study, we analyzed COVID-19 mortality for all municipalities in each of the 32 states in Mexico during the first seven months of the pandemic. This allowed to assess the association between COVID-19 mortality and population health characteristics, taking into consideration sociodemographic conditions, in order to evaluate if the prevalence of obesity in a community is associated with higher mortality. Over the last decade, the role of obesity as an underlying condition leading to increased severity of respiratory infections has been established. High prevalence of obesity among patients with severe influenza infections was noted during the H1N1 pandemic in 2009 [14,15]. This association has been strongly established in patients with SARS-CoV-2 infection [16,17]. As such, high prevalence of obesity in a population has been suggested to account for some of the differences in the impact of the COVID-19 pandemic [12,18].

Overweight and obesity represent one of the main public health issues in Mexico [19]. According to the most recent National Health and Nutrition Survey, the combined prevalence of overweight and obesity in adults older than 20 years old was 76.8% in women and 73.0% in men. Our results show that obesity prevalence in a municipality explains, in part, the differences in mortality rates observed between different municipalities in Mexico. At the individual level, COVID-19 patients with overweight and obesity have required ICU admission and have died more frequently than individuals with BMI between 18.5 and 25 kg/m^2. Obesity also has been associated with a greater need for intubation and longer hospitalization duration. While many reports have described the deleterious effect of obesity in patients with SARS-CoV-2 infection, some studies have not found this association [20,21]. As a result, the role and mechanisms leading to severe infections in persons with obesity require further investigation. Several explanations have been proposed for this association. Obesity is related to a chronic proinflammatory state with low levels of anti-inflammatory cytokines, as adiponectin, and high levels of proinflammatory cytokines, such as TNF-α, IL-6, MCP-1, IL-1β, and leptin [22]; these cytokines lead to low-grade inflammation and dysfunction of innate immunity predisposing individuals to the development of infections. Also, angiotensin-converting enzyme 2 (ACE2), the cell receptor for SARS-CoV-2, is highly

expressed in adipose and lung tissues in obese patients [23]; binding of this virus to ACE2 causes down-regulation of this receptor and accumulation of angiotensin II, which causes increased vascular permeability and vasoconstriction, leading to lung tissue damage and development of ARDS [17,22]. Obesity also leads to a procoagulant state, which may be enhanced by SARS-CoV-2 infection and, therefore, to worse clinical outcomes [24]. Finally, obesity is associated with other comorbidities, such as diabetes mellitus or hypertension, which are also risk factors for COVID-19 mortality [25].

Of relevance, diabetes prevalence was strongly associated (and independently from obesity) with higher COVID-19 mortality rates. A meta-analysis that included 33 studies reported a correlation between diabetes mellitus and severity of disease, with more patients requiring invasive ventilation and admission to ICU with higher mortality in this group as a result [25]. In addition to obesity, diabetes is also highly prevalent and is the second underlying cause of death in Mexico accounting for 14% of deaths [26,27]. Altogether, these observations indicate that in order to reduce the impact of SARS-CoV-2, a broad approach is required; interventions should address not only the transmission of the virus, but also a comprehensive assessment of the health condition of a population.

Although age and gender are relevant factors contributing to severity and mortality by SARS-CoV-2, our results were not consistent with this. Of note, our approach did not assess the individual characteristic of COVID-19 patients, but those of their residence location. Therefore, the observed results, such as the absence of association between the proportion of the population aged 60 years or more and mortality indicate that the population structure of a municipality does not explain the observed differences in mortality at different locations. Also, the proportion of residents in a municipality that speak native languages was not associated with COVID-19 mortality. This might be explained by the inclusion of other indicators (such as HDI) in our multivariate model and suggests that ethnic composition of a population does not explain differences observed between municipalities; in contrast, other indicators, such as income and education (which are included as part of the HDI) do explain, in part, the observed differences. Consistent with this observation, a systematic review found that although African American and Hispanic populations have had higher COVID-19 mortality rates compared with white populations, there were no differences in CFR associated with ethnicity [28]; differences in access to health care or exposure to SARS-CoV-2 were considered as potential explanations for the higher mortality in these minority groups. Remarkably, in Mexico, municipalities with higher HDI showed greater mortality than those with lower HDI. A state-level ecological study from India also found that COVID-19 mortality was associated with urbanization and several development indexes [29]. In addition, interpretation of these findings require to take into consideration the dynamic nature of SARS-CoV-2 spread across geographical areas; for example, the socioeconomic profile of German districts mostly affected by COVID-19 during the initial phase of the pandemic differed from those affected during the second phase [7]. As such, further analyses are required to determine if factors, such as economical activities, social interactions, or population mobility, might be associated to an elevated HDI and may explain the findings in our study.

A remarkable finding in our study was that altitude of a municipality was associated with COVID-19 incidence and mortality. Of note, municipalities located at low and high altitudes were associated with higher mortality compared to those located between 500 and 2000 meters above sea level. High altitude has previously been identified as a potential risk factor for severe respiratory infections. Low barometric pressure and, consequently, low oxygen pressure found at high altitudes leads to pulmonary and hematological physiological adaptations [30,31]; these could lead to an altered ability to respond to severe respiratory infections. Consistent with this, respiratory syncytial virus-associated hospitalizations have been reported to occur more frequently in children living at high altitudes [32]. Several studies have assessed the association between altitude and COVID-19, but results have been contradictory: high altitude has been associated with increased mortality in the United States and Mexico, while reports from South America suggest that high altitude may not have an effect on mortality or, could even be associated with lower COVID-19 fatality rate [33-35]. Of note, some of these reports were based on early data during the pandemic, when dissemination of SARS-CoV-2 was still ongoing and, as a result, the observed associations might have changed over time. In addition, adjustment for potential confounders was not included in some of them [34,35]. For example, an early analysis from Peru suggested that COVID-19 mortality was lower at high altitudes [35], while a study carried out subsequently in the same country reported that COVID-19 CFR was not reduced at high altitude [36]. A previous study that included data

of COVID-19 cases reported in Mexico up until May 13, 2020 also showed that municipalities located > 2,000 m above sea level had higher mortality rates than those at < 2,000 m [34]. Of interest, municipalities located at <1500 m showed higher mortality than those located between 1500 and 1999 m, a result consistent with our findings. The bimodal effect of altitude on mortality rate observed in Mexico suggest that other factors, in addition to physiological adaptation, might explain these results and deserve further study.

A limitation of this study is its ecological design, as well as retrospective analysis of data. A potential limitation is the inability to account for SARS-CoV-2 cases and deaths that may not have been reported. This can affect case fatality and mortality rate estimates [37]. Also, extension of epidemics does not occur synchronically in all countries and across all regions within a country; as such, analysis limited to short periods of time might not reflect geographic differences. To take these factors into account, our primary analysis was limited to municipalities with > 50,000 inhabitants, as well as analyzing a seven-month time frame which encompassed the complete first pandemic wave in Mexico. Secondary analyses, which included municipalities with > 25,000 inhabitants, and all municipalities in Mexico confirmed the observed associations.

Conclusions

Elevated diabetes and obesity prevalence are two major factors that explain differences in COVID-19 mortality rate between Mexican municipalities. In addition, municipalities with high HDI and those located at low (< 500 m) or high (> 2,000 m) altitude above sea level had increased mortality rates. Of relevance, both obesity and diabetes are preventable diseases. These results suggest that an integral and regionalized approach should be considered to successfully limit the impact of SARS-CoV-2.

Conflict of interests

Potential conflicts of interest. DEN has participated as a member of the speakers' bureau of AbbVie and speakers' bureau and advisory board for Sanofi Pasteur. All other authors declare that there are no competing interests regarding the publication of this manuscript.

Authors' Contributions

DEN contributed to the conception and design of the study; acquisition, analysis, and interpretation of data; drafting of the manuscript; and approval of the final version of the manuscript; NHA, CRJ, and AWS contributed to acquisition, and analysis of data; revision of the manuscript; and approval of the final version of the manuscript.

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