PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The epidemiological profile of hysterectomy in rural Chinese women: a population-based study
AUTHORS	Liu, Fangfang; Pan, Yaqi; Liang, Yongmei; Zhang, Chaoting; Deng, Qiuju; Li, Xiang; Liu, Mengfei; He, Zhonghu; Liu, Ying; Li, Jingjing; Ning, Tao; Guo, Chuanhai; Xu, Ruiping; Zhang, Lixin; Cai, Hong; Ke, Yang

VERSION 1 - REVIEW

REVIEWER	Xiaonan Xue Albert Einstein College of Medicine USA
REVIEW RETURNED	12-Dec-2016

GENERAL COMMENTS	This paper describes the age-specific prevalence of hysterectomy and its risk factors using data from an ongoing esophageal cancer cohort study conducted in rural area at Anyang, China. While the paper is descriptive in nature and is clearly written, I have some concerns with the timing of the outcome and exposure assessments. Specifically, it is not clear to me when the gynecologic tests were performed in order to determine the hysterectomy status of the participants, especially relative to the timing of the face to face interview. Further, for those who reported hysterectomy, was the time of the procedure recorded? If not, then some women could have the procedure done twenty years ago and some women could just have it? The paper examined the impact of age, BMI, smoking status and other time-dependent variables on the risk of having hysterectomy; however, as I explained above, if the age and BMI and other variables were measured after hysterectomy, then it is questionable to refer these variables as risk factors or predictors for hysterectomy and the relevance of this association needs to be justified. Also the terminology of age-specific prevalence may not be appropriate. Once a woman had hysterectomy, her hysterectomy status is fixed. Therefore, a larger portion of women at an older age group by default will have hysterectomy than women at a younger age group. It is probably more accurate to refer the rate of hysterectomy at each age group as age-specific cumulative incidence rate.

REVIEWER	Sapna Desai, PhD Independent researcher, India
REVIEW RETURNED	10-Jan-2017

GENERAL COMMENTS	This is an important contribution to the small yet growing body of

	literature on the epidemiology of hysterectomy in low-income settings. I have several comments on the methods and reporting to help strengthen the paper: Methods: (i) The authors need to provide more detail on the study design which have bearing on potential selection bias. For example: a) permanent residency needs to be defined more clearly with more discussion of the profile of women not eligible b) previous cancer diagnosis: if women were diagnosed with ovarian/uterine cancer would they have been ineligible? If yes, this could be a considerable contributor to selection bias and hence likely under-reporting of hysterectomy. (ii) It would be helpful to see more description of statistical methods and choice of variables. For example, forward logistic regression was used in building the final model (if it was). p values should be reported in the table in the multivariate analysis. For variables with multiple levels, how were overall p values computed? Since this drew from a larger study (which was not described adequately here and should be), was there an underlying sampling design accounted for in the estimates and standard error, ie using svy commands? Also, the prevalence estimate requires confidence intervals. Lastly, use of the term determinants is not suggested, given the cross-sectional design as well as the nature of the study. Predictors would be better. Discussion: iii. The background and parts of the study discussion could be strengthened considerably in a few ways: (a) more discussion of the public health importance of estimating hysterectomy prevalence, particularly longterm side effects (b) more consideration of the literature in developed country settings (there have been more estimates in India, Jordan and El Salvador, as well as Taiwan and Singapore that would be relevant). (c) deeper consideration of the risk factors in their local context with reference to relevant literature, as these have been known to vary quite widely by setting. (d) Similarly, the discussion on reasons for 'low' prevalence is weak at present and not grounded in either relevant comparisons or local context. Other relevant issues could be health systems factors (are gynaec services available, public/private sector access, affordability etc). In the authors' view, is the prevalence a reflection of relatively lower medical necessity or other factors? The authors refer to womanhood and the uterus, but this discussion is quite weak at present. The reference to one study in India regarding reasons for low prevalence may not be appropriate either. More discussion, as well as references to relevant literature, is warranted in the discussion of prevalence and in comparisons to other settings. (iv) Methodological limitations of the study deserve further discussion, particularly potential biases in the prevalence estimate due to the study recruitment method and other factors. Also, some discussion on age-standardisation to compare prevalence estimates across settings (ideally an age-standardised estimate could be computed). (v) Two minor points regarding age: The mean age at hysterectomy would be helpful to know and the age table should be presented as

	a histogram.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Q1. When the gynecologic tests were performed in order to determine the hysterectomy status of the participants, especially relative to the timing of the face to face interview.

Re: The gynecologic tests and face-to-face interviews were carried out on the same day. We have added the following statements about the timing of gynecologic tests and interviews into the Methods: "Data on…were collected through face-to-face interviews before gynecologic tests on the same day".

Q2. Further, for those who reported hysterectomy, was the time of the procedure recorded? If not, then some women could have the procedure done twenty years ago and some women could just have it?

Re: The time of hysterectomy was recorded. We have added the following statements into the Methods: "For cases reporting a hysterectomy, the time of the procedure along with the information on the indications for and surgical techniques used to perform hysterectomy were also recorded". Additionally, we have added the description of age at time of hysterectomy in the Results: "A total of 75 (68.18%, 75/110) cases provided further information on hysterectomy, with mean age at time of hysterectomy of 44 years (standard deviation: 7.6 years; range: 27-66 years) (Supplementary Figure S1)."

Q3. The paper examined the impact of age, BMI, smoking status and other time-dependent variables on the risk of having hysterectomy; however, as I explained above, if the age and BMI and other variables were measured after hysterectomy, then it is questionable to refer these variables as risk factors or predictors for hysterectomy and the relevance of this association needs to be justified.

Re: Thank you for the reviewer's constructive advice. We agree with the reviewer that it is one limitation of this study, like other similar studies (Koepsell et al., Am J Public Health 1980;70:40-7; Desai et al., Reproductive health matters 2011;19:42-51), to collect data on age, BMI and other variables after hysterectomy, if performed, thus the impact of these factors on the risk of having hysterectomy may not be accurate. Fortunately, only few variables seem to be time-dependent. Age at hysterectomy was recorded and the relevant description has been added in the Methods and Results. Since mean age at time of hysterectomy was 44 years (standard deviation: 7.6 years; range: 27-66 years), information of most variables included in this study such as marital status, education level, age at menarche, age at first birth, parity, history of fetal loss, use of intrauterine contraceptive devices, and history of cervicitis is likely to remain unchanged before or after a hysterectomy. The only concern is about BMI status, which may change after having a hysterectomy. We have added the following statements into the Discussion: "In terms of predictors for hysterectomy, it should be noted that data on sociodemographic factors and behavioral characteristics as well as information about BMI status were only gathered at the time of interview, hence whether there was any change in these questionnaire data before or after a hysterectomy, if performed, is unknown. The following discussion was based on the assumption that the information of aforementioned variables remained unchanged before the interview…Again, however, whether BMI status varied with undergoing hysterectomy is not determinable from the data at hand".

Q4. The terminology of age-specific prevalence may not be appropriate. Once a woman had hysterectomy, her hysterectomy status is fixed. Therefore, a larger portion of women at an older age group by default will have hysterectomy than women at a younger age group. It is probably more accurate to refer the rate of hysterectomy at each age group as age-specific cumulative incidence

rate.

Re: Use of the terminology of age-specific prevalence has been avoided. Since not all cases provided the time of hysterectomy, estimation of age-specific cumulative incidence rate may not be accurate. We have added the description of age at time of hysterectomy into the Results: “A total of 75 (68.18%, 75/110) cases provided further information on hysterectomy, with mean age at time of hysterectomy of 44 years (standard deviation: 7.6 years; range: 27-66 years) (Supplementary Figure S1).”

Reviewer 2:
Q1. For Methods, the authors need to provide more detail on the study design which has bearing on potential selection bias. For example: a) permanent residency needs to be defined more clearly with more discussion of the profile of women not eligible; b) previous cancer diagnosis: if women were diagnosed with ovarian/uterine cancer would they have been ineligible? If yes, this could be a considerable contributor to selection bias and hence likely under-reporting of hysterectomy.

Re: Thanks for the reviewer’s rigorous thinking. More details on the study design and eligibility criteria have been added in the Methods as follows: “The current investigation utilized a subset including 6 of the 9 target villages which were cluster-sampled in the parent cohort study conducted from 2009 to 2011. Eligibility criteria for subjects enrolled in this study were as follows: 1) female permanent residency in the target villages (registered in the China’s hukou system); 2) aged 25-68 69 years; 3) no prior diagnosis of cancer (9 residents were excluded before enrollment because of self-reported history of cancer including 1 with cervical cancer), mental disorder, or cardiovascular disease; and 4) no past history of HBV, HCV, or HIV infection.”
We agree that exclusion of residents with ovarian/uterine cancer may lead to selection bias. Fortunately, according to our records, this bias would be small. A total of 9 residents were excluded before enrollment because of self-reported history of cancer: 3 esophageal cancer, 2 breast cancer, 1 cervical cancer, 1 cardiac cancer, 1 skin cancer, and 1 leukemia (Some residents did not report their history of cancer before enrollment but reported it during gynecologic tests after enrollment. These participants were included as eligible subjects in this study). Since only one individual with a prior history of cervical cancer was excluded, the selection bias would be small and the subsequent under-reporting of hysterectomy can be estimable. The following sentence has been added in the Discussion: “the possibility of a selection bias (e.g. bias introduced by exclusion of individuals with a prior history of cervical cancer) and response bias of participants may reduce the generalizability of our findings to a wider population”.

Q2. It would be helpful to see more description of statistical methods and choice of variables. For example, forward logistic regression was used in building the final model (if it was). p values should be reported in the table in the multivariate analysis. For variables with multiple levels, how were overall p values computed? Since this drew from a larger study (which was not described adequately here and should be), was there an underlying sampling design accounted for in the estimates and standard error, ie using svy commands? Also, the prevalence estimate requires confidence intervals.

Re: More description of statistical methods and choice of variables has been added in the Methods as follows: “Prevalence estimates along with 95% confidence intervals (CI) were estimated using a null linear regression model implemented with the Generalized Estimating Equation (GEE) with a robust sandwich estimator of covariance to adjust for intracluster correlation (Zeger et al., Biometrics 1986; 42:121-30)...Potential risk factors that were statistically significant in univariate GEE regression analyses were entered in the final multivariate GEE regression models…Tests for linear trends were performed by treating ordered categorical variables as continuous variables in the GEE regression analyses”.
Additionally, P values have been added in the table in the multivariate analysis. For variables with

multiple levels, P trends were calculated by treating ordered categorical variables as continuous variables in the GEE regression analyses. 95% confidence intervals for the prevalence have been added in the Results and Figure 1.

Q3. Use of the term determinants is not suggested, given the cross-sectional design as well as the nature of the study. Predictors would be better.

Re: The term of determinants has been replaced with predictors.

Q4. More discussion of the public health importance of estimating hysterectomy prevalence, particularly longterm side effects.

Re: More discussion of long-term side effects of hysterectomy has been added in the Discussion as follows: “Approximately one quarter of hysterectomies were performed in women younger than 40 years of age in this study. Evidence on the long-term side effects of hysterectomy suggests that hysterectomies, especially those performed at young age, are associated with earlier onset of menopause and higher risk of cardiovascular disease, urinary incontinence and problems with sexual function (Hunter et al., BJOG : an international journal of obstetrics and gynaecology 2012;119:40-50; Hoga et al., Health Care Women Int. 2012;33:799-813; Farquhar et al., BJOG : an international journal of obstetrics and gynaecology 2005;112:956-62). Research is required across China to monitor trends and track long-term health effects of hysterectomy”.

Q5. More consideration of the literature in developed country settings (there have been more estimates in India, Jordan and El Salvador, as well as Taiwan and Singapore that would be relevant).

Re: More description of the literature in developed and developing country settings on prevalence of hysterectomy has been added in the Discussion as follows: “The overall prevalence of hysterectomy (3.3%) in our study was considerably lower than previous findings from studies conducted in developed countries such as the United States (26.2%), Ireland (22.2%), and Australia (26.2%, 22.2%, and 22.0%, respectively) (Spilsbury et al., BJOG : an international journal of obstetrics and gynaecology 2006;113:804-9; Wilcox et al., Obstet Gynecol 1994;83:549-55; McPherson et al., 1981;15:273-88; van Keep et al., Maturitas 1983;5:69-75), but closer to that identified in Taiwan (8.8%) and Singapore (7.5%) (Hsieh et al., Taiwan J Obstet Gynecol 2008;47:197-202; Lam et al., Ophthalmic epidemiology 2014;21:92-8). Data on hysterectomy is limited in developing settings. Our estimated prevalence was in the lower range reported by community-based studies from low- and middle-income countries such as India, El Salvador and Jordan (1.7%-9.8%) (Barghouti et al., Health Care Women Int. 2013;34:1015-23; Kaur et al., Climacteric : the journal of the International Menopause Society 2004;7:175-80; Shakhatreh et al., Saudi Med J 2005;26:830-5; Patel et al., BJOG : an international journal of obstetrics and gynaecology 2006;113:453-63; Ozel et al., Int Urogynecol J Pelvic Floor Dysfunct 2007;18:1065-9; Singh et al., Indian journal of community medicine : official publication of Indian Association of Preventive & Social Medicine 2008;33:196-7; Bhasin et al., The Indian journal of surgery 2011;73:131-5; Desai et al., Reproductive health matters 2011;19:42-51; Sarna et al., Global journal of health science 2013;5:139-49.), similar to percentage reported among women textile workers in Shanghai, China (3.9%) (Wong et al., Int Arch Occup Environ Health. 2006;79:251-8)”.

Q6. Deeper consideration of the risk factors in their local context with reference to relevant literature, as these have been known to vary quite widely by setting.

Re: More discussion of the risk factors in the local context with reference to relevant literatures has been added in the Discussion as follows: “In this study, prior pregnancy loss was associated with greater odds of hysterectomy; this finding is consistent with previous reports (Dharmalingam et al.,

Am J Public Health 2000;90:1455-8; Zhang et al., Maturitas 2005;52:328-36; Brett et al., Journal of women's health / the official publication of the Society for the Advancement of Women's Health Research 1997;6:309-16). Induced abortions have been commonly used in China since the 1970s as part of the national family planning programme. According to surveys conducted in China, approximately 50% of women had prior abortions, primarily aiming to limit family size (Sanderson et al., Int J Cancer 2001;92:899-905; Ye et al., Br J Cancer 2002;87:977-81)…".

Q7. The discussion on reasons for 'low' prevalence is weak at present and not grounded in either relevant comparisons or local context. Other relevant issues could be health systems factors (are gynaec services available, public/private sector access, affordability etc). In the authors' view, is the prevalence a reflection of relatively lower medical necessity or other factors? The authors refer to womanhood and the uterus, but this discussion is quite weak at present. The reference to one study in India regarding reasons for low prevalence may not be appropriate either. More discussion, as well as references to relevant literature, is warranted in the discussion of prevalence and in comparisons to other settings.

Re: More discussion on reasons for 'low' prevalence has been added in the Discussion as follows: "The low hysterectomy prevalence in this study population may be due to various reasons including limited availability of gynecology services, poor access to public/private sectors, and fear of surgical operations. Additionally, low affordability of medical care can be another explanation for the low prevalence. Based on data of China's National Health Survey in 2003, more than one-third of those who did not seek medical care while sick and over two-thirds of those who refused hospitalization after professional referral reported 'excessive cost' as the major factor influencing their decisions (Liu et al., ZEF- Discussion Papers on Development Policy No 155, Center for Development Research, Bonn. 2011)".

Q8. Methodological limitations of the study deserve further discussion, particularly potential biases in the prevalence estimate due to the study recruitment method and other factors. Also, some discussion on age-standardisation to compare prevalence estimates across settings (ideally an age-standardised estimate could be computed).

Re: We agree with the reviewer that the study recruitment method and some other factors may lead to bias in estimation of prevalence. This limitation has been added in the Discussion as follows: "First, the possibility of a selection bias (e.g. bias introduced by exclusion of individuals with a prior history of cervical cancer) and response bias of participants may reduce the generalizability of our findings to a wider population".
In terms of age-standardized prevalence of hysterectomy, we have added the following statements into Methods: "The China 2010 Population Census data and the World Health Organization world standard population data were used for calculating the adjusted prevalence of prior hysterectomy (Ahmad et al., World Health Organization 2001)". We have also added the following statements into Results: "Adjusted estimates of prevalence standardized by the age structure of the female population of China's 2010 Census and by the age distribution of the World Health Organization world standard population of 2001 were 3.21% and 3.03% respectively".
More description of the comparison of prevalence estimates across settings has been added in the Discussion as stated in Q5.

Q9. Two minor points regarding age: The mean age at hysterectomy would be helpful to know and the age table should be presented as a histogram.

Re: Mean age at hysterectomy has been provided and added into Results. The age table has been presented as a histogram (Please refer to Supplementary Figure S1).

VERSION 2 – REVIEW

REVIEWER	Sapna Desai, PhD Independent researcher, India
REVIEW RETURNED	27-Mar-2017

GENERAL COMMENTS	This is an important contribution to the literature on hysterectomy in Asia and low-income settings. In response to earlier comments, the authors have included important additional information about the methods, limitations of the design and implications for women's health. I have a few, mostly minor, comments: (i) In the key points, rather than (or in addition to) response bias, selection bias should be noted as an issue re generalizability. (ii) I am not sure re word limits - but a sentence or two on the setting (in the intro or methods) will be very helpful. Income, health indicators, health system etc. (iii) What is the hukou system - can a note be added? (iv) The association between prior fetal loss and hysterectomy is an interesting and important one that may have both biological and attitudinal links. Perhaps the authors can mention the need for more qualitative research, from both women and physicians' perspectives, on these issues. (v) Minor point and probably best for editorial - but one decimal point throughout is probably sufficient and easier to read. (vi) The discussion has improved considerably. Structurally, it would be helpful to have small headings as it is quite dense in terms of information. Also, please consider the sequence to improve readability and in reference to your objectives -- for example, should indications/surgical routes for hysterectomy be moved up, and predictors later, followed by the discussion on future research?

VERSION 2 – AUTHOR RESPONSE

Reviewer 2:
Q1. In the key points, rather than (or in addition to) response bias, selection bias should be noted as an issue re generalizability.

Re: The limitation of selection bias has been noted in the Discussion as follows: “First, the possibility of a selection bias (e.g. bias introduced by exclusion of individuals with a prior history of cervical cancer) may reduce the generalizability of our findings to a wider population. Second, due to the response bias of participants, there is no assurance that the epidemiological profile of hysterectomy observed here would hold true for the region as a whole…”.

Q2. I am not sure re word limits - but a sentence or two on the setting (in the intro or methods) will be very helpful. Income, health indicators, health system etc.

Re: The description of the setting has been added in the Methods as follows: “Anyang is an agricultural region of low-income with a per capita gross domestic product (GDP) of US$3,672 (2010).

Like other rural areas of China, the New Rural Cooperative Medical Scheme (NRCMS, a government-run voluntary insurance programme), initiated in 2003, is a major health insurance programme in rural Anyang. In 2013, the per capita premium was $57.8, and NRCMS accounted for 99% of all rural residents in China (Chinese Ministry of Health and Family Planning: http://www.nhfpc.gov.cn/jws/hzyl/list_3.shtml. 2013)".

Q3. What is the hukou system - can a note be added?

Re: A note of hukou system has been added in the Methods as follows: "female permanent residency in the target villages (registered in the China's unique household registration (Hukou) system)".

Q4. The association between prior fetal loss and hysterectomy is an interesting and important one that may have both biological and attitudinal links. Perhaps the authors can mention the need for more qualitative research, from both women and physicians' perspectives, on these issues.

Re: The following sentence has been added in the Discussion: "…More qualitative research is needed regarding the biological and attitudinal links between prior fetal loss and hysterectomy, from both women's and physicians' perspectives…"

Q5. Minor point and probably best for editorial - but one decimal point throughout is probably sufficient and easier to read.

Re: According to the editorial note "we are happy for the results to be kept as it is to two decimal places, rather than one", no change has been made for decimal places.

Q6. The discussion has improved considerably. Structurally, it would be helpful to have small headings as it is quite dense in terms of information. Also, please consider the sequence to improve readability and in reference to your objectives -- for example, should indications/surgical routes for hysterectomy be moved up, and predictors later, followed by the discussion on future research?

Re: We have rearranged the parts of discussion according to the reviewer's suggestions. Specially, contents about indications/surgical routes for hysterectomy have been moved before the contents about the predictors of hysterectomy. For small headings of Discussion, since most papers published in BMJ Open do not have structural subtitles for Discussion, we have not added small headings in Discussion. However, in order to improve readability, some guiding phrases have been added in the topic sentences of some paragraphs as follows: "For indications and surgical types for hysterectomy,…In terms of predictors for hysterectomy,…This study has some strengths and limitations…".

VERSION 3 – REVIEW

REVIEWER	Sapna Desai, PhD Independent researcher, India
REVIEW RETURNED	07-May-2017

GENERAL COMMENTS	This revised version is clear and well-presented. It is an important contribution to our understanding of hysterectomy in a range of settings.