

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The relationship between hormone replacement therapy and spinal osteoarthritis : A nationwide health survey analysis of the elderly Korean population
AUTHORS	Park, Jung-Ho; Hong, Jae-Young; Han, Kyungdo; Han, Seung-Woo; Chun, Eun Mi

VERSION 1 – REVIEW

REVIEWER	Yi-Xiang Wang The Chinese University of Hong Kong
REVIEW RETURNED	27-Jul-2017

GENERAL COMMENTS	<p>This study uses a large scale national data base, and addresses an important hypothesis. The conclusion agrees with the currently available evidences. This paper can be published after revision.</p> <p>The writing-up of this paper requires substantial improvement. The authors are suggested to have a better literature review. Some useful references include (but not limited to) the following: Imada K , Matsui H , Tsuji H . Oophorectomy predisposes to degenerative spondylolisthesis . J Bone Joint Surg Br 1995; 77(1): 126 – 130. Gruber HE, Yamaguchi D, Ingram J, et al, Expression and localization of estrogen receptor-beta in annulus cells of the human intervertebral disc and the mitogenic effect of 17-beta-estradiol in vitro. BMC Musculoskelet Disord 2002; 3:4. Wáng YX, Wáng JQ, Káplár Z. Increased low back pain prevalence in females than in males after menopause age: evidences based on synthetic literature review. Quant Imaging Med Surg. 2016;6(2):199-206.</p> <p>Wang YX. Postmenopausal Chinese women show accelerated lumbar disc degeneration compared with Chinese men. J Orthop Transl 2015;3:205-11. Menopause as a potential cause for higher prevalence of low back pain in women than in age-matched men. Journal of Orthopaedic Translation 2017; 8:1-4 Baron YM, Brincat MP, Galea R, Calleja N. Intervertebral disc height in treated and untreated overweight post-menopausal women. Hum Reprod 2005;20:3566e70.</p> <p>Wáng YX*, Káplár Z, Deng M, Leung JC. Lumbar degenerative spondylolisthesis epidemiology: a systemic review with a focus on</p>
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	<p>gender-specific and age-specific prevalence. J Orthop Translat. 2017;11: 39-52</p> <p>Marty-Poumarat C, Ostertag A, Baudoin C, Marpeau M, de Vernejoul MC, Cohen-Solal M. Does hormone replacement therapy prevent lateral rotatory spondylolisthesis in postmenopausal women? Eur Spine J 2012;21(6):1127-34.</p> <p>The express of English also needs major improvement. Some sentences are difficult to understand or maybe incorrect. Such as:</p> <p>" -Study included a large cross-sectional population and utilized sophisticated statistical methods, which may enhance the significance of the result."</p> <p>- firstly, the statistical methods used in this study are relatively straightforward; secondly, it may be incorrect to manipulate statistical methods to artificially increase significance of the result. "Hormone replacement therapy was closely related to spine OA morbidity."</p> <p>This sentence may infer that this is positive relationship, i.e. HRT increases spine OA morbidity. But actually, the results from this study shows HRT was associated less spine OA incidence or severity.</p> <p>'The spine OA group exhibited a significantly lower prevalence of HRT'- this sentence's expression is likely incorrect, though others may be able to understand it.</p> <p>Others, such as:.</p> <p>Page 10/26: The positive effect `` women of the same age not receiving HRT. Moreover, patients receiving long-term HRT have a lower risk of knee and hip OA on plain radiographs compared to women who do not take HRT.</p> <p>Page 11/26: We hypothesized that HRT may have a positive effect on the development of radiographic spinal OA. <the word 'positive' may be confusing here></p> <p>And, pls use the exact p-value (such as p=0.002) instead of p<0.05</p>
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REVIEWER	Arima, Kazuhiko Nagasaki University Graduate School of Biomedical Sciences
REVIEW RETURNED	16-Aug-2017

GENERAL COMMENTS	<p>Comment to the Authors</p> <p>Title: The relationship between hormone replacement therapy and symptomatic spine osteoarthritis (bmjopen-2017-018063)</p> <p>Journal: BMJ Open</p> <p>Type: Research (STROBE Compliant, Case-Control design)</p> <p>Authors: Jung-Ho Park, et al Jae-Young Hong (Contact)</p> <p>The objective of the authors was to identify the effect of hormone replacement therapy (HRT) on symptomatic spine osteoarthritis (OA). They designed a nested case-control study on nationwide survey, with 4,265 post-menopausal women.</p>
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	<p>They clearly showed a significant lower prevalence of spine OA in HRT group than that in no HRT group.</p> <p>They concluded that the populations receiving HRT showed a significantly lower prevalence of spine OA, and the duration of HRT was significantly related to OA spine prevalence. The authors suggested that their results would be helpful to physicians treating OA.</p> <p>Over all, this manuscript was well written and included clearly described key findings. In my opinion, this study provides an important clue to understand the nature of spine OA in post-menopausal women. There is some criticism for this manuscript. I hope to help the authors to strengthen the manuscript.</p> <p>Major</p> <ol style="list-style-type: none"> 1. In abstract and others (P. 03, L. 01, 02, P. 11, L. 10, 17), the authors use a word "incidence." The authors should describe in method the follow-up period. In this manuscript, it seems to be prevalence. In the case that all incidences of events were identified, an analysis based on the units of person-year will enhance the significance of their results. 2. In title and others (throughout the manuscript), it was hard to understand the "symptomatic spine OA" "spine OA" "OA" "solitary radiographic spine OA" "Sx" "OA Sx." A unification of terminology will help readers to understand with ease. <p>Minor</p> <p>(P. 06, L. 16) the authors described, "pain radiographic examination". Is it "plain"? Please reconsider it.</p> <p>(P. 09, L. 03) how many participants were with OA, smoking, and HRT? There was not the numbers in total. Especially the rate of smokers seems to be very low. If so, why?</p> <p>(P. 10, L. 08)(P. 11, L. 06) a reference of Nr. 17 was doubled.</p> <p>(P. 10, L. 08) the authors described, "effect women". Please reconsider it.</p> <p>(P. 11, L. 08) the authors described, "The OA group also had a significantly lower rate of HRT." It might be rare to treat patients with OA, using OC. Please reconsider it.</p> <p>(P. 11, L. 10, L. 14) the authors described "positive." Is it "protective"? Please reconsider it.</p> <p>(Table 1, 2, and 3) there was no total numbers or crude (unadjusted for age) results.</p> <p>(Table 1) It was difficult in SE of categorical variable. Please reconsider it.</p> <p>(Table 3) there was OR of age in adjusted for age. It should be 1. Please reconsider the method on this analysis.</p> <p>I did review it according to the journal's request to ensure studies are scientifically credible and were conducted ethically and in accordance with appropriate reporting guidelines. I did not judge on the priority or the breadth of appeal.</p> <p>I highly recommend asking for these authors to delete the "p < 0.05" in a sentence including the word of "significantly." It is doubled.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment: This study uses a large scale national data base, and addresses an important hypothesis. The conclusion agrees with the currently available evidences. This paper can be published after revision.

Response: Thank you for your favorable comment.

Comment: The writing-up of this paper requires substantial improvement. The authors are suggested to have a better literature review. Some useful references include (but not limited to) the following: Imada K , Matsui H , Tsuji H . Oophorectomy predisposes to degenerative spondylolisthesis . J Bone Joint Surg Br 1995; 77(1): 126 – 130.

Gruber HE, Yamaguchi D, Ingram J, et al, Expression and localization of estrogen receptor-beta in annulus cells of the human intervertebral disc and the mitogenic effect of 17-beta-estradiol in vitro. BMC Musculoskelet Disord 2002; 3:4.

Wáng YX, Wáng JQ, Káplár Z. Increased low back pain prevalence in females than in males after menopause age: evidences based on synthetic literature review. Quant Imaging Med Surg. 2016;6(2):199-206.

Wang YX. Postmenopausal Chinese women show accelerated lumbar disc degeneration compared with Chinese men. J Orthop Transl 2015;3:205-11.

Menopause as a potential cause for higher prevalence of low back pain in women than in age-matched men. Journal of Orthopaedic Translation 2017; 8:1-4

Baron YM, Brincat MP, Galea R, Calleja N. Intervertebral disc height in treated and untreated overweight post-menopausal women. Hum Reprod 2005;20:3566e70.

Wáng YX*, Káplár Z, Deng M, Leung JC. Lumbar degenerative spondylolisthesis epidemiology: a systemic review with a focus on gender-specific and age-specific prevalence. J Orthop Translat. 2017;11: 39-52

Marty-Poumarat C, Ostertag A, Baudoin C, Marpeau M, de Vernejoul MC, Cohen-Solal M. Does hormone replacement therapy prevent lateral rotatory spondylolisthesis in postmenopausal women? Eur Spine J 2012;21(6):1127-34.

Response: Thank you for your comment. We added several references and modified the introduction and discussion with new sentences.

Comment: The express of English also needs major improvement. Some sentences are difficult to understand or maybe incorrect. Such as: " -Study included a large cross-sectional population and utilized sophisticated statistical methods, which may enhance the significance of the result."- firstly, the statistical methods used in this study are relatively straightforward; secondly, it may be incorrect to manipulate statistical methods to artificially increase significance of the result.

Response: We revised the sentences according to your comment. We totally modified the manuscript with professional English editor.

Comment: "Hormone replacement therapy was closely related to spine OA morbidity." This sentence may infer that this is positive relationship, i.e. HRT increases spine OA morbidity. But actually, the results from this study shows HRT was associated less spine OA incidence or severity.

Response: We agree with your opinion. We modified the sentence according to your comment.

Comment: 'The spine OA group exhibited a significantly lower prevalence of HRT'- this sentence's expression is likely incorrect, though others may be able to understand it. Others, such as:. Page

10/26: The positive effect `` women of the same age not receiving HRT. Moreover, patients receiving long-term HRT have a lower risk of knee and hip OA on plain radiographs compared to women who do not take HRT. Page 11/26: We hypothesized that HRT may have a positive effect on the development of radiographic spinal OA.

Response: We agree with your opinion. We modified the sentence according to your comment.

Comment: And, pls use the exact p-value (such as $p=0.002$) instead of $p<0.05$

Response: We agree with your opinion. We provided the exact P-value in the tables. We removed the $p<0.05$ in the manuscript.

Reviewer: 2

Comment: The objective of the authors was to identify the effect of hormone replacement therapy (HRT) on symptomatic spine osteoarthritis (OA). They designed a nested case-control study on nationwide survey, with 4,265 post-menopausal women. They clearly showed a significant lower prevalence of spine OA in HRT group than that in no HRT group. They concluded that the populations receiving HRT showed a significantly lower prevalence of spine OA, and the duration of HRT was significantly related to OA spine prevalence. The authors suggested that their results would be helpful to physicians treating OA. Over all, this manuscript was well written and included clearly described key findings. In my opinion, this study provides an important clue to understand the nature of spine OA in post-menopausal women.

Response: Thank you for your favorable comment.

Comment: There is some criticism for this manuscript. I hope to help the authors to strengthen the manuscript.

Response: Thank you for your favorable comment. We are ready to revise the manuscript according to your comments.

Comment: 1. In abstract and others (P. 03, L. 01, 02, P. 11, L. 10, 17), the authors use a word "incidence." The authors should describe in method the follow-up period. In this manuscript, it seems to be prevalence. In the case that all incidences of events were identified, an analysis based on the units of person-year will enhance the significance of their results.

Response: We agree with your opinion. We modified the sentences according to your comment. We changed the term "incidence" to "prevalence".

Comment: 2. In title and others (throughout the manuscript), it was hard to understand the "symptomatic spine OA" "spine OA" "OA" "solitary radiographic spine OA" "Sx" "OA Sx." A unification of terminology will help readers to understand with ease.

Response: We agree with your opinion. We modified the sentences according to your comment. We simply changed the "symptomatic spine OA" to "spine OA" throughout the manuscript, and rephrase it radiographic and symptomatic when it is needed.

Comment: (P. 06, L. 16) the authors described, "pain radiographic examination". Is it "plain"? Please reconsider it.

Response: It was our mistake. We changed the sentence according to your comment.

Comment: (P. 09, L. 03) how many participants were with OA, smoking, and HRT? There was not the numbers in total. Especially the rate of smokers seems to be very low. If so, why?

Response: We added the absolute number in the manuscript and tables. The reason for relatively small numbers of smoking population was too small portion of smokers in HRT group (elderly women seldom smoke in Korea). We added sentence regarding your concern in the discussion which shows the limitation of the study.

Comment: (P. 10, L. 08)(P. 11, L. 06) a reference of Nr. 17 was doubled.

Response: We modified the doubled reference according to your comment. We omitted the later one to condense the manuscript.

Comment: (P. 10, L. 08) the authors described, "effect women". Please reconsider it.

Response: We omit the sentence according to your comment to minimize the misunderstandings.

Comment: (P. 11, L. 08) the authors described, "The OA group also had a significantly lower rate of HRT." It might be rare to treat patients with OA, using OC. Please reconsider it.

Response: We agree with your opinion. We removed the sentence according to your comment.

Comment: (P. 11, L. 10, L. 14) the authors described "positive." Is it "protective"? Please reconsider it.

Response: We agree with your opinion. We changed the sentence according to your comment.

Comment: (Table 1, 2, and 3) there was no total numbers or crude (unadjusted for age) results.

Response: We added the total number and crude in the manuscript & tables. And, we condensed the tables to provide more precise result.

Comment: (Table 1) It was difficult in SE of categorical variable. Please reconsider it.

Response: We agree with your opinion. However, we prefer to use SE in the result according to our statistician's opinion. If it is needed, we can add another variables.

Comment: (Table 3) there was OR of age in adjusted for age. It should be 1. Please reconsider the method on this analysis.

Response: We agree with your opinion. We changed the table 2 according to your comment. Initially, we separately calculate the OR of age without age adjustment. However, degenerative arthritis is an aging process, so we don't need to provide the evident relationship between age and OA in the manuscript. To minimize the misunderstandings, we omit the age (5year) variable in table 2 and result section.

Comment: I did review it according to the journal's request to ensure studies are scientifically credible and were conducted ethically and in accordance with appropriate reporting guidelines. I did not judge on the priority or the breadth of appeal. I highly recommend asking for these authors to delete the "p < 0.05" in a sentence including the word of "significantly." It is doubled.

Response: Thank you for your comment. We changed the sentence according to your comment.

VERSION 2 – REVIEW

REVIEWER	Yi-Xiang Wang The Chinese University of Hong Kong, Hong Kong No Competing Interest
REVIEW RETURNED	19-Sep-2017

GENERAL COMMENTS	<p>I still have concerns with the English expression of this manuscript. For example, this sentence in abstract: <All participants reported symptoms and disabilities related to spinal OA> can be interpreted as every participant had symptoms and disabilities related to spinal OA. Results in abstract:</p> <p><Demographic factors, marital status, education, income, and HRT all correlated with a decrease in spinal OA morbidity. > This sentence is very unclear.</p> <p>Also, in the introduction part, the author stated that: We hypothesized that HRT might prevent the onset of degenerative spinal disease and therefore might contribute to the prevention of low back pain. However, this hypothesis has already been proposed: Wang YX, Menopause as a potential cause for higher prevalence of low back pain in women than in age-matched men. Journal of Orthopaedic Translation 2017; 8:1-4 The work of this manuscript is to confirm this hypothesis. Therefore, this paper at < Journal of Orthopaedic Translation 2017; 8:1-4 https://doi.org/10.1016/j.jot.2016.05.012 > should be cited.</p> <p>Pls give a more detailed description of KNHANES-V (2010–2012) study, particularly how the participants were sampled.</p> <p>Overall, I support the publication of this paper. but a more careful revision should be done to improve this manuscript.</p>
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REVIEWER	Arima, Kazuhiko Nagasaki University Graduate School of Biomedical Sciences No Competing Interest
REVIEW RETURNED	16-Sep-2017

GENERAL COMMENTS	There are excellent improvements in the revised manuscript. I believe that their solid results and huge number of efforts for study
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	<p>might help the broad readership of BMJ Open to understand the nature of spinal osteoarthritis.</p> <p>In abstract, I highly recommend asking for these authors to delete the "p < 0.05" in a sentence including the word of "significantly." It is doubled. Alternatively in this manuscript, the exact p-value will be welcomed instead of p < 0.05.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Comment: There are excellent improvements in the revised manuscript. I believe that their solid results and huge number of efforts for study might help the broad readership of BMJ Open to understand the nature of spinal osteoarthritis.

Response: Thank you for your favorable comment.

Comment: In abstract, I highly recommend asking for these authors to delete the "p < 0.05" in a sentence including the word of "significantly." It is doubled. Alternatively in this manuscript, the exact p-value will be welcomed instead of p < 0.05.

Response: We agree with your opinion. We modified the abstract according to your comment.

VERSION 3 – REVIEW

REVIEWER	Yi-Xiang Wang The Chinese University of Hong Kong No Competing Interest
REVIEW RETURNED	13-Oct-2017
GENERAL COMMENTS	The authors have revised the article satisfactorily. There are a still a few minor typo etc, which can be improved during the copy-editing process of publication.