Author's response to reviews

Title: Relationship between daily isoflavone intake and sleep in Japanese adults: a cross-sectional study

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Author's response to reviews: see over
Hiromichi Kumagai, PhD  
Editor,  
*Nutrition Journal*  
November 10, 2015

Re: "Relationship between daily isoflavone intake and sleep in Japanese adults: a cross-sectional study" by Yufei Cui, Kaijun Niu, Cong Huang, Haruki Momma, Lei Guan, Yoritoshi Kobayashi, Hui Guo, Masahiko Chujo, Atsushi Otomo and Ryoichi Nagatomi.  
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Dear Dr. Hiromichi Kumagai:

I first would like to apologize that we sent you the older version of our manuscript and cover letter. I would appreciate if you could take the newest version of manuscript for further review.

Thank you very much for your considering the 2nd revised version of our manuscript. We are grateful to the referees and Dr. Hiromichi Kumagai for pointing out some constructive and very useful suggestions in our study. We have thoughtfully taken into account these comments. The response to referee 3, Masakazu Terauchi PhD. is given point by point in the list of change.

We hope that all these changes fulfill the requirements to make the manuscript acceptable for publication in *Nutrition Journal*.

Looking forward to hearing from you soon.

Yours sincerely,

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The following is a point-to-point response to the two reviewers' comments, and responses are in blue.

**Reviewer: Masakazu Terauchi PhD, MD.**

Comments to the Author

OVERALL COMMENTS
- This is a very interesting paper about the association between isoflavone intake and sleep hours in Japanese adults. The report being worth to be published in the journal, a critical question remains unaddressed.

MAIN COMMENTS

**Comments 1**
- As authors correctly pointed out, most of the studies of the effects of estrogen and isoflavones on sleep have been done in postmenopausal women (refs. 13, 14, 20, and 21). The effects of isoflavones as weak estrogen receptor agonists should be totally different among premenopausal women, women in enopausal transition, postmenopausal women, and men. Likewise, the effect of isoflavones on cognitive function was studied in older men and women (ref. 31), and that on IGF-1 was studied in women (ref. 32). The authors should further discuss the possible mechanisms of isoflavones being effective universally among the study population predominantly composed of relatively young men and fewer young (presumably premenopausal) women.

**Response 1**

As the reviewer suggested, we added another possible mechanism of isoflavone affecting on sleep in discussion. That is anti-oxidant effect of isoflavone. A previous study showed that isoflavone intake can decrease levels of oxidative stress in both men and women (Djuric et al. Cancer Lett. 2001). Furthermore, it have been shown that oxidative stress may be harmful to sleep quality, which could be improved by treatment of anti-oxidant (Singh et al. Indian J Chest Dis Allied Sci. 2009). Hence, we considered that isoflavone may affect sleep by the mediating role of anti-oxidant effect in general people.

Furthermore, effect of isoflavones on cognitive function was not only in older adults, but also in young men and women (File et al.
Psychopharmacology, 2001), suggesting cognitive function may also be a mechanism underlying the association between isoflavone and sleep status in general population. A new reference (ref. 32) reported positive relationship between isoflavones intakes and cognitive function among young men and women, was added into main text.

Page 15, line 299

“In addition, previous study has indicated that soy isoflavone supplementation decreases levels of oxidative stress in both men and women aged 22-56 years. Further, oxidative stress may be a risk factor of poor sleep quality because an interventional study has shown that anti-oxidant intake can improves the quality of sleep in sleep apnea syndrome patients. Hence, we considered that anti-oxidant effect of isoflavone may also be a possible mechanism underlying the association between isoflavone intakes and sleep status in present study.”

In addition, our study does not exclude the possibility that isoflavone intake would not be associated with sleep quality and duration in menopausal women who have higher level of estrogen. However, we could not examine the association of isoflavone intake with sleep status in menopausal women because of the insufficient sample size. Although statistical adjustment for gender in the multivariate analysis shows a general association of isoflavone intake and sleep duration and quality, further study is necessary to examine whether the weak estrogen mimetic action of isoflavone could modify or improve the sleep duration and quality in menopausal women. In line with our assumption, we inserted several lines for this point in the limitation in the discussion section.

Page 15, line 307

“First, our study does not exclude the possibility that isoflavone intake would not be associated with sleep quality and duration in menopausal women who have higher level of estrogen. However, we could not examine the association of isoflavone intake with sleep duration and quality in menopausal women because of the insufficient sample size. Although statistical adjustment for gender in the multivariate analysis shows a general association of isoflavone intake and sleep duration and quality,
further study is necessary to examine whether the weak estrogen mimetic action of isoflavone could modify or improve the sleep duration and quality in menopausal women.”