Response to the reviewer's comments

Reviewer 1

1) The authors have studied the sleep duration and the risk of diabetes across two generations. The following points are suggested to improve the manuscript: 2) Title: The title is misleading as the word generation indicates at least two generations. You can modify the same in young and older individuals or population etc.

Response

We agree with this comment. Then, we changed the title as follows.

"Age-dependent changes in the association between sleep duration and impaired glucose metabolism"

Additionally, we changed the word generations into population or subjects in the abstract or text.

3) Abstract: Same as above wrt generation. The first statement of the results should be modified. The short sleep duration is associated with the worsening of HbA1c and not vice versa. Please remove the adjectives (gentle J curve etc)

Response

We agree with the comment. Then, we changed the first statement of the results as follows.

from

"With deterioration of HbA1c, sleep duration became longer as age advanced, and this increase was greater in men than in women."

to

"As age advanced, sleep duration became longer and this increase in the 40s and 50s was two times greater in men than in women. This finding was accompanied by a deterioration in HbA1c levels."

The phrase "gentle J curve" was replaced with "non-linear relationship".

4) Introduction: Sleep duration tends to decrease with advancing age. Please modify your statement accordingly.

Response

As pointed out, overall sleep duration tends to decrease with advancing age. However, sleep duration can become longer individually. Therefore, we changed the sentence with a new reference of [21] as follows.

"In contrast, individual's sleep duration can become longer and its quality can be aggravated (e.g., more fragmented) as people become older[11,20], although it has been

shown that objectively measured sleep duration generally decreases with age[21]."

Reviewer 2

1) The title should be short and concise. According to recent studies that would favour future citations to the paper. What is really new in the paper? The sleep relation with diabetes? The studies in Japan?

Response

We agree with this comment. Then, we changed the title as follows.

"Age-dependent changes in the association between sleep duration and impaired glucose metabolism"

2) Abstract should be also quantitative as possible for rapid comparison with others studies, referring for instance to absolute values and avoiding sentences such as "and this increase was greate"..but how much? 1,2?, twofold? 200%? And also sentences such as "significantly positively associated"…hown much? 0.3? (30%)…once if the data it is not statistically significant no need to put it in the abs or in the paper. Also the main conclusion it is not clear..it is a suggestion or the results point out to this conclusion?

Response

We agree with this comment. Then, in the results of abstract and text, we deleted redundant and obscure expressions and described concrete numerical values that are highlighted with red, as much as possible.

3) The paper includes a very good number of recent references from the last 5 years (bout 30% of total references). However, in a certain way some references are lacking regarding for instance the effects of drugs related with sleep and the onset of diabetes. Some drugs used for sleeping and immunosupressors were described to induce diabetes. This association is relevant for the paper. This should be refereed and discussed. Also in the introduction it should be included why this paper is timely and relevant.

Response

We fully agree with this comment. Then, we added sentences and new references in the discussion section as follows.

"Finally, our study consisted of apparently healthy subjects who underwent an ordinary checkup. As people get older, they usually have more complications and chronic diseases, including cognitive impairment and mental disorders, such as depression. These etiologies often require some pharmacotherapies that predispose to disturbing homeostasis of sleep[41-43]. Prescription for insomnia increases as age advances, which also alters the

sleep circadian rhythm[44,45]. Additionally, chronic use of hypnotic might aggravate glucose metabolism, although a conflicting result has been reported[46]. Unfortunately, such pharmacotherapy and sleep medication were not investigated in this study."

Regarding explanation why this paper is timely and relevant, we added next phrases highlighted with red in the introduction section (page 5).

"Based on the findings mentioned above and the worldwide extension of the life span[22,23], we investigated whether the association between self-reported sleep duration …"

4) The figures could be globally improved, as possible, once WJD deserves high quality figures and with rigor to avoid lacking of interest for the data. Also the legends should be more completed information as possible to avoid looking in the text for information.

Response

In accordance with this comment, we added some information in the figure legends for the better understand, as follows.

"Figure legends

Figure 1. Sleep duration according to age groups and sex.

Each point and vertical bar represent the mean ± 1.96 SE. Sleep duration in men and women increased with increasing age (both $P < 0.0001$, ANOVA). Significant differences were observed in sleep duration between men and women in all age groups (all $P < 0.0001$, except for $P = 0.003$ in the 20s, t-test). The corresponding number of subjects is shown in the side of the bar.

Figure 2. HbA1c levels according to age groups divided by decades.

Each point and vertical bar represent the mean ± 1.96 SE. HbA1c levels in men and women increased with increasing age (both $P < 0.0001$, ANOVA). Significant differences were observed inHbA1c levels between men and women in all age groups (all $P < 0.0001$, t-test). The corresponding number of subjects is the same as that in Figure 1.

Figure 3. Relationship between HbA1c levels and sleep duration according to age and sex.

Each point and vertical bar represent the mean ± SE. P values for ANOVA were < 0.0001, 0.0001, 0.002, and 0.56 for young men, young women, older men, and older women, respectively. The corresponding number of subjects is shown in the side of the bar.

Figure 4. Relationship between HbA1c levels and sleep duration according to age groups divided by decades.
Each point and vertical bar represent the mean ± SE. Correlation coefficients and P values of Pearson's correlation were r = −0.03, P < 0.0001 for the 20s, r = −0.05, P < 0.0001 for the 30s, r = −0.01, P = 0.41 for the 40s, r = 0.01, P = 0.52 for the 50s, and r = −0.01, P = 0.32 for the 60–70s, respectively. The corresponding number of subjects is shown in the side of the bar.

Figure 5. Relationship between sleep duration and impaired glucose metabolism, and plausible underlying mechanisms.
AEBAS; abnormal eating behavior around sleep. "

5) The results section is not properly presented. The authors jump immediately do conclusion without describing the data. They do not refer to the absolute values and the observed decrease or increase is not quantified. This is important for rapid comparison with others studies…..in some parts of the results seems to be just a copy of the abstract.

Response

We agree with this comment. Then, we improved the results section. First of all, clinical characteristics of subjects are explained with describing the data. In addition, quantitative information was added as much as possible.

6) At a pedagogical point of view it would be worthy if the authors include a scheme figure proposing the major effects and the parameters affects by sleeping, reflecting, such as a mirror, the main message of the paper.

Response

We agree with this comment. Then, we made a new scheme, Figure 5, describing a summary of results and plausible underlying mechanisms.

Taken together, we added 16 new references along with revisions.