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REVIEW ARTICLE

Systematic review of areca (betel nut) use and adverse pregnancy outcomes

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KEYWORDS

Adverse outcomes; Areca; Betel nut; Pregnancy; Pregnancy complications

SYNOPSIS

A review of the evidence of adverse perinatal outcomes and areca use identified eight studies in the Asia–Pacific region showing an association with low birthweight.

ABSTRACT

Background: Betel nut is the fourth most commonly abused substance worldwide and has been associated with significant adverse health outcomes. Little is known about its effects on the fetus.

Objective: To perform a systematic review of studies investigating prenatal betel nut use and adverse perinatal outcomes.

Search strategy: Pubmed, Embase, and Cochrane databases were searched from

inception until July 2018 using the terms areca, betel nut, pregnancy, pregnancy complications, and infection.

Selection criteria: Eligible studies included case–control, cohort, and randomized control studies involving pregnant women.

Data collection and analysis: Where appropriate, bivariate meta-analysis was performed, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Main results: In total, 28 studies were screened and eight studies (including 15 270 women) were included in the review and meta-analysis. Preterm birth, low birthweight, and anemia were most commonly investigated. Meta-analysis revealed a significant association between betel nut use and low birthweight, with a pooled OR of 1.75 (95% CI, 1.35–2.27).

Conclusions: The review identified only eight eligible studies, all based in the Asia–Pacific region. There was a significant association between low birthweight and betel nut exposure in pregnancy. Further prospective studies are needed to confirm this association.

1 INTRODUCTION

Betel nut, also called areca nut, is the fourth most commonly abused substance worldwide, with approximately 10%–20% of the global population using some form of the substance [1, 2]. It is extremely common in many low and lower middle-income countries (LLMICs), especially among Asian, African, and Pacific island populations [1-4]. Betel nut is highly addictive among chronic consumers [2]. It is used more commonly by females and in many cultural and religious ceremonies, which adds to the prevalence of its consumption during pregnancy [2, 4].

Use of betel nut has been associated with several adverse health outcomes, including oral cancer, diabetes, hypertension, and cardiovascular disease [1, 4-6]. In particular, studies in Asia and Pacific island populations have shown that betel nut is a leading cause of oral cancer, and many countries in this region have the highest rates of oral cancer worldwide [7]. The main active ingredient in betel nut, arecoline, has been well-characterized in terms of its carcinogenic effects on the oral mucosa [2]. It increases both parasympathetic and sympathetic activity, resulting in hypertension, increased risk of arrhythmias, and bronchospasm [2, 6, 8, 9]. Betel nut

spitting has also been associated with the transmission of communicable diseases such as tuberculosis, which has prompted public health initiatives in many south and southeast Asian countries [1, 10, 11].

The United Nation's Sustainable Development Goals for 2030 include goals to reduce global maternal and neonatal mortality ratios, and goals to strengthen the prevention of substance abuse, especially in LLMICs [12]. In working toward these goals, it is important to understand the impact of substances such as betel nut on adverse pregnancy outcomes. In contrast to the well-documented effects of tobacco use on adverse pregnancy outcomes [1, 4, 6]. the potential associations between prenatal betel nut consumption and perinatal outcomes have not been well studied, despite the prevalence of betel nut use among pregnant women [2, 6]. The aim of the present systematic review and meta-analysis was therefore to investigate the association between betel nut use during pregnancy and the risk of adverse perinatal outcomes.

2 MATERIALS AND METHODS:

Search strategy and selection criteria

A search strategy was developed to identify studies investigating prenatal betel nut consumption and adverse perinatal outcomes in MEDLINE, Embase, and the Cochrane Database from inception to July 24th, 2018. The search terms were "areca," "betel nut," "pregnancy," and "pregnancy complications and infections" (Supplementary Table 1).

The review protocol for the study was registered in PROSPERO (CRD42018106450) and followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines; the checklist is provided in Supplementary Table 2. Ethics approval and informed consent were not required because the study was a review of previously published data.

Identifying studies for inclusion

The search identified observational studies, case–control studies, cohort studies, and randomized control trials involving pregnant women. Case reports, review articles, commentaries, letters, opinion pieces, and conference abstracts were

excluded. Studies were restricted to English language. Bibliographies from the identified articles were also reviewed to identify additional studies not captured by the initial search.

Studies were selected for review if they reported both betel nut use in pregnancy and adverse pregnancy outcomes. All eligible studies were uploaded to the online systematic review management system Covidence (Covidence, Melbourne, Australia). Two reviewers independently screened the titles and abstracts of articles retrieved from the literature search (MD, RH). Eligible full-text articles were again independently screened by two reviewers and any disagreements were resolved by a third reviewer (FB).

Quality assessment

The quality of the included studies was evaluated independently by two reviewers using the Newcastle–Ottawa scale (NOS) [13]. The NOS broadly scores studies using a points-based system, with a maximum score of 9 points based on three categories: selection of the study groups, comparability of the groups, and ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. These scores were used to rank study quality as “high,” “medium,” or ‘low” quality, where a NOS score of 7 or more indicates high quality or low risk of bias; a NOS score of 3–6 indicates moderate quality; and a score of less than 3 indicates low quality or high risk of bias.

Statistical methods

Two reviewers independently extracted data on both clinical and methodologic study characteristics for each included study by using a piloted standardized data extraction form. For each individual adverse outcome, the odds ratio (OR) and associated 95% confidence interval (CI) were calculated. Pooled estimates for two or more studies reporting the same adverse outcomes with similar study designs were calculated by using bivariate meta-analysis with a fixed effect model. Heterogeneity between the studies was assessed with Cochran *Q*, I^2 , and *H* statistics. I^2 values greater than 60%–70% were considered to indicate substantial heterogeneity. All analysis was performed by using Stata IC version 15.1 (StataCorp, College Station,

TX, USA).

3 RESULTS

The literature search identified 28 studies, of which 8 (including 15 270 women) met the inclusion criteria. Figure 1 shows the PRISMA flow diagram summarizing the screening and selection process, with the reasons for excluding studies from the review. The final eight studies comprised six cohort and two case–control studies, all of which were performed in LLMICs within the Asia–Pacific region (Taiwan, Papua New Guinea, and Palau) (Table 1).

Four of the studies were considered low risk of bias or applicability, with NOS scores between 7 and 8 (where 9 is the maximum score) [2, 4, 14, 15]. The other four studies [1, 16-18] scored from 2 to 6, with limitations in selection of the control cohort, adequacy and duration or follow-up of participants, and difficulty in ascertainment of exposure. Only three studies [2, 15, 16] obtained information about the quantity of betel nut use (Tables 2 and 3).

Among the eight studies, 17 adverse outcomes were assessed including preterm birth (delivery at <37 completed gestational weeks), low birthweight (<2.5 kilograms), anemia, spontaneous abortion, stillbirth, congenital abnormalities, pre-eclampsia, fetal distress in labor, and perinatal and neonatal death (Table 4). One study reported an overall composite of adverse outcomes, and another combined preterm birth and low birthweight.

Odds ratios for each adverse outcome were calculated for individual studies, and positive associations between betel nut use were found with low birthweight and anemia (Table 4). Only one study investigated pre-eclampsia, examining outcomes among 800 women (400 exposed and 400 non-exposed); however, it did not identify a significant association with betel nut exposure. No association between betel nut use and any other single outcome was found (Table 4).

Due to small number of studies and their differing outcomes and study design, it was not possible to calculate pooled estimates for all reported adverse outcomes. Anemia was reported in two cohort studies. One of these studies, including more

than 2000 women [5], found an association between anemia and betel nut exposure (OR, 1.72; 95% CI, 1.31–2.25). Due to the significant heterogeneity between the two studies (I^2 81.4%), a meta-analysis was not performed.

Low birthweight and preterm birth were reported in five (four cohort and one case–control) studies. A meta-analysis was performed for the four cohort studies investigating low birthweight and preterm birth (Table 5). Pooling the estimates for low birthweight, which included a total of 3545 women, indicated that betel nut use was associated with a 75% increased risk of low birthweight, with an OR of 1.75 (95% CI, 1.35–2.27). Pooling the results for preterm birth from the four cohort studies, including a total of 3892 women, gave an OR of 1.20 (95% CI, 0.91–1.62); however, this finding was not significant (Figure 2).

Only three studies prospectively quantified betel nut exposure through detailed questionnaires regarding the number of betel nuts used by participants [2, 15, 16]. Senn et al. [2] found that 56% of participants used less than five nuts per day, 13% used 5–10 per day, and the remaining 31% used more than 10 nuts per day [2]. Yang et al. [15] reported an average of 5.68 betel nuts per day, whereas Ome–Kaius et al. [16] found that 48% of women used more than 3 nuts per day.

No studies measured serum levels of arecoline. Only de Costa et al. [4] controlled for concurrent tobacco and alcohol use, excluding participants with dual use. Lastly, Senn et al. [2] collected data on participant knowledge regarding adverse effects and motivations for using betel nut during pregnancy, reporting that 80% of women in their study perceived no risk of betel nut use on pregnancy or fetal outcomes.

4 DISCUSSION

To our knowledge, this is the first systematic review to evaluate betel nut use during pregnancy. The review identified eight eligible studies, all of which were performed in the Asia–Pacific region where the practice of using betel nut is common [1, 2]. In total, 17 adverse perinatal outcomes were assessed in the eight studies. Because meta-analysis is commonly performed only when there are three or more homogenous studies, it was considered inappropriate to provide pooled estimates for most of these outcomes. Overall, meta-analysis was possible for only two adverse

outcomes, preterm birth and low birthweight.

Four of the eight studies were assessed as low risk for bias or applicability. The remaining studies showed limitations in selection of the control cohort, adequacy and duration of follow-up of participants, and ascertainment of exposure. Furthermore, there was heterogeneity in the outcomes measured and small participant numbers in many of the studies.

Betel nut exposure was not associated with 15 of the 17 reported outcomes. However, the pooled estimate for low birthweight among 3545 participants revealed a 75% increased risk of low birthweight with betel nut exposure during pregnancy. There was also a positive association between betel use and anemia. Low birthweight and anemia are large contributors to maternal and perinatal mortality and morbidity, particularly in LLMICs [19]. Thus, targeting betel nut consumption in this region may help to reduce anemia and low birthweight, improving maternal and neonatal outcomes. Meta-analysis of the four studies reporting preterm birth did not find a significant association with betel nut exposure. However, the slightly positive OR of 1.20 may reflect the limited numbers of study women and warrants further investigation. Similarly, the lack of association between betel nut use and other outcomes may reflect the relatively low number of women included in these studies, further highlighting the need for large, high-quality studies investigating maternal betel nut use.

The effect of betel nut on pregnancy outcomes is not fully understood; however, it has been postulated that betel nut may have a similar mechanism of action on the placenta and fetus as nicotine, which may account for the observed association with low birthweight [20]. Arecoline has been demonstrated to stimulate both the sympathetic and parasympathetic nervous system, resulting in increased systolic blood pressure, heart rate, and body temperature [6]. Furthermore, Kuo et al. [21] found that higher doses of arecoline inhibit endothelial cell growth, indicating that long-term or high-dose use may result in endothelial dysfunction and subsequent pathologies, including low birthweight. In addition, it is plausible that appetite suppression, which has been previously associated with betel nut consumption [22], may result in maternal anemia and in turn low birthweight. Despite these previously

reported associations, none of the eight studies reported controlling for important confounding factors, including maternal malaria infection, maternal nutritional status, diet, body mass index, or hypertensive disorders of pregnancy.

Importantly, there is much evidence to support the association of low birthweight with use of tobacco, which is commonly consumed with betel nut [1, 2, 14, 23]. Tobacco consumption was recorded by three of the five studies investigating low birthweight; however, it was controlled for only in one study, which excluded participants who smoked [4]. Thus, tobacco use may be a major confounder in the association between betel nut use and low birthweight.

The review has some limitations. First, betel nut use is most common in LLMICs, where there are significant limitations in data collection, research capacity, and funding, which contribute to a lack of quality research in this area. Second, the present search strategy may have limited representation from LLMICs because it was restricted to English search terms and studies. Third, quality was assessed by using the NOS because it allowed an assessment of non-randomized studies; however, previous studies have reported that this method has low inter-study reliability [24, 25]. Fourth, all eight studies were conducted in hospital settings, which may not comprehensively represent the populations in these LLMICs. Last, the review was most significantly limited by a lack of relevant research. There were few eligible studies and their quality was poor. The present findings highlight the need for increased research in this area. A further review should be conducted when more extensive and robust research is available.

5 Conclusion

Betel nut consumption is common worldwide and continues during pregnancy. Although it has been associated with several adverse health effects, there is limited evidence regarding adverse pregnancy outcomes. The present review identified only eight relevant studies, all based in low-income countries in the Asia–Pacific region. There was a significant association between low birthweight and betel nut exposure, and one study showed an association with anemia. However, the identified studies were limited by methodologic quality. The present findings highlight the need for large, prospective, high-quality studies investigating the association between

prenatal exposure to betel nut and adverse perinatal outcomes.

Author contributions

MD, LP, and RH conceived and designed the study. MD and RH carried out the review and data analysis, and drafted the manuscript. FB acted as the third reviewer and revised the manuscript. MD had primary responsibility for the final content. LP, AL, SW, FB, and ST provided intellectual input and technical support, and contributed to manuscript revision.

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Conflicts of interest

The authors have no conflicts of interest.

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Figure legends

Figure 1 PRISMA flow diagram of study selection.

Figure 2 Pooled odds ratios for the association of betel nut use in pregnancy and

preterm birth and low birthweight.

Supporting materials legends

Table S1 Predefined search strategy.

Table S2 Completed PRISMA checklist.

Table 1 Characteristics of the eight studies included in the review.

Author	Country	Study design	Study year	No. of cases	No. of controls	Quality (NOS score)	Case criteria	Control criteria	Outcomes
de Costa et al. [4]	PNG	Cohort, prospective	1981	400	400	High (8)	Women booked at Port Moresby general hospital, with a singleton pregnancy, who used betel nut prenatally (non-smokers with intake of alcohol and/or drugs apart from malaria prophylaxis)	Women booked at Port Moresby general hospital, with a singleton pregnancy, who did not use betel nut prenatally (non-smokers with intake of alcohol and/or drugs apart from malaria prophylaxis); age and gestation matched	Low birthweight; very low birthweight (<2200 g); anemia (Hb <10 g/L); pre-eclampsia; fetal distress in labor; Ventouse; assisted breech delivery; cesarean delivery; need for resuscitation; perinatal death; neonatal jaundice
Yang et al. [17]	Taiwan	Case–control, prospective	1994	62	124	Low (4)	Pregnant aboriginal women aged 15–50 y who used betel nut prenatally	Pregnant aboriginal women, aged 15–50 y years who did not chew betel nut prenatally	Adverse pregnancy outcomes (composite) [a]
Yang et al. [15]	Taiwan	Cohort, prospective	2003–2004	464	800	High (7)	Aboriginal women in southern and eastern Taiwan with singleton pregnancies who used betel nut prenatally	Aboriginal women in southern and eastern Taiwan with singleton pregnancies who did not use betel nut prenatally	Preterm birth; low birthweight; full-term low birthweight
Senn et al. [2]	Papua New	Cohort,	2007–	292	18	High (8)	Women who delivered	Women who delivered	Preterm birth; low

	Guinea	prospective	2008				at Alexshafen Health Center, Madang Province, with a singleton pregnancy who used betel nut prenatally	at Alexshafen Health Center, Madang Province, with a singleton pregnancy who did not use betel nut prenatally.	birthweight; full-term low birthweight
Yang et al. [18]	Taiwan	Case–control, prospective	1998	265	192	Low (3)	Aboriginal women delivering in a regional hospital in eastern Taiwan with adverse pregnancy outcomes (low birthweight, preterm, malformations) who used betel nut prenatally	Aboriginal women delivering in a regional hospital in eastern Taiwan without adverse pregnancy outcomes (low birthweight, preterm or malformations) who did not use betel nut prenatally	Preterm birth; low birthweight
Wang and Lee [14]	Taiwan	Cohort, retrospective	2005	19	8432	High (7)	Women who delivered with adverse pregnancy outcomes (preterm delivery or low birthweight) having used betel nut prenatally	Women who delivered with adverse pregnancy outcomes (preterm delivery or low birthweight) who did not use betel nut prenatally	Preterm birth and low birthweight (combined)
Ome–Kaius et al. [16]	Papua New Guinea	Cohort, prospective	2009–2013	2249	451	Medium (6)	Women who presented at 1 of 9 health facilities in Madang province, PNG, who used betel	Women who presented at 1 of 9 health facilities in Madang Province, PNG, who did not use	Preterm birth; abortion; stillbirth; congenital abnormalities; anemia (Hb <11 g/L)

							nut prenatally	betel nut prenatally	
Berger et al. [1]	Palau	Cohort, retrospective	2007–2013	893	278	Medium (6)	Native Palauan women who had a live singleton birth and used betel nut with tobacco prenatally	Native Palauan women who had a live singleton birth who did not use betel nut with tobacco prenatally	Preterm birth; low birthweight

Abbreviations: Hb, hemoglobin; PNG, Papua New Guinea.

[a] Composite adverse outcomes included stillbirth, preterm birth, spontaneous abortion, and fetal malformations.

Table 2 Quality assessment of cohort studies using the Newcastle–Ottawa scoring system [a].

Study	Newcastle–Ottawa score								
	Selection				Comparability	Outcome			Total
	Representative-ness of exposed cohort	Selection of control cohort	Ascertainment of exposure	Checked that outcome was not present at study outset	Comparability of cohorts based on design/analysis	Assessment of Outcome	Duration of follow-up	Adequacy of follow-up	
Berger et al. [1]	1	0	1	1	1	1	0	0	6
Senn et al. [2]	1	1	1	1	1	1	1	1	8
Ome–Kaius et al. [16]	0	0	1	1	1	1	1	1	6
de Costa et al. [4]	1	1	1	1	1	1	1	1	8
Wang and Lee [14]	1	1	0	1	1	1	1	1	7
Yang et al. [15]	1	1	1	1	1	1	1	0	7

[a] Each item can have a maximum of 1 point. Comparability can have a maximum of 2 points. Each study can have a maximum of 9 points.

Table 3 Quality assessment of case–control studies using the Newcastle–Ottawa scoring system [a].

Study	Newcastle–Ottawa score									
	Selection					Comparability	Outcome			Total
	Is the case definition adequate?	Representative-ness of cases	Selection of controls	Definition of controls	Demonstration that outcome was not present at study outset	Comparability of cases and controls based on design/analysis	Ascertainment of exposure	Same method of ascertainment for cases/controls	Non-response rate	
Yang et al. [17]	0	1	0	0	1	1	1	0	0	4
Yang et al. [18]	0	0	0	0	1	1	1	0	0	3

[a] Each item can have a maximum of 1 point. Comparability can have a maximum of 2 points. Each study can have a maximum of 9 points.

Table 4 Odds ratios for the association of betel nut use with reported adverse outcomes [a].

Adverse outcomes	Design	Country	Total no. of women	No. of cases	OR (95% CI)
Composite					
Yang et al. [17]	Case–control	Taiwan	186	62	1.96 (1.04–3.71)
Preterm birth					
Yang et al. [18]	Case–control	Taiwan	228	20	3.4 (0.97–11.98)
Yang et al. [15]	Cohort	Taiwan	1264	119	1.43 (0.98–2.10)
Senn et al. [2]	Cohort	PNG	310	21	0.56 (0.12–2.602)
Ome–Kaius et al. [16]	Cohort	PNG	114	89	1.23 (0.68–2.23)
Berger et al. [1]	Cohort	Palau	917	106	1.07 (0.66–1.72)
Overall LBW <2.5 kg					
Berger et al. [1]	Cohort	Palau	1171	96	1.49 (0.87–2.57)
de Costa et al. [4]	Cohort	PNG	800	62	1.42 (0.84–2.4)
Senn et al. [2	Cohort	PNG	310	57	1.86 (0.42–8.31)
Yang et al. [15]	Cohort	Taiwan	1264	128	2.12 (1.47–3.06)
Yang et al. [18]	Case–control	Taiwan	229	118	9.08 (1.13–72.9)
LBW <2.2 kg					
de Costa et al. [4]	Cohort	PNG	800	19	1.39 (0.55–3.48)
Term LBW <2.5 kg					
Berger et al. [1]	Cohort	Palau	1171	96	1.49 (0.87–2.57)
Yang et al. [15]	Cohort	Taiwan	1264	69	2.36 (1.44–3.85)
Senn et al. [2]	Cohort	PNG	310	50	3.43 (0.44–26.36)
PTB and LBW combined					
Wang and Lee [14]	Cohort	Taiwan	8432	810	0.57 (0.08–4.24)
Anemia					
de Costa et al. [4]	Cohort	PNG	800	376	1.08 (0.82–1.43)
Ome–Kaius et al. [16]	Cohort	PNG	1599	1170	1.72 (1.31–2.25)
Miscarriage					
Ome–Kaius et al. [16]	Cohort	PNG	2215	6	0.4 (0.07–2.20)
Stillbirth					
Ome–Kaius et al. [16]	Cohort	PNG	2215	40	1.83 (0.65–5.16)
Congenital abnormality					
Ome–Kaius et al. [16]	Cohort	PNG	2215	17	0.48 (0.17-1.37)
Pre-eclampsia					
de Costa et al. [4]	Cohort	PNG	800	84	0.85 (0.54–1.34)
Fetal distress in labor					
de Costa et al. [4]	Cohort	PNG	800	82	1 (0.63–1.58)
Ventouse					

de Costa et al. [4]	Cohort	PNG	800	52	0.84 (0.48–1.49)
Assisted Breech					
de Costa et al. [4]	Cohort	PNG	800	17	1.13 (0.43–2.95)
Cesarean delivery					
de Costa et al. [4]	Cohort	PNG	800	27	0.79 (0.37–1.72)
Resuscitation					
de Costa et al. [4]	Cohort	PNG	800	45	0.79 (0.43–1.45)
Perinatal death					
de Costa et al. [4]	Cohort	PNG	800	21	0.91 (0.38–2.16)
Neonatal jaundice					
de Costa et al. [4]	Cohort	PNG	800	130	0.59 (0.41–0.87)

Abbreviations: CI, confidence interval; LBW, low birthweight; OR, odds ratio; PNG, Papua New Guinea; PTB, preterm birth.

[a] Composite adverse outcomes included stillbirth, preterm birth, spontaneous abortion, fetal malformations.

Table 5. Pooled odds ratios for the association of betel nut use with preterm birth and low birthweight.

Outcome	**No. of participants in pooled studies**	**Number of studies**	**OR (95% CI)**	I^2, %
Preterm birth	3892	4	1.24 (0.95–1.62)	0
Low birthweight	3545	4	1.75 (1.35–2.27)	0

Abbreviations: CI, confidence interval; OR, odds ratio.

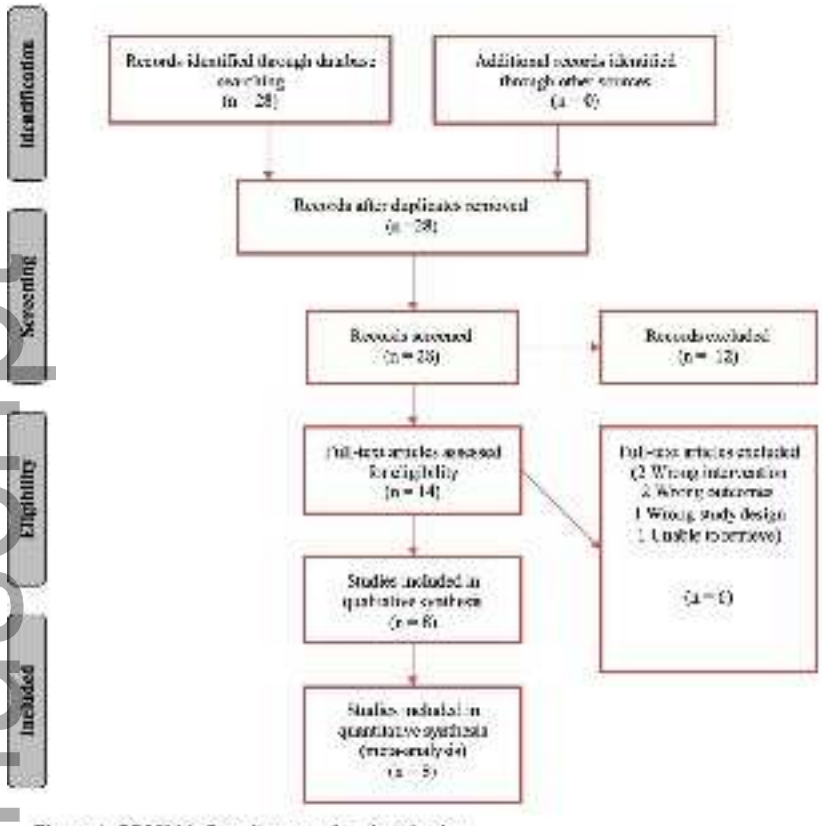

Figure 1. PRISMA flow diagram of study selection.

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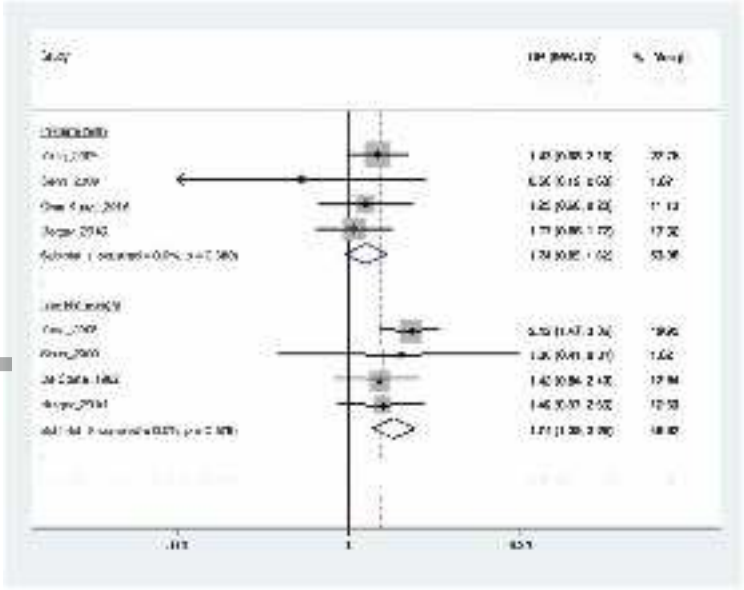

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