PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The prevalence and risk factors of senile pruritus: a systematic review and meta-analysis
AUTHORS	chen, shi; Zhou, Faquan; Xiong, Yiquan

VERSION 1 – REVIEW

REVIEWER	Reid, Colin University of British Columbia Okanagan Faculty of Health and Social Development, School of Health and Exercise Sciences
REVIEW RETURNED	30-May-2021

GENERAL COMMENTS	The is a systematic review of risk factors for, and prevalence of, senile pruritus in 6 countries. The authors review 17 studies that involved over 28,000 participants. Pooled estimates based on included studies are provided. It is concluded that the pooled estimate of SP prevalence is 20.4% but is not likely to be representative of the rest of the world. Identified risk factors included smoking, excessive drinking, and monophagism. The authors call for future research to establish prevalence of SP more broadly. This is a timely review, as evidence of the prevalence of SP has begun to accumulate and an assessment and summarization of the extant literature should be useful to advance the field. I have several comments to improve the manuscript. Sometimes the authors report that the participants were “over 60 years of age” (see page 6) and elsewhere they are described as “less than or equal to 60” (abstract). These are different age groups. This should be addressed. One inclusion criterion is “the study has incomplete data”. Please indicate how much missing data resulted in exclusion. Under “Quality of the studies” on page 6, please explain how to read the risk of bias scores (0-11). Is a higher scores indicative of more or less bias? Please explain briefly what “double arcsine transformation” is, and comment on the precise changes this transformation made to the variable in question (SP). Risk of Bias Assessment on page 9: Please explain the cutoff points for scoring risk of bias as moderate, high, or another level.

REVIEWER	Misery, Laurent University and Regional Hospital Centre Brest, Dermatology

REVIEW RETURNED	29-Jul-2021

GENERAL COMMENTS	This a very interesting and very well-done systematic review and meta-analysis on senile pruritus. The main concern is that the authors thnink that senile pruritus is only due to skin modifications while it is probably more secondary to the aging of the nerve endings in the skin, the presence of comborbities and the use of several treatments that are commonly use in elderly patients. Consequently, there is a need to deeply modify the discussion.

REVIEWER	Fleischer, Alan B. Jr University of Cincinnati
REVIEW RETURNED	20-Aug-2021

GENERAL COMMENTS	The authors undertook an ambitious project, to objectively quantify the prevalence of senile pruritus. Their methods and presentation were superb. The major limitation of the study is that the condition, senile pruritus, does not have rigid diagnostic criteria. Moreover, we now recognize the biopsychosocial model of chronic itch. Investigators in different countries and people in different societies may not be uniform in assessing the prevalence and/or severity of this condition. The widely divergent estimates suggest either that genetics may play a very powerful role in this condition. Alternatively definitions of investigators and the people studied may not be uniform. This reader suggests the latter is more responsible and the authors should make these clear in the discussion and limitation. These limitations make me less confident that the final estimate is close to a "true" estimate.

REVIEWER	Patil, Anant Dr D Y Patil Medical College
REVIEW RETURNED	15-Oct-2021

GENERAL COMMENTS	NA

REVIEWER	Smith, David University of Notre Dame, Psychology
REVIEW RETURNED	30-Nov-2021

GENERAL COMMENTS	BMJ-Open Manuscript ID bmjopen-2021-051694, entitled "The prevalence and risk factors of senile pruritus: A systematic review and meta-analysis", is an empirical research report of a meta-analytic investigation of the prevalence and risk factors for senile pruritus (SP). Examination of seventeen relevant studies suggested a high prevalence rate (21%) and significant risk factors, including smoking, excessive drinking, and monophagism. The study was preregistered with PROSPERO. The Introduction is concise yet sufficiently motivates interest in the study and includes relevant citations to the contemporary literature. 1. p. 6: The rationale for inclusion criterion #1 is not clear. Did the authors mean to exclude longitudinal and experimental (e.g., treatment) studies? Similarly, the rationale for the exclusion

	criterion that "the study populations were inpatients and outpatients" is not obvious. 2. p. 7: What data characteristics prompted the use of double arcsine transformations to generate prevalence rates? 3. 91% of the initial 8,518 studies were excluded based on screening of titles and abstracts. Can the authors provide information on the major categories of exclusion (e.g., a breakdown by language, age, etc.)? Similarly, 87% of the resulting 131 records were excluded without further comment. It would be interesting to know, for instance, how the database would have differed had the authors included languages other than Chinese. 4. A brief statement of how monophagism was operationalized in the relevant two studies would be gratefully received. 5. Would the authors be willing to pose a hypothesis (p. 13), albeit quite tentative, for the observed prevalence differences? As it stands, this is a purely descriptive effort. This could be similar to the hypotheses provided for the risk factors, which are given in the next paragraph.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
1. Sometimes the authors report that the participants were “over 60 years of age” (see page 6) and elsewhere they are described as “less than or equal to 60” (abstract). These are different age groups. This should be addressed.
We apologize for the mistake and has been revised in the revised manuscript (P5, L20-21).
2. One inclusion criterion is “the study has incomplete data”. Please indicate how much missing data resulted in exclusion.
Thanks for the comment. ‘The study has incomplete data’ refer to ‘the prevalence or risk factor effect value (mainly referred to as OR in this study) of SP wasn't clearly reported in the study, and the data provided by the study couldn't calculate the prevalence or risk factor effect value of SP’. This exclusion criteria has been supplemented in the revised manuscript (P6, L2-5).
3. Under “Quality of the studies” on page 6, please explain how to read the risk of bias scores (0-11). Is a higher scores indicative of more or less bias?
Thanks for the comment. Higher scores indicative of less bias and more quality. According to your comment, a description has been added to the revised manuscript (P9, L6-8).
4. Please explain briefly what “double arcsine transformation” is, and comment on the precise changes this transformation made to the variable in question (SP).
Thanks for the comment. Our responses are as follows:
① The commonly used meta-analysis method for single rate study is based on normal distribution. However, when n is small or p is close to 0 or 1, due to the discreteness of distribution, it is not appropriate to use the binomial data to approximate the normal distribution. At this point, data conversion is needed. Use the ‘double arcsine transformation’ to transform the raw prevalence estimates so that the data can follow an approximately normal distribution.
② Performs the double arcsine transformation, computes the weighted pooled estimate and performs the back-transformation on the pooled estimate. The confidence intervals for the pooled estimate are always admissible, avoid confidence intervals exceeding the range of 0 to 1.

③ See the article entitled ‘Metaprop: a Stata command to perform meta-analysis of binomial data’ for details. Reference have been added and the description of ‘double arcsine transformation’ has been added to the revised manuscript (P7, L1-2).
5. Risk of Bias Assessment on page 9: Please explain the cutoff points for scoring risk of bias as moderate, high, or another level.
Thanks for the comment. 0 to 3 indicates a low quality, 4 to 7 indicates a moderate quality, and 8 to 11 indicates a high quality. According to your comment, a description has been added to the revised manuscript (P9, L6-8).
Reviewer #2:
This a very interesting and very well-done systematic review and meta-analysis on senile pruritus. The main concern is that the authors think that senile pruritus is only due to skin modifications while it is probably more secondary to the aging of the nerve endings in the skin, the presence of comborbities and the use of several treatments that are commonly use in elderly patients. Consequently, there is a need to deeply modify the discussion.
Thanks for the comment. We can’t agree with you more. SP is not only caused by skin aging. In fact, SP also be secondary to some diseases, medication complication and degenerative change in peripheral nerve endings. Thank you for the reminder of the lack of discussion of other factors in the manuscript, we have added relevant discussion to the revised manuscript (P12, L2-9). We believe that the added discussion will make the reader more comprehensive about SP. Thank you for reminding of the parts we overlooked when writing.
Reviewer #3:
The authors undertook an ambitious project, to objectively quantify the prevalence of senile pruritus. Their methods and presentation were superb.
The major limitation of the study is that the condition, senile pruritus, does not have rigid diagnostic criteria. Moreover, we now recognize the biopsychosocial model of chronic itch. Investigators in different countries and people in different societies may not be uniform in assessing the prevalence and/or severity of this condition. The widely divergent estimates suggest either that genetics may play a very powerful role in this condition. Alternatively definitions of investigators and the people studied may not be uniform. This reader suggests the latter is more responsible and the authors should make these clear in the discussion and limitation. These limitations make me less confident that the final estimate is close to a "true" estimate.
Thanks for the comment. We also recognize that the major limitation of our study is the definitions of SP differed across the included studies. Although we have explained in the limitations and discussions, not further pointed out that due to different diagnostic criteria, biological, psychological, social, genetic and other factors and the different definitions of investigators and researchers, the "true" estimation of the prevalence of SP will be affected. Thank you for pointing it out, we modified at discussion (P 12, L 14-18) and limitations (P14, L14-19) in the revised manuscript according to your comment.
Reviewer #5:
1. p. 6: The rationale for inclusion criterion #1 is not clear. Did the authors mean to exclude longitudinal and experimental (e.g., treatment) studies? Similarly, the rationale for the exclusion criterion that "the study populations were inpatients and outpatients" is not obvious.
Thanks for the comment. Our responses are as follows:
① Longitudinal studies were not excluded from our study. However, since there is no longitudinal study meets the inclusion exclusion criteria, it is neglected to include it in inclusion criteria #
1. Longitudinal studies have been added to inclusion criteria # 1 according to your comment (P5, L19-20).
② Treatment studies were excluded from our study because the participants necessarily had skin disorders including SP, calculated prevalence of SP is overestimate. That's why studies in which the study participants was inpatient and outpatient were excluded.
2. p. 7: What data characteristics prompted the use of double arcsine transformations to generate prevalence rates?

Thanks for your comment. Our responses are as follows:
① The commonly used meta-analysis method for single rate study is based on normal distribution. However, when n is small or p is close to 0 or 1, due to the discreteness of distribution, it is not appropriate to use the binomial data to approximate the normal distribution. At this point, data conversion is needed. Use the 'double arcsine transformation' to transform the raw prevalence estimates so that the data can follow an approximately normal distribution.
② Performs the double arcsine transformation, computes the weighted pooled estimate and performs the back-transformation on the pooled estimate. The confidence intervals for the pooled estimate are always admissible, avoid confidence intervals exceeding the range of 0 to 1.
③ See the article entitled 'Metaprop: a Stata command to perform meta-analysis of binomial data' for details. Reference have been added and the description of 'double arcsine transformation' has been added to the revised manuscript (P7, L1-2).
3. 91% of the initial 8,518 studies were excluded based on screening of titles and abstracts. Can the authors provide information on the major categories of exclusion (e.g., a breakdown by language, age, etc.)? Similarly, 87% of the resulting 131 records were excluded without further comment. It would be interesting to know, for instance, how the database would have differed had the authors included languages other than Chinese.
Thanks for your comment. Our responses are as follows:
① 7, 740 records excluded by screening of titles and abstracts were based on age, design, and outcome. Based on your comment we have made simple instructions in the revised manuscript (P7, L17-18).
② The full-text screening is to exclude 114 studies by reading the full-text with reasons listed as follows: participants were not ≥ 60 years of age (n= 49), outcome was not senile pruritus (n= 44), not cross-sectional, case-control, cohort or longitudinal study (n= 9), non-Chinese and English study (n= 5), duplicate publication (n= 7). We have added it in the revised manuscript (P7, L19-20) (P8, L1) according to your comment.
③ In fact, we have no language restrictions when searching. We have read all the English abstracts of non-Chinese and English studies, 5 non-Chinese and English studies are excluded in the full-text screening (figure 1). We read these 5 studies by translation software and found no studies that met the inclusion and exclusion criteria, but in prudent view we ascribed their exclusion reasons to non-Chinese and English studies.
4. A brief statement of how monophagism was operationalized in the relevant two studies would be gratefully received.
Thanks for your comment. We also think that it is very meaningful to report the details of monophagism in the manuscript. Regrettably, the details of monophagism wasn't pointed out in the included study. But according to your reminder, we added discussion about deviance in the revised manuscript (P13, L18-20) (P14, L1-2).
5. Would the authors be willing to pose a hypothesis (p. 13), albeit quite tentative, for the observed prevalence differences? As it stands, this is a purely descriptive effort. This could be similar to the hypotheses provided for the risk factors, which are given in the next paragraph.
Thanks for your comment. Based on the current research status and evidence, we prefer to describe the status rather than pose hypotheses.

VERSION 2 – REVIEW

REVIEWER	Reid, Colin University of British Columbia Okanagan Faculty of Health and Social Development, School of Health and Exercise Sciences
REVIEW RETURNED	28-Jan-2022

GENERAL COMMENTS	The authors have adequately addressed my main concerns.

REVIEWER	Smith, David University of Notre Dame, Psychology
REVIEW RETURNED	30-Jan-2022

GENERAL COMMENTS	BMJ-Open Manuscript ID bmjopen-2021-051694.R1, entitled "The prevalence and risk factors of senile pruritus: A systematic review and meta-analysis", is a revised report of a meta-analytic investigation of the prevalence and risk factors for senile pruritus (SP). The authors were quite responsive to the initial round of reviews, addressing nearly all of my initial review points. I will only comment further on the following two points: Prior review point #2: I understand the double arcsine transformation is common in meta-analyses, and that it is implemented conveniently in Stata. It has come under some recent scrutiny (e.g., Lin & Xu, 2020), however, and the technical complaints are largely resolved by using simpler approaches, rather than even newer and more complex ones, so it is worth perhaps reconsidering the authors' use of the otherwise quite non-intuitive double arcsine transformation. Prior review point #5: I regret that the authors chose not to take this opportunity to propose some tentative hypotheses that might inspire future paths for research in this area. === Reference Lin, L, Xu, C. Arcsine-based transformations for meta-analysis of proportions: Pros, cons, and alternatives. Health Sci Rep. 2020; 9999:e178. https://doi.org/10.1002/hsr2.178