

RESEARCH PAPER

The demography and characteristics of SARS-CoV-2 seropositive residents and staff of nursing homes for older adults in the Community of Madrid: the SeroSOS study

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Abstract

Background: Nursing homes for older adults have concentrated large numbers of severe cases and deaths for coronavirus disease 2019 (COVID-19).

Methods: Point seroprevalence study of nursing homes to describe the demography and characteristic of severe acute respiratory syndrome by coronavirus 2 (SARS-CoV-2) immunoglobulin G (IgG)-positive residents and staff.

Results: Clinical information and blood samples were available for 9,332 residents (mean age 86.7 ± 8.1 years, 76.4% women) and 10,614 staff (mean age 45.6 ± 11.5, 86.2% women). Up to 84.4% of residents had frailty, 84.9% co-morbidity and 69.3% cognitive impairment; 65.2% of workers were health-aides. COVID-19 seroprevalence was 55.4% (95% confidence interval (CI), 54.4–56.4) for older adults and 31.5% (30.6–32.4) for staff. In multivariable analysis, frailty of residents was related with seropositivity (odds ratio (OR): 1.19, $P = 0.02$). In the case of staff, age > 50 years (2.10, $P < 0.001$), obesity (1.19, $P = 0.01$), being a health-aide (1.94, $P < 0.001$), working in a center with high seroprevalence in residents (3.49, $P < 0.001$) and contact with external cases of COVID-19 (1.52, $P < 0.001$) were factors associated with seropositivity. Past symptoms of COVID-19 were good predictors of seropositivity for residents (5.41, $P < 0.001$) and staff (2.52, $P < 0.001$).

Conclusions: Level of dependency influences risk of COVID-19 among residents. Individual and work factors, contacts outside the nursing home are associated with COVID-19 exposure in staff members. It is key to strengthen control measures to prevent the introduction of COVID-19 into care facilities from the community.

Keywords: COVID-19, SARS-CoV-2, seroprevalence, seropositivity, nursing homes, older adults, occupational

Key Points

- COVID-19 seroprevalence was 55.4% for older adults and 31.5% for staff in nursing homes after the first pandemic wave.
- More frail older adults had greater chances for being seropositive.
- Seropositivity in staff was related with age, body weight and type of work in the facility.
- Risk of infection in staff members was both related with exposure inside and outside the facility.

Introduction

The coronavirus infectious disease 2019 (COVID-19) is more severe with age, particularly for men and patients with underlying chronic diseases [1]. The nationwide sero-epidemiological study, undertaken in Spain during May and June 2020, found the infection fatality ratio of COVID-19 to be 6 and 14 times greater for men 70 to 79 years old and for men over 79 years old, respectively, as compared with younger people; but for older women, excess risk was lower, at only 3.5 and 8 times more than that for younger women, respectively [2].

From the beginning of the pandemic, nursing homes for older adults (NHOA) have seen more severe cases and deaths for severe acute respiratory syndrome by coronavirus 2 (SARS-CoV-2) infection than any other setting [3,4]. The factors related with this poorer outcome are age, health status, need for care and reduced mobility of most residents of NHOA [5]. For Spain, by mid-July 2020, the number of deaths with either confirmed, or suspected COVID-19 in NHOA was nearly 20,000. This enhanced health risk for institutionalized older people has been observed in almost all countries systematically studied [6,7].

Although the duration and effectiveness of antibody response against SARS-CoV-2 remains to be elucidated [8], animal studies have shown that primary infection protects from subsequent SARS-CoV-2 re-challenge [9], but according to case reports, reinfection in humans seems to still be possible [10–12]. While the determination of the precise frequency of these events requires a longer observation period [13], subjects with positive immunoglobulin G (IgG) against SARS-CoV-2 are considered to have some protection from severe infection, what may also lead to less viral transmission [14,15].

Although sero-epidemiological studies of the general population [16,17] and in health-care settings [18–20] have been published, there remains a lack of information about NHOA [21]. We present here the results for a large number of residents and staff members tested between July and October 2020, including their sero-status and factors related with their SARS-CoV-2 infections.

Methods

Design and participants

At the beginning of the COVID-19 pandemic, nearly 45,000 of older individuals [22] lived in one of the 476 long-term care facilities registered in the Community of

Madrid [23]. A point seroprevalence survey was designed for a sectorization strategy for the prevention of the spread of infection in NHOA [24].

All NHOA were contacted by the liaison geriatrician of the corresponding reference hospital; upon consent to participate, an appointment was set for blood extractions. Each NHAO was sampled in one visit or in two consecutive days, and only one blood sample was obtained for each participant for the purpose of the study.

A total of 362 NHOA agreed to participate in the study, of which 66 were specifically devoted to the care of patients with mental or physical chronic disabilities. According to the information provided by each center, 49,954 individuals were eligible for the study. This population was constituted by 24,117 residents and 25,837 staff members—of the staff, 16,846 were care providers. Blood samples were received from a total of 49,008 participants in NHOA. Among residents, clinical information was available for 16,964 individuals, and blood samples were analyzed in 25,405 subjects. For staff, clinical data were received in 18,049 instances and blood samples in 23,603. At the time of the study the total number of residents in NHOA registered in the official records of the Community of Madrid was 36,589; this means that we received and processed clinical information from 65.9% and blood samples from 69.4% of all older adults in nursing homes.

The final number of subjects with both clinical and laboratory information was 9,332 residents (among all residents, 38.7% had clinical data and 31.8% had laboratory data) and 10,614 staff (among all staff, 41.1% had clinical data and 38.6% had laboratory data). These constitute the populations for the analyses presented in this article (Figure 1).

The study was approved by the Regional Clinical Investigation Ethics Committee and the Regional Agency for Data Protection was consulted.

SARS-CoV-2 serological test

Determination of qualitative IgG response against SARS-CoV-2 nucleoprotein was done by chemiluminescent microparticle immunoassay (ARCHITECT; Abbott Laboratories, Abbott Park, IL, USA; reference 06R8620). For a relative light unit index of 1.4 for serum sample versus calibrator, the manufacturer of the test reported a sensitivity of 86.4% after 7 days from symptom onset and 100% after 14 days, and a specificity of 99.6%, using SARS-CoV-2 real time polymerase chain reaction (RT-PCR) as the gold standard [25,26].

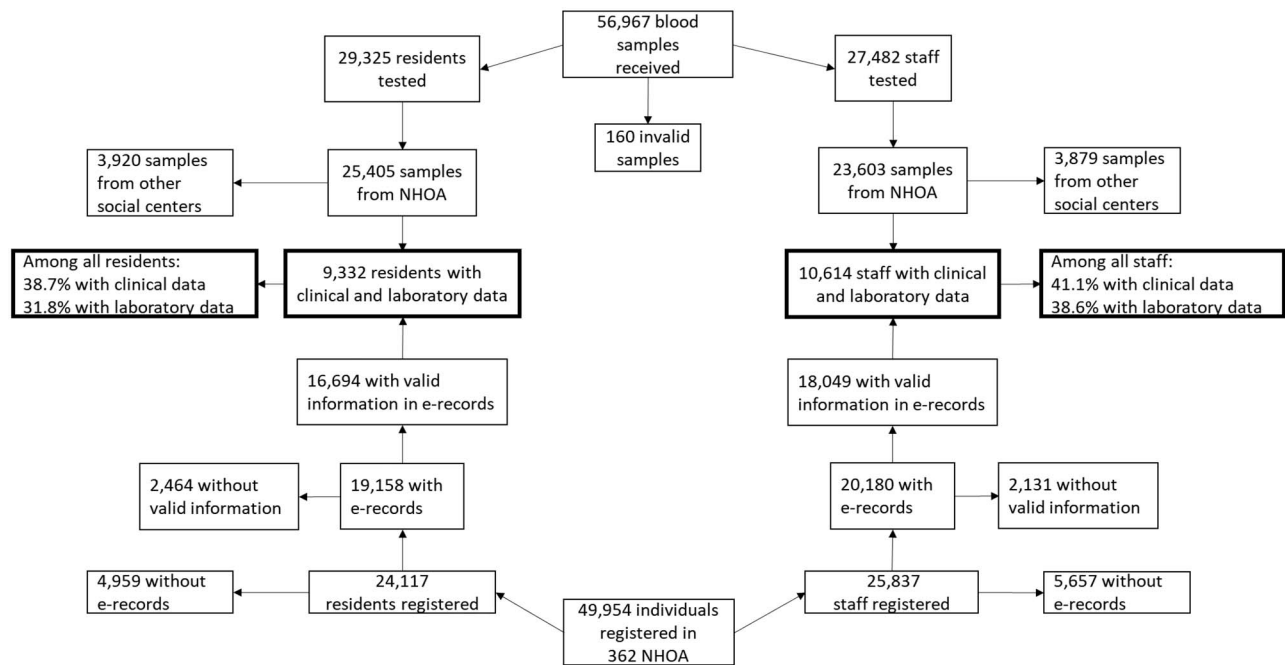


Figure 1. Disposition of studied individuals, by e-records registered and blood samples analyzed.

Clinical assessment

Co-morbidities were evaluated according to medical records at the facility, for residents, or as self-reported, by staff. Frailty for residents was assessed according to the validated [27] Clinical Frailty Scale (version 2.0) [28] that consists of levels from 1 (very fit) to 9 (terminally ill). For the analysis, these levels were grouped in a validated score of frailty: not frail (1–3), mildly frail or vulnerable (4–5), moderately-severely frail (6–8), terminally ill (9) [29].

Statistical analysis

In addition to descriptive statistics for all variables, bivariate analyses between positive and negative IgG reactivity were carried out. The Student's *t* test was used to compare normally distributed continuous variables. In the case of non-normally distributed variables, Mann–Whitney's *U* test was applied. Comparison of proportions for categorical variables was done either by chi-square or Fisher's exact tests. Multivariable logistic regression analyses using Back-Ward model were used to produce adjusted results for selected variables associated with a positive IgG result. The variance inflation factor was used to detect collinearity between variables. All statistical analyses were performed using SPSS[®] Version 20 (IBM[®], Chicago, USA).

Results

Description of the population of study

For the 9,332 older adults studied, the mean age was 87.7 ± 7.3 years for women and 83.5 ± 9.6 years for men

($P < 0.001$). In the distribution of the population by age, the oldest segment (more than 90 years) was more frequent than the other two segments ($P < 0.001$). Most residents (83.9%) had from mild to severe frailty; 69.3% had cognitive impairment; and 84.9% had at least one comorbidity (Table 1).

Among the 10,614 staff of the facilities studied, men were younger (43.4 ± 12.1 years) than women (46.0 ± 11.4 years) ($P < 0.001$). A greater proportion of workers were found in the segment of more than 50 years (40.2%) ($P < 0.001$, as compared with the other segments of age). One-third of staff self-reported as being current tobacco smokers and 78.4% were free of chronic conditions. Two-thirds of staff studied were health-aides in the residence (Table 2).

Nearly half of both residents and staff had a normal body mass index (BMI), but there were more underweight residents (9.0%) than staff (2.3%) ($P < 0.001$), and more obese staff (49.6%) than residents (43.9%) ($P < 0.001$). During the three previous months, a greater proportion of residents (28.2%) had presented symptoms compatible with COVID-19 than staff (26.0%) ($P = 0.001$). Conversely, while a history of a previous positive PCR was found for only 24.5% of residents, this proportion was 56.9% for workers ($P < 0.001$).

Seroprevalence

Between 7 July and 23 October 2020, a total of 5,172 residents and 3,344 staff were found to be IgG positive, for a seroprevalence of SARS-CoV-2 infection of 55.4% [95% confidence interval (CI), 54.4–56.4] for residents; and 31.5% [95% CI, 30.6–32.4] for staff ($P < 0.001$) (Tables 1 and 2).

Table 1. Characteristics and SARS-CoV-2 seroprevalence in residents of NHOA

Characteristics	Residents (%)	Seroprevalence (N%, [95% CI])	Univariable OR (95% CI)	P-value
Total	9,332 (100)	5,172 (55.4, [54.4–56.4])	—	—
Age (years old)				
<85	3,126 (33.5)	1,749 (56.0, [54.2–57.7])	Ref.	
85–90	2,606 (28.0)	1,456 (55.9, [53.9–57.8])	0.99 (0.90–1.11)	0.95
>90	3,590 (38.5)	1,965 (54.7, [53.1–56.4])	0.95 (0.86–1.05)	0.32
Sex				
Female	7,130 (76.4)	3,982 (55.8, [54.7–57.0])	1.08 (0.98–1.18)	0.14
Male	2,202 (23.6)	1,190 (54.0, [51.9–56.1])		
Ethnicity				
Caucasian	8,403 (98.8)	4,731 (56.3, [55.2–57.4])	Ref.	
African	8 (0.1)	2 (25.0, [3.2–65.1])	0.26 (0.05–1.28)	0.10
Latin American	70 (0.8)	35 (50.0, [37.8–62.2])	0.78 (0.48–1.24)	0.30
Arabic	7 (0.1)	2 (28.6, [3.7–71.0])	0.31 (0.06–1.60)	0.16
Asian	6 (0.1)	3 (50.0, [11.8–88.2])	0.78 (0.16–3.85)	0.76
Others	13 (0.2)	7 (53.8, [25.1–80.8])	0.91 (0.30–2.70)	0.86
Body mass index (kg/m ²)				
Underweight (<18.5)	510 (9.0)	265 (52.0, [47.5–56.4])	0.91 (0.75–1.10)	0.32
Normal weight (18.5–24.9)	2,650 (47.1)	1,440 (54.3, [52.4–56.2])	Ref.	
Pre-obesity (25.0–29.9)	1,627 (28.9)	867 (53.3, [50.8–55.7])	0.96 (0.85–1.08)	0.50
Obesity (≥30.0)	837 (15.0)	475 (56.8, [53.3–60.1])	1.10 (0.94–1.29)	0.22
Currently smoking	446 (5.2)	229 (51.3, [46.6–56.1])	0.84 (0.70–1.02)	0.08
Score of frailty				
Terminally ill (9)	45 (0.6)	13 (28.9, [16.4–44.3])	0.41 (0.21–0.79)	0.008
Moderately-severely frail (6–8)	4,531 (59.4)	2,542 (56.1, [54.6–57.6])	1.30 (1.14–1.47)	<0.001
Vulnerable-mildly frail (4–5)	1,868 (24.5)	980 (52.5, [50.2–54.7])	1.12 (0.97–1.30)	0.13
Not frail (1–3)	1,189 (15.6)	590 (49.6, [46.7–52.5])	Ref.	
Comorbidities				
With comorbidity	7,924 (84.9)	4,419 (55.8, [54.7–56.9])	1.10 (0.98–1.23)	0.11
1 comorbidity	2,458 (26.3)	1,367 (55.6, [53.6–57.6])	1.09 (0.96–1.24)	0.20
2 comorbidities	2,643 (28.3)	1,486 (56.2, [54.3–58.1])	1.12 (0.98–1.27)	0.09
3 or more comorbidities	2,823 (30.3)	1,566 (55.5, [53.6–57.3])	1.08 (0.95–1.23)	0.22
No comorbidities	1,408 (15.1)	753 (53.5, [50.8–56.1])	Ref.	
Cognitive impairment	6,135 (69.3)	3,436 (56.0, [54.8–57.3])	1.07 (0.98–1.17)	0.13
Flu-vaccine in 2019	6,916 (88.0)	3,859 (55.8, [54.6–57.0])	1.35 (1.18–1.55)	<0.001
COVID-19 symptoms in the last 3 months	2,515 (28.2)	2,046 (81.4, [79.8–82.9])	5.12 (4.57–5.71)	<0.001
Past SARS-CoV-2 positive IgG	850 (22.1)	719 (84.6, [82.0–87.0])	8.28 (6.78–10.11)	<0.001
Past SARS-CoV-2 positive PCR	1,839 (24.5)	1,490 (81.0, [79.2–82.8])	4.64 (4.08–5.27)	<0.001

A univariable analysis of residents found the proportion of seropositives similar for different age segments and between men and women. While BMI did not affect seropositivity, a lower level of frailty (1–3 points) was related with lower seroprevalence (49.6% [95% CI, 46.7–52.5]), but this parameter was higher (56.1% [95% CI, 54.6–57.6]) for more frail individuals (6–8 points) ($P < 0.001$). Conversely, neither the number of comorbidities, nor the associated cognitive impairment affected seropositivity. Positive IgG was found more frequently in subjects vaccinated than not vaccinated against influenza. The proportion of residents with positive IgG was very high for those with past symptoms of infection (81.4% [95% CI, 79.8–82.9], $P < 0.001$); past positive serology (84.6% [95% CI, 82.0–87.0], $P < 0.001$); or past positive SARS-CoV-2 PCR (81.0% [95% CI, 79.2–82.8]).

Yet for staff, significantly lower seroprevalence was observed for subjects below 40 years than for individuals above 50 years, and was also lower for women than for

men. Seroprevalence was lower for Caucasian and Arabic ethnicities than for African or Latin American. BMI was also directly associated with the frequency of past infection: with rising seroprevalences of 19.0% [95% CI, 14.0–25.0] for those underweight; 28.2% [95% CI, 26.8–29.5] for normal BMI; and 37.2% [95% CI, 34.8–39.6] for obese subjects ($P < 0.001$). While comorbidities did not affect the seropositivity of staff, the frequency of past infection was lower for smokers (12.6% [95% CI, 11.5–13.7]) than for non-smokers (40.8% [95% CI, 39.6–42.0]) ($P < 0.001$). Seroprevalence was greater for those vaccinated against influenza than for those not vaccinated.

The seroprevalence of staff who recalled contact with COVID-19 outside their NHOA was significantly higher than those without this antecedent. Recent or past symptoms of COVID were significantly associated with greater odds for seropositivity, as compared with asymptomatic individuals. Seroprevalence was 70.6% [68.0–73.1] for staff with a history of a positive SARS-CoV-2 PCR.

Table 2. Characteristics and SARS-CoV-2 seroprevalence in staff of NHOA

Characteristics	Staff (%)	Seroprevalence (N%, [95% CI])	Univariable OR (95% CI)	P-value
Total	10,614 (100)	3,344 (31.5, [30.6–32.4])	—	—
Age (years old)				
<40	3,185 (31.2)	850 (26.7, [25.2–28.3])	Ref.	
40–50	2,925 (28.6)	916 (31.3, [29.6–33.0])	1.25 (1.12–1.40)	<0.001
>50	4,114 (40.2)	1,444 (35.1, [33.6–36.6])	1.49 (1.34–1.64)	<0.001
Sex				
Female	9,150 (86.2)	2,932 (32.0, [31.1–33.0])	1.20 (1.07–1.36)	0.003
Male	1,464 (13.8)	412 (28.1, [25.9–30.5])		
Ethnicity				
Caucasian	7,417 (74.5)	1,985 (26.8, [25.8–27.8])	Ref.	
African	103 (1.0)	48 (46.6, [36.7–56.7])	2.39 (1.62–3.53)	<0.001
Latin American	1,677 (16.8)	779 (46.5, [44.0–48.9])	2.37 (2.13–2.65)	<0.001
Arabic	120 (1.2)	31 (25.8, [18.3–34.6])	0.95 (0.63–1.44)	0.82
Asian	32 (0.3)	14 (43.8, [26.4–62.3])	2.13 (1.06–4.29)	0.03
Others	611 (6.1)	283 (46.3, [42.3–50.4])	2.36 (2.00–2.79)	<0.001
BMI (kg/m ²)				
Underweight (<18.5)	210 (2.3)	40 (19.0, [14.0–25.0])	0.50 (0.35–0.70)	<0.001
Normal weight (18.5–24.9)	4,420 (48.1)	1,245 (28.2, [26.8–29.5])	Ref.	
Pre-obesity (25.0–29.9)	3,005 (32.7)	1,024 (34.1, [32.4–35.8])	1.32 (1.19–1.46)	<0.001
Obesity (≥30.0)	1,552 (16.9)	577 (37.2, [34.8–39.6])	1.51 (1.34–1.71)	<0.001
Currently smoking	3,342 (32.3)	420 (12.6, [11.5–13.7])	0.21 (0.19–0.23)	<0.001
Type of work in NHOA				
Health-aides	6,923 (65.2)	2,524 (36.5, [35.3–37.6])	2.01 (1.84–2.21)	<0.001
Others	3,690 (34.8)	819 (22.2, [20.9–23.6])		
Number of households at home				
≤3	6,344 (62.7)	1,935 (30.5, [29.4–31.7])	0.86 (0.79–0.94)	0.001
≥4	3,771 (37.3)	1,272 (33.7, [32.2–35.3])		
Average prevalence of COVID-19 among residents in NHOA of work				
High (>70%)	3,490 (34.4)	1,395 (40.0, [38.3–41.6])	3.07 (2.74–3.45)	<0.001
Medium (50–70%)	3,622 (35.7)	1,272 (35.1, [33.6–36.7])	2.50 (2.23–2.80)	<0.001
Low (<50%)	3,031 (29.9)	540 (17.8, [16.5–19.2])	Ref.	
Comorbidities	2,296 (21.6)	710 (30.9, [29.0–32.9])	0.97 (0.87–1.07)	0.502
Flu-vaccine in 2019	2,132 (21.2)	759 (35.6, [33.6–37.7])	1.25 (1.13–1.34)	<0.001
Past contact with COVID-19 cases outside the center	1,792 (17.4)	783 (43.7, [41.4–46.0])	1.89 (1.71–2.10)	<0.001
COVID-19 symptoms in the last 3 months	2,756 (26.0)	1,348 (48.9, [47.0–50.8])	2.81 (2.57–3.08)	<0.001
Past SARS-CoV-2 positive PCR	1,231 (56.9)	869 (70.6, [68.0–73.1])	1.28 (1.07–1.54)	0.008

Seropositivity of COVID-19 for staff was directly and significantly related with the average seroprevalence among residents in the NHOA of their workplace. For either a high (>70%), medium (50–70%) or low (<50%) seropositivity, the proportion of seropositive staff was 17.8% [95% CI, 16.5–19.2], 35.1% [95% CI, 33.6–36.7] and 40.0% [95% CI, 38.3–41.6], respectively ($P < 0.001$ for all comparisons). Also, for staff, both the type of work and the number of people residing in their households significantly affected their frequency of past COVID-19. As such, seroprevalence was 36.5% [95% CI, 35.3–37.6] for health-aides as compared with 22.2% [95% CI, 20.9–23.6] for other staff ($P < 0.001$); and 33.7% [95% CI, 32.2–35.3] for households of four or more, versus 30.5% [95% CI, 29.4–31.7] for households with three or less cohabitants ($P = 0.001$).

Multivariable analysis

The following variables were significantly and independently associated with COVID-19 seropositivity in NHOA residents: being moderately to severely frail, having had the flu

vaccine and COVID-19 symptoms. Being terminally ill was associated with being seronegative (Table 3).

Among workers, greater age and obesity were personal factors that increased chances for seropositivity, while Caucasian ethnicity or smoking habit was inversely correlated with seropositivity. With respect to factors related with exposure to COVID-19 among workers, seropositivity was associated with direct care of older adults, working in NHOA with high or medium seroprevalence, and exposure to COVID-19 in the community (Table 4).

Discussion

Early in the pandemic, special control measures for NHOA were enforced by the Public Health Council in the Community of Madrid. This organism used the results of seroprevalence for residents of each NHOA, according to the data presented here, for the governance of the internal organization of all sociosanitary centers in the Region [30].

Table 3. Multivariable analysis of variables associated with SARS-CoV-2 seropositivity in residents of NHOA

	OR (95% CI)	<i>P</i> -value
Score of frailty		
• Not frail (1–3)	Ref.	
• Vulnerable-mildly frail (4–5)	1.04 (0.88–1.22)	0.7
• Moderately-severely frail (6–8)	1.19 (1.03–1.38)	0.02
• Terminally ill (9)	0.36 (0.17–0.75)	0.006
Flu vaccine in 2019 (yes versus no)	1.23 (1.06–1.44)	0.008
COVID-19 symptoms in the last 3 months (yes versus no)	5.41 (4.73–6.18)	<0.001

Independent variables rendered by the logistic regression model (Nagelkerke *R*-square = 0.154; *P* < 0.001) including the OR, the 95% CI and the *P*-value (level of significance *P* ≤ 0.05).

Table 4. Multivariable analysis of variables associated with SARS-CoV-2 seropositivity in staff of NHOA

	OR (95% CI)	<i>P</i> -value
Age (years old)		
• >50	2.10 (1.84–2.41)	<0.001
• 40–50	1.44 (1.25–1.67)	<0.001
• <40	Ref.	
Caucasian (yes versus no)	0.61 (0.54–0.69)	<0.001
Obesity (BMI ≥ 30 kg/m ²) (yes versus no)	1.19 (1.03–1.36)	0.01
Currently smoker (yes versus no)	0.23 (0.20–0.27)	<0.001
Flu-vaccine in 2019 (yes versus no)	1.13 (0.99–1.28)	0.07
Health-aide (yes versus no)	1.94 (1.72–2.19)	<0.001
Seroprevalence in residents in NHOA of work:		
• High (>70%)	3.49 (3.01–4.03)	<0.001
• Medium (50–70%)	2.66 (2.23–3.08)	<0.001
• Low (<50%)	Ref.	
Past contact with COVID-19 cases outside the center (yes versus no)	1.52 (1.32–1.74)	<0.001
COVID-19 symptoms in the last 3 months (yes versus no)	2.52 (2.24–2.84)	<0.001

Independent variables rendered by the logistic regression model (Nagelkerke *R*-square = 0.154; *P* < 0.001) including the OR, the 95% CI and the *P*-value (level of significance *P* ≤ 0.05).

The characteristics of a congregant setting determine the occurrence of COVID-19 outbreaks [31]. For NHOA, close contact among residents, and particularly the close contact of residents and aides increases the odds of contagion [32]. Although community-acquired infections among outsiders usually contribute to the introduction of SARS-CoV-2 into the NHOA [33], the risk of infection inside these settings may be nearly three times greater for residents than for members of the staff [34]. Our extensive serological study of Madrid found a frequency of IgG antibodies against SARS-CoV-2 nucleocapsid of 55.4% [54.4–56.4] for residents and of 31.5% [30.6–32.4] for staff of NHOA.

The SARS-CoV-2 seroprevalence we found for older adults in nursing homes in Madrid is in accordance with other similar studies. A survey of Northern Italy, from March and April 2020, found positive serology for SARS-CoV-2 for 41.5% of residents living in long-term care facilities [35]. An epidemiological intervention in March 2020, for an outbreak occurring in a NHOA located in Madrid, found that 60.0% of surviving residents and 45.5% of staff were seropositive [21].

The seroprevalence we found for staff is in line with findings in a study done in the USA, where nearly one-third of health-care providers in nursing homes reported

COVID-19 symptoms [36]. This high risk for COVID-19 has also been described for emergency medical technicians (38.3%), correctional staff (39.2%) [37], and hospital workforce (18% in the UK and 31% in the US) [38,39]. The highest frequencies of seropositives found in Spain so far are 11.2% for health-care-workers, 11.3% for home-caregivers and 8.2% for sociosanitary staff—although this includes personnel working in facilities with a lower level of exposure (day centers, occupational workshops, care homes, etc.) than NHOA—[40,41]. It may be argued that the level of protection for staff in hospitals has been greater than for NHOA, at least during the first pandemic wave. This finding is particularly regretful if we consider that workers in long-term care facilities seem to be at high risk for severe COVID-19 [42].

Both the high incidence of COVID-19 for residents in NHOA, and the recirculation of infection by the personnel [43], may have been a significant vector for the spread of SARS-CoV-2 in the community during the first pandemic wave in Madrid—a similar finding to that of a study done in the city of Kirkland, WA [44]. Also, the rapid dispersion of the infection in Northern Italy during the first weeks of the pandemic has been associated, among other factors, with the number of beds of long-term care facilities [45].

We found two factors internal to the NHOA that independently appeared to increase the risk of infection of the staff: working as a health-aide (odds ratio (OR): 1.94 [1.72–2.19], $P < 0.001$) and high level of seropositivity—greater than 50%—among older adults in the facility. As expected, a history of non-occupational contact with COVID-19 also contributed to greater seroprevalence (OR: 1.52 [1.32–1.74], $P < 0.001$). These findings confirm that interactions among residents and staff, with sites of infection found inside and outside the sociosanitary center, constitute the background that finally results in the surge of cases in NHOA.

We found that more frail older adults, probably because they need more care, are more exposed to COVID. In the case of staff, greater age and greater body weight were found to be related with the higher seropositivity, as already described [1–3,46–48]. These two factors, being older or overweighted, are known to increase the odds of a more symptomatic and severe COVID-19; in addition, other comorbidities, such as diabetes and hypertension that are more frequent in these subjects [49,50], also aggravate the course of SARS-CoV-2 infection [51]. A more symptomatic and severe COVID-19 constitutes a factor related with a more robust and durable antibody response [52–58] and may translate into greater odds for remaining seropositive for longer.

Ethnic factors have been related with having positive SARS-CoV-2 serology [37]. In our study, we confirm this association, and we believe that it may be caused, at least in part, by differences for the risk of SARS-CoV-2 infection outside the NHOA. For instance, 66.7% of Caucasians lived with fewer than 4 cohabitants, but 49.1% of non-Caucasians shared a home with 4 or more people ($P < 0.001$). Lower seropositivity for smokers was also observed, which is confirmed by other studies that associate tobacco use with a reduced risk for becoming infected with SARS-CoV-2 [46,59].

It is of note the small number of workers (21.2%) in NHOA that were protected against influenza while taking care of high-risk population. It is also intriguing the relationship between flu vaccination and the greater odds of being seropositive, particularly for residents. Several studies have shown that influenza vaccination of people aged 65 and over reduces the spread and severity of COVID-19 but has no effect on the risk of infection [60–64]. We found that more frail residents—those more exposed to COVID—were more likely to be vaccinated than non-frail subjects (87.4% versus 84.1%, $P = 0.004$).

Several limitations of the study should be acknowledged. A selection bias was introduced because of the greater mortality for IgG positive than for IgG negative subjects, that is likely resulting in the underestimation of seroprevalence, particularly among residents [65]. While being a point seroprevalence survey with one single assessment per participant, our period of study was extended for 3 months, so that waning immunity or ongoing infections may have affected

the results. Although the level of participation was very high, 76% of all NHOA registered in the Region, we do not have information about the reasons for refusal to participate.

In conclusion, this observational study offers useful information from extensive fieldwork performed in long-term care facilities. The seroprevalence information allows a description of factors that facilitate COVID-19, of which frailty is a major determinant among older adults. The seropositivity of staff was affected by the type of work and the number of infections within the nursing home, but also by the level of exposure in family settings and by social interactions. There is a critical link between the interior and the exterior factors of NHOA, and also for residents and staff, for the determination of the risk of outbreaks within these highly vulnerable facilities.

Contributors

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References

1. Burn E, Cristian Tebé C, Fernández-Bertolín S *et al.* The natural history of symptomatic COVID-19 in Catalonia, Spain: a multi-state model including 109,367 outpatient diagnoses, 18,019 hospitalisations, and 5,585 COVID-19 deaths among 5,627,520 people. medRxiv 2020. doi: [10.1101/2020.07.13.20152454](https://doi.org/10.1101/2020.07.13.20152454) (preprint): not peer reviewed.
2. Pastor-Barriuso R, Pérez-Gómez B, Hernán MA *et al.* Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study. *BMJ* 2020; 371: m4509.
3. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging* 2020; 12: 6049–57.
4. Zhang J, Lee K, Ang L, Leo Y, Young B. Risk Factors for Severe Disease and Efficacy of Treatment in Patients Infected With COVID-19: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis. *Clin Infect Dis* 2020; 71: 2199–206.
5. Hägg S, Jylhävä J, Wanconnsorsg Y *et al.* Frailty, and comorbidity as prognostic factors for short-term outcomes in patients with coronavirus disease 2019 in geriatric care. *JAMDA* 2020; 21: 1555–9.
6. Comas-Herrera A, Zalakaín J, Lemmon E *et al.* Mortality associated with COVID-19 in care homes: international evidence. International Long-Term Care Policy Network. London, UK: CPEC-LSE. 14 October 2020. <https://ltccovid.org/2020/04/12/mortality-associated-with-covid-19-ou-tbreaks-in-care-homes-early-international-evidence/> (11 January 2021, date last accessed).
7. Thompson D, Barbu M, Beiu C *et al.* The impact of COVID-19 pandemic on long-term care facilities worldwide: an overview on international issues. *Biomed Res Int* 2020; 2020: 8870249. doi: [10.1155/2020/8870249](https://doi.org/10.1155/2020/8870249).
8. Ripperger T, Uhrlaub J, Watanabe M *et al.* Orthogonal SARS-CoV-2 serological assays enable surveillance of low-prevalence communities and reveal durable humoral immunity. *Immunity* 2020; 53: 925–33.
9. Deng W, Bao L, Liu J *et al.* Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques. *Science* 2020; 369: 818–23.
10. Tillet R, Sevinsky J, Hartley P *et al.* Genomic evidence for reinfection with SARS-CoV-2: a case study. *Lancet Infect Dis* 2021; 21: 52–8.
11. Gupta V, Bhoyar RC, Jain A *et al.* Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2. *Clin Infect Dis* 2020. doi: [10.1093/cid/ciaa1451](https://doi.org/10.1093/cid/ciaa1451).
12. To K, Hung I, Chan K *et al.* Serum antibody profile of a patient with COVID-19 reinfection. *Clin Infect Dis* 2020. doi: [10.1093/cid/ciaa1368](https://doi.org/10.1093/cid/ciaa1368).
13. Ledford H. Coronavirus reinfections: three questions scientists are asking. *Nature* 2020; 585: 168–9.
14. Overbaugh J. Understanding protection from SARS-CoV-2 by studying reinfection. *Nat Med* 2020; 26: 1680–1.
15. Kim Y, Kim S, Park S *et al.* Critical role of neutralizing antibody for SARSCoV-2 reinfection and transmission. *Emerg Microb Infect* 2021; 10: 152–60.
16. Pollán M, Pérez-Gómez B, Pastor-Barriuso R *et al.* Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *Lancet* 2020; 396: 535–44.
17. Stringhini S, Wisniak A, Piumatti G *et al.* Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCO-V-POP): a population-based study. *Lancet* 2020; 396: 313–9.
18. Psychogiou M, Karabinis A, Pavlopoulou I *et al.* Antibodies against SARS-CoV-2 among health care workers in a country with low burden of COVID-19. *PLoS One* 2020; 15: e0243025. doi: [10.1371/journal.pone.0243025](https://doi.org/10.1371/journal.pone.0243025).
19. Iversen K, Bundgaard H, Hasselbalch R *et al.* Risk of COVID-19 in health-care workers in Denmark: an observational cohort study. *Lancet Infect Dis* 2020; 20: 1401–8.
20. Chen Y, Tong X, Wang J *et al.* High SARS-CoV-2 antibody prevalence among healthcare workers exposed to COVID-19 patients. *J Infect* 2020; 81: 420–6.
21. Bouza E, Pérez-Granda MJ, Escribano P *et al.* Outbreak of COVID-19 in a nursing home in Madrid. *J Infect* 2020; 81: 647–9.

22. Martínez-Peromingo J, Serra-Rexach J. Long-term care facilities and the COVID-19 pandemic: lessons learned in Madrid. *J Am Geriatr Soc* 2020; 68: 1920–2.
23. Comunidad de Madrid. Registro de Centros de Servicio Sociales. https://datos.comunidad.madrid/catalogo/dataset/servicios_sociales_registro_centros (1 February 2021, date last accessed).
24. González de Villaumbrosia C, Martínez-Peromingo J, Ortiz-Imedio J *et al.* Implementation of an algorithm of cohort classification to prevent the spread of COVID-19 in nursing homes. *J Am Med Dir Assoc* 2020; 21: 1811–4.
25. Bryan A, Pepper G, Wener M *et al.* Performance characteristics of the Abbott Architect SARS-CoV-2 IgG assay and seroprevalence in Boise, Idaho. *J Clin Microbiol* 2020; 58: e00941–20. doi: 10.1128/JCM.00941-20.
26. Maine GN, Lao KM, Krishnan SM *et al.* Longitudinal characterization of the IgM and IgG humoral response in symptomatic COVID-19 patients using the Abbott Architect. *J Clin Virol* 2020; 133: 104663. doi: 10.1016/j.jcv.2020.104663.
27. Pulok MH, Theou O, van der Valk AM, Rockwood K. The role of illness acuity on the association between frailty and mortality in emergency department patients referred to internal medicine. *Age Ageing* 2020; 49: 1071–9.
28. Rockwood K, Theou O. Using the clinical frailty scale in allocating scarce health care resources. *Can Geriatr J* 2020; 23: 254–9.
29. Gregorevic K, Hubbard R, Katz B, Lim W. The clinical frailty scale predicts functional decline and mortality when used by junior medical staff: a prospective cohort study. *BMC Geriatr* 2016; 16: 117–23.
30. Consejería de Sanidad, Comunidad de Madrid. Guía de Medidas Frente a la Infección por Coronavirus en Centros Residenciales Sociosanitarios de Mayores. 11 January 2021. https://www.comunidad.madrid/sites/default/files/doc/servicios-sociales/guia_11_01_21_0.pdf (1 February 2021, date last accessed).
31. McMichael TM, Currie DW, Clark S *et al.* Epidemiology of COVID-19 in a long-term care facility in King County, Washington. *N Engl J Med* 2020; 382: 2005–11.
32. Kossover RA, Chi CJ, Wise ME, Tran AH, Chande ND, Perz JF. Infection prevention and control standards in assisted living facilities: are residents' needs being met? *J Am Med Dir Assoc* 2014; 15: 47–53.
33. Malikov K, Huang Q, Shi S, Stall NM, Tuite AR, Hillmer MP. Temporal associations between community incidence of COVID-19 and nursing home outbreaks in Ontario, Canada. *J Am Med Dir Assoc* 2020; S1525-8610: 31060–4.
34. Telford CT, Onwubiko U, Holland DP *et al.* Preventing COVID-19 outbreaks in long-term care facilities through preemptive testing of residents and staff members - Fulton County, Georgia, march-may 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 1296–9.
35. Vena A, Berruti M, Adessi A *et al.* Prevalence of antibodies to SARS-CoV-2 in Italian adults and associated risk factors. *J Clin Med* 2020; 9: 2780.
36. Fell A, Beaudoin A, D'Heilly P *et al.* SARS-CoV-2 exposure and infection among health care personnel - Minnesota March 6-July 11, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 1605–10.
37. Sami S, Akinbami LJ, Petersen LR *et al.* Prevalence of SARS-CoV-2 antibodies in first responders and public safety personnel, New York City, New York, USA, May-July 2020. *Emerg Infect Dis* 2021; 27: 796–804.
38. Pallett S, Rayment M, Patel A *et al.* Point-of-care serological assays for delayed SARS-CoV-2 case identification among health-care workers in the UK: a prospective multicentre cohort study. *Lancet Respir Med* 2020; 8: 885–94.
39. Self WH, Tenforde MW, Stubblefield WB *et al.* CDC COVID-19 response team; IVY network. Seroprevalence of SARS-CoV-2 among frontline health care personnel in a multistate hospital network - 13 academic medical centers, April-June 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 1221–6.
40. Instituto de Salud Carlos III. Estudio ENE-COVI, Cuarta Ronda. Estudio Nacional de Sero-epidemiología de la Infección por SARS-CoV-2 en España. 15 December 2020. <https://www.mscbs.gob.es/gabinetePrensa/notaPrensa/pdf/15.12151220163348113.pdf> (1 February 2021, date last accessed).
41. Garcia-Basteiro AL, Moncunill G, Tortajada M *et al.* Seroprevalence of antibodies against SARS-CoV-2 among health care workers in a large Spanish reference hospital. *Nat Commun* 2020; 11: 3500.
42. Greene J, Gibson DM. Workers at long-term care facilities and their risk for severe COVID-19 illness. *Prev Med* 2021; 143: 106328. doi: 10.1016/j.ypmed.2020.106328.
43. Ladhani S, Chow J, Janarthanan R *et al.* Increased risk of SARS-CoV-2 infection in staff working across different care homes: enhanced CoVID-19 outbreak investigations in London care homes. *J Infect* 2020; 81: 621–4.
44. Chen MK, Chevalier JA, Long EF. Nursing home staff networks and COVID-19. *Proc Natl Acad Sci U S A* 2021; 118: e2015455118. doi: 10.1073/pnas.2015455118.
45. Buja A, Paganini M, Cocchio S, Scioni M, Rebba V, Baldo V. Demographic and socio-economic factors, and health-care resource indicators associated with the rapid spread of COVID-19 in Northern Italy: an ecological study. *PLoS One* 2020; 15: e0244535. doi: 10.1371/journal.pone.0244535.
46. de Lusignan S, Dorward J, Correa A *et al.* Risk factors for SARSCoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. *Lancet Infect Dis* 2020; 20: 1034–42.
47. Stefan N, Birkenfeld AL, Schulze MB. Global pandemics interconnected – obesity, impaired metabolic health and COVID-19. *Nat Rev Endocrinol* 2021; 17: 135–49.
48. Popkin B, Du S, Green W *et al.* Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. *Obes Rev* 2020; 21: e13128. doi: 10.1111/obr.13128.
49. Zhou F, Yu T, Du R *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–62.
50. Wu C, Chen X, Cai Y *et al.* Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 180: 934–43.
51. Muscogiuri G, Pugliese G, Barrea L, Savastano S, Colao A. Obesity: the “Achilles heel” for COVID-19? *Metabolism* 2020; 108: 154251.
52. Weisberg SP, Connors TJ, Zhu Y *et al.* Distinct antibody responses to SARS-CoV-2 in children and adults across

- the COVID-19 clinical spectrum. *Nat Immunol* 2021; 22: 25–31.
53. Klein SL, Pekosz A, Park HS *et al.* Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. *J Clin Invest* 2020; 130: 6141–50.
 54. Sasisekharan V, Pentakota N, Jayaraman A, Tharakaraman K, Wogan GN, Narayanasami U. Orthogonal immunoassays for IgG antibodies to SARS-CoV-2 antigens reveal that immune response lasts beyond 4 mo post illness onset. *Proc Natl Acad Sci U S A* 2021; 118: e2021615118. doi: [10.1073/pnas.2021615118](https://doi.org/10.1073/pnas.2021615118).
 55. Okba N, Müller M, Li W *et al.* Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. *Emerg Infect Dis* 2020; 26: 1478–88.
 56. Ibarrodo FJ, Fulcher JA, Goodman-Meza D *et al.* Rapid decay of anti-SARS-CoV-2 antibodies in persons with mild COVID-19. *N Engl J Med* 2020; 383: 1085–7.
 57. Patel M, Thornburg N, Stubblefield W *et al.* Change in antibodies to SARS-CoV-2 over 60 days among health care personnel in Nashville, Tennessee. *JAMA* 2020; 324: 1781–2.
 58. Long QX, Tang XJ, Shi QL *et al.* Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020; 26: 1200–4.
 59. Simons D, Shahab L, Brown J, Perski O. The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 7). *Addiction* 2020. doi: [10.1111/add.15276](https://doi.org/10.1111/add.15276).
 60. Amato M, Werba JP, Frigerio B *et al.* Relationship between influenza vaccination coverage rate and COVID-19 outbreak: an Italian ecological study. *Vaccines (Basel)* 2020; 8: 535.
 61. Fink G, Orlova-Fink N, Schindler T *et al.* Inactivated trivalent influenza vaccination is associated with lower mortality among patients with COVID-19 in Brazil. *BMJ Evid Based Med* 2020. doi: [10.1136/bmjebm-2020-111549](https://doi.org/10.1136/bmjebm-2020-111549).
 62. Belingheri M, Paladino ME, Latocca R, De Vito G, Riva MA. Association between seasonal flu vaccination and COVID-19 among healthcare workers. *Occup Med (Lond)* 2020; 70: 665–71.
 63. Ragni P, Marino M, Formisano D *et al.* Association between exposure to influenza vaccination and COVID-19 diagnosis and outcomes. *Vaccines (Basel)* 2020; 8: 675.
 64. Reche PA. Potential cross-reactive immunity to SARS-CoV-2 from common human pathogens and vaccines. *Front Immunol* 2020; 11: 586984. doi: [10.3389/fimmu.2020.586984](https://doi.org/10.3389/fimmu.2020.586984).
 65. Nikolich-Zugich J, Knox K, Rios C, Natt B, Bhattacharya D, Fain M. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. *Gero Sci* 2020; 42: 505–14.

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