Associations between measures of social distancing and SARS-CoV-2 seropositivity: a nationwide population-based study in the Netherlands

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ABSTRACT

This large nationwide population-based seroepidemiological study provides evidence on the effectiveness of physical distancing (>1.5m) and indoor group size reductions on SARS-CoV-2 infection. Additionally, young adults may play an important role in viral spread, opposed to children up until 12 years of age with whom close contact is permitted.

KEYWORDS: COVID-19 pandemic; SARS-CoV-2 seroprevalence; social distancing; transmission; the Netherlands

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is an unprecedented global crisis. Stringent measures to suppress the spread of its causative agent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have been implemented to reduce incidence of disease and prevent health systems from becoming overwhelmed. Assessment of the impact of social-distancing measures is vital for informing public health decisions, particularly since the worldwide availability of vaccines is still very limited in this phase.

In the Netherlands, the first case of COVID-19 was reported on February 27, 2020. Key governmental interventions implemented since mid-March, 2020, included: keeping physical distance (≥1.5m) from adults for those aged >12 years, whereas close contact between children <18years was permitted; closure of schools, restaurants/bars/cafés, cultural institutions, sport facilities; working from home if possible; prohibition of contact professions; closure of nursing homes to visitors; and reducing group sizes – i.e., maximum of three visitors at home as well as three persons from different households outside, and prohibition of all events and gatherings, except for weddings, funerals, religious gatherings (maximum of 30 persons), legally required meetings and work-related meetings necessary for continuation of daily activities (maximum of 100 persons). In May, daycare and primary schools were re-opened, and contact professions were allowed to resume. Measures were further relaxed from June until the end of summer, while adhering to physical distancing measures and obligation of wearing a non-medical mask in public transportation.

Seroprevalence of antibodies against SARS-CoV-2, acquired from validated laboratory assays and well-designed population-based studies, provide an important indicator of cumulative infection [1, 2]. In combining seroprevalence with questionnaire data, the current nationwide population-based study (PIENTER-Corona, PICO) [3] – performed after the first epidemic wave in the Netherlands in

June, 2020 – enabled us to identify risk factors for infection to support assessment of the impact of globally-applied social distancing measures.

METHODS

Randomly-selected participants of all age groups from the first PICO-serosurvey in April, 2020 [3, 4], – who were initially sampled from the PIENTER3-serosurvey cohort, established in 2016/17 [4] – were invited for the current study in June, 2020, and 2,317 enrolled (of initially 4,926 invited). To enhance countrywide geographical coverage, and given the low anticipated seroprevalence, the study sample from April, 2020, was supplemented with an additional sample of 4,496 (of 26,854) randomly-selected persons from the population registry, resulting in a total cohort of 6,813 participants in the current study (combined response rate 21.4% (for further details on sampling, see **Supplement–p3-4**)). Participants were requested to collect a fingerstick blood sample in a microtainer (SARSTEDT) and return it by mail. An (online) questionnaire was completed on potential SARS-CoV-2 exposure (number and age group of non-household close contacts (<1.5m) the day before filling out the questionnaire, attendance of indoor meetings with >20 persons, nursing home visits, working from home last week, profession, close contact (voluntary) work with patients/clients and children, and household size); and sociodemographic characteristics (sex, age, ethnic background, religion, educational level, postal codes were used to determine geographical sites).

Quantitative measures of serum IgG antibodies against SARS-CoV-2 Spike-S1 antigen were derived via a validated immunoassay [5] (see **Supplement-p6-7** for further details on the assay). Based on low anticipated seroprevalence [3], we aimed for a specificity of 99.9% to keep false positive rates to a minimum. Mixture model analyses (using a validation panel as prior distribution) showed that such specificity could be obtained (at a cut-off for seropositivity of 0.04 log(AU)/mL) with associated sensitivity of 94.3% (95% confidence interval (CI) 90.6-96.7) (**Supplement–p6-16**). Applying this cut-off, all seroprevalence estimates (and 95% CIs) for the general Dutch population took into account the survey design, included weighting factors to match the distribution of the general Dutch population (based on sex, age, ethnic background and degree of urbanization; **Supplement–p6**), and were controlled for test characteristics subsequently [6, 7]. Smooth age-specific seroprevalence was modelled with B-splines (second degree, three percentile-placed internal knots, following lowest Akaike's Information Criteria (AIC)).

Risk factors for seropositivity were identified using random-effects logistic regression – taking into account municipality as a unit of clustering. In the main analysis, all participants without missing data for the tested determinants were included (n=6,331). Odds ratios (OR) and 95% CIs were derived from univariable analyses, and two-way interactions with age were tested for significance. Variables with an overall p<0.15 were tested in multivariable analysis, in which stepwise-backward selection was applied yielding a final model including only independent risk factors (based on lowest AIC). Sensitivity analyses were performed applying forward selection; and by testing models without the variable 'being religious' (n=6,487) – as it comprised the most missing values – without 'educational level' (n=6,339) and without non-household contact data (n=6,338) – the latter two to test potential associations with profession.

Analyses were performed using Stan v.2.21 (mixture modelling), and SAS v.9.4 (SAS Institute Inc., USA). The study was approved by the Medical Ethics Committee MEC-U (Clinical Trial Registration NTR8473) and all participants provided written informed consent.

RESULTS

Median inclusion date was June 14, 2020 (range: June 9–Augustus 24; 90% was enrolled by June 22) (note: sociodemographic characteristics available from non-responders were compared to responders and shown in **Supplement–p4-5**). The cohort comprised 55% women and regions were equally represented following population size (**Supplement–p5-7**). Half of the participants reported to have had ≥2 non-household close contacts the day before filling out the questionnaire. Since the start of the epidemic, one quarter had attended an indoor meeting with >20 persons, and 8% had visited a nursing home. Among 18-66 year-olds, 36% (voluntarily) worked in close contact with clients/patients, 18% was a healthcare worker, and 40% had been (partly) working from home last week.

After the first epidemic wave, overall seroprevalence in the Dutch population was 4.5% (95% CI 3.8-5.2). No statistically significant differences were observed between sexes or ethnic backgrounds. Estimates were low (0-2%) in children aged 1-12 years, high (9%) in young adults in their early twenties, and 4-7% in individuals ≥35 years (**Figure1A**). Low urbanized areas were hit hardest, predominantly in the South-East (up till 16%) (**Supplement–p17**).

All potential risk factors for seropositivity tested in univariable analyses are shown in **Figure1B** (see **Supplement–p18-20** for additional details). Close contact (voluntary) work with children and work with clients/patients were not associated with seropositivity. Social distancing-related risk factors in the multivariable model included (**Figure1B, 1C, and Supplement–p18-19**): non-household close contacts with ≥50% persons ≥10 years, but not close contact with ≥50% children <10 years, as compared to no contacts (see also **Figure1D**); attending indoor meetings with >20 persons; working in a nursing home (rather than visiting); increased household size; and age, with low adjusted odds in children ≤12 years, whilst over 2.5 times higher odds in adults aged 18-30 and ≥50 years as compared to 12-year-olds (**Figure1C**). Notably, total number of non-household close contacts did not remain in the final model after including the variable nature of close contact. Sensitivity analyses yielded similar results (**Supplement–p21**).

DISCUSSION

Here, we provide evidence from a large population-based study on the effectiveness of physical distancing (>1.5m) as well as indoor group size reductions on SARS-CoV-2 infection. These data suggest that close contact with children up until 12 years of age may pose little risk for infection.

Our results on physical distancing are in line with the few previous reports mostly derived from healthcare settings and households [8]. Seroprevalence rates were low in children aged ≤12 years despite close contact, and similar to observations from other European countries with comparable nationwide estimates [1, 9]. Interestingly, the likelihood of infection among persons in close contact with children was not statistically significantly increased, most likely indicating a low contribution in transmission, as suggested previously [10-13]. In contrast, particularly young adults, who engage in relatively more social interaction as opposed to older age groups [14] and often living in larger (student) households in the Netherlands, most probably play an increased role. Applying physical distancing measures within households may not always be feasible, however stressing its relevance in outbreak management could help to reduce (ongoing) transmission. Further, like in ample other countries [15], these data underline the increased risk of infection among nursing home workers. Hence, while working with the most vulnerable, this requires specific attention.

Our study has strengths and limitations. Strength is that our study provides a large population sample covering a full age-range from young to old, combining a sound indicator of prior infection, i.e., seropositivity, with extensive questionnaire data. Also, samples could be classified accurately since antibodies were measured with a highly specific and sensitive immunoassay. A limitation includes the relatively low response rate, which may have introduced potential selection bias, e.g., participation of relatively more health-conscious individuals possibly adhering to social distancing measures, healthcare workers and persons from Dutch descent, however we expect little effect on our main outcome. Further, some variables might be proxies of risk of viral exposure, e.g., on contacts, thus associations should be interpreted with care as they may not reflect causal effects.

In conclusion, these results underscore the effectiveness of the social distancing-related measures to reduce SARS-CoV-2 transmission in an era of limited availability of vaccines. Additionally, our data suggest a diminished role of young children in viral spread, which combined with a proactive testing policy, might justify to keep primary schools open, while young adults may seem to play a more considerable role.

NOTES

CONTRIBUTORS: EV wrote the manuscript. FvK, HdM, EV, LM, RvB, GdH, and JB conceived the study. EV conducted the epidemiological data analyses, MvB performed the mixture modelling and supervised the epidemiological analyses together with HdM and HB. RvB, and GdH supervised the laboratory analyses. EV, LM, CvH, and GdH processed the data. FvK was principal investigator of the study. EV and FvdK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the interpretation of data, and read, edited and approved the final manuscript.

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POTENTIAL CONFLICT OF INTEREST: None declared.

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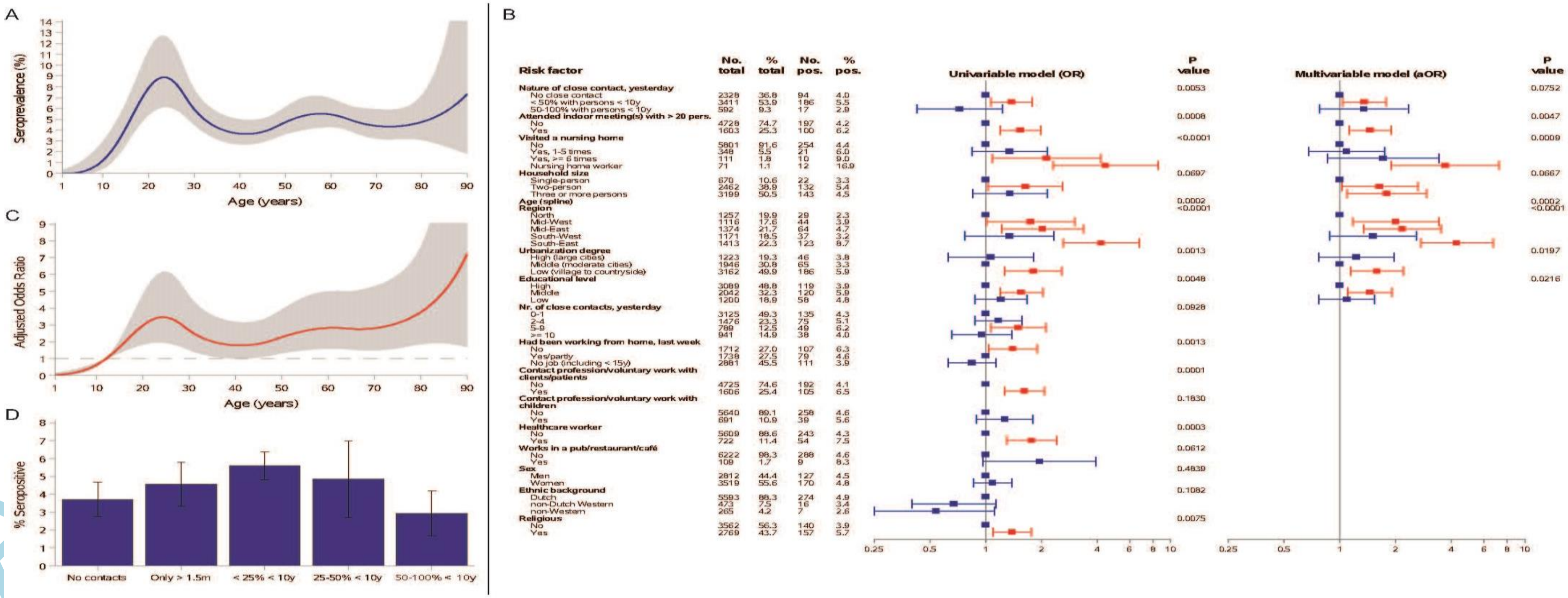
FIGURE LEGEND

Figure1. **A**. shows the weighted smooth age-specific SARS-CoV-2 seroprevalence with 95% confidence envelope in the general population of the Netherlands after the first epidemic wave. **B** displays the risk factor analyses for SARS-CoV-2 seropositivity. Number (and %) of total participants per potential risk factor-category are provided as well as the number (and %) of seropositive participants, and P-values. Forest plots are shown of crude odds ratios (OR) for univariable analyses and adjusted odds ratios (aOR) for the multivariable analysis, and depicted by squares and 95% confidence intervals (95% CIs) with lines: those in red are significantly associated with seropositivity and those in blue are non-significant. Time window of attending indoor meetings with > 20 persons and visiting a nursing home concerned the beginning of the epidemic in the Netherlands (February 27, 2020) until the day of filling out the questionnaire or until closure (for visitors) of nursing homes (March 20, 2020), respectively. Nature and number of non-household close contacts yesterday, and working from home last week, concerned the day or week, respectively, before filling out the questionnaire. Receiver Operating Characteristic curve analysis of the multivariable model yielded an Area Under the Curve (as a measure of goodness-of-fit) of 0.72. **C**. shows the aOR with 95% confidence envelope for age (which was included with a flexible (spline) function) derived from the multivariable model, with 12 year as reference category. **D**. displays the percentage of SARS-CoV-2 seropositive participants (and 95% CIs) by number and nature of non-household close contact the day before filling out the questionnaire. Nature of non-household close contact was defined as the proportion of non-household close contacts with children aged < 10 years of the total number of non-household close contacts. Abbreviations: aOR, adjusted odds ratio; no., number; OR, odds ratio, pers., persons; pos., positive; y, year.

Figure 1


A
Seroprevalence (%)
Age (years)
C
Adjusted Odds Ratio
Age (years)
D
% Seropositive
No contacts
Only > 1.5m
< 25% < 10y
25-50% < 10y
50-100% < 10y
B
Risk factor
No. total
% total
No. pos.
% pos.
Univariable model (OR)
P value
Multivariable model (aOR)
P value