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Article

Association between Mortality and Cardiovascular Diseases in Vulnerable Mexican Populations, A Retrospective Study of the COVID-19 Pandemic

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Abstract: Cardiovascular diseases (CVD´s) continue as the primary cause of death worldwide. During the past couple of years, and with the surge of the COVID-19 pandemic, deaths linked to CVD´s were -slightly overshadowed by those deaths related to COVID-19, albeit during the highest peaks of the pandemic. The present study derived form understanding the correlation between both diseases, from the standpoint of patients already diagnosed with CVD´s (n = 41883) and what comorbidities had the highest influence on overall patient death (n = 3637).

Obesity, hypertension, and diabetes are all linked to worsening the outcome of COVID-19 positive patients, hence they were considered when looking at the overview of all CVD positive patients. Our finding showed that 1697 deaths were related to diabetes ($p < 0.001$), 987 deaths were related to obesity ($p < 0.001$), and lastly 2499 deaths were attributed to hypertension ($p < 0.001$) individually. Using logistic regression modeling, we found diabetes (OR: 1.744, $p < 0.001$) and hypertension (OR: 2.179, $p < 0.001$) had a high impact on patient deaths. Hence, having a CVD diagnosis, with hypertension and/or diabetes seems to increase the likely-hood of complication leading to death in COVID-19 positive patients.

Keywords: cardiovascular diseases; Mexico COVID-19; Mexico metropolitan area

1. Introduction

The Metropolitan Area of the Valley of Mexico is the largest metropolitan area in North America, and the most important economic, political, and social hub in the country. It houses over 22 million people or roughly 20% of the country's total population [1]. Given the size and importance of the area, the federal government has devoted much of the resources of the national health care system to tackle many public health issues. The area is host to many of the Tier-1 national health care facilities in the nation, hence promoting health-related tourism [2–5].

One of the biggest challenges the world has faced ever since the last century has been the increase in mortality related to cardiovascular disease (CVD´s) [6,7], and Mexico has

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been no exception to these phenomena, particularly since the second half of the past century [8]. To make things ever more hard pressing, since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, Mexico has been one of the most hard-hit countries in the world, with an observed case-fatality ratio of 9% at its highest [9,10]. Fortunately, as face-mask mandates came into effect, and new effective vaccines become available [11], this percentage dropped to around 5.5%. Unfortunately, it is still double than the next following country in case-fatality ratio (Indonesia with 2.6%) with about 253.8 deaths per 100,000 population [12]. Unsurprisingly, CVD´s and particular associated comorbidities, such as hypertension, obesity, and diabetes, were early in the pandemic detected as linked to high mortality [13,14]. One reason behind CVD's high mortality during the COVID-19 pandemic is that hypertension, obesity, and diabetes, upregulate highly inflammatory states in the individual, and as a result in combination with COVID-19 activate hyper-inflammatory reactions, resulting in a potential dysregulation of the immune system [15].

During a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which gives rise to the COVID-19, the angiotensin-converting-enzyme 2 (ACE2) receptor; expressed in many human tissues, including the lungs, heart, kidneys, liver, and nervous system, play a crucial role in mediating viral entry [16]. ACE2 is the major regulator of the renin–angiotensin–aldosterone system, which aids as a homeostatic regulator of vascular function [17]. Interestingly, a high increase of adipose tissue, as seen in patients with obesity, seems to correlate with an imbalance of the renin–angiotensin–aldosterone system, resulting in a final upregulation of angiotensin II [14,18]. Other studies have also shown that ACE2 deficiency relates to reduce insulin secretion and islet fibrosis, ultimately aggravating a diabetic state [17,19].

Primarily in the lungs, ACE2 converts angiotensin I into angiotensin II [20,21], which further acts on the AT1 receptor further, leading to a proinflammatory cascade causing inflammation, vasoconstriction, aldosterone release, and increasing oxidative stress [22]. This proinflammatory cascade, once aggravated, can promote endothelial dysfunction. For the case of CVD´s and related comorbidities: obesity, diabetes, and hypertension, this cascade becomes an exacerbated problem [15,23].

Through this study, we opted to analyze data from the collected COVID-19 pandemic from early 2020, through the first trimester of 2022, obtained from the Mexico metropolitan area health care system. Selecting for those patients positive for CVD´s and given particular attention to the vulnerable or at high-risk populations such as those affected by comorbidities such as obesity, diabetes, and hypertension, as well as a COVID-19 diagnosis.

2. Materials and Methods

Publicly available data was obtained from the health care ministry of Mexico City, which included > 5.5 million total entries, from 2020 to the first trimester (march) of 2022 [24]. First, we sorted the data for all individuals which were deemed as positive for CVD´s. Our final count was 41882 individuals. Individual frequencies were next calculated for gender (female / male), age groups, COVID-19 diagnosis (test results: positive / negative / unknown - untested), patient type (hospitalized / ambulatory), hypertension (yes / no / not reported), diabetes, hypertension (yes / no / not reported), obesity hypertension (yes / no / not reported), death (yes / no), and year (2020 / 2021 / 2022).

2.1. Deaths by patient type and diagnosis

For all CVD´s positive patients, death was taken as a critical variable. We recorded death by year as it related to COVID-19 diagnosis. Next, we compared death to patient type, and finally, comprehensively, we compared all 3.

2.2. COVID-19 and Death results by comorbidities

All CVD´s positive patients were then divided into COVID-19 diagnosis, and further divided as they related to comorbidities in the following manner: hypertension/diabetes,

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hypertension/obesity, and obesity/diabetes. Next, similarly as with comorbidities, we calculated only the subpopulation of death patients.

2.3. Age groups, gender and results

All CVD´s positive patients, we divided for each individual comorbidity, patient type, mortality, and COVID-19 diagnosis by age group and gender.

2.4. Chi-squared correlations and Binary logistic regression

For all CVD´s positive patients, we did statistical correlations on each individual comorbidity, as they related to death for each group. Next, we built a binary logistic regression model to determine de amount of influence each comorbidity and a positive COVID-19 diagnosis would have on CVD´s patients mortality. All statistical analyzes including binary logistic regression, Pearson's chi-squared and an R ratio of 0.05, were done using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Parallel set was further made in RStudio v. 1.3.1093 with R v. 4.0.3. The following packages were used: reshape2 v. 1.4.4, tidyverse v. 1.3.0, ggforce v. 0.3.3. These packages can be downloaded from CRAN (https://cran.r-project.org/).

3. Results

Publicly obtained data from 2020 to the first trimester (march) of 2022 recorded > 5.5 million patient entries, which were then sorted for patients positive for CVD´s. The latter group comprised 41882 entries with 3697 patient reported deaths, total female entries represented 51.8%, highest number of entries (n = 8691) were for individual ranging from 51 to 60 years (20.8%), with a close second (n = 8147) for older individual from 61 to 70 years (19.5%). The total number of COVID-19 positive patients (n = 15363) represented 36.7%, additionally ambulatory patients (n = 32108) represented 76.3%. Regarding comorbidities, 19405 patients (46.3%) were positive for hypertension, moreover 11879 patients (28.4%) were positive for diabetes, and 9612 patients (23%) were positive for obesity. Finally, while 2022 is still in course, during the first 2 years, there were a total of 34573 patients with 16565 patients in 2020 (48%), and 18008 patients in 2021 (52%). Data in Table 1.

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Table 1. Profile for CVD positive patients (n = 41883).

		n	%
Gender	Female	21701	51.8%
	Male	20182	48.2%
Age groups	0 - 17	2029	4.8%
	18 - 30	3797	9.1%
	31 - 40	3957	9.4%
	41 - 50	6205	14.8%
	51 - 60	8691	20.8%
	61- 70	8147	19.5%
	71 - 80	5779	13.8%
	81 and more	3278	7.8%
COVID-19	Positive	15363	36.7%
	Negative	24659	58.9%
	Unknown / untested	1861	4.5%
Patient Type	Ambulatory	32108	76.3%
	Hospitalized	9974	23.7%
Hypertension	Yes	19405	46.3%
	No	22477	53.7%
	Not reported	1	0.0%
Diabetic	Yes	11879	28.4%
	No	30003	71.6%
	Not reported	1	0.0%
Obesity	Yes	9612	23.0%
	No	32270	77.0%
	Not reported	1	0.0%
Death	Yes	3637	8.7%
	No	38246	91.3%
Year	2020	16565	39.6%
	2021	18008	43.0%
	2022*	7309	17.5%

*Data for the first trimester of 2022

We next recorded death, COVID-19 diagnosis, and patient type. Table 2 A. shows the relation of CVD´s positive patients and a COVID-19 diagnosis by years. When we take into consideration COVID-19 positive diagnosis, we can observe the average is around 73% through all the years recorded. Another interesting factor observed is the hospitalization and its relation to mortality. Out of the total 3637 deaths, we observed only 255 in ambulatory patients (Table 2 B). When we further analyze mortality, patient type, and COVID-19 diagnosis, we confirmed the highest mortality in hospitalized patients; for those (hospitalized) positive to COVID-19, there were 2373 cases, meanwhile for negative to COVID-19 there were 790 cases. This was a striking difference as compared to ambulatory patients, where we recorded 168 cases in COVID-19 positive and only 58 cases in COVID-19 negative, for unknown / untested patients there were 248 deaths (Table 2 C).

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Table 2A. COVID-19 diagnosis (Deaths by year).

Year	Positive		Negative		Unknown/untested		Total
	n	%	n	%	n	%	
2020	1358	67%	494	24.40%	175	8.60%	2027
2021	1009	72.70%	311	22.40%	68	4.90%	1388
2022*	174	78.40%	43	19.40%	5	2.30%	222
*Data for the first trimester of 2022							3637

Table 2B. Patient Type (Deaths).

Death	Yes		No		Total
	n	%	n	%	
Ambulatory	255	0.80%	31853	99.2	32108
Hospitalized	3382	34.60%	6392	65.40%	9774
Total	3637		38245		41882

Table 2C. COVID-19 Diagnosis/Patient Type (Deaths).

COVID-19	Patient Type	Death				Total
		Yes		No		
		n	%	n	%	
Positive	Hospitalized	2373	49.68%	2404	50.32%	4777
	Ambulatory	168	1.59%	10418	98.41%	10586
Negative	Hospitalized	790	18.41%	3501	81.59%	4291
	Ambulatory	58	0.28%	20310	99.72%	20368
Unknown / Untested	All	248	13.30%	1612	86.67%	1860
					Total	41882

Next, we related COVID-19 diagnosis to comorbidities (Tables 3 A-C, and Figure 1 by years), followed by the subset of patient death in a similar relation (Table 3 A.1-C.1). We directly related comorbidities by pairs (hypertension / diabetes, hypertension / obesity, and obesity / diabetes). Finally, we integrated deaths into COVID-19 diagnosis, and all 3 comorbidities (Table 4 A, Figures 2 and 3). First, for COVID-19 positive diagnosis, the relation of hypertension and diabetes was: 3691 cases were positive for both, 4108 cases were positive only for hypertension, 1212 were positive only for diabetes and 6352 were negative for both. When we looked at the death cases, we could clearly observe that hypertension is an important factor as 949 cases were positive for both and 830 cases were positive for hypertension only, meanwhile COVID-19 positive deaths with negative hypertension showed 244 cases for diabetic patients and 518 cases for both negative. Next, we continued using hypertension as the primary comorbidity, but now in relation to obesity. For COVID-19 positive patients, 2462 cases were positive for both conditions, 5337 were only positive for hypertension, while 1393 were only positive for obesity, and 6171 were negative for both. When we look at mortality, we again saw higher cases of death as compared to non-hypertensive individuals: 578 cases were positive for both conditions, 1201 cases were positive only for hypertension, 158 cases were only positive for obesity. In an interesting turn of events, there were 604 cases for when both conditions were negative. It is important to take into consideration that these 604 are a combination of patients

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negative for both conditions and those with diabetes, which did not fall under any other category. In order for us to continue exploring these cases, we next did the relation between obesity and diabetes. For COVID-19 positive patients, 1543 were positive for both conditions, 2312 were only positive for obesity, 3360 were only positive for diabetes and 8148 were negative for both. Finally, when looking at deaths, obesity did not seem to have as high influence as diabetes: 378 cases were positive for both conditions, 358 were only positive for obesity, 815 cases were only positive for diabetes, and 990 cases were negative for both conditions. Finally, we integrated all 3 comorbidities into the subpopulation of death patients. From these results, we observed the highest mortality in the COVID-19 positive group, which was also positive for both diabetes and hypertension but negative for obesity (n = 631). The next 2 groups with the highest mortalities were also positive for COVID-19, negative for diabetes, negative for obesity; the group positive for hypertension had 570 recorded deaths and the group negative for hypertension had 420 deaths. The least number of deaths recorded overall were in the patients with all conditions negative (n = 58). Interestingly, through the course of the pandemic, the use of personal protective equipment, safe distancing, and newly developed vaccines have helped mediate the deadly effects of COVID-19, therefore considering these measures took time to take full effect we took the data from Table 4 A. and sub grouped it by year the relations of deaths by individual comorbidities (Tables 4. A1-3). These results showed a steady drop in the total number of deaths: in year 2020 the total number of deaths recorded was n = 2027, from which the highest amount n = 315 were for COVID-19, diabetes, and hypertension, remarkably the next high incidence was n = 312 for COVID-19 and hypertension. In year 2021, the total amount of deaths dropped to n=1388, over a 31% decrease from the previous year, and from which the highest incidence recorded was n = 262, was again for COVID-19 positive patients, diabetes, and hypertension, moreover the second highest recorded level of incidence n = 214, was COVID-19 positive patients and hypertension. For the first trimester of 2022, the highest incidence was n = 54 for patients COVID-19, diabetes, and hypertension positive, followed by n = 44 for COVID-19 and hypertension positive patients, results presented in Figure 1.

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Table 3 A. COVID-19 (Hypertension / Diabetes)

COVID-19	Hyper tension	Diabetes	n	%	Total
Positive	Yes	Yes	3691	47.33%	7799
		No	4108	52.67%	
	No	Yes	1212	16.02%	7564
		No	6352	83.98%	
Negative	Yes	Yes	4671	43.83%	10656
		No	5985	56.17%	
	No	Yes	1696	12.11%	14003
		No	12307	87.89%	
Unknown / Untested	All	Yes	609	32.74%	1860
		No	1251	67.26%	
				Total	41882

Table 3 A.1 Death related to COVID-19 (Hypertension / Diabetes)

COVID-19	Hyper tension	Diabetes	n	%	Total
Positive	Yes	Yes	949	53.34%	1779
		No	830	46.66%	
	No	Yes	244	32.02%	762
		No	518	67.98%	
Negative	Yes	Yes	310	55.66%	557
		No	247	44.34%	
	No	Yes	76	26.12%	291
		No	215	73.88%	
Unknown / Untested	All	Yes	118	47.58%	248
		No	130	52.42%	
				Total	3637

Table 3 B. COVID-19 (Hypertension / Obesity)

COVID-19	Hyper tension	Obsesity	n	%	Total
Positive	Yes	Yes	2462	31.57%	7799
		No	5337	68.43%	
	No	Yes	1393	18.42%	7564
		No	6171	81.58%	
Negative	Yes	Yes	3149	29.55%	10656
		No	7507	70.45%	
	No	Yes	2218	15.84%	14003
		No	11785	84.16%	
Unknown / Untested	All	Yes	390	20.97%	1860
		No	1470	79.03%	
				Total	41882

Table 3 B.1 Death related to COVID-19 (Hypertension / Obesity)

COVID-19	Hyper tension	Obesity	n	%	Total
Positive	Yes	Yes	578	32.49%	1779
		No	1201	67.51%	
	No	Yes	158	20.73%	762
		No	604	79.27%	
Negative	Yes	Yes	164	29.44%	557
		No	393	70.56%	
	No	Yes	46	15.81%	291
		No	245	84.19%	
Unknown / Untested	All	Yes	41	16.53%	248
		No	207	83.47%	
				Total	3637

Table 3 C. COVID-19 (Obesity/ Diabetes)

COVID-19	Obesity	Diabetes	n	%	Total
Positive	Yes	Yes	1543	40.03%	3855
		No	2312	59.97%	
	No	Yes	3360	29.20%	11508
		No	8148	70.80%	
Negative	Yes	Yes	1955	36.43%	5367
		No	3412	63.57%	
	No	Yes	4412	22.87%	19292
		No	14880	77.13%	
Unknown / Untested	All	Yes	609	32.74%	1860
		No	1251	67.26%	
				Total	41882

Table 3 C.1. Death related to COVID-19 (Obesity / Diabetes)

COVID-19	Obesity	Diabetes	n	%	Total
Positive	Yes	Yes	378	51.36%	736
		No	358	48.64%	
	No	Yes	815	45.15%	1805
		No	990	54.85%	
Negative	Yes	Yes	118	56.19%	210
		No	92	43.81%	
	No	Yes	268	42.01%	638
		No	370	57.99%	
Unknown / Untested	All	Yes	118	47.58%	248
		No	130	52.42%	
				Total	3637

To further show the influence of each individual comorbidity, and a positive diagnosis for COVID-19 to death, we did a binary logistic regression. Our results showed no statistical correlation between obesity and death ($p = 0.755$). Meanwhile, a positive

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COVID-19 diagnosis showed the overall strongest correlation ($p < 0.01$, OR: 4.377), followed by hypertension ($p < 0.01$, OR: 2.179) and diabetes ($p < 0.001$, OR: 1.744).

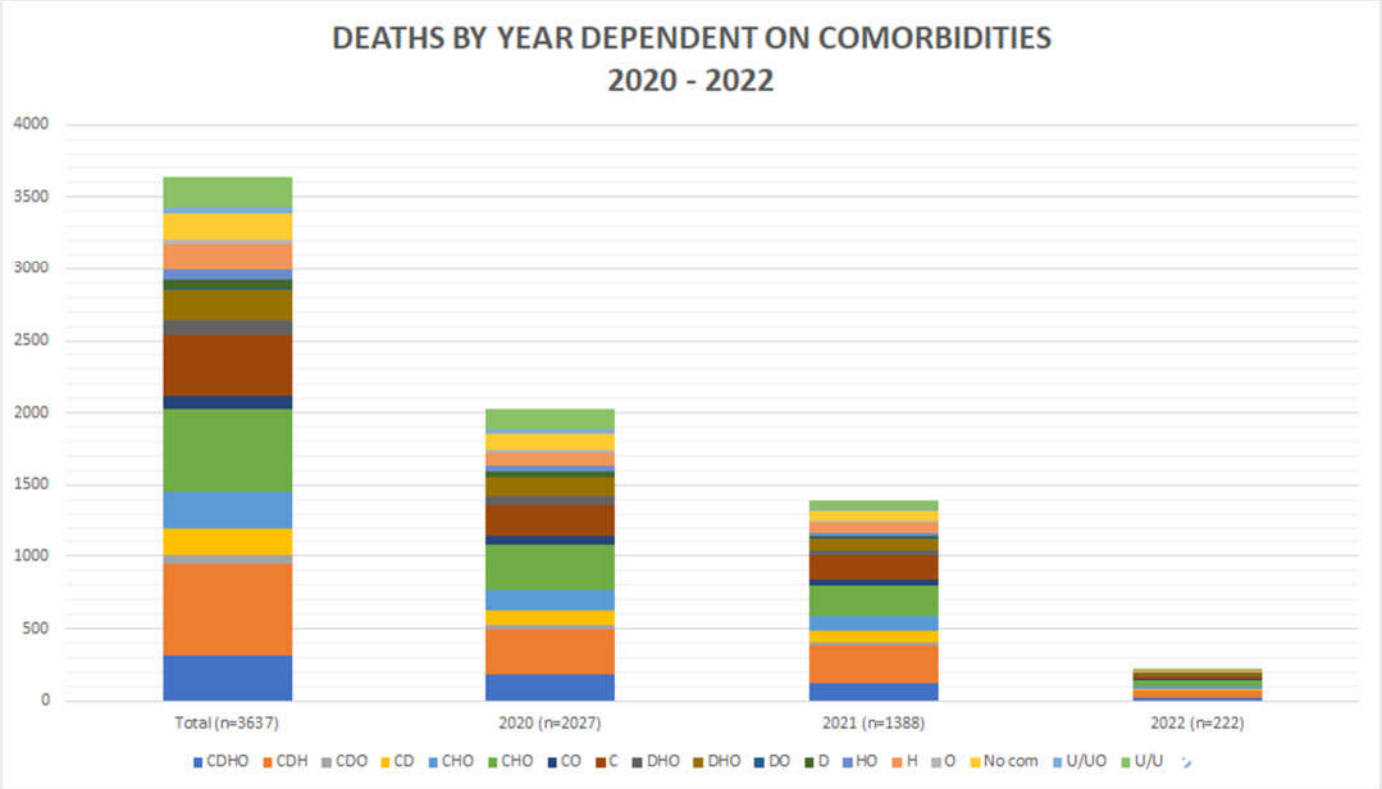

Figure 1. Deaths dependent on comorbidities 2020 – 2022 (first trimester). Individual labels C=COVID-19, D=Dia*betes, H=Hypertension, O=Obesity, No com=No comorbidities, U/U=Unknown/Untested.

A breakdown of the cases by comorbidity, COVID-19 diagnosis, and death was further analyzed by gender and age group (Supplemental Table 1). We observed hypertension positive cases at its highest values for in both males and females between 51 to 60 years (f = 2187, m = 2270) and 61 to 70 (f = 2352, m = 2547), for diabetes positive cases the highest values seen were for in both males and females between 51 to 60 years (f = 1416, m = 1468) and 61 to 70 (f = 1608, m = 1775), for obese patients the highest cases observed were in both males and females between 51 to 60 years (f = 1367, m = 1076) followed by females 61 to 70 years (n = 1150). Previously, we observed that hospitalized patients contributed to most deaths when we distributed them by age and gender the highest case incidence were in males ages 51 to 60 years (n = 993), both females and males 61 to 70 years (f = 906, m = 1399), and females and males 71 to 80 (f = 977, m = 1349). Interestingly, the highest COVID-19 positive cases seen were in males 51 to 60 years (n = 1668) and males 61 to 70 years (n = 1768). Finally, the highest total death count recorded was in males ages 61 to 70 (n = 570), males aged 71 to 80 years (n = 655), and older males aged 81+ (n =459). Finally, we correlated individual comorbidities to death, demonstrating high correlations, as all 3 comorbidities had p-values of < 0.01 (Supplemental Table 2). Parallel set visualization of the data is shown in Figure 2. Figure 3 represents total deaths individually and combined comorbidities by Venn diagram, as presented in Table 4A.

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Table 4 A. Total Deaths related to COVID-19 (Diabetes / Hypertension / Obesity)

COVID-19	Diabetes	Hyper tension	Obesity	n	%	Total
Positive	Positive	Yes	Yes	318	33.51%	949
			No	631	66.49%	
		No	Yes	60	24.59%	244
			No	184	75.41%	
	Negative	Yes	Yes	260	31.33%	830
			No	570	68.67%	
		No	Yes	98	18.92%	518
			No	420	81.08%	
Negative	Positive	Yes	Yes	101	32.58%	310
			No	209	67.42%	
		No	Yes	17	22.37%	76
			No	59	77.63%	
	Negative	Yes	Yes	63	25.51%	247
			No	184	74.49%	
		No	Yes	29	13.49%	215
			No	186	86.51%	
Unknown / Untested	All	All	Yes	38	15.32%	248
			No	210	84.68%	
					Total	3637

Table 4 A.1 Total Deaths in 2020 related to COVID-19 (Diabetes / Hypertension / Obesity)

COVID-19	Diabetes	Hyper tension	Obesity	n	%	Total
Positive	Positive	Yes	Yes	178	36.11%	493
			No	315	63.89%	
		No	Yes	35	26.92%	130
			No	95	73.08%	
	Negative	Yes	Yes	143	31.43%	455
			No	312	68.57%	
		No	Yes	60	21.43%	280
			No	220	78.57%	
Negative	Positive	Yes	Yes	64	33.51%	191
			No	127	66.49%	
		No	Yes	8	17.78%	45
			No	37	82.22%	
	Negative	Yes	Yes	41	30.60%	134
			No	93	69.40%	
		No	Yes	15	12.10%	124
			No	109	87.90%	
Unknown / Untested	All	All	Yes	30	17.14%	175
			No	145	82.86%	
					Total	2027

Table 4 A.2 Total Deaths in 2021 related to COVID-19 (Diabetes / Hypertension / Obesity)

COVID-19	Diabetes	Hyper tension	Obesity	n	%	Total
Positive	Positive	Yes	Yes	123	31.95%	385
			No	262	68.05%	
		No	Yes	22	21.78%	101
			No	79	78.22%	
	Negative	Yes	Yes	101	32.06%	315
			No	214	67.94%	
		No	Yes	32	15.38%	208
			No	176	84.62%	
Negative	Positive	Yes	Yes	35	31.82%	110
			No	75	68.18%	
		No	Yes	8	33.33%	24
			No	16	66.67%	
	Negative	Yes	Yes	19	20.00%	95
			No	76	80.00%	
		No	Yes	12	14.63%	82
			No	70	85.37%	
Unknown / Untested	All	All	Yes	11	16.18%	68
			No	57	83.82%	
					Total	1388

Table 4 A.3. Total Deaths in the first trimester of 2022 related to COVID-19 (Diabetes / Hypertension / Obesity)

COVID-19	Diabetes	Hyper tension	Obesity	n	%	Total
Positive	Positive	Yes	Yes	17	23.94%	71
			No	54	76.06%	
		No	Yes	3	23.08%	13
			No	10	76.92%	
	Negative	Yes	Yes	16	26.67%	60
			No	44	73.33%	
		No	Yes	6	20.00%	30
			No	24	80.00%	
Negative	Positive	Yes	Yes	2	22.22%	9
			No	7	77.78%	
		No	Yes	1	14.29%	7
			No	6	85.71%	
	Negative	Yes	Yes	3	16.67%	18
			No	15	83.33%	
		No	Yes	2	22.22%	9
			No	7	77.78%	
Unknown / Untested	All	All	Yes	0	0.00%	5
			No	5	100.00%	
					Total	222

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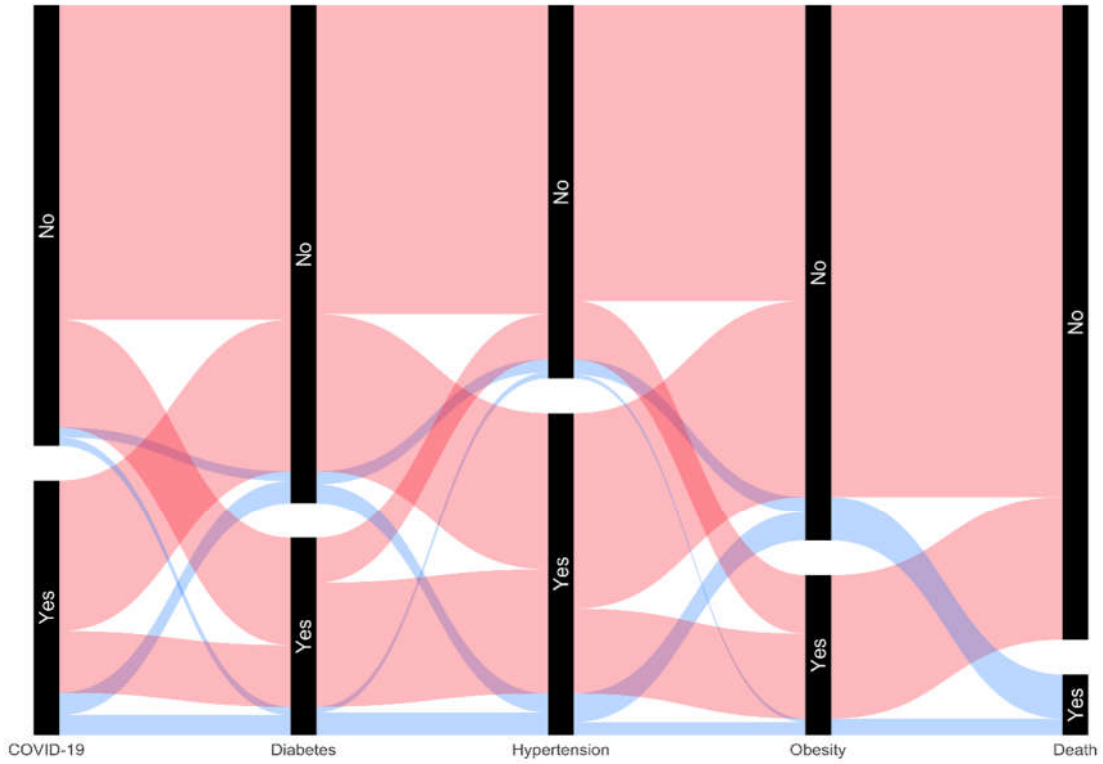

Figure 2. Parallel set visualization of Total CVD´s positive patients and different comorbidities, including death.

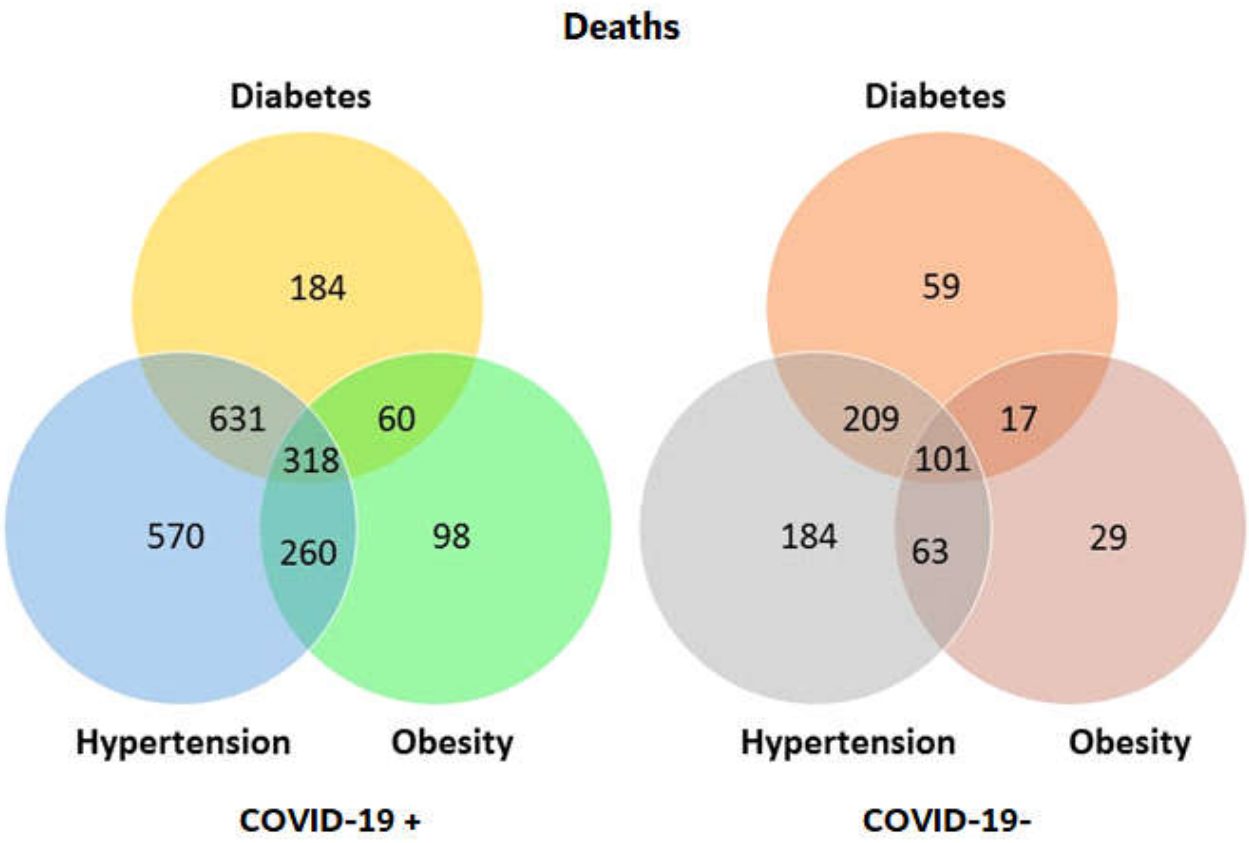

Figure 3. Diagrams of total deaths for CVD´s positive patients, divided by COVID-19 diagnosis with values of comorbidities either individually or combined.

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4. Discussion

In a recent statement by the American Heart Association, there is mention that CVD´s continues to be one of the most frequent cause of mortality worldwide [25]. In the US alone, reports have shown that CVD´s account for the death of 1 person each 36 seconds and for 1 in 3 death in women [26,27]. Given the recent COVID-19 pandemic, it is likely that deaths attributed to COVID-19 during the highest peaks of the pandemic could have overshadowed the mortality from CVD´s (including patients with related comorbidities). Thankfully, the development and worldwide distribution of novel vaccines, vaccine acceptancy, safe distancing practices, and the overall better conscientization of the public, has made mortality by COVID-19 diminished significantly [9,11,28–31]. For Mexico, this has eventually resulted in a drop from the 9% COVID-19 case-fatality-ratio, at its highest, to just above 5% [12].

Through this work, we have analyzed individuals confirmed to have CVD´s and whom received ambulatory consultation, treatment, or were hospitalized in the Mexico city metropolitan area. Importantly, the Mexico city metropolitan area roughly includes 20% of the total population of Mexico and it houses some of the most important reference hospitals in the country. Hence, many individuals travel to Mexico to receive medical attention [2–5]. Over the course of 2 years and 3 months, CVD´s positive patients amounted to 41882, with 51.8% of patients being female, and 3637 recorded deaths (38% female) or 8.68%, from which only 36.7% of these patients were positive for COVID-19 (Table 1).

Over the course of the COVID-19 pandemic, several studies have showed that CVD´s positive patients are at higher risk of death, particularly when these include comorbidities such as hypertension, obesity, and diabetes, making them particularly vulnerable groups [13,18,32,33]. In a recent study, which included 46321 hospitalized individuals positive for COVID-19 (with CVD´s), the mortality rates were found to be 4-times higher in patients with comorbidities such as diabetes (OR: 2.41 $p < 0.001$) and hypertension (OR: 2.60 $p < 0.001$) [34]. Our study, focused on patients positive for CVD´s, finding similar trends for both, diabetes (OR: 1.744, $p < 0.001$) and hypertension (OR: 2.179, $p < 0.001$), as well as observing that 92% of deaths (n = 3382, Table 2 B) were in hospitalized patients, from which n = 2393 were COVID-19 positive. We further ran chi-squared correlations deaths for individual comorbidities contributions (Supplemental Table 2), we found that out of the n=3637 deaths, n = 987 were attributed directly to obesity ($p < 0.001$), while n = 2499 were attributed to hypertension ($p < 0.001$), and n = 1697 related to diabetes ($p < 0.001$). Interestingly, in our study, the total reported hospitalized patients (regardless of condition) were n = 9774, meaning that 34.6% of hospitalized patients died.

Table 5. Binary logistic regression analysis on death and comorbidities.

	B	Std error	Wald	gl	p (values)	OR	95% C.I. for OR	
							Inferior	Superior
Diabetes	0.556	0.038	208.724	1	<0.001	1.744	1.617	1.880
Hypertension	0.779	0.040	369.788	1	<0.001	2.179	2.013	2.359
Obesity	-0.013	0.041	0.097	1	0.755	0.987	0.910	1.070

Model summary: −2 log likelihood = 22019.540, Cox and Snell R square = 0.063, and Nagelkerke R square = 0.140.

An interesting observation was seen with the total number of deaths (Table 2 A and Tables 3 and 4, A-C.1), which were the steady drop overtime, from 2020 to 2021 31% decrease. During COVID-19 pandemic, overall data has shown that COVID-19 vaccination, have had a great impact on case reduction. Alongside this data, it is important to note that since late December 2020, the Mexican government began massive efforts to vaccinate the population, beginning with at risk population. In addition, official government reports during late November 2021 showed that approximately 58% of the population in Mexico had received at least one dose of vaccination [35]. As the global situation has felt more eased in part by vaccine availability, vaccines alone are not the end-all solution, use of

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personal protective equipment and social distancing are crucial in stopping the infection chain of COVID-19. Relaxing of these measures has given rise to emerging COVID-19 variants [36]. More recently, as a new surge of COVID-19 infections have emerged in the northeast part of the US. states such as New York and Massachusetts are on high alert with reconsideration of face mask mandates [37]. A recent report commented that in several countries where there were removal of COVID-19 restrictions, there have been subsequent increases not only in overall cases but also in hospitalizations and deaths, albeit case severity is still under investigation [38].

Finally, while CVD´s positive patients are an at risk population, particularly when additional comorbidities are present. It is important to ponder the reverse question, are post COVID-19 patients at risk for CVD´s? While this was not the focus of the current study, a recent study by Al-Aly et al., showed that COVID-19 survivors regardeles of age or race had an increase risk of developing CVD´s amphazising that physicians should include COVID-19 diagnosis as part of history of CVD´s [39]. Interestingly, in inflammaory Heart Diseases were independently confirmed for a group of professional athletes,just over half of the tested athletes have had a previous COVID-19 diagnosis, from this individuals 45 showed either abnornal ECG´s and, or elevated Troponins were, which caused concerned, hence restricting their play. We should note that long-tern follow-up is ongoing [40]. In another study, about half of the 1216 participants form over 69 countries (age 52 - 79), whom also had a prior COVID-19 diagnosis showed abnormal electrocardiography, their results showed left and right ventricular abnormalities in 479 (39%) and 397 (33%) patients, myocardial infarction in 36 (3%), myocarditis in 35 (3%), and takotsubo cardiomyopathy in 19 (2%) [41].

Having a CVD diagnosis, particularly with comorbidities seems to increase the likely-hood of complication leading to death in COVID-19 posiive patients. Meanwhile having a COVID-19 diagnosis seems to increase the risk of developing CVD´s in the long-run, while both conditions continue under investigation, individuals in general should strive to pursue healthy lifestyles to reduce the potential of developing CVD´s, and take preventive meassures such as the use of face-masks and vaccines in otder to minimie the potential to get COVID-19. These prespectives are important to enhance the quality of life in individuals and minimize any potential complication one could develop of these or other related diseases.

5. Limitations

Understanding vulnerable populations is a multi-complex variable problem. Currently, we have centered our study to consider for the particular population of CVD´s positive patients the relation to mortality based on 3 of the upmost important comorbidities (diabetes, hypertension, obesity) as determined by several studies, as well as the influence of COVID-19. Further analysis with other comorbidities, pharmacological intake, social, economic, educational, and stress related factors (including religious beliefs), should be done in order to help model risk factors in these and other vulnerable populations, as uncertainty for this pandemic and any future one is still at large.

6. Conclusions

Mexico was one of the most affected countries worldwide by the COVID-19 pandemic. Particularly, Mexico city was among the most affected cities in the country. Our findings suggest that, while obesity does not seem to contribute significantly to CVD and COVID-19 related mortality, both diabetes and hypertension seem to act as key contributors to CVD´s positive patients mortality, when confronted with a positive COVID-19 diagnosis. It is essential for public health officials and policy makers to enhance medical follow-up strategies for these particular vulnerable groups, as a punctual diagnosis and pharmacological and non-pharmacological treatment for patients may act as protective factors against COVID-19. Adittionally, evidence have shown that COVID-19 vaccination, plays a crucial role in this particular populations for mortality reduction. Therefore,

vaccination strategies should keep including these populations as a priority in order to reduce mortality, as potential surges of COVID-19 (and its variations) may continue to rise along the years to come.

Supplementary Materials:

- Supplemental Table 1 Individual comorbidities (hypertension, diabetes and obesity), Patient type, COVID-19 diagnosis, and death reported by gender and age
- Supplemental Table 2 Individual comorbidities correlated to death in CVD´s patients

Author Contributions: GRP-R, JD-G, ENG-T and JFI conceptualized and supervised the study, contributed to the overall design of the survey experiment, analysis and interpretation of the data, JD-G, JFI wrote the first draft of the manuscript. GG-T, KAG-H, ZG-B contributed to the overall design of the experiment, JAR-R, HF-V, JEM-C, AEE-R contributed to the analysis and statistic interpretation of the data. AL-L. AMR-E. and JR-J contributed to the discussion. All the authors had access to all the data in this study and had final responsibility for the decision to submit for publication.

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References

1. Juárez-Pérez, C.A.; Cabello-López, A.; Aguilar-Madrid, G.; Trujillo-Reyes, Ó.; Torres-Valenzuela, A.; Fascinetto-Dorantes, R.; Jiménez-Ramírez, C.; Skjönsberg, Å. Commute times and audiometric findings among adult population in Mexico City. *Gac. Mexico* **2022**, *157*, doi:10.24875/GMM.M21000576.
2. León-Cortés, J.L.; Leal Fernández, G.; Sánchez-Pérez, H.J. Health reform in Mexico: Governance and potential outcomes. *Int. J. Equity Health* **2019**, *18*, 1–6, doi:10.1186/s12939-019-0929-y.
3. Secretaría de Salud *PERSONAL DE SALUD 03 DE NOVIEMBRE DE 2020*; CDMX, 2020;
4. Abeldaño Zuñiga, R.A.; González Villoria, R.A.M. Social Participation Strategies and Resilience in Mexican Population Affected by the 2017 Earthquakes. *Disaster Med. Public Health Prep.* **2020**, *14*, 335–342, doi:10.1017/dmp.2019.59.
5. Delgado-Gallegos, J.L.; Montemayor-Garza, R.J.; Padilla-Rivas, G.R.; Franco-Villareal, H.; Islas, J.F. Prevalence of stress in healthcare professionals during the covid-19 pandemic in Northeast Mexico: A remote, fast survey evaluation, using an adapted covid-19 stress scales. *Int. J. Environ. Res. Public Heal.* **2020**, *17*, doi:10.3390/ijerph17207624.
6. Chiong, M.; Wang, Z. V; Pedrozo, Z.; Cao, D.J.; Troncoso, R.; Ibacache, M.; Criollo, A.; Nemchenko, A.; Hill, J. a; Lavandero, S. Cardiomyocyte death: mechanisms and translational implications. *Cell Death Dis.* **2011**, *2*, e244, doi:10.1038/cddis.2011.130.
7. Litviňuková, M.; Talavera-López, C.; Maatz, H.; Reichart, D.; Worth, C.L.; Lindberg, E.L.; Kanda, M.; Polanski, K.; Heinig, M.; Lee, M.; et al. Cells of the adult human heart. *Nature* **2020**, *588*, 466, doi:10.1038/s41586-020-2797-4.
8. Acosta-Cázares, B.; Escobedo-de la Peña, J. High burden of cardiovascular disease risk factors in Mexico: An epidemic of ischemic heart disease that may be on its way? *Am. Heart J.* **2010**, *160*, 230–236, doi:10.1016/j.ahj.2010.05.016.
9. Delgado-Gallegos, J.L.; Padilla-Rivas, G.R.; Zúñiga-Violante, E.; Avilés-Rodríguez, G.; Arellanos-Soto, D.; Gastelum-Arias, L.J.; Franco Villareal, H.; Cosío-León, M. de los Á.; Romo-Cardenas, G.S.; Moreno-Treviño, M.G.; et al. Determinants of COVID-19 Vaccine Hesitancy: A Cross-Sectional Study on a Mexican Population Using an Online Questionnaire (COV-AHQ). *Front. Public Heal.* **2021**, *9*, doi:10.3389/fpubh.2021.728690.
10. Padilla-Rivas, G.R.; Delgado-Gallegos, J.L.; Montemayor-Garza, R.D.J.; Franco-Villareal, H.; Cosio-León, M.D.L.Á.; Avilés-Rodriguez, G.; Zuñiga-Violante, E.; Romo-Cardenas, G.S.; Islas, J.F. Dataset of the adapted COVID STRESS SCALES for Healthcare professionals of the Northeast region of Mexico . *Data Br.* **2021**, *34*, 106733, doi:10.1016/j.dib.2021.106733.
11. Haque, A.; Pant, A.B. Efforts at COVID-19 vaccine development: Challenges and successes. *Vaccines* **2020**, *8*, 1–16, doi:10.3390/vaccines8040739.
12. John Hopkins University Mortality Rate - John Hopkins Coronavirus Resource Center Available online: https://coronavirus.jhu.edu/map.html (accessed on May 1, 2022).
13. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* **2020**, *395*, 1054–1062, doi:10.1016/S0140-6736(20)30566-3.

14. Bello-Chavolla, O.; Bahena-López, J.; Antonio-Villa, N.; Vargas-Vázquez, A.; González-Díaz, A.; Márquez-Salinas, A.; Fermín-Martínez, C.; Naveja, J.; Aguilar-Salinas, C. Predicting mortality due to SARS-CoV-2: A mechanistic score relating obesity and diabetes to COVID-19 outcomes in Mexico Omar. *J Clin Endocrinol Metab.* **2020**, *105*, 1–13.
15. Henry, B.M.; Vikse, J.; Benoit, S.; Favaloro, E.J.; Lippi, G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clin. Chim. Acta* **2020**, *507*, 167–173, doi:10.1016/j.cca.2020.04.027.
16. Edler, C.; Schröder, A.S.; Aepfelbacher, M.; Fitzek, A.; Heinemann, A.; Heinrich, F.; Klein, A.; Langenwalder, F.; Lütgehetmann, M.; Meißner, K.; et al. Dying with SARS-CoV-2 infection—an autopsy study of the first consecutive 80 cases in Hamburg, Germany. *Int. J. Legal Med.* **2020**, *134*, 1275–1284, doi:10.1007/s00414-020-02317-w.
17. Ye, M.; Wysocki, J.; William, J.; Soler, M.J.; Cokic, I.; Batlle, D. Glomerular Localization and Expression of Angiotensin-Converting Enzyme 2 and Angiotensin-Converting Enzyme: Implications for Albuminuria in Diabetes. *J. Am. Soc. Nephrol.* **2006**, *17*, 3067–3075, doi:10.1681/ASN.2006050423.
18. Iannelli, A.; Favre, G.; Frey, S.; Esnault, V.; Gugenheim, J.; Bouam, S.; Schiavo, L.; Tran, A.; Alifano, M. Obesity and COVID-19: ACE 2, the Missing Tile. *Obes. Surg.* **2020**, *30*, 4615–4617, doi:10.1007/s11695-020-04734-7.
19. Tikellis, C.; Wookey, P.J.; Candido, R.; Andrikopoulos, S.; Thomas, M.C.; Cooper, M.E. Improved Islet Morphology after Blockade of the Renin- Angiotensin System in the ZDF Rat. *Diabetes* **2004**, *53*, 989–997, doi:10.2337/diabetes.53.4.989.
20. Shori, A.B.; Baba, A.S. Antioxidant activity and inhibition of key enzymes linked to type-2 diabetes and hypertension by Azadirachta indica-yogurt. *J. Saudi Chem. Soc.* **2013**, *17*, 295–301, doi:10.1016/j.jscs.2011.04.006.
21. Shiuchi, T.; Cui, T.-X.; Wu, L.; Nakagami, H.; Takeda-Matsubara, Y.; Iwai, M.; Horiuchi, M. ACE Inhibitor Improves Insulin Resistance in Diabetic Mouse Via Bradykinin and NO. *Hypertension* **2002**, *40*, 329–334, doi:10.1161/01.HYP.0000028979.98877.0C.
22. Beyerstedt, S.; Casaro, E.B.; Rangel, É.B. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur. J. Clin. Microbiol. Infect. Dis.* **2021**, *40*, 905–919, doi:10.1007/s10096-020-04138-6.
23. Kumar, A.; Narayan, R.K.; Kumari, C.; Faiq, M.A.; Kulandhasamy, M.; Kant, K.; Pareek, V. SARS-CoV-2 cell entry receptor ACE2 mediated endothelial dysfunction leads to vascular thrombosis in COVID-19 patients. *Med. Hypotheses* **2020**, *145*, 110320, doi:10.1016/j.mehy.2020.110320.
24. Mexico, G. de la C. de Casos a nivel nacional asociados a COVID-19No Title Available online: https://datos.cdmx.gob.mx/dataset/casos-asociados-a-covid-19 (accessed on Apr 25, 2022).
25. American Heart Institute Heart disease likely to remain #1 killer in U.S. indefinitely due to long-term COVID-19 impact Available online: https://newsroom.heart.org/news/heart-disease-likely-to-remain.
26. CDC Heart Disease Facts Available online: https://www.cdc.gov/heartdisease/facts.htm (accessed on May 18, 2022).
27. Virani, S.S.; Alonso, A.; Aparicio, H.J.; Benjamin, E.J.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Cheng, S.; Delling, F.N.; et al. Heart Disease and Stroke Statistics—2021 Update. *Circulation* **2021**, *143*, doi:10.1161/CIR.0000000000000950.
28. Skjefte, M.; Ngirbabul, M.; Akeju, O.; Escudero, D.; Hernandez-Diaz, S.; Wyszynski, D.F.; Wu, J.W. COVID-19 vaccine acceptance among pregnant women and mothers of young children: results of a survey in 16 countries. *Eur. J. Epidemiol.* **2021**, *36*, 197–211, doi:10.1007/s10654-021-00728-6.
29. Fisher, K.A.; Bloomstone, S.J.; Walder, J.; Crawford, S.; Fouayzi, H.; Mazor, K.M. Attitudes Toward a Potential SARS-CoV-2 Vaccine. *Ann. Intern. Med.* **2020**, *173*, 964–973, doi:10.7326/M20-3569.
30. Lai, J.; Ma, S.; Wang, Y.; Cai, Z.; Hu, J.; Wei, N.; Wu, J.; Du, H.; Chen, T.; Li, R.; et al. Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019. *JAMA Netw. open* **2020**, *3*, e203976, doi:10.1001/jamanetworkopen.2020.3976.
31. Ratneswaren, A. The I in COVID: The importance of community and patient involvement in COVID-19 research. *Clin. Med. (Northfield. Il).* **2020**, *20*, e120–e122, doi:10.7861/clinmed.2020-0173.
32. Sahni, S.; Gupta, G.; Sarda, R.; Pandey, S.; Pandey, R.M.; Sinha, S. Impact of metabolic and cardiovascular disease on COVID-19 mortality: A systematic review and meta-analysis. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2021**, *15*, 102308, doi:10.1016/j.dsx.2021.102308.
33. Suárez, V.; Suarez Quezada, M.; Oros Ruiz, S.; Ronquillo De Jesús, E. Epidemiología de COVID-19 en México: del 27 de febrero al 30 de abril de 2020. *Rev. Clínica Española* **2020**, 1–9, doi:10.1016/j.rce.2020.05.007.
34. Cordero, A.; Santos García-Gallego, C.; Bertomeu-González, V.; Fácila, L.; Rodríguez-Mañero, M.; Escribano, D.; Castellano, J.M.; Zuazola, P.; Núñez, J.; Badimón, J.J.; et al. Mortality associated with cardiovascular disease in patients with COVID-19. *REC CardioClinics* **2021**, *56*, 30–38, doi:10.1016/j.rccl.2020.10.005.
35. Gobierno de Mexico VACUNACIÓN CONTRA COVID-19 PARA ADOLESCENTES DE 12 A 17 AÑOS Available online: http://vacunacovid.gob.mx/wordpress/vacuna-covid19-adolescentes/ (accessed on Nov 20, 2021).
36. Bartsch, S.M.; O'Shea, K.J.; Chin, K.L.; Strych, U.; Ferguson, M.C.; Bottazzi, M.E.; Wedlock, P.T.; Cox, S.N.; Siegmund, S.S.; Hotez, P.J.; et al. Maintaining face mask use before and after achieving different COVID-19 vaccination coverage levels: a modelling study. *Lancet Public Heal.* **2022**, *7*, e356–e365, doi:10.1016/S2468-2667(22)00040-8.
37. U.S.news Creeping COVID-19 Cases Result in Few Schools Mask Mandates Available online: https://www.usnews.com/news/world/articles/2022-05-11/creeping-covid-19-cases-result-in-few-schools-mask-mandates.
38. Stokel-Walker, C. COVID restrictions are lifting — what scientists think. *Nature* **2022**, *603*, 563–563, doi:10.1038/d41586-022-00620-7.

39. Abbasi, J. The COVID Heart-One Year after SARS-CoV-2 Infection, Patients Have an Array of Increased Cardiovascular Risks. *JAMA - J. Am. Med. Assoc.* **2022**, *327*, 1113–1114, doi:10.1001/jama.2022.2411.
40. Martinez, M.W.; Tucker, A.M.; Bloom, O.J.; Green, G.; Difiori, J.P.; Solomon, G.; Phelan, D.; Kim, J.H.; Meeuwisse, W.; Sills, A.K.; et al. Prevalence of Inflammatory Heart Disease among Professional Athletes with Prior COVID-19 Infection Who Received Systematic Return-to-Play Cardiac Screening. *JAMA Cardiol.* **2021**, *6*, 745–752, doi:10.1001/jamacardio.2021.0565.
41. Dweck, M.R.; Bularga, A.; Hahn, R.T.; Bing, R.; Lee, K.K.; Chapman, A.R.; White, A.; Salvo, G. Di; Sade, L.E.; Pearce, K.; et al. Global evaluation of echocardiography in patients with COVID-19. *Eur. Heart J. Cardiovasc. Imaging* **2020**, *21*, 949–958, doi:10.1093/ehjci/jeaa178.