


BMJ Open Influence of prior comorbidities and chronic medications use on the risk of COVID-19 in adults: a population-based cohort study in Tarragona, Spain

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ABSTRACT

Objective To investigate possible relationships between pre-existing medical conditions (including common comorbidities and chronic medications) and risk for suffering COVID-19 disease in middle-aged and older adults.

Design Population-based retrospective cohort study.

Setting Twelve primary care centres (PCCs) in Tarragona (Spain).

Participants 79 083 people (77 676 community-dwelling and 1407 nursing-home residents), who were all individuals aged >50 years affiliated to the 12 participating PCCs.

Outcomes Baseline cohort characteristics (age, sex, vaccinations, comorbidities and chronic medications) were established at study start (1st. March 2020) and primary outcome was time to COVID-19 confirmed by PCR among cohort members throughout the epidemic period (from 1st. March 2020 to 23rd. May 2020). Risk for suffering COVID-19 was evaluated by Cox regression, estimating multivariable HRs adjusted for age, sex, comorbidities and medications use.

Results During the study period, 2324 cohort members were PCR-tested, with 1944 negative and 380 positive results, which means an incidence of 480.5 PCR-confirmed COVID-19 cases per 100 000 persons-period. Assessing the total study cohort, only age (HR 1.02; 95% CI 1.01 to 1.03; p=0.002), nursing-home residence (HR 21.83; 95% CI 16.66 to 28.61; p<0.001) and receiving diuretics (HR 1.35; 95% CI 1.04 to 1.76; p=0.026) appeared independently associated with increased risk. Smoking (HR 0.62; 95% CI 0.41 to 0.93; p=0.022), ACE inhibitors (HR 0.68; 95% CI 0.47 to 0.99; p=0.046) and antihistamine (HR 0.47; 95% CI 0.22 to 1.01; p=0.052) were associated with a lower risk. Among community-dwelling individuals, cancer (HR 1.52; 95% CI 1.03 to 2.24; p=0.035), chronic respiratory disease (HR 1.82; 95% CI 1.08 to 3.07; p=0.025) and cardiac disease (HR 1.53; 95% CI 1.06 to 2.19; p=0.021) emerged to be also associated with an increased risk. Receiving ACE inhibitors (HR 0.66; 95% CI 0.44 to 0.99; p=0.046) and influenza vaccination (HR 0.63; 95% CI 0.44 to 0.91; p=0.012) was associated with decreased risk.

Strengths and limitations of this study

- This is a population-based cohort study involving 79 083 adults aged ≥50 years in Tarragona (Southern Catalonia, Spain).
- Cohort members were retrospectively followed up across the first wave of COVID-19 epidemic period from 1st. March 2020 to 23rd. May 2020.
- Relationships between PCR-confirmed COVID-19 incidence and chronic comorbidities and chronic medications use were assessed by multivariable Cox regression models.
- Despite the large size of study cohort, the number of events was relatively low, which limits statistical power (especially in subgroup analyses).
- PCR testing was not routinely performed (prioritised for patients with severe case), and asymptomatic/oligosymptomatic cases were underestimated.

Conclusion Age, nursing-home residence and multiple comorbidities appear predisposing for COVID-19. Conversely, receiving ACE inhibitors, antihistamine and influenza vaccination could be protective, which should be closely investigated in further studies specifically focused on these concerns.

INTRODUCTION

Currently, population-based clinical data on the SARS-CoV-2 coronavirus (COVID-19 disease) pandemic are limited. Furthermore, the available clinical information comes mainly from hospitalised and therefore more severe patients (especially those who required intensive care or those who died)^{1–4} and there are few community data, from primary care, covering a larger sample of the population. In fact, there is very scarce data assessing incidence and risk for suffering infection in relation to the pre-existing clinical characteristics of the population (ie, baseline risk profile

according to previous underlying conditions/medications use).^{5 6}

Earlier studies regarding clinical characteristics and prevalence of comorbidities in patients infected with SARS-CoV-2 reported that diabetes mellitus, obesity, cardiovascular disease (including hypertension), chronic respiratory diseases and smoking were major risk factors associated with severe COVID-19.¹⁻⁴

A more recent systematic review and meta-analysis has reported that COVID-19 patients with cardiovascular disease, hypertension, diabetes, congestive heart failure, chronic kidney disease and cancer have a greater risk of mortality compared with patients with COVID-19 without these comorbidities.⁷ However, these results (mainly based on hospitalised cases and observational data) were likely to be confounded by age or other conditions (including sociodemographic) and therefore concerns have been raised about the possibility that some of these comorbidities/underlying conditions increase the risk for severe disease, but they were not really related 'per se' to an increased risk of infection.

Unlike most previous studies that examined risk factors for poor prognosis, few published studies have reported characteristics associated with susceptibility to SARS-CoV-2 infection. On this, recently published primary care cohort study from the Oxford Royal College of General Practitioners in the UK has reported similar risk factors associated with positive PCR testing as observed for severe outcomes of COVID-19 in hospital settings (except for smoking) and has provided some evidence of potential sociodemographic factors associated with a positive PCR testing (including socioeconomic deprivation, population density and ethnicity).⁵

Considering the relationship between sociodemographic aspects and susceptibility for COVID-19, some studies reported that male sex and older age are associated with a higher risk of infection and a worse prognosis. However, evidence on sociodemographic and clinical disparities related to the susceptibility for SARS-COV-2 infection is limited and new studies collecting these data are needed.^{5 6 8}

Taking this situation into account, we designed this study whose objective was to investigate the incidence and risk of suffering from COVID-19 infection in adults over 50 years in Tarragona (Southern Catalonia, Spain) with pre-existing comorbidities or using chronic medications, over the first 12 weeks' pandemic period in the study area.

METHODS

Design, setting and study population

This is a retrospective cohort study involving 79 083 people aged ≥ 50 years old in the region of Tarragona (a residential-industrial urban area in Southern Catalonia, Spain, with an overall population of 210 672 all-age inhabitants). The cohort consisted of individuals ≥ 50 years old date of birth before 1st. January 1970) affiliated in the 12 participating primary care centres (PCCs) managed by

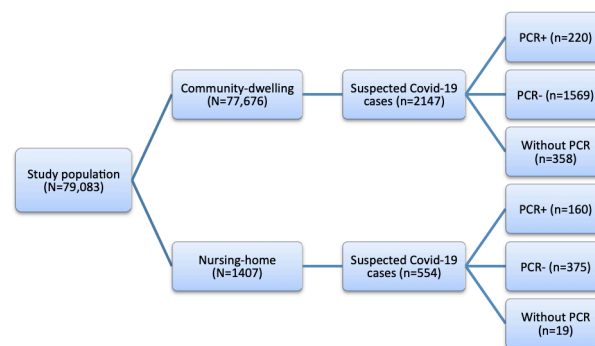


Figure 1 Flow diagram of the study.

the Institut Català de la Salut (ICS) in the study area. In the study setting (concretely 'Tarragonés', 'Alt Camp' and 'Conca de Barberà' counties), there are 16 PCCs overall. Of them, 12 PCCs (those included in this study) are managed by the ICS, whereas the remaining 4 PCCs are managed by other providers and were not included in the present study. The study cohort represents approximately 75% of overall inhabitants aged 50 years or older in the study area according to census data.⁹ Reference laboratory and hospital for the 12 participating PCCs were the Hospital Universitari Joan XXIII and its Microbiological Service in Tarragona city.

Figure 1 shows the distribution of the cohort members between nursing-home residents and community dwellings; and also the number of suspected cases and the PCR tests (positive and negative) performed in the aforementioned population subgroups.

Cohort members were retrospectively followed up from 1st. March 2020 (the beginning of the epidemic period in the region) until the occurrence of any study event (COVID-19 diagnosis) or until the end of the 12-week follow-up (23 May 2020). The study was approved by the ethical committee of the Institution (Ethics Committee IDIAP Jordi Gol, Barcelona, file 20/065-PCV) and was conducted according to the Helsinki Declaration and Spanish legislation on biomedical studies, data protection and respect for human rights.¹⁰

Data sources

The CAPAMIS Research Database, a pre-existing institutional database that we had previously used for other cohort studies carried out in our region,¹¹ was rapidly updated to become the primary data source for this epidemiological study. Briefly, this research database collects information from the electronic clinical records system (in operation since the 2000s) which is used, at the institutional level, by the PCCs in the region. It includes administrative and clinical data, such as diagnoses, coded according to the International Classification of Diseases 10th Revision (ICD-10) and it allowed us to identify sociodemographic characteristics, comorbidities, history of vaccinations and use of active drugs among cohort members to establish their baseline characteristics at the beginning of the study period (March 1, 2020).

At the start of the COVID-19 pandemic in our region, two new alerts related to laboratory records (results of diagnostic tests for SARS-CoV-2 infection) and ICD-10 codes for COVID-19 suspicion (B34.2: Unspecified coronavirus infection; B97.29: Other coronavirus as the cause of diseases classified elsewhere) were added to the electronic clinical records system. The registries provided from both data sources were linked to build an anonymised research database, which is the one we have used for this study.

Outcomes

Primary outcome was time (from study start) to COVID-19 confirmed by positive Polymerase Chain Reaction (PCR) test among cohort members throughout the study period (from March 1, 2020 to May 23, 2020). We also reported, in the descriptive analysis, cases with a negative result in the PCR test (laboratory-excluded cases) and cases of presumed COVID-19 (people who were assigned a code of clinical suspicion of the disease but no PCR test was performed).

The guidelines of the Department of Health of the *Generalitat de Catalunya* were followed for the laboratory diagnosis of COVID-19 by reverse transcription PCR (RT-PCR).¹² In summary, the Cobas SARS-CoV-2 RT-PCR technique with European Conformity and Food and Drug Administration (CE-FDA) marking was performed from samples collected by nasal and pharyngeal swabs with transport medium for viruses and refrigerated at 4°C for a maximum of 48 hours; sensitivity and specificity close to 100% have been reported for this test.¹³ When the epidemic period began, there was little availability of PCR tests, and they were prioritised for severe cases (requiring hospital admission) and for nursing-home residents (since there were several outbreaks in nursing homes), while among suspected cases of outpatient management, fewer PCR tests were conducted.

Exposure

Baseline use of common chronic medications, which could be hypothetically related to the physiopathological mechanism of SARS-CoV-2 infection or virulence (eg, antihypertensive, antiplatelet/anticoagulant and/or anti-inflammatory drugs), were considered as main explanatory variables possibly related to the occurrence of COVID-19 for the present study. It was determined by a review of the PCCs' electronic clinical records system that contains specially designated fields for medications prescribed. Thus, active medication treatments in each cohort member on 1 March 2020, coded according to the Anatomical, Therapeutic, and Chemical classification system (ATC) of the WHO,¹⁴ were identified from the patient treatment plan registered in the PCC's clinical records system, and included the following therapeutic groups: antihypertensive (diuretics, beta-blockers, ACE inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers, statins, anticoagulants (warfarin and new oral anticoagulant drugs), antiplatelet

drugs, antidiabetic drugs (insulin, oral antidiabetic drugs), inhaled respiratory drugs, antineoplastic agents, systemic corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), chloroquine/hydroxychloroquine, antihistamines, proton-pump inhibitors and benzodiazepines (see online supplemental appendix).

Covariates

Besides age, sex, residence (community-dwelling/nursing-home) and vaccinations' history (influenza vaccination in prior autumn or pneumococcal vaccination at any time), the following comorbidities/underlying conditions, obtained from the registries in the electronic PCCs clinical records on 1 March 2020, were considered: neurological disease (including dementia and stroke), cancer (solid organ or haematological neoplasia diagnosed in the past 5 years), chronic renal failure, systemic autoimmune rheumatic diseases (including rheumatoid arthritis and lupus), chronic respiratory disease (including chronic bronchitis/emphysema and/or asthma), chronic heart disease (including congestive heart failure, coronary artery disease and other cardiopathies), atrial fibrillation, chronic liver disease (including chronic hepatitis and cirrhosis), hypertension, diabetes mellitus, hypercholesterolaemia, obesity and smoking (see online supplemental appendix). Comorbidities were chosen on the basis of immunocompromise degree and risk for severe respiratory illness as usually used in other studies about community-acquired pneumonia.¹¹

Statistical analyses

We calculated the incidence rates (IRs), with their corresponding 95% confidence intervals (CIs)—estimated assuming a Poisson distribution for uncommon events—for PCR-confirmed COVID-19 per 100 000 person-period (12 weeks). The baseline characteristics of the individuals, based on whether or not they had COVID-19, were compared using χ^2 or Fisher's test as appropriate, in bivariate analyses.

Cox regression analyses were used to calculate unadjusted and multivariable-adjusted hazard ratios (HRs) to estimate the association between baseline exposure conditions and the time to PCR-confirmed COVID-19 diagnosis among cohort members throughout the epidemic period (from March 1, 2020 to May 23, 2020). The multivariable Cox models were made with all above-mentioned exposure variables and covariables (ie, age, sex, residence, vaccinations history, comorbidities/underlying conditions and medications use). The method to select a subset of covariables to include in the final model was the purposeful selection. The final models include significant, confounders and all covariables judged clinically or epidemiologically relevant. A main analysis was performed for the entire study cohort (N=79 083) as well as two subgroup analyses for community-dwelling individuals (n=77 676) and for nursing-home residents (n=1 407). The level of statistical significance was established at

Table 1 Incidence of PCR-confirmed COVID-19 cases according to baseline demographic and clinical characteristics (comorbidities/medications) in the total study cohort (N=79083): Tarragona region (Southern Catalonia, Spain), March 1, 2020– May23, 2020

Characteristic	Study population (N=79083) n (%)	PCR-confirmed COVID-19 cases (n=380)	
		Univariate analysis n (%) p value	Incidence rate
Sociodemographic			
Age			
50–64 years	42 684 (54.0)	101 (26.6) <0.001	236.6 (193.6–288.7)
65–79 years	26 013 (32.9)	95 (25.0)	365.2 (295.4–452.9)
≥80 years	10 386 (13.1)	184 (48.4)	1771.6 (1527.1–2055.1)
Sex			
Men	37 626 (47.6)	158 (41.6) 0.019	419.9 (358.6–491.7)
Women	41 457 (52.4)	222 (58.4)	535.5 (464.8–616.4)
Community-dwelling	77 676 (98.2)	220 (57.9) <0.001	283.2 (245.8–326.0)
Nursing-home residence	1 407 (1.8)	160 (42.1)	11 371.7 (9711.4–13316.3)
Comorbidities			
Neurological disease	2 317 (2.9)	66 (17.4) <0.001	2848.5 (2236.1–3617.6)
Renal disease	4 476 (5.7)	49 (12.9) <0.001	1094.7 (812.3–1445.0)
Cancer	6 630 (8.4)	49 (12.9) 0.001	739.1 (548.4–975.6)
Rheumatic disease	872 (1.1)	2 (0.5) 0.281	229.4 (27.8–828.0)
Respiratory disease	7 272 (9.2)	63 (16.6) <0.001	866.3 (667.1–1126.2)
Cardiac disease	13 435 (17.0)	123 (32.4) <0.001	915.5 (762.6–1098.6)
Atrial fibrillation	3 786 (4.8)	55 (14.5) <0.001	1452.7 (1077.9–1917.6)
Liver disease	1 465 (1.9)	8 (2.1) 0.714	546.1 (235.4–1075.8)
Diabetes	13 317 (16.8)	102 (26.8) <0.001	765.9 (626.5–934.4)
Hypertension	34 945 (44.2)	223 (58.7) <0.001	638.1 (553.9–734.5)
Hypercholesterolaemia	27 314 (34.5)	133 (35.0) 0.850	486.9 (411.0–576.5)
Obesity	21 678 (27.4)	96 (25.3) 0.347	442.8 (362.2–540.3)
Smoking	12 750 (16.1)	27 (7.1) <0.001	211.8 (139.6–309.2)
Chronic medications use			
Diuretics	8 481 (10.7)	111 (29.2) <0.001	1308.8 (1090.2–1570.6)
Beta-blockers	9 571 (12.1)	68 (17.9) 0.001	710.5 (557.7–902.3)
ACEIs	16 419 (20.8)	92 (24.2) 0.097	560.3 (453.3–694.8)
ARBs	8 869 (11.2)	39 (10.3) 0.556	439.7 (314.0–598.0)
Calcium channel blockers	6 490 (8.2)	52 (13.7) <0.001	801.2 (594.5–1057.6)
Statins	16 134 (20.4)	69 (18.2) 0.277	427.7 (335.7–543.1)
Oral anticoagulants	3 912 (4.9)	46 (12.1) <0.001	1175.9 (857.2–1575.7)
Antiplatelet drugs	9 154 (11.6)	86 (22.6) <0.001	939.5 (760.0–1165.0)
Insulin	3 042 (3.8)	39 (10.3) <0.001	1282.1 (915.4–1743.6)
Oral antidiabetic drugs	10 585 (13.4)	69 (18.2) 0.006	651.9 (511.7–827.9)
Inhaled respiratory drugs	6 293 (8.0)	61 (16.1) <0.001	969.3 (746.4–1260.1)
Antineoplastic agents	1 614 (2.0)	8 (2.1) 0.929	495.7 (213.6–976.5)
Systemic corticosteroids	1 252 (1.6)	5 (1.3) 0.676	399.4 (129.4–930.5)
NSAIDs	4 321 (5.5)	12 (3.2) 0.047	277.7 (143.6–486.0)
Chloroquine	168 (0.2)	0 (0.0) 0.367	0 (–)
Antihistamines	3 264 (4.1)	7 (1.8) 0.025	214.5 (86.0–446.1)
Proton-pump inhibitors	17 931 (22.7)	142 (37.4) <0.001	791.9 (668.4–937.6)

Continued

Table 1 Continued

Characteristic	Study population (N=79 083) n (%)	PCR-confirmed COVID-19 cases (n=380)	
		Univariate analysis n (%) p value	Incidence rate
Benzodiazepines	13 046 (16.5)	96 (25.3) <0.001	735.9 (601.9–897.7)
Vaccination's history			
Influenza vaccine in prior autumn	22 606 (28.6)	205 (53.9) <0.001	906.8 (787.1–1043.8)
Pneumococcal vaccinated	26 183 (33.1)	213 (56.1) <0.001	813.5 (706.1–936.3)

P values in univariate analysis were calculated by χ^2 , or Fisher's test as appropriate, comparing percentages in the study population versus COVID-19 cases; IR denotes incidence rates per 100 000 persons-period (12 weeks); CIs denotes confidence intervals for incidence rates and were calculated assuming a Poisson distribution for uncommon events.

ACEIs, ACE inhibitors; ARBs, angiotensin II receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs.

$p < 0.05$ (two-tailed). IBM SPSS Statistics for Windows V.24 (IBM Corp.) was used to analyse the data.

This methodology is very similar to the one reported in a previous article from the authors published in *Journal of Clinical Hypertension* (JCH).¹⁵ Both articles are part of the same project. Unlike the one published in JCH, the current article reports results referring to the total study population, distinguishing between community-dwelling and nursing-home residents and extends the analysis period until May 23.

RESULTSE

Across the study period, an amount of 2324 cohort members were PCR tested. Of them, 380 (16.4%) presented a positive result (PCR-confirmed COVID-19) and 1944 (83.6%) presented a negative result. Additionally, 377 cohort members with presumptive COVID-19 (clinical suspicion alone) were not PCR tested.

As compared with the structure of the study population (54% aged 50–64 years vs 46% aged ≥ 65 years, 47.6% men vs 52.4% women, 98.2% community-dwelling vs 1.8% nursing-home residents), PCR testing was more frequently performed among elderly people and nursing-home residents. Indeed, PCR was tested (positive plus negative results) in 930 (40%) people aged 50–64 years versus 1394 (60%) in aged ≥ 65 years ($p < 0.001$), 1023 (44%) in men versus 1301 (56%) in women ($p = 0.007$) and 1789 (77%) in community-dwelling versus 535 (23%) in nursing-home residents ($p < 0.001$).

Of the 380 PCR-confirmed COVID-19 cases, 158 (41.6%) occurred in men and 222 (58.4%) in women. By age groups, 101 (26.6%) occurred in people aged 50–64 years, 95 (25%) in aged 65–79 years and 184 (48.4%) in 80 years or older. By residence, 160 cases (42.1%) occurred in nursing-home residents and 220 (57.9%) in community-dwelling individuals. This means an overall IR of 480.5 PCR-confirmed COVID-19 cases per 100 000 persons-period (236.6 in 50–64 years vs 365.2 in 65–79 years vs 1771.6 in 80 years or older; 419.9 in men vs 535.5 in women)

The most prevalent pre-existing comorbidities/underlying conditions among the 380 patients with COVID-19 were hypertension (58.7%), hypercholesterolaemia (35%), chronic cardiac disease (32.4%), diabetes (26.8%) and obesity (25.3%).

By underlying conditions, maximum IRs (per 100 000 persons-period) emerged among those persons with neurological diseases (2848.5) followed by atrial fibrillation (1452.7), chronic renal failure (1094.7), chronic heart disease (915.5), chronic respiratory disease (866.3), diabetes (765.9), cancer (739.1) and hypertension (638.1). Lower IRs were observed among persons with rheumatic diseases (229.4) and smokers (211.8). According to pre-existing active medications, maximum IRs (per 100 000) appeared among those receiving diuretics (1308.8), insulin (1282.1), oral anticoagulants (1175.9) and inhaled-respiratory therapy (969.3) (table 1).

Table 2 shows unadjusted and multivariable-adjusted analyses evaluating risk for suffering PCR-confirmed COVID-19 in the total study cohort. In the unadjusted analysis, many underlying conditions and medications use were associated with an increased risk. However, after multivariable adjustment, only age (HR 1.02; 95% CI 1.01 to 1.03; $p = 0.002$), nursing-home residence (HR 21.83; 95% CI 16.66 to 28.61; $p < 0.001$) and receiving diuretics (HR 1.35; 95% CI 1.04 to 1.76; $p = 0.026$) appeared significantly associated with an increased risk. Conversely, smoking (HR 0.62; 95% CI 0.41 to 0.93; $p = 0.022$), receiving ARBs (HR 0.68; 95% CI: 0.47 to 0.99; $p = 0.046$) and antihistamines (HR 0.47; 95% CI 0.22 to 1.01; $p = 0.052$) appeared associated with a reduced risk.

Among community-dwelling individuals ($n = 77 676$), 1789 people were PCR tested. Of them, 1569 (87.7%) presented a negative result and 220 (12.3%) a positive result. Additionally, 358 people were codified as presumptive COVID-19 cases (clinical suspicion without PCR performed). Table 3 shows the distribution of PCR-confirmed COVID-19 cases and specific IRs by demographic characteristics, underlying conditions and

**Table 2** Cox regression analyses assessing unadjusted and adjusted risks to suffer PCR-confirmed COVID-19 in the total study cohort (N=79083): Tarragona region (Southern Catalonia, Spain) from 1st. March 2020 to 23rd. May 2020

Characteristic	LC-COVID-19 cases (n=349)	
	Unadjusted HR (95% CI) P value	Adjusted HR (95% CI) P value
Sociodemographic		
Age (continuous years)	1.07 (1.07 to 1.08) <0.001	1.02 (1.01 to 1.03) 0.002
Sex: women	1.28 (1.04 to 1.57) 0.019	0.95 (0.76 to 1.18) 0.624
Nursing-home residence	42.14 (34.37 to 51.66) <0.001	21.83 (16.66 to 28.61) <0.001
Comorbidities		
Neurological disease	7.03 (5.39 to 9.16) <0.001	1.31 (0.97 to 1.77) 0.074
Renal disease	2.47 (1.83 to 3.34) <0.001	0.91 (0.66 to 1.26) 0.556
Cancer	1.62 (1.20 to 2.19) 0.002	1.17 (0.86 to 1.60) 0.315
Rheumatic disease	0.47 (0.12 to 1.90) 0.293	0.54 (0.13 to 2.19) 0.386
Respiratory disease	1.97 (1.50 to 2.58) <0.001	1.29 (0.89 to 1.87) 0.184
Cardiac disease	2.34 (1.89 to 2.90) <0.001	1.04 (0.80 to 1.34) 0.790
Atrial fibrillation	3.38 (2.54 to 4.50) <0.001	1.17 (0.74 to 1.84) 0.514
Liver disease	1.14 (0.57 to 2.30) 0.712	1.16 (0.57 to 2.35) 0.684
Diabetes	1.81 (1.45 to 2.27) <0.001	1.10 (0.73 to 1.65) 0.646
Hypertension	1.80 (1.46 to 2.20) <0.001	0.98 (0.74 to 1.29) 0.869
Hypercholesterolaemia	1.02 (0.83 to 1.26) 0.851	0.88 (0.70 to 1.11) 0.269
Obesity	0.89 (0.71 to 1.13) 0.344	0.87 (0.68 to 1.11) 0.262
Smoking	0.40 (0.27 to 0.59) <0.001	0.62 (0.41 to 0.93) 0.022
Chronic medications use		
Diuretics	3.45 (2.76 to 4.30) <0.001	1.35 (1.04 to 1.76) 0.026
Beta blockers	1.59 (1.22 to 2.06) 0.001	0.96 (0.72 to 1.29) 0.790
ACEIs	1.22 (0.96 to 1.54) 0.098	0.85 (0.65 to 1.13) 0.260
ARBs	0.90 (0.65 to 1.26) 0.552	0.68 (0.47 to 0.99) 0.046
Calcium channel blockers	1.77 (1.32 to 2.38) <0.001	1.31 (0.95 to 1.79) 0.096
Statins	0.87 (0.67 to 1.12) 0.276	0.82 (0.60 to 1.11) 0.200
Oral anticoagulants	2.65 (1.95 to 3.61) <0.001	1.26 (0.76 to 2.07) 0.371
Antiplatelet drugs	2.24 (1.76 to 2.85) <0.001	1.35 (1.00 to 1.81) 0.051
Insulin	2.87 (2.06 to 3.99) <0.001	1.47 (0.98 to 2.21) 0.065
Oral antidiabetic drugs	1.44 (1.11 to 1.86) 0.007	1.05 (0.69 to 1.59) 0.823
Inhaled respiratory drugs	2.22 (1.69 to 2.92) <0.001	1.24 (0.84 to 1.81) 0.275
Antineoplastic agents	1.03 (0.51 to 2.08) 0.929	1.06 (0.51 to 2.20) 0.876
Systemic corticosteroids	0.83 (0.34 to 2.00) 0.677	0.57 (0.23 to 1.40) 0.218
NSAIDs	0.57 (0.32 to 1.00) 0.051	1.04 (0.58 to 1.87) 0.901
Antihistamines	0.44 (0.21 to 0.92) 0.029	0.47 (0.22 to 1.01) 0.052
Proton-pump inhibitors	2.04 (1.66 to 2.51) <0.001	0.93 (0.72 to 1.19) 0.557
Benzodiazepines	1.72 (1.36 to 2.16) <0.001	1.25 (0.98 to 1.60) 0.072
Vaccination's history		
Influenza vaccine in prior autumn	2.93 (2.40 to 3.59) <0.001	1.02 (0.79 to 1.32) 0.878
Pneumococcal vaccination	2.58 (2.11 to 3.16) <0.001	1.02 (0.78 to 1.33) 0.904

HRs denotes hazard ratios and were calculated for those who had the condition as compared with those who had not the condition. In adjusted analysis, the HRs were adjusted for age (continuous years), sex, residence, comorbidities/underlying conditions and chronic medications use. CIs denotes confidence intervals.

ACEIs, ACE inhibitors; ARBs, angiotensin II receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs .

Table 3 Incidence of PCR-confirmed COVID-19 cases according to baseline demographic and clinical characteristics (comorbidities/medications) in subgroup analysis restricted to community-dwelling individuals (n=77 676): Tarragona region (Southern Catalonia, Spain), March 1, 2020– May 23, 2020

Characteristic	Study population (N=77 676) n (%)	PCR-confirmed COVID-19 cases (n=220)	
		Univariate analysis n (%) p value	Incidence rate
Sociodemographic			
Age			
50–64 years	42 533 (54.8)	99 (45.0) <0.001	232.8 (190.4–284.0)
65–79 years	25 713 (33.1)	72 (32.7)	280.0 (219.8–355.6)
≥80 years	9 430 (12.1)	49 (22.3)	519.6 (385.6–685.9)
Sex			
Men	37 145 (47.8)	108 (49.1) 0.706	290.8 (237.8–354.7)
Women	40 531 (52.2)	112 (50.9)	276.3 (230.2–331.6)
Comorbidities			
Neurological disease	1 951 (2.5)	11 (5.0) 0.018	563.8 (281.3–1009.2)
Renal disease	4 240 (5.5)	26 (11.8) <0.001	613.2 (400.4–901.4)
Cancer	6 463 (8.3)	32 (14.5) 0.001	495.1 (334.2–708.0)
Rheumatic disease	860 (1.1)	1 (0.5) 0.354	116.3 (2.9–647.7)
Respiratory disease	7 075 (9.1)	47 (21.4) <0.001	664.3 (484.3–890.2)
Cardiac disease	12 925 (16.6)	68 (30.9) <0.001	526.1 (413.0–668.2)
Atrial fibrillation	3 561 (4.6)	26 (11.8) <0.001	730.1 (476.8–1073.3)
Liver disease	1 438 (1.9)	6 (2.7) 0.334	417.2 (153.1–909.6)
Diabetes	12 926 (16.6)	50 (22.7) 0.015	386.8 (287.0–510.6)
Hypertension	33 996 (43.8)	112 (50.9) 0.032	329.5 (274.4–395.3)
Hypercholesterolaemia	26 766 (34.5)	74 (33.6) 0.797	276.5 (217.0–351.1)
Obesity	21 344 (27.5)	57 (25.9) 0.602	267.1 (205.6–347.2)
Smoking	12 640 (16.3)	19 (8.6) 0.002	150.3 (90.5–234.5)
Chronic medications use			
Diuretics	8 028 (10.3)	51 (23.2) <0.001	635.3 (471.4–838.6)
Beta-blockers	9 312 (12.0)	40 (18.2) 0.005	429.6 (306.7–584.2)
ACEIs	16 031 (20.6)	41 (18.6) 0.462	255.8 (182.6–347.8)
ARBs	8 709 (11.2)	29 (13.2) 0.354	333.0 (223.1–479.5)
Calcium channel blockers	6 316 (8.1)	27 (12.3) 0.024	427.5 (281.7–624.1)
Statins	15 911 (20.5)	47 (21.4) 0.746	295.4 (215.3–395.8)
Oral anticoagulants	3 741 (4.8)	27 (12.3) <0.001	721.7 (475.6–1053.7)
Antiplatelet drugs	8 810 (11.3)	40 (18.2) 0.001	454.0 (324.2–617.5)
Insulin	2 904 (3.7)	20 (9.1) <0.001	688.7 (420.8–1060.6)
Oral antidiabetic drugs	10 352 (13.3)	34 (15.5) 0.353	328.4 (228.9–456.5)
Inhaled respiratory drugs	6 095 (7.8)	42 (19.1) <0.001	689.1 (492.0–937.2)
Antineoplastic agents	1 581 (2.0)	2 (0.9) 0.236	126.5 (15.3–456.7)
Systemic corticosteroids	1 216 (1.6)	5 (2.3) 0.397	411.2 (133.2–958.1)
NSAIDs	4 305 (5.5)	12 (5.5) 0.955	278.7 (144.1–487.8)
Antihistamines	3 221 (4.1)	6 (2.7) 0.290	186.3 (68.4–406.1)
Proton-pump inhibitors	17 315 (22.3)	74 (33.6) <0.001	427.4 (335.5–542.8)
Benzodiazepines	12 654 (16.3)	49 (22.3) 0.016	387.2 (287.3–511.1)
Vaccination's history			
Influenza vaccine in prior autumn	21 570 (27.8)	70 (31.8) 0.179	324.5 (254.8–412.1)
Pneumococcal vaccinated	25 224 (32.5)	100 (45.5) <0.001	396.4 (324.3–483.7)

P values in univariate analysis were calculated by χ^2 , or Fisher's test as appropriate, comparing percentages in the study population versus COVID-19 cases; IR denotes incidence rates per 100 000 persons-period (12 weeks); CIs denotes confidence intervals for incidence rates and were calculated assuming a Poisson distribution for uncommon events.

ACEIs, ACE inhibitors; ARBs, angiotensin II receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs .

**Table 4** Cox regression analyses assessing unadjusted and adjusted risks to suffer PCR-confirmed COVID-19 among community-dwelling individuals (n=77676): Tarragona region (Southern Catalonia, Spain), March 1, 2020– May 23, 2020

Characteristic	LC-COVID-19 cases (n=201)	
	Unadjusted HR (95% CI) p value	Adjusted HR (95% CI) p value
Sociodemographic		
Age (continuous years)	1.03 (1.02 to 1.04) <0.001	1.01 (0.99 to 1.02) 0.573
Sex: women	0.95 (0.73 to 1.24) 0.708	0.97 (0.73 to 1.28) 0.807
Comorbidities		
Neurological disease	2.04 (1.12 to 3.75) 0.021	1.06 (0.56 to 2.01) 0.857
Renal disease	2.32 (1.54 to 3.50) <0.001	1.22 (0.77 to 1.94) 0.398
Cancer	1.88 (1.29 to 2.73) 0.001	1.52 (1.03 to 2.24) 0.035
Rheumatic disease	0.41 (0.06 to 2.91) 0.371	0.41 (0.06 to 2.97) 0.375
Respiratory disease	2.72 (1.97 to 3.75) <0.001	1.82 (1.08 to 3.07) 0.025
Cardiac disease	2.24 (1.69 to 2.99) <0.001	1.53 (1.06 to 2.19) 0.021
Atrial fibrillation	2.79 (1.86 to 4.21) <0.001	1.06 (0.48 to 2.33) 0.882
Liver disease	1.49 (0.66 to 3.35) 0.336	1.24 (0.54 to 2.83) 0.608
Diabetes	1.47 (1.08 to 2.02) 0.016	1.26 (0.70 to 2.28) 0.441
Hypertension	1.33 (1.02 to 1.74) 0.034	1.06 (0.72 to 1.55) 0.785
Hypercholesterolaemia	0.96 (0.73 to 1.28) 0.798	0.88 (0.64 to 1.20) 0.405
Obesity	0.92 (0.68 to 1.25) 0.599	0.75 (0.54 to 1.03) 0.076
Smoking	0.49 (0.30 to 0.78) 0.003	0.49 (0.30 to 0.80) 0.004
Chronic medications use		
Diuretics	2.62 (1.92 to 3.58) <0.001	1.54 (1.04 to 2.27) 0.031
Beta blockers	1.63 (1.16 to 2.30) 0.005	1.02 (0.69 to 1.52) 0.909
ACEIs	0.88 (0.63 to 1.24) 0.462	0.66 (0.44 to 0.99) 0.046
ARBs	1.20 (0.81 to 1.78) 0.356	0.75 (0.47 to 1.19) 0.222
Calcium channel blockers	1.58 (1.06 to 2.36) 0.026	1.21 (0.78 to 1.87) 0.395
Statins	1.05 (0.76 to 1.46) 0.747	0.72 (0.49 to 1.06) 0.094
Oral anticoagulants	2.77 (1.85 to 4.14) <0.001	1.58 (0.71 to 3.48) 0.261
Antiplatelet drugs	1.74 (1.23 to 2.45) 0.002	1.30 (0.84 to 2.02) 0.243
Insulin	2.58 (1.63 to 4.08) <0.001	1.79 (1.00 to 3.21) 0.059
Oral antidiabetic drugs	1.19 (0.82 to 1.71) 0.356	0.73 (0.40 to 1.32) 0.295
Inhaled respiratory drugs	2.78 (1.99 to 3.89) <0.001	1.41 (0.81 to 2.45) 0.225
Antineoplastic agents	0.44 (0.11 to 1.78) 0.250	0.36 (0.09 to 1.49) 0.159
Systemic corticosteroids	1.46 (0.60 to 3.55) 0.400	1.03 (0.41 to 2.58) 0.945
NSAIDs	0.99 (0.55 to 1.76) 0.959	1.17 (0.65 to 2.12) 0.600
Antihistamines	0.65 (0.29 to 1.46) 0.294	0.51 (0.23 to 1.16) 0.109
Proton-pump inhibitors	1.77 (1.34 to 2.34) <0.001	1.11 (0.79 to 1.57) 0.555
Benzodiazepines	1.48 (1.07 to 2.03) 0.017	1.26 (0.90 to 1.76) 0.186
Vaccination's history		
Influenza vaccine in prior autumn	1.21 (0.91 to 1.61) 0.182	0.63 (0.44 to 0.91) 0.012
Pneumococcal vaccination	1.73 (1.33 to 2.26) <0.001	1.29 (0.86 to 1.92) 0.214

HRs denotes hazard ratios and were calculated for those who had the condition as compared with those who did not have the condition. In multivariable-adjusted analysis, HRs were adjusted for age (continuous years), sex, residence, comorbidities/underlying conditions and chronic medications use. CIs denote confidence intervals.

ACEIs, ACE inhibitors; ARBs, angiotensin II receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs .

Table 5 Univariate and multivariate analyses on laboratory-confirmed COVID-19 cases according to baseline demographic and clinical characteristics (comorbidities/medications) in subgroup analysis restricted to nursing-home residents (n=1407): Tarragona region (Southern Catalonia, Spain) from 1st. March 2020 to 23rd. May 2020

Characteristic	Study population (N=1407) n (%)	PCR-confirmed COVID-19 cases (n=160)	
		Univariate analysis n (%) p value	Multivariate analysis HR (95% CI) p value
Sociodemographic			
Age			
50–64 years	151 (10.7)	2 (1.3) <0.001	1.00 (reference)
65–79 years	300 (21.3)	23 (14.4)	6.66 (1.53 to 29.02) 0.012
≥80 years	956 (67.9)	135 (84.4)	13.16 (3.09 to 56.00) <0.001
Sex			
Men	481 (34.2)	50 (31.3) 0.406	1.00 (reference)
Women	926 (65.8)	110 (68.8)	0.85 (0.59 to 1.24) 0.402
Comorbidities			
Neurological disease	366 (26.0)	55 (34.4) 0.010	1.25 (0.89 to 1.76) 0.193
Renal disease	236 (16.8)	23 (14.4) 0.388	0.68 (0.43 to 1.08) 0.104
Cancer	167 (11.9)	17 (10.6) 0.605	0.74 (0.43 to 1.26) 0.264
Rheumatic disease	12 (0.9)	1 (0.6) 0.739	0.86 (0.12 to 6.43) 0.885
Respiratory disease	197 (14.0)	16 (10.0) 0.121	0.72 (0.39 to 1.31) 0.280
Cardiac disease	510 (36.2)	55 (34.4) 0.601	0.76 (0.52 to 1.09) 0.137
Atrial fibrillation	225 (16.0)	29 (18.1) 0.434	1.25 (0.71 to 2.20) 0.436
Liver disease	27 (1.9)	2 (1.3) 0.512	0.70 (0.17 to 2.88) 0.618
Diabetes	391 (27.8)	52 (32.5) 0.158	1.08 (0.63 to 1.85) 0.786
Hypertension	949 (67.4)	111 (69.4) 0.581	0.89 (0.60 to 1.33) 0.562
Hypercholesterolaemia	548 (38.9)	59 (36.9) 0.568	0.90 (0.64 to 1.26) 0.525
Obesity	334 (23.7)	39 (24.4) 0.841	1.10 (0.75 to 1.61) 0.617
Smoking	8 (5.0)	110 (7.8) 0.158	1.47 (0.68 to 3.17) 0.323
Chronic medications use			
Diuretics	453 (32.2)	60 (37.5) 0.127	1.19 (0.83 to 1.70) 0.342
Beta blockers	259 (18.4)	28 (17.5) 0.753	0.90 (0.57 to 1.41) 0.642
ACEIs	388 (27.6)	51 (31.9) 0.196	1.01 (0.69 to 1.47) 0.981
ARBs	160 (11.4)	10 (6.3) 0.030	0.45 (0.23 to 0.90) 0.023
Calcium channel blockers	174 (12.4)	25 (15.6) 0.184	1.34 (0.85 to 2.12) 0.214
Statins	223 (15.8)	22 (13.8) 0.440	0.99 (0.59 to 1.64) 0.964
Oral anticoagulants	171 (12.2)	19 (11.9) 0.909	0.81 (0.41 to 1.59) 0.534
Antiplatelet drugs	344 (24.4)	46 (28.7) 0.179	1.30 (0.85 to 1.98) 0.227
Insulin	138 (9.8)	19 (11.9) 0.350	1.05 (0.59 to 1.86) 0.880
Oral antidiabetic drugs	233 (16.6)	35 (21.9) 0.055	1.56 (0.88 to 2.77) 0.131
Inhaled respiratory drugs	198 (14.1)	19 (11.9) 0.396	0.93 (0.53 to 1.64) 0.808
Antineoplastic agents	33 (2.3)	6 (3.8) 0.212	3.27 (1.34 to 7.94) 0.009
Systemic corticosteroids	36 (2.6)	0 (-) 0.029	NA
NSAIDs	16 (1.1)	0 (-) 0.150	NA
Antihistamines	43 (3.1)	1 (0.6) 0.058	0.21 (0.03 to 1.54) 0.125
Proton-pump inhibitors	616 (4.8)	68 (42.5) 0.729	0.82 (0.57 to 1.18) 0.286
Benzodiazepines	392 (27.9)	47 (29.4) 0.650	1.02 (0.72 to 1.46) 0.911
Vaccination's history			
Influenza vaccine in prior autumn	1036 (73.6)	135 (84.4) 0.001	1.61 (0.98 to 2.59) 0.071
Pneumococcal vaccination	959 (68.2)	113 (6.6) 0.477	0.77 (0.53 to 1.10) 0.148

Continued



Table 5 Continued

Characteristic	Study population (N=1407) n (%)	PCR-confirmed COVID-19 cases (n=160)	
		Univariate analysis n (%) p value	Multivariate analysis HR (95% CI) p value

P values in univariate analysis were calculated by χ^2 (or Fisher's test as appropriate) comparing percentages in the study population versus COVID-19 cases; HR denotes multivariable-adjusted hazard ratios (Cox regression) calculated for those who had the condition as compared with those who did not have the condition, being adjusted by age (continuous), sex, pre-existing comorbidities and medications use. ACEIs, ACE inhibitors; ARBs, angiotensin II receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs.

medications use among community-dwelling individuals. In the multivariable analysis focused on these community-dwelling individuals, chronic respiratory disease (HR 1.82; 95% CI 1.08 to 3.07; $p=0.025$), cardiac disease (HR 1.53; 95% CI 1.06 to 2.19; $p=0.021$), cancer (HR 1.52; 95% CI 1.03 to 2.24; $p=0.035$), receiving diuretics (HR 1.54; 95% CI 1.04 to 2.27; $p=0.031$) and insulin (HR: 1.79; 95% CI: 1.00 to 3.21; $p=0.049$) were associated with an increased risk, whereas smoking (HR 0.49; 95% CI 0.30 to 0.80; $p=0.004$), receiving ACE inhibitors (HR 0.66; 95% CI 0.44 to 0.99; $p=0.046$) and influenza vaccination in prior autumn (HR 0.63; 95% CI 0.44 to 0.91; $p=0.012$) were associated with a decreased risk (table 4).

Among nursing-home residents ($n=1407$), where several outbreaks occurred, a total of 554 possible COVID-19 cases were observed. Of them, 375 were excluded by a PCR negative result, 160 were confirmed by positive PCR and 19 were not PCR tested. Table 5 shows univariate and multivariate analyses on PCR-confirmed COVID-19 cases in subgroup analysis restricted to nursing-home residents. In the multivariable analysis, increasing age and receiving antineoplastic agents were associated with an increased risk, whereas receiving ARBs was associated with a decreased risk (HR 0.45; 95% CI 0.23 to 0.90; $p=0.023$).

DISCUSSION

In the current context of COVID-19 clinical uncertainties, there is not clear evidence about possible clinical predisposing or protecting factors related to SARS-CoV-2 infection. In the present study, the overall incidence rate of PCR-confirmed COVID-19 (480.5 cases per 100 000 persons-period) may be considered intermediate/low as compared with other Spanish regions.¹⁶

Considering sociodemographic variables, apart from nursing-home residence that increased more than 20 times the adjusted risk for PCR-confirmed COVID-19, we found that age increased by approximately 2% for each year the adjusted risk for suffering COVID-19. Despite COVID-19 being more frequent in women, sex did not alter significantly the risk of infection in multivariable analysis.

None comorbidity appeared to be independently associated with a significant increased risk for PCR-confirmed COVID-19 in the multivariable analysis evaluating the total study population. Nevertheless, pre-existing cancer, chronic respiratory disease and cardiac disease emerged to be significantly associated with an increased risk in

subgroup analysis focused on community-dwelling individuals. Hypertension, diabetes and/or obesity did not emerge to be independently associated with a significant increased risk for suffering COVID-19 in our adjusted analyses. There is general consensus considering these conditions as major risk conditions related to poor prognosis in hospitalised patients with COVID-19,^{1-4 7 16-20} but there is lacking data assessing the role of these conditions to predispose for suffering infection.^{2 16}

Surprisingly, smoking was associated with a statistically significant decreased risk for suffering COVID-19 in both multivariable analyses assessing the total study cohort and the subgroup of community-dwelling individuals. This surprising data is not unique^{5 21} and merits further investigations. Opposite findings about poor prognosis among smokers with COVID-19 have been reported.^{2 16 22} Obviously, it must not be forgotten that smoking has severe pathological consequences (being a serious danger for health) and nicotine is a drug responsible for smoking addiction. Nevertheless, as it has been hypothesised elsewhere,²³ a potential protective role for nicotinic agents (under controlled conditions) against COVID-19 infection should be explored.

While angiotensin receptors have been related to the physiopathological mechanisms of SARS-CoV-2 infection,^{24 25} receiving ACEIs/ARBs emerged associated with a reduced risk in this study. Since the beginning of the COVID-19 global pandemic, concerns have been raised about the possibility that receiving ACEIs/ARBs could predispose individuals to severe COVID-19.^{26 27} These concerns were based on the fact that ACE2 receptors facilitates SARS-CoV-2 cell invasion. This negative effect was previously established during other earlier SARS-CoV outbreaks.²⁴⁻²⁷ Most recent studies have concluded that there is no clinical or experimental evidence supporting that ACEIs or ARBs augment the susceptibility to SARS-CoV-2 or aggravate the severity and outcomes of COVID-19 at present.²⁸⁻³¹ Conversely, ACEIs and ARBs may be associated with lower incidence and/or improved outcome in patients with lower respiratory tract infections,³² and lower risk of all-cause mortality among hospitalised patients with COVID-19.³³ Our findings are in accordance with the above mentioned findings and supports that the use of RAAS inhibitors could be beneficial in reducing risk for COVID-19 infection.

Other cardiovascular medications (ie, statins, antiplatelet and/or oral anticoagulant drugs) used before COVID-19 exposition did not significantly alter the risk for COVID-19

in the present study. The use of anticoagulant therapy has been proposed to reduce risk of thrombotic events during and after COVID-19, but studies analysing the influence of the use of these drugs before infection are scarce and mostly focused on interactions with antiviral therapy.³⁴ Considering specifically statins, it has been reported that adjuvant treatment and continuation of pre-existing statin therapy could improve the clinical course of patients with COVID-19, either by their immunomodulatory action or by preventing cardiovascular damage.³⁵

Receiving NSAIDs or corticosteroids (which have been associated with good outcomes when using in patients with severe COVID-19)³⁶ did not significantly alter risk for suffering infection in our study cohort. A pre-print study has reported that prior use of oral steroid medications was associated with decreased COVID-19 positive testing risk, but increased inpatient admission risk.⁶ Available publications recommend caution until further evidence emerges surrounding the use of these drugs in COVID-19 patients.³⁷

Considering controversy about chloroquine/hydroxychloroquine use,³⁸ none COVID-19 case was observed among 168 people receiving this drug (because systemic rheumatoid disease), but this study has lack statistical power to assess it.

Antihistamine use was associated with an almost statistically significant reduction risk of COVID-19 in the total study cohort, which would require further investigation. At present, there is no clear evidence that currently available antihistamines increase or decrease the risk of severe COVID-19 disease. Of note, H1 receptors are expressed on the surface of the smooth musculature of the respiratory tract, neutrophils, eosinophil, macrophages, monocytes and T and B lymphocytes; however, it is not evaluated what the clinical significance of the effect of these drugs may be at this level.³⁹ Considering H2, famotidine use has been associated with improved clinical outcomes in hospitalised patients with COVID-19.⁴⁰

Community-dwelling individuals who received influenza vaccination in prior autumn appeared to be at decreased risk of suffering PCR-confirmed COVID-19 in our adjusted analysis. Although this finding may be possibly related to residual confounding due to unmeasured factors (eg, lifestyle or healthcare-related factors), it merits further investigations exploring a possible immunity-related mechanism explanation (which could be important for future prevention strategies). In this way, it has been hypothesised that the resultant immunity against prior influenza infection or vaccination would, at least in part, foster immunity against SARS-CoV-2 because of cross reactivity of immunity between influenza and coronavirus (due to similarities in their structures).⁴¹

Major strengths in this study were its population-based design (a large cohort involving more than 79 000 people) and the use of multivariable analysis methods to estimate accurately possible relationships between suffering COVID-19 and common chronic medical conditions and medications use among middle aged and older adults (who suffer the greatest burden of severe disease). The study

has also several limitations, mainly related to its observational nature and retrospective design. Assessing COVID-19, the most specific outcome is a laboratory-confirmed by PCR testing infection. However, this outcome depends on the reliability of RT-PCR performed (ie, quality of the nasopharyngeal swabs specimen, timing of collection, sensitivity of tests used) and guidelines for testing over study period. On this concern, the availability of PCR tests was scarce at the beginning of the epidemic period in our setting and they were not routinely performed for all presumptive cases, being PCR tests prioritised for hospitalised or patients with severe case. Obviously, residual confounding in incidence and risk estimates related to selection bias may not be excluded considering that PCR testing was not uniformly performed.

Of note, most COVID-19 cases included in this study were those who were severe enough to warrant medical attention during the epidemic period. Thus, it must be highlighted that those cohort members who were asymptomatic but SARS-CoV-2 infected, those that were oligosymptomatic and those that had mild symptoms (who mostly were in self-isolation and self-medicating in accordance with the recommendations of the health authorities at the time) were largely underestimated in the present study.

We did subgroup analysis (community-dwelling/nursing-home) and multivariable adjustments but, as all observational studies, a residual confounding due to unmeasured factors (eg, epidemiological, social, job and/or health care-related factors) may not be completely excluded. We have not data about need for hospitalisation and clinical course (hospitalisation/intensive care unit admission or death) and, consequently, the study was not able to assess severity degree of cases. Despite the large size of the study cohort, there were relatively few events (n=380) that limits the statistical power, especially in the subgroup analysis. The study was conducted in a single geographical area and, logically, specific incidence data may not be directly extrapolated to other geographical regions with distinct epidemic conditions. Nevertheless, adjusted-risk estimates may be helpful to better characterise risk profile for suffering COVID-19 among middle-aged and older adults in relation with common chronic medications use, providing new arguments to explore possible preventive/treatment research lines.

In summary, our data support that increasing age, nursing-home residence, pre-existing cancer, chronic respiratory and cardiac disease are independent major predisposing conditions to suffer COVID-19 among middle-aged and older adults. Patients receiving diuretics were also at increased risk. Conversely, smokers (who suffered the lowest incidence), patients receiving RAAS inhibitors (and possibly antihistamines) and those community-dwelling individuals that received influenza vaccination in prior autumn appear at decreased risk, which should be closely investigated in future studies specifically focused on these concerns. We note that for most common chronic medications/treatments there is lacking data reporting the possible influence of previous

use of these medications on the risk for developing COVID-19.

On a clinical and public health-oriented point of view, meanwhile an efficacious treatment or vaccination against COVID-19 will be available; universal influenza vaccination, RAAS inhibitors in cardiovascular patients and possibly anti-histamine drugs in patients with allergies could be complementary tools partially protecting against COVID-19.

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