Hysterectomy and Risk of Cardiovascular Disease: A Meta-analysis

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Abstract

Background: The association of hysterectomy with risk of cardiovascular disease(CVD) remains unclear. Objective: To evaluate the relationship between hysterectomy and the risk of CVD. Search Strategy: Five databases and reference lists of relevant studies were systematically searched up to January 2020. Selection Criteria: Observational studies evaluating the relationship between hysterectomy and risk of CVD or its subordinate diseases and non-hysterectomy controls were retained. Data Collection and Analysis: Pooled relative risks (RRs) and 95% CI were calculated by random effects model. Subgroup analyses and meta-regressions were performed to explore potential sources of heterogeneity. Small-study effects were estimated by Egger's test and funnel plot. Main Results: Fourteen articles were included in our meta-analysis. The pooled RR (95% CI) of ischemic heart disease risk for hysterectomy versus non-hysterectomy was 1.20 (95% CI: 1.08-1.35). In association between ischemic heart disease and hysterectomy with ovarian preservation or hysterectomy with oophorectomy, significant positive associations were observed. A significant association was also found with having hysterectomy before 50y (1.19; 95% CI:1.01-1.41), but not with after 50y (1.16; 95% CI: 0.87-1.54). Hysterectomy might increase the risk of hypertension and unclassified CVD, but have no influence on other subordinate diseases of CVD. Conclusions: hysterectomy, whether preserving ovaries or not, might increase the risk of ischemic heart disease and hypertension, not of stroke. Hysterectomy might increase the risk of ischemic heart disease and stroke in women who had surgery below 50y. Keywords: hysterectomy, cardiovascular disease, hysterectomy with ovarian preservation, hysterectomy with oophorectomy, age at operation, meta-analysis.

Tweetable Abstract

Hysterectomy, whether keeping ovaries or not, might increase the risk of ischemic heart disease and hypertension, not of stroke.

1 Introduction

Hysterectomy is a common surgery in women especially for benign gynecological diseases owing to its low perioperative morbidity and definite therapeutic effect.[1, 2] Although in recent years, endometrial ablation has become mature gradually, it cannot completely replace hysterectomy because the re-operation rates after endometrial ablation including repeat ablation and hysterectomy increase progressively over time.[2] Studies have shown that hysterectomy is associated with increased risks of many diseases, such as bipolar disorder[3], fallopian tube prolapse[4], osteoporosis[5], dementia[6] and colorectal cancer[7]. In addition, the association between hysterectomy and the risk of cardiovascular disease (CVD) was found.[8-16]

In the 19th century, the incidence of coronary artery disease (CAD) was found higher in male than female.[17-19] Researchers later confirmed that male predominance depended on age[20] and it disappeared in people over 60. Meanwhile, it was found that the serum cholesterol of women over 50 years old was significantly higher than that of young women.[21, 22] It was speculated that this phenomenon was due to the ovarian involution after menopause. Therefore, many observational studies assessing the association between oophorectomy and CAD were conducted, regardless of the influence of hysterectomy.[23] In the process of exploring this problem, negative effects of hysterectomy on CAD and other cardiovascular diseases were recognized.[17, 23]

Although a lot of researches were conducted, the epidemiological evidence of the relationship between hysterectomy and CVD is controversial.[10-14, 16, 24-27] Since hysterectomy leads to ovarian failure by interfering with blood and nerve supply of the ovaries, some studies showed hysterectomy would increase the risk of CVD.[10-14, 16, 28-30] However, Some researchers found hysterectomy was not associated with risk of CVD.[24-27]They considered that the increased CVD risk may because of the more adverse initial risk of CVD rather the hysterectomy itself.[24-26, 31] Therefore, we conducted a meta-analysis to assess: (1) the relation between unclassified hysterectomy and risk of CVD; (2) the relationship between hysterectomy with ovarian preservation and risk of CVD; (3) the association between hysterectomy with oophorectomy and risk of CVD; (4) whether the age of hysterectomy will influence CVD risk.

2 Methods

2.1 Data sources

This study was conducted by MOOSE guidelines[32]. A search of the literature up to January 2020 was performed from the databases of PubMed, Web of Science, Wan fang, VIP (Chinese scientific and technical journal database) and CNKI (National Knowledge Infrastructure of China). The following search terms were used:exposure ("hysterectomy" or "surgical removal of the uterus") and outcomes ("heart disease" or "CVD" or "cardiovascular disease" or "CAD" or "CHD" or "coronary artery disease" or "coronary heart disease" or "ischemic heart disease" or "hypertension" or "high blood pressure" or "stroke" or "arrhythmias" or "myocardial infarction" or "angina pectoris" or "heart failure"). The language was restricted to English and Chinese. Furthermore, relevant studies which were not captured by our database searches but listed as the bibliographies of selected articles were also included.

2.2 Study selection

All included studies were reviewed independently by two investigators (Z.W. and X.L.), and the results were reviewed by the third investigator (D.Z.). The inclusion criteria were restricted to (1) observational studies (cohort studies, case-control studies and cross-sectional studies); (2) the exposure of interest was hysterectomy; (3) the outcome of interest was CVD or its subordinate diseases; (4) hazard ratio (*HR*) or odds ratio (*OR*) or risk ratio (*RR*) and 95% confidence interval (*95% CI*) were available; (5) the controls were women without hysterectomy; (6) the most recent and complete article was adopted when data were duplicated in more than once for the same outcome.

2.3 Data extraction

Information was collected for each study including the following aspects: (1) name of the first author; (2) publication year; (3) study type; (4) continent where the study was conducted; (5) mean age or range; (6) outcome of the diseases; (7) ovaries status (hysterectomy with ovarian preservation; hysterectomy with unilateral oophorectomy; hysterectomy with bilateral oophorectomy; hysterectomy with oophorectomy); (8) age at operation; (9) *OR* , *RR* or*HR* with *95% CI* including accompanying oophorectomy or not and age at operation; (10) case number and sample size; (11) adjusted covariates. If more than one *RRs* provided, we extracted *RRs (95% CI)* which controlled the influential confounding factors to the greatest extent. Two investigators (Z.W. and X.L.) independently extracted data and any disagreements were resolved by discussing with the third investigator (D.Z.).

2.4 Data synthesis

We chose the ischemic heart disease as the main disease to analysis. The studies included were summarized according to their *RRs* with corresponding *95% CI* . The study-specific *log RRs* were weighted by the inverse of their variance, and the weighted values were used to assess the association between hysterectomy and risk of CVD. Furthermore, pooling was also performed for studies on different ovaries status (hysterectomy with oophorectomy or hysterectomy with ovarian preservation) and studies on age at hysterectomy (divided by 50 years old). In our analysis, hysterectomy with unilateral oophorectomy was classified as the category of hysterectomy with ovarian preservation, and hysterectomy with bilateral oophorectomy was classified as hysterectomy with oophorectomy. Overall *RRs* with *95% CI* in each study, instead of stratum-specific values (eg, separate estimates for hysterectomy with oophorectomy and hysterectomy with ovarian preservation), were used to assess total pooled *RR* of this meta-analysis. If an overall value was not presented in the article, the stratum-specific values were used following the principle that the populations in the different strata did not overlap.

Assessment for among-study heterogeneity was performed by calculatingI^2 which represents no, low, moderate and high heterogeneity when its values are 0, 25, 50 and 75% respectively.[33] The fixed-effect model was used if moderate or lower heterogeneity (I^2 [?]50%) was found. If I^2 >50%, the random-effect model was adopted. Pre-specified characteristics including publication year, continent and study design for exploring potential sources of heterogeneity were used in meta-regressions and subgroup analyses.[34] The sensitivity analysis which useI^2 >50% as the criteria was applied to evaluate the excluded studies that have substantial impact on between-study heterogeneity.[35] We also assessed the relationship between hysterectomy with or without oophorectomy and CVD, age at operation and CVD. The influence analysis was performed with one study removed at a time to assess whether the results could have been affected markedly by a single study.[36] The small-study effects were detected by Egger test[37] and funnel plot. All statistical analyses were carried out with STATA version 15.0 (Stata Corporation, College Station, TX, USA). All reported 2-tailed P values were considered statistically significant when P[?]0.05.

3 Results

3.1 Literature search and study characteristics

A total of 6706 articles were identified by search strategy. Seven additional articles were found in reference lists of retrieved studies. After removing the duplications and uncorrelated articles which were checked by screening titles and abstracts, 264 articles were included. We excluded 250 articles because: reviews (n=11); full texts were not available (n=30); the association of interest was not evaluated (n=71); *OR* , *RR* or *HR* and corresponding *95% CI* were not available (n=138). Ultimately, 14 articles[10-16, 24-27, 31, 38, 39] which fulfilled the inclusion criteria were included in the meta-analysis (Figure 1).

Of the 17 studies about ischemic heart disease, there are 9 cohort studies, 3 cross-sectional studies, and 5 case-control studies. Twelve studies investigated the relationship between hysterectomy with ovarian preservation and ischemic heart disease, 4 studies researched the relationship between hysterectomy with oophorectomy and ischemic heart disease. The relationships between surgery before 50 years old or surgery after 50 years old and risk of ischemic heart disease were investigated in 8 studies and 6 studies respectively.

Furthermore, 6 studies explored the relationship between hysterectomy and CVD. And 5 studies for association with ovarian preservation and CVD. Nine studies evaluated the relation between hysterectomy with oophorectomy and CVD. Six studies assessing the relationship between hysterectomy and hypertension were found. Four studies and three studies were respectively used to evaluate the association between hysterectomy with ovarian preservation and hypertension, and the relationship between hysterectomy with oophorectomy and hypertension. There are 5 studies included to assess the relation of hysterectomy and heart failure, 3 studies for arrhythmia and 8 studies for stroke. More details about the included studies were shown in Table S1.

3.2 Ischemic heart disease

3.2.1 Pooled *RR* The pooled *RR (95% CI)* of ischemic heart disease risk for hysterectomy versus no hysterectomy was 1.20 (*95% CI* : 1.08-1.35; I^2 =73.0%;$P_{heterogeneity}$ = 0.000; Figure 2).

3.2.2 Subgroup analysis and meta-regression In subgroup analysis stratified by study design, the pooled *RR* was 1.15 (*95% CI* : 1.03-1.29; I^2 =77.3%;$P_{heterogeneity}$ = 0.000) in cohort studies; 1.27 (*95% CI* : 0.70-2.28; I^2 =78.8%;$P_{heterogeneity}$ = 0.001) in case-control studies; 1.61 (*95% CI* : 1.09-2.38; I^2 =0%;$P_{heterogeneity}$

= 0.487) in cross-sectional studies, respectively. In subgroup analysis stratified by continent, the pooled RR was 1.22 (*95% CI* : 0.90-1.66;I^2 =60.1%;$P_{heterogeneity}$ = 0.028) in North America; 1.20 (*95% CI* : 1.02-1.41; I^2 =80.9%;$P_{heterogeneity}$ = 0.000) in Europe and 1.20 (*95% CI* : 1.01-1.42; I^2 =41.5%;$P_{heterogeneity}$ = 0.181) in Asian. We also conducted the subgroup analysis stratified by publication year, more details were shown in Table S2. Meta-regressions of publication year (P =0.353), continent (P =0.801), study design (P =0.797), sample size (P =0.446), case number (P =0.992) were conducted to explore the between-study heterogeneity.

3.2.3 Sensitivity analysis In sensitivity analysis, after excluding 2 studies of 2 articles[14, 39], the pooledRR was 1.21 (*95% CI* : 1.12-1.31) and theI^2 dropped from 73.0% to 36.9%.

3.2.4 Influence analysis and publication bias Influence analysis showed that 1 study[14] had an excessive influence on the pooledRR (Figure S1). After excluding the excessive influential study, the pooled result did not change obviously (RR : 1.24; *95% CI* : 1.12-1.37; I^2 = 53.8%;$P_{heterogeneity}$ = 0.006). No significant small-study effect was found by visual inspection of the funnel plot (Figure S2) and Egger test (P =0.394).

3.2.5 Ovarian status, age at operation In the analysis between hysterectomy with ovarian preservation and risk of ischemic heart disease, the pooled RR was 1.33 (*95% CI* : 1.05-1.68;I^2 =54.4%;$P_{heterogeneity}$ = 0.012). The pooled RR was 1.31 (*95% CI* : 1.02-1.67; I^2 =0%;$P_{heterogeneity}$ = 0.446) in the relationship between hysterectomy with oophorectomy and risk of ischemic heart disease. The pooled RR was 1.19 (*95% CI* : 1.01-1.41;I^2 =47.0%;$P_{heterogeneity}$ = 0.067) in the association between having surgery before 50 years old and risk of ischemic heart disease; 1.16 (*95% CI* : 0.87-1.54;I^2 =73.6%;$P_{heterogeneity}$ = 0.002) for the association between having surgery after 50 years old and risk of ischemic heart disease. More details were shown in Table 1.

3.3 Other cardiovascular diseases

The pooled RRs were 1.16 (*95% CI* : 1.03-1.30;I^2 =91%; $P_{heterogeneity}$= 0.000) from 6 studies; 1.31 (*95% CI* : 1.10-1.56;I^2 =79.5%;$P_{heterogeneity}$ = 0.000) from 6 studies for the relationship between hysterectomy and CVD, hysterectomy and hypertension, respectively.

As for ovarian status, the pooled RR was 1.18 (*95% CI* : 1.03-1.36; I^2 =93%;$P_{heterogeneity}$ = 0.000) for hysterectomy with ovarian preservation and CVD risk. We also conducted the relationship between hysterectomy with ovarian preservation and hypertension (RR : 1.36; *95% CI* : 1.14-1.64;I^2 =82.6%;$P_{heterogeneity}$ = 0.001) and the association between hysterectomy with oophorectomy and hypertension (RR : 1.39; *95% CI* : 1.05-1.84; I^2 =11.8%;$P_{heterogeneity}$ = 0.322).

In the women who had hysterectomy before 50 years old, the pooledRR was 1.18 (*95% CI* : 1.08-1.30;I^2 =5.1%; $P_{heterogeneity}$= 0.378) for stroke.

More details were shown in Table 2.

4 Discussion

4.1 Main findings

4.1.1 Hysterectomy and risk of ischemic heart disease

This meta-analysis indicated that compared to non-hysterectomy, hysterectomy increased the risk of ischemic heart disease by 20%. In the results of subgroup analyses by study design, a significant association was observed in cohort studies as well as in cross-sectional studies. In the subgroup analysis of continent, hysterectomy was significantly associated with increased risk of ischemic heart disease among studies conducted in Europe and Asia.

In our research, 31% increase was found in the relationship between hysterectomy with oophorectomy and ischemic heart disease. A 33% increase in ischemic heart disease was shown in persons who underwent hysterectomy with ovarian preservation.

4.1.2 Hysterectomy and risk of other cardiovascular diseases

In relationship between hysterectomy and CVD, we found a 16% increased risk. And a 18% increase was found in risk of CVD in women who have hysterectomy without oophorectomy compared to people without hysterectomy.

Statistical significances were found in the relationship between hysterectomy and risk of hypertension, hysterectomy with oophorectomy and hypertension, hysterectomy with ovarian preservation and hypertension.

And in our research, it showed hysterectomy, whether with oophorectomy or not, did not influence the risk of stroke. Our result was consistent with other studies.[10, 27, 40, 41] There was evidence that hysterectomy was associated with increased risk of CAD but not of stroke were restricted among women who did not have hysterectomy and oophorectomy simultaneously.[10] Because lacking of data about the time of oophorectomy relative to hysterectomy, we did not do the further exploration.

4.2 Biologic plausibility

More than 50% of hysterectomy is accompanied by oophorectomy because oophorectomy is the only unambiguous method to prevent ovarian cancer.[14, 24, 42, 43] It is well known that the risk of CVD in women is lower than that in men due to the presence of estrogen before menopause, but after entering menopause, the risk of CVD is unbiased in men and women.[11, 44] The possible reason for this result is the decrease of estrogen level due to the oophorectomy.[45] Considering the surgical menopause due to oophorectomy, the American College of Obstetrics and Gynecology suggests premenopausal women choose hysterectomy with ovarian preservation if no genetic risk of ovarian cancer.[46]And some studies showed that ovarian preservation is beneficial to cardiovascular and nerve system.[47-50] While in our results, the statistical significance was shown when the ovaries are preserved. As we all know, no recognized endocrine factors that have direct influence on the cardiovascular system can be produced from uterus.[13] This association may be interpreted as a decrease of ovarian blood flow due to hysterectomy, leading to premature ovarian failure.[14, 45] And the decline of ovarian reserve function subsequently promotes the consumption of follicles and finally accelerates arteriosclerosis.[51, 52] In addition, there are a series of studies to prove that hysterectomy with ovarian preservation can also reduce the endogenous hormones.[51-53]

4.3 Between-study heterogeneity

Between-study heterogeneity is common in meta-analysis.[54] Moderate to high heterogeneity was found in this analysis of hysterectomy and the risk of ischemic heart disease. To explore the potential sources of between-study heterogeneity, we performed the subgroup analyses and meta-regressions with the covariates of publication year, continent and study design. However, we did not find the factors as the important determinants in the between-study heterogeneity.

We also conducted a leave-one-out sensitivity analysis to reduce the heterogeneity. After excluding two studies, the heterogeneity decreased and the results remained significant. It showed our result was stable.

4.4 Strengths

As far as we know, this is the first meta-analysis to explore the association between hysterectomy and CVD risk. There are several strengths in our meta-analysis. Firstly, there were a large number of participants involved in our meta-analysis which guaranteed a much greater possibility of reaching reasonable conclusions. Secondly, age at operation and ovarian status were two unnegligible factors making the relationship between hysterectomy and CVD difficult to analyze.[45] Thus our results were more credible because we assessed whether the ovarian status and age of operation could affect the risk of CVD. Thirdly, considering the definition of CVD varies in different studies, it's inaccurate to assess the risk of overall CVD. In our meta-analysis, we assessed kinds of cardiovascular diseases separately to avoid this deviation. Fourthly, a significant positive association was found from cohort studies in subgroup analysis, indicating a potential causal relationship between hysterectomy and risk of ischemic heart disease. Fifthly, there were no small-study effects in our meta-analysis.

4.5 Limitations

Some limitations should be considered. Firstly, time of oophorectomy relative to hysterectomy is an important factor on CVD risk.[10, 14] However, because of the insufficiency of data, we did not assess the association between the different time of oophorectomy relative to hysterectomy (having oophorectomy before hysterectomy, having hysterectomy and oophorectomy at the same time and having oophorectomy after hysterectomy) and the risk of CVD. Secondly, whether hysterectomy with oophorectomy is worse in risk of CVD than hysterectomy with ovarian preservation or not is still controversial.[26, 48] In our meta-analysis, we found a 33% increase of ischemic heart disease risk in hysterectomy with ovarian preservation and a 31% increase in hysterectomy with oophorectomy. A statistical test is needed to assess whether there is a difference between hysterectomy only and hysterectomy with oophorectomy. But due to the deficiency of the data, we cannot compare the statistical difference between the two situations. Thirdly, moderate to high between-study heterogeneity was found, but it was not completely explained by subgroup analyses and meta-regressions. Presumably, confounders were different in each study, that may be an important determinant in the heterogeneity. And the underlying confounders may have contributed to the heterogeneity.

5 Conclusion In summary, hysterectomy, whether the ovarian preservation or not, might increase the risk of ischemic heart disease and hypertension, not of stroke. Hysterectomy might increase the risk of ischemic heart disease and stroke in women who had surgery before 50y; in women who had surgery after 50y, the results were nonsignificant.

Disclosure of interests

The authors don't have any conflict of interest.

Contribution to authorship

D.Z. and Z.W. formed the conception; Z.W. and X.L. planned and carried out the work; Z.W. analysed the data; Z.W. wrote the article; Z.W. and X.L. edited the manuscript.

Details of ethics approval

Ethics approval was not required for this work.

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Supporting Information

Additional Supporting Information may be found online:

Figure S1: Influence analysis

Figure S2: publication bias (small-study effects)

Table S1: Characteristics of 14 included studies on hysterectomy and risk of CVD

Table S2: Subgroup analyses of the association between hysterectomy and ischemic heart diseases

Appendix S1: PubMed/Web of Science search strategy for studies related to hysterectomy and risk of cardiovascular disease (CVD)

Appendix S2: Wan fang/VIP/CNKI search strategy for studies related to hysterectomy and risk of cardiovascular disease (CVD)

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`Figure 2.docx` available at https://authorea.com/users/343761/articles/470354-hysterectomy-and-risk-of-cardiovascular-disease-a-meta-analysis