

Peer Review Information

Journal: Nature Human Behaviour

Manuscript Title: Sleep characteristics across the lifespan in 1.1 million persons from the Netherlands, UK and USA: a systematic review and meta-analysis

Corresponding author name(s): Henning Tiemeier

Editorial Notes:

Redactions – transferred manuscripts (mention of the other journal) This manuscript has been previously reviewed at another journal. This document only contains reviewer comments, rebuttal and decision letters for versions considered at Nature Human Behaviour. Mentions of the other journal have been redacted.

Reviewer Comments & Decisions:

Decision Letter, initial version:
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12th February 2020

Dear Prof Tiemeier,

Thank you once again for your manuscript, entitled "Sleep characteristics across the lifespan in 1.1 million persons from the general population of the Netherlands, UK and USA. A systematic-review and individual participant meta-analysis," and for your patience during the peer review process.

Having considered both rounds of reviews from **[REDACTED]**, which you kindly supplied, we would be interested in considering a revised version of your manuscript which addresses the second round reviewer concerns. We would also need to see a point-by-point response to the second round reviews.

Please note that we do not ask you to extend the meta-analysis to other countries (as suggested by Ref #2), or to split your paper into two or three papers (as suggested by Ref #4). However, we would ask you to fully address all other reviewer comments, and in general to ensure that all claims or recommendations in the manuscript are justified on the basis of the data.

I apologize again for the delay in the evaluation of this manuscript.

We hope to receive your revised manuscript within four to eight weeks. If you cannot send it within this time, please let us know. We will be happy to consider your revision so long as nothing similar has

been accepted for publication at Nature Human Behaviour or published elsewhere.

With your revision, please:

- Include a "Response to reviewers" document detailing, point-by-point, how you addressed each Round 2 **[REDACTED]**, referee comment. If no action was taken to address a point, you must provide a compelling argument. This response will be sent back to the reviewers along with the revised manuscript.
- Highlight all changes made to your manuscript or provide us with a version that tracks changes.

Please use the link below to submit your revised manuscript and related files:

[REDACTED]

Note: This URL links to your confidential home page and associated information about manuscripts you may have submitted, or that you are reviewing for us. If you wish to forward this email to co-authors, please delete the link to your homepage.

We look forward to seeing the revised manuscript and thank you for the opportunity to review your work. Please do not hesitate to contact me if you have any questions or would like to discuss these revisions further.

Sincerely,
Jamie

Dr Jamie Horder
Associate Editor
Nature Human Behaviour

Author Rebuttal to Initial comments
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Dear Dr. Jamie Horder,

Hereby we would like to submit a revised manuscript and a point-by-point response to the comments of the reviewers invited by **[REDACTED]**. We hope that by addressing their points we have improved the manuscript and you would find it of interest for the readers of Nature Human Behavior.

The main additions to the paper are:

- We provide a careful analysis of sources of heterogeneity among the studies from the Netherlands.
- We have now studied changes in sleep patterns across time (1993-2017) in the studies from the Netherlands and the USA.

- Descriptive tables of main sleep characteristics across all available strata are now provided in the supplement.

We would be grateful to receive further suggestions for improvement, and if you have additional questions or concerns, do not hesitate to contact us.

On behalf of the team,
Desana Kocevka

Manuscript NATHUMBEHAV-20018806. **Sleep characteristics across the lifespan in 1.1 million persons from the general population of the Netherlands, UK and USA.**

Response to reviewers provided by [REDACTED]:

Reviewer: 1

Isao Muraki

Job Title: Assistant processor

Institution: Public Health, Graduate School of Medicine, Osaka University

In the present research, the authors conducted pooling individual data analysis of Dutch population regarding sleep characteristics. Their findings may help promoting the improvement of sleep duration and quality in general population. In the current manuscript, the authors have solved most comments for the previous one.

Response: We thank the reviewer for this compliment.

Major comments

1. Since sleep duration and sleep quality may be changing through periods in several countries due to social changes such as economic crisis like the subprime mortgage crisis in 2007-2008 and widespread use of smartphone like the iPhone (Hoyos C et al. Curr Sleep Medicine Rep 2015;1:195–204, Sheehan CM et al. Sleep 2019;42:zsy221), relatively large difference in survey period of included studies may cause some bias. Please additionally show the stratified results by survey period.

Response: We thank the reviewer for bring up this important point. We now show pooled and sex-stratified data on total sleep time, difficulty initiating sleep and difficulty

maintaining sleep stratified by data-collection years, for the Netherlands and the US (which is partially the same data as from the Sheehan paper). These results are also described in the results and discussed in the discussion section.

Methods Page 18: *“Fourth, since sleep may change in due to social changes like economic crisis or increasing use of blue-light emitting screens, we assessed if changes in average sleep duration (TST), as well as the prevalence of DIS and DMS occurred in the Netherlands and USA.”*

Results Page 24:

“Changes in sleep patterns with calendar year

In the data from the Netherlands there was some evidence for a decrease in sleep duration from the 90s to the 00's, TST values between 1993-1997 averaged around 7.3 hours per night, whereas after 2004 values ranged between 6.7 to 7.1 hour, with the exception of 2009 which is fully based on the LASA Study (Supplemental Figure 6). In the USA, TST values between 2004 and 2017 were more stable, ranging between 7.07 in 2017 and 7.19 in 2007. There were no changes in the prevalence of insomnia symptoms across the studies years in the Netherlands and in USA (Supplemental Figure 7).”

Discussion Page 27: *“In the Netherlands, there was some evidence for a 18-36 minutes decrease in the average sleep duration from the 90s to the 00's, but this could also have resulted from between-study heterogeneity. We did not observe changes in average sleep duration in the USA, although one study (Sheehan et al.) did show an increase in the prevalence of adults sleeping <6hrs per night.”*

2. Individuals over 90 years seems to sleep longer than those aged 80 years or so, but the estimates for those aged over 90 years may be strongly affected by the healthy survivor bias. Since the number of participants over 90 years are limited, excluding those aged over 90 years may be better to minimize such a survivor bias.

Response: Excluding the persons aged more than 90 years (n=130) did not change the results.

Results Page 22: *“Results were similar if participants above 90 years of age (n=130) were excluded (data not shown).”*

Minor comments

1. In supplementary table 1, median and range of age rather than mean and

standard deviation can be important to understand study characteristics.

Response: Thank you for this valuable suggestion. We have now added the median and range in the tables.

2. In supplementary table 1 and 2, it may be easy to compare study characteristics when studies are listed in order of median age of each study population rather than in alphabetic order of study name which is a usual way.

Response: Thank you for this valuable suggestion. We have now reordered Supplementary Table 1 and 2 by ascending age of the study population.

Reviewer: 2
Naja Hulvej Rod
Professor of Epidemiology
University of Copenhagen

1. It is an interesting and well-conducted systematic review and IPD meta-analysis of sleep studies from the Netherlands. A total of 36 studies were included in IPD meta-analysis based on data from 200,358 people. The findings from these studies were compared with sleep data from the UK Biobank and the National Health Interview Survey in the USA. While large and comprehensive in coverage, it is puzzling, why the authors have chosen to only include data from the Netherlands. The study would have been more original, if it had been a IPD meta-analysis of all published studies on sleep characteristics, maybe within a short time frame.

Response: We thank the reviewer for the comments. Sleep parameters and sleep patterns vary substantially across countries. People living in the US have, on average, a shorter sleep duration, than people living in UK, Netherlands, but also than those in Germany or Belgium; people living in Spain or Italy go to bed later than people living in the UK or Netherlands, who in turn go to bed later than people in the US.¹ We think that combining data from different populations in one individual participant meta-analysis would not have yielded a meaningful reference chart, the chart would not have been applicable to any given population. Presenting data from populations of two other Western countries to contrast with our results from the Netherlands, however, facilitates generalization.

For reviewer purpose only: 1. Walch OJ, Cochran A, Forger DB. A global quantification of “normal” sleep schedules using smartphone data. Science advances. 2016 May 1;2(5):e1501705.

Discussion Page 30: *“However, current recommendations are applicable only to self-reported average sleep duration, and international differences point to the need for country-specific recommendations for adequate sleep.”*

See also comment from Associate Editor Jamie Horder: Please note that we do not ask you to extend the meta-analysis to other countries (as suggested by Ref #2), or to split your paper into two or three papers (as suggested by Ref #4).

2. Looking more into sources of heterogeneity between studies would also have added to the originality of the study.

Response: This is an important point raised by the reviewer, that was previously not addressed in the paper. We have now thoroughly explored the role of age, sex and cohort in the heterogeneity of quantitative sleep variables and insomnia symptoms. This is now explained in the methods and results.

Methods Page 17: *“Heterogeneity was evaluated by calculating the I^2 statistic, which indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity. Also, we describe how the I^2 changed with subgroup analyses (by age group, sex and cohort). In addition, we evaluated the differences between the pooled estimates of sleep duration and insomnia symptom as estimated by a fixed effect versus random effects meta-analysis.”*

Results Page 20: *“Heterogeneity estimates were high: I^2 ranged between 97-99% for TIB, 90-99% for TST, and 96-99% for SE (Supplemental table 1b). However, when meta-analyses were stratified by sex, heterogeneity estimates decreased as low as 0% for TIB (women ages 26-40 years), 54% for TST (women 18-25 years) and 0% for SE (both men and women aged >65 years). For some age strata, however, sex stratification had only minor effects on heterogeneity estimates, as I^2 remained high (see forest plots in Supplemental Figure XX). Importantly, age- and sex-specific TIB, TST, SE estimates changed only marginally from the fixed effect to the random effects model (Supplementary Table 5).”*

Results Page 21: *“Heterogeneity ranged from 0-99% for DIS, 0-97% for DMS, and 17-97% for EMA, depending on age group (see Supplemental Table 2b). Heterogeneity of insomnia symptoms were low in pediatric cohorts aged 5 years or younger. When studies of adults were additionally stratified by sex, I^2 decreased as low as 48% for DIS in men aged 65+ years, 54% for DMS in women aged 26-40 years, and 0% for EMA in men 18-25 years. However, residual heterogeneity was substantial in most other strata (see Supplementary Table 7 and Supplementary Figure 5a-c). Pooled prevalence estimates (shown in Supplementary Table 7) were, however, comparable between fixed*

effect and random effect models, with the exception of DIS in 18-25 and 26-40-year-olds (from 23.4% to 9.5%), DMA in 6-13-year-olds (from 9% to 17%), and EMA in 26-40 (from 14% to 11%) and 41-65-year-olds (from 21% to 17%)."

Discussion Page 26: "Second, heterogeneity between studies may have introduced misclassification bias (e.g. different definitions of bedtimes and waketimes can influence TIB estimates). Analyses of sources of heterogeneity indicated that age and sex partly account for the heterogeneity between the studies from the Netherlands. Other socio-demographic variables, within and beyond those assessed in this study, likely also influence sleep estimates resulting in residual heterogeneity. Though access to IPD improves data quality through standardization of definitions, this study was not sufficiently powered to tease out all these influences on heterogeneity. Nevertheless, we provided crude estimates for the socio-demographic strata that could be valuable reference for future studies or clinical practice. Third, we could not assess potential confounding by underlying sleep disorders (e.g. sleep apnea), psychiatric disorders, substance abuse and other chronic medical conditions that could disturb sleep and the ability to go out of bed (e.g. hypertension, diabetes mellitus), environmental or occupational factors (noise, shift work). These factors may have contributed to heterogeneity in the sleep estimates."

3. The research question is to 'obtain reliable reference charts for sleep characteristics in the general population across the life course...' ; but it is unclear how these sleep characteristics can be used as reference charts? If a population experiences many sleep problems, would it then be more/less acceptable for a person to experience similar problems than if the population experiences low levels of sleep problems? I don't think it is plausible to call them reference charts, which seems to refer to normal development (e.g. like reference charts for weight development during childhood). I suggest this is modified throughout the manuscript.

Response: We apologize if we have given the impression that our study provides *recommendations*. We did not mean to do so. With reference charts, we merely mean to provide estimates of how the population sleeps - not whether this is sufficient or desirable. We characterize the distribution of measures of sleep quantity (sleep duration, time in bed, and sleep efficiency), which vary substantially by age (i.e. developmental effect), and (like weight) are variably distributed in the general population. Reference charts are, of course, not able to determine the prevalence's of insomnia symptoms or other sleep complaints. This has been now made clearer in the manuscript.

Abstract Page 5: *“The study has three main objectives: 1) to obtain reliable reference charts for sleep duration; 2) estimate the prevalence of sleep complaints in the general population across the lifespan; and 3) to identify risk indicators of poor sleep.”*

Introduction Page 9: *“Estimating reference ranges for sleep duration can help compare an individual’s sleep characteristics with that of men or women of the same age in the general population and quantify the prevalence of insufficient sleep at a population level.”*

Introduction Page 10: *“In order to obtain valuable population percentile curves and reference values we described sleep duration, time in bed and sleep efficiency across age and sex.”*

Discussion Page 28: *“Despite the premise that ‘optimal’ sleep duration likely differs per outcome, individual and circumstances, providing reference values for sleep length can be useful in clinical or prevention practice.”*

Discussion Page 30: *“The estimated population reference charts for sleep timing, sleep duration and efficiency across the lifespan, will help guide personalized advice on sleep.”*

5. The systematic review and IPD meta-analysis seem to follow all relevant guidelines and is well conducted and presented. It would have been interesting to also see the heterogeneity between studies and over time and explore sources of this heterogeneity.

Response: We thank the reviewer for this suggestion, we have now addressed this point. Please see our answer to comment 2 for quotes of changes in the paper.

6. The rational for focusing solely on data from the Netherlands is not well argued for and needs further elaboration.

Response:

See also our answer to point 1, which we only partly repeat here.

We selected the Netherlands, a country with many population-based studies, but recognize the need to also describe sleep in other population, hence we have made comparisons with general-populations studies from the UK and US.

Sleep parameters and sleep patterns vary substantially across countries. Combining data from different populations in one individual participant meta-analysis would not have yielded a meaningful reference chart; the chart would not have been applicable to any given population. However, we decided to increase the facilitate the scope of results by also including data from two other countries.

We now elaborate on this issue, but please also see above for further changes to the manuscript.

Methods Page 11: *“In order to chart sleep characteristics for the population of the Netherlands, we conducted a systematic literature search to identify population-based cohorts assessing sleep characteristics via questionnaires.”*

Methods Page 12: *“These samples were not meta-analytically pooled with the data from the Netherlands, as this would further increase heterogeneity, thereby resulting in estimates that cannot be better generalized to other populations.”*

Discussion Page 30: *“However, current recommendations are applicable only to self-reported average sleep duration, and international differences point out the need for country specific recommendations for adequate sleep.”*

7. The participants are adequately described and compared to general population measures. The population, however, seems to not be completely representative of the general population. This is particularly important when presenting descriptive results and the impact of this lack of generalizability should be further elaborated. Maybe the results could be weighted to fit the general population?

Response: We indeed observed slight overrepresentation of females and persons with middle educational level, however these differences were minor (1-9%), and are not likely to have influenced the sleep estimates we report. In addition, in the population from the USA survey estimates have been weighted for the population stratification in the USA, but changes in sleep estimates resulting from these adjustments were negligible. Hence, we decided to use unweighted estimates for this sample. However, we now provide estimates from random effects meta-analysis (Supplemental Table 5 and 6) next to the pooled raw estimates (Table 1 and 2), which should partly account for the heterogeneity between the studies. We think that this is preferable to reporting population weighted outcomes, because the latter may falsely lead the reader to conclude that all biases have been accounted, while they cannot sufficiently adjust possible selection effects.

8. The calculation of sleep efficiency based to two self-reported measures of sleep duration and time to bed and awakening seem quite vulnerable to misclassification bias, and one may question whether it is a valid measure. Especially, because the authors make relatively strong conclusion about quite small differences in this measure.

Response: We agree that the ratio between time in bed in self-reported sleep duration might be particularly prone to misclassification bias.

Discussion Page 26: *"In addition, as SE is based on two self-reported measures, these variables might be particularly prone to error, and should be interpreted with caution."*

9. Changes over time is not addressed, but would be very relevant to present, as there seem to be an increase in sleep problems over time.

Response: Thank you for this suggestion. This data is now presented in the paper, and comparisons of time period changes in sleep characteristics in the Netherlands with those observed in the USA cohort are also presented. Please also refer to our answer to comment 1 of the first reviewer, which include the changes in the manuscript.

10. Confidence bans should be added to the figures.

Response: We thank the reviewer for this valuable suggestion, we have now added the confidence intervals to Figure 4.

11. They show a marginally lower (2%) sleep efficiency in women than in men, but such small differences seem irrelevant from at clinical or public health perspective. The beta of 0,02% also seem to be wrongly written, as the difference is 2% when you look at the numbers. This essentially goes for all the numbers presented in suppl table 4.

Response: The numbers in the tables reporting means and prevalences are unadjusted values (Table 1 and 2), whereas in the linear mixed models (Supplemental Table 4 and 5) estimates are adjusted for all factors included in the models, as well as accounting for missing values and additionally account for clustering within cohorts (random intercept and slope for study are included).

We agree that unadjusted differences of 2% are not likely to be clinically relevant. This is now addressed in the paper.

Discussion Page 27: *"Fifth, multivariable adjusted models indicated that the reported differences in sleep patterns across socio-demographic groups were small, thus their clinical implications may be limited."*

12. Again, relatively strong conclusions about differences according to health indicators are drawn from quite small actual differences (see page 21 mid). This needs to be modified.

Response: We understand the concern of the reviewer. These findings are only described in the results, and are intentionally not further interpreted in the discussion. Though unadjusted differences may be of some value, we agree that confounding likely plays an important role. Therefore, we find it important to describe both unadjusted and adjusted results in the paper. We have also explicitly addressed this in the discussion.

Discussion page 27: *"Fifth, adjusted differences indicated that the reported differences in sleep patterns across socio-demographic groups were small, thus their clinical implications may be limited."*

13. There is a nice summary of the results. They highlight that more than half of the teenagers sleep an hour less than recommended and that especially sleep initiation is a problem. While one of their stated aims is to 'identify risk indicators of poor sleep', it is interesting that they don't even mention the large and increasing literature on screens, digital devices and sleep impairment, especially among young people. I suggest that this literature is incorporated into the discussion section.

Response: We agree with the reviewer that screen exposure might be one of the reasons why we observed highest prevalence of insufficient sleep in teenagers. We did, however, not have data on this exposure information to quantify these effects. We have now addressed this in the Discussion.

Discussion Page 26: *"Third, we could also not assess potential confounding by underlying sleep disorders (e.g. sleep apnea), psychiatric disorders, substance abuse and other chronic medical conditions that could disturb sleep and the ability to go out of bed (e.g. hypertension, diabetes mellitus), environmental (screen exposure, noise) or occupational factors (noise, shift work)."*

Discussion Page 28: *"In teenagers, the prevalence of insufficient sleep and sleepiness was much higher than in any other age group. This could likely be explained by developmental bedtime delay (as evidenced by our analyses of sleep timing), but could also be influenced by adolescent lifestyle and environment such as social and peer pressure, screen exposure or social life."*

14. Confounding is not a relevant concern in descriptive studies, and the discussion about potential confounders seems irrelevant.

Response: We agree but consider it valuable to discuss confounding effects because they are likely to have contributed to the observed heterogeneity. We have revised this part of the discussion. It now reads:

Discussion Page 26: *“Third, we could also not assess potential confounding by underlying sleep disorders (e.g. sleep apnea), psychiatric disorders, substance abuse and other chronic medical conditions that could disturb sleep and the ability to go out of bed (e.g. hypertension, diabetes mellitus), environmental or occupational factors (noise, shift work). In addition, differential recruitment strategies may have resulted in differential prevalence of disturbed sleep in the sample. These factors would likely further explain residual heterogeneity in the sleep estimates.”*

15. Regarding literature, it is puzzling why they are not referring to the landmark meta-analyses from Cappuccio et al. when discussion the potential health consequences of sleep problems. There are also a number of previous studies reporting prevalence of sleep problems in different populations, but they are not systematically referred to or compared with.

These important references are now cited. It is beyond the scope of the paper to summarize all individual studies describing sleep patterns in smaller samples with specific age groups or geographical regions.

Discussion Page 28: *“Studies included in our meta-analysis have shown that participants aged 18-65 years old sleeping both less than 6 hours and less than 7 hours per night have higher cardiovascular risk as compared to those sleeping 7 to 8 hours per night, as also confirmed by landmark meta-analyses on the associations between sleep and cardio-metabolic health().”*

16. The title promises more than what is presented in the paper, as one is expecting a meta-analysis of 1.1 million persons.

Response: We understand the concern of the reviewer. To avoid confusion, we have removed the “systematic review and individual participant meta-analysis” from the title, as these methods only refer to the data from the Netherlands. This is still described in the methods and results.

The title now reads: ***“Sleep characteristics across the lifespan in 1.1 million persons from the general population of the Netherlands, UK and USA.”***

17. Under ‘What this study adds’ the authors state that they provide ‘population reference curves... that might contribute to personalized sleep advice’. How these curves can be used as references charts is unclear to me and especially how they can feed into personalized sleep advice is not well described. I suggest this part is modified.

Response: This was a part relevant for the [REDACTED] formatting that has now been removed from the manuscript. Information on how reference curves can be used is presented in the discussion.

Discussion Page 29: “For example, a 28-year-old woman reporting to spend 9 hours in bed is in the 90th percentile of the female population of similar age, whereas, a 28-year-old man with the same TIB, would be in the 95th percentile of the male population of similar age.”

Reviewer: 3

Ninad Chaudhary

Job Title: Research Scientist

Institution: University of Alabama at Birmingham

Comments

I would like to commend the authors for such extensive work on this manuscript. The authors have conducted a comprehensive systematic review and meta-analysis to derive the prevalence of sleep characteristics in the general population across the lifespan. The authors also determined the association of insomnia symptoms, total sleep time and sleep efficiency with demographics and health profile. The study is primarily based on the Netherland population with comparison in UK and US population. While the literature is extensive and it is not feasible to verify the articles in this systematic review in such a short period of time, I am happy with the search and literature review algorithm of the authors and random check of the articles meet the suggested inclusion criteria. As this is a revised version, I have avoided overlap with prior reviewer comments and would defer the decision of completeness of responses to the editor.

Response: We thank the reviewer for the kind comments and highly valuing the paper.

1. One of the proposed rationale for this the manuscript is – “In addition, these recommendations target healthy populations, whereas the general population represents the continuum between health and disease” and “Ideally, recommendations for sleep duration in the general population should be described over multiple physiologically and clinically relevant aspects, including age, sex, demographics, or lifestyle”. However, the manuscript does not really measure sleep characteristics based on any clinical aspects including lifestyle. The paper also lacks any information on clinical comorbidities to support the rationale that most of the participants are at one or other end of the continuum.

The authors also suggest that the study population in this study may be different from the general healthy population on which NSF recommendations are based which may not be true. Any healthy population is the continuum between health and disease. The results of the study also suggest the same. The author's conclusion that this study provides reference charts for sleep duration for research, clinical and preventive seems to be overstated based on that.

Response: We thank the reviewer for these critically evaluating the introduction of our paper. With the "continuum between health and disease" we were referring to the fact that in the general population studies we included in the meta-analysis, no exclusion criteria were applied. We agree, however, that some these statements needed reevaluation and rewording. We have adapted the introduction accordingly.

Abstract Page 6: "In the largest descriptive sleep study to date, we provide age- and sex-specific population reference charts for sleep duration and efficiency which can help guide personalized advice on sleep length and preventive practices in industrialized countries, as well as be used in future research."

Introduction Page 8: "In addition, these recommendations were targeted for healthy populations, whereas the general population may represent a broader continuum between health and disease."

2. Do individuals from UK Biobank and US NHIS meet NSF recommendations? Are the percent of individuals not meeting the recommendations similar to the Netherland population?

Response: These results are described in the Results page 24: "The proportion adults reporting TST shorter than recommended for age was the highest in the US (30.3%), compared to 24.5% in the Netherlands, and 25.0% in the UK. The proportion of adults sleeping less than the "acceptable" values were below 10% in all three countries."

3. The calculation of sleep efficiency is reliant only on time in bed and total sleep time which are both prone to measurement errors. The authors excluded those who had % SE higher than 110 and converted the values between 100- 110% to 100% which inadvertently added to measurement bias. The potential reason for asking both these questions in a survey would have been to account for other sleep complaints i.e. DIS and early morning awakening. There is a possibility that those who had %SE > 100 can be unique individuals with some insomnia sub-phenotype and may not be purely error.

Response: We thank the reviewer for this suggestion. Most of the SE values above 110% were from a single study (Lifelines), therefore we suspected these might be more an error artefact. We have excluded these values, and addressed this in the manuscript.

Discussion Page 24: "In addition, as SE is based on two self-reported measures, these variables might be particularly prone to error, and should be interpreted with caution."

4. Even though %SE has been recoded such that maximum value is 100% - some of the values in tables suggest the maximum value is greater than 100% (Table 1)

Response: We have double-checked the values, and we assure the reviewer that values above 100% have been excluded. In addition, we now provide median, minimum and maximum values in the table.

5. It is not clear if the authors included UK and US population in the association analysis or using this data only for comparison.

Response: We included the UK and US population for international comparisons, and we have not pooled results with the data from the Netherlands. This is now explained in the methods.

Methods Page 12: "To evaluate differences of sleep characteristics across countries, we included two large population-based datasets from adults in the UK Biobank (n=498,320) and the National Health Interview Survey (NHIS) from the USA (n=409,617). These samples were not meta-analytically pooled with the data from the Netherlands, as this would further increase heterogeneity, thereby resulting in estimates that cannot be generalized to any population."

6. Along the same lines of point # 3 Additional Supplementary table by age and gender with missing information for each insomnia variable will be helpful. It is difficult to decipher what is the general missing pattern based on each symptom by age and gender. While use of the weights based on the distribution of age in the pooled data would have been more appropriate, as the authors have adjusted for age and gender – the higher missing values in a particular age group may bias the results.

Response: We have added a Supplement table 16 where we provide the number of missing information per age and sex group for the main variables of interest (TST, TIB, SE, DIS, DMS, EMA). In addition, please note linear mixed models adequately account for missing values.

Methods Page 18: *"The distribution of missing data across age and sex is shown in Supplementary Table 16."*

7. Based on the approach, the authors seem to be interested in the change in sleep complaints due to each demographic/health characteristic. Considering that, sleep complaints regressed on each characteristic deriving unadjusted estimates could be more informative. The adjusted model seems redundant here as there are multiple factors that are not available (especially substance use, psychiatric symptoms, hypertensive measures that form huge comorbid burden along with insomnia) and not accounted for. Being a descriptive study, there is no perfect way that the confounding bias will be addressed.

Response: We thank the reviewer for this suggestion. We now added the unadjusted means and prevalences stratified by education, ethnicity, partner and employment in Supplement Table 9 and 10. Nevertheless, we also kept the results from the adjusted model, as such analyses account for multiple confounders, missing values, and heterogeneity between studies.

Results Page 21: "). Unadjusted estimates stratified by ethnic origin, educational level, employment and presence of a partner are presented in Supplementary Table 9."

Results Page 22: "Estimates stratified by BMI and smoking status is presented in Supplementary Table 10."

8. Did the random effect have significant estimates? If not, adjusting for study may be more helpful.

Response: This is an excellent suggestion. The random effects were indeed significant in all models.

Methods Page 16: *"The random effects for study were significant in all models."*

9. There are concerns related to the definition of ethnicity. A country of birth may not be an appropriate surrogate marker for ethnicity as it may not account for immigration patterns. Also, ethnicity may not useful for international comparisons owing to differences in how it is an important factor in the US-based population but may not be that relevant in the UK population. I would suggest that the authors should drop the assessment from the paper or measure it in a different way.

Response: Please note, we did not make any international comparisons based on ethnic origins. We agree that the present ethnicity definition would not have captured the immigration/racial composition across the three countries. Therefore, this definition of ethnicity was operationalized only in the sample from the Netherlands and is in line with the definitions of the Statistics Netherlands.

In the Netherlands the immigration patterns are more recent than in the US, thus country of birth or birth of parents is an arguably reliable estimate of ethnicity. Instead of fully omitting this analysis, we have now clearly described in the manuscript that conclusions based on ethnicity are based on the population from the Netherlands only.

Methods Page 14: "Ethnic origin was based on self-report of the country of birth of the participant or his/her parent(25) and categorized into European origin - Dutch, European origin – other, and non-European origin.(23)"

10. There is a recent article that self-assessed average sleep duration underestimated objectively measured sleep duration using actigraphy while wake-bed time differences are overestimated in older population (PMID: 31616945). How does the current study findings stand in the light of this paper?

Response: This indeed what we also found in our population. Unfortunately, we did not have actigraphy data in younger adults (e.g. 18-60 years) to assess age differences in this overestimation.

11. The number "5,932" in Supplementary Figure 1a seems incorrect.

Response: We thank the reviewer for pointing out this error. This number should have been 8.508 and is now corrected.

Reviewer: 4

Yu Sun Bin

Job Title: Research Fellow

Institution: University of Sydney

Comments:

Thank you for asking me to review this paper. The idea of producing population norms for sleep is an excellent one but this aim is lost in a very dense manuscript which mixes purposes and methods. In addition to describing norms, the manuscript also describes associations between sociodemographic characteristics and sleep parameters and compares Dutch sleep to sleep in 2

other countries. The methods include a combination of (1) systematic review of Dutch studies of various types not necessarily representative, (2) actigraphic measurement of actigraphic sleep from the UK Biobank, and (3) self-reported sleep from US National Health Surveys.

I think the manuscript would be improved if split into 2, maybe even 3, papers with their quite distinct aims: (1) a systematic review on the state of sleep health in the Netherlands, and (2) on sleep norms, perhaps comparing and contrasting self-reported values to those that are objective measures. The first paper on the state of sleep health in the Netherlands would be an important one in that country. However, the second suggestion still runs into the major issue of trying to combine different measures of sleep which were not collected in the same population - that is, it is unclear to what extent the derived norms are specific to the Dutch, and it is unclear to what extent the norms are specific to the British or American populations especially given that sleep was measured using different methods in each population.

Unfortunately large numbers of participants cannot overcome these methodological issues to make the descriptive results as useful as the authors would like them to be.

Comment from Associate Editor Jamie Horder: Please note that we do not ask you to extend the meta-analysis to other countries (as suggested by Ref #2), or to split your paper into two or three papers (as suggested by Ref #4).

Response: We argue that the present combination of multiple population-based samples provides a good estimate of a large representative national sample for population norms or reference charts. This is a unique effort and can partly overcome that all surveys and population-based studies conducted in high-income countries currently struggle to obtain population-based (defined by a primary study base) samples that are also representative. Sometimes, nationally representative samples are obtained with oversampling (or weighing) on certain characteristics. Yet, this typically comes with low response rates, which introduces bias through self-selection and high motivation. Finally, we fully agree that the samples from the UK and the US cannot be combined with the Dutch norms and this data must be interpreted carefully. However, these samples demonstrate the limits but also the possibilities of generalization to other high-income countries.

We are happy to read that the Associate Editor agrees that the study should not be split. It is important to discuss population characteristics such as age, gender and socio-economic status that are strongly related to sleep characteristics and some users may want to take in to account when interpreting sleep norms. Thus, these two aims are intrinsically related.

Decision Letter, first revision:

2nd July 2020

*Please ensure you delete the link to your author homepage in this e-mail if you wish to forward it to your co-authors.

Dear Prof Tiemeier,

Thank you once again for submitting your revised manuscript, entitled "Sleep characteristics across the lifespan in 1.1 million persons from the general population of the Netherlands, UK and USA" and for your patience during the re-review process. I apologize again for the delay.

Your manuscript has now been evaluated by our referees, and in the light of their advice I am delighted to say that we can in principle offer to publish it.

First, however, we would like you to revise your paper to address the points made by the reviewers, and to ensure that it complies with our Guide to Authors at <http://www.nature.com/nathumbehav/info/gta>.

You will see that both of the reviewers raise a number of points which you should address in the final version with further discussion or minor changes.

Nature Human Behaviour offers a transparent peer review option for new original research manuscripts submitted from 1st December 2019. We encourage increased transparency in peer review by publishing the reviewer comments, author rebuttal letters and editorial decision letters if the authors agree. Such peer review material is made available as a supplementary peer review file.

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To assist you with finalizing your manuscript for publication, I attach a checklist that lists all of our editorial policies and formatting requirements. I also attach a template document, which you may find useful as it gives examples of our format.

Please attend to *every item* in the checklist, and upload a copy of the completed checklist with your

submission. ***I have highlighted in the checklist items that require your attention along with recommended actions*** - these should appear as Comments in the file. If you have any difficulty viewing this file, please let me know. I also mention here a few points that are frequently missed and can cause delays:

- 1) Ensure that all corresponding authors have linked their ORCID to their account on our online manuscript handling system. This is very frequently missed and invariably causes delays in formal acceptance.
- 2) Ensure that you provide all of the materials requested in the attached checklist and below with your final submission. Please note that the Licence to Publish needs to be hand-signed.
- 3) Please double check that your manuscript matches PRISMA requirements. For some of the PRISMA items, e.g. "IPD integrity" A1 & A3, I found it difficult to find where you had addressed them in the manuscript. Please include an updated PRISMA checklist with the final submission.

We hope to hear from you within 10 days; please let us know if the revision process is likely to take longer.

To submit your revised manuscript, you will need to provide the following:

- Cover letter
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- Manuscript text (not including the figures) in .docx or .tex format
- Individual figure files (one figure per file)
- Extended Data & Supplementary Information, as instructed
- Reporting summary
- Editorial policy checklist
- License to publish
- Third-party rights table (if applicable)
- Suggestions for cover illustrations (if desired)
- PRISMA checklist

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Please use the following link for uploading these materials:

[REDACTED],

If you have any further questions, please feel free to contact me.

With best regards,
Jamie

Dr Jamie Horder
Senior Editor
Nature Human Behaviour

Reviewer #1:

Remarks to the Author:

Thank you for the opportunity to review this important manuscript again. The authors have conducted a comprehensive systematic review and meta-analysis to derive the prevalence of sleep characteristics in the general population across the lifespan. The authors also determined the association of insomnia symptoms, total sleep time, and sleep efficiency with demographics and health profile. The study is primarily based on the Netherlands population with comparison in UK and US population. The authors have satisfactorily responded to my earlier comments. Compared to prior submission, the authors have updated the finding by studying the heterogeneity between the studies.

Below are a couple of comments/concerns for authors to consider further:

1. The challenge of such a big pooled estimate analysis of 36 studies is that poor heterogeneity is expected. This is mostly due to unavoidable inherent selection bias within and between the studies, including variable missing pattern. Unfortunately, the heterogeneity statistics for this study are poorer than expected which raises the important concern about the pooled estimates. I could not locate supplemental table 1b in the supplementary information but based on the forest plot, chi-square statistic is high too. While the larger part of the author's message is still important, I believe the authors may consider the following:

- a. Considering variable and lower heterogeneity within the sex strata, interpret the results as gender stratified and avoiding the interpretation as overall population
- b. Association of insomnia symptoms with other factors (social determinants and health indicators) should be stratified by gender

If the authors are interested in the interpretation of the overall population, the authors should emphasize more on the limitations due to the heterogeneity, mainly the possible reasons, and how the interpretation of the overall population is biased and sex-strata estimates could be a better representative.

Minor comments:

2. Page 10 Line 250 ... "We additionally.... ": Based on the supplementary figure 1b, the authors see to have sought IPD for 44 studies and not 47 studies as mentioned in the text.
3. It is not clear what the message/interpretation of Figure 1 with respect to sleep efficiency?
4. Page 26 Line 608: "Analyses of sources of heterogeneity indicated that age and sex partly account for the heterogeneity between the studies from the Netherlands" – I do not think sub-group analysis really answers that. Age could be possible but gender does not seem to be.

Reviewer #2:

Remarks to the Author:

Kocevska et al. present the most detailed study of sleep characteristics to date. This is done by

carefully analyzing previous large-scale studies. I find the manuscript very interesting and important for the field. The authors also provided detailed responses to comments from four previous reviewers. These responses sufficiently address these reviewer's concerns. Beyond this, I only have three suggestions for items which the authors could discuss further:

- 1) Much of the manuscript focuses on testing how sleep compares with current guidelines. There are certain cases where they find a sizeable deviation from these guidelines. Should the recommendations be revisited? How could their data impact further discussion on setting guidelines? I do think that such a discussion would help readers, and can be done in a way that also recognizes that the point of the study was not to set new guidelines but to provide more information.
- 2) The finding of TST being longer in women than men is an interesting one. Although not large, it does match the results of other studies for example from smartphone apps. Again, possible reasons for this or implications? Should this gender difference be considered in setting guidelines?
- 3) Changes in sleep time between different age groups occur because of changes in bedtime not waketime. Again, more discussion of this result could be helpful.

Author Rebuttal, first revision:

Response to reviewers

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If the authors are interested in the interpretation of the overall population, the authors should emphasize more on the limitations due to the heterogeneity, mainly the possible reasons, and how the interpretation of the overall population is biased and sex-strata estimates could be a better representative.

Response: We thank the reviewer for this thorough assessment of the heterogeneity in our meta-analysis. We understand the concerns the reviewer has, and we have tried to emphasize the important role heterogeneity can play for the interpretation of our findings throughout the Discussion. In addition, in the Results we acknowledge that heterogeneity was somewhat decreased when the data was stratified by age *and* sex, however, in most strata heterogeneity remained high. Please note that the heterogeneity estimates for each sex and age strata can be found in Supplement Tables 5 and 7. This indicates, as the reviewer points out, that between study heterogeneity resulting

from varying sampling strategies, missingness etc. remains an important source of heterogeneity. Therefore, the assessment of the changes in heterogeneity estimates by stratification further inform the reader. In addition, please note that all descriptive results throughout the paper are presented an age- and sex-stratified manner, as are most of the interpretations based on the pooled data (e.g. comparisons with recommendations, international comparisons etc.). Finally, we would like to point out to the reviewer, that the models of demographic and health determinants were also adjusted for age, sex, and a random effect for study, which should account for the heterogeneity originating from age and sex. Stratifying these associations for sex would not solve any issues introduced by between-study heterogeneity. Therefore, to avoid further complicating the interpretation of these findings we have decided not to present sex-stratified associations between demographic and health determinants. Some changes were made to the manuscript to make sure that the issue of heterogeneity is sufficiently addressed in the discussion.

Discussion page 25: *"Our study is the largest descriptive sleep study to date, however pooling a large number of individual studies inevitably results in high heterogeneity, thus absolute estimates should be interpreted with caution."*

Discussion page 26: *"Analyses of sources of heterogeneity indicated that age and sex only partly account for the heterogeneity between the studies from the Netherlands, and that most remaining heterogeneity likely originates from between study differences in sampling, source population, regions or missing patterns."*

"In addition, differential recruitment strategies may have resulted in differential prevalence of disturbed sleep in the sample. These factors may have contributed to heterogeneity in the sleep estimates"

Minor comments:

2. Page 10 Line 250 ... "We additionally.... ": Based on the supplementary figure 1b, the authors see to have sought IPD for 44 studies and not 47 studies as mentioned in the text.

Response: We thank the reviewer for pointing out this error. We have now corrected it.

3. It is not clear what the message/interpretation of Figure 1 with respect to sleep efficiency?

Response: Figure 1 presents percentile curves of sleep duration and sleep efficiency across the lifespan. The changes in sleep efficiency across the lifespan are presented in the results, however, because recommended values for self-reported sleep efficiency do not exist, these values could not be classified as "acceptable" or "appropriate", as done for sleep duration. The percentile curves, however, could be useful in comparing individual's sleep efficiency with respect to the overall population of same age. In the limitation section the potential error that is inherent to the subjective measurement of sleep efficiency is discussed, see page 26.

Results page 18: *"SE decreases from mean $\pm$ SD= 97 $\pm$ 5% in childhood to 91 $\pm$ 8% in teenage years. This SE decline continues into adulthood, however 25% of >65-year-olds reported sleeping over 95% of their TIB."*

Discussion page 26: *"Moreover, absolute numbers should be interpreted with caution because age or reporter could influence sleep estimates (e.g. parents may underreport their children's sleep onset latency and wake time during the night, resulting in higher SE estimates). In addition, as SE is based on two self-reported measures, these variables might be particularly prone to error, and should be interpreted with caution."*

4. Page 26 Line 608: "Analyses of sources of heterogeneity indicated that age and sex partly account for the heterogeneity between the studies from the Netherlands" – I do not think sub-group analysis really answers that. Age could be possible but gender does not seem to be.

Response: We thank the reviewer for this comment. We, however, disagree that the subgroup analyses do not inform on the sources of heterogeneity. The changes in heterogeneity across the different age and sex subgroups (Supplemental Table 5 and 7) as compared to the overall unstratified analysis, give an indication that these variables play a substantial role in some strata. This is now made more explicit and discussed in the paper.

Results page 19: *"However, when the meta-analyses were stratified by sex, heterogeneity estimates decreased to values as low as 0% for TIB (women ages 26-40 years), 54% for TST (women 18-25 years) and 0% for SE (both men and women aged >65 years). For some age strata, however, sex and age stratification had minor effects on heterogeneity estimates, as I^2 remained high (up to 100%) (see forest plots in Supplemental Figure 4a-c)."*

Results page 20: *"When studies of adults were additionally stratified by sex, I^2 decreased to values as low as 48% for DIS in men aged 65+ years, 54% for DMS in women aged 26-40 years, and 0% for EMA in men 18-25 years. However, residual heterogeneity was substantial in most other strata (see Supplementary Table 7 and Supplementary Figure 5a-c)."*

Discussion page 25: *"Our study is the largest descriptive sleep study to date, however, pooling a large number of individual studies inevitably results in high heterogeneity, thus absolute estimates should be interpreted with caution."*

Discussion page 26: *"Analyses of sources of heterogeneity indicated that age and sex only partly account for the heterogeneity between the studies from the Netherlands, and that most remaining heterogeneity likely originates from study differences in sampling, source population, regions or missing patterns."*

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Kocevska et al. present the most detailed study of sleep characteristics to date. This is done by carefully analyzing previous large-scale studies. I find the manuscript very interesting and important for the field. The authors also provided detailed responses to comments from four previous reviewers. These responses sufficiently address these reviewer's concerns. Beyond this, I only have three suggestions for items which the authors could discuss further:

1) Much of the manuscript focuses on testing how sleep compares with current guidelines. There are certain cases where they find a sizeable deviation from these guidelines. Should the recommendations be revisited? How could their data impact further discussion on setting guidelines? I do think that such a discussion would help readers, and can be done in a way that also recognizes that the point of the study was not to set new guidelines but to provide more information.

Response: We thank the reviewer for this suggestion. We had already included some statements on the potential ways these guidelines could be flawed; however, they have also been useful in research over the past years. Hence, we were careful not to discard them completely.

Nevertheless, in the Discussion, we now try to convey the need to focus recommendations more in the direction of improving sleep quality, rather than duration, as this is a characteristic that is highly variable between individuals, and also under strong genetic control.

Discussion page 25:

"Our results suggest that: i) the population of the Netherlands reported sleeping within "acceptable" sleep duration range at all ages, but more than half of teenagers slept almost an hour less than recommendations; ii) actigraphic sleep duration and efficiency are consistently lower than self-reported estimates, which limits the applicability of current recommendations to objective sleep variables,"

Discussion page 30:

"This indicates that recommendations for appropriate sleep duration and quality should be sex-specific."

"However, current recommendations are applicable only to self-reported average sleep duration, and international differences point to the need for country specific recommendations for adequate sleep. Given that poor sleep (i.e. low sleep quality or insomnia symptoms) is more common than short sleep (i.e. TST below "acceptable" values) in Europe and in the US, recommendations for improving sleep might need to focus more on sleep quality."

Discussion page 30-31: *"We also show that the lowest prevalence of poor sleep in the general population occurs in those spending 7 to 8 hours in bed. This finding, together with the relatively high prevalence of poor sleep despite*

nearly appropriate sleep duration, warrants defining new targets for sleep hygiene advice. In other words, by recommending optimal sleep duration we are unlikely to accomplish better sleep at a population level."

2) The finding of TST being longer in women than men is an interesting one. Although not large, it does match the results of other studies for example from smartphone apps. Again, possible reasons for this or implications? Should this gender difference be considered in setting guidelines?

Response: We thank the reviewer for this interesting insight. We have now addressed it in the Discussion.

Discussion page 30: *"This indicates that recommendations for appropriate sleep duration and quality should be sex-specific."*

3) Changes in sleep time between different age groups occur because of changes in bedtime not waketime. Again, more discussion of this result could be helpful.

Response: We have now addressed this in the Discussion.

Discussion page 29: *"Importantly, our data also show that wake time is remarkably stable across the lifespan, thus any interventions targeting sleep duration, but also those targeting sleep quality, should primarily be aimed at adaptations of bed time."*

Final Decision Letter:

Dear Professor Tiemeier,

We are pleased to inform you that your Article "Sleep characteristics across the lifespan in 1.1 million persons from the Netherlands, UK and USA: a systematic review and meta-analysis", has now been accepted for publication in Nature Human Behaviour.

I apologize for the delay in the final stage of manuscript processing.

Before your manuscript is typeset, we will edit the text to ensure it is intelligible to our wide readership and conforms to house style. We look particularly carefully at the titles of all papers to ensure that they are relatively brief and understandable.

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We look forward to publishing your paper.

With best regards,
Jamie

Dr Jamie Horder
Senior Editor
Nature Human Behaviour

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