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Influence of prior comorbidities and chronic medications use on the risk of COVID19 in adults: a population based cohort study in Tarragona, Spain

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Complete List of Authors:	Vila-Córcoles, Angel; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona; IDIAP Jordi Gol, Unitat de Suport a la recerca Camp de Tarragona-Reus Ochoa-Gondar, Olga; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona; IDIAP Jordi Gol, Unitat de suport a la recerca Camp de Tarragona-Reus Satué, EVA; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona; IDIAP Jordi Gol, Unitat de suport a la recerca Camp de Tarragona-Reus Torrente-Fraga, Cristina; Institut Catala De La Salut, Information and Communication Technologies Gomez-Bertomeu, Frederic; Institut Catala De La Salut, Department of Microbiology. Hospital Universtari Joan XXIII Vila-Rovira, Angel; IDIAP Jordi Gol, Unitat de suport a la recerca Camp de Tarragona-Reus Hospital-Guardiola, Immaculada; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona de Diego-Cabanes, Cinta; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona Bejarano, Ferran; Institut Catala De La Salut, Department of Pharmacology. Primary Healthcare Service Camp de Tarragona Basora-Gallisà, Josep; IDIAP Jordi Gol, Direction
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TITLE PAGE

Title: Influence of prior comorbidities and chronic medications use on the risk of COVID19 in adults: a population based cohort study in Tarragona, Spain.

Author and Co-author's name

1) Angel Vila-Corcoles,

2) Olga Ochoa-Gondar,

3) Eva Satue-Gracia,

4) Cristina Torrente-Fraga,

5) Frederic Gomez-Bertomeu,

6) Angel Vila-Rovira,

7) Immaculada Hospital-Guardiola,

8) Cinta de Diego-Cabanes,

9) Ferran Bejarano-Romero

10) Josep Basora-Gallisa.

Name, postal address, email, telephone, and fax numbers of the corresponding author.

Name: Eva Mª Satué Gracia

Postal address: C/ Rambla Nova, 124, Esc D, 1A, 43001, Tarragona (Spain)

Email: esatue.tgn.ics@gencat.cat

Telephone number. +0034977254021

Fax number: +0034977226411

Full names, institutions, city, and country of all co-authors.

1) FULL NAME: Angel Vila-Corcoles, MD (avila.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.
INSTITUTION 2: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.
CITY: Barcelona
COUNTRY: Spain.

2) FULL NAME: Olga Ochoa-Gondar, MD (oochoa.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.

CITY: Tarragona
COUNTRY: Spain.
INSTITUTION 2: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.
CITY: Barcelona
COUNTRY: Spain.

3) . Eva Satue-Gracia, MD (esatue.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.
INSTITUTION 2: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.
CITY: Barcelona
COUNTRY: Spain.

4) FULL NAME: Cristina Torrente-Fraga, DM (ctorrente.tgn.ics@gencat.cat)

INSTITUTION 1: Department of information and communication technologies. DAP Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.

5) FULL NAME: Frederic Gomez-Bertomeu, MD (ffgomez.hj23.ics@gencat.cat)

INSTITUTION 1: Department of Microbiology. Hospital Universitari Joan XXIII. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.
6) FULL NAME: Angel Vila-Rovira, DM (vilapf@gmail.com)

INSTITUTION 1: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.
CITY: Barcelona

COUNTRY: Spain.

7) FULL NAME: Immaculada Hospital-Guardiola, PhD (ihospitalg.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona

COUNTRY: Spain

8) FULL NAME: Cinta de Diego-Cabanes, MD (mcdiego.tgn.ics@gencat.cat)

INSTITUTION 1:Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona

COUNTRY: Spain

9) FULL NAME: Ferran Bejarano-Romero, PhD (fbejarano.tgn.ics@gencat.cat)

INSTITUTION 1: Department of Pharmacology. DAP Camp de Tarragona. Institut Catala de la Salut.

CITY: Tarragona

COUNTRY: Spain

10) FULL NAME: Josep Basora-Gallisa, PhD (jbasora@idiapjgol.org)

INSTITUTION 1: Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)

CITY: Barcelona

COUNTRY: Spain.

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Influence of prior comorbidities and chronic medications use on the risk of COVID19 in adults: a population based cohort study in Tarragona, Spain)

ABSTRACT

OBJECTIVE: To investigate possible relationships between pre-existing medical conditions (including common comorbidities and chronic medications) and risk for suffering COVID19 infection in middle-aged and older adults.

DESIGN: Population-based retrospective cohort study.

SETTING: twelve primary care centres (PCCs) in Tarragona (Southern Catalonia, Spain).

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

OUTCOMES: Baseline cohort characteristics (age, sex, vaccinations, comorbidities and chronic medications) were established at study start (01/03/2020) and primary outcome was PCR-confirmed COVID19 occurred among cohort members across 01/03/2020-23/05/2020. Risk for suffering COVID19 was evaluated by Cox regression, estimating multivariable hazard ratios (HRs) adjusted for age, sex, comorbidities and medications use.

RESULTS: During study period, 380 PCR-confirmed COVID19 cases were observed, which means an incidence of 480.5 per 100,000 persons-period. Assessing the total study cohort only age/years (HR: 1.02; 95% CI: 1.01-1.03; p=0.002), nursing-home residence (HR: 21.83; 95% CI: 16.66-28.61; p<0.001) and receiving diuretics (HR: 1.35; 95% CI: 1.04-1.76; p=0.026) appeared independently associated with increased risk, whereas smoking (HR: 0.62; 95%CI: 0.41-0.93; p=0.022) and receiving angiotensin receptor blockers(HR: 0.68; 95%CI: 0.47-0.99; p=0.046) and antihistamine (HR: 0.47; 95% CI: 0.22-1.01; p=0.052) were related with a reduced risk. Among community-dwelling individuals, pre-existing cancer (HR: 1.52; 95% CI: 1.03-2.24; p=0.035), chronic respiratory disease (HR: 1.82; 95% CI: 1.08-3.07; p=0.025) and cardiac disease (HR: 1.53; 95% CI: 1.06-2.19; p=0.021) emerged also associated with an increased risk for COVID19, WHEREAS receiving ACE-inhibitors (HR: 0.66; 95% CI: 0.44-0.99; p=0.046) and flu vaccination in prior autumn (HR: 0.63; 95% CI: 0.44-0.91; p=0.012) were associated with decreased risk.

CONCLUSION: Age, nursing-home residence and multiple comorbidities appear predisposing for COVID19. Conversely, receiving angiotensin-receptor blockers/inhibitors, antihistamine and influenza vaccination could be protective, which should be closely investigated in further studies specifically focused on these concerns.

KEYWORDS: Coronavirus Infections, COVID19, Incidence, Risk, Disease Prevention.

Strengths and limitations of this study (per article summary)

- This is a population-based cohort study including 79,083 adults >50 years (77,676 community-dwelling and 1407 nursing-home residents) in Tarragona (Southern Catalonia, Spain) who were retrospectively followed between 01/03/2020-23/05/2020.

- Relationships between PCR-confirmed COVID19 incidence and chronic comorbidities/medications were assessed by multivariable analysis methods, estimating risk ratios adjusted by age, sex and baseline underlying conditions.

- Main limitations are related with its observational nature and retrospective design.

- Despite the large size of study cohort, events were relatively few (n=380) which limits statistical power, especially in subgroup analyses.

- Data provides new arguments to explore possible preventive research lines.

INTRODUCTION

At present, available population-based clinical data on the current coronavirus SARS-COV-2 pandemic (COVID19) is limited.[1,2] Most available clinical information is hospital-based data derived from severe cases(hospital/ICU admitted/deaths),[2-8] and there is few population- or community-based data involving a wide representative sample of the exposed population.[2,6,9] Many studies reported distribution of severe/fatal COVID19 cases according to clinical and demographical characteristics,[3,4,5,7,8] but there is lacking data assessing incidence and risk for suffering infection in relation with pre-existing clinical characteristics of the population (i.e, baseline risk profile according to previous underlying conditions/medications use). In fact, there is uncertainty about possible factors predisposing/protecting against COVID19 infection.

This study was aimed to analyse incidence and risk for suffering COVID19 in relation with pre-existing comorbidities and, especially, common chronic medications use among the general adult population over 50 years in Tarragona (Southern Catalonia, Spain) across the first 12-weeks pandemic period in the study area.

METHODS

Design, setting and study population

This is a population-based retrospective cohort study including 79,083 individuals affiliated to 12 participant primary care centres (PCCs) in the Tarragona area (an industrial-urban area in the Mediterranean coast of Southern Catalonia, Spain). Cohort members were all persons ≥50 years affiliated to any of the 12 PCCs managed by the Institut Català de la Salut in the study region (Tarragonès, Alt Camp and Conca Barberà counties), serving an assigned population of 210,672 all-age inhabitants , with the same reference Microbiological Laboratory Service (Hospital Joan XXIII) in Tarragona city. Cohort members were retrospectively followed since 01/03/2020 (the beginning of epidemic period in the region), until the occurrence of any study event (Covid19 diagnosis) or until the end of 12-weeks follow-up (23/05/2020). 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 pre-existing CAPAMIS Research Database, an institutional clinical research database previously used for other cohort studies in the study area,[11] was quickly updated for using as main data source in this COVID19 epidemiological investigation. Briefly, this research database compiles data from the institutional PCCs' clinical records system (working since the 2000s),

including administrative data and clinical information coded according to the International Classification of Diseases 10th Revision (ICD-10). It was used to identify sociodemographical characteristics, comorbidities, vaccinations history and active medications use among cohort members and to establish baseline characteristics of study population at study start (01/03/2020).

When COVID19 epidemic period started in the study area, two electronic alerts including COVID19's laboratory registries plus ICD-10 codes for COVID19 suspicion (B34.2: unspecified Coronavirus infection; B97.29: Other coronavirus as the cause of diseases classified elsewhere) were added to the electronic PCCs clinical records system and, later, both data sources were linked to construct an anonymized research database used for this report.

Outcomes

Primary outcome was COVID-19 diagnosed by polymerase chain reaction (PCR) occurred among cohort members across the study period (from 01/03/2020 to 23/05/2020). For descriptive results we also report laboratory-excluded cases (PCR performed with a negative result) and presumptive COVID19 cases (persons coded as clinical suspicion alone without PCR tested). For laboratory diagnosis of COVID19 by RT-PCR, guidelines of the Health Department of the Generalitat de Catalunya were followed.[12] Briefly, from the samples collected by nasal and pharyngeal swab with transport medium for viruses and refrigerated at 4°C for a maximum of 48 hours, the RT-PCR technique Cobas© SARS-CoV-2 with CE-FDA marking was performed with a sensitivity and specificity close to 100%.[13] At the beginning of epidemic period, the availability for PCR testing was scarce, being prioritized for severe case patients admitted in the hospital and nursing-home residences (where several outbreaks occurred), whereas less PCR test were made among possible cases managed as outpatient.

Exposure

Baseline use of common chronic medications, which could be hypothetically related with physiopathological mechanism of SARS-COV-2 infection or virulence (e.g., antihypertensive, antiplatelet/anticoagulant and/or anti-inflammatory drugs), were considered as main explanatory variables possibly related with the occurrence of COVID19 for the present study. It was determined by a review of the PHCCs' electronic clinical records system which contains specially designated fields for medications prescribed. Thus, active medication treatments in each cohort member on 01/03/2020, coded according to the Anatomical, Therapeutic, and Chemical classification system (ATC) of the World Health Organization,[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, angiotensin converting enzyme 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 (NSADs), chloroquine/hydroxychloroquine, antihistamines, proton-pump inhibitors and benzodiazepines (see Appendix).

Covariates

Besides age, sex, residence (community-dwelling/nursing-home), and vaccinations' history (flu vaccination in prior autumn or pneumococcal vaccination at any time), the following comorbidities/underlying conditions were considered according to data registered in the electronic PCCs clinical records on 01/03/2020: neurological disease (including dementia and stroke), cancer (solid organ or haematological neoplasia diagnosed in 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, hypercholesterolemia, obesity and smoking (see Appendix).

Statistical analyses

Incidence rates (IRs) for PCR-confirmed COVID19 were calculated per 100,000 person-period (12 weeks). Confidence intervals (CIs) for IRs were calculated assuming a Poisson distribution for uncommon events. In bivariate analyses, baseline characteristics according to suffer or not COVID19 were compared using Chi-squared or Fisher's test as appropriate.

Cox regression analyses were used to calculate unadjusted and multivariable-adjusted hazards ratios (HRs) and estimate the association between baseline exposure conditions and the time to the first outcome (PCR-confirmed COVID19 infection) during the study period.[15] The multivariable Cox models were made with all above mentioned exposure variables and co-variables (i.e, age, sex, residence, vaccinations history, comorbidities/underlying conditions and medications use). The method to select a subset of co-variables to include in the final model was the purposeful selection.[15] The final models include significant, confounders and all co-variables judged clinically or epidemiologically relevant. We performed a main analysis including the total study cohort (N=79,083) and two subgroup analyses restricted to community-dwelling individuals (N=77,676) and nursing-home residents (N=1407). Statistical significance was set at $p < 0.05$ (two-tailed). Data was performed by using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA).

RESULTS:

Across the study period an amount of 2324 cohort members were PCR tested. Of them, 380 (16.4%) presented a positive result (PCR-confirmed COVID19) and 1944 (83.6%) presented a negative result. Additionally, 377 cohort members with presumptive COVID19 (clinical suspicion alone) were not PCR tested.

Of the 380 PCR-confirmed COVID19 cases, 158 (41.6%) occurred in men and 222 (58.4%) in women. By age groups, 101 (26.6%) occurred in people 50-64 years, 95 (25%) in 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 COVID19 cases per 100,000 persons-period (236.6 in 50-64 yrs vs 365.2 in 65-79 yrs *vs* 1771.6 in 80 yrs or older; 419.9 in men *vs* 535.5 in women)

The most prevalent pre-existing comorbidities/underlying conditions among the 380 COVID19 patients were hypertension (58.7%), hypercholesterolemia (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 COVID19 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: 1.01-1.03; p=0.002), nursing-home residence (HR: 21.83; 95% CI: 16.66-28.61; p<0.001) and receiving diuretics (HR: 1.35; 95% CI: 1.04-1.76; p=0.026) appeared significantly associated with an increasing risk. Conversely, smoking (HR: 0.62; 95%CI: 0.41-0.93; p=0.022), receiving angiotensin II receptor blockers (HR: 0.68; 95%CI: 0.47-0.99; p=0.046) and antihistamines (HR: 0.47; 95% CI: 0.22-1.01; 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 COVID19 cases (clinical suspicion without PCR performed). Table 3 shows distribution of PCR-confirmed COVID19 cases and specific-IRs by demographical characteristics, underlying conditions and medications use among community-dwelling individuals. In the multivariable analysis focused on these community-dwelling individuals, chronic respiratory disease (HR: 1.82; 95% CI: 1.08-3.07; p=0.025), cardiac disease

(HR: 1.53; 95% CI: 1.06-2.19; p=0.021) cancer (HR: 1.52; 95% CI: 1.03-2.24; p=0.035) receiving diuretics (HR: 1.54; 95% CI: 1.04-2.27; p=0.031) and insulin (HR: 1.79; 95% CI: 1.00-3.21; p=0.049) were associated with an increasing risk, whereas smoking (HR: 0.49; 95% CI: 0.30-0.80; p=0.004), receiving ACE-inhibitors (HR: 0.66; 95% CI: 0.44-0.99; p=0.046) and influenza vaccination in prior autumn (HR: 0.63; 95% CI: 0.44-0.91; 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 COVID19 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 analysis on PCR-confirmed COVID19 cases in subgroup analysis restricted to nursing-home residents. In the multivariable analysis, increasing age and receiving antineoplastic agents were associated with an increasing risk, whereas receiving angiotensin II receptor blockers was associated with a decreased risk (HR: 0.45; 95% CI: 0.23-0.90; p=0.023).

DISCUSSION

In the current context of COVID19 clinical uncertainties, there is not clear evidence about possible clinical predisposing or protecting factors related with SARS-COV-2 infection.

In the present study, the overall incidence rate of PCR-confirmed COVID19 (480.5 cases per 100,000 persons-period) may be considered intermediate as compared with other Spanish or European regions.[1,16] During study period, approximately 3% of cohort members were PCR tested (with 380 positive and 1944 negative result). Assuming this data, and considering that PCR test were scarcely available in the study area for patients with less severe symptoms during the first weeks of the epidemic period, the true incidence of COVID19 was logically underestimated. Nevertheless, considering the relatively low number of presumptive cases (clinical suspicion alone without PCR performed), our data also suggests that the overall number of infected population (definitive plus presumptive) may be considerably lower than speculated.[16]

Specific-IRs by comorbidities and medications use largely reflect the excess baseline-risk profile related with the great number of cases observed among elderly persons and, especially, nursing-home residents (where several outbreaks occurred and supported approximately forty percent of overall COVID19 cases).

Considering sociodemographical variables, apart of nursing-home residence that increased more than twenty-times the adjusted-risk for PCR-confirmed COVID19, we found that age increased approximately a 2% for each year the adjusted-risk for suffering COVID19 infection. Despite COVID19 was more frequent in women, sex did not alter significantly the risk of infection in multivariable analysis.

None comorbidity appeared independently associated with a significant increased risk for PCR-confirmed COVID19 in the multivariable analysis evaluating the total study population. Nevertheless, pre-existing cancer, chronic respiratory disease and cardiac disease emerged significantly associated with an increased risk in subgroup analysis focused on community-dwelling individuals. Hypertension, diabetes and/or obesity did not emerge independently associated with a significant increasing risk for suffering COVID19 in our adjusted analyses. There is general consensus considering these conditions as major risk conditions related with poor prognosis in hospitalised COVID19 patients,[7,8,16-20] 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 COVID19 in both multivariable analyses assessing the total study cohort and the subgroup of community-dwelling individuals. This surprising data is not unique[21] and merits further investigations. Opposite findings about poor prognosis among smokers with COVID19 have been reported.[2,4,16,22] 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 hypothesized elsewhere,[23] a potential protective role for nicotinic agents (under controlled conditions) against COVID19 infection should be explored.

Considering main exposure variables (i.e, common medications use), receiving diuretics appeared significantly associated with an increasing risk for COVID19. In contrast, while angiotensin receptors have been related with 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 COVID19 global pandemic, concerns have been raised about the possibility that receiving ACEIs/ARBs could predispose individuals to severe COVID19.[26,27] These concerns were based on the fact that ACE2 receptors facilitates SARS-CoV-2 cell invasion; however, 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.[9,28-31] 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 COVID19 hospitalized patients.[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 COVID19 infection.

Other cardiovascular medications (i.e., statins, antiplatelet and/or oral anticoagulant drugs) used before COVID19 exposition did not significantly alter the risk for COVID19 infection in the present study. The use of anticoagulant therapy has been proposed to reduce risk of thrombotic events during and after COVID19 infection, 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 NSADs or corticosteroids (which have been associated with good outcomes when using in severe COVID19 patients)[36] did not significantly alter risk for suffering infection in our study cohort. 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 COVID19 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 COVID19 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 disease from COVID19. 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 hospitalized COVID19 patients.[40]

Community-dwelling individuals who received influenza vaccination in prior autumn appeared at-decreased risk to suffer PCR-confirmed COVID19 in our adjusted analysis. Although this finding may be possibly related with residual confounding due to unmeasured factors (e.g, life-style or health care-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 hypothesized 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 flu 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 COVID19 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 with its observational nature and retrospective design. Assessing COVID19, the most specific outcome is a laboratory-confirmed by PCR testing infection. However, this outcome depends on the reliability of RT-PCR performed (i.e, 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 prioritized for hospitalised or severe case patients. Obviously, residual confounding in incidence and risk estimates related to selection bias may not be excluded considering that PCR testing was not uniformly performed.

We did subgroup analysis (community-dwelling/nursing-home) and multivariable-adjustments but, as all observational studies, a residual confounding due to unmeasured factors (e.g, 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/ICU 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 where relatively few events (n=380) which limits statistical power, especially in 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 characterize risk profile for suffering COVID19 infection 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 supports that increasing age, nursing-home residence, pre-existing cancer, chronic respiratory and cardiac disease are independent major predisposing conditions to suffer COVID19 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 COVID19 infection. Meanwhile an efficacious treatment or vaccination will be available, RAAS-inhibitors and influenza vaccination (and possibly antihistamines and/or nicotine-related therapy) could be complementary tools partially protecting against COVID19.

Author's contributions: AVC designed the study and wrote the manuscript; CTF and FGB obtained data; ESG, IHG and CDC assessed outcomes; OOG and AVR did statistical analyses; FBR revised pharmacological data; AVC and JBG coordinated the study.

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Data availability statement: Data are available upon reasonable request

Patient and Public Involvement statement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

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Table 1. Incidence and risk of PCR-confirmed COVID19 cases according to baseline demographical and clinical characteristics (comorbidities/medications) in the total study cohort (N=79,083). Tarragona area (Southern Catalonia, Spain), 01/03/2020-23/05/2020.

Characteristic	Study population (N=79083) n (%)	PCR-confirmed COVID19 cases (n=380)	
		Univariate analysis n (%) p-value	Incidence rate
Sociodemographical			
Age: 50-64 yrs	42684 (54.0)	101 (26.6) <0.001	236.6 (193.6-288.7)
65-79 yrs	26013 (32.9)	95 (25.0)	365.2 (295.4-452.9)
≥80 yrs	10386 (13.1)	184 (48.4)	1771.6 (1527.1-2055.1)
Sex Men	37626 (47.6)	158 (41.6) 0.019	419.9 (358.6-491.7)
Women	41457 (52.4)	222 (58.4)	535.5 (464.8-616.4)
Community-dwelling	77676 (98.2)	220 (57.9) <0.001	283.2 (245.8-326.0)
Nursing-home residence	1407 (1.8)	160 (42.1)	11371.7 (9711.4-13316.3)
Comorbidities			
Neurological disease	2317 (2.9)	66 (17.4) <0.001	2848.5 (2236.1-3617.6)
Renal disease	4476 (5.7)	49 (12.9) <0.001	1094.7 (812.3-1445.0)
Cancer	6630 (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	7272 (9.2)	63 (16.6) <0.001	866.3 (667.1-1126.2)
Cardiac disease	13435 (17.0)	123 (32.4) <0.001	915.5 (762.6-1098.6)
Atrial fibrillation	3786 (4.8)	55 (14.5) <0.001	1452.7 (1077.9-1917.6)
Liver disease	1465 (1.9)	8 (2.1) 0.714	546.1 (235.4-1075.8)
Diabetes	13317 (16.8)	102 (26.8) <0.001	765.9 (626.5-934.4)
Hypertension	34945 (44.2)	223 (58.7) <0.001	638.1 (553.9-734.5)
Hypercholesterolemia	27314 (34.5)	133 (35.0) 0.850	486.9 (411.0-576.5)
Obesity	21678 (27.4)	96 (25.3) 0.347	442.8 (362.2-540.3)
Smoking	12750 (16.1)	27 (7.1) <0.001	211.8 (139.6-309.2)
Chronic medications use			
Diuretics	8481 (10.7)	111 (29.2) <0.001	1308.8 (1090.2-1570.6)
Beta blockers	9571 (12.1)	68 (17.9) 0.001	710.5 (557.7-902.3)
ACEIs	16419 (20.8)	92 (24.2) 0.097	560.3 (453.3-694.8)
ARBs	8869 (11.2)	39 (10.3) 0.556	439.7 (314.0-598.0)
Calcium channel blockers	6490 (8.2)	52 (13.7) <0.001	801.2 (594.5-1057.6)
Statins	16134 (20.4)	69 (18.2) 0.277	427.7 (335.7-543.1)
Oral anticoagulants	3912 (4.9)	46 (12.1) <0.001	1175.9 (857.2-1575.7)
Antiplatelet drugs	9154 (11.6)	86 (22.6) <0.001	939.5 (760.0-1165.0)
Insulin	3042 (3.8)	39 (10.3) <0.001	1282.1 (915.4-1743.6)
Oral antidiabetic drugs	10585 (13.4)	69 (18.2) 0.006	651.9 (511.7-827.9)
Inhaled respiratory drugs	6293 (8.0)	61 (16.1) <0.001	969.3 (746.4-1260.1)
Antineoplastic agents	1614 (2.0)	8 (2.1) 0.929	495.7 (213.6-976.5)
Systemic corticosteroids	1252 (1.6)	5 (1.3) 0.676	399.4 (129.4-930.5)
NSADs	4321 (5.5)	12 (3.2) 0.047	277.7 (143.6-486.0)
Chloroquine	168 (0.2)	0 (0.0) 0.367	0 (-)
Antihistamines	3264 (4.1)	7 (1.8) 0.025	214.5 (86.0-446.1)
Proton-Pump Inhibitors	17931 (22.7)	142 (37.4) <0.001	791.9 (668.4-937.6)
Benzodiazepines	13046 (16.5)	96 (25.3) <0.001	735.9 (601.9-897.7)
Vaccination's history			
Flu vaccine in prior autumn	22606 (28.6)	205 (53.9) <0.001	906.8 (787.1-1043.8)
Pneumococcal vaccinated	26183 (33.1)	213 (56.1) <0.001	813.5 (706.1-936.3)

NOTE: P-values in univariate analysis were calculated by chi-squared, or Fisher's test as appropriate, comparing percentages in the study population vs COVID19 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.

Table 2. Cox regression analyses assessing unadjusted and adjusted risks to suffer PCR-confirmed COVID19 in the total study cohort (N=79,083). Tarragona area (Southern Catalonia, Spain) from 01/03/2020 to 23/05/2020.

Characteristic	LC-COVID19 cases (n=349)	
	Unajusted HR (95% CI) p-value	**Adjusted HR (95% CI) p-value**
Sociodemographical		
Age (continuous yrs)	1.07 (1.07-1.08) <0.001	1.02 (1.01-1.03) 0.002
Sex: women	1.28 (1.04-1.57) 0.019	0.95 (0.76-1.18) 0.624
Nursing-home residence	42.14 (34.37-51.66) <0.001	21.83 (16.66-28.61) <0.001
Comorbidities		
Neurological disease	7.03 (5.39-9.16) <0.001	1.31 (0.97-1.77) 0.074
Renal disease	2.47 (1.83-3.34) <0.001	0.91 (0.66-1.26) 0.556
Cancer	1.62 (1.20-2.19) 0.002	1.17 (0.86-1.60) 0.315
Rheumatic disease	0.47 (0.12-1.90) 0.293	0.54 (0.13-2.19) 0.386
Respiratory disease	1.97 (1.50-2.58) <0.001	1.29 (0.89-1.87) 0.184
Cardiac disease	2.34 (1.89-2.90) <0.001	1.04 (0.80-1.34) 0.790
Atrial fibrillation	3.38 (2.54-4.50) <0.001	1.17 (0.74-1.84) 0.514
Liver disease	1.14 (0.57-2.30) 0.712	1.16 (0.57-2.35) 0.684
Diabetes	1.81 (1.45-2.27) <0.001	1.10 (0.73-1.65) 0.646
Hypertension	1.80 (1.46-2.20) <0.001	0.98 (0.74-1.29) 0.869
Hypercholesterolemia	1.02 (0.83-1.26) 0.851	0.88 (0.70-1.11) 0.269
Obesity	0.89 (0.71-1.13) 0.344	0.87 (0.68-1.11) 0.262
Smoking	0.40 (0.27-0.59) <0.001	0.62 (0.41-0.93) 0.022
Chronic medications use		
Diuretics	3.45 (2.76-4.30) <0.001	1.35 (1.04-1.76) 0.026
Beta blockers	1.59 (1.22-2.06) 0.001	0.96 (0.72-1.29) 0.790
ACEIs	1.22 (0.96-1.54) 0.098	0.85 (0.65-1.13) 0.260
ARBs	0.90 (0.65-1.26) 0.552	0.68 (0.47-0.99) 0.046
Calcium channel blockers	1.77 (1.32-2.38) <0.001	1.31 (0.95-1.79) 0.096
Statins	0.87 (0.67-1.12) 0.276	0.82 (0.60-1.11) 0.200
Oral anticoagulants	2.65 (1.95-3.61) <0.001	1.26 (0.76-2.07) 0.371
Antiplatelet drugs	2.24 (1.76-2.85) <0.001	1.35 (1.00-1.81) 0.051
Insulin	2.87 (2.06-3.99) <0.001	1.47 (0.98-2.21) 0.065
Oral antidiabetic drugs	1.44 (1.11-1.86) 0.007	1.05 (0.69-1.59) 0.823
Inhaled respiratory drugs	2.22 (1.69-2.92) <0.001	1.24 (0.84-1.81) 0.275
Antineoplastic agents	1.03 (0.51-2.08) 0.929	1.06 (0.51-2.20) 0.876
Systemic corticosteroids	0.83 (0.34-2.00) 0.677	0.57 (0.23-1.40) 0.218
NSADs	0.57 (0.32-1.00) 0.051	1.04 (0.58-1.87) 0.901
Antihistamines	0.44 (0.21-0.92) 0.029	0.47 (0.22-1.01) 0.052
Proton-Pump Inhibitors	2.04 (1.66-2.51) <0.001	0.93 (0.72-1.19) 0.557
Benzodiazepines	1.72 (1.36-2.16) <0.001	1.25 (0.98-1.60) 0.072
Vaccination's history		
Flu vaccine in prior autumn	2.93 (2.40-3.59) <0.001	1.02 (0.79-1.32) 0.878
Pneumococcal vaccination	2.58 (2.11-3.16) <0.001	1.02 (0.78-1.33) 0.904

NOTE: 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 denote confidence intervals.

Table 3. Incidence and risk of PCR-confirmed COVID19 cases according to baseline demographical and clinical characteristics (comorbidities/medications) in subgroup analysis restricted to community-dwelling individuals (N=77,676). Tarragona area (Southern Catalonia, Spain), 01/03/2020-23/05/2020.

Characteristic	Study population (N=77676) n (%)	PCR-confirmed COVID19 cases (n=220)	
		Univariate analysis n (%) p-value	Incidence rate
Sociodemographical			
Age: 50-64 yrs	42533 (54.8)	99 (45.0) <0.001	232.8 (190.4-284.0)
65-79 yrs	25713 (33.1)	72 (32.7)	280.0 (219.8-355.6)
≥80 yrs	9430 (12.1)	49 (22.3)	519.6 (385.6-685.9)
Sex Men	37145 (47.8)	108 (49.1) 0.706	290.8 (237.8-354.7)
Women	40531 (52.2)	112 (50.9)	276.3 (230.2-331.6)
Comorbidities			
Neurological disease	1951 (2.5)	11 (5.0) 0.018	563.8 (281.3-1009.2)
Renal disease	4240 (5.5)	26 (11.8) <0.001	613.2 (400.4-901.4)
Cancer	6463 (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	7075 (9.1)	47 (21.4) <0.001	664.3 (484.3-890.2)
Cardiac disease	12925 (16.6)	68 (30.9) <0.001	526.1 (413.0-668.2)
Atrial fibrillation	3561 (4.6)	26 (11.8) <0.001	730.1 (476.8-1073.3)
Liver disease	1438 (1.9)	6 (2.7) 0.334	417.2 (153.1-909.6)
Diabetes	12926 (16.6)	50 (22.7) 0.015	386.8 (287.0-510.6)
Hypertension	33996 (43.8)	112 (50.9) 0.032	329.5 (274.4-395.3)
Hypercholesterolemia	26766 (34.5)	74 (33.6) 0.797	276.5 (217.0-351.1)
Obesity	21344 (27.5)	57 (25.9) 0.602	267.1 (205.6-347.2)
Smoking	12640 (16.3)	19 (8.6) 0.002	150.3 (90.5-234.5)
Chronic medications use			
Diuretics	8028 (10.3)	51 (23.2) <0.001	635.3 (471.4-838.6)
Beta blockers	9312 (12.0)	40 (18.2) 0.005	429.6 (306.7-584.2)
ACEIs	16031 (20.6)	41 (18.6) 0.462	255.8 (182.6-347.8)
ARBs	8709 (11.2)	29 (13.2) 0.354	333.0 (223.1-479.5)
Calcium channel blockers	6316 (8.1)	27 (12.3) 0.024	427.5 (281.7-624.1)
Statins	15911 (20.5)	47 (21.4) 0.746	295.4 (215.3-395.8)
Oral anticoagulants	3741 (4.8)	27 (12.3) <0.001	721.7 (475.6-1053.7)
Antiplatelet drugs	8810 (11.3)	40 (18.2) 0.001	454.0 (324.2-617.5)
Insulin	2904 (3.7)	20 (9.1) <0.001	688.7 (420.8-1060.6)
Oral antidiabetic drugs	10352 (13.3)	34 (15.5) 0.353	328.4 (228.9-456.5)
Inhaled respiratory drugs	6095 (7.8)	42 (19.1) <0.001	689.1 (492.0-937.2)
Antineoplastic agents	1581 (2.0)	2 (0.9) 0.236	126.5 (15.3-456.7)
Systemic corticosteroids	1216 (1.6)	5 (2.3) 0.397	411.2 (133.2-958.1)
NSADs	4305 (5.5)	12 (5.5) 0.955	278.7 (144.1-487.8)
Antihistamines	3221 (4.1)	6 (2.7) 0.290	186.3 (68.4-406.1)
Proton-Pump Inhibitors	17315 (22.3)	74 (33.6) <0.001	427.4 (335.5-542.8)
Benzodiazepines	12654 (16.3)	49 (22.3) 0.016	387.2 (287.3-511.1)
Vaccination's history			
Flu vaccine in prior autumn	21570 (27.8)	70 (31.8) 0.179	324.5 (254.8-412.1)
Pneumococcal vaccinated	25224 (32.5)	100 (45.5) <0.001	396.4 (324.3-483.7)

NOTE: P-values in univariate analysis were calculated by chi-squared, or Fisher's test as appropriate, comparing percentages in the study population *vs* COVID19 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.

Table 4. Cox regression analyses assessing unadjusted and adjusted risks to suffer PCR-confirmed COVID19 among community-dwelling individuals (N=77,676). Tarragona area (Southern Catalonia, Spain), 01/03/2020-23/05/2020.

Characteristic	LC-COVID19 cases (n=201)	
	Unadjusted HR (95% CI) p-value	**Adjusted HR (95% CI) p-value**
Sociodemographical		
Age (continuous yrs)	1.03 (1.02-1.04) <0.001	1.01 (0.99-1.02) 0.573
Sex: women	0.95 (0.73-1.24) 0.708	0.97 (0.73-1.28) 0.807
Comorbidities		
Neurological disease	2.04 (1.12-3.75) 0.021	1.06 (0.56-2.01) 0.857
Renal disease	2.32 (1.54-3.50) <0.001	1.22 (0.77-1.94) 0.398
Cancer	1.88 (1.29-2.73) 0.001	1.52 (1.03-2.24) 0.035
Rheumatic disease	0.41 (0.06-2.91) 0.371	0.41 (0.06-2.97) 0.375
Respiratory disease	2.72 (1.97-3.75) <0.001	1.82 (1.08-3.07) 0.025
Cardiac disease	2.24 (1.69-2.99) <0.001	1.53 (1.06-2.19) 0.021
Atrial fibrillation	2.79 (1.86-4.21) <0.001	1.06 (0.48-2.33) 0.882
Liver disease	1.49 (0.66-3.35) 0.336	1.24 (0.54-2.83) 0.608
Diabetes	1.47 (1.08-2.02) 0.016	1.26 (0.70-2.28) 0.441
Hypertension	1.33 (1.02-1.74) 0.034	1.06 (0.72-1.55) 0.785
Hypercholesterolemia	0.96 (0.73-1.28) 0.798	0.88 (0.64-1.20) 0.405
Obesity	0.92 (0.68-1.25) 0.599	0.75 (0.54-1.03) 0.076
Smoking	0.49 (0.30-0.78) 0.003	0.49 (0.30-0.80) 0.004
Chronic medications use		
Diuretics	2.62 (1.92-3.58) <0.001	1.54 (1.04-2.27) 0.031
Beta blockers	1.63 (1.16-2.30) 0.005	1.02 (0.69-1.52) 0.909
ACEIs	0.88 (0.63-1.24) 0.462	0.66 (0.44-0.99) 0.046
ARBs	1.20 (0.81-1.78) 0.356	0.75 (0.47-1.19) 0.222
Calcium channel blockers	1.58 (1.06-2.36) 0.026	1.21 (0.78-1.87) 0.395
Statins	1.05 (0.76-1.46) 0.747	0.72 (0.49-1.06) 0.094
Oral anticoagulants	2.77 (1.85-4.14) <0.001	1.58 (0.71-3.48) 0.261
Antiplatelet drugs	1.74 (1.23-2.45) 0.002	1.30 (0.84-2.02) 0.243
Insulin	2.58 (1.63-4.08) <0.001	1.79 (1.00-3.21) 0.059
Oral antidiabetic drugs	1.19 (0.82-1.71) 0.356	0.73 (0.40-1.32) 0.295
Inhaled respiratory drugs	2.78 (1.99-3.89) <0.001	1.41 (0.81-2.45) 0.225
Antineoplastic agents	0.44 (0.11-1.78) 0.250	0.36 (0.09-1.49) 0.159
Systemic corticosteroids	1.46 (0.60-3.55) 0.400	1.03 (0.41-2.58) 0.945
NSADs	0.99 (0.55-1.76) 0.959	1.17 (0.65-2.12) 0.600
Antihistamines	0.65 (0.29-1.46) 0.294	0.51 (0.23-1.16) 0.109
Proton-Pump Inhibitors	1.77 (1.34-2.34) <0.001	1.11 (0.79-1.57) 0.555
Benzodiazepines	1.48 (1.07-2.03) 0.017	1.26 (0.90-1.76) 0.186
Vaccination's history		
Flu vaccine in prior autumn	1.21 (0.91-1.61) 0.182	0.63 (0.44-0.91) 0.012
Pneumococcal vaccination	1.73 (1.33-2.26) <0.001	1.29 (0.86-1.92) 0.214

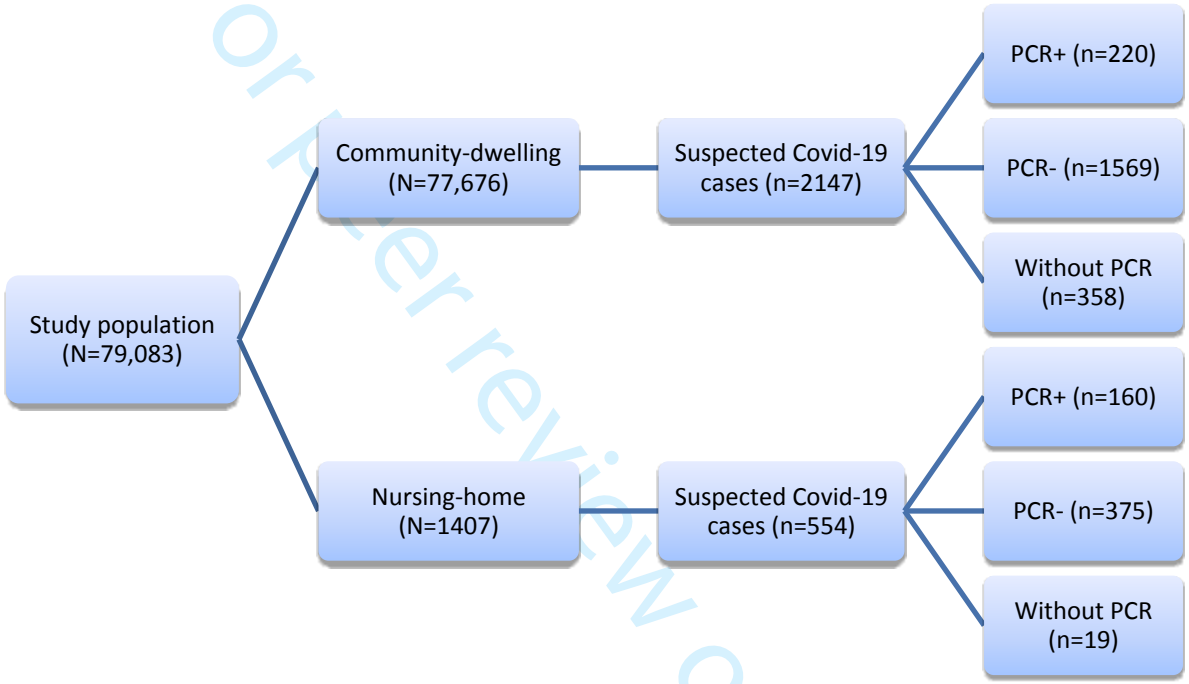
NOTE: HRs denotes Hazard ratios, and were calculated for those who had the condition as compared with those who had not the condition. In multivariable-adjusted analysis, HRs were adjusted for age (continuous years), sex, residence, comorbidities/underlying conditions and chronic medications use. CIs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

Table 5. Univariate and multivariate analyses on laboratory-confirmed COVID19 cases according to baseline demographical and clinical characteristics (comorbidities/medications) in subgroup analysis restricted to nursing-home residents (N=1407). Tarragona area (Southern Catalonia, Spain) from 01/03/2020 to 23/05/2020.

Characteristic	Study population (N=1407) n (%)	PCR-confirmed COVID19 cases (n=160)	
		Univariate analysis n (%) p value	Multivariate analysis HR (95% CI) p value
Sociodemographical			
Age: 50-64 yrs	151 (10.7)	2 (1.3) <0.001	1.00 (reference)
65-79 yrs	300 (21.3)	23 (14.4)	6.66 (1.53-29.02) 0.012
≥80 yrs	956 (67.9)	135 (84.4)	13.16 (3.09-56.00) <0.001
Sex: Men	481 (34.2)	50 (31.3) 0.406	1.00 (reference)
Women	926 (65.8)	110 (68.8)	0.85 (0.59-1.24) 0.402
Comorbidities			
Neurological disease	366 (26.0)	55 (34.4) 0.010	1.25 (0.89-1.76) 0.193
Renal disease	236 (16.8)	23 (14.4) 0.388	0.68 (0.43-1.08) 0.104
Cancer	167 (11.9)	17 (10.6) 0.605	0.74 (0.43-1.26) 0.264
Rheumatic disease	12 (0.9)	1 (0.6) 0.739	0.86 (0.12-6.43) 0.885
Respiratory disease	197 (14.0)	16 (10.0) 0.121	0.72 (0.39-1.31) 0.280
Cardiac disease	510 (36.2)	55 (34.4) 0.601	0.76 (0.52-1.09) 0.137
Atrial fibrillation	225 (16.0)	29 (18.1) 0.434	1.25 (0.71-2.20) 0.436
Liver disease	27 (1.9)	2 (1.3) 0.512	0.70 (0.17-2.88) 0.618
Diabetes	391 (27.8)	52 (32.5) 0.158	1.08 (0.63-1.85) 0.786
Hypertension	949 (67.4)	111 (69.4) 0.581	0.89 (0.60-1.33) 0.562
Hypercholesterolemia	548 (38.9)	59 (36.9) 0.568	0.90 (0.64-1.26) 0.525
Obesity	334 (23.7)	39 (24.4) 0.841	1.10 (0.75-1.61) 0.617
Smoking	8 (5.0)	110 (7.8) 0.158	1.47 (0.68-3.17) 0.323
Chronic medications use			
Diuretics	453 (32.2)	60 (37.5) 0.127	1.19 (0.83-1.70) 0.342
Beta blockers	259 (18.4)	28 (17.5) 0.753	0.90 (0.57-1.41) 0.642
ACEIs	388 (27.6)	51 (31.9) 0.196	1.01 (0.69-1.47) 0.981
ARBs	160 (11.4)	10 (6.3) 0.030	0.45 (0.23-0.90) 0.023
Calcium channel blockers	174 (12.4)	25 (15.6) 0.184	1.34 (0.85-2.12) 0.214
Statins	223 (15.8)	22 (13.8) 0.440	0.99 (0.59-1.64) 0.964
Oral anticoagulants	171 (12.2)	19 (11.9) 0.909	0.81 (0.41-1.59) 0.534
Antiplatelet drugs	344 (24.4)	46 (28.7) 0.179	1.30 (0.85-1.98) 0.227
Insulin	138 (9.8)	19 (11.9) 0.350	1.05 (0.59-1.86) 0.880
Oral antidiabetic drugs	233 (16.6)	35 (21.9) 0.055	1.56 (0.88-2.77) 0.131
Inhaled respiratory drugs	198 (14.1)	19 (11.9) 0.396	0.93 (0.53-1.64) 0.808
Antineoplastic agents	33 (2.3)	6 (3.8) 0.212	3.27 (1.34-7.94) 0.009
Systemic corticosteroids	36 (2.6)	0 (-) 0.029	NA (-) -
NSADs	16 (1.1)	0 (-) 0.150	NA (-) -
Antihistamines	43 (3.1)	1 (0.6) 0.058	0.21 (0.03-1.54) 0.125
Proton-Pump Inhibitors	616 (4.8)	68 (42.5) 0.729	0.82 (0.57-1.18) 0.286
Benzodiazepines	392 (27.9)	47 (29.4) 0.650	1.02 (0.72-1.46) 0.911
Vaccination's history			
Flu vaccine in prior autumn	1036 (73.6)	135 (84.4) 0.001	1.61 (0.98-2.59) 0.071
Pneumococcal vaccination	959 (68.2)	1130.6) 0.477	0.77 (0.53-1.10) 0.148

NOTE: p-values in univariate analysis were calculated by chi-squared (or Fisher's test as appropriate) comparing percentages in the study population *vs* COVID19 cases; HR denotes multivariable-adjusted Hazard ratios (Cox regression) calculated for those who had the condition as compared with those who had not the condition, being adjusted by age (continuous), sex, pre-existing comorbidities and medications use.

FIGURE 1. Flow diagram of the study.



APPENDIX. Criteria used to identify comorbidities and active medications in the study population.

Comorbidities and underlying conditions with ICD-10 codes [International Classification of Diseases, 10th Revision]	
Neurological disease:	
Dementia	F01-F03
Ictus	I63, I61
Chronic renal failure	N18-N19
Cancer (solid organ or haematological neoplasia) in past 5 years	C00-C97
Rheumatologic disease:	
Rheumatoid arthritis, enteropathic arthropathies and juvenile arthritis	M05-M09
Systemic lupus erythematosus	M32
Chronic pulmonary/respiratory disease:	
Chronic bronchitis/emphysema	J41-J44
Asthma	J45-J46
Other chronic pulmonary diseases	P27, E84, J47
Chronic heart disease:	
Congestive heart failure	I50
Coronary artery disease	I20-I22, I25
Other chronic heart diseases	I05-I08, I11,I35-I37,I42, I51.7
Atrial Fibrillation	I48
Chronic liver disease:	
Chronic viral hepatitis	B18
Cirrhosis	K74
Alcoholic hepatitis	K70
Diabetes mellitus	E10-E14
Hypertension	I10, I11, I12 o I15
Hypercholesterolemia	E78
Obesity	E66
Smoking	F17
Drugs identified in the patient treatment with codes of the Anatomical, Therapeutic, and Chemical classification system (ATC codes) of the World Health Organization:	
Diuretics	C03
Beta blockers	C07
Angiotensin converter enzyme inhibitors (ACEIs)	C09A, C09B
Angiotensin II receptor blockers (ARBs)	C09C, C09D
Calcium channel blockers	C08CA
Statins	C10AA
Oral anticoagulant drugs	B01AA, B01AE, B01AF
Antiplatelet drugs	B01AC
Insulin	A10A
Oral antidiabetic drugs	A10B
Inhaled respiratory drugs	R03A, R03B
Antineoplastic agents	L01, L02B, L03, L04
Corticosteroids for systemic use	H02A
Non-steroids anti inflammatory drugs (NSADs)	M01A
Chloroquine/Hydroxychloroquine	P01BA01, P01BA02
Antihistamines for systemic use	R06
Proton pump inhibitors	A02BC
Benzodiazepines	N05BA, N05CD, N05CF

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (p. 4) ✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (p. 4) ✓
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (p. 6) ✓
Objectives	3	State specific objectives, including any prespecified hypotheses (p. 6) ✓
Methods		
Study design	4	Present key elements of study design early in the paper (p. 6) ✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p. 6-7) ✓
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (p. 6) ✓
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed NOT APPLICABLE□
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (p. 7-8) ✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (p. 6-7 and Appendix) ✓
Bias	9	Describe any efforts to address potential sources of bias (p. 12-13) ✓
Study size	10	Explain how the study size was arrived at. NOT APPLICABLE (all people included)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (p. 8) ✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (p. 8) ✓
		(*b*) Describe any methods used to examine subgroups and interactions (p. 8) ✓
		(*c*) Explain how missing data were addressed N/A ✓
		(*d*) If applicable, explain how loss to follow-up was addressed. NOT AAPPLICABLE
		(*e*) Describe any sensitivity analyses (p. 8) ✓
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (p. 9) ✓
		(b) Give reasons for non-participation at each stage. NOT APPLICABLE
		(c) Consider use of a flow diagram (Figure 1) ✓
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p.19, Table 1) ✓
		(b) Indicate number of participants with missing data for each variable of interest. NA
		(c) Summarise follow-up time (eg, average and total amount) (p. 6) ✓
Outcome data	15*	Report numbers of outcome events or summary measures over time (p. 9)✓
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (p. 19-23, Tables 1-5) ✓
		(*b*) Report category boundaries when continuous variables were categorized (p.19,21,23, Tables 1,3,5) ✓
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (p. 22-23; Tables 4-5) ✓
Discussion		
Key results	18	Summarise key results with reference to study objectives (p. 13) ✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (p. 10-13) ✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p. 10-13) ✓
Generalisability	21	Discuss the generalisability (external validity) of the study results (p. 13) ✓
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (p. 14) ✓

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Influence of prior comorbidities and chronic medications use on the risk of COVID19 in adults: a population based cohort study in Tarragona, Spain

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Complete List of Authors:	Vila-Córcoles, Angel; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona; IDIAP Jordi Gol, Unitat de Suport a la recerca Camp de Tarragona-Reus Ochoa-Gondar, Olga; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona; IDIAP Jordi Gol, Unitat de suport a la recerca Camp de Tarragona-Reus Satué, EVA; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona; IDIAP Jordi Gol, Unitat de suport a la recerca Camp de Tarragona-Reus Torrente-Fraga, Cristina; Institut Catala De La Salut, Information and Communication Technologies Gomez-Bertomeu, Frederic; Institut Catala De La Salut, Department of Microbiology. Hospital Universtari Joan XXIII Vila-Rovira, Angel; IDIAP Jordi Gol, Unitat de suport a la recerca Camp de Tarragona-Reus Hospital-Guardiola, Immaculada; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona de Diego-Cabanes, Cinta; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona Bejarano, Ferran; Institut Catala De La Salut, Department of Pharmacology. Primary Healthcare Service Camp de Tarragona Basora-Gallisà, Josep; IDIAP Jordi Gol, Direction
Primary Subject Heading:	Infectious diseases
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TITLE PAGE

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

Author and Co-author's name

1) Angel Vila-Corcoles,

2) Olga Ochoa-Gondar,

3) Eva Satue-Gracia,

4) Cristina Torrente-Fraga,

5) Frederic Gomez-Bertomeu,

6) Angel Vila-Rovira,

7) Immaculada Hospital-Guardiola,

8) Cinta de Diego-Cabanes,

9) Ferran Bejarano-Romero

10) Josep Basora-Gallisa.

Name, postal address, email, telephone, and fax numbers of the corresponding author.

Name: Eva Mª Satué Gracia

Postal address: C/ Rambla Nova, 124, Esc D, 1A, 43001, Tarragona (Spain)

Email: esatue.tgn.ics@gencat.cat

Telephone number. +0034977254021

Fax number: +0034977226411

Full names, institutions, city, and country of all co-authors.

1) FULL NAME: Angel Vila-Corcoles, MD (avila.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.
INSTITUTION 2: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.
CITY: Barcelona
COUNTRY: Spain.

2) FULL NAME: Olga Ochoa-Gondar, MD (oochoa.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.
INSTITUTION 2: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.
CITY: Barcelona
COUNTRY: Spain.

3) FULL NAME: Eva Satue-Gracia, MD (esatue.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.
INSTITUTION 2: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.

CITY: Barcelona
COUNTRY: Spain.

4) FULL NAME: Cristina Torrente-Fraga, DM (ctorrente.tgn.ics@gencat.cat)

INSTITUTION 1: Department of information and communication technologies. DAP Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.

5) FULL NAME: Frederic Gomez-Bertomeu, MD (ffgomez.hj23.ics@gencat.cat)

INSTITUTION 1: Department of Microbiology. Hospital Universitari Joan XXIII. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.

6) FULL NAME: Angel Vila-Rovira, DM (vilapf@gmail.com)

INSTITUTION 1: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.
CITY: Barcelona

COUNTRY: Spain.

7) FULL NAME: Immaculada Hospital-Guardiola, PhD (ihospitalg.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona

COUNTRY: Spain

8) FULL NAME: Cinta de Diego-Cabanes, MD (mcdiego.tgn.ics@gencat.cat)

INSTITUTION 1:Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona

COUNTRY: Spain

9) FULL NAME: Ferran Bejarano-Romero, PhD (fbejarano.tgn.ics@gencat.cat)

INSTITUTION 1: Department of Pharmacology. DAP Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain

10) FULL NAME: Josep Basora-Gallisa, PhD (jbasora@idiapjgol.org)

INSTITUTION 1: Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)

CITY: Barcelona

COUNTRY: Spain.

KEYWORDS: Coronavirus Infections, COVID-19, Incidence, Risk, Disease Prevention

WORD COUNT: 3832 words (including abstract)

Contributors: AVC designed the study and wrote the manuscript; CTF and FGB obtained data; ESG, IHG and CDC assessed outcomes; OOG and AVR did statistical analyses; FBR revised pharmacological data; AVC and JBG coordinated the study.

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INTEREST CONFLICTS: All authors, none declared.

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

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>50 years affiliated to the 12 participating PCCs.

OUTCOMES: Baseline cohort characteristics (age, sex, vaccinations, comorbidities and chronic medications) were established at study start (01/03/2020) and primary outcome was time to COVID-19 confirmed by PCR among cohort members throughout epidemic period (from 01/03/2020 to 23/05/2020). Risk for suffering COVID-19 was evaluated by Cox regression, estimating multivariable hazard ratios (HRs) adjusted for age, sex, comorbidities and medications use.

RESULTS: During 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: 1.01-1.03; p=0.002), nursing-home residence (HR: 21.83; 95% CI: 16.66-28.61; p<0.001) and receiving diuretics (HR: 1.35; 95% CI: 1.04-1.76; p=0.026) appeared independently associated with increased risk. Smoking (HR: 0.62; 95%CI: 0.41-0.93; p=0.022), ACE-inhibitors (HR: 0.68; 95%CI: 0.47-0.99; p=0.046) and antihistamine (HR: 0.47; 95% CI: 0.22-1.01; p=0.052) were associated with a lower risk. Among community-dwelling individuals, cancer (HR: 1.52; 95% CI: 1.03-2.24; p=0.035), chronic respiratory disease (HR: 1.82; 95% CI: 1.08-3.07; p=0.025) and cardiac disease (HR: 1.53; 95% CI: 1.06-2.19; p=0.021) emerged also associated with an increased risk. Receiving ACE-inhibitors (HR: 0.66; 95% CI: 0.44-0.99; p=0.046) and flu vaccination (HR: 0.63; 95% CI: 0.44-0.91; p=0.012) were associated with decreased risk.

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.

KEYWORDS: Coronavirus Infections, COVID-19, Incidence, Risk, Disease Prevention.

- Strengths and limitations of this study (per article summary)

- This is a population-based cohort study involving 79,083 adults>50 years in Tarragona (Southern Catalonia, Spain)

- Cohort members were retrospectively followed across the first wave of COVID-19 epidemic period from 01/03/2020 to 23/05/2020.

- 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 r~~elatively low, which limits statistical power (especially in subgroup analyses).

- PCR testing was not routinely performed (prioritized for severe case patients) and asymptomatic/oligosymtomatic cases were underestimated.

INTRODUCTION

At present, available population-based clinical data on the current coronavirus SARS-COV-2 pandemic (COVID-19 disease) is limited. Most available clinical information is hospital-based data derived from severe cases (hospital/ICU admitted/deaths),[1-4] but there is few population- or community-based data involving a wide representative sample of the exposed population. In fact, there is very scarce data assessing incidence and risk for suffering infection in relation with pre-existing clinical characteristics of the population (i.e, 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 to 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 sociodemographical) and therefore concerns have been raised about the possibility that some of these comorbidities/underlying conditions increase risk for severe disease, but they were not really related “per se” with 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 United Kingdom 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 socio-demographic aspects and susceptibility for COVID-19, some studies reported that sex men older age are associated with a higher risk of infection and a worse prognosis But evidence on sociodemographical and clinical disparities related with the susceptibility for SARS-COV-2 infection is limited and new studies collecting this data are needed.[5,6,8]

In this context, this study was aimed to analyse incidence and risk for suffering COVID-19 in relation with pre-existing comorbidities and, especially, common chronic medications use among the general adult population over 50 years in Tarragona (Southern Catalonia, Spain) across 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 persons ≥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). Cohort members were all persons >50 years-old (birth day data before 01/01/1970) affiliated in the 12 participating primary care centres (PCCs) managed by 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 a 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 from 01/03/2020 (the beginning of epidemic period in the region), until the occurrence of any study event (COVID-19 diagnosis) or until the end of 12-weeks follow-up (23/05/2020). 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 pre-existing CAPAMIS Research Database, an institutional clinical research database previously used for other cohort studies in the study area[11] was quickly updated for use as the main data source in this COVID-19 epidemiological investigation. Briefly, this research database compiles data from the institutional PCCs' clinical records system (working since the 2000s), including administrative data and clinical information coded according to the International Classification of Diseases 10th Revision (ICD-10). It was used to identify sociodemographical characteristics, comorbidities, vaccinations history and active medications use among cohort members and to establish baseline characteristics of study population at study start (01/03/2020).

When COVID-19 epidemic period started in the study area, two electronic alerts including COVID-19's laboratory registries plus 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 PCCs clinical records system and, later, both data sources were linked to construct an anonymized research database used for this report.

Outcomes

Primary outcome was COVID-19 diagnosed by polymerase chain reaction (PCR) occurred among cohort members across the study period (from 01/03/2020 to 23/05/2020). For descriptive results we also report laboratory-excluded cases (PCR performed with a negative result) and presumptive COVID-19 cases (persons coded as clinical suspicion alone without PCR tested). For laboratory diagnosis of COVID-19 by RT-PCR, guidelines of the Health Department of the Generalitat de Catalunya were followed.[12] Briefly, from the samples collected by nasal and pharyngeal swab with transport medium for viruses and refrigerated at 4°C for a maximum of 48 hours, the RT-PCR technique Cobas© SARS-CoV-2 with CE-FDA marking was performed with a sensitivity and specificity close to 100%.[13] At the beginning of the epidemic period, the availability for PCR testing was scarce, being prioritized for severe cases admitted in the hospital and nursing-home residences (where several outbreaks occurred), whereas less PCR tests were made among possible cases managed as outpatient.

Exposure

Baseline use of common chronic medications, which could be hypothetically related with physiopathological mechanism of SARS-COV-2 infection or virulence (e.g., antihypertensive, antiplatelet/anticoagulant and/or anti-inflammatory drugs), were considered as main explanatory variables possibly related with the occurrence of COVID-19 for the present study. It was determined by a review of the PHCCs' electronic clinical records system which contains specially designated fields for medications prescribed. Thus, active medication treatments in each cohort member on 01/03/2020, coded according to the Anatomical, Therapeutic, and Chemical classification system (ATC) of the World Health Organization,[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, angiotensin converting enzyme 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 (NSADs), chloroquine/hydroxychloroquine, antihistamines, proton-pump inhibitors and benzodiazepines (see Appendix).

Covariates

Besides age, sex, residence (community-dwelling/nursing-home), and vaccinations' history (flu vaccination in prior autumn or pneumococcal vaccination at any time), the following comorbidities/underlying conditions were considered according to data registered in the electronic PCCs clinical records on 01/03/2020: neurological disease (including dementia and stroke), cancer (solid organ or haematological neoplasia diagnosed in 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, hypercholesterolemia, obesity and smoking (see 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

Incidence rates (IRs) for PCR-confirmed COVID-19 were calculated per 100,000 person-period (12 weeks). Confidence intervals (CIs) for IRs were calculated assuming a Poisson distribution for uncommon events. In bivariate analyses, baseline characteristics according to suffer or not COVID-19 were compared using Chi-squared or Fisher's test as appropriate.

Cox regression analyses were used to calculate unadjusted and multivariable-adjusted hazards ratios (HRs) and estimate the association between baseline exposure conditions and the time to PCR-confirmed COVID-19 occurred among cohort members throughout the epidemic period (from 01/03/2020 to 23/05/2020).[15] The multivariable Cox models were made with all above mentioned exposure variables and co-variables (i.e, age, sex, residence, vaccinations history, comorbidities/underlying conditions and medications use). The method to select a subset of co-variables to include in the final model was the purposeful selection.[15] The final models include significant, confounders and all co-variables judged clinically or epidemiologically relevant. We performed a main analysis including the total study cohort (N=79,083) and two subgroup analyses restricted to community-dwelling individuals (N=77,676) and nursing-home residents (N=1407). Statistical significance was set at $p < 0.05$ (two-tailed). Data was performed by using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA).

RESULTS:

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 44% 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 vs 1394 (60%) in aged >65 years (p<0.001), 1023 (44%) in men vs 1301 (56%) in women (p=0.007) and 1789 (77%) in community-dwelling vs 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 50-64 years, 95 (25%) in 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 yrs vs 365.2 in 65-79 yrs *vs*1771.6 in 80 yrs or older; 419.9 in men *vs*535.5 in women)

The most prevalent pre-existing comorbidities/underlying conditions among the 380 COVID-19 patients were hypertension (58.7%), hypercholesterolemia (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: 1.01-1.03; p=0.002), nursing-home residence (HR: 21.83; 95% CI: 16.66-28.61; p<0.001) and receiving diuretics (HR: 1.35; 95% CI: 1.04-1.76; p=0.026) appeared significantly associated with an increasing risk. Conversely, smoking (HR: 0.62; 95%CI: 0.41-0.93; p=0.022), receiving angiotensin II receptor blockers (HR: 0.68; 95%CI: 0.47-0.99; p=0.046) and antihistamines (HR: 0.47; 95% CI: 0.22-1.01; 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 distribution of PCR-confirmed COVID-19 cases and specific-IRs by demographical characteristics, underlying conditions and medications use among community-dwelling individuals. In the multivariable analysis focused on these community-dwelling individuals, chronic respiratory disease (HR: 1.82; 95% CI: 1.08-3.07; p=0.025), cardiac disease (HR: 1.53; 95% CI: 1.06-2.19; p=0.021) cancer (HR: 1.52; 95% CI: 1.03-2.24; p=0.035) receiving diuretics (HR: 1.54; 95% CI: 1.04-2.27; p=0.031) and insulin (HR: 1.79; 95% CI: 1.00-3.21; p=0.049) were associated with an increasing risk, whereas smoking (HR: 0.49; 95% CI: 0.30-0.80; p=0.004), receiving ACE-inhibitors (HR: 0.66; 95% CI: 0.44-0.99; p=0.046) and influenza vaccination in prior autumn (HR: 0.63; 95% CI: 0.44-0.91; 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 analysis 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 increasing risk, whereas receiving angiotensin II receptor blockers was associated with a decreased risk (HR: 0.45; 95% CI: 0.23-0.90; 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 with 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 sociodemographical variables, apart of nursing-home residence that increased more than twenty-times the adjusted-risk for PCR-confirmed COVID-19, we found that age increased approximately a 2% for each year the adjusted-risk for suffering COVID-19. Despite COVID-19 was more frequent in women, sex did not alter significantly the risk of infection in multivariable analysis.

None comorbidity appeared 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 significantly associated with an increased risk in subgroup analysis focused on community-dwelling individuals. Hypertension, diabetes and/or obesity did not emerge independently associated with a significant increasing risk for suffering COVID-19 in our adjusted analyses. There is general consensus considering these conditions as major risk conditions related with poor prognosis in hospitalised COVID-19 patients,[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 hypothesized 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 with 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; however, 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 COVID-19 hospitalized patients.[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 (i.e., 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 NSADs or corticosteroids (which have been associated with good outcomes when using in severe COVID-19 patients)[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 disease from COVID-19. 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 hospitalized COVID-19 patients.[40]

Community-dwelling individuals who received influenza vaccination in prior autumn appeared at-decreased risk to suffer PCR-confirmed COVID-19 in our adjusted analysis. Although this finding may be possibly related with residual confounding due to unmeasured factors (e.g, life-style or health care-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 hypothesized 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 flu 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 with 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 (i.e, 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 prioritized for hospitalised or severe case patients. 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 (e.g, 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/ICU 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 where relatively few events (n=380) which limits statistical power, especially in 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 characterize 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 supports 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.

Since 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 antihistamine drugs in allergic patients could be complementary tools partially protecting against COVID-19.

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Data availability statement: Data are available upon reasonable request

Patient and Public Involvement statement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

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TABLES

Table 1. Incidence of PCR-confirmed COVID-19 cases according to baseline demographical and clinical characteristics (comorbidities/medications) in the total study cohort (N=79,083). Tarragona region (Southern Catalonia, Spain), 01/03/2020-23/05/2020.

Characteristic	Study population (N=79083) n (%)	PCR-confirmed COVID-19 cases (n=380)	
		Univariate analysis n (%) p-value	Incidence rate
Sociodemographical			
Age: 50-64 yrs	42684 (54.0)	101 (26.6) <0.001	236.6 (193.6-288.7)
65-79 yrs	26013 (32.9)	95 (25.0)	365.2 (295.4-452.9)
≥80 yrs	10386 (13.1)	184 (48.4)	1771.6 (1527.1-2055.1)
Sex Men	37626 (47.6)	158 (41.6) 0.019	419.9 (358.6-491.7)
Women	41457 (52.4)	222 (58.4)	535.5 (464.8-616.4)
Community-dwelling	77676 (98.2)	220 (57.9) <0.001	283.2 (245.8-326.0)
Nursing-home residence	1407 (1.8)	160 (42.1)	11371.7 (9711.4-13316.3)
Comorbidities			
Neurological disease	2317 (2.9)	66 (17.4) <0.001	2848.5 (2236.1-3617.6)
Renal disease	4476 (5.7)	49 (12.9) <0.001	1094.7 (812.3-1445.0)
Cancer	6630 (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	7272 (9.2)	63 (16.6) <0.001	866.3 (667.1-1126.2)
Cardiac disease	13435 (17.0)	123 (32.4) <0.001	915.5 (762.6-1098.6)
Atrial fibrillation	3786 (4.8)	55 (14.5) <0.001	1452.7 (1077.9-1917.6)
Liver disease	1465 (1.9)	8 (2.1) 0.714	546.1 (235.4-1075.8)
Diabetes	13317 (16.8)	102 (26.8) <0.001	765.9 (626.5-934.4)
Hypertension	34945 (44.2)	223 (58.7) <0.001	638.1 (553.9-734.5)
Hypercholesterolemia	27314 (34.5)	133 (35.0) 0.850	486.9 (411.0-576.5)
Obesity	21678 (27.4)	96 (25.3) 0.347	442.8 (362.2-540.3)
Smoking	12750 (16.1)	27 (7.1) <0.001	211.8 (139.6-309.2)
Chronic medications use			
Diuretics	8481 (10.7)	111 (29.2) <0.001	1308.8 (1090.2-1570.6)
Beta blockers	9571 (12.1)	68 (17.9) 0.001	710.5 (557.7-902.3)
ACEIs	16419 (20.8)	92 (24.2) 0.097	560.3 (453.3-694.8)
ARBs	8869 (11.2)	39 (10.3) 0.556	439.7 (314.0-598.0)
Calcium channel blockers	6490 (8.2)	52 (13.7) <0.001	801.2 (594.5-1057.6)
Statins	16134 (20.4)	69 (18.2) 0.277	427.7 (335.7-543.1)
Oral anticoagulants	3912 (4.9)	46 (12.1) <0.001	1175.9 (857.2-1575.7)
Antiplatelet drugs	9154 (11.6)	86 (22.6) <0.001	939.5 (760.0-1165.0)
Insulin	3042 (3.8)	39 (10.3) <0.001	1282.1 (915.4-1743.6)
Oral antidiabetic drugs	10585 (13.4)	69 (18.2) 0.006	651.9 (511.7-827.9)
Inhaled respiratory drugs	6293 (8.0)	61 (16.1) <0.001	969.3 (746.4-1260.1)
Antineoplastic agents	1614 (2.0)	8 (2.1) 0.929	495.7 (213.6-976.5)
Systemic corticosteroids	1252 (1.6)	5 (1.3) 0.676	399.4 (129.4-930.5)
NSADs	4321 (5.5)	12 (3.2) 0.047	277.7 (143.6-486.0)
Chloroquine	168 (0.2)	0 (0.0) 0.367	0 (-)
Antihistamines	3264 (4.1)	7 (1.8) 0.025	214.5 (86.0-446.1)
Proton-Pump Inhibitors	17931 (22.7)	142 (37.4) <0.001	791.9 (668.4-937.6)
Benzodiazepines	13046 (16.5)	96 (25.3) <0.001	735.9 (601.9-897.7)
Vaccination's history			
Flu vaccine in prior autumn	22606 (28.6)	205 (53.9) <0.001	906.8 (787.1-1043.8)
Pneumococcal vaccinated	26183 (33.1)	213 (56.1) <0.001	813.5 (706.1-936.3)

NOTE: P-values in univariate analysis were calculated by chi-squared, or Fisher's test as appropriate, comparing percentages in the study population vs 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.

Table 2. Cox regression analyses assessing unadjusted and adjusted risks to suffer PCR-confirmed COVID-19 in the total study cohort (N=79,083). Tarragona region (Southern Catalonia, Spain) from 01/03/2020 to 23/05/2020.

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

NOTE: 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 denote confidence intervals.

Table 3. Incidence of PCR-confirmed COVID-19 cases according to baseline demographical and clinical characteristics (comorbidities/medications) in subgroup analysis restricted to community-dwelling individuals (N=77,676). Tarragona region (Southern Catalonia, Spain), 01/03/2020-23/05/2020.

Characteristic	Study population (N=77676) n (%)	PCR-confirmed COVID-19 cases (n=220)	
		Univariate analysis n (%) p-value	Incidence rate
Sociodemographical			
Age: 50-64 yrs	42533 (54.8)	99 (45.0) <0.001	232.8 (190.4-284.0)
65-79 yrs	25713 (33.1)	72 (32.7)	280.0 (219.8-355.6)
≥80 yrs	9430 (12.1)	49 (22.3)	519.6 (385.6-685.9)
Sex Men	37145 (47.8)	108 (49.1) 0.706	290.8 (237.8-354.7)
Women	40531 (52.2)	112 (50.9)	276.3 (230.2-331.6)
Comorbidities			
Neurological disease	1951 (2.5)	11 (5.0) 0.018	563.8 (281.3-1009.2)
Renal disease	4240 (5.5)	26 (11.8) <0.001	613.2 (400.4-901.4)
Cancer	6463 (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	7075 (9.1)	47 (21.4) <0.001	664.3 (484.3-890.2)
Cardiac disease	12925 (16.6)	68 (30.9) <0.001	526.1 (413.0-668.2)
Atrial fibrillation	3561 (4.6)	26 (11.8) <0.001	730.1 (476.8-1073.3)
Liver disease	1438 (1.9)	6 (2.7) 0.334	417.2 (153.1-909.6)
Diabetes	12926 (16.6)	50 (22.7) 0.015	386.8 (287.0-510.6)
Hypertension	33996 (43.8)	112 (50.9) 0.032	329.5 (274.4-395.3)
Hypercholesterolemia	26766 (34.5)	74 (33.6) 0.797	276.5 (217.0-351.1)
Obesity	21344 (27.5)	57 (25.9) 0.602	267.1 (205.6-347.2)
Smoking	12640 (16.3)	19 (8.6) 0.002	150.3 (90.5-234.5)
Chronic medications use			
Diuretics	8028 (10.3)	51 (23.2) <0.001	635.3 (471.4-838.6)
Beta blockers	9312 (12.0)	40 (18.2) 0.005	429.6 (306.7-584.2)
ACEIs	16031 (20.6)	41 (18.6) 0.462	255.8 (182.6-347.8)
ARBs	8709 (11.2)	29 (13.2) 0.354	333.0 (223.1-479.5)
Calcium channel blockers	6316 (8.1)	27 (12.3) 0.024	427.5 (281.7-624.1)
Statins	15911 (20.5)	47 (21.4) 0.746	295.4 (215.3-395.8)
Oral anticoagulants	3741 (4.8)	27 (12.3) <0.001	721.7 (475.6-1053.7)
Antiplatelet drugs	8810 (11.3)	40 (18.2) 0.001	454.0 (324.2-617.5)
Insulin	2904 (3.7)	20 (9.1) <0.001	688.7 (420.8-1060.6)
Oral antidiabetic drugs	10352 (13.3)	34 (15.5) 0.353	328.4 (228.9-456.5)
Inhaled respiratory drugs	6095 (7.8)	42 (19.1) <0.001	689.1 (492.0-937.2)
Antineoplastic agents	1581 (2.0)	2 (0.9) 0.236	126.5 (15.3-456.7)
Systemic corticosteroids	1216 (1.6)	5 (2.3) 0.397	411.2 (133.2-958.1)
NSADs	4305 (5.5)	12 (5.5) 0.955	278.7 (144.1-487.8)
Antihistamines	3221 (4.1)	6 (2.7) 0.290	186.3 (68.4-406.1)
Proton-Pump Inhibitors	17315 (22.3)	74 (33.6) <0.001	427.4 (335.5-542.8)
Benzodiazepines	12654 (16.3)	49 (22.3) 0.016	387.2 (287.3-511.1)
Vaccination's history			
Flu vaccine in prior autumn	21570 (27.8)	70 (31.8) 0.179	324.5 (254.8-412.1)
Pneumococcal vaccinated	25224 (32.5)	100 (45.5) <0.001	396.4 (324.3-483.7)

NOTE: P-values in univariate analysis were calculated by chi-squared, or Fisher's test as appropriate, comparing percentages in the study population *vs* 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.

Table 4. Cox regression analyses assessing unadjusted and adjusted risks to suffer PCR-confirmed COVID-19 among community-dwelling individuals (N=77,676). Tarragona region (Southern Catalonia, Spain), 01/03/2020-23/05/2020.

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

NOTE: HRs denotes Hazard ratios, and were calculated for those who had the condition as compared with those who had not 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.

Table 5. Univariate and multivariate analyses on laboratory-confirmed COVID-19 cases according to baseline demographical and clinical characteristics (comorbidities/medications) in subgroup analysis restricted to nursing-home residents (N=1407). Tarragona region (Southern Catalonia, Spain) from 01/03/2020 to 23/05/2020.

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
Sociodemographical			
Age: 50-64 yrs	151 (10.7)	2 (1.3) <0.001	1.00 (reference)
65-79 yrs	300 (21.3)	23 (14.4)	6.66 (1.53-29.02) 0.012
≥80 yrs	956 (67.9)	135 (84.4)	13.16 (3.09-56.00) <0.001
Sex: Men	481 (34.2)	50 (31.3) 0.406	1.00 (reference)
Women	926 (65.8)	110 (68.8)	0.85 (0.59-1.24) 0.402
Comorbidities			
Neurological disease	366 (26.0)	55 (34.4) 0.010	1.25 (0.89-1.76) 0.193
Renal disease	236 (16.8)	23 (14.4) 0.388	0.68 (0.43-1.08) 0.104
Cancer	167 (11.9)	17 (10.6) 0.605	0.74 (0.43-1.26) 0.264
Rheumatic disease	12 (0.9)	1 (0.6) 0.739	0.86 (0.12-6.43) 0.885
Respiratory disease	197 (14.0)	16 (10.0) 0.121	0.72 (0.39-1.31) 0.280
Cardiac disease	510 (36.2)	55 (34.4) 0.601	0.76 (0.52-1.09) 0.137
Atrial fibrillation	225 (16.0)	29 (18.1) 0.434	1.25 (0.71-2.20) 0.436
Liver disease	27 (1.9)	2 (1.3) 0.512	0.70 (0.17-2.88) 0.618
Diabetes	391 (27.8)	52 (32.5) 0.158	1.08 (0.63-1.85) 0.786
Hypertension	949 (67.4)	111 (69.4) 0.581	0.89 (0.60-1.33) 0.562
Hypercholesterolemia	548 (38.9)	59 (36.9) 0.568	0.90 (0.64-1.26) 0.525
Obesity	334 (23.7)	39 (24.4) 0.841	1.10 (0.75-1.61) 0.617
Smoking	8 (5.0)	110 (7.8) 0.158	1.47 (0.68-3.17) 0.323
Chronic medications use			
Diuretics	453 (32.2)	60 (37.5) 0.127	1.19 (0.83-1.70) 0.342
Beta blockers	259 (18.4)	28 (17.5) 0.753	0.90 (0.57-1.41) 0.642
ACEIs	388 (27.6)	51 (31.9) 0.196	1.01 (0.69-1.47) 0.981
ARBs	160 (11.4)	10 (6.3) 0.030	0.45 (0.23-0.90) 0.023
Calcium channel blockers	174 (12.4)	25 (15.6) 0.184	1.34 (0.85-2.12) 0.214
Statins	223 (15.8)	22 (13.8) 0.440	0.99 (0.59-1.64) 0.964
Oral anticoagulants	171 (12.2)	19 (11.9) 0.909	0.81 (0.41-1.59) 0.534
Antiplatelet drugs	344 (24.4)	46 (28.7) 0.179	1.30 (0.85-1.98) 0.227
Insulin	138 (9.8)	19 (11.9) 0.350	1.05 (0.59-1.86) 0.880
Oral antidiabetic drugs	233 (16.6)	35 (21.9) 0.055	1.56 (0.88-2.77) 0.131
Inhaled respiratory drugs	198 (14.1)	19 (11.9) 0.396	0.93 (0.53-1.64) 0.808
Antineoplastic agents	33 (2.3)	6 (3.8) 0.212	3.27 (1.34-7.94) 0.009
Systemic corticosteroids	36 (2.6)	0 (-) 0.029	NA (-) -
NSADs	16 (1.1)	0 (-) 0.150	NA (-) -
Antihistamines	43 (3.1)	1 (0.6) 0.058	0.21 (0.03-1.54) 0.125
Proton-Pump Inhibitors	616 (4.8)	68 (42.5) 0.729	0.82 (0.57-1.18) 0.286
Benzodiazepines	392 (27.9)	47 (29.4) 0.650	1.02 (0.72-1.46) 0.911
Vaccination's history			
Flu vaccine in prior autumn	1036 (73.6)	135 (84.4) 0.001	1.61 (0.98-2.59) 0.071
Pneumococcal vaccination	959 (68.2)	1130.6) 0.477	0.77 (0.53-1.10) 0.148

NOTE: p-values in univariate analysis were calculated by chi-squared (or Fisher's test as appropriate) comparing percentages in the study population *vs* COVID-19 cases; HR denotes multivariable-adjusted Hazard ratios (Cox regression) calculated for those who had the condition as compared with those who had not the condition, being adjusted by age (continuous), sex, pre-existing comorbidities and medications use.

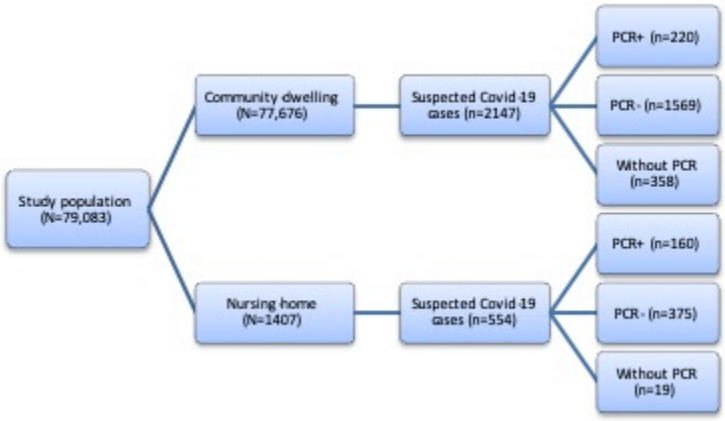

FIGURE 1. Flow diagram of the study.

APPENDIX. Criteria used to identify comorbidities and active medications in the study population.

Comorbidities and underlying conditions with ICD-10 codes [International Classification of Diseases, 10th Revision]	
Neurological disease:	
Dementia	F01-F03
Ictus	I63, I61
Chronic renal failure	N18-N19
Cancer (solid organ or haematological neoplasia) in past 5 years	C00-C97
Rheumatologic disease:	
Rheumatoid arthritis, enteropathic arthropathies and juvenile arthritis	M05-M09
Systemic lupus erythematosus	M32
Chronic pulmonary/respiratory disease:	
Chronic bronchitis/emphysema	J41-J44
Asthma	J45-J46
Other chronic pulmonary diseases	P27, E84, J47
Chronic heart disease:	
Congestive heart failure	I50
Coronary artery disease	I20-I22, I25
Other chronic heart diseases	I05-I08, I11,I35-I37,I42, I51.7
Atrial Fibrillation	I48
Chronic liver disease:	
Chronic viral hepatitis	B18
Cirrhosis	K74
Alcoholic hepatitis	K70
Diabetes mellitus	E10-E14
Hypertension	I10, I11, I12 o I15
Hypercholesterolemia	E78
Obesity	E66
Smoking	F17
Drugs identified in the patient treatment with codes of the Anatomical, Therapeutic, and Chemical classification system (ATC codes) of the World Health Organization:	
Diuretics	C03
Beta blockers	C07
Angiotensin converter enzyme inhibitors (ACEIs)	C09A, C09B
Angiotensin II receptor blockers (ARBs)	C09C, C09D
Calcium channel blockers	C08CA
Statins	C10AA
Oral anticoagulant drugs	B01AA, B01AE, B01AF
Antiplatelet drugs	B01AC
Insulin	A10A
Oral antidiabetic drugs	A10B
Inhaled respiratory drugs	R03A, R03B
Antineoplastic agents	L01, L02B, L03, L04
Corticosteroids for systemic use	H02A
Non-steroids anti inflammatory drugs (NSADs)	M01A
Chloroquine/Hydroxychloroquine	P01BA01, P01BA02
Antihistamines for systemic use	R06
Proton pump inhibitors	A02BC
Benzodiazepines	N05BA, N05CD, N05CF

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (p. 4) ✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (p. 4) ✓
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (p. 6) ✓
Objectives	3	State specific objectives, including any prespecified hypotheses (p. 6) ✓
Methods		
Study design	4	Present key elements of study design early in the paper (p. 6) ✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p. 6-7) ✓
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (p. 6) ✓
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed NOT APPLICABLE□
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (p. 7-8) ✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (p. 6-7 and Appendix) ✓
Bias	9	Describe any efforts to address potential sources of bias (p. 12-13) ✓
Study size	10	Explain how the study size was arrived at. NOT APPLICABLE (all people included)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (p. 8) ✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (p. 8) ✓
		(*b*) Describe any methods used to examine subgroups and interactions (p. 8) ✓
		(*c*) Explain how missing data were addressed N/A ✓
		(*d*) If applicable, explain how loss to follow-up was addressed. NOT AAPPLICABLE
		(*e*) Describe any sensitivity analyses (p. 8) ✓
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (p. 9) ✓
		(b) Give reasons for non-participation at each stage. NOT APPLICABLE
		(c) Consider use of a flow diagram (Figure 1) ✓
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p.19, Table 1) ✓
		(b) Indicate number of participants with missing data for each variable of interest. NA
		(c) Summarise follow-up time (eg, average and total amount) (p. 6) ✓
Outcome data	15*	Report numbers of outcome events or summary measures over time (p. 9)✓
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (p. 19-23, Tables 1-5) ✓
		(*b*) Report category boundaries when continuous variables were categorized (p.19,21,23, Tables 1,3,5) ✓
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (p. 22-23; Tables 4-5) ✓
Discussion		
Key results	18	Summarise key results with reference to study objectives (p. 13) ✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (p. 10-13) ✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p. 10-13) ✓
Generalisability	21	Discuss the generalisability (external validity) of the study results (p. 13) ✓
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (p. 14) ✓

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Influence of prior comorbidities and chronic medications use on the risk of COVID19 in adults: a population based cohort study in Tarragona, Spain

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Complete List of Authors:	Vila-Córcoles, Angel; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona; IDIAP Jordi Gol, Unitat de Suport a la recerca Camp de Tarragona-Reus Ochoa-Gondar, Olga; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona; IDIAP Jordi Gol, Unitat de suport a la recerca Camp de Tarragona-Reus Satué, EVA; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona; IDIAP Jordi Gol, Unitat de suport a la recerca Camp de Tarragona-Reus Torrente-Fraga, Cristina; Institut Catala De La Salut, Information and Communication Technologies Gomez-Bertomeu, Frederic; Institut Catala De La Salut, Department of Microbiology. Hospital Universtari Joan XXIII Vila-Rovira, Angel; IDIAP Jordi Gol, Unitat de suport a la recerca Camp de Tarragona-Reus Hospital-Guardiola, Immaculada; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona de Diego-Cabanes, Cinta; Institut Catala De La Salut, Primary Healthcare Service Camp de Tarragona Bejarano, Ferran; Institut Catala De La Salut, Department of Pharmacology. Primary Healthcare Service Camp de Tarragona Basora-Gallisà, Josep; IDIAP Jordi Gol, Direction
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TITLE PAGE

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

Author and Co-author's name

1) Angel Vila-Corcoles,

2) Olga Ochoa-Gondar,

3) Eva Satue-Gracia,

4) Cristina Torrente-Fraga,

5) Frederic Gomez-Bertomeu,

6) Angel Vila-Rovira,

7) Immaculada Hospital-Guardiola,

8) Cinta de Diego-Cabanes,

9) Ferran Bejarano-Romero

10) Josep Basora-Gallisa.

Name, postal address, email, telephone, and fax numbers of the corresponding author.

Name: Eva Mª Satué Gracia

Postal address: C/ Rambla Nova, 124, Esc D, 1A, 43001, Tarragona (Spain)

Email: esatue.tgn.ics@gencat.cat

Telephone number. +0034977254021

Fax number: +0034977226411

Full names, institutions, city, and country of all co-authors.

1) FULL NAME: Angel Vila-Corcoles, MD (avila.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.
INSTITUTION 2: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.
CITY: Barcelona
COUNTRY: Spain.

2) FULL NAME: Olga Ochoa-Gondar, MD (oochoa.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.
INSTITUTION 2: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.
CITY: Barcelona
COUNTRY: Spain.

3) FULL NAME: Eva Satue-Gracia, MD (esatue.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.
INSTITUTION 2: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.

CITY: Barcelona
COUNTRY: Spain.

4) FULL NAME: Cristina Torrente-Fraga, DM (ctorrente.tgn.ics@gencat.cat)

INSTITUTION 1: Department of information and communication technologies. DAP Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.

5) FULL NAME: Frederic Gomez-Bertomeu, MD (ffgomez.hj23.ics@gencat.cat)

INSTITUTION 1: Department of Microbiology. Hospital Universitari Joan XXIII. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain.

6) FULL NAME: Angel Vila-Rovira, DM (vilapf@gmail.com)

INSTITUTION 1: Unitat de Suport a la Recerca Camp de Tarragona-Reus. IDIAP Jordi Gol.
CITY: Barcelona

COUNTRY: Spain.

7) FULL NAME: Immaculada Hospital-Guardiola, PhD (ihospitalg.tgn.ics@gencat.cat)

INSTITUTION 1: Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona

COUNTRY: Spain

8) FULL NAME: Cinta de Diego-Cabanes, MD (mcdiego.tgn.ics@gencat.cat)

INSTITUTION 1:Primary Health Care Service Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona

COUNTRY: Spain

9) FULL NAME: Ferran Bejarano-Romero, PhD (fbejarano.tgn.ics@gencat.cat)

INSTITUTION 1: Department of Pharmacology. DAP Camp de Tarragona. Institut Catala de la Salut.
CITY: Tarragona
COUNTRY: Spain

10) FULL NAME: Josep Basora-Gallisa, PhD (jbasora@idiapjgol.org)

INSTITUTION 1: Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)

CITY: Barcelona

COUNTRY: Spain.

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INTEREST CONFLICTS: All authors, none declared.

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

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>50 years affiliated to the 12 participating PCCs.

OUTCOMES: Baseline cohort characteristics (age, sex, vaccinations, comorbidities and chronic medications) were established at study start (01/03/2020) and primary outcome was time to COVID-19 confirmed by PCR among cohort members throughout epidemic period (from 01/03/2020 to 23/05/2020). Risk for suffering COVID-19 was evaluated by Cox regression, estimating multivariable hazard ratios (HRs) adjusted for age, sex, comorbidities and medications use.

RESULTS: During 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: 1.01-1.03; p=0.002), nursing-home residence (HR: 21.83; 95% CI: 16.66-28.61; p<0.001) and receiving diuretics (HR: 1.35; 95% CI: 1.04-1.76; p=0.026) appeared independently associated with increased risk. Smoking (HR: 0.62; 95%CI: 0.41-0.93; p=0.022), ACE-inhibitors (HR: 0.68; 95%CI: 0.47-0.99; p=0.046) and antihistamine (HR: 0.47; 95% CI: 0.22-1.01; p=0.052) were associated with a lower risk. Among community-dwelling individuals, cancer (HR: 1.52; 95% CI: 1.03-2.24; p=0.035), chronic respiratory disease (HR: 1.82; 95% CI: 1.08-3.07; p=0.025) and cardiac disease (HR: 1.53; 95% CI: 1.06-2.19; p=0.021) emerged also associated with an increased risk. Receiving ACE-inhibitors (HR: 0.66; 95% CI: 0.44-0.99; p=0.046) and flu vaccination (HR: 0.63; 95% CI: 0.44-0.91; p=0.012) were associated with decreased risk.

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.

KEYWORDS: Coronavirus Infections, COVID-19, Incidence, Risk, Disease Prevention.

- Strengths and limitations of this study (per article summary)

- This is a population-based cohort study involving 79,083 adults>50 years in Tarragona (Southern Catalonia, Spain)

- Cohort members were retrospectively followed across the first wave of COVID-19 epidemic period from 01/03/2020 to 23/05/2020.

- 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 r~~elatively low, which limits statistical power (especially in subgroup analyses).

- PCR testing was not routinely performed (prioritized for severe case patients) and asymptomatic/oligosymtomatic cases were underestimated.

INTRODUCTION

Currently population-based clinical data on the SARS-COV-2 coronavirus (COVID-19 disease) pandemic is limited. Furthermore, the available clinical information comes mainly from hospitalized 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 with pre-existing clinical characteristics of the population (i.e, 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 to 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 risk for severe disease, but they were not really related “per se” with 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 United Kingdom 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 socio-demographic aspects and susceptibility for COVID-19, some studies reported that sex men older age are associated with a higher risk of infection and a worse prognosis But evidence on sociodemographic and clinical disparities related with the susceptibility for SARS-COV-2 infection is limited and new studies collecting this 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 ≥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 (birth day data before 01/01/1970) affiliated in the 12 participating primary care centres (PCCs) managed by 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 a 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 from 01/03/2020 (the beginning of epidemic period in the region), until the occurrence of any study event (COVID-19 diagnosis) or until the end of 12-weeks follow-up (23/05/2020). 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 (03/01/2020).

At the start of the COVID19 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 anonymized 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 test (PCR) among cohort members throughout study period (from 01/03/2020 to 23/05/2020). 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 was performed).

The guidelines of the Department of Health of the *Generalitat de Catalunya* were followed for the laboratory diagnosis of COVID-19 by RT-PCR.[12] In summary, the Cobas © SARS-CoV-2 RT-PCR technique with 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; a 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 prioritized for severe cases (requiring hospital admission) and for nursing-home residents (since there were several outbreaks in residences), while among suspected cases of outpatient management, conducted fewer PCR-tests.

Exposure

Baseline use of common chronic medications, which could be hypothetically related with physiopathological mechanism of SARS-COV-2 infection or virulence (e.g., antihypertensive, antiplatelet/anticoagulant and/or anti-inflammatory drugs), were considered as main explanatory variables possibly related with the occurrence of COVID-19 for the present study. It was determined by a review of the PHCCs' electronic clinical records system which contains specially designated fields for medications prescribed. Thus, active medication treatments in each cohort member on 01/03/2020, coded according to the Anatomical, Therapeutic, and Chemical classification system (ATC) of the World Health Organization,[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, angiotensin converting enzyme 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 (NSADs), chloroquine/hydroxychloroquine, antihistamines, proton-pump inhibitors and benzodiazepines (see Appendix).

Covariates

Besides age, sex, residence (community-dwelling/nursing-home), and vaccinations' history (flu 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 01/03/2020, were considered: neurological disease (including dementia and stroke), cancer (solid organ or haematological neoplasia diagnosed in 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, hypercholesterolemia, obesity and smoking (see 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 Chi-squared or Fisher's test as appropriate, in bivariate analyses.

Cox regression analyses were used to calculate unadjusted and multivariable-adjusted hazards ratios (HRs) and estimate the association between baseline exposure conditions and the time to PCR-confirmed COVID-19 occurred among cohort members throughout the epidemic period (from 01/03/2020 to 23/05/2020). The multivariable Cox models were made with all above mentioned exposure variables and co-variables (i.e, age, sex, residence, vaccinations history, comorbidities/underlying conditions and medications use). The method to select a subset of co-variables to include in the final model was the purposeful selection. The final models include significant, confounders and all co-variables 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=1407). The level of statistical significance was established at $p < 0.05$ (two-tailed). IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) 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.

RESULTS:

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 44% 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 vs 1394 (60%) in aged >65 years (p<0.001), 1023 (44%) in men vs 1301 (56%) in women (p=0.007) and 1789 (77%) in community-dwelling vs 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 50-64 years, 95 (25%) in 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 yrs vs 365.2 in 65-79 yrs *vs*1771.6 in 80 yrs or older; 419.9 in men *vs*535.5 in women)

The most prevalent pre-existing comorbidities/underlying conditions among the 380 COVID-19 patients were hypertension (58.7%), hypercholesterolemia (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: 1.01-1.03; p=0.002), nursing-home residence (HR: 21.83; 95% CI: 16.66-28.61; p<0.001) and receiving diuretics (HR: 1.35; 95% CI: 1.04-1.76; p=0.026) appeared significantly associated with an increasing risk. Conversely, smoking (HR: 0.62; 95%CI: 0.41-0.93; p=0.022), receiving angiotensin II receptor blockers (HR: 0.68; 95%CI: 0.47-0.99; p=0.046) and antihistamines (HR: 0.47; 95% CI: 0.22-1.01; 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 distribution of PCR-confirmed COVID-19 cases and specific-IRs by demographical characteristics, underlying conditions and medications use among community-dwelling individuals. In the multivariable analysis focused on these community-dwelling individuals, chronic respiratory disease (HR: 1.82; 95% CI: 1.08-3.07; p=0.025), cardiac disease (HR: 1.53; 95% CI: 1.06-2.19; p=0.021) cancer (HR: 1.52; 95% CI: 1.03-2.24; p=0.035) receiving diuretics (HR: 1.54; 95% CI: 1.04-2.27; p=0.031) and insulin (HR: 1.79; 95% CI: 1.00-3.21; p=0.049) were associated with an increasing risk, whereas smoking (HR: 0.49; 95% CI: 0.30-0.80; p=0.004), receiving ACE-inhibitors (HR: 0.66; 95% CI: 0.44-0.99; p=0.046) and influenza vaccination in prior autumn (HR: 0.63; 95% CI: 0.44-0.91; 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 analysis 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 increasing risk, whereas receiving angiotensin II receptor blockers was associated with a decreased risk (HR: 0.45; 95% CI: 0.23-0.90; 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 with 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 sociodemographical variables, apart of nursing-home residence that increased more than twenty-times the adjusted-risk for PCR-confirmed COVID-19, we found that age increased approximately a 2% for each year the adjusted-risk for suffering COVID-19. Despite COVID-19 was more frequent in women, sex did not alter significantly the risk of infection in multivariable analysis.

None comorbidity appeared 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 significantly associated with an increased risk in subgroup analysis focused on community-dwelling individuals. Hypertension, diabetes and/or obesity did not emerge independently associated with a significant increasing risk for suffering COVID-19 in our adjusted analyses. There is general consensus considering these conditions as major risk conditions related with poor prognosis in hospitalised COVID-19 patients,[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 hypothesized 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 with 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; however, 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 COVID-19 hospitalized patients.[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 (i.e., 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 NSADs or corticosteroids (which have been associated with good outcomes when using in severe COVID-19 patients)[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 disease from COVID-19. 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 hospitalized COVID-19 patients.[40]

Community-dwelling individuals who received influenza vaccination in prior autumn appeared at-decreased risk to suffer PCR-confirmed COVID-19 in our adjusted analysis. Although this finding may be possibly related with residual confounding due to unmeasured factors (e.g, life-style or health care-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 hypothesized 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 flu 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 with 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 (i.e, 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 prioritized for hospitalised or severe case patients. 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 (e.g, 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/ICU 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 where relatively few events (n=380) which limits statistical power, especially in 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 characterize 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 supports 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.

Since 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 antihistamine drugs in allergic patients could be complementary tools partially protecting against COVID-19.

Author's contributions: AVC designed the study and wrote the manuscript; CTF and FGB obtained data; ESG, IHG and CDC assessed outcomes; OOG and AVR did statistical analyses; FBR revised pharmacological data; AVC and JBG coordinated the study.

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Ethics approval: 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.

Data availability statement: Data are available upon reasonable request

Patient and Public Involvement statement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

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TABLES

Table 1. Incidence of PCR-confirmed COVID-19 cases according to baseline demographical and clinical characteristics (comorbidities/medications) in the total study cohort (N=79,083). Tarragona region (Southern Catalonia, Spain), 01/03/2020-23/05/2020.

Characteristic	Study population (N=79083) n (%)	PCR-confirmed COVID-19 cases (n=380)	
		Univariate analysis n (%) p-value	Incidence rate
Sociodemographical			
Age: 50-64 yrs	42684 (54.0)	101 (26.6) <0.001	236.6 (193.6-288.7)
65-79 yrs	26013 (32.9)	95 (25.0)	365.2 (295.4-452.9)
≥80 yrs	10386 (13.1)	184 (48.4)	1771.6 (1527.1-2055.1)
Sex Men	37626 (47.6)	158 (41.6) 0.019	419.9 (358.6-491.7)
Women	41457 (52.4)	222 (58.4)	535.5 (464.8-616.4)
Community-dwelling	77676 (98.2)	220 (57.9) <0.001	283.2 (245.8-326.0)
Nursing-home residence	1407 (1.8)	160 (42.1)	11371.7 (9711.4-13316.3)
Comorbidities			
Neurological disease	2317 (2.9)	66 (17.4) <0.001	2848.5 (2236.1-3617.6)
Renal disease	4476 (5.7)	49 (12.9) <0.001	1094.7 (812.3-1445.0)
Cancer	6630 (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	7272 (9.2)	63 (16.6) <0.001	866.3 (667.1-1126.2)
Cardiac disease	13435 (17.0)	123 (32.4) <0.001	915.5 (762.6-1098.6)
Atrial fibrillation	3786 (4.8)	55 (14.5) <0.001	1452.7 (1077.9-1917.6)
Liver disease	1465 (1.9)	8 (2.1) 0.714	546.1 (235.4-1075.8)
Diabetes	13317 (16.8)	102 (26.8) <0.001	765.9 (626.5-934.4)
Hypertension	34945 (44.2)	223 (58.7) <0.001	638.1 (553.9-734.5)
Hypercholesterolemia	27314 (34.5)	133 (35.0) 0.850	486.9 (411.0-576.5)
Obesity	21678 (27.4)	96 (25.3) 0.347	442.8 (362.2-540.3)
Smoking	12750 (16.1)	27 (7.1) <0.001	211.8 (139.6-309.2)
Chronic medications use			
Diuretics	8481 (10.7)	111 (29.2) <0.001	1308.8 (1090.2-1570.6)
Beta blockers	9571 (12.1)	68 (17.9) 0.001	710.5 (557.7-902.3)
ACEIs	16419 (20.8)	92 (24.2) 0.097	560.3 (453.3-694.8)
ARBs	8869 (11.2)	39 (10.3) 0.556	439.7 (314.0-598.0)
Calcium channel blockers	6490 (8.2)	52 (13.7) <0.001	801.2 (594.5-1057.6)
Statins	16134 (20.4)	69 (18.2) 0.277	427.7 (335.7-543.1)
Oral anticoagulants	3912 (4.9)	46 (12.1) <0.001	1175.9 (857.2-1575.7)
Antiplatelet drugs	9154 (11.6)	86 (22.6) <0.001	939.5 (760.0-1165.0)
Insulin	3042 (3.8)	39 (10.3) <0.001	1282.1 (915.4-1743.6)
Oral antidiabetic drugs	10585 (13.4)	69 (18.2) 0.006	651.9 (511.7-827.9)
Inhaled respiratory drugs	6293 (8.0)	61 (16.1) <0.001	969.3 (746.4-1260.1)
Antineoplastic agents	1614 (2.0)	8 (2.1) 0.929	495.7 (213.6-976.5)
Systemic corticosteroids	1252 (1.6)	5 (1.3) 0.676	399.4 (129.4-930.5)
NSADs	4321 (5.5)	12 (3.2) 0.047	277.7 (143.6-486.0)
Chloroquine	168 (0.2)	0 (0.0) 0.367	0 (-)
Antihistamines	3264 (4.1)	7 (1.8) 0.025	214.5 (86.0-446.1)
Proton-Pump Inhibitors	17931 (22.7)	142 (37.4) <0.001	791.9 (668.4-937.6)
Benzodiazepines	13046 (16.5)	96 (25.3) <0.001	735.9 (601.9-897.7)
Vaccination's history			
Flu vaccine in prior autumn	22606 (28.6)	205 (53.9) <0.001	906.8 (787.1-1043.8)
Pneumococcal vaccinated	26183 (33.1)	213 (56.1) <0.001	813.5 (706.1-936.3)

NOTE: P-values in univariate analysis were calculated by chi-squared, or Fisher's test as appropriate, comparing percentages in the study population vs 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.

Table 2. Cox regression analyses assessing unadjusted and adjusted risks to suffer PCR-confirmed COVID-19 in the total study cohort (N=79,083). Tarragona region (Southern Catalonia, Spain) from 01/03/2020 to 23/05/2020.

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

NOTE: 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 denote confidence intervals.

Table 3. Incidence of PCR-confirmed COVID-19 cases according to baseline demographical and clinical characteristics (comorbidities/medications) in subgroup analysis restricted to community-dwelling individuals (N=77,676). Tarragona region (Southern Catalonia, Spain), 01/03/2020-23/05/2020.

Characteristic	Study population (N=77676) n (%)	PCR-confirmed COVID-19 cases (n=220)	
		Univariate analysis n (%) p-value	Incidence rate
Sociodemographical			
Age: 50-64 yrs	42533 (54.8)	99 (45.0) <0.001	232.8 (190.4-284.0)
65-79 yrs	25713 (33.1)	72 (32.7)	280.0 (219.8-355.6)
≥80 yrs	9430 (12.1)	49 (22.3)	519.6 (385.6-685.9)
Sex Men	37145 (47.8)	108 (49.1) 0.706	290.8 (237.8-354.7)
Women	40531 (52.2)	112 (50.9)	276.3 (230.2-331.6)
Comorbidities			
Neurological disease	1951 (2.5)	11 (5.0) 0.018	563.8 (281.3-1009.2)
Renal disease	4240 (5.5)	26 (11.8) <0.001	613.2 (400.4-901.4)
Cancer	6463 (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	7075 (9.1)	47 (21.4) <0.001	664.3 (484.3-890.2)
Cardiac disease	12925 (16.6)	68 (30.9) <0.001	526.1 (413.0-668.2)
Atrial fibrillation	3561 (4.6)	26 (11.8) <0.001	730.1 (476.8-1073.3)
Liver disease	1438 (1.9)	6 (2.7) 0.334	417.2 (153.1-909.6)
Diabetes	12926 (16.6)	50 (22.7) 0.015	386.8 (287.0-510.6)
Hypertension	33996 (43.8)	112 (50.9) 0.032	329.5 (274.4-395.3)
Hypercholesterolemia	26766 (34.5)	74 (33.6) 0.797	276.5 (217.0-351.1)
Obesity	21344 (27.5)	57 (25.9) 0.602	267.1 (205.6-347.2)
Smoking	12640 (16.3)	19 (8.6) 0.002	150.3 (90.5-234.5)
Chronic medications use			
Diuretics	8028 (10.3)	51 (23.2) <0.001	635.3 (471.4-838.6)
Beta blockers	9312 (12.0)	40 (18.2) 0.005	429.6 (306.7-584.2)
ACEIs	16031 (20.6)	41 (18.6) 0.462	255.8 (182.6-347.8)
ARBs	8709 (11.2)	29 (13.2) 0.354	333.0 (223.1-479.5)
Calcium channel blockers	6316 (8.1)	27 (12.3) 0.024	427.5 (281.7-624.1)
Statins	15911 (20.5)	47 (21.4) 0.746	295.4 (215.3-395.8)
Oral anticoagulants	3741 (4.8)	27 (12.3) <0.001	721.7 (475.6-1053.7)
Antiplatelet drugs	8810 (11.3)	40 (18.2) 0.001	454.0 (324.2-617.5)
Insulin	2904 (3.7)	20 (9.1) <0.001	688.7 (420.8-1060.6)
Oral antidiabetic drugs	10352 (13.3)	34 (15.5) 0.353	328.4 (228.9-456.5)
Inhaled respiratory drugs	6095 (7.8)	42 (19.1) <0.001	689.1 (492.0-937.2)
Antineoplastic agents	1581 (2.0)	2 (0.9) 0.236	126.5 (15.3-456.7)
Systemic corticosteroids	1216 (1.6)	5 (2.3) 0.397	411.2 (133.2-958.1)
NSADs	4305 (5.5)	12 (5.5) 0.955	278.7 (144.1-487.8)
Antihistamines	3221 (4.1)	6 (2.7) 0.290	186.3 (68.4-406.1)
Proton-Pump Inhibitors	17315 (22.3)	74 (33.6) <0.001	427.4 (335.5-542.8)
Benzodiazepines	12654 (16.3)	49 (22.3) 0.016	387.2 (287.3-511.1)
Vaccination's history			
Flu vaccine in prior autumn	21570 (27.8)	70 (31.8) 0.179	324.5 (254.8-412.1)
Pneumococcal vaccinated	25224 (32.5)	100 (45.5) <0.001	396.4 (324.3-483.7)

NOTE: P-values in univariate analysis were calculated by chi-squared, or Fisher's test as appropriate, comparing percentages in the study population *vs* 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.

Table 4. Cox regression analyses assessing unadjusted and adjusted risks to suffer PCR-confirmed COVID-19 among community-dwelling individuals (N=77,676). Tarragona region (Southern Catalonia, Spain), 01/03/2020-23/05/2020.

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

NOTE: HRs denotes Hazard ratios, and were calculated for those who had the condition as compared with those who had not 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.

Table 5. Univariate and multivariate analyses on laboratory-confirmed COVID-19 cases according to baseline demographical and clinical characteristics (comorbidities/medications) in subgroup analysis restricted to nursing-home residents (N=1407). Tarragona region (Southern Catalonia, Spain) from 01/03/2020 to 23/05/2020.

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
Sociodemographical			
Age: 50-64 yrs	151 (10.7)	2 (1.3) <0.001	1.00 (reference)
65-79 yrs	300 (21.3)	23 (14.4)	6.66 (1.53-29.02) 0.012
≥80 yrs	956 (67.9)	135 (84.4)	13.16 (3.09-56.00) <0.001
Sex: Men	481 (34.2)	50 (31.3) 0.406	1.00 (reference)
Women	926 (65.8)	110 (68.8)	0.85 (0.59-1.24) 0.402
Comorbidities			
Neurological disease	366 (26.0)	55 (34.4) 0.010	1.25 (0.89-1.76) 0.193
Renal disease	236 (16.8)	23 (14.4) 0.388	0.68 (0.43-1.08) 0.104
Cancer	167 (11.9)	17 (10.6) 0.605	0.74 (0.43-1.26) 0.264
Rheumatic disease	12 (0.9)	1 (0.6) 0.739	0.86 (0.12-6.43) 0.885
Respiratory disease	197 (14.0)	16 (10.0) 0.121	0.72 (0.39-1.31) 0.280
Cardiac disease	510 (36.2)	55 (34.4) 0.601	0.76 (0.52-1.09) 0.137
Atrial fibrillation	225 (16.0)	29 (18.1) 0.434	1.25 (0.71-2.20) 0.436
Liver disease	27 (1.9)	2 (1.3) 0.512	0.70 (0.17-2.88) 0.618
Diabetes	391 (27.8)	52 (32.5) 0.158	1.08 (0.63-1.85) 0.786
Hypertension	949 (67.4)	111 (69.4) 0.581	0.89 (0.60-1.33) 0.562
Hypercholesterolemia	548 (38.9)	59 (36.9) 0.568	0.90 (0.64-1.26) 0.525
Obesity	334 (23.7)	39 (24.4) 0.841	1.10 (0.75-1.61) 0.617
Smoking	8 (5.0)	110 (7.8) 0.158	1.47 (0.68-3.17) 0.323
Chronic medications use			
Diuretics	453 (32.2)	60 (37.5) 0.127	1.19 (0.83-1.70) 0.342
Beta blockers	259 (18.4)	28 (17.5) 0.753	0.90 (0.57-1.41) 0.642
ACEIs	388 (27.6)	51 (31.9) 0.196	1.01 (0.69-1.47) 0.981
ARBs	160 (11.4)	10 (6.3) 0.030	0.45 (0.23-0.90) 0.023
Calcium channel blockers	174 (12.4)	25 (15.6) 0.184	1.34 (0.85-2.12) 0.214
Statins	223 (15.8)	22 (13.8) 0.440	0.99 (0.59-1.64) 0.964
Oral anticoagulants	171 (12.2)	19 (11.9) 0.909	0.81 (0.41-1.59) 0.534
Antiplatelet drugs	344 (24.4)	46 (28.7) 0.179	1.30 (0.85-1.98) 0.227
Insulin	138 (9.8)	19 (11.9) 0.350	1.05 (0.59-1.86) 0.880
Oral antidiabetic drugs	233 (16.6)	35 (21.9) 0.055	1.56 (0.88-2.77) 0.131
Inhaled respiratory drugs	198 (14.1)	19 (11.9) 0.396	0.93 (0.53-1.64) 0.808
Antineoplastic agents	33 (2.3)	6 (3.8) 0.212	3.27 (1.34-7.94) 0.009
Systemic corticosteroids	36 (2.6)	0 (-) 0.029	NA (-) -
NSADs	16 (1.1)	0 (-) 0.150	NA (-) -
Antihistamines	43 (3.1)	1 (0.6) 0.058	0.21 (0.03-1.54) 0.125
Proton-Pump Inhibitors	616 (4.8)	68 (42.5) 0.729	0.82 (0.57-1.18) 0.286
Benzodiazepines	392 (27.9)	47 (29.4) 0.650	1.02 (0.72-1.46) 0.911
Vaccination's history			
Flu vaccine in prior autumn	1036 (73.6)	135 (84.4) 0.001	1.61 (0.98-2.59) 0.071
Pneumococcal vaccination	959 (68.2)	1130.6) 0.477	0.77 (0.53-1.10) 0.148

NOTE: p-values in univariate analysis were calculated by chi-squared (or Fisher's test as appropriate) comparing percentages in the study population *vs* COVID-19 cases; HR denotes multivariable-adjusted Hazard ratios (Cox regression) calculated for those who had the condition as compared with those who had not the condition, being adjusted by age (continuous), sex, pre-existing comorbidities and medications use.

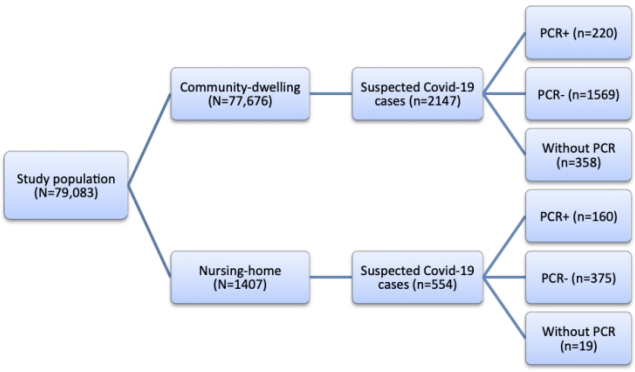

Figure 1. Flow diagram of the study

209x297mm (150 x 150 DPI)

APPENDIX. Criteria used to identify comorbidities and active medications in the study population.

Comorbidities and underlying conditions with ICD-10 codes [International Classification of Diseases, 10th Revision]	
Neurological disease:	
Dementia	F01-F03
Ictus	I63, I61
Chronic renal failure	N18-N19
Cancer (solid organ or haematological neoplasia) in past 5 years	C00-C97
Rheumatologic disease:	
Rheumatoid arthritis, enteropathic arthropathies and juvenile arthritis	M05-M09
Systemic lupus erythematosus	M32
Chronic pulmonary/respiratory disease:	
Chronic bronchitis/emphysema	J41-J44
Asthma	J45-J46
Other chronic pulmonary diseases	P27, E84, J47
Chronic heart disease:	
Congestive heart failure	I50
Coronary artery disease	I20-I22, I25
Other chronic heart diseases	I05-I08, I11,I35-I37,I42, I51.7
Atrial Fibrillation	I48
Chronic liver disease:	
Chronic viral hepatitis	B18
Cirrhosis	K74
Alcoholic hepatitis	K70
Diabetes mellitus	E10-E14
Hypertension	I10, I11, I12 o I15
Hypercholesterolemia	E78
Obesity	E66
Smoking	F17
Drugs identified in the patient treatment with codes of the Anatomical, Therapeutic, and Chemical classification system (ATC codes) of the World Health Organization:	
Diuretics	C03
Beta blockers	C07
Angiotensin converter enzyme inhibitors (ACEIs)	C09A, C09B
Angiotensin II receptor blockers (ARBs)	C09C, C09D
Calcium channel blockers	C08CA
Statins	C10AA
Oral anticoagulant drugs	B01AA, B01AE, B01AF
Antiplatelet drugs	B01AC
Insulin	A10A
Oral antidiabetic drugs	A10B
Inhaled respiratory drugs	R03A, R03B
Antineoplastic agents	L01, L02B, L03, L04
Corticosteroids for systemic use	H02A
Non-steroids anti inflammatory drugs (NSADs)	M01A
Chloroquine/Hydroxychloroquine	P01BA01, P01BA02
Antihistamines for systemic use	R06
Proton pump inhibitors	A02BC
Benzodiazepines	N05BA, N05CD, N05CF

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (p. 4) ✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (p. 4) ✓
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (p. 6) ✓
Objectives	3	State specific objectives, including any prespecified hypotheses (p. 6) ✓
Methods		
Study design	4	Present key elements of study design early in the paper (p. 6) ✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p. 6-7) ✓
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (p. 6) ✓
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed NOT APPLICABLE□
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (p. 7-8) ✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (p. 6-7 and Appendix) ✓
Bias	9	Describe any efforts to address potential sources of bias (p. 12-13) ✓
Study size	10	Explain how the study size was arrived at. NOT APPLICABLE (all people included)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (p. 8) ✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (p. 8) ✓
		(*b*) Describe any methods used to examine subgroups and interactions (p. 8) ✓
		(*c*) Explain how missing data were addressed N/A ✓
		(*d*) If applicable, explain how loss to follow-up was addressed. NOT AAPPLICABLE
		(*e*) Describe any sensitivity analyses (p. 8) ✓
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (p. 9) ✓
		(b) Give reasons for non-participation at each stage. NOT APPLICABLE
		(c) Consider use of a flow diagram (Figure 1) ✓
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p.19, Table 1) ✓
		(b) Indicate number of participants with missing data for each variable of interest. NA
		(c) Summarise follow-up time (eg, average and total amount) (p. 6) ✓
Outcome data	15*	Report numbers of outcome events or summary measures over time (p. 9)✓
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (p. 19-23, Tables 1-5) ✓
		(*b*) Report category boundaries when continuous variables were categorized (p.19,21,23, Tables 1,3,5) ✓
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (p. 22-23; Tables 4-5) ✓
Discussion		
Key results	18	Summarise key results with reference to study objectives (p. 13) ✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (p. 10-13) ✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p. 10-13) ✓
Generalisability	21	Discuss the generalisability (external validity) of the study results (p. 13) ✓
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (p. 14) ✓

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.