Household exposure to SARS-CoV-2 and association with COVID-19 severity: a Danish nationwide cohort study

Marcella, M Broccia, (ORCID: 0000-0002-5257-7448), MD[1,2]; Victoria Elizabeth, VE, de Knegt (0000-0001-9918-2593), MD[3]; Elisabeth Helen Anna, EHA, Mills (0000-0002-7499-3880), MD[4]; Amalie Lykkemark, AL, Møller (0000-0003-2952-2809), MScPH [2]; Filip, F, Gnesin (0000-0002-3566-5155), MS[2]; Thea K, TK, Fischer, MD, Prof[5]; Nertila, N, Zylyftari (0000-0002-8562-6760), MD[2]; Stig Nikolaj, SN, Blomberg (0000-0002-5073-6820) MSc[6]; Mikkel Porsborg, MP, Andersen (0000-0001-6162-5205), MScPH, PhD[2]; Morten, M, Schou, MD[7]; Emil, E, Fosbøl (0000-0002-2048-4167), MD, PhD[8]; Kristian, K, Kragholm, MD, PhD[7,9]; Helle Collatz, HC, Christensen (0000-0003-3302-7149), MD, PhD[10]; Laura Bech, LB, Polcwiartek (0000-0002-1251-6675), MD[11]; Matthew, M, Phelps (0000-0003-0344-2026), MPH, PhD[12]; Lars, L, Køber (0000-0002-6635-1466), MD, Prof[9]; Christian, C, Torp-Pedersen (0000-0003-2892-6131), MD, DMSc, Prof[2,4]

[1]Department of Obstetrics and Gynaecology, Aalborg University Hospital, Reberbansgade 15, 9000 Aalborg, Denmark

[2]Department of Cardiology, Nordsjællands Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark

[3]Department of Pediatrics, Hvidovre Hospital, Kettegård alle 30, 2650 Hvidovre, Denmark

[4]Department of Cardiology, Aalborg University Hospital, Hobrovej 18-22, 9000 Aalborg, Denmark

[5]Department of Clinical Research, Nordsjællands Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark

[6]Emergency Medical Services, University of Copenhagen, Region Hovedstaden (Capital Region of Denmark),

[7]Department of Cardiology, Herlev Gentofte Hospital, Hospitalsvej 1, 2900 Hellerup, Denmark

[8]Department of Cardiology, Rigshospitalet, Blegdamsvej 9, 2100 København Ø, Denmark

[9]Unit of Clinical Biostatistics and Epidemiology, Aalborg University Hospital, Reberbansgade 15, 9000 Aalborg, Denmark

[10]Danish Clinical Quality Program (RKKP) ▪ National Clinical Registries, Frederiksberg Hospital, Denmark

[11]Department of Pediatrics, Aalborg University Hospital, Reberbansgade 15, 9000 Aalborg, Denmark
[12]The Danish Heart Foundation, 1120 Copenhagen, Denmark

Corresponding author

Marcella Broccia, MD, PhD student

Department of Obstetrics and Gynaecology

Aalborg University Hospital

Reberbansgade 15, 9000 Aalborg, Denmark

Home cell phone number: +45 28 90 97 38

E-mail: marcellabroccia@hotmail.com

Summary: Almost one quarter of multi-person households with a primary infection had secondary cases within the same household. We found no association between household transmission of severe acute respiratory syndrome coronavirus 2 and Coronavirus disease 2019 severity

Abstract

Background Households are high-risk settings for the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Severity of Coronavirus disease 2019 (COVID-19) is likely associated with the infectious dose of SARS-CoV-2 exposure. We therefore aimed to assess the association between SARS-CoV-2 exposure within households and COVID-19 severity.

Methods We performed a Danish nationwide register-based cohort study including laboratory-confirmed SARS-CoV-2 infected individuals from 22 February to 6 October 2020. Household exposure to SARS-CoV-2 was defined as having one individual tested positive for SARS-CoV-2 within the household. Cox proportional-hazards models were used to estimate the association between 'critical COVID-19' within and between households with and without secondary cases.

Results From 15,063 multi-person households, 19,773 SARS-CoV-2 positive individuals were included; 11,632 were categorized as index cases without any secondary household cases, 3,431 as index cases with secondary cases, i.e. 22.8% of multi-person households, and 4,710 as secondary cases. 'Critical COVID-19' occurred in 2.9 % of index cases living with no secondary cases, 4.9 % of index cases with secondary cases, and 1.3 % of secondary cases. The adjusted hazard ratio for 'critical COVID-19' among index cases versus secondary cases within the same household was 2.50 (95%CI=1.88-3.34), 2.27 (95%CI=1.77-2.93) for index cases in households with no secondary cases versus secondary cases, and 1.1 (95%CI=0.93-1.30) for index cases with secondary cases versus index cases without secondary cases.

Conclusion We found no increased hazard ratio of 'critical COVID-19' among household members of infected SARS-CoV-2 index cases.

Key words: Corona, infectious dose, viral load, transmission, death.

Introduction

The severity of Coronavirus disease 2019 (COVID-19) infection is likely associated with the infectious dose of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) one is exposed to. This is true for measles, chickenpox, and polio, where it has been shown that continuous exposure through infected household members can result in more severe disease in subsequently infected family members.[1-3] One study found that high viral loads of SARS-CoV-2 detected from patient respiratory tracts were positively associated with severe lung disease and suggests that high viral load is a possible predictor of disease severity.[4] This raises the question of whether continuous exposure to SARS-CoV-2 may lead to a high viral load and increased disease severity making household transmission a risk factor.

A Singaporean study of close contacts (household, work and social) of 1,114 polymerase chain reaction (PCR) confirmed index cases found a higher secondary attack rate among household contacts than among work and social contacts.[5] Furthermore, a higher risk of becoming infected with SARS-CoV-2 within households was present if the index case was symptomatic rather than asymptomatic.[5] Although, infected individuals are also capable of transmitting the SARS-CoV-2 prior to symptom onset and without the develop of symptoms.[6] A U.S. prospective study reported that household transmission of SARS-CoV-2 is high, suggesting that households are high-risk exposure areas.[7] In addition, a Swedish observational cohort study reported that COVID-19 deaths among adults aged 70 or older was increased by 60% if they lived with a household member younger than 66 years compared to living with a household member older than 65. [8] This suggests that isolation at home with younger household members confers a considerable risk of exposure.[8]

The COVID-19 pandemic has become a rapidly evolving public health crisis, which by the end of December 2020 has led to well over 1.5 million deaths worldwide.[9] Many countries, including Denmark, are now facing a second surge, with the number of daily COVID-19 cases shattering previous records and an increasing positive test rate.[9,10] It has become a key public health priority to identify potential groups at risk of severe COVID-19 infection in order to protect vulnerable individuals in the population, prevent overburdening of the healthcare system, and reduce overall mortality.[11] In order to lower transmission, health authorities advocate for self-isolation as well as other precautionary measures. This can be a challenge considering that, across the world, the average size of households is above 1.0.[12] In addition, it remains unknown whether household transmission is associated with COVID-19 severity.

We aimed to investigate the association between COVID-19 severity and continuous exposure to SARS-CoV-2 by a proxy measure of living in a household with other SARS-CoV-2 infected members.

Methods

Setting and data collection

This cohort study is based on Danish nationwide registries.[13] The study population comprised all Danish individuals in multi-person households (>1 person) tested positive for SARS-CoV-2 from 22 February 2020 to 6 October 2020 and their household members. All Danish residents receive a unique Civil Personal Registration number, which can be used to facilitate linkage between all national administrative registers on an individual level.[14,15]

Data on diagnostic SARS-CoV-2 test date and results were obtained from the Danish Microbiology Database.[16,17] Data regarding the date of birth, sex, ethnicity, place of residence, date of death, and number of persons within the household was acquired from the Danish Civil Registration System.[14] Older adults living in care homes are logged in the Danish Civil Registration System as living in one-persons households and were therefore not included in the study. Data regarding in- and out-patient hospital contacts, diagnosis codes according to the International Classification of Disease, 10th Revision (ICD-10)[18], and surgical procedure codes according to the Danish version of the Nordic Medico-Statistical Committee Classification and Surgical Procedures[19] were obtained from the Danish National Patient Registry[20].

Assessment of SARS-CoV-2 exposure and national test-strategy

Household exposure to SARS-CoV-2 was used as a proxy measure of continuous exposure to the virus and was defined as having an index case in the household i.e. the first household member tested positive for SARS-CoV-2.

Index cases were categorized as having a secondary case within the household or not (Figure 1). We defined secondary cases as cases tested positive for SARS-CoV-2 within five weeks of the index case's positive SARS-CoV-2 test date to account for the incubation period and virus excretion after possible symptom onset.[21,22]

SARS-CoV-2 tests were performed by means of quantitative reverse-transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swab specimens and, for hospitalized patients with lower respiratory tract symptoms, by tracheal suction. All patients hospitalized with symptoms of infection were routinely tested for SARS-CoV-2.

Accessibility to testing varied over the study period, reflecting change in national test-strategy and available testing capacity. Small numbers of COVID-19 tests were performed in Denmark from 28 January 2020 to 11 March 2020, mostly limited to individuals returning from countries with detected SARS-CoV-2.[23] The first positive test was reported on 27 February 2020.[23] On 12 March 2020, testing criteria were broadened to include patients with moderate to severe symptoms in need of hospitalization and specific risk groups.[23] Patients with mild symptoms of COVID-19 were ordered to self-quarantine at home without a test. From 1 April 2020, all patients with symptoms of COVID-19 could be sent for testing[23], and, since 19 May 2020, test capacity was extended to an open testing of all individuals, asymptomatic individuals included.[24]

Assessment of covariates

Comorbidity was defined as a medical history of myocardial infarction, heart failure, hypertension, atrial fibrillation, stroke, peripheral artery disease, diabetes mellitus, chronic obstructive pulmonary disease, cancer, rheumatic disease, or chronic renal disease according to the Charlson Comorbidity Index within 10 years before the end of the study period.[25] Ethnicity was categorized into three groups; Danish, immigrant (born abroad by non-Danish parents), and descendant (born in Denmark by non-Danish parents). Age was included as a continuous variable.

Ascertainment of severe COVID-19 infection

COVID-19 severity was evaluated by a composite outcome 'critical COVID-19' defined as the presence of one or more of the following three criteria: 1. hospitalization with the diagnosis 'Severe acute respiratory syndrome' (ICD-10: B97.2A), a diagnosis given to individuals in need of hospitalization due to COVID-19 symptoms regardless of required supplemental oxygen; 2. intensive care unit (ICU) admission identified by procedure codes for intensive care observation or therapy (Danish procedure codes: NABE and NABB) or Mechanical ventilation (Danish procedure codes: BGDA) within 30 days of the positive SARS-CoV-2 test date; and/or 3. death within 30 days of the positive SARS-CoV-2 test date.

Statistical analyses

Characteristics of individuals are presented as counts with percentages and, additionally, as means for age (Table 1). Baseline characteristics of individuals in the supplementary analyses are presented in Table S1-S3.

For the analyses, individuals were followed from positive SARS-CoV-2 test until outcome, death, or end of the study period whatever came first. A Cox regression model was performed to estimate crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) for 'critical COVID-19' among: 1. index cases vs. secondary cases within the same household; 2.index cases from households without secondary cases vs. secondary cases across households, and; 3. index cases with secondary cases vs. index cases without secondary cases across households (Figure 2). We adjusted for the following potential confounders; sex, age, ethnicity and comorbidities. Supplementary analyses (Figure 2) were performed by repeating the cox regression model with the confounders described above with: 1) exclusion of adults aged 80 years or older; 2) restriction to the time period from 22 February 2020 to 18 May 2020 - corresponding to the period with limited test access; and 3) restriction to the time period from 19 May 2020 to 6 October 2020 - corresponding to the period with open test access. All analyses were carried out as complete-case analyses and performed with R software version 3.6.1.[26]

Patient and public involvement

No patients or members of the public were formally involved in the design, analysis, or interpretation of this study. The findings of this study will be disseminated to the general public in a press release and through seminars and conferences.

Results

From 15,063 multi-person households with infections, 19,773 SARS-CoV-2 positive individuals were included; 11,632 were categorized as index cases with no secondary household cases, 3,431 as index cases with secondary household cases, and 4,710 as secondary cases, i.e. 22.8 % of multi-person households with an index case also had at least one secondary case. Patient selection is shown in Figure S1. There were 98.9% complete cases after exclusion of 349 individuals with missing data (place of residence) and 2,657 individuals where multi-household members tested positive for SARS-CoV-2 on the same day and it was not possible to determine an index case. The median time between the index case and subsequent cases within a household was three days and the interquartile range was [2;5].

Study population characteristics

Of the 15,063 multi-person households, 45.5% had 3-4 members and 13.9% >4 members. Table 1 shows baseline characteristics of the study population. Compared to index cases with and index cases without secondary cases, secondary cases tended to be younger with a higher proportion of individuals under 19 years of age, were more often descendants, and came predominantly from households with three or more members. Furthermore, 71.0 % of secondary cases were tested and identified during the open test period. Index cases with secondary cases were characterized by a high proportion of immigrants and belonging to the age-interval 40 to 79 years of age. Moreover, they were more likely to have comorbidities. Of note, index cases with secondary cases had the highest mortality rate and incidences of both ICU admissions and hospitalizations with 'Severe acute respiratory syndrome' (ICD-10: B97.2A), which remained after exclusion of individuals 80 years or above and in both testing periods (Table S1-S3). Index cases with no secondary cases made up the largest sub-cohort and were characterised by Danish ethnicity and living in households with two to four members.

The population that tested positive in the early limited test period (Table S2) was characterized by a general higher proportion of females, the presence of comorbidities, and Danish ethnicity. Furthermore, almost 25% were aged 60 or above. Characteristics of the population that tested positive in the open test period (Table S3) included lower incidences of comorbidities, ICU admissions, and mortality rates. Compared to the limited test period, the proportion of descendants was more than double in the open period (Table S3).

Association between continuous SARS-CoV-2 exposure and critical COVID-19

'Critical COVID-19' occurred in 2.9 % of index cases living with no secondary cases, 4.9 % of index cases living with secondary cases, and 1.3 % of secondary cases (Table 1).

Figure 2 and Table S4 summarize crude and adjusted HR for 'critical COVID-19' among index cases with and without secondary cases vs. secondary cases (analysis 1 and 2) and among index cases with vs. without secondary cases across households (analysis 3). Overall, both index cases with and without secondary cases had increased adjusted HRs for 'critical COVID-19' compared to secondary cases within and across households, except in the open test period where test capacity was extended to all individuals in Denmark. The adjusted HRs for index cases with secondary cases compared to secondary cases was highest in the main crude and in the analysis during the limited test period. In contrast, the latter analysis had a less pronounced adjusted HR when index cases without secondary cases were compared with secondary cases. In the analyses among index cases with versus without secondary cases across households, the only significant result was an increased adjusted HR during the limited test period.

Discussion

This cohort study reveals that the presence of SARS-CoV-2 positive individuals within households did not pose a higher risk of 'critical COVID-19' infection among subsequently infected household members. Our findings are in contrast to the increased risk of severe infection and household exposure to measles, chickenpox, and polio.[1-3] Likewise, no association between household transmission and increased risk of critical infection with SARS-CoV-1 or Middle East Respiratory Syndrome has, to the best of our knowledge, been described.

Our results reflect the national test strategy with different access to testing across time. The most pronounced findings were in the limited test period, where only high-risk groups more likely to become severely ill had access to testing. This is supported by our findings of a higher proportion of older adults and individuals with comorbidities during the limited test period. Contrariwise, no significant results were found in the open test period with broad access, and is probably more representative of the general Danish population. Of secondary cases, 71% were tested in the open period. Thus, results of the limited test period might be confounded by indication due to the restricted test capacity and hence an unknown number of unidentified COVID-19 positive individuals. Antibody serology among routine blood donors from 6 April 2020 to 3 May 2020 suggests that 0.8-2.3% of the Danish population had developed antibodies by then, with a ratio of expected seropositive to PCR-confirmed cases of between 7 and 20.[27]

Our percentage of multi-person households with more than one confirmed SARS-CoV-2 case (22.8%) is higher than the secondary attack rate (16.6%) reported in a systematic review and meta-analysis including 54 studies.[28] Likewise, our study had a higher percentage of PCR-positive secondary cases prompted by symptoms than the 13.7% of Singaporean household contact groups.[5] The Singaporean study had more households with >2 members compared to our study (77,4% vs 59.5%).[5] However, our confirmed SARS-CoV-2 cases also included asymptomatic individuals. Furthermore, our households with secondary cases had a proportion of 34% immigrants or descendants. Ethnic minorities have proven more vulnerable; they tend to live in smaller dwellings with more people compared to ethnic Danes, often are care or healthcare workers or work in public transport and may have difficulty understanding danish and thus have worse access to healthcare information.[29]

Fewer sub-outcomes of 'critical COVID-19' occurred in the open testing period (25 deaths vs. 176 deaths in the restricted period), likely reflecting developments in COVID-19 treatments over time. In addition, the estimated prevalence of COVID-19 in the general population seems to have remained at a stable low level between June and the end of August, with cases only starting to rise again in September.[10] Furthermore, the broader test strategy is reflected in a fall in the percentage of positive tests in the open compared to the limited period, e.g. in week 15 (6-12 April 2020), 7.2% of tests were positive with at most 6000 patients tested daily.[30] Subsequent mathematical modelling, based on the differences between positive tests in the general population (where test numbers have also greatly increased) and routine tests upon hospitalization, indicate that since September there has been an increase in positive tests reflecting a higher incidence, although the outbreak until mid-October does not yet seem to have reach the heights seen in April.[10] Overall, residual confounding as number of square meters per household member, multigenerational contact in households and insufficient self-isolation cannot be ruled out.

Strengths and limitations

Denmark has a long history of data collection on its citizens, providing a unique opportunity for a register-based study.[15] We were thus able to include a large nationwide cohort. The use of diagnostic and procedure codes to identify individuals with 'Severe acute respiratory syndrome' (ICD-10: B97.2A) and admission to intensive care was an efficient way of identifying individuals with increased disease severity. Of note, the diagnosis 'Severe acute respiratory syndrome' (ICD-10: B97.2A)' covers different severity levels. However, this should exclude any COVID-19 positive individuals hospitalized for other unrelated reasons. Also, the use of three different procedure codes for the identification of patients admitted to intensive care ensured that all relevant individuals were identified. Our data was, however, dependent on correct and timely registration in the national database. The database is updated monthly, and, therefore, did not include the latest COVID-19 cases or individuals that not yet had developed critical infection or succumbed to the virus. Furthermore, individuals living in care homes were not included due to lack of identification. If one considers a care home as a multi-person household, lack of inclusion will likely have underestimated our results as the incidence of 'critical COVID-19' is probably higher in this group.

One limitation of our study design is the assumption that individuals living in multi-person households were tested in chronological order of infection. However, some household members could have had a shorter time of symptom onset than others concurrently infected, others asymptomatic, leading to a misclassification of index and secondary cases with possible underestimation of our results. Furthermore, we did not take into account the possibility of family members choosing to isolate outside the home, which could have underestimated our results regarding secondary attack rates. Also, a grade of selection bias is possible, since the possibility and desire for testing was most likely based on the presence or absence of symptoms, and perhaps the severity of infected household members. In addition, we are unaware of the performance of the swab test in individuals with weak or no symptoms. Lower sensitivity and specificity in these individuals would result in false negative cases, resulting in both an underestimation of the number of infected individuals reported and, again, affect their classification within the household set-ups used in this study. Lastly, this study had limitations related to the observational nature which could be accommodated by a face-to-face epidemiological investigation.

Conclusion

In this study we found no increased hazard ratio of 'critical COVID-19' among household members of infected SARS-CoV-2 index cases.

Acknowledgements

Contributors: MB, CTP and ALM conceived and designed the analysis; MB, CTP and MPA collected the data; MB, CTP, EHAM, FG, MPA, MP and ALM did the data analysis; MB, CTP, FG, EHAM, ALM, VK interpreted the results of the data; MB, VK, EHAM, TKF wrote the first draft of the work; all authors revised the work critically for intellectual content; all authors approved the final version of the work to be published; all authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The authors thank Statistics Denmark for their help regarding data accessibility. Likewise, the authors acknowledge The Danish Departments of Clinical Microbiology (KMA) and Statens Serum Institut for carrying out laboratory analyses, registration, and release of the national SARS-CoV-2 surveillance data. The Danish law states that registry-based studies conducted for the sole purpose of scientific research do not require ethical approval or informed consent. Approval to use data sources for research purposes was granted by the data responsible institute (the Capital Region of Denmark) in accordance with the General Data Protection Regulation. Approval number: P-2019-191.

Funding: The study sponsors had no role in study design, in the collection, analysis, and interpretation of data, neither in the writing of the article or decision to submit the paper for publication.

Competing interests: Prof. C. Torp-Pedersen reports grants for randomized/epidemiological studies from Bayer and Novo Nordisk, outside the submitted work; Prof. L. Køber reports speaker's fees/honorarium from Novo, Novartis, Boehringer and AstraZeneca, unrelated to this manuscript; Doctor E. Fosbøl reports independent research grant from Novo Nordisk unrelated to this work. Doctor N. Zylyftari has received funding from the European Union´s Horizon 2020 research and innovation program ESCAPE-NET and Helsefonden, unrelated to this study. All other authors report no other relationships or activities that could appear to have influenced the submitted work.

References

1. Aaby P, Bukh J, Lisse IM, et al. Overcrowding and intensive exposure as determinants of measles mortality. *Am J Epidemiol* 1984; 120:49-63. doi: 10.1093/oxfordjournals.aje.a113874. PMID: 6741923.
2. Poulsen A, Qureshi K, Lisse I, et al. A household study of chickenpox in Guinea-Bissau: intensity of exposure is a determinant of severity. *J Infect* 2002; 45(4):237-42. doi: 10.1053/jinf.2002.1049. PMID: 12423611.
3. Nielsen NM, Aaby P, Wohlfahrt J, et al. Intensive exposure as a risk factor for severe polio: a study of multiple family cases. Scand J Infect Dis. 2001; 33:301-5. doi: 10.1080/003655401300077360. PMID: 11347591.
4. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020; 63:364-374. doi: 10.1007/s11427-020-1643-8. Epub 2020 Feb 9. PMID: 32048163; PMCID: PMC7088566.
5. Tek Ng O, Marimuthu K, Koh V, et al. SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: a retrospective cohort study. *Lancet Infect Dis* 2020: S1473-3099(20)30833-1. doi: 10.1016/S1473-3099(20)30833-1. Epub ahead of print. PMID: 33152271.
6. Rasmussen AL, Popescu SV. SARS-CoV-2 transmission without symptoms. *Science* 2021; 371(6535):1206-1207. doi: 10.1126/science.abf9569. PMID: 33737476.
7. Grijalva CG, Rolfes MA, Zhu Y, et al. Transmission of SARS-COV-2 Infections in Households - Tennessee and Wisconsin, April-September 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69:1631-1634. doi: 10.15585/mmwr.mm6944e1. PMID: 33151916; PMCID: PMC7643897.
8. Brandén M, Aradhya S, Kolk M, et al. Residential context and COVID-19 mortality among adults aged 70 years and older in Stockholm: a population-based, observational study using individual-level data. *Lancet Healthy Longev* 2020; published online Oct 27. doi:10.1016/S2666-7568(20)30016-7.
9. Johns Hopkins Coronavirus Resource Center. https://coronavirus.jhu.edu/ (1 November 2020, date last accessed).

10. Statens Serum Institut. Ekspertrapport af d. 23. Oktober 2020. Incidens og fremskrivning ad COVID-19 tilfælde. Stathttps://www.ssi.dk/-/media/ssi-files/ekspertrapport-af-den-23-oktober-2020-incidens-og-fremskrivning-af-covid19-tilflde.pdf?la=da (19 December 2020, date last accessed).
11. World Health Organization. Managing the COVID-19 infodemic: Promoting healthy behaviours and mitigating the harm from misinformation and disinformation. Joint statement by WHO, UN, UNICEF, UNDP, UNESCO, UNAIDS, ITU, UN Global Pulse, and IFRC. https://www.who.int/news/item/23-09-2020-managing-the-covid-19-infodemic-promoting-healthy-behaviours-and-mitigating-the-harm-from-misinformation-and-disinformation. (19 December 2020, date last accessed).
12. United Nations. Department of Economic and Social Affairs. Population Division. Household Size & Composition Around the World 2017. Data booklet (ST/ESA/SER.A/405).
13. Thygesen LC, Daasnes C, Thaulow I, et al. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011; 39:12-6. doi: 10.1177/1403494811399956. PMID: 21898916.
14. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; 39:22-5. doi: 10.1177/1403494810387965. PMID: 21775345.
15. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019; 11:563-591. doi: 10.2147/CLEP.S179083. PMID: 31372058; PMCID: PMC6634267.
16. Voldstedlund M, Haarh M, Mølbak K; MiBa Board of Representatives. The Danish Microbiology Database (MiBa) 2010 to 2013. *Euro Surveill* 2014; 19:20667. doi: 10.2807/1560-7917.es2014.19.1.20667. PMID: 24434175.
17. Registry analyses of Danish Covid-19 patients. https://laegemiddelstyrelsen.dk/en/about/danish-medicines-agencys-data-analytics-center-dac/registration-analyses-of-danish-covid-19-patients/ (28 July 2020, date last accessed).
18. World Health Organization. The International Classification of Diseases and Related Health Problems, Tenth Revision. Geneva, Switzerland: World Health Organization, 2007.
19. The Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures. 2011. http://norden.diva-portal.org/smash/get/diva2:968721/FULLTEXT01.pdf (19 December 2020, date last accessed).

20. Schmidt M, Schmidt SAJ, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; 7:449-90. doi: 10.2147/CLEP.S91125. PMID: 26604824; PMCID: PMC4655913.

21. Koff AG, Laurent-Rolle M, Hsu JC, Malinis M. Prolonged incubation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a patient on rituximab therapy. *Infect Control Hosp Epidemiol* 2020; 7:1-2. doi: 10.1017/ice.2020.1239. PMID: 33023685; PMCID: PMC7578652.

22. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe* 2021;2(1):e13-e22. doi: 10.1016/S2666-5247(20)30172-5. PMID: 33521734; PMCID: PMC7837230.

23. Sundhedsstyrelsen. Retningslinjer for håndtering af COVID-19 i sundhedsvæsenet. 21. October 2020. https://www.sst.dk/da/Udgivelser/2020/Retningslinjer-for-haandtering-af-COVID-19. (19 December 2020, date last accessed).

24. Sundheds- og Ældreministeriet. Alle borgere får mulighed for at blive testet for COVID-19. 18-05-2020. https://sum.dk/Aktuelt/Nyheder/Coronavirus/2020/Maj/Alle-borgere-faar-mulighed-for-at-blive-testet-for COVID-19.aspx. (19 December 2020, date last accessed).

25. Thygesen SK, Christiansen CF, Christensen S, et al. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011; 11:83. doi: 10.1186/1471-2288-11-83. PMID: 21619668; PMCID: PMC3125388.

26. R Core Team (2019). R: A language and environment for statistical computing. R and Foundation for Statistical Computin, Vienna, Austia. URL https://www.R-project.org/.

27. Erikstrup C, Hother CE, Pedersen OBV, et al. Estimation of SARS-CoV-2 infection fatality rate by real-time antibody screening of blood donors. *Clin Infect Dis* 2020: ciaa849. doi: 10.1093/cid/ciaa849. Epub ahead of print. PMID: 32584966; PMCID: PMC7337681.

28. Madewell ZJ, Yang Y, Longini IM, et al. Household Transmission of SARS-CoV-2: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2020; 3:e2031756. doi: 10.1001/jamanetworkopen.2020.31756. PMID: 33315116; PMCID: PMC7737089.

29. Ligebehandlingsafdelingen, Institut for menneske rettigheder. Corona rammer skævt – etnicitet og smitte. Juni 2020.

https://menneskeret.dk/sites/menneskeret.dk/files/media/billeder/udgivelser/ligebehandling_2020/rapport_corona_rammer_skaevt.pdf. (4 April 2021, date last accessed).

30. Sundhedsstyrelsen. COVID-19 i Danmark. Status ved indgangen til 8. epidemiuge. 22. april 2020. https://www.sst.dk/-/media/Udgivelser/2020/Corona/Status-og-strategi/COVID19-8-epidemiuge.ashx?la=da&hash=1EE6DCA211CAF1E9D7FA085FADA69F17C505436B. (19 December 2020, date last accessed).

Tables

Table 1. Characteristics of the study population

Characteristics	Level	Index cases without secondary cases (n=11632)	Index cases with secondary cases (n=3431)	Secondary cases (n=4710)	Total (n=19773)
Composite outcome of critical COVID-19	Yes	341 (2.9)	167 (4.9)	60 (1.3)	568 (2.9)
Death within 30 days	Yes	127 (1.1)	59 (1.7)	15 (0.3)	201 (1.0)
Intensive care unit admission (NABE, NAB, BGA)	Yes	169 (1.5)	95 (2.8)	24 (0.5)	288 (1.5)
Severe acute respiratory syndrome (ICD-10: B97.2A)	Yes	264 (2.3)	129 (3.8)	48 (1.0)	441 (2.2)
Time period of positive test*	Limited test period	4,668 (40.1)	1,124 (32.8)	1,368 (29.0)	7,160 (36.2)
	Open test period	6,964 (59.9)	2,307 (67.2)	3,342 (71.0)	12,613 (63.8)
Sex	Female	6,350 (54.6)	1,767 (51.5)	2,474 (52.5)	10,591 (53.6)
	Male	5,282 (45.4)	1,664 (48.5)	2,236 (47.5)	9,182 (46.4)
Age	0-18	1,647 (14.2)	356 (10.4)	1,456 (30.9)	3,459 (17.5)
	19-39	4,037 (34.7)	933 (27.2)	1,067 (22.7)	6,037 (30.5)
	40-59	4,142 (35.6)	1,436 (41.9)	1,483 (31.5)	7,061 (35.7)

	60-79	1,584 (13.6)	595 (17.3)	609 (12.9)	2,788 (14.1)
	80-102	222 (1.9)	111 (3.2)	95 (2.0)	428 (2.2)
	Mean	39.96	44.65	35.87	39.80
Ethnicity	Danish	9,095 (78.2)	2,309 (67.3)	3,062 (65.0)	14,466 (73.2)
	Immigrant	1,782 (15.3)	858 (25.0)	943 (20.0)	3,583 (18.1)
	Descendant	755 (6.5)	264 (7.7)	705 (15.0)	1,724 (8.7)
Household members	2	4,807 (41.3)	1,302 (37.9)	1,302 (27.6)	7,411 (37.5)
	3-4	5,325 (45.8)	1,535 (44.7)	2,217 (47.1)	9,077 (45.9)
	>4	1500 (12.9)	594 (17.3)	1191 (25.3)	3,285 (16.6)
Comorbidities cf. Charlson Comorbidity Index	Yes	1428 (12.3)	558 (16.3)	516 (11.0)	2,502 (12.7)

*The 'limited test period' from 22 February 2020 to 18 May 2020 covers a period of SARS-CoV-2 test accessibility for individuals at risk, while the 'open test period' from 19 May 2020 to 6 October 2020 covers SARS-CoV-2 test accessibility for all individuals in Denmark.

Figure legends

Figure 1. Various types of SARS-CoV-2 positive household members.

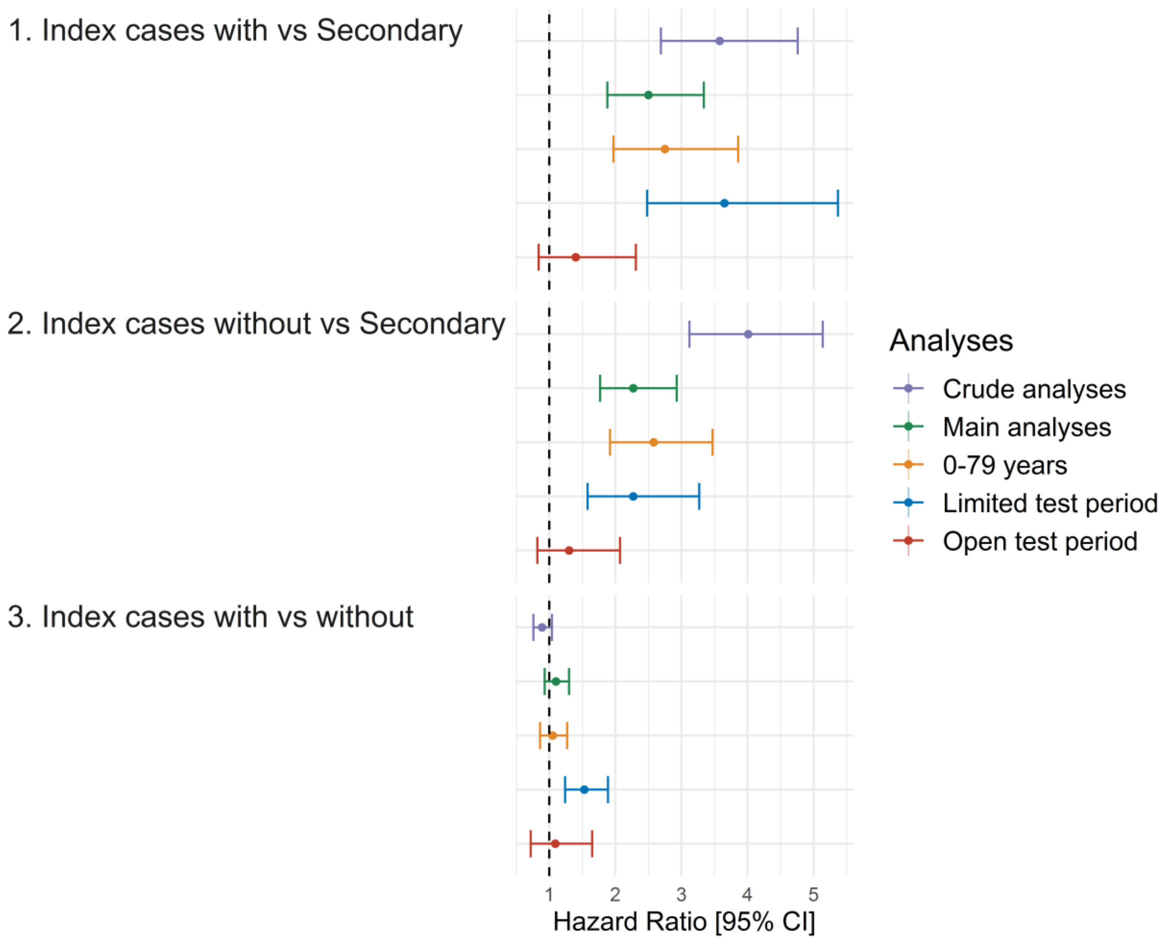
Figure 2. Association between SARS-CoV-2 exposure and critical COVID-19 specified by hazard ratios

Sub-cohorts were categorized as index cases with secondary cases (n = 3,431), index cases without any secondary household cases (n = 11,632), and secondary cases (n = 4,710). Table S4 shows the corresponding results in numbers.

Figure 1


Index case without
secondary cases
n = 11,632
Index case with
secondary cases
n = 3,431
Secondary cases
n = 4,710

Figure.2



1. Index cases with vs Secondary
2. Index cases without vs Secondary
3. Index cases with vs without
Analyses
Crude analyses
Main analyses
0-79 years
Limited test period
Open test period
1
2
3
4
5
Hazard Ratio [95% CI]