PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A potential impact of physical distancing on physical and mental health. A rapid narrative umbrella review of meta-analyses on the link between social connection and health
AUTHORS	Morina, Nexhmedin; Kip, Ahlke; Hoppen, Thole; Priebe, Stefan; Meyer, Thomas

VERSION 1 – REVIEW

REVIEWER	Thomas K.M. Cudjoe Johns Hopkins University School of Medicine United States of America
REVIEW RETURNED	05-Aug-2020

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript (A potential impact of social distancing on physical and mental health. A rapid narrative umbrella review of meta-analyses on the link between social isolation and health). The current study is a narrative umbrella review of meta-analyses which summarized the existing evidence on the association of social isolation with physical and mental health outcomes. A total of 25 meta-analyses with a total of 692 studies and 3+ million participants were included. This study is important in that it provides a current review of a relevant body of work particularly amid the current COVID-19 pandemic. The study is unique in that it offers a succinct and timely overview of the state of research examining while providing context and highlighting the implications of "social distancing" measures. This study would be of interest to a global audience of researchers, clinicians and policy makers as they study, care, and make decisions that influence societal health and well-being. In particular, the study should provide greater clarity between social isolation, loneliness, and other terms used to characterize social connection (i.e. living alone) and the association with physical and mental health outcomes. It is critically important that authors make this differentiation as the pathways or theoretical frameworks that link social isolation to health outcomes may differ. #Major Comments Of the meta-analyses that met study criteria authors should consider further differentiation between social isolation and loneliness. Throughout the manuscript, the authors use the term "social distancing". The author should consider revising this terminology to—physical distancing. Numerous researchers and the World Health Organization have encouraged the use of this term to provide greater clarity. The authors should consider whether including literature about living alone is appropriate for this review. Previously investigators (Perissinotto, C. M., & Covinsky, K. E. (2014). Living alone, socially isolated or lonely—What are we measuring?.) have suggested that

	social connections are more complex than this description of living arrangement. The Background section could be improved by providing further context regarding the epidemiology of social isolation, loneliness etc. The terminology and framing of social connections in the background section could might benefit from the organizing frameworks and definitions included in the recent report on Social Isolation and Loneliness- National Academies of Sciences, Engineering, and Medicine. "Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System." (2020). Line 52 characterizes social isolation by three indicators (number of contacts, loneliness, living alone). To my knowledge, this is not widely accepted. The aforementioned NAM report presents a coherent dichotomy of terms, which focus on structure function and quality of social connections as the umbrella terminology. The literature reviewed in this meta-analysis is largely focused on loneliness and living alone rather than social isolation. The results should make this distinction as the pathways may differ. Reframing the indicators based on social connection-structure, function, quality could facilitate this distinction. Continuing to frame social isolation by indicators is not clear. Line 3 page 16- The authors can further strengthen this manuscript by providing the methodological shortcomings in an appendix. #Minor comments The conclusion stated in the Abstract on Line 47-52 and on page 18 could be further clarified and/or expanded to emphasize the potential implications of current physical distancing on current and future health outcomes. The considerations of these findings are broader than “government decision”—authors can further strengthen conclusion by describing implications more broadly. Findings noted on Line 6 and 8 on page 5 should be cited. The majority of the literature available and reviewed on this subject involves adults. The authors should further support not applying an age restriction. Table 1 utilizes the Social Connection terminology to note living arrangement, loneliness, or social contact though this does not align with the framing of indicators for social isolation discussed in the background section. Table 1 should also use specific terms to characterize the age of study participants—consider different term or description than “Mainly 50+” or “Adults(mainly)”- a footnote could be used for this specific information. Line 27-31 pg 16 Implications The authors could further strengthen this section by including a more expansive contextualization of social connection interventions than provided. Line 40-43 pg 17 Authors should be specific about groups they believe are impacted- “socially disadvantaged groups” lacks specificity and may differ in the global context. Language about restrictions on Line 22 should be updated to months Line 42 Is “translate” the proper word choice. Consider increase one’s risk or perpetuate. Line 49 Is “wide” the proper word choice. Consider broad

REVIEWER	KJ Smith University of Surrey, UK
REVIEW RETURNED	07-Aug-2020

GENERAL COMMENTS	A comprehensive review examining previous meta-analyses that have studied the association between loneliness, social isolation and living alone with physical and mental health outcomes. However, I

	feel there are a number of important considerations that the authors should address before this paper would be suitable for publication: 1.) Loneliness, social isolation and living alone (while at times related) are theoretically (and statistically) considered to be different constructs; and suggesting these are synonymous outcomes that are all indicative of a broader construct of social isolation is not in line with the way that experts working in this field conceptualise these issues. I feel that a major re-working of the paper is needed to emphasise this, rather than suggesting they are different ways of measuring the same thing (e.g., in the introduction you talk about social isolation health outcomes and then refer to papers that actually measured loneliness). 2.) Furthermore, suggesting that these outcomes are indicative of the impact of social distancing need to be backed up by evidence. Social distancing is not the same thing as social isolation; while research into social isolation may be able to act as a proxy for the potential impact of social distancing, they are very different things. Again, I feel that you should re-work the whole piece being really mindful of presenting your constructs in a balanced way. 3.) There are multiple issues in this paper of you making overarching statements that are not supported by evidence (e.g., "social distancing with it's inevitable increase of social isolation may therefore have a negative impact on physical and mental health"). Please be mindful to make sure you present a balanced and evidence-based theoretical rationale, rather than presenting things that you have assumed will be the case without supporting evidence. 4.) Could you please link into the exact PROSPERO protocol, and give the number of your registered protocol (p5 a generic link to PROSPERO is not sufficient). 5.) Could you please outline how many, and which authors completed the screening (you only give details about full-text extraction, and you should also report details for screening). Could you also clarify what you inter-rater agreement was at the full-text stage (if applicable)? 6.) In line with reporting standards for a systematic review could you please append your exact searches that you ran? 7.) Having looked at the data extraction I am not sure how well you have done this. I think this needs to be done very clearly in terms of what studies found relating to the different predictors you have examined (i.e., present results stratified by a.) loneliness b.) social isolation and/or c.) living alone as these are not the same thing!). 8.) A lot of the studies are cross-sectional; and some are longitudinal (which arguably are better for examining your question of interest). Could you determine what findings are longitudinal and whether they may be able to tell us more about the impact that you three predictors have on the outcomes? You make big statements in the discussion about the 'impact' of loneliness, social isolation and living alone; so it would be good if you unpicked which results are 'associations' (but may not imply causation) and which examine 'risk' (and so tell us more about possible causation). 9.) Could you clarify whether the results you present are adjusted for important confounders or not (and if so, which ones)? 10.) The discussion is not very substantive and there are large sections with no evidence presented where the authors seem to just present their opinion. Would it be possible to present an evidence-based discussion as much as is possible? 11.) The conclusion relies heavily on an assumption that social distancing is directly linked with social isolation, loneliness and/or living alone (which you even state in the discussion may not be the

	case). I would suggest that the discussion be re-worked to be more cognisant of this.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Thank you for the opportunity to review this manuscript (A potential impact of social distancing on physical and mental health. A rapid narrative umbrella review of meta-analyses on the link between social isolation and health). The current study is a narrative umbrella review of meta-analyses which summarized the existing evidence on the association of social isolation with physical and mental health outcomes. A total of 25 meta-analyses with a total of 692 studies and 3+ million participants were included. This study is important in that it provides a current review of a relevant body of work particularly amid the current COVID-19 pandemic. The study is unique in that it offers a succinct and timely overview of the state of research examining while providing context and highlighting the implications of “social distancing” measures. This study would be of interest to a global audience of researchers, clinicians and policy makers as they study, care, and make decisions that influence societal health and well-being. In particular, the study should provide greater clarity between social isolation, loneliness, and other terms used to characterize social connection (i.e. living alone) and the association with physical and mental health outcomes. It is critically important that authors make this differentiation as the pathways or theoretical frameworks that link social isolation to health outcomes may differ.

Response: We are grateful to the reviewer for his positive feedback as well as his comments, which we found very helpful. In response to the comment mentioned above, we now provide greater clarity with respect to the terms used to characterise social connection and the association with health outcomes. Please see below for further information.

#Major Comments

Of the meta-analyses that met study criteria authors should consider further differentiation between social isolation and loneliness.

Throughout the manuscript, the authors use the term “social distancing”. The author should consider revising this terminology to—physical distancing. Numerous researchers and the World Health Organization have encouraged the use of this term to provide greater clarity.

Response: As suggested by the reviewer, we have replaced the term social distancing with the term physical distancing throughout the manuscript. In the introduction, we now report that physical distancing is mostly referred to as social distancing.

The authors should consider whether including literature about living alone is appropriate for this review. Previously investigators (Perissinotto, C. M., & Covinsky, K. E. (2014). Living alone, socially isolated or lonely—What are we measuring?.) have suggested that social connections are more complex than this description of living arrangement.

Response: We agree with the reviewer that social connections are more complex than the description of living arrangement. And in fact, the publication by Perissinotto & Covinsky that the reviewer mentioned above, was our first citation (and is now second). Yet, we argue that it is nonetheless informative to summarise the literature on the association between living alone and health otcomes, which clearly indicates that living alone is associated with worse health outcomes. Given the fact that we report results separately for living alone and other forms of social connections (i.e., loneliness and low number of social contacts), we believe that including the literature on living alone and reporting it separately (as we do in Table 1), enriches the paper.

In response to this comment, however, we now report in the discussion section:

"*the results on the association between living alone and health outcomes need to be interpreted with caution. As reported above, living alone is not necessarily indicative of feeling lonely*.[2]"

The reader can furthermore read in the introduction section "*Living alone describes a basic characteristic of an individual's social situation which can be associated with reduced social relationships, but is not necessarily so*"

The Background section could be improved by providing further context regarding the epidemiology of social isolation, loneliness etc.

Response: In response to this comment, we now report the following on P. 5?:

"Literature suggests that many individuals are socially isolated or lonely or both and that social isolation and loneliness may occur unequally across age groups. For example, Hawkley and colleagues[6] reported that loneliness decreased with age through the early 70s and then increased again. Several studies indicate that at least a fifth of adults report frequent loneliness [7, 8] and that more than 40 percent of adults aged 60 and older report feeling lonely.[9]"

The terminology and framing of social connections in the background section could might benefit from the organizing frameworks and definitions included in the recent report on Social Isolation and Loneliness- National Academies of Sciences, Engineering, and Medicine. "Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System." (2020).

Response: We appreciate the reviewer's suggestion, which we now consider in the current version of the manuscript (see below).

Line 52 characterizes social isolation by three indicators (number of contacts, loneliness, living alone). To my knowledge, this is not widely accepted. The aforementioned NAM report presents a coherent dichotomy of terms, which focus on structure function and quality of social connections as the umbrella terminology.

Response: The terminology in the field of social connections is indeed inconsistent, which we also mention in the manuscript. Originally, we stated that three indicators of social isolation are commonly used in research: low number of social contacts, living alone, and loneliness. As such, number of social contacts and living alone represent structural indicators, whereas loneliness represents a quality measure of social connections, as suggested by Holt-Lunstad et al. (2018) and also referred to in the recent report on Social Isolation and Loneliness by the National Academies of Sciences, Engineering, and Medicine (2020). (We thank the reviewer again for drawing our attention towards this relevant publication). Our decision to focus on these three indicators was based on work conducted by Holt-Lundstad and others. For example, Holt-Lunstad et al. (2015; Perspect Psychol Sci) report that living alone and having few social network ties are both markers of social isolation (P. 227) and the authors further focus on loneliness as a subjective emotional state. However, the comment made by the reviewer helped us to further improve the terminology throughout the paper. In responseto the comment, we replaced the term low number of social contacts with the term "few social network ties", a term also used in the above mentioned report on Social Isolation and Loneliness. And as indicated above, this is also in line with Holt-Lunstad et al (2015) that also focused on these three indicators of social connections: few social network ties, living alone, and loneliness. We do acknowledge that Holt-Lunstad et al (2015) in their presentation of results termed these three indicators a) social isolation, b) living alone, and c) loneliness. In the introduction, however, and as mentioned above, the authors report that living alone and having few social network ties are both markers of social isolation (P. 227). Accordingly, we find

is more useful to use the term “few social network ties” when referring to the number of social contacts because the term “social isolation” is also used as an umbrella term for both “few social network ties” and “living alone”. And recall that the term “few social network ties” is also used in the above mentioned report on Social Isolation and Loneliness to indicate the number of social contacts.

The literature reviewed in this meta-analysis is largely focused on loneliness and living alone rather than social isolation. The results should make this distinction as the pathways may differ. Reframing the indicators based on social connection-structure, function, quality could facilitate this distinction. Continuing to frame social isolation by indicators is not clear.

Response: Social isolation (which we in this context label as “few social network ties”) is actually not less often reported than living alone. In fact, both forms are reported in 10 (i.e., 40%) of the included meta-analyses. Yet, in response to this comment, we now report in the results section how often few social network ties, living alone, and loneliness were examined in the respective meta-analyses on physical and mental health.

In addition, we now clearly report in the introduction section that social network ties and living alone represent structural indicators, whereas loneliness represents a quality measure of social connections, as recommended by Holt-Lunstad et al (2018). Furthermore, we report under “Selection and characteristics of included studies” the following:

“*We considered as structural indicators of social isolation social network ties defined as an objectively quantifiable variable of one’s social contacts irrespective of its perceived quality and living alone as an objective characteristic of the living situation. Furthermore, we defined loneliness as a quality indictor representing the subjective emotional appraisal of the extent and quality of social relationships.*[5]“

Line 3 page 16- The authors can further strengthen this manuscript by providing the methodological shortcomings in an appendix.

Response: In the manuscript we refer to the methodological shortcomings of the primary research studies. Accordingly, we are talking about 276 primary studies that were included in the 10 meta-analyses on physical health and 416 primary studies with respect to mental health, i.e., a total of 692 studies. Given the nature of this rapid review, we are not able to examine the quality of 692 studies. Furthermore, we want to point out that the assessment of the quality of the primary studies is not common practice when conducting an umbrella review. What is common practice, however, is the assessment of the quality of the included meta-analyses. This assessment we report on P. 16-17.

#Minor comments

The conclusion stated in the Abstract on Line 47-52 and on page 18 could be further clarified and/or expanded to emphasize the potential implications of current physical distancing on current and future health outcomes. The considerations of these findings are broader than “government decision”—authors can further strengthen conclusion by describing implications more broadly.

Response: We have now added the following in the conclusion subsection:

“*In addition, the existing knowledge on the association between social connection and physical and mental health should be considered in clinical practice. Finally, more experimental research is needed to increase our understanding of the causal relationship between social connection and physical and psychological well-being.*”

Findings noted on Line 6 and 8 on page 5 should be cited.

Response: We believe that the reviewer refers to the following sentence:

"Living alone describes a basic characteristic of an individual's social situation which can be associated with reduced social relationships, but is not necessarily so." We now cite

Holt-Lunstad J. Why Social Relationships are important for Physical Health: A Systems Approach to Understanding and Modifying Risk and Protection. *Annu Rev Psychol.* 2018; 69:437-458.

The majority of the literature available and reviewed on this subject involves adults. The authors should further support not applying an age restriction.

Response: It is true that the majority of the included studies were conducted with adults. However, when designing this umbrella review, we found it crucial to inform the reader about the literature available involving all ages. We believed that this would constitute a strength of the paper. We would not feel comfortable to provide an ex post justification because of the outcome of the systematic search (i.e., the fact that there is less research with children and adolescents).

Table 1 utilizes the Social Connection terminology to note living arrangement, loneliness, or social contact though this does not align with the framing of indicators for social isolation discussed in the background section. Table 1 should also use specific terms to characterize the age of study participants—consider different term or description than "Mainly 50+" or "Adults(mainly)"- a footnote could be used for this specific information.

Response: In the revised version, the same terminology with respect to social connections is used in Table 1 and other parts of the paper, i.e., social network ties, living alone, and loneliness. Furthermore, we now report more specific terms to characterize age in Table 1, including the use of footnotes where necessary.

Line 27-31 pg 16 Implications The authors could further strengthen this section by including a more expansive contextualization of social connection interventions than provided.

Response: In response to the reviewers comment, we have added the following:

"Altogether, the literature on interventions to reduce loneliness and social isolation indicates that a policy focus on social connection is a cost-effective strategy for enhancing health at the population level due to the potential pay-offs in health care costs that would otherwise occur. Existing volunteer friendly visiting programs or psychosocial group interventions[48] may need to be redesigned to the point that they can be readily implemented in in accordance with existing rules of physical distancing. Creative programs and interventions to foster social connections, including technology-based social networking programs, are needed.[49] Furthermore, existing policies should ensure that populations at greater risk, such as the poor and the elderly, receive most support.[1]"

Line 40-43 pg 17 Authors should be specific about groups they believe are impacted- "socially disadvantaged groups" lacks specificity and may differ in the global context.

Response: We now provide examples for socially disadvantaged groups: "*(e.g., individuals in need of mental or physical health care or individuals with low income)"*.

Language about restrictions on Line 22 should be updated to months Line 42 Is "translate" the proper word choice. Consider increase one's risk or perpetuate.

Response: We thank the reviewer for reading the manuscript so carefully. We adjusted both words accordingly.

Line 49 Is "wide" the proper word choice. Consider broad

Response: We replaced the word wide by broad.

Reviewer: 2

A comprehensive review examining previous meta-analyses that have studied the association between loneliness, social isolation and living alone with physical and mental health outcomes. However, I feel there are a number of important considerations that the authors should address before this paper would be suitable for publication:

1.) Loneliness, social isolation and living alone (while at times related) are theoretically (and statistically) considered to be different constructs; and suggesting these are synonymous outcomes that are all indicative of a broader construct of social isolation is not in line with the way that experts working in this field conceptualise these issues. I feel that a major re-working of the paper is needed to emphasise this, rather than suggesting they are different ways of measuring the same thing (e.g., in the introduction you talk about social isolation health outcomes and then refer to papers that actually measured loneliness).

Response: We are grateful to the reviewer for her helpful comments. With respect to the terminology used to describe indicators of social connections, we now report in the introduction section:

"*Three indicators of social isolation (also referred to as social connections) are commonly used in research: few social network ties, living alone, and loneliness.[2-4] Social network ties is a behavioral measure that can – at least in theory – be objectively quantified. Living alone describes a basic characteristic of an individual's social situation which can be associated with reduced social relationships, but is not necessarily so.[5] Loneliness, on the other hand, is an individual's subjective assessment of the quality and quantity of their social relationships, reflecting a belief that they have too few or too poor relationships, or both. Accordingly, social network ties and living alone represent structural indicators, whereas loneliness represents a quality measure of social connections.[4, 5]*"

Furthermore, we report under "Selection and characteristics of included studies" the following:

"*We considered as structural indicators of social isolation social network ties defined as an objectively quantifiable variable of one's social contacts irrespective of its perceived quality and living alone as an objective characteristic of the living situation. Furthermore, we defined loneliness as a quality indictor representing the subjective emotional appraisal of the extent and quality of social relationships.[5]*"

With respect to the last part of the comment, we made sure that whenever we address the association between social isolation and health outcomes, that we refer to papers that actually address social isolation rather than loneliness only.

2.) Furthermore, suggesting that these outcomes are indicative of the impact of social distancing need to be backed up by evidence. Social distancing is not the same thing as social isolation; while research into social isolation may be able to act as a proxy for the potential impact of social distancing, they are very different things. Again, I feel that you should re-work the whole piece being really mindful of presenting your constructs in a balanced way.

Response: We are grateful to the reviewer for this very relevant comment. (Note that the editor made a similar comment, and therefore we share the same response twice). We now report clearly how physical distancing may increase the risk of social isolation and that physical distancing does not necessarily translate into social isolation. (Please note that in response to a comment made by Reviewer #1, we now use the term physical distancing rather than social distancing.) On P. 4-5 we now report the following:

"*A recent general population survey revealed that physical distancing can increase social isolation and loneliness.[1] This may happen when people are prevented from travelling, physical meetings with significant others, and in some cases even from leaving their home other than for essential activities.*

Of note, some individuals can be physically isolated and not feel lonely and others can feel lonely even if they are not isolated. Furthermore, many individuals are able to remain socially connected by means of remote communication while physically isolated. Accordingly, we should not assume that physical distancing inevitably leads to social isolation and loneliness. However, physical distancing is likely to have a disproportionate effect on those most vulnerable, in particular older adults, individuals in need of intensive physical or mental health care, and individuals with limited access to technology who lack the means of engaging in creative forms of contact with loved ones. Older patients, for example, may lose access to important parts of their usual routine (e.g., day care programs or informal gatherings with significant others). Similarly, caregivers residing with patients need also to physically isolate themselves due to the ramifications of quarantines."

3.) There are multiple issues in this paper of you making overarching statements that are not supported by evidence (e.g., "social distancing with it's inevitable increase of social isolation may therefore have a negative impact on physical and mental health"). Please be mindful to make sure you present a balanced and evidence-based theoretical rationale, rather than presenting things that you have assumed will be the case without supporting evidence.

Response: We agree with the reviewer and have adjusted the manuscript accordingly, as reported in the comment above. Of note, we have deleted the word "inevitable increase" altogether.

4.) Could you please link into the exact PROSPERO protocol, and give the number of your registered protocol (p5 a generic link to PROSPERO is not sufficient).

Response: After submitting details of our umbrella review for registration in PROSPERO, we received the following response on May 7th: "*With the current extremely high demand for registration, we will aim to respond within 10 working days for UK submissions but for submissions from outside the UK it will be considerably longer - possibly around three months. But we will process your application as soon as possible. During this time the record will be locked and you will not be able to access it.*"

Upon enquiring about the status, they wrote (in capital letters): "WE ARE RECEIVING *MANY EMAILS ENQUIRING ABOUT PROGRESS. AS REPLYING TO THESE TAKES TIME AWAY FROM THE PROCESSING OF RECORDS, WE ASK THAT YOU ONLY EMAIL SHOULD IT BE ABSOLUTELY NECESSARY. YOU CAN BE ASSURED THAT THE TEAM ARE WORKING PARTICULARLY HARD TO PROCESS RECORDS AS QUICKLY AS IS POSSIBLE. WE THANK YOU FOR YOUR UNDERSTANDING IN ADVANCE.*"

Given the nature of this rapid review due to the current corona crisis, we submitted the manuscript for publication hoping that PROSPERO will reply soon. As of September 28th, they yet have to reply. As soon as we get a reply from them, we will inform the editor's office.

5.) Could you please outline how many, and which authors completed the screening (you only give details about full-text extraction, and you should also report details for screening). Could you also clarify what you inter-rater agreement was at the full-text stage (if applicable)?

Response: We report under "Authors' Contributions" that "NM and AK carried out the literature searches and screening" and that "NM, THH, and TM carried out the data extraction. AK and TM assessed the quality of the included meta-analyses."

6.) In line with reporting standards for a systematic review could you please append your exact searches that you ran?

Response: We now report the full search string for Medline and PsycINFO on P. 7.

7.) Having looked at the data extraction I am not sure how well you have done this. I think this needs to be done very clearly in terms of what studies found relating to the different predictors you have examined (i.e., present results stratified by a.) loneliness b.) social isolation and/or c.) living alone as these are not the same thing!).

Response: Table 1 first informs what form of social connections was assessed in the respective meta-analysis. For example, with respect to Besora-Moreno et al. (2020; top of the list) it informs that this meta-analysis focused on "living alone" only, whereas Holt-Lunstad et al. (2015) focused on all three forms of social connections, i.e.: living alone, few social network ties, and loneliness. The results are then reported separately for living alone. However, the authors of 3 meta-analyses (i.e., 3 out of 25) did not report separate data for the three indicators of social connections (i.e., living alone, few social network ties, and loneliness). Instead, they reported the data combined for "Few social network ties or loneliness", which can bee seen in Table. Another paper, Heidari Gorji et al. (2019), reported their results in three categories:

a. Any type of poor social connection
b. Living alone or few social network ties
c. Loneliness

And we found it more informative to report the data accordingly.

8.) A lot of the studies are cross-sectional; and some are longitudinal (which arguably are better for examining your question of interest). Could you determine what findings are longitudinal and whether they may be able to tell us more about the impact that you three predictors have on the outcomes? You make big statements in the discussion about the 'impact' of loneliness, social isolation and living alone; so it would be good if you unpicked which results are 'associations' (but may not imply causation) and which examine 'risk' (and so tell us more about possible causation).

Response: In Table 1, we have a separate column labelled "Study design", which indicates whether the presented results were collected in a cross-sectional or longitudinal manner. However, we believe that the reviewer's comment relates to the text. In response, we now report the cross-sectional and longitudinal results separately, see P. 15-16.

In the discussion section we further report that the findings are strengthened by the fact that several meta-analyses were conducted with longitudinal studies. However, we also point out that all findings are based on observational studies and thus do not provide evidence on the causal direction of the association.

9.) Could you clarify whether the results you present are adjusted for important confounders or not (and if so, which ones)?

Response: We agree that statistical adjustment for confounders is highly relevant for the interpretation of the results. Unfortunately, an in-depth overview per meta-analysis is not possible, because only very few papers have explicitly compared adjusted with unadjusted studies, and/or specified the respective covariates. However, some authors have indicated that they preferred effect sizes with minimal or with maximal adjustment during data extraction. We have now marked meta-analyses in Table 1 that preferably used adjusted or unadjusted effect sizes, using two different superscript letters. Moreover, we included the following information in the note under Table 1:

"*Most meta-analyses included studies both with adjusted and with unadjusted effect sizes (typically controlling for potential confounders like age, sex, education, socioeconomic status, chronic conditions, depression or anxiety). Unless specified in the table, the authors did not indicate a preference for adjusted or for unadjusted effect sizes*".

Besides, we would like to refer to the Risk of Bias (RoB) assessments that many of the included meta-analyses have performed. RoB assessments typically indicate low risk of bias if the original study reported adequate consideration and statistical correction for all potential confounders. Whether a RoB assessment was adequately carried out, reported, and considered by each meta-analysis was among the AMSTAR-2 criteria that we used to derive the quality scores. As noted on P. 17, "*inadequate assessment of risk of bias and/or lack of consideration of risk of bias represented the most frequent critical weaknesses of included meta-analyses*". Therefore, the quality scores given to each meta-analysis provide an additional indication whether confounding has been considered carefully in the respective meta-analysis.

10.) The discussion is not very substantive and there are large sections with no evidence presented where the authors seem to just present their opinion. Would it be possible to present an evidence-based discussion as much as is possible?

Response: In response to this comment and other comments, we have adjusted many parts of the discussion section. In doing so, we now provide several references that back up our discussion. For example: in the original version we had only stated that for establishing a causal relationship between social isolation and health outcomes experimental studies are required. Now, we inform the reader where they can find some information about experimental research with animals that suggests that social isolation increases mortality, and experimental research with humans indicating that loneliness/exclusion leads to different health relevant physiological responses than being randomly assigned to a support condition. Furthermore, we provide more information on the literature on interventions to reduce loneliness and social isolation, as suggested by Reviewer #1.

11.) The conclusion relies heavily on an assumption that social distancing is directly linked with social isolation, loneliness and/or living alone (which you even state in the discussion may not be the case). I would suggest that the discussion be re-worked to be more cognisant of this.

Response: We are grateful to the reviewer for this comment. We have adjusted the conclusion accordingly.

VERSION 2 – REVIEW

REVIEWER	K Smith University of Surrey
REVIEW RETURNED	11-Oct-2020

GENERAL COMMENTS	While I thank the authors for addressing the questions posed previously I do not feel that they have adequately addressed the major concerns that myself and another reviewer had, and I continue to have major concerns particularly with: a.) The definition of social isolation and b.) assumptions made within the paper that are not backed up with evidence. 1.) Instead of helping to clarify issues around social isolation and loneliness and definitions, the paper now reads as almost contradictory in parts as you haven't been consistent in how you have addressed reviewer concerns (i.e., you now acknowledge early on that loneliness and social isolation are not the same thing, but then later on state your definition of social isolation includes loneliness). By defining social isolation as one thing early on, and then using 'social isolation' as a term to capture a range of indicators and then separating out again later on this will end up confusing

	your reader. I would suggest that either a.) You ONLY look at social isolation or b.) You consistently separate out the outcomes of social isolation, loneliness and living alone or c.) use the terminology 'social connectedness' instead of social isolation. I would suggest that you read the following paper to clarify the differences between these three indicators (as this paper really clearly lays out the differences between these indicators): Victor, C., Scambler, S., Bond, J., & Bowling, A. (2000). Being alone in later life: loneliness, social isolation and living alone. Reviews in Clinical Gerontology, 10(4), 407-417. 3.) There is also the continued issue of making big statements without any underlying evidence (An example is here: However, physical distancing is likely to have a disproportionate effect on those most vulnerable, in particular older adults, individuals in need of intensive physical or mental health care, and individuals with limited access to technology who lack the means of engaging in creative forms of contact with loved ones. Older patients, for example, may lose access to important parts of their usual routine (e.g., day care programs or informal gatherings with significant others). Similarly, caregivers residing with patients need also to physically isolate themselves due to the ramifications of quarantines). This is also a big issue on page 21 where you make a lot of assumptions about social isolation and physical distancing with no evidence to back this up. Please make sure that you are presenting a balanced and evidence-based rationale for your work. 4.) The paper reads as though issues around social isolation and loneliness primarily affect older adults, which is known not to be the case. More up-to-date evidence is showing that loneliness has peaks in adolescence and oldest age, or that age doesn't make any difference to the experience of loneliness. Furthermore, it isn't clear what the narrative on loneliness in older adults is adding to your introduction when this is not something you explore within the paper itself. This could be more interesting as a discussion point (i.e., while we know loneliness can impact people across the lifespan, and physical distancing measures have been implemented for all people (with some countries encouraging additional measures for older adults) - what does that mean for the extent to which your results are useful for policy-makers?) 5.) Minor point: Please don't use the word 'elderly' when referring to older adults; the preferred terminology is 'older adults'. This is something used within the discussion. 6.) Minor point: Some of your studies could have an overlap in samples as they look at similar outcomes (e.g., Steptoe and Kivimaki and Valtorta et al). I think that this could be made clearer in the methods, results and discussion. I would also suggest you avoid adding up the total number of participants included in the different meta-analyses (also because a lot of different meta-analyses will include the same studies looking at the same participants, just looking at a different outcome).

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2:

While I thank the authors for addressing the questions posed previously I do not feel that they have adequately addressed the major concerns that myself and another reviewer had, and I continue to have major concerns particularly with:
a.) The definition of social isolation and b.) assumptions made within the paper that are not backed up with evidence.
Response: We have carefully addressed both points raised by the reviewer as outlined below.

1.) Instead of helping to clarify issues around social isolation and loneliness and definitions, the paper now reads as almost contradictory in parts as you haven't been consistent in how you have addressed reviewer concerns (i.e., you now acknowledge early on that loneliness and social isolation are not the same thing, but then later on state your definition of social isolation includes loneliness). By defining social isolation as one thing early on, and then using 'social isolation' as a term to capture a range of indicators and then separating out again later on this will end up confusing your reader. I would suggest that either a.) You ONLY look at social isolation or b.) You consistently separate out the outcomes of social isolation, loneliness and living alone or c.) use the terminology 'social connectedness' instead of social isolation. I would suggest that you read the following paper to clarify the differences between these three indicators (as this paper really clearly lays out the differences between these indicators): Victor, C., Scambler, S., Bond, J., & Bowling, A. (2000). Being alone in later life: loneliness, social isolation and living alone. Reviews in Clinical Gerontology, 10(4), 407-417.
Response: We thank the reviewer for this helpful comment. In the previous version of the manuscript, we had defined social isolation as an umbrella term capturing multiple ways in which an individual connects to other individuals and had also indicated that this term is "also referred as social connection". We had further written that "Social isolation is a broad term without a consistent definition in the literature", which is also stated in the above mentioned paper by Victor et al. (2000). However, we fully agree with the reviewer that it is much more beneficial to use the term 'social connection' instead of social isolation when applying an umbrella term capturing multiple ways in which an individual connects to others. The reviewer suggested "social connectedness", yet, we would rather use the slightly different term 'social connection' instead as this term has been used in some influential publications (e.g., Holt-Lunstad, Annual Review of Psychology, 2018).
Consequently, our terminology in the current version of the manuscript is as follows (and as outlined on P. 4-5 and P. 15):

1. Social connection = an umbrella term representing the extent to which an individual connects to others,
    a. Social isolation = a behavioral measure of a person's social network that can – at least in theory – be objectively quantified (previously we had used the label "social network ties" in this respect),
    b. Living alone = a measure of the type of household in which an individual lives,
    c. Loneliness = an individual's subjective assessment of the quality and quantity of their social relationships, reflecting a belief that they have too few or too poor relationships, or both.

We have now made sure that throughout the revised manuscript these terms are used in line with the definitions outlined here and on P. 4-5.

3.) There is also the continued issue of making big statements without any underlying evidence (An example is here: However, physical distancing is likely to have a disproportionate effect on those most vulnerable, in particular older adults, individuals in need of intensive physical or mental health care, and individuals with limited access to technology who lack the means of engaging in creative forms of contact with loved ones. Older patients, for example, may lose access to important parts of their usual routine (e.g., day care programs or informal gatherings with significant others). Similarly, caregivers residing with patients need also to physically isolate themselves due to the ramifications of quarantines). This is also a big issue on page 21 where you make a lot of assumptions about social isolation and physical distancing with no evidence to back this up. Please make sure that you are presenting a balanced and evidence-based rationale for your work.
Response: In response to this comment, we have deleted the example mentioned by the reviewer. Furthermore, we have reduced the number of assumptions in the discussion section (i.e., P. 21).

Throughout the paper, we have made sure to indicate that further research, including experimental research, is required to increase our understanding of the relationship between social connection and physical and psychological well-being.

4.) The paper reads as though issues around social isolation and loneliness primarily affect older adults, which is known not to be the case. More up-to-date evidence is showing that loneliness has peaks in adolescence and oldest age, or that age doesn't make any difference to the experience of loneliness. Furthermore, it isn't clear what the narrative on loneliness in older adults is adding to your introduction when this is not something you explore within the paper itself. This could be more interesting as a discussion point (i.e., while we know loneliness can impact people across the lifespan, and physical distancing measures have been implemented for all people (with some countries encouraging additional measures for older adults) - what does that mean for the extent to which your results are useful for policy-makers?)
Response: We have now reduced the focus on older people in the introduction section. In fact, we now focus on older people only once on P. 6 where we report that social isolation and loneliness may occur unequally across age groups. The point here is not to focus on older people, but rather to inform the reader how prevalent lack of social connection is. In this respect, we cite 4 quite recent studies on this issue:
Hawkley et al. Are US older adults getting lonelier? Age, period, and cohort differences. Psychology & Aging. 2019.
DiJulio et al.. Loneliness and social isolation in the United States, the United Kingdom, and Japan: An international survey. The Economist & Kaiser Family Foundation; 2018.
Anderson & Thayer. Loneliness and social connections: A national survey of adults 45 and older. AARP Foundation; 2018.
Perissinotto et al. Loneliness in older persons: a predictor of functional decline and death. Archives of internal medicine. 2012.

5.) Minor point: Please don't use the word 'elderly' when referring to older adults; the preferred terminology is 'older adults'. This is something used within the discussion.
Response: We had indeed used this term once on P. 20. However, based on the suggestion by the reviewer to reduce the focus on older adults throughout the paper, we deleted that word altogether.

6.) Minor point: Some of your studies could have an overlap in samples as they look at similar outcomes (e.g., Steptoe and Kivimaki and Valtorta et al). I think that this could be made clearer in the methods, results and discussion. I would also suggest you avoid adding up the total number of participants included in the different meta-analyses (also because a lot of different meta-analyses will include the same studies looking at the same participants, just looking at a different outcome).
Response: We are thankful for this significant comment. In response, we deleted the information on the total number of participants included in the different meta-analyses (e.g., we deleted the following sentence in the abstract "A total of more than 3 million individuals had participated in the 692 primary studies". More importantly, we now report with respect to the meta-analyses on physical health the following (P. 15):

"*However, there was some overlap in samples in meta-analyses that examined cardiovascular disease[17,18] and early mortality.[4,19] Steptoe and Kivimäki[18] and Valtorta et al.[19] shared one primary study. In addition, Holt-Lunstad et al.[4] and Rico-Uribe et al.[20] shared 12 primary studies.*"
Similarly, we added the following information regarding the meta-analyses on mental health (P. 16):

"*There was some overlap in samples in the four meta-analyses focusing on cognitive functioning or risk of dementia.[27-30] Kuiper et al.[29] shared two primary studies with Evans et al.[28], four with Lara et al.[30], and three with Penninkilampi et al.[27] Penninkilampi et al.[27] further shared two primary studies Lara et al.[30]*"

VERSION 3 – REVIEW

REVIEWER	K Smith UoS, UK
REVIEW RETURNED	11-Feb-2021

GENERAL COMMENTS	All comments have been addressed