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Maternal vitamin D intake during pregnancy and risk of asthma and wheeze in children: A systematic review and meta-analysis of observational studies

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Abstract

Aims: To summarize the relationship between vitamin D and infant asthma or wheeze.

Materials and Methods: We used PubMed and Embase to search articles through July 2017 with selection criteria for relevant studies. Random-effect models were used to pool the results of included studies.

Results: Ten articles with 14 independent reports of 2,073 incident cases of asthma and 1,875 cases of wheeze among 23,030 pairs of mother and child were included in our meta-analysis. Compared to those who didn't take vitamin D, the mothers who had vitamin D supplementation during pregnancy stage could reduce the risk of asthma or wheeze in infants. The combined odds ratio of infant wheeze was 0.65 (95% CI=0.54-0.79) and asthma was 0.78 (95% CI=0.69-0.89). The results almost didn't change in the subgroup analyses.

Conclusions: It suggests that increasing maternal vitamin D intake during pregnancy might have a protective effect on suffering from wheeze and asthma for children.

Key words: Vitamin D; pregnancy; asthma; wheeze; meta-analysis

1.Introduction

Childhood asthma is a chronic disease of respiratory tract that usually starts in early life of human being.[1] Its characteristics include variable and recurrent symptoms, reversible airflow obstruction and bronchial spasm. Wheeze is one of common symptoms for asthma attack, especially in young children. And wheeze starts even in the first several weeks of new arrival.[2] In addition, infants who only have wheeze with respiratory infections are more likely to develop asthma. Wheeze and asthma both are the most common problems that will affect the health of newborns, and the main reasons of early children being hospitalized and going to the emergency department for treating.[3, 4] A number of risk factors are established to be associated with wheeze and asthma, such as maternal smoking during pregnancy and maternal asthma,[5, 6, 7, 8] moreover, vitamin D has been reported to play an important role in the progression of wheeze and asthma in recent years.

Vitamin D is a kind of nutrient as well as a hormone,[9] also, it is a role in calcium homeostasis and metabolism. As time goes by, accumulating evidences suggest that vitamin D has the function to improve lung development and immune system of children who are in the fetal and early postnatal period.[10, 11, 12, 13, 14] When the immune system is impaired, allergy or sensitive immune responses induced by air pollutants, pollen or cold are thought to be the main causes of asthma in children. Furthermore, observational studies have shown an association between low levels of vitamin D and an increased risk of allergic sensitization [15] or respiratory tract infections.[16] Therefore, maternal or children vitamin D supplementation may help to reduce the risk of wheeze and asthma in young children. Some epidemiology studies have explored the relationship of vitamin D, wheeze and asthma. However, the above conclusions are still controversial.[9, 17, 18] Devereux and colleagues[9] found that the higher maternal vitamin intake could reduce the risk of wheeze in early childhood while Magnus and colleagues[16] reported no significant association between the level of maternal vitamin D and early childhood asthma. The effect of maternal vitamin D supplementation on asthma and wheeze in early childhood is still unclear.

In this study, we conducted a meta-analysis of published epidemiological studies to summarize the conclusion of the above relation and to quantify the association between maternal vitamin D intake and risk of asthma or wheeze in their infants.

2.Materials and methods

We planned this review in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[19]

2.1 Literature search

We conducted a literature search of PubMed and Embase for observational studies through July 2017 by using the following search terms without restriction: “vitamin D”, “wheeze”, “asthma”, “children” and “pregnancy”. In addition, we have reviewed

reference list from the relevant articles to identify additional articles that are not searched at first. We have set no limitation on region, ethnic group or religion of people. Also, we only considered the articles published in the English language.

2.2 Studies selection

All the references from electronic database were mixed and collected in Endnote. Articles were included if they met the following criteria: (1) vitamin D was the only variable in the study, (2) people who intake vitamin D in study should be pregnant women, (3) it should show clear methods of how to collect the data, (4) it should have a clear result, such as odds ratio (OR) with 95% confidence interval (CI), to show the relation between vitamin D and wheeze or asthma, (5) it should be nonrandomized study design. Studies were not included if: (1) non-human studies, (2) studies just summarized or inferred the relation between vitamin D and wheeze or asthma, didn't provide any data, (3) studies put asthma and wheeze together and just gave one result for both.

2.3 Data extraction

The following data were extracted from articles: the name of the first author, the year of publication, the country, follow-up year, number of subjects and cases, study design, odds ratios (ORs) with 95% confidence intervals (CIs) and adjusted covariates. We separate the data of asthma and wheeze in two forms.

2.4 Quality assessment

We followed Newcastle-Ottawa Quality Assessment Scale to assess the quality of studies, it is a validated scale, which has a maximum of 9 points, used for nonrandomized studies in meta-analysis. The 9 points scale includes: 4 for selection of participants and measurement of exposure, 2 for comparability of cohorts on the foundation of the design or analysis, and 3 for assessment of results and time of follow-up. We assigned scores of 0~3, 4~6, 7~9 for low, moderate and high quality of studies.

2.5 Statistical analysis

In this meta-analysis, we used ORs and 95% CIs to measure the association of interest; also, hazard ratios and relative risks were considered equivalent to ORs. When ORs were showed separately in subgroup with different level of vitamin D, we combined the results from every subgroup to calculate a common OR for final analysis. The lowest level of vitamin D intake was regarded as "basic vitamin D intake" while other levels of vitamin D intake were defined as "more vitamin D intake". Random effects model was the method that we used to calculate the overall combined OR.[20]

Heterogeneity was tested by Q and I² statistic.[21] It was confirmed with a significant level of P<0.10. The I² measures the proportion of total variation from studies caused by heterogeneity, but not chance; also, its values of 25%, 50% and 75%

show cutoff points for low, moderate and high degrees of heterogeneity.[22] In sensitivity analyses, we used one-leave-out[23] analyses for every study to examine the influence of each study on pooled result. Furthermore, subgroup analyses for location, publication year, study design and number of participants were conducted to examine the stability of the original results. For publication bias, Begg's test and Egger's test were used to assess.[24, 25] In addition, all statistical analyses were showed using STATA version 12.0, and all tests were two sided with a significance level of 0.05.

3.Results

3.1 Literature search

Fig.1 shows the process of study identification and collection. The search included 952 citations from PubMed and 727 citations from Embase before 1 August 2017. After 562 duplicates were excluded, 1117 citations were collected for screening through title and abstract; then, 1097 citations were excluded because they were randomized studies or irrelevant studies. After reading the full text of 10 articles, 10 articles were excluded due to a lack of sufficient data, such as odds ratio. Eventually, 14 independent reports in 10 articles were included in our final meta-analysis. [9, 16, 17, 26, 27, 28, 29, 30, 31, 32]

3.2 Study Characteristics

All the main information of the studies was extracted in Table S1 and S2 prospectively. All included studies were cohort studies or case-control studies, and they were all published from 2007 to July 2017. To be more specific, four studies were conducted in the UK, [9, 26, 27, 28] one in Denmark,[29] Finland,[30] Norway, [16] US,[17] Canada,[31] and Japan. [32] The sample size of studies ranged between 581 and 5632, and the number of asthma or wheeze case ranged from 79 to 504. Among them, four studies reported asthma and wheeze separately, the total reports were 14. All studies have adjusted covariates, such as child sex, birth weight, maternal smoking during pregnancy, maternal asthma, breastfeeding duration, and so on.

3.3 Vitamin D intake during pregnancy and wheeze

Figure 2 shows the results from random-effects model combining the risk estimates of wheeze. In the whole seven studies, six studies reported an inverse relationship between maternal vitamin D intake during pregnancy and offspring wheeze, and one showed no significant association of interest. Overall, the combined odds ratio of wheeze was 0.65 (95% CI=0.54-0.79, $I^2=78.9\%$, $P=0.000$) for increasing the maternal vitamin D intake during pregnancy in comparison with those didn't take vitamin D.

3.4 Vitamin D intake during pregnancy and asthma

The results from random-effects model combining the risk estimates of asthma are showed in Figure 3. In the whole seven studies, the results from five studies indicated that increasing maternal vitamin D intake reduced the risk of offspring asthma, and

two showed the relationships were not significant. All in all, the combined odds ratio of asthma was 0.78 (95% CI=0.69-0.89, $I^2=63.3\%$, $P=0.002$) for increasing the maternal vitamin D intake during pregnancy when compared with those not taking vitamin D.

3.5 Subgroup and sensitivity analysis

Subgroup analysis by location, publication year, study design and number of participants were conducted to examine the stability of the results (Table S3 and Table S4). The associations between increasing maternal vitamin D intake and the risk of offspring wheeze were similar in most subgroup analyses. However, it showed that location and publication year might be sources of heterogeneity for wheeze. The result of wheeze sorted by study location showed that the OR for Americans was 0.53 (95% CI=0.43-0.67), which was much lower than ORs from other areas. Also, the ORs of wheeze in the studies with participants ≤ 1000 (0.73, 0.57-0.93) was much higher than those of participants > 1000 (0.58, 0.44-0.76).

The association between increasing maternal vitamin D intake and the risk of offspring asthma in subgroup analyses were almost the same as the relationship between vitamin D supplementation and infant wheeze. Nevertheless, publication year might be a source of heterogeneity because the ORs of asthma in studies which were published before 2014 (OR=0.82, 0.71-0.94) were much higher than those published after 2014 (0.65, 0.49-0.85).

In addition, sensitivity analysis was made by excluding a single study in turn. The final pooled OR didn't materially change, with a range from 0.65 (0.53-0.81) to 0.74 (0.63-0.87) for wheeze and 0.76 (0.68-0.85) to 0.86 (0.76-0.95) for asthma.

3.6 Publication bias

Visual inspection of funnel plots failed to identify substantial asymmetry (Figure S1 and S2). We didn't find any publication bias by Begg's rank correlation test and Egger's linear regression test for wheeze (Begg's test $Z=1.87$, $P=0.06$; Egger's test $t=2.11$, $P=0.06$) and asthma (Begg's test $Z=1.56$, $P=0.12$; Egger's test $t=0.87$, $P=0.41$).

4. Discussion

It is no doubt that wheeze and asthma are big problems that affect the health of young children. The possible roles of vitamin D in reduction the risk of childhood wheeze or asthma have been evaluated in epidemiological studies and the results were inconsistent. Our systematic review and meta-analysis provides evidence to support maternal vitamin D intake or supplementation for the reduction of wheeze or asthma in their infants.

Two systematic reviews and meta-analyses of maternal vitamin D status and childhood asthma published recently yielded different results.[33, 34] Wei and his colleagues found that lower maternal vitamin D during pregnancy was not associated with children asthma or wheeze. They didn't evaluate the effects of maternal vitamin D supplementation. However, Song et al reported that a U-shaped relationship

between maternal blood 25(OH)D levels and risk of children asthma. The lowest risk of childhood asthma was at 70 nmol/L of 25(OH)D in maternal blood. In present study, different from above two meta-analyses, more concerns are paid on the effects of vitamin D supplementation during maternal pregnancy. We included all studies of maternal vitamin D supplementary intake, with or without levels of blood 25(OH)OD. And our results indicated increasing maternal vitamin D intake during pregnancy would have a protective effect on offspring wheeze and asthma. Moreover, result from each study was similar to the pooled result; however, we found one study [28] had different results with the ORs of 1.00 (95% CI=0.98-1.02) for wheeze and 0.98 (95% CI=0.92-1.04) for asthma. Possible reason of this phenomenon was that this study only evaluated serum 25-hydroxyvitamin D level in maternal late-pregnancy. Perhaps, the impacts of vitamin D supplementation on pulmonary development are not significantly in late-pregnancy.

In our subgroup analyses, we obtained two findings in wheeze. Firstly, in wheezing illness analyses, the pooled OR for people from Europe (0.78, 95% CI=0.63-0.96) was clearly higher than those for people from Asia (0.65, 95% CI=0.48-0.87) or America (0.53, 95% CI=0.43-0.67). Possible reason was that one of the American studies and the only Asian study (Japan) included relative higher doses of vitamin D supplementation in their analysis. In their studies, a higher dosage of vitamin D intake led to a lower OR value. Therefore, the pooled OR of their studies would be lower than other studies'. However, we just found two studies from America and one from Asia, which needed to be confirmed further with more studies. Of course, it may be associated with the culture or diet differences among these populations. The second finding was that the pooled OR for the studies with participants ≤ 1000 (0.73, 95% CI=0.57-0.93) was much higher than pooled OR of those with participants > 1000 (0.58, 95% CI=0.44-0.76). Furthermore, we found ORs from the studies with participants > 1000 were generally lower than those from the studies with participants ≤ 1000 . It may be because the bigger number of participants would lead to a general result. Besides, it also confirmed that vitamin D intake in pregnancy could have a protective effect on wheeze and asthma for children, as larger number participants could provide more reliable results. As to asthma, we could find that some differences between studies published before 2014 and after 2014. The OR was much lower in studies published after 2014 than that before 2014, and no heterogeneity was found among these three studies, thus it could declare that vitamin D may have a protective effect on asthma.

The mechanisms that underlie these associations are complex. Several potential mechanisms may be used to explain the associations of vitamin D and wheeze or asthma. Firstly, some recent studies show VDR gene is related to lung disease.[17] In addition, VDR gene is a kind of gene with vitamin D, and both asthma and wheeze are lung diseases. Therefore, it shows that vitamin D levels will influence VDR gene, thereby affecting asthma or wheeze. Secondly, lower vitamin D levels may cause airway smooth muscle to increase and reduce lung function.[35] Once lung function drops, there will be a higher risk to suffer from wheeze or asthma. The last mechanism we found is vitamin D could modulate antigen-presenting cells, such

as macrophages; regulate T cells, which express inhibitory cytokines (IL-10); and inactivate the activation of antigen-specific T cell.[17]

Our study has several strengths. We collected only prospective studies with an average quality score of 7.6, which could proof the high quality of our meta-analysis. Besides, we included studies that were published in the last ten years, and most of which were published in last five years. In our meta-analysis, some limitations should be cleared. Firstly, either wheeze or asthma was confirmed by questionnaire, it would cause a bias when recorded the data. Secondly, daily maternal vitamin D intake was also confirmed by specific questions, bias of memories may exist, thus it would influence the exposure assessment and affect the final result.

5.Conclusion

In summary, our meta-analysis suggests that increasing maternal vitamin D intake during pregnancy should lower the risk of offspring wheeze and asthma. Vitamin D may have a protective effect on suffering from wheeze and asthma.

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No.

Conflicts of interest

No conflicts of interest were reported.

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JUST ACCEPTED

Figure Legends

Figure 1 Flow diagram of literature search and study selection

Figure 2 The relationship between vitamin D of pregnancy among mother and risk of wheeze in children

Figure 3 The relationship between vitamin D of pregnancy among mother and risk of asthma in children

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Supplementary Material

Table S1 Characteristics of studies for asthma included in meta-analysis

Table S2 Characteristics of studies for wheeze included in meta-analysis

Table S3 Stratified analyses on associations of vitamin D of pregnancy among mother and risk of asthma in children

Table S4 Stratified analyses on associations of vitamin D of pregnancy among mother and risk of wheeze in children

Figure S1 Funnel plot of vitamin D of pregnancy among mother and risk of asthma in children

Figure S2 Funnel plot of vitamin D of pregnancy among mother and risk of wheeze in children





