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Maternal vitamin D status and childhood asthma, wheeze and eczema: a systematic review and meta-analysis

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Abstract

Background

Maternal vitamin D status has been reported to be associated with childhood allergic diseases. However, this association remains to be fully elucidated.

Methods

A systematic review and meta-analysis was conducted using prospective cohort studies that examined the association between maternal vitamin D status and childhood allergic diseases including wheeze, eczema and asthma. We searched electronic databases of PubMed, EMBASE, the Cochrane library, the Wanfang (Chinese) database, the VIP (Chinese) database, and Chinese National Knowledge Infrastructure (CNKI) up to August 2014. Odds ratios and 95% confidence intervals (CIs) from individual studies were synthesized using a fixed effects model.

Results

Four studies on the association between maternal vitamin D status and childhood asthma (3666 mother-child pairs), four studies on the association between maternal vitamin D status and childhood wheeze (2225 mother-child pairs) and three papers on the association between maternal vitamin D status and childhood eczema (2172 mother-child pairs) met our inclusion criteria. Maternal vitamin D status during pregnancy was associated with childhood eczema (pooled OR=0.904, 95% CI=0.831-0.983). However, the meta-analysis showed no statistical

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association between maternal vitamin D status and childhood asthma (pooled OR=0.981, 95% CI=0.944-1.019) or childhood wheeze (pooled OR=0.995, 95% CI=0.982-1.009).

Conclusions

Our meta-analysis found that lower maternal vitamin D during pregnancy was associated with an increased risk of childhood eczema but was not associated with childhood asthma or wheeze. The role of maternal vitamin D as an important protective factor for the development of childhood eczema remains to be elucidated.

Key words

Maternal, vitamin D, childhood, allergy

Introduction

The prevalence of allergic diseases began to increase worldwide in the 1960s [1]. The rising worldwide trend of allergic disorders in children and adults is a major public health concern [2]. Recently, many research efforts have attempted to explain the immunomodulatory mechanism and pattern of epidemiology of allergic diseases. However, the precise immune pathways driving this phenomenon are still under debate, and available data are conflicting [3-7]. At present, most studies seem to suggest that vitamin D protects against allergic diseases.

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Vitamin D is both a nutrient and a hormone [8]. It acts as a hormone and is well recognized for its role in allergic diseases. Maternal vitamin D deficiency, as indicated by low circulating 25-hydroxyvitamin D [25(OH)D] levels, is common during pregnancy worldwide [9,10,11]. Poor vitamin D status in children may be linked to poor maternal vitamin D status during pregnancy because the developing fetus depends entirely on its mother for its supply of vitamin D [12, 13].

Allergic diseases are the most common chronic diseases among children [14].

The prevalence of allergic diseases is increasing worldwide, the complexity and severity of allergic diseases continue to increase especially in children and young adults, who are bearing the greatest burden of the trends,, indicating the importance of early exposures. In recent years, vitamin D has been a focus of growing interest in public health nutrition [15-16]. This also raises the question of whether vitamin D status in utero and early life has effects on the development of allergic diseases. Therefore, our aim was to systematically review and update data from birth cohort studies regarding the effect of maternal vitamin D during pregnancy on childhood allergic diseases.

Methods

The preferred reporting items for systematic reviews and meta- analysis (PRISMA) statement was consulted during the preparation of this review.

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Identification and selection of studies

Search strategy

Two reviewers (Zhenzhen Wei, Xiaodan Yu) independently searched targeted studies on maternal vitamin D status and childhood allergic outcomes. PubMed, EMBASE, the Cochrane library, the Wanfang (Chinese) database, the VIP (Chinese) database and Chinese National Knowledge Infrastructure (CNKI) were searched for relevant studies up to August 2015. Language restrictions were not applied. The following key words were applied in the search for eligible articles: "vitamin D" and ('antenatal" or "pregnancy" or "prenatal") and ("allergy" or "allergic disease" or "asthma" or "wheeze" or "eczema"). Authors manually searched for further relevant studies.

Data collection and analysis

Two reviewers (Zhenzhen Wei, Xiaodan Yu) independently evaluated the title, abstract, and keywords of every record identified with the search strategy. The following inclusion criteria for published studies were applied: (1) the studies included pregnant women who were assessed for vitamin D status (the studies included vitmain D status during pregnancy, comprising maternal serum 25(OH)D, cord serum 25(OH)D and vitamin D intake from food and supplements), and the outcomes included childhood allergic outcomes; (2) the study was a prospective cohort study; and (3) the studies reported relative risks (RRs), odds ratios (ORs) or hazard ratios (HRs) with their 95% confidence intervals (CIs) or provided enough data to calculate the effect size. However, we excluded articles in which ORs were only reported by

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category of vitamin D. Discrepancies between the reviewers were resolved by discussion until a consensus was reached (Figure 1).

Data extraction was performed using specific forms. All data were extracted independently by two reviewers (Zhenzhen Wei, Xiaodan Yu). In cases of discrepancies in the data collection process, a consensus was reached through discussion. The information extracted from each study included the study design, allergic disease, the first author's name, year of publication, country of origin, sample size, measurement method of maternal vitamin D status, gestational age at the time of vitamin D measurement, odds ratio and the potential confounding factors in the adjustment (Table 1). As allergic outcomes are relatively rare, the distinction between the different estimates of relative risk (i.e., odds ratio, rate ratio, risk ratio) was ignored, and all measures were interpreted as relative risk.

Assessment of study quality

All studies were evaluated using the Newcastle–OttawaScale (NOS) [17]. The NOS is a nine-point scale which assigns points based on the selection process of cohorts(0–4 points), the comparability of the cohorts(0–2 points), and the identification of the exposures and the outcomes of research participants (0–3 points). This measure is recommended by the Cochrane Non-Randomized Studies Methods Working Group. A score of seven and above was defined as high quality.

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Statistical analysis

Odds ratios and 95% confidence intervals from included studies were pooled separately to assess the association between maternal vitamin D status and childhood allergic outcomes. Heterogeneity of treatment effects was evaluated graphically with forest plots and statistically with a Q test and I^2, and heterogeneity was considered to be present if the P value of the Q test was <0.1 and the I^2 statistic was >50%. If there was no heterogeneity, the pooled OR was evaluated using a fixed effects model. Otherwise, a random effects model was used. Potential publication bias was assessed via visual inspection of the symmetry of the funnel plots. Quantitative analysis for publication bias included the Begg's test and the Egger's test. The trim and fill method was adapted for analysis of sensitivity. All analyses were performed using Stata 12.0 (Stata Corp, College station, TX) statistical software.

Results

Description of studies

Figure 1 summarizes the processes of literature identification and selection of studies evaluating the relation between maternal vitamin D status and childhood asthma, wheeze and eczema outcomes. The initial search yielded 63 citations. After review of the title and abstract, 30 studies were excluded. After review of the title and abstract, 27 studies were excluded because they were review articles (7), animal studies (1), or did not report the outcomes of interest (19). Ultimately, we excluded studies only focusing on ORs with stratified categories of vitamin D, there were 6 studies providing ORs with 95% CI [7,

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18-22]. The characteristics of the 6 trials that fulfilled the predefined inclusion criteria are detailed in Table 1.

Four studies, which together included 3666 mother-child pairs, evaluated the association between maternal vitamin D during pregnancy and childhood asthma [7, 19-21]. No evidence of heterogeneity across studies was detected (χ^2=4.213, P=0.239). Figure 2 (Part A) presents the forest plot for the association between maternal vitamin D status and childhood asthma. The fixed effects model indicated that maternal vitamin D status during pregnancy was not associated with an increased risk of asthma in offspring (pooled OR=0.981, 95% CI=0.944-1.019).

Four cohort studies, which together included a total of 2225 mother-child pairs, evaluated the association between maternal vitamin D status and childhood wheeze [7, 18-20]. The Q test of heterogeneity did not show statistical significance (χ^2=3.846, P=0.279). Figure 2 (Part B) shows the forest plot for the association between maternal vitamin D status and childhood wheeze. There was no association detected between maternal vitamin D status and childhood wheeze (pooled OR=0.995, 95% CI=0.982-1.009).

Three studies assessed the association between maternal vitamin D status and childhood eczema [18, 21, 22], and together they included 2172 mother-child pairs. There was no evidence of statistical heterogeneity for these studies (χ^2=0.773, P=0.680). Figure 2 (Part C) presents the association between maternal vitamin D status and childhood eczema. In a fixed effects meta-analysis, the association between maternal vitamin D status and childhood eczema was statistically significant (pooled OR=0.904, 95% CI=0.831-0.983).

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Sensitivity analysis

We used the trim and fill method to perform sensitivity analyses. The pooled ORs and 95% CIs were not materially altered, suggesting that the results from this meta-analysis were statistically robust.

Bias diagnostics

No bias was detected in the analyses of the association between maternal vitamin D status during pregnancy and childhood asthma (Begg's test, P=0.734; Egger's test, P=0.541) (Figure 3), childhood wheeze (Begg's test, P=1.000; Egger's test, P=0.804) (Figure 4), and childhood eczema (Begg's test, P=1.000; Egger's test, P=0.725) (Figure 5).

Discussion

Our systematic review and meta-analysis showed a modest association between low maternal vitamin D levels and an increased risk of childhood eczema in offspring. However, the pooled results did not provide evidence of any apparent association between maternal vitamin D status and childhood asthma or wheeze.

The quality of a meta-analysis depends on the quality of the studies included. In this systematic review and meta-analysis, we included only studies focusing on mother-child pairs from prospective cohort studies. It should be noted that no statistically significant heterogeneity was detected across the prospective cohort studies included in this

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meta-analysis. Consequently, we adopted a fixed effects model to examine the pooled effects of association between maternal vitamin D status and childhood allergic outcomes. Sensitivity analyses indicated that the results from the meta-analysis were robust and not substantially altered when individual studies were excluded.

This systematic review and meta-analysis is the most recent and quantitative review of the topic reported to date. Previously, several reviews focused on maternal vitamin D (vitamin D from dietary intake) with allergic diseases (asthma and wheeze) [23-25]. Studies from Nurmatov U and Castro-Rodriguez J A indicated an association between maternal vitamin D intake and childhood wheeze [23] and eczema [24], however, Cassim R did not find any association between cord vitamin D and asthma [25]. Our systematic review and meta-analysis focuses on observational studies documenting the associations between maternal vitamin D levels and several childhood allergic outcomes (asthma, wheeze and eczema). Most studies included in this review used direct serological measures of vitamin D to accurately confirm vitamin D status, although 5 of 6 the studies in the review assessed maternal vitamin D status in only the last trimester of pregnancy.

A number of potential mechanisms through which maternal vitamin D exposure may lead to childhood allergic outcomes have been proposed. Several recent genetic association studies [26-29] suggest that polymorphisms of the vitamin D receptor gene are related to asthma as well as a range of autoimmune conditions. The presence of 1,25-$(OH)_2$D has also been found to modulate antigen-presenting cells (such as inhibition of macrophages) [30-32], enhance the proliferation of regulatory T cells [33], and induce a T helper subset balance toward Th2 dominance [34,35]. Although some studies have shown an increased Th2

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response in the presence of vitamin D, others have reported that vitamin D may either suppress or enhance the Th2 response [35-37]. Evidence also indicates that vitamin D is an important regulator of lung growth in utero [38-40].

Some limitations of this review should be acknowledged. First, the methods of vitamin D assessments (dietary and supplementation intake vs. biomarkers in serum or umbilical cord blood) were inconsistent across the studies. Dietary and supplementation information was mainly based on data from maternal questionnaires, which are vulnerable to recall bias. Second, our rigorous inclusion criteria significantly limited the number of analyzed studies, which restricted the possibility of a more comprehensive analysis. Another potential limitation of this systematic review is the lack of data on the race/ethnicity and sunlight exposure of participants in the original studies, which prevented us from stratifying the findings by sunlight exposure or race/ethnicity [41]. Finally, the observed associations between maternal vitamin D status and childhood allergic outcomes could be affected by confounding factors [42] as not all studies in this review generated adjusted ORs. However, since confounding factors can influence the strength of the results of the studies [42], most of the studies included in this meta-analysis were investigated for possible confounding factors whenever possible (Table 1). Several factors such as parents' history of allergy and season of birth were identified as potential confounders of the association of maternal vitamin D with childhood allergic diseases. Only one study from Anderson P. Jones did not adjusted for confounding factors in this study [18].

Conclusions and future research directions

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In summary, this systematic review and meta-analysis of observational studies showed that low vitamin D level during pregnancy was associated with risk of childhood eczema but not with childhood asthma or wheeze. Despite growing interest in the relationships between maternal vitamin D status during pregnancy and childhood allergic outcomes, the epidemiological evidence thus far remains insufficient to provide clinical guidance. The results of this meta-analysis provide further justification for the trials of vitamin D intervention during pregnancy that are currently underway.

Further confirmation of these findings in intervention trials is required. Additionally, further research is required to better understand the role in these childhood diseases of vitamin D status during different trimesters of pregnancy.

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Table 1. Characteristics of studies on maternal vitamin D status and childhood allergic outcomes

Study design	disease	First author's name	Age	Diagnosis	Year of publication	Country of origin	Sample size	Measurement method of vitamin D status	Assessment times	Odds ratio and 95% confidence intervals	Quality score	Adjustment factors
Prospective cohort study	asthma	Nour Baïz	5 years old	doctor's diagnosis	2014	France	239	Cord blood 25(OH)D	Last trimester	1.07 (0.78-1.45)	8	a
Prospective cohort study	asthma	Carlos A	5 years old	doctor's diagnosis	2011	New Zealand	922	Cord blood 25(OH)D	Last trimester	0.99 (0.94-1.04)	8	b
Prospective cohort study	asthma	Katharine C Pike	6 years old	doctor's diagnosis	2012	UK	836	Serum 25-OH D	Last trimester	0.98 (0.92-1.04)	8	c
Prospective cohort study	asthma	M. Erkkola	5 years old	doctor's diagnosis	2009	Finland	1669	Food and supplement	First, second and last trimester	0.79 (0.64-0.99)	8	d
Prospective cohort study	wheeze	Nour Baïz	5 years old	parental report	2014	France	239	Cord blood 25(OH)D	Last trimester	1.15 (0.79-1.691)	8	e

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Prospective cohort study	wheeze	Carlos A	15 months	parental report	2011	New Zealand	922	Cord blood 25(OH)D	Last trimester	0.96 (0.92-1.00)	8	f
Prospective cohort study	wheeze	Katharine C Pike	6 years old	parental report	2012	UK	833	Serum 25-hydroxyvitamin D	Last trimester	0.99 (0.94-1.05)	8	g
Prospective cohort study	wheeze	Anderson P. Jones	12 months	parental report	2012	Australia	231	Cord blood 25(OH)D	Last trimester	1.00 (0.98-1.01)	7	h
Prospective cohort study	eczema	Anderson P. Jones	12 months	doctor's diagnosis	2012	Australia	231	Cord blood 25(OH)D	Last trimester	0.857 (0.739-0.995)	7	i
Prospective cohort study	eczema	M. Erkkola	5 years old	parental report	2009	Finland	1669	Food and supplement	First, second and third trimester	0.93 (0.84-1.04)	8	d
Prospective cohort study	eczema	K. Weisse	12 months	Parental report	2013	Germany	272	Serum 25-hydroxyvitamin D	Last trimester	0.89 (0.63-1.32)	8	j

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a. Adjusted for city, mother's age, maternal history of allergy, prepregnancy body mass index, any smoking during pregnancy, any passive smoke exposure during the first 3 years of life, number of siblings, household income, newborn's sex and weight, and season.

b. Adjusted for season of birth plus 13 potential confounders (study site, maternal age at birth, New Zealand Deprivation Index, maternal history of asthma, paternal history of asthma, gestational age, gender, child's ethnicity, any smoking during pregnancy, any passive smoke exposure at 3 months of age, number of children younger than 16 years in the household at the time the child was 3 months old, endotoxin on bedroom floor at the time the child was 3 months old [in quartiles], and duration of exclusive breastfeeding).

c. Adjusted for maternal education, maternal asthma, paternal asthma and paternal rhinitis.

d. Adjusted for sex, area of birth, duration of gestation, maternal age, maternal basic education, maternal smoking during pregnancy, number of siblings, parental asthma, parental allergic rhinitis, atopic eczema before the age of 6 months (except for the end-point of atopic eczema), and pets inside the house before the age of 1 year.

e. Adjusted for city, mother's age, maternal history of allergy, prepregnancy body mass index, any smoking during pregnancy, any passive smoke exposure during the first 3 years of life, number of siblings, household income, newborn's sex and weight, season of birth, and exclusive breast-feeding for 4 months or longer.

f. Adjusted for season of birth.

g. Adjusted for maternal education, smoking during pregnancy, maternal asthma, paternal asthma, and maternal rhinitis.

h. Unadjusted.

i. Adjusted for season of birth, infant gender, pet ownership, maternal age, and maternal ethnicity

j. Adjusted for gender of the child, number of siblings, cord blood total IgE, family history of atopy, log cotinine (34th week of pregnancy), breast feeding, UV intensity of month of birth and vitamin D supplementation during the first year of life.

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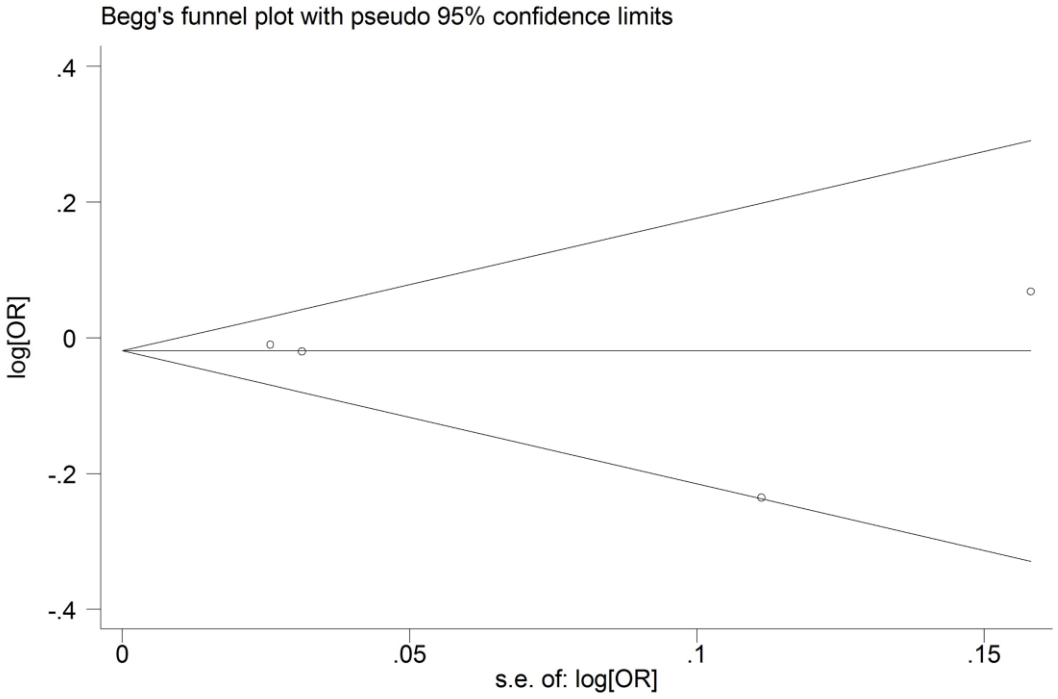
Figure 3: Funnel plot of the association between maternal vitamin D status and childhood asthma. Begg's funnel plot with pseudo 95% confidence limits.

Figure 4: Funnel plot of the association between maternal vitamin D status and childhood wheeze. Begg's funnel plot with pseudo 95% confidence limits.

Figure 5: Funnel plot of the association between maternal vitamin D status and childhood eczema. Begg's funnel plot with pseudo 95% confidence limits.



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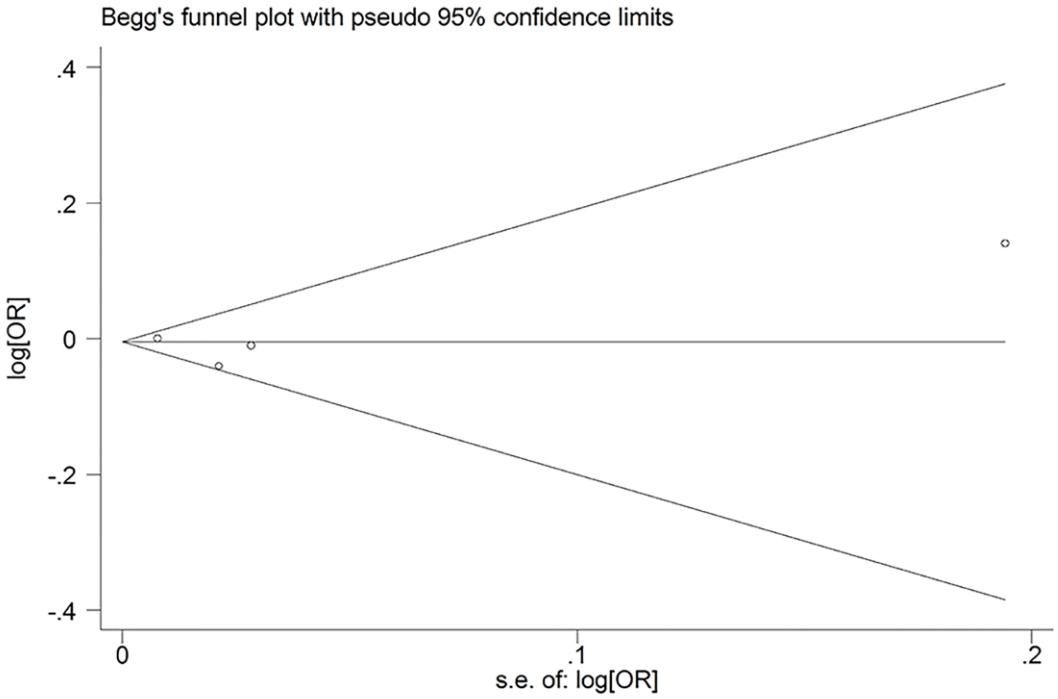

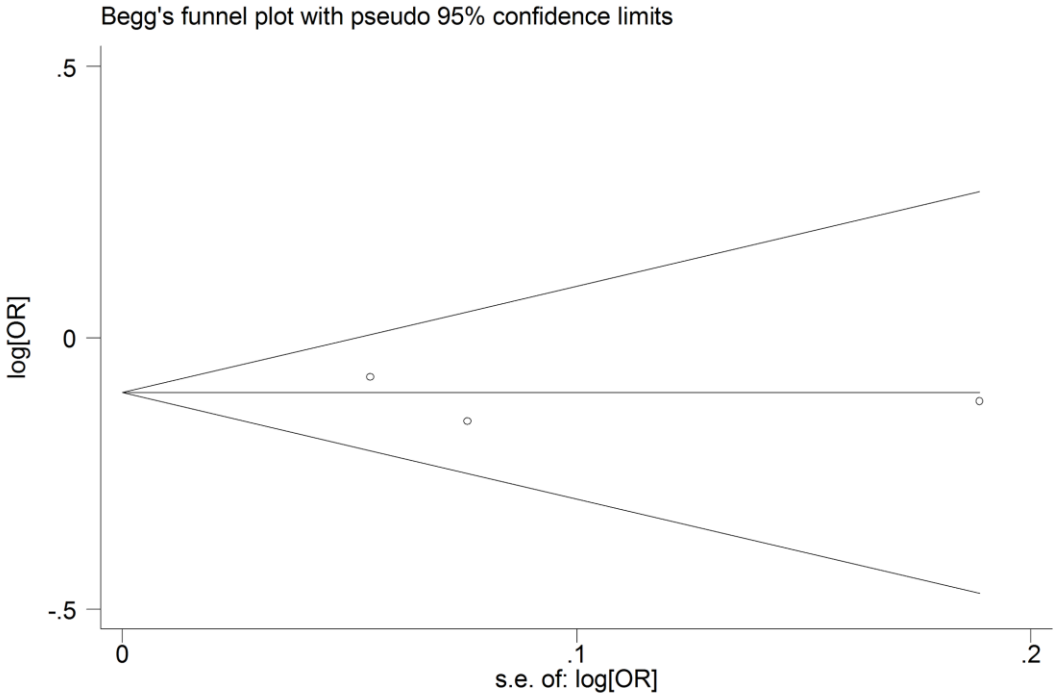

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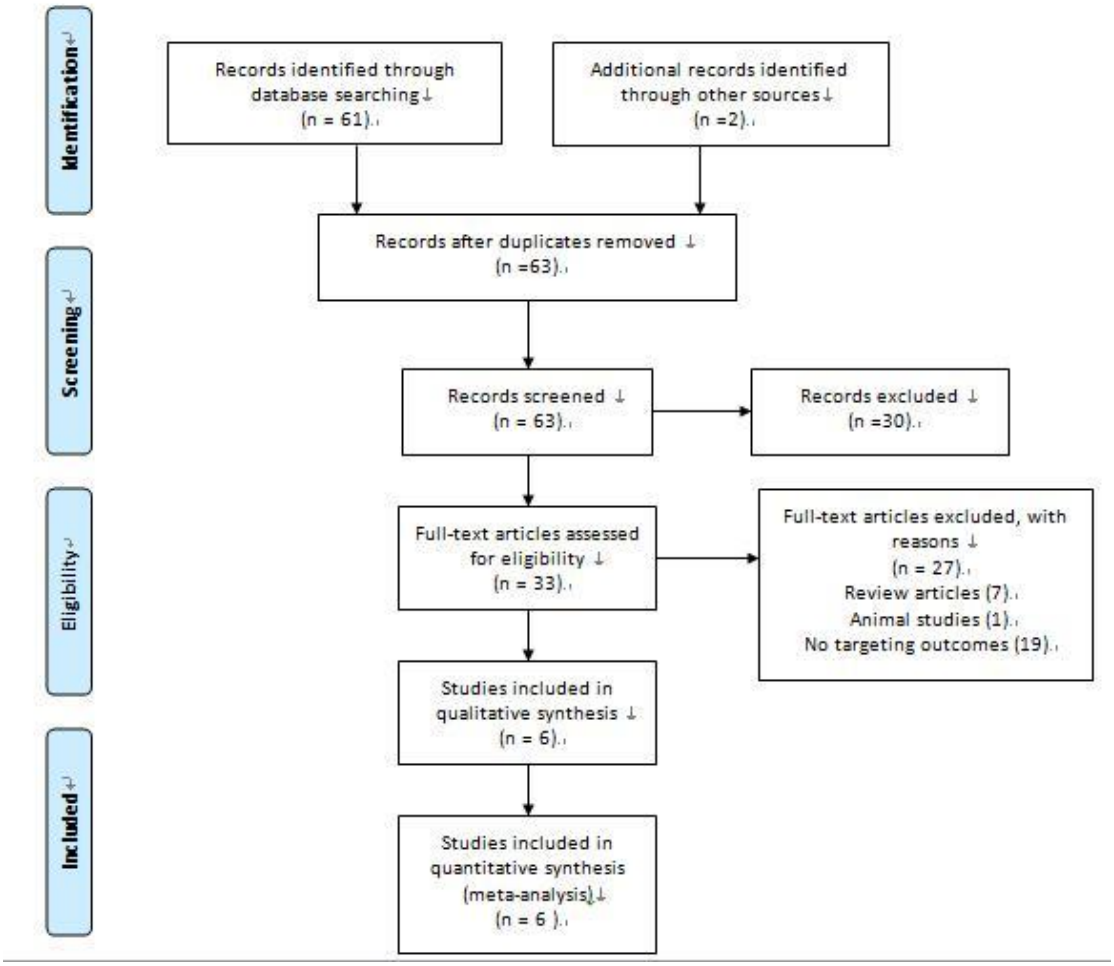

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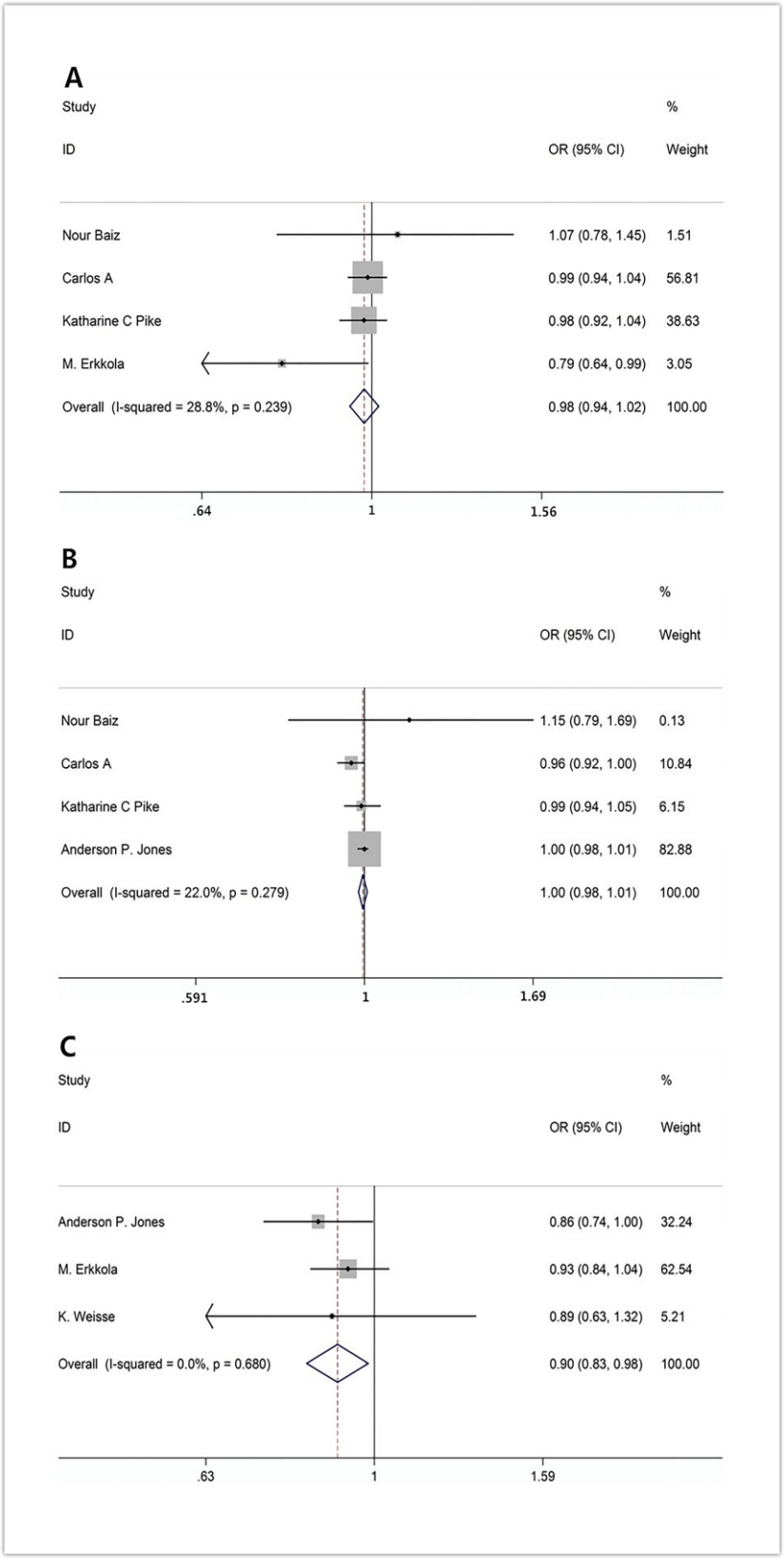

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