



Published by  
Department of Public Health and Preventive  
Medicine, Faculty of Medicine,  
Udayana University

# The association between Vitamin D serum level and sleep quality among pregnant women in Asia: A systematic review

Gredel Faustine<sup>1</sup>, Felicia Kurniawan<sup>2</sup>, Regina<sup>3\*</sup>

<sup>1</sup>Bachelor of Medicine Study Programme, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia.

<sup>2</sup>Department of Public Health Sciences and Nutrition, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia.

<sup>3</sup>Department of Dermatology and Venereology, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia.

\*Correspondence to: [regina@atmajaya.ac.id](mailto:regina@atmajaya.ac.id)

## ABSTRACT

**Background and purpose:** Studies have investigated that Vitamin D serum level is associated with sleep quality and circadian rhythms in pregnant women in Asia, but the results remained controversial. This systematic review is conducted to explore the association between Vitamin D serum level and sleep quality among pregnant women population in Asia.

**Methods:** We conducted systematic literature review based on the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines. Relevant studies that discussed the association between Vitamin D serum level and sleep quality was retrieved from *Pubmed*, *EBSCO*, and *Proquest*. The outcome variable was sleep-quality which measured with Pittsburg Sleep Quality Index (PSQI) questionnaires and the independent variable was the serum 25(OH)D levels. A total 2,285 articles were excluded, leaving 3 final articles to be analyzed. The risk of bias was assessed with the New-Castle Ottawa Quality Assessment Scale (NOS).

**Results:** Three studies included in this review with a total of 1,359 pregnant women in Asia, ranging from 18 to 68 years old. All three studies were controlled for covariates. Out of three studies, two studies showed a significant result of the association between Vitamin D serum level with sleep quality with a p-value <0,05. Causal reasons remained unexplained considering the studies were completed in cross-sectional and cohort design.

**Conclusion:** This study gives an overview of the role of Vitamin D in the sleep quality of pregnant women in Asia. Future research should focus on conducting more comprehensive studies with stringent criteria to further explore this association in diverse Asian populations

**Keywords:** Vitamin D, sleep quality, pregnant women, Asia

## INTRODUCTION

Sleep disturbances are common in pregnancy, with pain, discomfort, and frequent urination as the main factors that contributed to sleep difficulties in pregnancies.<sup>1</sup> Changes in physical, psychological, and hormonal affect the sleep quality in pregnancy.<sup>2</sup> One study that was conducted in a large sample of pregnant women across all months of pregnancy shows that 76% of women experienced poor sleep quality.<sup>1</sup> Another study with larger samples in Poland reported that 77.09% of pregnant women in their first trimester of pregnancy suffered from sleep problems.<sup>2</sup> Asians including Filipino, Japanese, Chinese, and mixed groups had shorter mean sleep duration compared to the white group according to a study with multi-ethnic samples.<sup>3</sup> A study conducted by Rahmawati et al. in Cimanggis and Sukmajaya, Indonesia, revealed that nearly all third-trimester pregnant women experienced poor sleep quality (93.6%).<sup>4</sup>

Sleep disturbances are associated with disadvantageous pregnancy outcomes, such as preeclampsia, longer labor times, higher cesarean section rates, preterm birth, and intrauterine growth restriction.<sup>5</sup> It is necessary to investigate the factors that affect them, then control them to reach a better sleep quality in pregnancy.

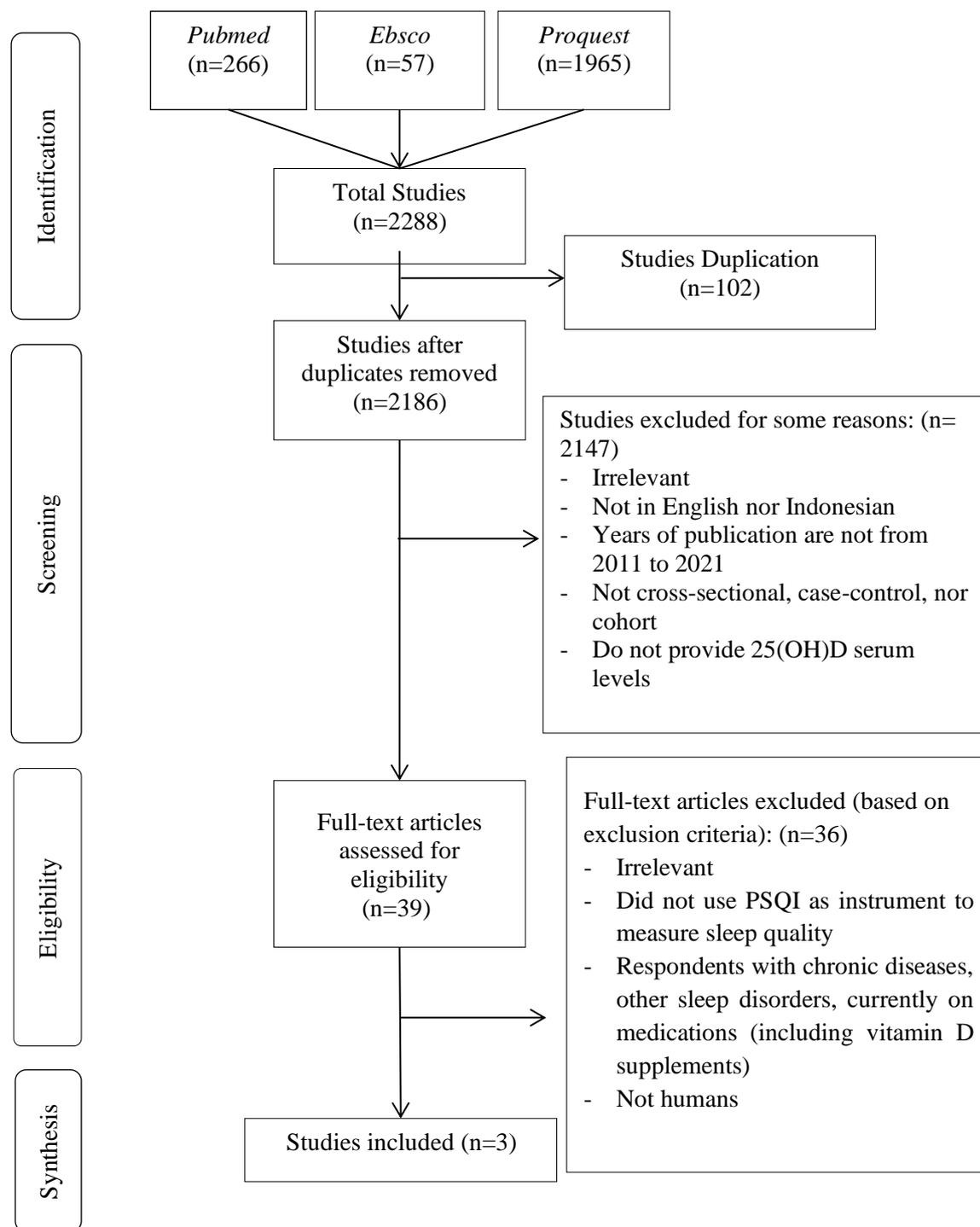
Vitamin D was suggested to have linked with sleep disturbances in humans. A cross-sectional study reported respondents with lower vitamin D levels had shorter sleep duration.<sup>6</sup> Vitamin D receptors are found in almost all tissues in the body, including the hypothalamus, prefrontal cortex, and brain stem, which regulate sleep. A systematic review discussed the association between vitamin D serum level and sleeps quality but was not specified in pregnant women.<sup>7</sup> Several studies examined vitamin D serum level and sleep quality in pregnant women, however, the result remained controversial.<sup>8-10</sup>

Vitamin D is a fat-soluble vitamin that has roles in maintaining calcium and phosphate concentration in serum, which takes part in bone growth. About 50-90% of Vitamin D is obtained from sunlight, others are food and supplements.<sup>8</sup> Vitamin D is synthesized in the skin by ultraviolet B, then converted to the functionally active form. The 25(OH)D is the most common form found in the circulation, thus becoming the best indicator to measure vitamin D serum level.<sup>7,8</sup> Other factors, such as lifestyle and skin colors also affect vitamin D concentration in serum, making Vitamin D deficiency (VDD) more susceptible to happen, around 1 billion people in the world live with VDD. VDD is linked with cardiovascular, infectious, and other diseases, including sleep disturbances.<sup>7,8</sup> According to the World Health Organization (WHO), VDD is frequently found in pregnant women, associated with an increased risk of adverse pregnancy outcomes.<sup>11</sup>

The urgency of this research lies in the significant impact that sleep disturbances can have on pregnancy outcomes, and the potential role of Vitamin D levels to mitigate these effects. By investigating the association between Vitamin D serum levels and sleep quality in pregnant women in Asia, this study aims to provide valuable insights for improving pregnancy outcomes and potentially reducing the risk of sleep disturbances in pregnant women.

## METHOD

This systematic review was conducted based on the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement guidelines as shown in Figure 1 below.



**Figure 1. PRISMA Flow Diagram (Study Selection Process)**

We searched 3 databases systematically for the relevant literature (*Pubmed*, EBSCO, and *Proquest*). Keywords were identified using a controlled vocabulary. Terms we used included sleep quality-related (e.g., sleep) and vitamin D-related (e.g., calcidiol, 25-hydroxyvitamin D, vitamin D serum, and cholecalciferol), as

listed in the table 1.

**Table 1. Keywords for the literature search**

Database	Keywords	No of articles
Pubmed	("sleep quality"[All Fields] OR "sleep"[All Fields]) AND ("Vitamin D"[MeSH Terms] OR "Cholecalciferol"[MeSH Terms] OR "Vitamin D Serum"[Title/Abstract] OR "25 hydroxyvitamin D"[Title/Abstract] OR "Cholecalciferol"[Title/Abstract] OR "Calcidiol"[Title/Abstract])	266
Proquest	((("sleep quality") OR ("sleep"))) AND ("Vitamin D Serum" OR "25 Hydroxyvitamin D" OR "Cholecalciferol" OR "Calcidiol")	1965
Ebsco	((("sleep quality") OR ("sleep"))) AND ("Vitamin D Serum" OR "25 Hydroxyvitamin D" OR "Cholecalciferol" OR "Calcidiol")	71

This study included relevant studies that were searched using selected keywords, written in English or Bahasa Indonesia, ranging from 2011 to 2021. All studies were original articles with cross-sectional, case-control, and cohort study design. The 25(OH)D serum levels must be provided in their study with pregnant women in Asia as their samples. Articles that did not include their research methods, irrelevant, did not use *Pittsburg Sleep Quality Index* (PSQI) as the instrument to measure sleep quality, respondents with chronic diseases and other sleep disorders (e.g., *obstructive sleep apnea*), respondents that were currently on medications, including Vitamin D supplements, and subjects were not humans, were excluded.

The characteristics of the selected studies were listed in the table with the name of the authors, title, purpose, and conclusion as the components. Information that was considered important were also extracted, the data included last name of the first author, publication year, country, study design, total numbers of respondents and age, sleep quality assessment method, Vitamin D levels assessment method, the cutoff value of 25(OH)D in ng/mL, and result (significant or not) with  $p$ -value  $<0,05$  as the benchmark.

We used *Newcastle Ottawa Scale* (NOS) to help us assess the study quality. The components were categorized into three major components, such as selection, comparability, and outcome. The assessment process finished with total points each study gained. The risk of bias was considered low when points gained

were 7 to 8, moderate when 6, and high when 5 or less.

All three studies, had ethical clearance. Woo et al. did not require ethical approval as it was a retrospective analysis, while Cheng et al. and Gunduz et al. obtained approval from their respective institutional review boards (IRBs). This ensures that all ethical standards were met in the conduct of these studies.

## RESULT

Total studies obtained from a comprehensive search in *Pubmed*, *EBSCO*, and *Proquest* were 2288 studies. 102 studies were eliminated by duplication reason, leaving 2186 studies to be filtered based on inclusion and exclusion criteria. 2147 studies were then excluded after matching the inclusion criteria, leaving 39 studies. Ultimately, 3 studies were chosen after eliminating others based on the exclusion criteria. A total of 1,359 respondents were obtained from those 3 studies. The characteristics of the studies and data extraction table (demographic characteristics) were listed in Table 2 and 3.

**Table 2. Title, purpose and result of the studies**

Author	Title	Purpose	Result
Cheng	<i>Plasma Vitamin D Deficiency Is Associated with Poor Sleep Quality and Night-Time Eating at Mid-Pregnancy in Singapore</i>	Investigate the associations between maternal plasma 25OHD status and sleep quality and circadian eating patterns during pregnancy	Maternal plasma 25OHD deficiency was associated with poor sleep quality and pNT feeding during the late-second trimester of pregnancy in Singapore.
Gunduz	<i>Sleep deprivation in the last trimester of pregnancy and inadequate vitamin D: Is there a relationship?</i>	Test the hypothesis that serum vitamin D levels are low in pregnant women who have poor sleep quality in their last trimester.	Inadequate vitamin D and poor sleep quality are prevalent in pregnant women, but low levels of vitamin D are not associated with poor sleep quality.
Woo	<i>Vitamin D Deficiency and Sleep Quality in Minority Pregnant Women</i>	To examine if vitamin D deficiency was associated with poor sleep quality in a sample of African American and Hispanic pregnant women. We also examined if race moderates the relationship between serum 25(OH)D levels and sleep quality among participants in this sample.	Serum 25(OH)D levels were significant predictors of sleep quality after controlling for covariates (i.e., race, maternal age, pre-pregnancy body mass index, gestational age at data collection).

**Table 3. Study characteristics and findings**

Author	Year	Location	Study Design	Total Respondents (Age)	Sleep Quality Assessment Method	Vitamin D Assessment Method	Cutoffs value of 25(OH)D (ng/mL)	Result
Cheng	2017	Singapore	Cohort	1152 (42-68)	PSQI	<i>Isotope-dilution liquid chromatography–tandem mass spectrometry</i>	>30.05 20.03-30.05 <20.03	Significant*
Gunduz	2016	Ankara, Turkey	Cross-sectional	92 (18-45)	PSQI	<i>High-performance liquid chromatography</i>	<20 <32	Not Significant <sup>+</sup>
Woo	2020	South Korea	Cross-sectional	115 (18-43)	PSQI	<i>Radioimmunoassay (RIA)</i>	<20	Significant*

Meanwhile, studies quality assessments using NOS are provided as well on Table 4. Based on the quality assessment, two studies obtained 7 points, thus the risk of bias was low, meanwhile one had a moderate risk of bias with 6 points.

**Table 4. Studies Quality Assessment (NOS)**

Author, Year	Selection				Comparability	Outcome			Total
	<i>Representativeness of the exposed cohort</i>	<i>Non-exposed cohort</i>	<i>Ascertainment of the exposure</i>	<i>Outcome of interest was not present</i>		<i>Assessment of the outcome</i>	<i>Follow-up</i>	<i>Adequacy of Follow up</i>	
Cheng, 2017	-	*	*	-	**	-	*	*	6
	<i>Representativeness of the sample</i>	<i>Sample Size</i>	<i>Non-Respondents</i>	<i>Ascertainment of the exposure</i>	<i>factors are controlled</i>	<i>Assessment of the outcome</i>	<i>Statistical test</i>		
Gunduz, 2016	-	-	*	**	**	*	*		7
Woo, 2020	-	*	-	**	**	*	*		7

Two studies were cross-sectional and one was a cohort. The origin countries of those studies were Singapore, Turkey, and South Korea. Out of three studies that were examined according to the existing criteria, there were two studies<sup>9,10</sup> that showed the significant result of the association of Vitamin D serum levels and sleep quality among pregnant women in Asia, one study<sup>8</sup> reported there was no significant association.

The study by Cheng, et al. controlled factors that affected the result, such as race, age, Body Mass Index (BMI), education, income, parity, night shift status, physical activity, the total score of *Edinburgh Postnatal Depression Scale* (EPDS), and gestational weight gain per week. 25(OH)D deficiency (<50 nmol/L) associated with poor sleep quality with  $p$ -value <0,001 and odds ratio (OR) 4.14 (95% CI:2.01-8.51). 25(OH)D insufficiency (50-75 nmol/L) was also reported associated with poor sleep quality with  $p$ -value=0,0048 and OR=1.51 (95% CI:0.91-2.50). The study then explained that 25(OH)D deficiency association with poor sleep quality was more significant compared to insufficiency. This study also examined 25(OH)D status with midnight eating activity in pregnancy, the result was significant in 25(OH)D deficiency group, but not in 25(OH)D insufficient group, with  $p$ -value=0.901 and OR=0.96 (95% CI:0.99-3.64).<sup>10</sup>

The Gunduz, et al. compared the Vitamin D deficiency group with the non-deficiency group, and there were no significant differences between the Vitamin D deficiency group and non-deficiency with  $p$ -value >0.05. All factors, such as age, job, relationship with a partner, BMI, weight gain, primiparous, duration of labor, and labor methods, were controlled before concluded.<sup>8</sup>

There was a significant result when Woo, et al. conducted the study about the association between 25(OH)D serum levels and sleep quality. Like the others, the result was concluded after controlling covariates, such as race, BMI before pregnancy, gestational age and maternal age ( $p$ -value=0.002). The study concluded that race was not associated with both 25(OH)D serum levels and sleep quality.<sup>9</sup>

All studies used PSQI by Buysse, a validated questionnaire for assessing sleep quality. Subjects answered the questionnaire independently. Woo, et al. used both English PSQI and Spanish, all studies had the same cutoff score for categorizing the good or poor sleep quality. A score of more than 5 indicating as poor sleep quality.<sup>8,9,10</sup> A study conducted by Gunduz, et al. reported that 43.5% (40 participants) had poor sleep quality.<sup>9</sup> Meanwhile, woo, et al. reported that 58.2% (67 women) got a score of more than 5 on PSQI, or translated as poor sleep quality.<sup>9</sup> Gunduz, et al. did not find any association between sleep quality and other factors (age, BMI before pregnancy, weight gain during pregnancy, labor duration, primiparous, labor methods, jobs, and relationship with partners. Only families with low income showed a significant association to poor sleep quality ( $P$ -value = 0.001).<sup>8</sup> Woo, et al. elaborated that the Asian African race had a significant association with PSQI score.<sup>9</sup>

Vitamin D serum levels were assessed with participants' blood samples. All three studies used different cut-off categories of Vitamin D serum levels. Cheng, et al. used 75 nmol/L to describe normal Vitamin D level, 50-75 nmol/L for insufficiency, less than 50 nmol/L for deficiency. It shows that 59.2% (527 respondents) had enough Vitamin D, 27.4% (244) were in insufficiency, and 13.4% (119) were having Vitamin D deficiency.<sup>10</sup> Gunduz, et al. examined pregnant women's (36 weeks gestation age) blood from a vein, collected and centrifuged, then kept it safe at 80 degrees Celsius. The cut-off value was 20 ng/mL for deficiency (78% of participants) and 32 ng/mL for insufficiency (55.4% of participants).<sup>8</sup> Woo, et al. examined Vitamin D with *Radioimmunoassay* (RIA) from *Quest Diagnostics* 2015, which was the most common method used in the

clinics to examine 25(OH)D. This study used the same cut-off value as Gunduz, et al.'s, with 60.8% of respondents suffered from Vitamin D deficiency in this study.<sup>9</sup> All three studies used less than 20 ng/mL to describe Vitamin D deficiency.<sup>8-10</sup>

## DISCUSSION

This systematic review discussed the relationship between Vitamin D serum levels and sleep quality among pregnant women in Asia. Our review synthesized findings from three key studies: Cheng et al. (2017), Gunduz et al. (2016), and Woo et al. (2020).<sup>8-10</sup>

Among the studies reviewed, Cheng et al. and Woo et al. found significant association between 25(OH)D plasma concentrations and sleep quality measures in pregnant women, suggesting that Vitamin D status may influence sleep patterns during pregnancy,<sup>9,10</sup> however, Gunduz et al. did not observe a significant association, which they attributed to limitations such as a small sample size, only mature babies were included, and the use of self-reported sleep measures.<sup>8</sup>

Our systematic review indicates that while there is considerable interest and some evidence suggesting an association between Vitamin D serum levels and sleep quality among pregnant women in Asia, the overall findings are not definitive. The majority of studies reviewed do suggest a potential link, but the evidence is limited by the variability in study designs, methodological limitations such as reliance on self-reported sleep measures, and strict criteria. This study does not establish a causal relationship between Vitamin D serum levels and sleep quality due to the cross-sectional and cohort study designs utilized. Cohort studies, which provide relatively strong evidence on association, are crucial for understanding the longitudinal impact over time. These factors underscore the need for more rigorous and standardized research to establish a clearer understanding of this relationship in diverse Asian populations.

When comparing our findings with previous research, it becomes evident that the association between Vitamin D and sleep quality among pregnant women varies considerably across different studies. This variability may be attributed to differences in sample sizes, geographic locations, and methodological approaches.<sup>8-10</sup>

The studies by Gunduz et al. (2016), Cheng et al. (2017), and Woo et al. (2020) underscore the prevalence of Vitamin D deficiency among pregnant women across diverse regions and populations.<sup>8-10</sup> Gunduz et al. and Cheng et al. reported a high prevalence of Vitamin D deficiency among pregnant women, attributed to rapid urbanization and associated lifestyle changes despite year-round sunlight exposure.<sup>8,10</sup> Woo et al. identified limited sunlight exposure, dark skin, and pre-pregnancy BMI  $\geq 40$  as factors contributing to Vitamin D deficiency among minority pregnant women.<sup>9</sup> In Indonesia, a systematic review and meta-analysis revealed that 25%, 63%, and 78% of Indonesian pregnant women suffer from Vitamin D insufficiency, deficiency, and hypovitaminosis D, respectively.<sup>12</sup> Similar factors contributing to high prevalence rates include limited sunlight exposure, rapid urbanization reducing physical activity and outdoor exposure, dark skin, inadequate dietary Vitamin D intake, and absence of Vitamin D fortification in foods.<sup>12,13</sup>

Humans' behavioral rhythms, including sleep and eat are synchronized with the surroundings in 24 hours period. Synchronization process initiated by a circadian central clock, located in hypothalamus suprachiasmatic

nucleus that captures sunlight through eyes, then affecting peripheral movements through hormonal and neural, disrupted central and peripheral rhythms then causing circadian disturbances. Other theories explained that circadian sleep rhythm is regulated by Vitamin D. VDR found in humans' brains, especially in parts that control sleep. Those three studies explored pregnant women. Maternal plasma 25(OH)D connected to sleep quality, related to the theory that said 25(OH)D plasma concentration is the biomarker for circadian behavior status in pregnancy.<sup>10</sup> Positive linear correlations of 25(OH)D and sleep quality were also found in a study involving pre- and post-menopause in Southern England, however, PSQI was not used in this study.<sup>14</sup>

The findings of our systematic review have several implications for clinical practice in prenatal care. Considering the potential impact of Vitamin D on sleep quality, healthcare providers in Asia, including Indonesia, should prioritize monitoring and maintaining optimal Vitamin D levels in pregnant women. Strategies such as maintaining adequate Vitamin D levels through dietary intake, Vitamin D supplements, or sunlight exposure during pregnancy has been shown to significantly improve sleep quality in Asian pregnant women, thereby enhancing sleep quality and overall maternal health outcomes.<sup>15-17</sup>

Until recently, Indonesian pregnant women still do not regularly practice Vitamin D supplementation because it is not made mandatory by the National Health Minister.<sup>18</sup> Moreover, Southeast Asian females often wear traditional heavy clothing such as hijab or Shari, which can limit exposure to sunlight necessary for Vitamin D synthesis.<sup>19</sup> Furthermore, many Asian females are cautious about sun exposure due to concerns about skin damage and sunburn, often using sunscreen or carrying an umbrella to mitigate sun exposure.<sup>20,21</sup>

Therefore, it is crucial to recommend regular Vitamin D supplementation and educate pregnant women about its benefits during prenatal care visits. Implementing guidelines or public health campaigns that emphasize the importance of maintaining optimal Vitamin D levels could potentially mitigate the high prevalence of Vitamin D deficiency among pregnant women in Indonesia and other Asian countries. By addressing these barriers and promoting awareness, healthcare providers can support better maternal health outcomes through improved sleep quality and overall well-being.

A strength of this systematic review is its focused examination of the association specific to pregnant women in Asia, without comorbid sleep disorders. To our knowledge, this is the first systematic review to discuss this issue. However, the review is limited by the strict inclusion criteria and outcome measures, such as the reliance on the PSQI for sleep quality assessment and 25(OH)D for Vitamin D assessment. These criteria may have excluded relevant studies that used alternative measures or focused on broader populations. Despite these limitations, self-reported measures like the PSQI are generally more reliable and effective in capturing the subjective experiences and perceptions of sleep quality, which are essential for comprehending the impact of sleep disturbances on daily life and overall well-being.<sup>22</sup>

Future studies should focus on several key areas to enhance understanding of the link between Vitamin D and sleep quality among pregnant women in Asia. Firstly, conducting larger studies with diverse populations across different Asian regions will ensure that findings are applicable more broadly and can account for regional variations. Additionally, exploring alternative methods to measure sleep quality and Vitamin D status beyond the PSQI questionnaire and blood levels (25(OH)D) could provide a more comprehensive understanding of their connection. Incorporating objective measures like sleep monitors alongside subjective assessments can offer deeper insights into this relationship, thereby guiding effective strategies for improving sleep quality

through Vitamin D management during pregnancy in Asia.

## CONCLUSION

This systematic review concluded that after controlling other important factors, Vitamin D serum levels are most likely associated with sleep quality in pregnant women. It is proven by the majority of the studies that provided significant results to this association ( $p$ -value  $<0.05$ ).

To improve sleep quality, healthcare providers should consider Vitamin D levels in prenatal care and provide guidance on maintaining optimal levels. Public health campaigns should emphasize the importance of Vitamin D for overall health during pregnancy. Future research should focus on conducting more comprehensive studies with stringent criteria to further explore this association in diverse Asian populations. This will contribute to a deeper understanding of factors influencing sleep quality during pregnancy.

## AUTHOR CONTRIBUTION

GF, FK, and RR designed the study. GF collected and analysed the data, wrote the first draft, and edited the manuscript. FK and RR provided feedback and input to the manuscript and data analysis. RR reviewed the study proposal and manuscript critically. All authors approved the final manuscript.

## CONFLICT OF INTEREST

None

## FUNDING

None

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