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Original Article

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Characterizing a two-pronged epidemic in Mexico of non-communicable diseases and SARS-Cov-2: factors associated with increased case-fatality rates

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Abstract

Background: People with a previous diagnosis of non-communicable diseases (NCDs) are more likely to develop serious forms of COVID-19 or die. Mexico is the country with the fourth highest fatality rate from SARS-Cov-2, with high mortality in younger adults.
Objectives: To describe and characterize the association of NCDs with the case-fatality rate (CFR) adjusted by age and sex in Mexican adults with a positive diagnosis for SARS-Cov-2.
Methods: We studied Mexican adults aged $\geq$20 years who tested positive for SARS-Cov-2 during the period from 28 February to 31 July 2020. The CFR was calculated and associations with history of NCDs (number of diseases and combinations), severity indicators and type of institution that treated the patient were explored. The relative risk (RR) of death was estimated using Poisson models and CFR was adjusted using logistic models.
Results: We analysed 406 966 SARS-Cov-2-positive adults. The CFR was 11.2% (13.7% in men and 8.4% in women). The CFR was positively associated with age and number of NCDs (p trend $<$0.001). The number of NCDs increased the risk of death in younger adults when they presented three or more NCDs compared with those who did not have any NCDs [RR, 46.6; 95% confidence interval (CI), 28.2, 76.9 for women; RR, 16.5; 95% CI, 9.9, 27.3 for men]. Lastly, there was great heterogeneity in the CFR by institution, from 4.6% in private institutions to 18.9% in public institutions.

Conclusion: In younger adults, higher CFRs were associated with the total number of NCDs and some combinations of type 2 diabetes, chronic kidney disease, chronic obstructive pulmonary disease and cardiovascular disease.

Key words: Hypertension, diabetes, cardiovascular disease, COVID-19, SARS-Cov-2, mortality

Key Messages

- The relative risk (RR) of death increases with the number of non-communicable diseases (NCDs).
- NCDs increase the RR of death differentially by age groups, with the highest RR seen in young adults.
- Some combinations of NCDs are associated with greater increases in case-fatality rates (CFRs).
- There is great heterogeneity in the CFR by type of healthcare institution.

Background

The severe acute respiratory syndrome coronavirus 2 disease (COVID-19)[1] can produce mild respiratory symptoms that remit naturally.[2] However, in some cases, it can also evolve into acute respiratory distress syndrome, causing multiple-organ failure and death.[3]

As of 8 November 2020, >50.3 million people have been infected with SARS-Cov-2 worldwide and >1.254 million have died from this cause. When comparing the mortality rate per 100 000 inhabitants during this period, Mexico had the sixth highest mortality rate and had officially tested 2.568 million people, reaching 961 938 positive cases.[4]

People with a previous diagnosis of non-communicable diseases (NCDs) such as high blood pressure (HBP), type 2 diabetes (T2D), cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD),[5,6] as well as those who are older or male, are more likely to develop serious conditions of COVID-19 or die from this cause.[7] In China, the fatality rate (number of deaths per 100 infected) for COVID-19 was 2.3%. However, it was 6.0% for people with hypertension, 7.3% for adults with diabetes and 10.5% for people with cardiovascular disease.[8] On the one hand, differences were observed in the hazard ratio (HR) of people who developed severe symptoms or died, being higher in men (HR 1.6) than in women (HR 1.0) and in people ≥65 years old (HR 1.9) as opposed to those <65 years old (HR 1.0).[9] Epidemiological studies have shown that the risk of mortality from SARS-Cov-2 increases 2.5 times when the patient has HBP, 1.9 times when they have diabetes[10] and 7.9 times when they have CVD.[11]

In Mexico, the association between obesity and diabetes with a higher risk of SARS-Cov-2 infection,[12] severity and need for hospitalization has been documented.[13] A recent study has also documented a higher risk of complications at the beginning of hospitalization among patients with SARS-Cov-2 who also had co-morbidities like obesity, hypertension and diabetes.[14]

In a country like Mexico, where 49% of adults have hypertension,[15] 14% have diabetes[16] and 24% develop CVD,[17] it is important to quantify the risk of death among the population with NCDs and COVID-19. It is also important to consider the role of the health system in providing care to patients with SARS-Cov-2 in cases with and without other NCDs. Understanding the magnitude of this association and its related characteristics can improve targeted strategies that aim to identify adults who are most likely to be infected and die of SARS-Cov-2. Our objective is to describe and characterize the association between NCDs and case-fatality rates (CFRs), adjusting by factors that increase the risk of death, such as age and sex, in Mexican adults with a positive diagnosis of SARS-Cov-2.

Methods

Study design and participants

Our study population consisted of Mexican adults aged ≥20 years who tested positive for SARS-Cov-2 and were registered in the Epidemiological Surveillance System for Respiratory Diseases database (SISVER, Spanish acronym). This database includes epidemiological information at the national level, with mandatory reporting of diseases like SARS-Cov-2 for all public or private health units and laboratories. The information was obtained from the Ministry of Health's website (https://www.gob.mx/salud/documentos/datos-abiertos-152127).[18] This data set is

open to the public and is continuously updated. We analysed data from the beginning of the epidemic (28 February 2020) to 31 July 2020. The database contains information on all outpatients and those hospitalized, as well as on deaths from SARS-Cov-2 in Mexico.[18]

Confirmation of COVID-19 cases

Adults were suspected of having COVID-19 if they reported at least two of the following symptoms within the past 7 days: fever, headache and cough, accompanied by at least one of the following signs: arthralgia, conjunctivitis, pain in the chest, dyspnea, myalgia, odynophagia or rhinorrhea. For all suspected cases, two protocols were followed: testing for SARS-Cov-2 and epidemiological surveillance.[18] As authorized by the National Committee for Epidemiological Surveillance (CONAVE, Spanish acronym),[18] cases were confirmed using the polymerase chain reaction test based on the Berlin protocol.[19]

NCD assessment

An adult was considered to have an NCD when the patient reported having been previously diagnosed with: HBP, T2D, obesity (OB), CVD, chronic kidney disease (CKD) or COPD. We selected these NCDs because they are those with the highest prevalence in Mexico and because of their association with greater severity of COVID-19.[15–17] The instrument used to collect the information was an official standardized questionnaire used by the federal government's Epidemiological Surveillance System.[18] It collects: socio-demographic information (age and sex), personal pathological history (presence of NCDs, date on which the symptoms associated with the infection began and exposure to tobacco), treatment characteristics and indicators of severity such as the presence of pneumonia, need for hospitalization, assistance in the Intensive Care Unit and the use of assisted mechanical intubation (IMA). We classified information on NCDs by number, as follows: no NCDs, one NCD, two NCDs and three or more NCDs.

Institution in which healthcare was provided

We included the institution in which patients received care in the analysis. We categorized the healthcare institutions as Private, Ministry of Navy (SEMAR), Federal Ministry of Health (SS), (Red Cross+DIF+Municipal+University), Ministry of National Defense (SEDENA), not specified, State Secretaries of Health, Petroleos Mexicanos (PEMEX), Institute of Security and Social Services for State Workers (ISSSTE) and Mexican Institute of Social Security (IMSS).

Statistical analysis

Fatality due to SARS-Cov-2 was calculated through the CFR and expressed in percentages (*number of deaths from COVID/total patients identified with COVID in the period described* $\times$ *100)* with their 95% confidence intervals (95% CIs).

The CFR was disaggregated by sex, age and NCDs. To assess trends between age groups and the number of NCDs, tests were performed using robust estimates by Bootstrap. The relative risk (RR) was estimated using Poisson models and the probability of death (CFR adjusted) using logistic regression, which in both cases were adjusted in the models for age, sex, the presence of pre-existing diseases (asthma, immunosuppression, other co-morbidities non-specified) and dummy variables for health institutions. Robust estimates were used in all models. Data analysis was performed using the statistical software STATA[20] and the statistical software R.[21]

Results

The database used in this study included information on 842 025 adults aged $\geq$20 years who were tested for COVID-19. Of these, 3600 (0.4%) observations were eliminated for not having information related to NCD diagnosis. We analysed only information on confirmed SARS-Cov-2 cases ($n = 406\,966$). Of these, 53.2% were men (mean age, 47.0 years: 95% CI, 46.9, 47.1) and 46.5% women (mean age, 45.6 years; 95% CI, 45.6, 45.7).

Participants' characteristics by sex are described in Table 1. The prevalence of NCDs was similar between the sexes. The most common NCD was HBP (20.6%; 95% CI, 20.5, 20.8), followed by obesity (19.8%; 95% CI, 19.6, 19.8) and diabetes (16.8%; 95% CI, 16.7%, 16.9). Furthermore, 55.8% (95% CI, 55.6, 56.0) reported having no NCDs, whereas 25.9% (95% CI, 25.8, 26.1) reported having one, 12.1% (95% CI, 12.0, 12.3) reported having two and 5.9% (95% CI, 5.9, 6.0) had three or more. Over half of the cases were reported by units from the Ministry of Health (53.7%; 95% CI, 53.5, 53.8), followed by the IMSS (33.0%; 95% CI, 32.8, 33.1).

Table 2 shows the CFR for SARS-Cov-2 by sex and NCDs. In the total population, the average CFR was 12.1% (95% CI, 12.0, 12.2) and was higher among men (CFR 14.6%; 95% CI, 14.5, 14.8) than women (CFR 9.1%; 95% CI, 9.0, 9.3). Trend analyses showed that the

Table 1 Characteristics of Mexican adults with diagnosis of COVID-19 and non-communicable diseases (NCDs) by sex

	Total			Women			Men		
	n	%	(95% CI)	*N*	%	(95% CI)	*n*	%	(95% CI)
Total	406 996	100	–	190 088	46.7	(46.5, 46.8)	216 908	53.2	(53.1, 53.4)
Age in years									
20–39	154 375	37.9	(37.7, 38.0)	75 687	39.8	(39.5, 40.0)	78 688	36.2	(36.0, 36.4)
40–59	169 361	41.6	(41.4, 41.7)	78 012	41.0	(40.8, 41.2)	91 349	42.1	(41.9, 42.3)
60–79	72 409	17.7	(17.6, 17.9)	31 508	16.5	(16.4, 16.7)	40 901	18.8	(18.6, 19.0)
≥80	10 851	2.6	(2.6, 2.7)	4881	2.5	(2.4, 2.6)	5970	2.7	(2.6, 2.8)
NCDs									
Cardiovascular disease									
No	398 168	97.8	(97.7, 97.8)	186 293	98.0	(97.9, 98.0)	211 875	97.6	(97.6, 97.7)
Yes	8828	2.1	(2.1, 2.2)	3795	1.9	(1.9, 2.0)	5033	2.3	(2.2, 2.3)
Hypertension									
No	323 624	79.5	(79.3, 79.6)	150 661	79.2	(79.0, 79.4)	172 963	79.7	(79.5, 79.9)
Yes	83 372	20.4	(20.3, 20.6)	39 427	20.7	(20.5, 20.9)	43 945	20.2	(20.0, 20.4)
Chronic kidney diseases									
No	398 660	97.9	(97.9, 97.9)	186 490	98.1	(98.0, 98.1)	212 170	97.8	(97.7, 97.8)
Yes	8336	2.0	(2.0, 2.0)	3598	1.8	(1.8, 1.9)	4738	2.1	(2.1, 2.2)
Diabetes									
No	339 625	83.4	(83.3, 83.5)	158 970	83.6	(83.4, 83.7)	180 655	83.2	(83.1, 83.4)
Yes	67 371	16.5	(16.4, 16.6)	31 118	16.3	(16.2, 16.5)	36 253	16.7	(16.5, 16.8)
Obesity									
No	328 251	80.6	(80.5, 80.7)	151 476	79.6	(79.5, 79.8)	176 775	81.4	(81.3, 81.6)
Yes	78 745	19.3	(19.2, 19.4)	38 612	20.3	(20.1, 20.4)	40 133	18.5	(18.3, 18.6)
Chronic obstructive pulmonary disease									
No	400 352	98.3	(98.3, 98.4)	186 895	98.3	(98.2, 98.3)	213 457	98.4	(98.3, 98.4)
Yes	6644	1.6	(1.5, 1.6)	3193	1.6	(1.6, 1.7)	3451	1.5	(1.5, 1.6)
Number of NCDs									
0	241 589	59.3	(59.2, 59.5)	113 244	59.5	(59.3, 59.7)	128 345	59.1	(58.9, 59.3)
1	100 464	24.6	(24.5, 24.8)	45 600	23.9	(23.7, 24.1)	54 864	25.2	(25.1, 25.4)
2	45 673	11.2	(11.1, 11.3)	21 545	11.3	(11.1, 11.4)	24 128	11.1	(10.9, 11.2)
≥3	19 270	4.7	(4.6, 4.7)	9699	5.1	(5.0, 5.2)	9571	4.4	(4.3, 4.4)
Severity indicators									
Pneumonia									
No	321 109	78.8	(78.7, 79.0)	157 201	82.7	(82.5, 82.8)	163 908	75.5	(75.3, 75.7)
Yes	85 881	21.1	(20.9, 21.2)	32 884	17.2	(17.1, 17.4)	52 997	24.4	(24.2, 24.6)
Attention mode									
Ambulatory	294 586	72.3	(72.2, 72.5)	146 841	77.2	(77.0, 77.4)	1477 45	68.1	(67.9, 68.3)
Hospital admission	112 410	27.6	(27.4, 27.7)	43 247	22.7	(22.5, 22.9)	69 163	3.2	(31.6, 32.0)
Mechanically assisted intubation									
No	396 337	97.3	(97.3, 97.4)	186 528	98.1	(98.0, 98.1)	209 809	96.7	(96.6, 96.8)
Yes	10 659	2.6	(2.5, 2.6)	3560	1.8	(1.8, 1.9)	7099	3.2	(3.1, 3.3)
Admitted to unit and intensive care									
No	398 193	97.8	(97.7, 97.8)	187 060	98.4	(98.3, 98.4)	211 133	97.3	(97.2, 97.4)
Yes	8803	2.1	(2.1, 2.2)	3028	1.5	(1.5, 1.6)	5775	2.6	(2.5, 2.7)
Institutions of the health system									
Private	11 992	2.9	(2.8, 2.9)	4790	2.5	(2.4, 2.5)	7202	3.3	(3.2, 3.3)
SEMAR	3184	0.7	(0.7, 0.8)	1040	0.5	(0.5, 0.5)	2144	0.9	(0.9, 1.0)
SS	218 544	53.6	(53.5, 53.8)	104 574	55.0	(54.7, 55.2)	113 970	52.5	(52.3, 52.7)
Others	762	0.1	(0.1, 0.2)	380	0.1	(0.1, 0.2)	382	0.1	(0.1, 0.1)
SEDENA	2831	0.6	(0.6, 0.7)	943	0.4	(0.4, 0.5)	1888	0.8	(0.8, 0.9)
Not specified	3148	0.7	(0.7, 0.8)	1416	0.7	(0.7, 0.7)	1732	0.7	(0.7, 0.8)
SMH	9186	2.2	(2.2, 2.3)	4537	2.3	(2.3, 2.4)	4649	2.1	(2.0, 2.2)
PEMEX	5106	1.2	(1.2, 1.2)	1793	0.9	(0.8, 0.9)	3313	1.5	(1.4, 1.5)

(Continued)

Table 1 Continued

	Total			Women			Men		
	n	%	(95% CI)	*N*	%	(95% CI)	*n*	%	(95% CI)
ISSSTE	18 026	4.4	(4.3, 4.4)	8401	4.4	(4.3, 4.5)	9625	4.4	(4.3, 4.5)
IMSS	134 217	32.9	(32.8, 33.1)	62 214	32.7	(32.5, 32.9)	72 003	33.1	(32.9, 33.3)

Data from General Direction of Health Information (DGIS), 2020.

Ministry of Health, Ministry of the Navy (SEMAR), Federal Ministry of Health (SS), Other (Red Cross, DIF, Municipal, Universitary), Ministry of National Defense (SEDENA), Statal Ministry of Health (SMH), Petroleos Mexicanos (PEMEX), Institute of Security and Social Services for State Workers (ISSSTE), Mexican Institute of Social Security (IMSS).

CFR increased with age and number of NCDs (trend test $p < 0.001$). In women, the CFR was 1.2% in the 20- to 39-year-old age group and 40.8% in the ≥80 years group, whereas, for men, it was 2.6% and 47.9%, respectively.

In the group of patients without NCDs and stratified by sex, the CFR was lower in women (3.4%; 95% CI, 3.3, 3.5) than in men (8.0%; 95% CI, 7.8, 8.1). When stratifying by type of institution, the CFR was higher in the IMSS (CFR , 10.7%; 95% CI, 10.5, 10.9), followed by the ISSSTE (CFR, 9.5%; 95% CI, 8.9, 10.1). In patients with at least three NCDs, the CFR was higher in women (CFR, 29.9%; 95% CI, 29.0, 30.0) than in men (CFR, 35.8%; 95% CI, 34.8, 36.7), whereas, when stratifying by type of institution, the CFR was higher in the IMSS (CFR, 44.0%; 95% CI, 42.9, 45.1), followed by the ISSSTE (CFR, 37.5%; 95% CI, 35.0, 40.1). The trend test by number of NCDs was $p < 0.001$ (Table 3).

Figure 1 shows that the CFR increases with the number of NCDs in a triple interaction ($p < 0.01$) with sex and age. Adults aged 20–29 years with at least three NCDs have a greater risk compared with those without NCDs, in women (RR, 46.6; 95% CI, 28.2, 76.9) and men (RR, 16.5; 95% CI, 9.9, 27.3). Moreover, the risk among adults aged ≥80 years with at least three NCDs compared with those without NCDs is 1.2 in women (95% CI, 1.0, 1.3) and 1.0 in men (95% CI, 0.9, 1.1). The model is shown in Supplementary Appendix 1, available as Supplementary data at *IJE* online, and Table 1.

The CFR for SARS-Cov-2 in men and women by number and all possible combinations of NCDs is shown in Supplementary Appendix 2, available as Supplementary data at *IJE* online, and Table 1. For two NCDs, the combination with the greatest CFR was T2D+CKD (CFR, 44.0; 95% CI, 39.2, 48.8); for three NCDs, it was T2D+COPD+CVD (CFR, 57.5; 95% CI, 38.4, 75.8).

When categorizing by number of NCDs (from none to at least three), and disaggregating by age group, a greater risk of mortality for older age was found in all categories, except for T2D+COPD and CVD+CKD combinations. The combinations with the highest CFR (from 50.0% to 75.0%) were: CVD+HBP+CKD+T2D+OB, CVD+CKD+COPD, CVD+T2D+COPD, CVD+HBP+CKD+OB+COPD, HBP+CKD+T2D+OB+COPD, CVD+CKD+T2D+COPD; and 31 combinations with CFR between 30.0% and 49.0% were observed. The lowest CFRs were with OB or no NCDs (Figure 2). We did not see a specific pattern by sex (Supplementary Appendix 3, available as Supplementary data at *IJE* online, and Figures 1 and 2).

Figures 3–5 show the CFR by age groups for each NCD (T2D, HBP, OB, CKD, COPD and CVD) individually and combined with other NCDs. Figure 3a and b shows that younger adults had a higher RR of death when they had T2D combined with one or more NCDs (women: RR, 12.5; 95% CI, 7.1, 22.2; men: RR, 5.8, CI 95% 3.1, 10.9). A similar pattern was observed in all diseases and combinations in the age group of ≥60 years. The model is shown in Supplementary Appendix 1, available as Supplementary data at *IJE* online, and Table 2.

Discussion

In our analysis, the CFR was associated with sex, age and number of NCDs (HBP, obesity, CVD, CKD or COPD). We observed greater CFR heterogeneity among institutions.

There is evidence that a country's average age can explain up to 66% of the variation in CFR for COVID-19.[22] Much of the variation between countries is due to the age of people evaluated and diagnosed with the virus. In our analysis, the average age of the population infected with SARS-Cov-2 was 45 years, similarly to that in China (49 years) but younger than that in Italy (62 years).[2] This could be due to the fact that the median age is similar in Mexico (30 years)[3] and China (35 years),[4] but higher in Italy (46 years).[4]

Adults with underlying NCDs are more likely to experience more severe symptoms or die from a SARS-Cov-2 infection.[23] In our analysis, 40.5% of adults with SARS-Cov-2 had at least one NCD. This is lower than the

Table 2 Case-fatality rate (CFR) in Mexican adults diagnosed with COVID-19 and non-communicable diseases (NCDs) by sex.

	Total					Women					Men					Women[a] vs men		
	n	CFR %	(95% CI)	RR[b]	(95% CI)[d]	n	CFR %	(95% CI)	RR[c]	(95% CI)[d]	*N*	CFR %	(95% CI)[d]	RR[c]	(95% CI)	RR by sex	(95% CI)[d]	*P*-value[f]
Sex	406 996	11.2	(11.1, 11.3)	–	–	190 088	8.4	(8.3, 8.6)	–	–	216 908	13.7	(13.6, 13.9)	–	–	1.5	(1.4, 1.5)	<0.001
Age group																		
20–39[a]	154 375	1.7	(1.6, 1.8)	1	–	75 687	1.1	(1.0, 1.1)	1	–	78 688	2.3	(2.1, 2.5)	1	–	2.0	(1.9, 2.2)	<0.001
40–59	169 361	9.8	(9.6, 9.9)	5.5	(5.3, 5.7)	78 012	6.7	(6.7, 6.8)	6.1	(5.6, 6.5)	91 349	12.4	(12.2, 12.6)	5.2	(4.9, 5.4)	1.7	(1.7, 1.8)	<0.001
60–79	72 409	30.2	(29.9, 30.6)	16.8	(16.2, 17.5)	31 508	25.7	(25.6, 5.8)	23.2	(21.6, 24.8)	40 901	33.7	(33.5, 34.0)	14.1	(13.5, 14.8)	1.3	(1.2, 1.3)	<0.001
≥80	10 851	43.2	(42.3, 44.2)	24.2	(23.1, 25.2)	4881	39.0	(38.9, 9.0)	35.1	(32.6, 37.9)	5970	46.7	(46.5, 46.9)	19.6	(18.6, 20.6)	1.1	(1.1, 1.2)	<0.001
p trend			$p < 0.001$					$p < 0.001$					$p < 0.001$			$p < 0.001$		
NCCDs																		
Cardiovascular disease																		
No[a]	398 168	10.9	(10.8, 11.0)	1	–	186 293	8.1	(8.0, 8.2)	1	–	211 875	13.3	(12.0, 14.6)	1	–	1.5	(1.5, 1.5)	<0.001
Yes	8828	27.7	(26.7, 28.6)	1.1	(1.0, 1.1)	3795	24.0	(23.8, 4.1)	1.2	(1.1, 1.3)	5033	30.4	(29.2, 31.7)	1.1	(1.1, 1.2)	1.2	(1.1, 1.3)	<0.001
Hypertension																		
No[a]	323 624	7.9	(7.8, 8.0)	1	–	150 661	5.1	(5.0, 5.2)	1	–	172 963	10.4	(9.9, 10.8)	1	–	1.7	(1.6, 1.7)	<0.001
Yes	83 372	24.2	(23.9, 24.5)	1.4	(1.4, 1.5)	39 427	21.2	(21.0, 1.3)	1.6	(1.6, 1.7)	43 945	26.9	(26.5, 27.3)	1.3	(1.3, 1.3)	1.3	(1.2, 1.3)	<0.001
Chronic kidney diseases																		
No[a]	398 660	10.7	(10.6, 10.8)	1	–	186 490	7.9	(7.8, 8.1)	1	–	212 170	13.1	(11.7, 14.5)	1	–	1.5	(1.5, 1.5)	<0.001
Yes	8336	37.5	(36.5, 38.6)	2.0	(2.0, 2.1)	3598	34.8	(34.7, 34.9)	2.4	(2.3, 2.6)	4738	39.6	(38.2, 41.0)	1.8	(1.8, 1.9)	1.1	(1.0, 1.1)	<0.001
Diabetes																		
No[a]	339 625	8.3	(8.2, 8.4)	1	–	158 970	5.6	(5.5, 5.8)	1	–	180 655	10.7	(10.2, 11.2)	1	–	1.6	(1.6, 1.7)	<0.001
Yes	67 371	26.0	(25.6, 26.3)	1.7	(1.6, 1.7)	31 118	22.7	(22.6, 22.8)	1.9	(1.9, 2.0)	36 253	28.7	(28.3, 29.2)	1.5	(1.5, 1.6)	1.2	(1.2, 1.3)	<0.001
Obesity																		
No[a]	328 251	10.5	(10.4, 10.6)	1	–	151 476	7.5	(7.4, 7.6)	1	–	176 775	13.1	(12.6, 13.4)	1	–	1.5	(1.5, 1.5)	<0.001
Yes	78 745	14.5	(14.2, 14.7)	1.4	(1.4, 1.4)	38 612	12.1	(11.9, 12.2)	1.5	(1.4, 1.5)	40 133	16.8	(16.4, 17.2)	1.4	(1.3, 1.4)	1.4	(1.4, 1.5)	<0.001
Chronic obstructive pulmonary disease																		
No[a]	400 352	10.9	(10.8, 11.0)	1	–	186 895	8.1	(7.9, 8.2)	1	–	213 457	13.3	(11.7, 14.9)	1	–	1.5	(1.5, 1.5)	<0.001
Yes	6644	33.3	(32.2, 34.5)	1.1	(1.1, 1.2)	3193	30.0	(29.8, 30.1)	1.2	(1.1, 1.2)	3451	36.5	(34.9, 38.1)	1.1	(1.0, 1.1)	1.2	(1.1, 1.3)	<0.001
Number of NCCDs																		
0[a]	241 589	5.8	(5.7, 5.9)	1	–	113 244	3.4	(3.3, 3.5)	1		128 345	8.0	(7.7, 8.3)	1		1.9	(1.8, 1.9)	<0.001
1	100 464	14.3	(14.1, 14.5)	1.6	(1.5, 1.6)	45 600	10.6	(10.5, 10.7)	1.8	(1.7, 1.9)	54 864	17.4	(17.1, 17.7)	1.5	(1.4, 1.5)	1.5	(1.5, 1.6)	<0.001
2	45 673	24.1	(23.7, 24.5)	2.0	(1.9, 2.1)	215 45	20.7	(20.6, 20.8)	2.5	(2.4, 2.6)	241 28	27.2	(26.8, 27.5)	1.7	(1.7, 1.8)	1.3	(1.2, 1.3)	<0.001
>2	19 270	32.8	(32.1, 33.5)	2.4	(2.4, 2.5)	9699	29.9	(29.8, 30.0)	3.2	(3.0, 3.3)	9571	35.8	(35.4, 36.1)	2.1	(2.0, 2.2)	1.2	(1.1, 1.2)	<0.001
p trend			$p < 0.001$					$p < 0.001$					$p < 0.001$					
Severity indicators																		
Pneumonia																		
No[a]	321 109	3.6	(3.5, 3.6)	1	–	157 201	2.5	(2.4, 2.6)	1	–	163 908	4.6	(4.1, 5.0)	1	–	1.7	(1.6, 1.7)	<0.001

(Continued)

Table 2 Continued

	Total					Women					Men					Women[a] vs men		
	n	CFR %	(95% CI)	RR[b]	(95% CI)[d]	n	CFR %	(95% CI)	RR[c]	(95% CI)[d]	*N*	CFR %	(95% CI)[d]	RR[c]	(95% CI)	RR by sex	(95% CI)[d]	*P*-value[f]
Yes	85 881	40.0	(39.7, 40.3)	6.6	(6.5, 6.8)	32 884	36.7	(36.6, 36.8)	8.1	(7.8, 8.4)	52 997	42.1	(41.6, 42.4)	5.9	(5.7, 6.0)	1.1	(1.1, 1.1)	<0.001
Attention mode																		
Hospital admission																		
No[a]	294 586	1.7	(1.6, 1.7)	1	–	146 841	1.1	(1.1, 1.2)	1	–	147 745	2.2	(1.9, 2.6)	1	–	1.9	(1.7, 2.0)	<0.001
Yes	112 410	36.3	(36.0, 36.6)	12.9	(12.5, 13.3)	43 247	33.2	(33.2, 33.3)	16.7	(15.9, 17.7)	69 163	38.2	(37.8, 38.6)	11.0	(10.5, 11.4)	1.1	(1.1, 1.1)	<0.001
Mechanically assisted intubation																		
No[a]	396 337	9.6	(9.5, 9.7)	1	–	186 528	7.2	(7.1, 7.3)	1	–	209 809	11.7	(10.7, 12.7)	1	–	1.5	(1.4, 1.5)	<0.001
Yes	10 659	73.1	(72.2, 73.9)	4.1	(4.0, 4.2)	3560	72.8	(72.6, 72.9)	4.8	(4.6, 5.0)	7099	73.2	(72.2, 74.2)	3.8	(3.7, 3.9)	1	(0.9, 1.0)	0.0614
Admitted to unit and intensive care																		
No[a]	398 193	10.3	(10.3, 10.4)	1	–	187 060	7.8	(7.7, 7.9)	1	–	211 133	12.6	(11.3, 13.9)	1	–	1.5	(1.4, 1.5)	<0.001
Yes	8803	51.9	(50.9, 53.0)	2.8	(2.7, 2.9)	3028	48.8	(48.7, 48.9)	3.1	(2.9, 3.2)	5775	53.6	(52.3, 54.9)	2.7	(2.6, 2.7)	1.1	(1.0, 1.1)	<0.001
Institutions of the health system[e]																		
Private	11 992	4.6	(4.3, 5.0)	1		4790	3.7	(3.2, 4.3)	1		7202	5.2	(4.3, 6.2)	1	–	1.5	(1.2, 1.7)	<0.0001
SEMAR	3184	5.9	(5.1, 6.7)	1.4	(1.2, 1.6)	1040	7.0	(6.4, 7.5)	1.9	(1.4, 2.4)	2144	5.4	(4.4, 6.4)	1.2	(0.9, 1.4)	1	(0.7, 1.3)	0.4882
SS	218 544	6.3	(6.2, 6.4)	1.5	(1.4, 1.6)	104 574	4.4	(3.9, 5.0)	1.4	(1.2, 1.6)	113 970	8.1	(7.1, 9.0)	1.6	(1.5, 1.8)	1.7	(1.6, 1.8)	<0.0001
Others	762	8.0	(6.1, 9.9)	1.3	(1.0, 1.7)	380	5.5	(4.9, 6.0)	1.2	(0.8, 1.9)	382	10.4	(9.5, 11.4)	1.4	(1.0, 1.9)	1.6	(1.0, 2.6)	0.0225
SEDENA	2831	11.2	(10.1, 12.4)	2.2	(1.9, 2.5)	943	11.1	(10.5, 11.6)	2.5	(2.0, 3.1)	1888	11.3	(10.3, 12.2)	2.1	(1.8, 2.4)	1.1	(0.9, 1.4)	0.0623
Not specified	3148	11.8	(10.7, 13.0)	2.3	(2.1, 2.6)	1416	7.9	(7.4, 8.5)	2.3	(1.8, 2.8)	1732	15.1	(14.1, 16.0)	2.4	(2.1, 2.8)	1.5	(1.3, 1.9)	<0.0001
SMH	9186	11.9	(11.2, 12.6)	2.5	(2.3, 2.8)	4537	8.7	(8.2, 9.3)	2.5	(2.2, 3.0)	4649	15.0	(14.1, 16.0)	2.6	(2.3, 2.9)	1.5	(1.3, 1.6)	<0.0001
PEMEX	5106	14.9	(14.0, 15.9)	2.3	(2.1, 2.6)	1793	14.3	(13.7, 14.8)	2.6	(2.2, 3.1)	3313	15.3	(14.3, 16.2)	2.2	(2.0, 2.5)	1.2	(1.1, 1.4)	0.0032
ISSSTE	18 026	17.9	(17.4, 18.5)	2.9	(2.7, 3.2)	8401	13.7	(13.1, 14.2)	2.9	(2.5, 3.3)	9625	21.6	(20.7, 22.6)	2.9	(2.7, 3.3)	1.4	(1.3, 1.5)	<0.0001
IMSS	134 217	18.9	(18.7, 19.1)	3.8	(3.5, 4.1)	62 214	14.7	(14.1, 15.2)	4.0	(3.5, 4.6)	72 003	22.6	(21.6, 23.6)	3.7	(3.4, 4.1)	1.4	(1.3, 1.4)	<0.0001

[a]Reference category.
[b]RR = relative risk adjusted by age and sex.
[c]RR adjusted by age.
[d]RR = relative risk with 95% confidence interval.
[e]Ministry of Health. Ministry of the Navy (SEMAR), Federal Ministry of Health (SS), Other (Red Cross, DIF, Municipal, Universitary), Ministry of National Defense (SEDENA), Statal Ministry of Health (SMH), Petroleos Mexicanos (PEMEX), Institute of Security and Social Services for State Workers (ISSSTE), Mexican Institute of Social Security (IMSS).
[f]Differences women vs men.
Data from General Direction of Health Information (DGIS), Ministry of Health, 2020.

Table 3 Case-fatality rate (CFR) in Mexican adults diagnosed with COVID-19 and categorized by number of non-communicable diseases (NCDs)

Variables	No NCDs					One NCD					Two NCDs					Three NCDs				Among NCDs
	N	CFR %	(95% CI)	RR	*n*	CFR %	(95% CI)	RR	(95% CI)	*N*	CFR %	(95% CI)	RR	(95% CI)	*n*	CFR %	(95% CI)	RR	(95% CI)	*p* trend
Sex[c]																				
Women[a]	113 244	3.4	(3.3, 3.5)	1.0	45 600	10.6	(10.3, 10.9)	1.8	(1.7, 1.9)	21 545	20.7	(20.2, 21.3)	2.5	(2.5, 2.4)	9699	29.9	(29.0, 30.8)	3.2	(3.0, 3.3)	<0.0001
Men	128 345	8.0	(7.8, 8.1)	1.0	54 864	17.4	(17.1, 17.7)	1.5	(1.4, 1.5)	24 128	27.2	(26.6, 27.7)	1.7	(1.7, 1.7)	9571	35.8	(34.8, 36.7)	2.1	(2.0, 2.2)	<0.0001
Age group[d] **(years)**																				
20–39[a]	120 764	0.9	(0.9, 1.0)	1.0	27 670	3.4	(3.2, 3.7)	3.5	(3.2, 3.8)	4924	8.3	(7.5, 9.0)	8.2	(8.2, 7.3)	1017	16.3	(14.0, 18.5)	16.1	(13.8, 18.7)	<0.0001
40–59	93 176	6.0	(5.9, 6.2)	1.0	47 162	11.3	(11.0, 11.6)	1.8	(1.8, 1.9)	20 849	16.9	(16.4, 17.4)	2.8	(2.8, 2.7)	8174	25.5	(24.5, 26.4)	4.2	(4.0, 4.4)	<0.0001
60–79	24 373	24.9	(24.3, 25.4)	1.0	22 093	29.4	(28.8, 30.0)	1.1	(1.1, 1.2)	17 169	34.1	(33.4, 34.8)	1.4	(1.4, 1.3)	8774	39.6	(38.6, 40.6)	1.6	(1.6, 1.7)	<0.0001
≥80	3276	39.4	(37.7, 41.1)	1.0	3539	44.5	(42.8, 46.1)	1.1	(1.0, 1.2)	2731	45.0	(43.1, 46.9)	1.1	(1.1, 1.1)	1305	45.9	(43.1, 48.6)	1.1	(1.1, 1.2)	<0.0001
Severity indicators																				
Pneumonia[a]																				
No[a]	208 529	1.7	(1.7, 1.8)	1.0	73 721	4.7	(4.5, 4.8)	1.6	(1.5, 1.7)	28 437	9.8	(9.5, 10.2)	2.3	(2.3, 2.2)	10 422	15.7	(15.0, 16.4)	3.2	(3.0, 3.4)	<0.0001
Yes	33 056	31.8	(31.3, 32.3)	1.0	26 742	40.9	(40.3, 41.5)	1.1	(1.1, 1.1)	17 235	47.7	(46.9, 48.4)	1.2	(1.2, 1.2)	8848	52.9	(51.9, 54.0)	1.3	(1.3, 1.4)	<0.0001
Attention mode																				
Hospital admission[a]																				
No[a]	198 400	0.8	(0.7, 0.8)	1.0	65 886	2.3	(2.2, 2.5)	1.7	(1.6, 1.9)	22 767	5.2	(4.9, 5.5)	2.6	(2.6, 2.4)	7533	9.1	(8.4, 9.7)	3.8	(3.5, 4.2)	<0.0001
Yes	43 189	29.0	(28.6, 29.4)	1.0	34 578	37.1	(36.6, 37.6)	1.1	(1.1, 1.1)	22 906	42.9	(42.2, 43.5)	1.2	(1.2, 1.2)	11 737	48.0	(47.1, 48.9)	1.3	(1.3, 1.4)	<0.0001
Mechanically assisted intubation[a]																				
No[a]	238 182	4.9	(4.8, 5.0)	1.0	96 958	12.2	(11.9, 12.4)	1.5	(1.5, 1.6)	43 224	21.2	(20.8, 21.6)	2.0	(2.0, 1.9)	17 973	29.5	(28.8, 30.1)	2.5	(2.4, 2.6)	<0.0001
Yes	3407	68.6	(67.0, 70.2)	1.0	3506	73.6	(72.2, 75.1)	1.0	(1.0, 1.0)	2449	75.2	(73.5, 76.9)	1.0	(1.0, 1.0)	1297	79.1	(76.8, 81.3)	1.1	(1.0, 1.1)	<0.0001
Admitted to unit and intensive care[e]																				
No[a]	238 685	5.3	(5.2, 5.4)	1.0	97 496	13.1	(12.9, 13.3)	1.5	(1.5, 1.6)	43 750	22.8	(22.4, 23.2)	2.0	(2.0, 1.9)	18 262	31.2	(30.5, 31.9)	2.5	(2.4, 2.5)	<0.0001
Yes	2904	46.2	(44.3, 48.0)	1.0	2968	52.6	(50.8, 54.4)	1.0	(1.0, 1.1)	1923	54.6	(52.4, 56.8)	1.1	(1.1, 1.0)	1008	61.7	(58.7, 64.7)	1.2	(1.1, 1.3)	<0.0001
Institutions of the health systemb[e,b]																				
Private[a]	7994	1.9	(1.6, 2.2)	1.0	2555	6.6	(5.6, 7.6)	2.1	(1.6, 2.6)	1038	14.2	(12.1, 16.3)	3.2	(3.2, 2.5)	405	21.9	(17.9, 26.0)	4.2	(3.2, 5.5)	<0.0001
SEMAR	2407	2.0	(1.5, 2.6)	1.0	461	13.6	(10.5, 16.8)	3.4	(2.3, 5.1)	215	21.8	(16.3, 27.3)	3.7	(3.7, 2.4)	101	29.7	(20.7, 38.6)	4.8	(3, 7.9.0)	
SS	136 772	3.1	(3.0, 3.2)	1.0	53 198	8.9	(8.6, 9.1)	1.9	(1.8, 1.9)	21 062	15.3	(14.8, 15.8)	2.4	(2.4, 2.3)	7512	20.7	(19.8, 21.6)	3.1	(2.9, 3.3)	<0.0001
Others	413	2.6	(1.1, 4.2)	1.0	190	12.6	(7.8, 17.3)	2.9	(1.4, 5.7)	101	13.8	(7.0, 20.6)	2.0	(2.0, 0.8)	58	20.6	(10.1, 31.2)	3.0	(1.3, 6.8)	<0.0001
SEDENA	1827	7.2	(6.0, 8.4)	1.0	603	15.2	(12.3, 18.1)	1.2	(0.9, 1.6)	300	24.6	(19.7, 29.5)	1.4	(1.4, 1.0)	101	19.8	(11.9, 27.6)	1.2	(0.7, 1.9)	<0.0001
Not specified	1681	6.7	(5.5, 7.9)	1.0	907	14.7	(12.4, 17.0)	1.4	(1.1, 1.8)	398	20.8	(16.8, 24.8)	1.6	(1.6, 1.2)	162	26.5	(19.7, 33.3)	1.7	(1.2, 2.4)	<0.0001
SMH	5308	7.1	(6.4, 7.8)	1.0	2253	14.2	(12.7, 15.6)	1.3	(1.1, 1.5)	1076	20.9	(18.4, 23.3)	1.4	(1.4, 1.2)	549	31.3	(27.4, 35.2)	1.6	(1.4, 1.9)	<0.0001
PEMEX	1502	6.9	(5.6, 8.2)	1.0	1970	12.2	(10.7, 13.6)	1.3	(1.1, 1.6)	984	21.6	(19.0, 24.2)	1.7	(1.7, 1.3)	650	31.8	(28.2, 35.4)	2.1	(1.7, 2.6)	<0.0001
ISSSTE	9079	9.5	(8.9, 10.1)	1.0	4756	20.9	(19.8, 22.1)	1.4	(1.3, 1.6)	2799	30.5	(28.8, 32.2)	1.7	(1.7, 1.6)	1392	37.5	(35.0, 40.1)	2.1	(1.9, 2.3)	<0.0001
IMSS	74 606	10.7	(10.5, 10.9)	1.0	33 571	22.7	(22.2, 23.1)	1.4	(1.3, 1.4)	17 700	34.7	(34.0, 35.4)	1.6	(1.6, 1.5)	8340	44.0	(42.9, 45.1)	1.9	(1.8, 1.9)	<0.0001

Data from General Direction of Health Information (DGIS), Ministry of Health, 2020.

[a]Reference category.

[b]Ministry of Health, Ministry of the Navy (SEMAR), Federal Ministry of Health (SS), Other (Red Cross, DIF, Municipal, Universitary), Ministry of National Defense (SEDENA), Statal Ministry of Health (SMH), Petroleos Mexicanos (PEMEX), Institute of Security and Social Services for State Workers (ISSSTE), Mexican Institute of Social Security (IMSS).

[c]Adjusted by age continuous.

[d]Adjusted by sex.

[e]Adjusted by age continuous and sex.

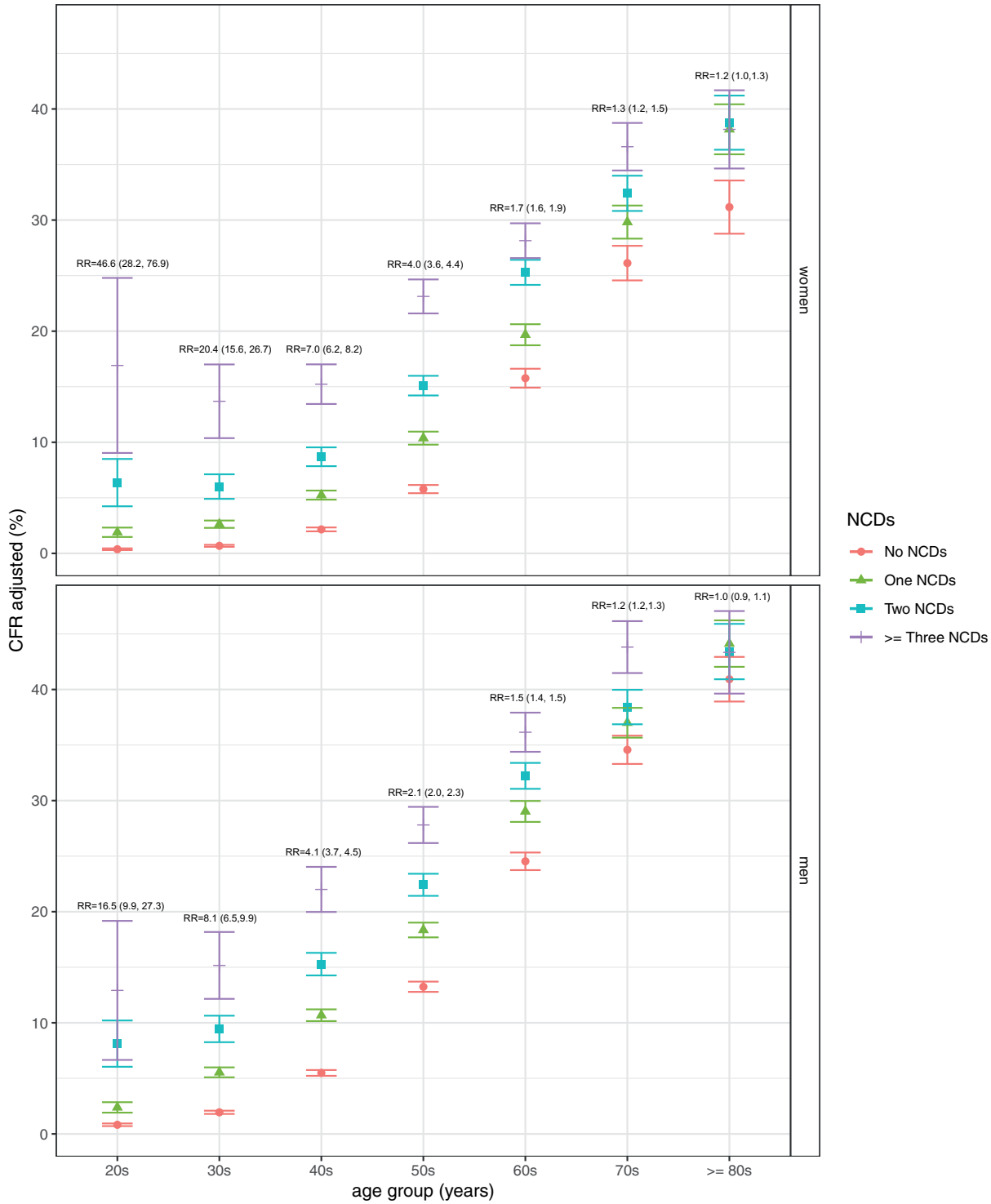

Figure 1 Case-fatality rate (CFR) estimate in adults with COVID-19 and number of non-communicable diseases (NCDs), categorized by age groups and sex. Estimations adjusted by categories of the institutions of the health system, asthma, immunosuppression and other non-specified co-morbidities. RR, relative risk (95% IC) no NCDs vs three or more NCDs. Data from General Direction of Health Information (DGIS), Ministry of Health, 2020.

prevalence found in the general Mexican adult population, in which 49.2% have at least one NCD.[24]

On the other hand, men have fewer antibodies that decrease the expression of IL-6, which is linked to deregulation of the immune system and lung damage. Likewise, men have higher concentrations of angiotensin-converting enzyme 2 (ACE2) in the alveolar membrane of the lungs through which SARS-CoV-2 enters and infects its host.[25] Consistently with

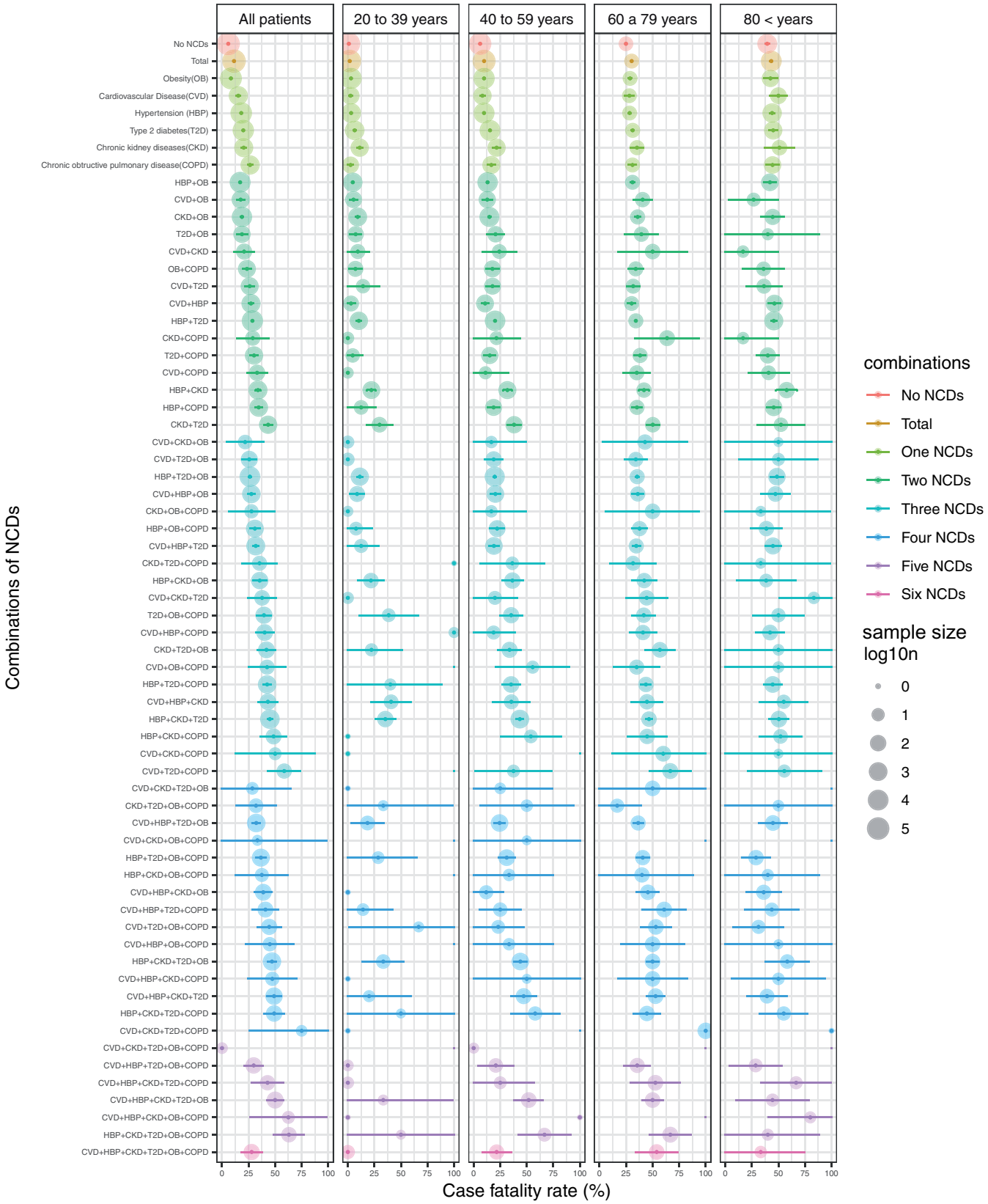

Figure 2 Case-fatality rate and combinations of non-communicable diseases (NCDs) by age groups. Data from General Direction of Health Information (DGIS), Ministry of Health, 2020.

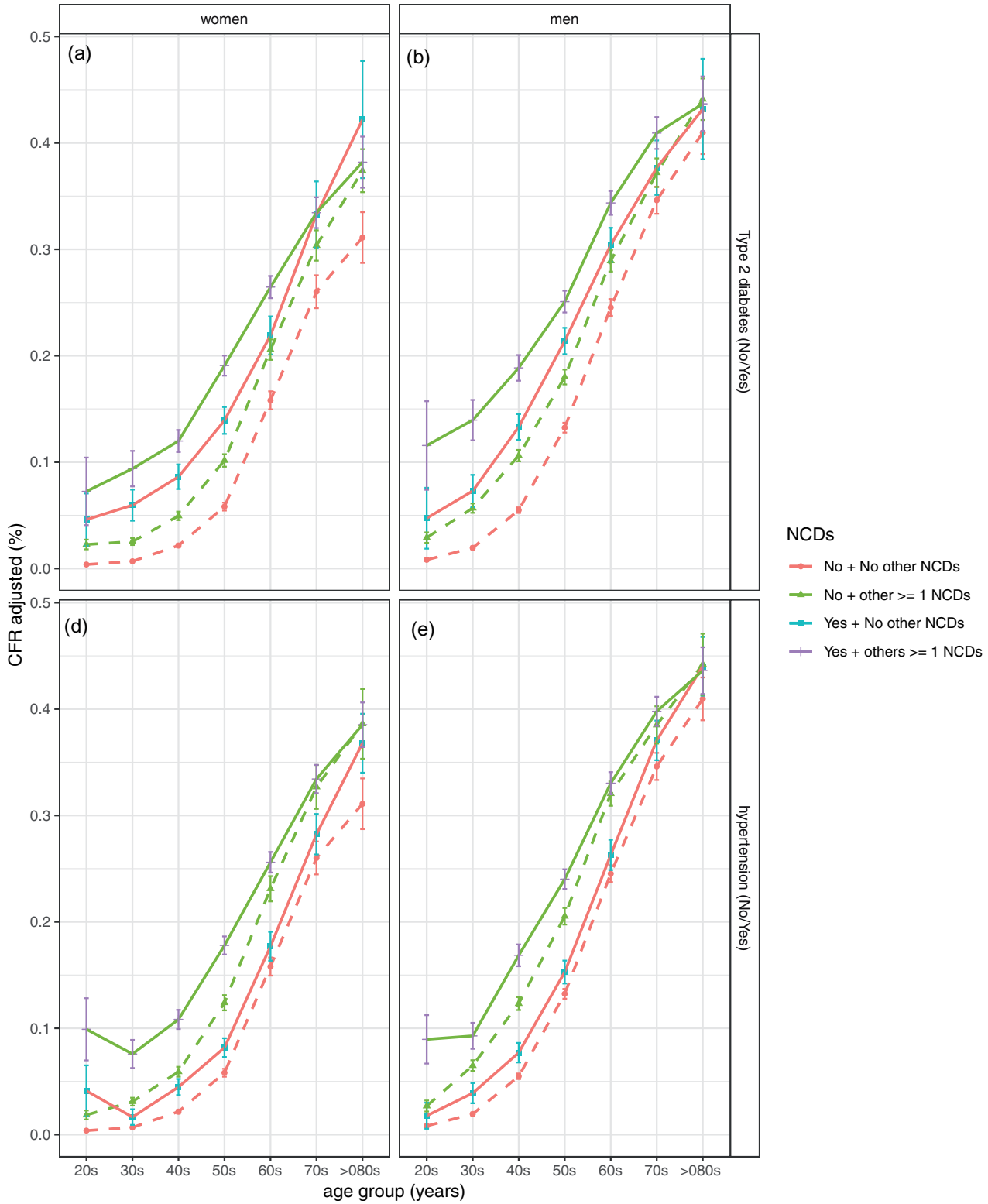

Figure 3 Case-fatality rate (CFR) in adults with COVID-19 with/without diabetes or hypertension, with/without other non-communicable diseases (NCDs). Estimations adjusted by categories of the institutions of the health system, asthma, immunosuppression and other non-specified co-morbidities. Data from General Direction of Health Information (DGIS), Ministry of Health, 2020.

this infection mechanism and men's diminished immune-system response, the CFR in our study was higher in men (CFR, 14.6) than in women (CFR, 9.1).

The number of chronic co-morbidities influences the risk of being infected with SARS-Cov-2 and dying from it.[26] People with more NCDs and of older age have a

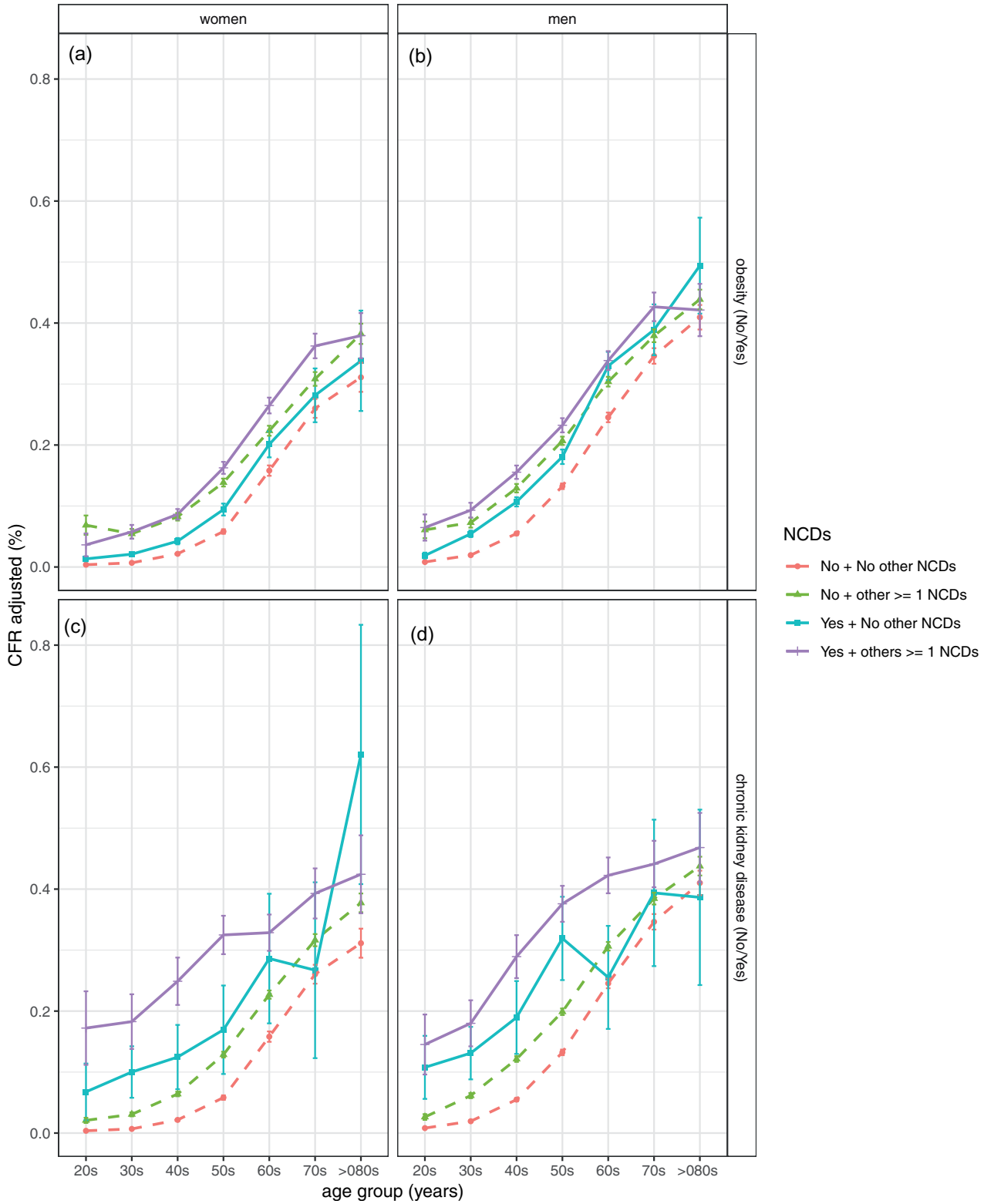

Figure 4 Case-fatality rate (CFR) in adults with COVID-19 with/without obesity or chronic kidney disease, with/without other non-communicable diseases (NCDs). Estimations adjusted by categories of the institutions of the health system, asthma, immunosuppression and other non-specified comorbidities. Data from General Direction of Health Information (DGIS), Ministry of Health, 2020.

higher risk of death.[10] In China, reports indicate that, among people ≥60 years old, the risk of death was greater among those with two or more NCDs (RR, 2.59) in comparison to those with only one NCD (RR, 1.79).[11–16] This is consistent with our findings, where risk of death was also greater in adults ≥60 years old and those with

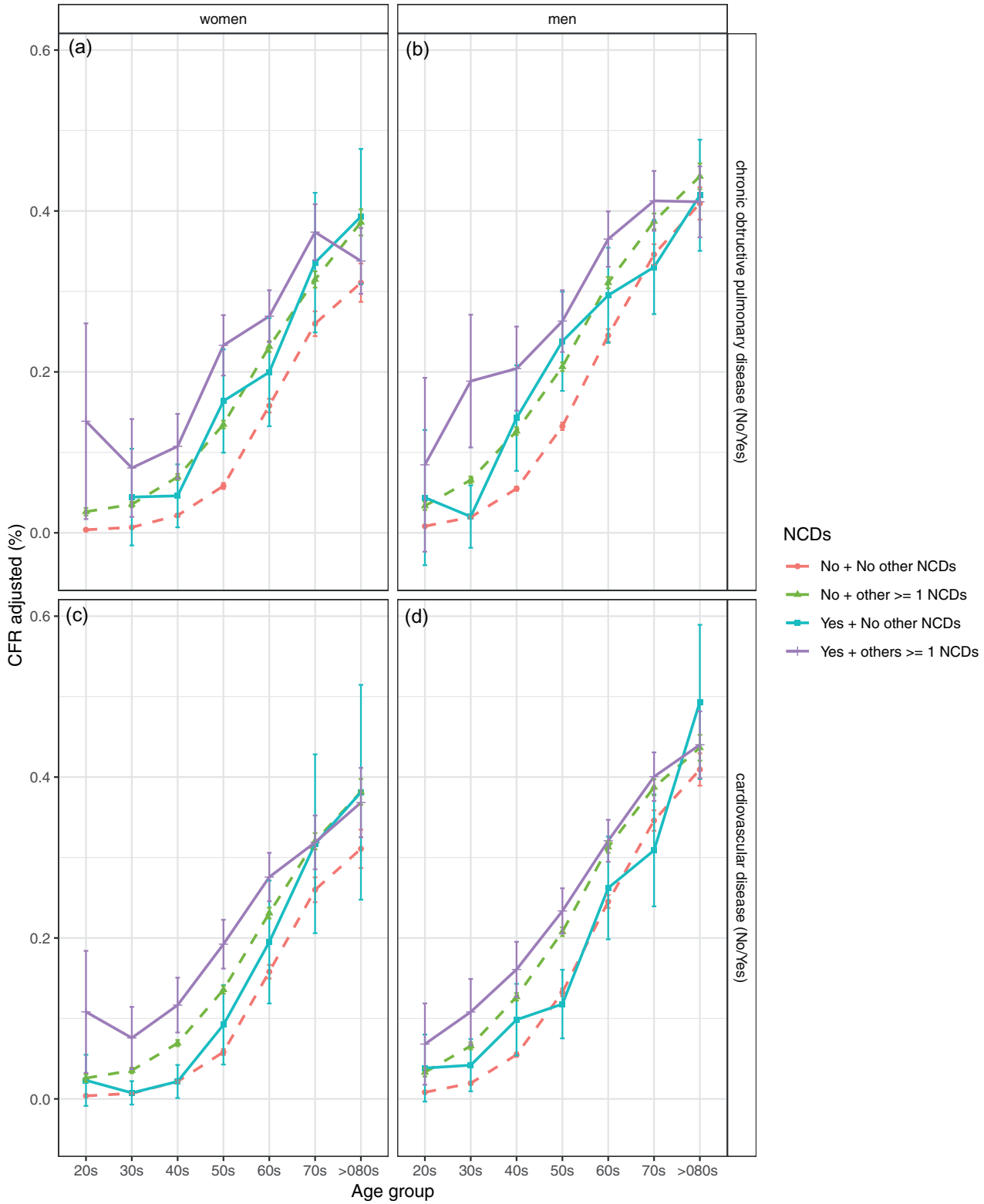

Figure 5 Case-fatality rate (CFR) in adults with COVID-19 with/without chronic obstructive pulmonary disease or cardiovascular disease, with/without other non-communicable diseases (NCDs). Estimations adjusted by categories of the institutions of the health system, asthma, immunosuppression and other non-specified co-morbidities. Data from General Direction of Health Information (DGIS), Ministry of Health, 2020.

two or more NCDs (RR, 24.1) vs those with one (RR, 14.3).

Regardless of age, adults with SARS-Cov-2 and comorbidities are at increased risk of death. Adults with SARS-Cov-2 and COPD have a higher expression of the functional receptor in the lower respiratory tract and this explains the extent of damage and the increased risk of death in patients with COPD and SARS-CoV-2.[27] COPD combined with CVD or CKD significantly increases the risk of death, due to the systemic inflammatory response induced by hypoxia, as well as the homeostatic imbalance caused by CKD.[28–30] The combination of three NCDs with the highest CFR among Mexicans was CVD+T2D+COPD. This combination is one of the most common in adults worldwide[28] and can be attributed to the fact that multiorgan failure is associated with elevated plasminogen levels, leading to coronary thrombosis and pulmonary embolism.[31] In general, we found that a greater number of NCDs increases the CFR because it reflects multiple-organ dysfunction, severity and worse prognosis.[32,33]

We observe a triple interaction between the number of NCDs, age and sex. In the group aged 20–29 years, the RR of death when having at least three NCDs compared with not having any NCDs was higher in women (RR, 46.6) than in men (RR, 16.5), unlike that in the age group ≥80 years old, in which the RR was similar between women (RR, 1.0) and men (RR, 1.2). The greater RR in women aged 20–29 years is explained by the low CFR when they did not have any NCDs (women, 0.37%; men, 0.82%) and the higher CFR observed in women when they presented with at least three NCDs (women, 16.9%; men, 12.9%). In the youngest age group (20–29 years), women with at least NCDs had a higher CFR than men. This can be explained because the youngest have risk behaviours such as high alcohol and tobacco consumption that contribute to the generation of NCDs at very early ages[34] but, in Mexico, these risk behaviours are more frequent in women than in men.[35,36]

We observed similar associations in other publications that use the same sources.[13–14–15–37] However, our research was an exhaustive analysis that focused on the effect of six NCDs. This considers that they have a similar physiopathology, based on expression of ACE2 and a deficient immune system in diabetics that delays the phagocytic and antibacterial activity of neutrophils and macrophages together with oxidative stress that also exacerbates the chronic inflammatory processes.[37,38] Thus, the smoking variable was eliminated because we do not believe it captures the tobacco habit in a robust way, as proposed by international expert recommendations.[39]

In Mexico, the difference observed in the CFR by institution providing health services may be due to the type of users treated (with formal employment or without employment, with different levels of poverty and different ages of the beneficiaries). It could also be due to the limited material and personnel infrastructure that local public institutions have (less testing capacity, especially at the beginning of the pandemic). In comparison, federal public institutions and private institutions have more availability of therapeutic supplies and intensive-care equipment. In our study, the CFR was lower in private institutions and federal public institutions. To explain these differences in more detail, a more comprehensive analysis is needed in the future.[40,41]

Limitations

We acknowledge that the main limitation of our study lies within its design, considering it is an observational study. This impedes us from making precise inferences or assuming causal relationships. We lacked information on clinical biomarkers at the time of registration to evaluate the baseline health status of the patients with SARS-Cov-2. With this information, we could have estimated, with less error and/or confounders, the effect of NCDs on mortality from SARS-Cov-2.

Another possible limitation is due to the data source, which was compiled through the Ministry of Health Epidemiologic Surveillance System and favours surveillance of high-risk cases or specific risk factors. This increases the probability of registering cases with severe symptoms and under-representing cases with lower risk who have moderate symptoms.

A third limitation of this study is that, to preserve the confidentiality of participants, the database does not include the specific medical unit in which the patients received care. It did not allow us to control for the specific effect of each healthcare unit and the clustering of observations at the healthcare unit, which may affect mainly the variance of our estimates.

A strength of our study is that it is the first to examine the association between CFR and NCDs in SARS-Cov-2 patients by correcting for the institution of care in all data of Mexican adults registered as SARS-Cov-2-positive. Our findings are consistent with those of other publications that state that NCDs increase mortality in SARS-Cov-2 cases. It therefore contributes to a better understanding of the interaction between SARS-Cov-2 and pre-existing NCDs.

Conclusion

We found that, among Mexican adults, mortality from SARS-Cov-2 increases with the number of NCDs. The

combination of diseases such as T2D, CKD, COPD and CVD that were diagnosed in young people may mean that Mexicans are exposed early to risk factors like alcohol and tobacco intake, adiposity and poor diet, and in greater magnitude. This accelerates disease onset and may explain the higher mortality in young Mexicans. Our findings are consistent with the scientific literature and contribute to the understanding of these associations. More studies are needed to understand the heterogeneity observed by mortality and type of health institution. The evidence generated by this study can be useful for decision makers in the health sector, at both population and clinical levels.

Ethics approval

The study does not require ethical review because it is based on open, anonymized data from the Mexican Ministry of Health.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

E.M.F., M.R.V., S.B.C. and I.C.N.: conceptualized the research; E.M.F. and B.H.: analysed the data; M.R.V., J.E.M. and I.C.N.: investigation; M.R.V., J.E.M., I.C.N., E.M.F. and I.C.N.: methodology; M.R.V., J.E.M., I.C.N. and E.M.F.: supervision; E.M.F., M.R.V., J.E.M., B.H., S.B.C., V.E.V.D. and I.C.N.: writing, review and editing.

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Conflict of interest

None declared.

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