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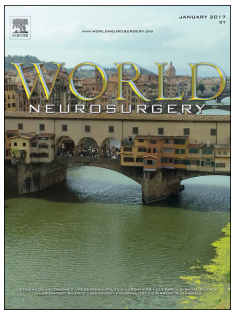

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Relationship Between Oral Contraceptives and The Risk of Gliomas and Meningiomas :A Dose-response Meta-analysis and Systematic Review

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***Abbreviations list*:** OCs, Oral contraceptives. MeSH, medical subject headings. ORs, odds ratios.NOS, Newcastle-Ottawa scale.ICD, International Classification of Diseases.

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Abstract

Objective: Glioma and meningioma are the most common primary brain tumors in adults. Epidemiological studies on the relationship between female hormone exposure and exogenous hormone use and the risk of meningioma and glioma in females have yielded inconsistent results.

Methods: Two investigators comprehensively retrieved three electronic databases,including Pubmed, Embase database, and Cochrane library. Finally, a total of 11 case-control studies were enrolled for meta-analysis. Meanwhile ,a dose-response meta-analyses were conducted.

Results: Compared with the non-OCs female users, the female OCs users might have reduced risk of glioma (RR 0.87,95%CI0.77-0.97; $I^2$42.6%). However, there was no obvious evidence of an association between OCs use and the risk of meningioma in females (RR 0.99,95%CI0.87-1.13;$I^2$42.7%). Using OCs over 10years in females may significantly decrease the risk of glioma to 30% (RR 0.7,95%CI0.6 -0.81; $I^2$0%). The dose-response meta-analyses indicated that the risk of glioma in females significantly decreased when the duration of oral OCs use was over7.5 year.

Conclusions In conclusion, OCs use may not increase the risks of glioma and meningioma in females. Instead, the long-term use of OCs may significantly decrease the risk of glioma, and the benefits are even more pronounced when the “time window” is beyond7.5 years. Nonetheless, the pooled results in this study suggest that OCs use may not elevate the risk of meningioma. Therefore, our conclusion should be validated and supplemented in future larger studies.

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Keywords: oral contraceptives; Glioma; Meningioma; Meta-analysis

Introduction

Glioma and meningioma are the most common primary brain tumors in adults[1], but their precise pathogenesis has not been well established yet. High dose ionizing radiation[2-3], genetic susceptibility[4-5]and some rare genetic diseases[6]have been identified as the risk factors, but only in a small proportion of cases. Other factors, such as mobile phone use [7-8], head trauma [9], family history [10-11] and oral contraceptive (OC)use[12-13],have also been proposed as the risk factors, but they have not been validated yet.As reported in several studies, the incidence of meningioma and glioma is different depending on the sex. For example, meningioma is more frequently seen in women, with a female-to-male ratio of up to 3.5:1 in some age groups[14], while glioma hasa higherincidence in males (7.10 per 100,000 person-years) than in females (5.01 per 100,000 person-years) [1]. Therefore, many scholars suggest that hormones may be one of the important factors affecting the development of these tumors. It is shown by some experimental evidence that, estrogen exposure may protect againstglioma by inhibiting glioma cell proliferation and promoting cell apoptosis [15-17].In contrast, estrogen may also increase the risk of meningioma, and it is reported that meningioma cell lines exposed to estradiol or progesterones how higher proliferation rates[18]. Generally speaking, exogenous hormones, such as OC and hormone replacement therapy (HRT), have been extensively applied among the non-menopausal and postmenopausal females. HRT application displays a declining trend across postmenopausal women, whereas OC use shows an increasing trend[19].OCs, the most common drug contraception method that can achieve a high contraception success rate, are mostly made up of synthetic estrogen and progesterone. However, there are inconsistent results from epidemiological studies on the relationship of female hormone exposure and exogenous hormone use with the risks of meningioma and glioma in females, and there is no evidence of a trend toward longer duration of hormone use[20-23].To address these gaps, a systematic meta-analysis was conducted in the present work to investigate the association between OCs use and the risks of meningioma and glioma. In addition, a dose-response meta-analysis was also carried out to evaluate the effect of the duration of OCs use on the risks of meningioma and glioma.

Methods

Search Strategy

The present meta-analysis was performed following the protocols and guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[24].The databases, including Pubmed, Embase database and Cochrane library, were systemically searched to identify relevant articles published in English from inception to October 6th, 2020.In addition, the library was manually retrieved to avoid omitting any eligible article. To ensure a

comprehensive search, three sets of medical subject headings (MeSH) were adopted, including "Contraceptive Agents, Hormonal", "Meningioma" and "Glioma". Moreover, relevant previous meta-analyses and systematic reviews were also retrieved and included in the study[25-28]. The search strategy is displayed in ***Appendix 1***.

Study Selection

The study inclusion criteria were as follows: 1) Females had a history of hormonal contraceptive agent use, no history of glioma or meningioma or precancerous lesions. 2) The exposure was the use of hormonal contraceptive agents.3) Subjects who never used hormonal contraceptive agents were adopted as a control.4)The outcome was the risk of incidence of glioma or meningioma.5) The study type was limited to observational study or randomized controlled trial (RCT). 6).There were available data on the maximum adjustment risk ratios (RRs), odds ratios (ORs), hazard ratios (HRs), together with corresponding 95% confidence interval (CI) in the study. Meanwhile, the study exclusion criteria were shown below: 1). Females with nohistory of using hormonal contraceptive agents or with a history of glioma or meningioma or precancerous lesions were excluded. 2). The exposure was not the use of hormonal contraceptive agents.3) The outcome was the risk of incidence of non-glioma or non-meningioma.4).Conference abstracts, letters, and case reports were excluded.

Data extraction and quality assessment

The following data, including first author, publication year, study type, country, date of recruitment, age, patient number, gliomaconfirmation, intervention, control number and outcomes, were extracted using the unified data list. In the meantime, the numbers of all participants and cases in the intervention and control groups were also recorded. Any disagreement or dispute in the process of data extraction was resolved through mutual negotiation. Besides, the Newcastle-Ottawa scale (NOS) [29] was utilized to assess the study quality, and the total score was 9. Specifically, studies with a NOS score over 6 stars were considered as high quality studies, while those with a NOS score less than 6 stars as low quality studies.

Statistical Analysis

The primary outcome in this study was qualitative analysis on the relationship of OCs use with the risks of glioma and meningioma. Generally, HR equaled to RR and was thus roughly considered as RR [30].Meanwhile, ORs were transformed into RRs by the following

formula: RR=OR/[(1–P_0)+(P_0×OR)], where P_0stands for the incidence of outcome in unexposed group[31].Besides, the corresponding 95CI was transformed by the formula: SElog(RR)=SElog(OR)×log(RR)/log(OR) [32]. The data were presented as RRs. Statistical heterogeneity was evaluated by the I^2 statistic [33], where the I^2 values of 25%, 50% and 75% represented low, moderate and high inconsistency, respectively. Moreover, subgroup analysis and meta-regression were also performed to explore the potential sources of heterogeneity and to compare different groups. Sensitivity analysis was implemented by eliminating one study each time to test its impact on the pooled results. To more conservatively estimate the pooled RRs, the random effect model was adopted, since it was more capable of explaining the heterogeneity between studies. Further, the funnel plot was drawn to assess the publication bias by Begg's test and Egger's test [34-35].

The secondary outcome in this study was the systematic assessment of the impact of OCs use duration on the risk of glioma or meningioma. To this end, a quantitative dose-response meta-analysis was conducted. For the maximum excavation of available studies, the robust error meta-regression method described by Xu and Doi [36] was adopted to establish the potential dose-response relationship of oral hormonal contraceptives use with the risk of glioma or meningioma. In this "one-stage" framework method, each included study was treated as a cluster across the whole population, which required that the studies include at least two categories. In this study, the restricted cubic spline was employed to fit the potential non-linear trend with three knots, and the nonlinear P-value was calculated by testing the second spline coefficient of zero. The nonlinear model was adopted when P for nonlinear ≤0.05; otherwise, the linear model was adopted. Generally speaking, the included studies should take the category of lowest dose as a reference. The original author was contacted when the number of cases in a category was missing. In addition, when the open intervals were studied, their amplitudes were assumed to be the same as those of adjacent categories [36]. All data were analyzed by Stata 12.0.

Results

A total of 440 studies were retrieved from three electronic databases including PubMed, Embase, and the Cochrane library, as shown in ***Figure 1***. No additional study was found by manual search. Among these440 studies, 50 were excluded due to duplication, while354were removed due to irrelevance after title and abstract reading. For the remaining 36 studies, the full-texts were carefully read and 16 were excluded due to the following reasons: a) reviews(n=7); b) the outcome was brain tumor (n=2); c) the subjects had no history of hormonal contraceptive (n=3); d) both male and female were exposed(n=1);e) letters and abstracts (n=3).Finally,

20observational studies [21-22,37-54] were enrolled in the present meta-analysis, including 13 population-based case-controlled studies and 7 cohort studies. The baseline characteristics of all the enrolled studies are shown in ***Table 1***. Among the 20 observational studies enrolled, 12 reported the relationship between OCs use and the risk of glioma, whereas13 reported the association between OCs use and the risk of meningioma. Quality assessment of the included studies is presented in ***Supplementary Table 1***. Of these 20 studies, nine studies scored 8 stars; ten studies scored 7 stars; one study scored 6 stars. All studies scored higher than 6 stars and were considered as the high-quality studies.

Meta-analysis

OCs Users Vs. Non-OCs Users

As shown in ***Figure 2***, 12 studies involving 1,844,503 participants reported the association between OCs use and the risk of glioma. Compared with the non-OCs female users, the female OCs users might have reduced risk of glioma (RR 0.87,95%CI0.77-0.97; $I^2$42.6%).In addition, 13 studies recruiting 1,948,360 participants mentioned the association between OCs use and the risk of meningioma,as shown in ***Figure 2***. Compared with the non-OCs female users, there was no obvious evidence of an association between OCs use and the risk of meningioma in females (RR 0.99,95%CI0.87-1.13;$I^2$42.7%).

The funnel plot showing the relationship between OCs use and the risks of glioma and meningioma in females is displayed in ***Supplementary Figure 1***.Obviously, the funnel plot was asymmetrical, but there was no obvious evidence of publication bias upon Begg's (p=0.837)or Egger's test (p=0.843).Moreover, to explore the potential heterogeneity among diverse studies, this study carried out subgroup analysis and meta-regression, as exhibited in ***Table 2***. Additionally, subgroup-analysis stratified by publication year, sample size, country, tumor confirmation and study design was carried out. As a result, the publication year after 2010, the sample size less than 500, the included studies from Europe and tumor confirmation by the International Classification of Diseases(ICD) were the potential sources of heterogeneity in glioma. Simultaneously, the publication year before 2010, the sample size less than 500, the included studies from America, and tumor ascertainment by the medical records were the possible sources of heterogeneity in meningioma. Nonetheless, the above-mentioned factors made no contribution to inter-study heterogeneity, as suggested by meta-regression analysis. Sensitivity analysis on the relationship between OCs use and the risks of glioma and meningioma in females is shown in ***Supplementary Figure 2.***The pooled results only changed mildly when one study was removed a time.

Duration of OCs use

As observed from ***Figure 3***, compared with non-OCs users, there was no significant increase in the risk of glioma among females who used OCs for less than 1 year (RR 0.86, 95%CI 0.7-1.06;$I^2$41.8%).

However, OCs use for1-10years in females might significantly decrease the risk of glioma to17%(RR 0.83,95%CI0.0.74-0.93;$I^2$0%).Similarly, it was indicated that OCs use for over 10 years might decrease the risk of glioma in females compared with that in non-OCs users (RR 0.7,95%CI0.6 -0.81; $I^2$0%).

It was illustrated from ***Figure 4*** that, compared with non-OCs users, there was no significant increase in the risk of meningioma among females who used OCs for less than 1 year (RR 0.99,95% CI0.8-1.22; $I^2$0%). In addition, similar results were found in the groups with OCs use for 1-10 years and over 10 years, with (RR1.16,95%CI0.95-1.42;$I^2$0%) and (RR0.99,95% CI0.78-1.25;$I^2$0%), respectively.

Dose-response Meta-analyses

According to ***Figure 5***, 11 studies involving1,844,146 participants satisfied the dose-response for the relationship between OCs use and the risk of glioma. The results showed that there was a positive non-linear correlation between the duration of OCs use and the risk of glioma ($P_{nonlinear}$=0.004). With the increase in the years of oral OCs use, the risk of glioma in females decreased gradually. Specifically, the risk of glioma in females significantly decreased when the duration of oral OCs use was over7.5 years, while there was no significant association between OCs use and the risk of glioma when the duration was less than 7.5 years.

It was found in ***Figure 6*** that, 9 studies involving1,527,165participants met the dose-response for the relationship between OCs use and the risk of meningioma. Clearly, there was a non-linear correlation between the duration of OCs use and the risk of meningioma ($P_{nonlinear}$=0.033). However, with the increase in the years of oral OCs use, there was no distinct evidence on the relationship between OCs use and the risk of meningioma.

Discussion

Findings in the present meta-analysis involving 2,138,608 participants suggested that, the use of OCs might not increase the risk of glioma or meningioma. Conversely, as time went by, long-term use of OCs might significantly decrease the risk of glioma, and the "critical point" seemed to be 7.5 years. However, results of qualitative analysis indicated that OCs use might not increase the risk of meningioma, and similar results were reported in dose-response analysis.

OCs are the most common drug contraception method that can achieve a high contraceptive success rate, and they are mostly made up of synthetic estrogen and progesterone. OCs, one of the sources of exogenous hormone intake, are still controversial about their relationship with the risks of meningioma and glioma. A study by Andersen L et al. [45]suggested that, long-term hormonal contraceptive use might increase the risk of glioma, which was possibly related to the fact that progesterone promoted the proliferation of high-grade astrocytoma cells [55] and the levels of growth factors [56], and the progesterone receptor (PR) mRNA or protein expression increases as the glioma grade elevates[57].However, a study by Krishnamachari B et al. [39] showed that, OCs use decreased the risk of glioma, which was because that the hormone promoted the expression of Th2 cytokines that had certain protective effects on glioblastoma[58]. Further, some epidemiological and observational studies also reveal that, hormonal regulation plays a certain role in meningioma genesis and development. The PR expression level is found to be negatively correlated with histological grade and the high meningioma relapse rate; besides, oral contraception may down-regulate PR expression, thereby leading to an increased risk of meningioma[41,59-60]. Nonetheless, Guevara P et al. discovered that the PR level was not related to the relapse of meningioma[61]. Furthermore, the biological data-based studies in vitro indicate that, estradiol or progesterone application promotes meningioma cell proliferation[62], whereas estrogen suppresses glioma cell growth[63-64].In recent years, Peyre M et al. first illustrated the specific mutational landscape in progesterone-related meningioma occurrence from the molecular biology perspective, where the hormone-induced PIK3CA gene mutations were found to be involved. But our pooled results revealed that OCs use was not related to the risk of meningioma. The diverse types of hormones are well recognized to exert different functions in meningioma and glioma, but no further precise analysis can be conducted due to the limited existing data. Future research must focus on hormone type differentiation. Moreover, the mechanisms by which OCs use affects the risks of glioma and meningioma should be further clarified in more future studies.

Note worthily, our meta-analysis has the following strengths. Firstly, to the best of our knowledge, this is the first systemic and qualitative meta-analysis. Meanwhile, the results of

qualitative meta-analysis were further validated by the dose-response meta-analysis. Secondly, OCs use is one of the complementary sources of exogenous sex hormones, which has not been well explained to be related to meningioma or glioma. This study partially explained the problem. More importantly, this study found that long-term use of oral OCs might reduce the risk of glioma, which provided a direction for future study. Thirdly, the quality of our enrolled studies was high, which guaranteed the reliability of the results.

Inevitably, several limitations should be noted in this study. Firstly, due to the limited number of existing studies, subgroup analysis stratified by race, age and parity was not performed. Secondly, although the results of most studies were adjusted according to the maximum covariates, the influence of residual confounding variables was not excluded. Thirdly, most studies did not report the specific sex hormone components in OCs, therefore, difference in the sex hormone contraceptive might lead to a certain difference in the pooled results. Fourthly, it was suggested that OCs use did not elevate the risk of meningioma according to the limited existing data, but the risk of other possible diseases was not eliminated.

In conclusion, OCs use may not increase the risks of glioma and meningioma in females. Instead, the long-term use of OCs may significantly decrease the risk of glioma, and the benefits are even more pronounced when the “time window” is beyond7.5 years. Nonetheless, the pooled results in this study suggest that OCs use may not elevate the risk of meningioma. Therefore, our conclusion should be validated and supplemented in future larger studies.

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Figure legends

Figure 1. Flowchart of the study retrieval process.

Figure 2. Forest plots of OCs use and the risks of glioma and meningioma regardless of the use duration.

Figure 3. Forest plots of OCs use and the risk of glioma according to the different use duration.

Figure 4. Forest plots of OCs use and the risk of meningioma according to the differentuse duration.

Figure 5. The dose-response of glioma.

Figure 6. The dose-response of meningioma.

Supplementary Figure 1. Funnel plot of the risks of glioma and meningioma.

Supplementary Figure 2. Sensitivity analysis on the risk of glioma and meningioma.

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Pubmed

1. Search: "Contraceptive Agents"[Mesh] **42381**
2. Search: (((((Agents, Contraceptive) OR (Contraceptives)) OR (Contraceptive Effect)) OR (Effect, Contraceptive)) OR (Contraceptive Effects)) OR (Effects, Contraceptive) **147,472**
3. 1 or 2 **147,472**
4. Search: "Glioma"[Mesh] **84,046**
5. Search: ((((((((((((Gliomas) OR (Glial Cell Tumors)) OR (Glial Cell Tumor)) OR (Tumor, Glial Cell)) OR (Tumors, Glial Cell)) OR (Mixed Glioma)) OR (Glioma, Mixed)) OR (Gliomas, Mixed)) OR (Mixed Gliomas)) OR (Malignant Glioma)) OR (Glioma, Malignant)) OR (Gliomas, Malignant)) OR (Malignant Gliomas) **105,523**
6. 4 or 5 **105,523**
7. Search: "Meningioma"[Mesh] **19,335**
8.(((Meningiomas) OR (Xanthomatous Meningioma)) OR (Meningioma, Xanthomatous)) OR (Meningiomas, Xanthomatous)) OR (Xanthomatous Meningiomas)) OR (Angioblastic Meningioma)) OR (Angioblastic Meningiomas)) OR (Meningioma, Angioblastic)) OR (Meningiomas, Angioblastic)) OR (Angiomatous Meningioma)) OR (Angiomatous Meningiomas)) OR (Meningioma, Angiomatous)) OR (Meningiomas, Angiomatous)) OR (Clear Cell Meningioma)) OR (Clear Cell Meningiomas)) OR (Meningioma, Clear Cell)) OR (Meningiomas, Clear Cell)) OR (Fibrous Meningioma)) OR (Fibrous Meningiomas)) OR (Meningioma, Fibrous)) OR (Meningiomas, Fibrous)) OR (Hemangioblastic Meningioma)) OR (Hemangioblastic Meningiomas)) OR (Meningioma, Hemangioblastic)) OR (Meningiomas, Hemangioblastic)) OR (Hemangiopericytic Meningioma)) OR (Hemangiopericytic Meningiomas)) OR (Meningioma, Hemangiopericytic)) OR (Meningiomas, Hemangiopericytic)) OR (Intracranial Meningioma)) OR (Intracranial Meningiomas)) OR (Meningioma, Intracranial)) OR (Meningiomas, Intracranial)) OR (Intraorbital Meningioma)) OR (Intraorbital Meningiomas)) OR (Meningioma, Intraorbital)) OR (Meningiomas, Intraorbital)) OR (Intraventricular Meningioma)) OR (Intraventricular Meningiomas)) OR (Meningioma, Intraventricular)) OR (Meningiomas, Intraventricular)) OR (Malignant Meningioma)) OR (Malignant Meningiomas)) OR (Meningioma, Malignant)) OR (Meningiomas, Malignant)) OR (Meningiomas, Multiple)) OR (Meningioma, Multiple)) OR (Multiple Meningioma)) OR (Multiple Meningiomas)) OR (Meningiomatosis)) OR (Meningiomatoses)) OR (Meningotheliomatous Meningioma)) OR (Meningioma, Meningotheliomatous)) OR (Meningiomas, Meningotheliomatous)) OR (Meningotheliomatous Meningiomas)) OR (Microcystic Meningioma)) OR (Meningioma, Microcystic)) OR (Meningiomas, Microcystic)) OR (Microcystic Meningiomas)) OR (Olfactory Groove Meningioma)) OR (Groove Meningiomas, Olfactory)) OR (Meningioma, Olfactory Groove)) OR (Meningiomas, Olfactory Groove)) OR (Olfactory Groove Meningiomas)) OR (Papillary Meningioma)) OR (Meningioma, Papillary)) OR (Meningiomas, Papillary)) OR (Papillary Meningiomas)) OR (Parasagittal Meningioma)) OR (Meningioma, Parasagittal)) OR (Meningiomas, Parasagittal)) OR (Parasagittal Meningiomas)) OR (Posterior Fossa Meningioma)) OR (Meningioma, Posterior Fossa)) OR (Meningiomas, Posterior Fossa)) OR (Posterior Fossa Meningiomas)) OR (Psammomatous Meningioma)) OR (Meningioma, Psammomatous)) OR (Meningiomas, Psammomatous)) OR (Psammomatous Meningiomas)) OR (Secretory

Meningioma)) OR (Meningioma, Secretory)) OR (Meningiomas, Secretory)) OR (Secretory Meningiomas)) OR (Sphenoid Wing Meningioma)) OR (Meningioma, Sphenoid Wing)) OR (Meningiomas, Sphenoid Wing)) OR (Sphenoid Wing Meningiomas)) OR (Meningioma, Sphenoid Wing)) OR (Meningiomas, Sphenoid Wing)) OR (Sphenoid Wing Meningiomas)) OR (Wing Meningioma, Sphenoid)) OR (Wing Meningiomas, Sphenoid)) OR (Spinal Meningioma)) OR (Meningioma, Spinal)) OR (Meningiomas, Spinal)) OR (Spinal Meningiomas)) OR (Transitional Meningioma)) OR (Meningioma, Transitional)) OR (Meningiomas, Transitional)) OR (Transitional Meningiomas)) OR (Benign Meningioma)) OR (Benign Meningiomas)) OR (Meningioma, Benign)) OR (Meningiomas, Benign)) OR (Cerebral Convexity Meningioma)) OR (Cerebral Convexity Meningiomas)) OR (Convexity Meningioma, Cerebral)) OR (Convexity Meningiomas, Cerebral)) OR (Meningioma, Cerebral Convexity)) OR (Meningiomas, Cerebral Convexity) **26,074**
9.7 or 8 **26,074**
10.6 or 9 **126,441**
11.3 and 10 **269**

Embase

1. 'hormonal contraceptive agent'/exp **76,584**
2. contraceptive AND agents, AND hormonal OR (hormonal AND contraceptive) OR (hormonal AND contraceptive AND agents) OR (hormonal AND contraceptives) **14,925**
3. #1 OR #2 **85,731**
4. 'meningioma'/exp **32,898**
5. meningeal AND neoplasms OR meningeoma OR (meningeal AND tumor) OR (meningeal AND tumour) OR (meninges AND tumor) OR (meninges AND tumour) OR meningothelioma OR (multiple AND meningioma) OR (petroclival AND meningioma) OR (retrochiasmatic AND meningioma) OR (suprasellar AND meningioma) **10,495**
6. #4 OR #5 **37,881**
7. 'glioma'/exp **140,685**
8. brain AND glioma OR (cerebral AND glioma) OR ganglioglioma OR (glia AND tumor) OR (glia AND tumour) OR (glial AND tumor) OR (glial AND tumour) OR (high AND grade AND glioma) OR (low AND grade AND glioma) OR (recurrent AND glioma) **77,746**
9. #7 OR #8 **160,085**
10. #6 OR #9 **189,743**
11. #3 AND #10 **171**

Cochrane

1. MeSH descriptor: [Contraceptive Agents, Hormonal] explode all trees **384**
2. (Contraceptive Agents, Female Hormonal) OR (Hormonal Contraceptive Agents) OR

(Contraceptive Agents, Male Hormonal) **997**

3. #1 or #2 **701**
4. MeSH descriptor: [Glioma] explode all trees **1173**
5. (Gliomas, Malignant) OR (Malignant Glioma) OR (Malignant Gliomas) OR (Gliomas) **1726**
6. (Glioma, Mixed) OR (Mixed Gliomas) OR (Mixed Glioma) OR (Gliomas, Mixed) OR (Glioma, Malignant)**715**
7. #5 or #6 **1121**
8. #4 or #7 **1896**
9. MeSH descriptor: [Meningioma] explode all trees **64**
10. (Meningioma, Angiomatous) OR (Angiomatous Meningioma) OR (Meningiomas, Angiomatous) OR (Angiomatous Meningiomas) OR (Fibrous Meningioma) **5**
11. (Meningiomas, Fibrous) OR (Meningioma, Fibrous) OR (Fibrous Meningiomas) OR (Transitional Meningioma) OR (Transitional Meningiomas) **8**
12. (Posterior Fossa Meningiomas) OR (Malignant Meningioma) OR (Meningiomas, Malignant) OR (Malignant Meningiomas) OR (Meningioma, Malignant)**66**
13. (Meningiomas, Olfactory Groove) OR (Meningioma, Olfactory Groove) OR (Olfactory Groove Meningiomas) OR (Groove Meningiomas, Olfactory) OR (Olfactory Groove Meningioma) **2**
14. (Meningioma, Microcystic) OR (Microcystic Meningioma) OR (Meningiomas, Microcystic) OR (Microcystic Meningiomas) OR (Meningioma, Clear Cell) **32**
15. (Clear Cell Meningiomas) OR (Clear Cell Meningioma) OR (Meningiomas, Clear Cell) OR (Meningiomas, Secretory) OR (Meningioma, Secretory) **33**
16. (Secretory Meningiomas) OR (Secretory Meningioma) OR (Meningiomas) OR (Xanthomatous Meningiomas) OR (Xanthomatous Meningioma) **276**
17. (Meningioma, Xanthomatous) OR (Meningiomas, Xanthomatous) OR (Meningiomas, Parasagittal) OR (Meningioma, Parasagittal) OR (Parasagittal Meningiomas) **1**
18. (Parasagittal Meningioma) OR (Meningiomas, Benign) OR (Benign Meningiomas) OR (Benign Meningioma) OR (Meningioma, Benign)**38**
19. (Meningiomas, Spinal) OR (Spinal Meningioma) OR (Meningioma, Spinal) OR (Spinal Meningiomas) OR (Meningioma, Hemangiopericytic)**12**
20. (Hemangiopericytic Meningiomas) OR (Meningiomas, Hemangiopericytic) OR (Hemangiopericytic Meningioma) OR (Meningioma, Intracranial) OR (Intracranial Meningiomas)**75**
21. (Intracranial Meningioma) OR (Meningiomas, Intracranial) OR (Psammomatous Meningioma) OR (Meningiomas, Psammomatous) OR (Psammomatous Meningiomas)75
22. (Meningioma, Psammomatous) OR (Sphenoid Wing Meningiomas) OR (Wing Meningiomas, Sphenoid) OR (Wing Meningioma, Sphenoid) OR (Meningioma, Sphenoid Wing) **1**
23. (Sphenoid Wing Meningioma) OR (Meningiomas, Sphenoid Wing) OR (Meningiomas, Cerebral Convexity) OR (Convexity Meningioma, Cerebral) OR (Convexity Meningiomas, Cerebral) **1**
24. (Cerebral Convexity Meningiomas) OR (Cerebral Convexity Meningioma) OR (Meningioma, Cerebral Convexity) OR (Meningotheliomatous Meningiomas) OR

(Meningiomas, Meningotheliomatous) **0**

25. (Meningotheliomatous Meningioma) OR (Meningioma, Meningotheliomatous) OR (Multiple Meningiomas) OR (Meningioma, Multiple) OR (Multiple Meningioma) **53**

26. (Meningiomas, Multiple) OR (Meningiomas, Hemangioblastic) OR (Hemangioblastic Meningiomas) OR (Meningioma, Hemangioblastic) OR (Hemangioblastic Meningioma) **53**

27. (Meningioma, Papillary) OR (Papillary Meningioma) OR (Meningiomas, Papillary) OR (Papillary Meningiomas) OR (Intraventricular Meningioma)**2**

28. (Meningioma, Intraventricular) OR (Meningiomas, Intraventricular) OR (Intraventricular Meningiomas)**1**

29. #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 **183**

30. #9 or #29 **206**

31. #8 or #30 **2046**

32. #3 and #31 **0**

Tble1.The Detailed Characters of The Included 20 Observational Studies

First Author , year	Study Type	Country	The Date of Recruitment	Age, year	Patients Number (G/M)	Ascertainment	Intervention	Control or Total Number	Outcome
Anic.GM [37] ,2014	PCC	USA	NA	52.6y	507/247	Medical Records	OCs	659	Gliomas/ Meningiomas
Felini MJ [38] ,2009	PCC	USA	1991-1994 1997-1999 2001-2004	56.3y	619/	International Classification of Diseases	OCs	650	Gliomas
Hatch EE [22] ,2005	PCC	USA	1994-1998	51.8y	212/151	International Classification of Diseases	OCs	436	Gliomas/ Meningiomas
Krishnamachari B [39] ,2014	PCC	USA	2003-2008	51.4y	968	International Classification of Diseases	OCs	1322	Gliomas
Wigertz A [40] ,2006	PCC	Sweden	2000-2002	20-69y	115/178	International Classification of Diseases	OCs	323	Gliomas/ Meningiomas
Custer B [41] ,2006	PCC	USA	1995-1998	NA	/143	Medical Records	OCs	286	Meningiomas
Huang K [21] ,2004	PCC	USA	1995-1997	52y	341	International Classification of Diseases	OCs	527	Gliomas
Lee E [42] ,2006	PCC	USA	1987-1992	NA	/219	Medical Records	OCs	260	Meningiomas

Cea-Soriano L[43] ,2011	Cohort	Spain	1996-2008	12-89y	549	Medical Records	OCs	7347	Meningiomas
Korhonen K[44] ,2010	PCC	Finland	2000-2002	54y	/264	International Classification of Diseases	OCs	505	Meningiomas
Andersen L[45] ,2014	PCC	Denmark	2000-2009	15-49y	317/	International Classification of Diseases	OCs	2126	Gliomas
Benson VS[46] ,2008	Cohort	UK	1996-2001	55.9y	646/390	International Classification of Diseases	OCs	1,249,670	Gliomas/ Meningiomas
Claus EB[47] ,2013	PCC	USA	2006-2011	57.2y	/1127	Medical Records	OCs	1092	Meningiomas
Jhawar BS[48] ,2003	Cohort	USA	1976-1996	54.2y	/125	Medical Records	OCs	121,700	Meningiomas
Michaud DS[49] ,2010	Cohort	UK	1990s	50.4y	193/194	International Classification of Diseases	OCs	276,212	Gliomas/ Meningiomas
Navarro Silvera.SA[50] ,2005	Cohort	USA	1980-2000	48.5y	125/	International Classification of Diseases	OCs	89,830	Gliomas
Wang SS[51] ,2011	PCC	USA	1993-2001	NA	357/	Medical Records	OCs	822	Gliomas
Kabat GC[52] ,2011	Cohort	USA	1995-2003	50-71y	174/	Medical Records	OCs	225,355	Gliomas

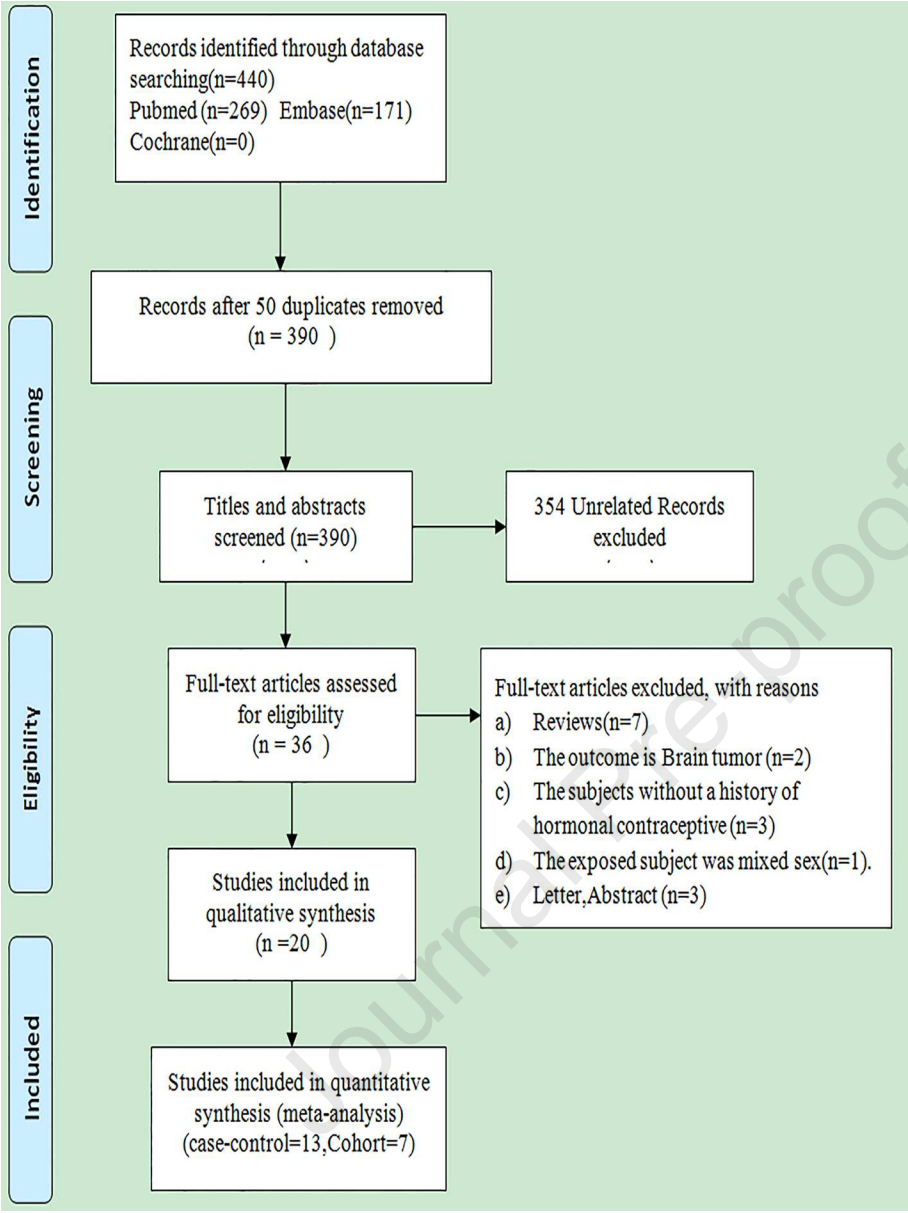
Preston-Martin S[53], 1995	PCC	USA	1978-1985	20-74y	/81	Medical Records	OCs	155	Meningiomas
Johnson DR[54],2011	Cohort	USA	1986–2004	69.3y	/125	International Classification of Diseases	OCs	291,021	Meningiomas

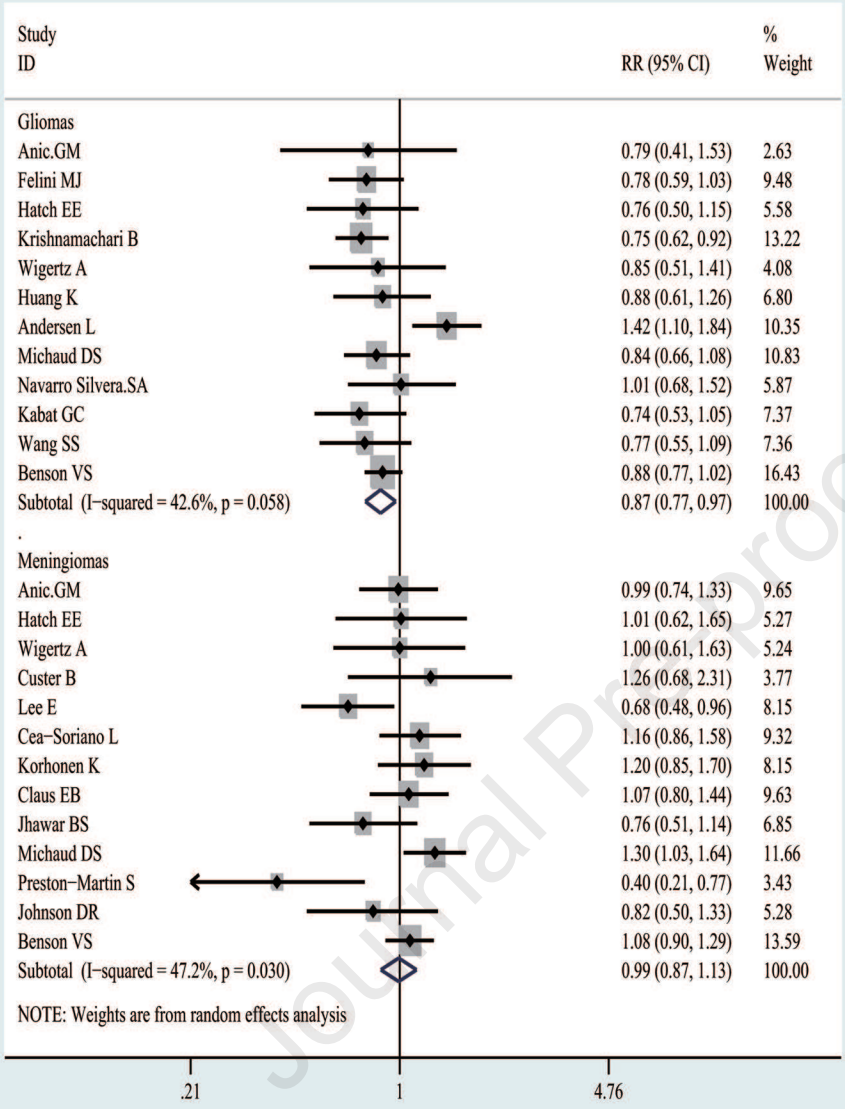
PCC, Population-based Case-Control. OCs, oral contraceptives.NA: No Applicable.

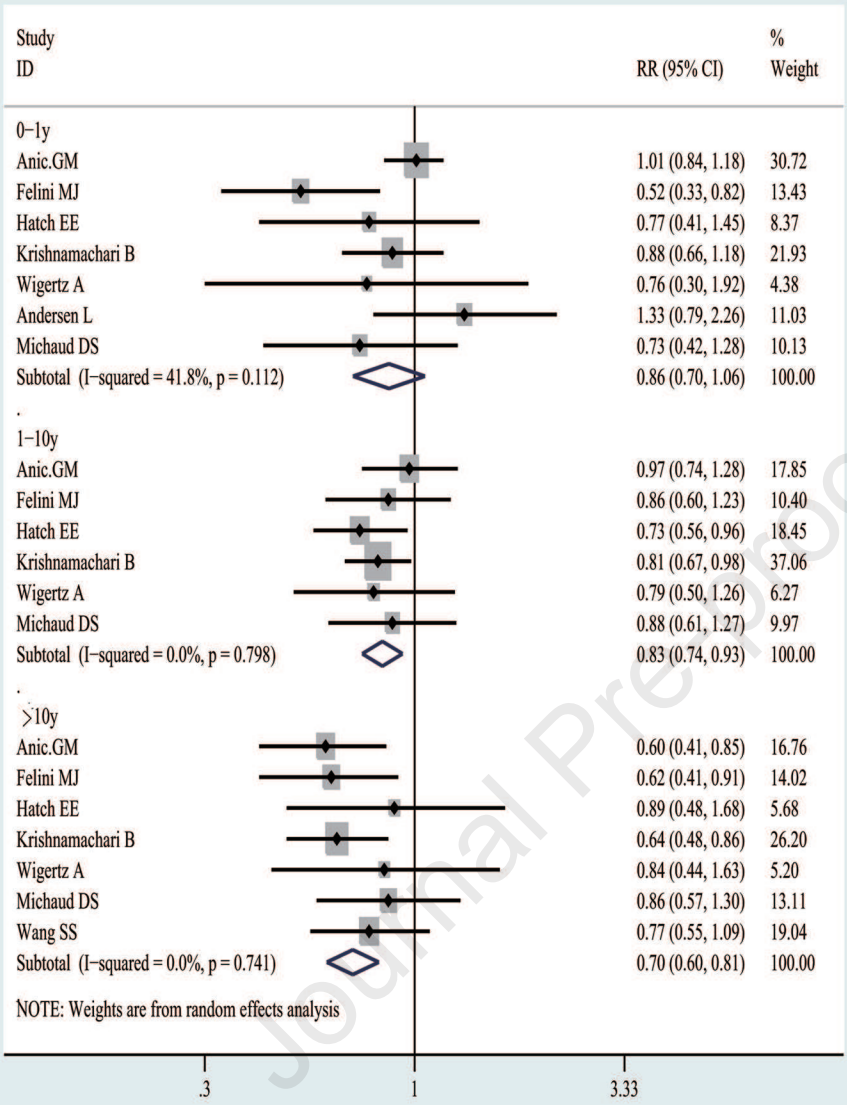
Table.2 Subgroup analyses and Meta-regression of the OCs usage of the risk of Gliomas and Meningiomas

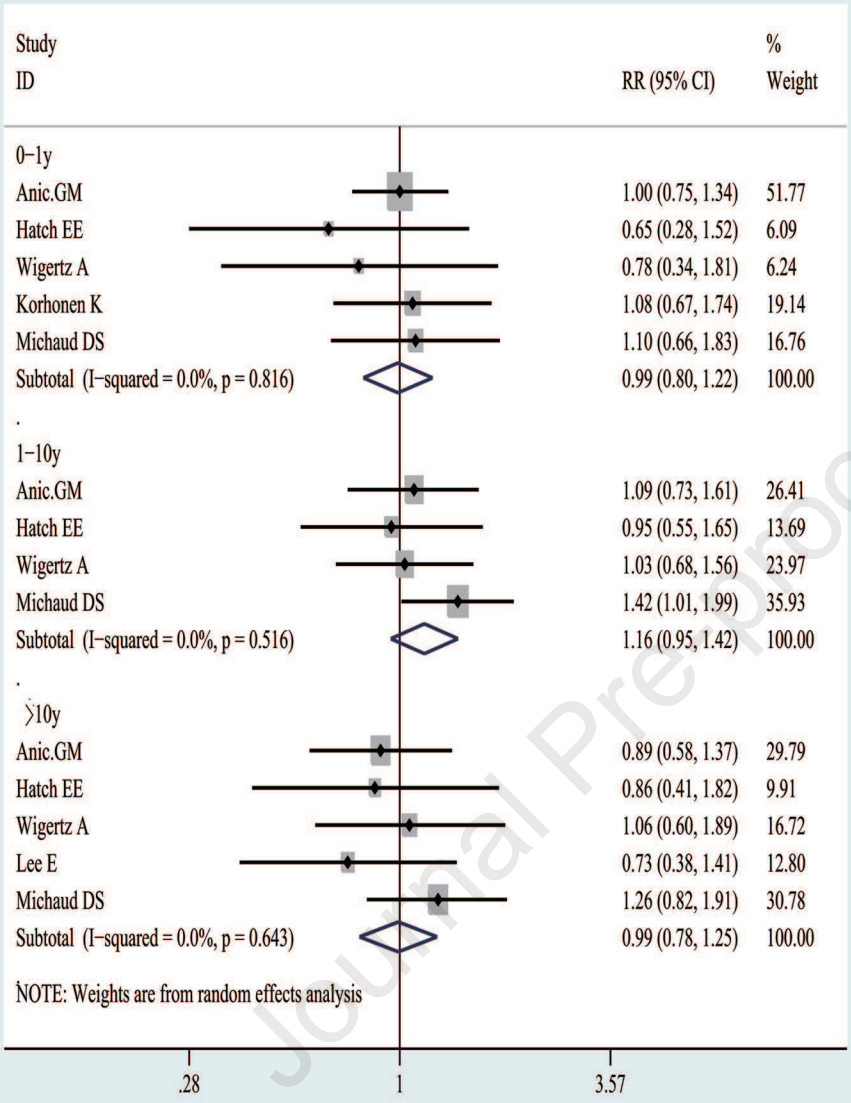
	Gliomas					***Meningiomas***				
Type	N	RR(95%CI)	I^2	P^a	P^b	N	RR(95%CI)	I^2	P^a	P^b
Published Year	12				***0.859***	13				***0.967***
Before 2010	6	0.86(0.78-0.96)	0%	0.908		7	0.86(0.68-1.09)	58.2%	0.026	
After 2010*	6	0.87(0.69-1.1)	71.6%	0.003		6	1.13(1.0-1.28)	0%	0.535	
Sample Size					***0.541***					***0.426***
＜500	5	0.93(0.70-1.23)	66.4%	0.018		6	0.88(0.65-1.20)	60.6%	0.026	
≥500	7	0.83(0.76-0.91)	0%	0.777		7	1.07(0.95-1.20)	16%	0.038	
Country					***0.531***					***0.712***
America	9	0.80(0.72-0.88)	0%	0.964		8	0.93(0.75-1.16)	62.5%	0.009	
Europe	3	1.04(0.72-1.48)	81%	0.005		5	1.07(0.94-1.21)	0%	0.471	
Ascertainment					***0.478***					***0.561***
ICD	8	0.9(0.78-1.05)	59%	0.017		5	1.13(1.00-1.28)	0	0.457	
Medical Records	4	0.76(0.62-0.93)	0%	0.998		8	0.90(0.74-1.10)	52.4%	0.04	
Study Design					***0.596***					***0.505***
PCC	8	0.87(0.72-1.05)	0%	0.013		8	0.94(0.76-1.14)	49.1%	0.056	
Cohort	4	0.87(0.77-0.97)	0%	0.686		5	1.07(0.90-1.26)	40.8%	0.149	

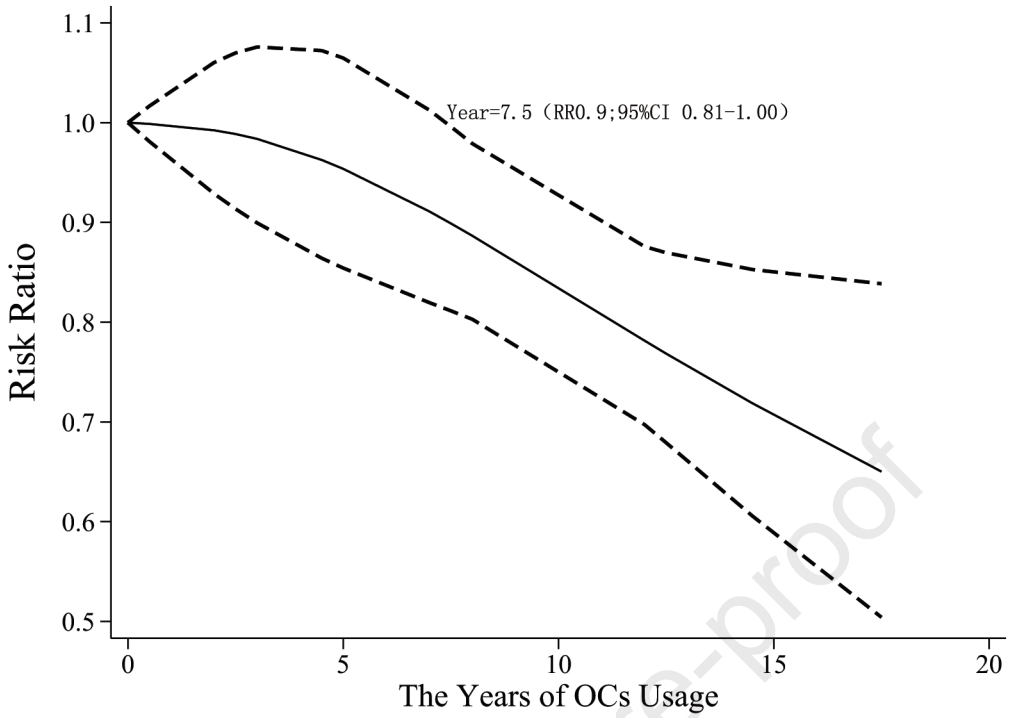
* indicated including 2010. ICD, International Classification of Diseases. P^a for heterogeneity within each subgroup. P^b for heterogeneity between subgroups with meta-regression analysis.

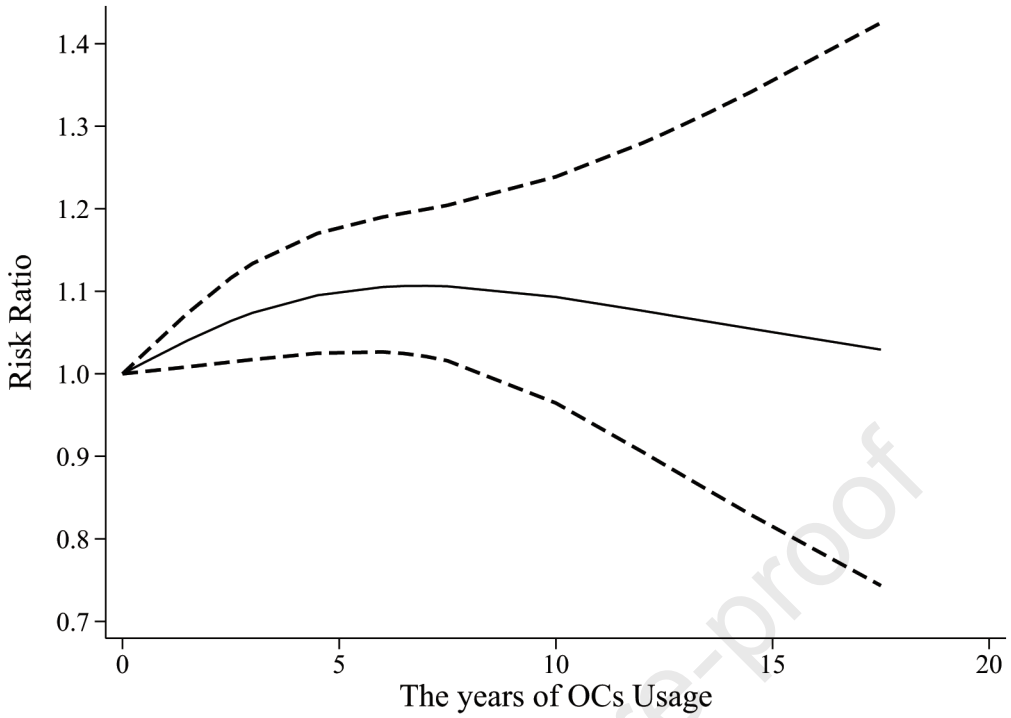












***Abbreviations list*:** OC, Oral contraceptive. MeSH, medical subject headings. ORs, odds ratios.NOS, Newcastle-Ottawa scale.ICD, International Classification of Diseases.

Declaration of interests

■ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

■The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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