PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Predictors of Incident SARS-CoV-2 Infections in an International Prospective Cohort Study
AUTHORS	Lin, Anthony; Vittinghoff, Eric; Olgin, J; Peyser, Noah; Aung, Sidney; Joyce, Sean; Yang, Vivian; Hwang, Janet; Avram, Robert; Nah, Gregory; Tison, Geoffrey; Beatty, Alexis; Runge, Ryan; Wen, David; Butcher, Xochitl; Horner, Cathy; Eitel, Helena; Pletcher, Mark; Marcus, GM

VERSION 1 – REVIEW

REVIEWER	Caniza, Miguela St Jude Children's Hospital Memphis , Global Pediatric Medicine and Infectious Diseases
REVIEW RETURNED	21-Jun-2021

GENERAL COMMENTS	The study " Predictors of Incident SARS-CoV-2 Infections in Participants of the Covid-19 Citizen Science Study" by Lin AL et al presents the results of a prospective cohort study of adults to identify personal risk factors for contracting SARS-CoV-2 using a mobile-based study collecting daily, weekly, and monthly surveys in a prospective and time-updated manner. A multisite and multi-country response indicated that increase age was protective, increase number of household contacts, attending events in crowed places had higher risk of contracting SARS-CoV-2. Comments Interesting and informative study. Title. Appropriate Abstract. Appropriate Introduction. Appropriate Methods. Indicate if English language was the only language used. Results. Indicate what percent of participants were compliant with the requests for data in the periodic surveys. Most of the participating countries were of more affluent sites, any reasons? Discussion Please comment the significance of no participation of large parts of world, was this because of lack of penetration of the research participation offering, or because of the language barrier?

REVIEWER	Athens, Josie University of Otago, Preventive and Social Medicine
REVIEW RETURNED	04-Jul-2021

GENERAL COMMENTS	The manuscript presents results from a prospective study looking at factors associated with SARS-CoV-2 infection. The study was conducted electronically worldwide, and given its magnitude,

	cautions should be taken about presenting information and interpreting the results. The aims of the study are clear and relevant, and the methods to analyse data is adequate. My main concern is about how the authors interpret their results and thus reach conclusions. To make conclusions from p-values and ignore the actual effects of their predictors is not acceptable nowadays. For example, the effect of age, which they conclude is significant, is only 2% (OR 0.98), and its confidence interval includes the null value of one. The p-value was significant because of the large sample size. To conclude that older age "protects" against SARS-CoV-2 infection is thus, wrong and biased. The authors discuss some of the limitations of the platform that they used to collect data but I would like to see more discussion and to acknowledge selection bias particularly in the older population; it is well known about infections in caring homes and that was not even discussed. What is the minimum effect size that the authors consider as clinically significant? I would like for this to be decided a priori for an unbiased discussion of the results. In their discussion, the authors state "Our study demonstrated an increased association of SARS-CoV-2 infection in individuals who reported higher number of recent contacts". "Demonstration" is a strong word in science and I did not find any demonstration, whatsoever in the manuscript; please be careful on your selection of words particularly on topics of public health with such an impact as COVID-19.

REVIEWER	Sera, Francesco London School of Hygiene and Tropical Medicine, Social and Environmental Health Research
REVIEW RETURNED	09-Jul-2021

GENERAL COMMENTS	I read with interest this paper presenting the results of a longitudianl study investigating the predictors of incident SARS-CoV-2 infections in a US cohort. The paper is well structured and clear. The longitudinal design allows to mitigate information and selection bias. The statistical methods (e.g. pooled logistic regression) are coherent with the study design. The results are interesting as confirm the role of social contacts on increasing the likelihood of SARS-CoV-2 infections. I have only one minor points to discuss with the authors, and it's related to the external validity of the results presented in this research. The prevalence of subjects in the cohort working in helathcare without SARS-CoV-2 infections is 20.1, and it seems quite high to me. It seems that in the cohort there could be an over representation of subjects with a greater attention to covid-19. This could also explain some results on mask wearing and hand washing on which the exposre range could be limited affecting the power. I think the author should discuss possible effect of selection bias due to over-represenation of healtcare workers.

	As a note I would avoid to use the term significant or not significant on describing the results, especially considering the low power of this study as only 112 outcomes were identified. The results on mask wearing and other behaviours could be due to low power of this study.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

The study " Predictors of Incident SARS-CoV-2 Infections in Participants of the Covid-19 Citizen Science Study" by Lin AL et al presents the results of a prospective cohort study of adults to identify personal risk factors for contracting SARS-CoV-2 using a mobile-based study collecting daily, weekly, and monthly surveys in a prospective and time-updated manner. A multisite and multi-country response indicated that increase age was protective, increase number of household contacts, attending events in crowed places had higher risk of contracting SARS-CoV-2.
Comments
Interesting and informative study.
Title. Appropriate
Abstract. Appropriate
Introduction. Appropriate

Thank you for your time and careful review of our study. We appreciate your insights.

Methods. Indicate if English language was the only language used.

English was the language used in the health surveys. We have now clarified that point in the Methods section:

"Surveys were written in English and met the Flesch-Kincaid criteria for 8th grade reading level."

Results. Indicate what percent of participants were compliant with the requests for data in the periodic surveys. Most of the participating countries were of more affluent sites, any reasons?

Thank you for this comment. We have included the mean ± standard deviation of all participants who responded to survey requests at least once weekly and at least once monthly, and have included tables in the supplementary materials regarding week-by-week and month-by-month details:

"The mean proportion of participants who completed at least one health survey during a study week was 88.6% ± 5.0% and the mean proportion of participants who completed at least one health survey during a study month was 98.1% ± 1.6%."

While enrollment was available to all adults over 18, recruitment was limited by press releases, social media, and word-of-mouth. We suspect that more affluent countries may have had more access to those forms of communication to self-enroll in the Covid-19 Citizen Science Study. Additionally, the health surveys were conducted through a smartphone application, which may have made participation more difficult for members of less affluent sites. To address this potential source of bias, we mention in our limitations section that:

"As the study required smartphone ownership and use, it is possible that the Covid-19 Citizen Science Study participants represent a more affluent and more technologically savvy population compared to the general population."

Discussion
Please comment the significance of no participation of large parts of world, was this because of lack of penetration of the research participation offering, or because of the language barrier?

Thank you for this insightful question. While our diverse recruitment methods were able to reach participants from nearly 100 different countries and every state in the United States, we unfortunately were not able to reach every international country. While recruitment efforts are ongoing to continue to add to the geographical diversity of the Covid-19 Citizen Science Study, the health surveys have not been translated to languages other than English at this time. We suspect that both language and differing levels of penetration in our recruitment methods may account for the differences seen in the geographic distribution of our Covid-19 Citizen Science participants. Additionally, as mentioned above, the requirement of a smartphone to engage with our platform may skew the study population towards a more affluent subset when compared to the general international population. While we acknowledge these limitations may limit generalizability to countries not as well-represented in the Covid-19 Citizen Science Study, internal validity of the study was preserved due to the purposeful study design to follow the same participant over time to identify differences in behaviors and exposures between those who contracted SARS-CoV-2 and those who did not:

"As the study required smartphone ownership and use, it is possible that the Covid-19 Citizen Science Study participants represent a more affluent and more technologically savvy population compared to the general population. Though this would limit generalizability instead of internal validity, our diverse recruitment methods were meant to mitigate risks of sampling bias. The distribution of study participants throughout nearly 100 different countries and every state in the US provides fairly unprecedented geographical diversity for a study that also ascertains participant-reported behaviors."

Reviewer 2:

The manuscript presents results from a prospective study looking at factors associated with SARS-CoV-2 infection. The study was conducted electronically worldwide, and given its magnitude, cautions should be taken about presenting information and interpreting the results.

The aims of the study are clear and relevant, and the methods to analyse data is adequate. My main concern is about how the authors interpret their results and thus reach conclusions.

To make conclusions from p-values and ignore the actual effects of their predictors is not acceptable

nowadays. For example, the effect of age, which they conclude is significant, is only 2% (OR 0.98), and its confidence interval includes the null value of one. The p-value was significant because of the large sample size. To conclude that older age "protects" against SARS-CoV-2 infection is thus, wrong and biased. The authors discuss some of the limitations of the platform that they used to collect data but I would like to see more discussion and to acknowledge selection bias particularly in the older population; it is well known about infections in caring homes and that was not even discussed.

Thank you for bringing up this important point. We agree with you and, as this is a prospective cohort study, we do not try to make a conclusion about causality for any of the associations observed in the study. Regarding older populations, we reference prior studies demonstrating higher rates of hospitalization, morbidity, and mortality in the elderly, and postulate as to why we observe a decreased odd ratio in our large population study in the context of the research performed prior to ours:

"While the lower risk among older individuals may at first glance appear counter-intuitive, this may be consistent with similar protective behaviors and compliance with social distancing behaviors, especially given data reporting high incidence of SARS-CoV-2 in nursing homes[29] as well as disproportionately higher rates of hospitalization and death in older populations infected with SARS-CoV-2.[30,31] If such phenomena were operative, the fact that we were unable to detect differences in such behaviors (such as significant relationships between hand hygiene or mask-wearing) may be due to collinearity with age and/or suboptimal ascertainment of the actual protective approaches utilized by older individuals."

What is the minimum effect size that the authors consider as clinically significant? I would like for this to be decided a priori for an unbiased discussion of the results.

We did not prespecify a minimum effect size precisely to avoid enabling preconceived assumptions to direct our results. Instead, we a priori sought to identify predictors in multivariable models that would emerge with statistical significance. As above, we are careful to avoid causal language. We have also addressed this specifically in the revised limitations:

"Because identification of predictors was determined by testing for statistical significance, we acknowledge that the effect sizes for some of the identified covariates may be small and of questionable clinical relevance. However, this approach enabled us to be as inclusive as possible without constraining potentially relevant predictors based on preconceived assumptions."

In their discussion, the authors state "Our study demonstrated an increased association of SARS-CoV-2 infection in individuals who reported higher number of recent contacts". "Demonstration" is a strong word in science and I did not find any demonstration, whatsoever in the manuscript; please be careful on your selection of words particularly on topics of public health with such an impact as COVID-19.

Thank you for this point of clarity. We have changed the words "demonstrate[d]" to "observed" and "suggest" to be more specific in the language used:

“Our study observed an increased association of SARS-CoV-2 infection in individuals who reported higher numbers of recent contacts. In a similar vein, increased attendance of events of 10 or more people and restaurant visits were associated with increased odds for developing SARS-CoV-2. Given our general understanding of disease transmission for respiratory viruses and recent research characterizing the asymptomatic transmission of SARS-CoV-2,[25,26] these findings are bolstered by biologic plausibility. They add to previous research supporting the use of government mandated physical distancing policies to reduce SARS-CoV-2 incidence[27,28] and suggest that behaviors to minimize human-to-human interaction could be effective means to lower one’s individual risk of contracting SARS-CoV-2. To our knowledge, this is the first longitudinal cohort to determine that such behaviors among individuals prior to infection actually influence risk.”

Reviewer 3:

I read with interest this paper presenting the results of a longitudinal study investigating the predictors of incident SARS-CoV-2 infections in a US cohort.

The paper is well structured and clear. The longitudinal design allows to mitigate information and selection bias. The statistical methods (e.g. pooled logistic regression) are coherent with the study design.

The results are interesting as confirm the role of social contacts on increasing the likelihood of SARS-CoV-2 infections.

Thank you for your careful review of our study and we appreciate your insightful comments.

I have only one minor points to discuss with the authors, and it's related to the external validity of the results presented in this research.
The prevalence of subjects in the cohort working in healthcare without SARS-CoV-2 infections is 20.1, and it seems quite high to me. It seems that in the cohort there could be an over representation of subjects with a greater attention to covid-19. This could also explain some results on mask wearing and hand washing on which the exposure range could be limited affecting the power. I think the author should discuss possible effect of selection bias due to over-representation of healthcare workers.

Thank you for this insightful observation. The prevalence of healthcare workers was higher likely due to the nature of the study being conducted by a large academic medical center. We have raised this point in our discussion as well:

“…the higher prevalence of healthcare workers in the study population may have resulted in participants having higher rates of mask wearing and hand washing, but also higher risk for infection, thereby degrading any associations between predictor and outcome.”

As a note I would avoid to use the term significant or not significant on describing the results, especially considering the low power of this study as only 112 outcomes were identified. The results on mask wearing and other behaviors could be due to low power of this study.

Thank you for this comment. Given the low number of positive cases compared to the total study population, we agree that negative results (lack of associations) will tend to be less informative than positive results (observations with $p<0.05$). Therefore, we place less emphasis in the manuscript overall on the negative results observed in the study (such as mask wearing and other behaviors as you've mentioned), and focus our discussion largely on the positive results observed during the study period:

"…these negative results should be interpreted cautiously in the context of the study design and insufficient power may render negative results (or lack of associations) less informative than the statistically significant relationships (positive results) that have been observed thus far (even if in the absence of a longitudinal cohort with time-updated assessments as described here)."

Thank you again for your time and consideration.

VERSION 2 – REVIEW

REVIEWER	Athens, Josie University of Otago, Preventive and Social Medicine
REVIEW RETURNED	27-Aug-2021

GENERAL COMMENTS	The authors addressed all the concerns and observations that I had on the first revision.

REVIEWER	Sera, Francesco London School of Hygiene and Tropical Medicine, Social and Environmental Health Research
REVIEW RETURNED	22-Aug-2021

GENERAL COMMENTS	My concerns have been addressed thoughtfully in the revisions. I have no futher comments.