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Original Article

Vitamin D Supplementation and Sun Exposure Maintain Blood Pressures of Pregnant Women and Increase Birth Weight in a Randomized Controlled Trial

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Abstract

Background: Vitamin D supplementation or sun exposure increase pregnant women's Calcidiol levels, lower the blood pressures and increase birth weight. We aimed to compare the effects between sun exposure and vitamin D supplementation on pregnant women's Calcidiol levels, blood pressures and newborns' anthropometric indices.

Methods: This randomized clinical trial was conducted on 108 pregnant women at 20 wk of gestation on 2021's dry season in Semarang City, Indonesia. The subjects were randomly and evenly divided into 3 groups of 36 subjects (sunlight exposure, vitamin D supplement, and control). Vitamin D group received 1000 IU daily and sun exposure group was recommended to have 15–30 min for 3 times/week for 17 wk. Compliance was monitored every 2 d through home visits. Calcidiol levels, blood pressures, in all groups were compared before and after intervention. The increments and the newborn anthropometric indices were compared between the groups and controlled for confounding factors.

Results: At baseline, all groups had vitamin D deficiency, different mean Calcidiol levels, systolic, and diastolic blood pressures. The mean Calcidiol levels increased in the sun exposure and vitamin D group after the intervention. Systolic blood pressure decreased in the vitamin D group only (P=0.019). The mean birth weight was the highest in the vitamin D group (3,172±181.8 g) compared to the sun exposure (3,091±362.5g) and control groups (2,861 ± 208.0 g).

Conclusion: Vitamin D supplementation and sun exposure increased Calcidiol levels and birth weights. Vitamin D supplementation maintained systolic blood pressure.

Keywords: Vitamin D; Sun exposure; Pregnancy; Blood pressure; Birth weight

Introduction

Vitamin D deficiency in pregnant women is a global public health problem, especially in the sub-tropical region (1). The prevalence of vitamin D deficiency in pregnant women ranges from 27 to 91% in the United States, 39 to 65% in Canada, 45 to 100% in Asia, 19 to 96% in Europe, and 25 to 87% in Australia and New Zealand (2). However, in tropical areas, many pregnant women also have vitamin D deficiency, such as in Guizhou, China, which reached 38.4% (3).

Vitamin D deficiency in pregnant women also occurs in Indonesia, which lies on the equator and sunlight is available throughout the year (4). Among the first trimester pregnant women living in Jakarta, 90% had vitamin D deficiency (5). The results of study among pregnant women in their third trimester in West Sumatra showed that the prevalence of vitamin D deficiency was 61.25%, and more than 85% of the pregnant women had low vitamin D intake (6). Another study on the first-trimester pregnant women showed that the prevalence of vitamin D deficiency was 82.8% (7), while a study on the third trimester of pregnancies in Tanah Datar and Solok Regencies (West Sumatra) reported that the prevalence of vitamin D deficiency was 35% (8).

Vitamin D deficiency increased low birth weight risk in addition to decrease body length, head circumference, and chest circumference in neonates (9). A pure experimental study in Iran on 130 pregnant women with mean Calcidiol levels of 30 ng/mL showed that vitamin D supplementation increased newborns' weight, length, and head circumference (10). Vitamin D levels in pregnancy play an important role in the mother and fetus's health status (11).

Vitamin D in the body comes from food, vitamin D fortified food, vitamin D supplements, and the change of provitamin D into vitamin D in the skin by ultraviolet B (UVB) radiation (12). There are two forms of vitamin D, namely D2 (ergocalciferol) and D3 (cholecalciferol) transported to the liver and oxidized into 25 hydroxyvitamin D (25(OH)D) or Calcidiol (2). Calcidiol is an active metabolite of vitamin D transported from the maternal circulation into fetus through placenta to meet fetal vitamin D need (13).

Vitamin D supplementation and sunlight exposure to pregnant women are important for fetal growth and development. Sun exposure is a good and safe source of vitamin D as it does not cause intoxication (14). A 30-minute sunlight exposure 3 times/ week for 12 wk on women at childbearing age in Bogor (West Java) increased serum Calcidiol from 15.7 ± 4.1 ng/mL to 18.2 ± 4.6 ng/mL. Sun exposure can lower systolic blood pressure from 122.6 to 111.4 mmHg (P=0.004) and diastolic blood pressure from 80.3 to 74.3 mmHg (P=0.011). Thus, this quasi-experimental study showed that sun exposure could improve vitamin D status and blood pressure (15).

Vitamin D adequacy in pregnant women needs health workers' attention as they are at high-risk group (16). In Indonesia, Calcidiol levels in pregnant women have not been examined routinely. While sunlight is abundant in Indonesia, most women avoid direct sunlight exposure. This study was the first study in Semarang City, Indonesia, which aimed to compare the effect of sun exposure and vitamin D supplementation on Calcidiol levels and pregnant women' blood pressures and newborns' anthropometric indices.

Materials and Methods

The research was conducted after receiving ethical approval from the Faculty of Public Health, Diponegoro University, Semarang, Indonesia, with the number of 165/EA/KEPK-FKM/2021. This Randomized Control Trial (RCT) has also been registered at ISRCTN registry no. 87262826. This unblinded randomized control trial was conducted on pregnant mothers at 20 wk of gestation from 3 primary healthcare centers in Srondol, Ngesrep, Padangsari, Semarang City, Central Java, Indonesia. This study was conducted in May-Oct 2021, which was a dry season in Indonesia. The inclusion criteria include pregnant women at 20 wk of gestation, systolic blood pressure between 110–140 mmHg, diastolic blood pressure between 70–90 mmHg, and serum Calcidiol levels were less than 30 ng/mL.

For minimal sample size calculation, we used 80% power, 5% alpha, and standard deviation of 20 ng/mL (17), which resulted in the largest calculated sample size after trying all of the dependent variables in this study. For 3 groups comparison, the minimal sample size was 93 subjects. However, we had 108 subjects, who fulfilled the inclusion criteria, and were divided into 3 groups using computerized random allocation. Each group of sun exposure, vitamin D, and control, had 36 subjects, respectively. Serum Calcidiol level was measured by ELFA (Enzyme Linked Fluorescent Assay) method.

All three groups received iron, vitamin C, and calcium supplementation as routinely done in ANC (Ante Natal Care) program. Subjects in the sun exposure group were asked to get 15-minute sunbathing between 10:00 a.m. and 3:00 p.m. on face, arms, back, or legs for at least 3 times/ week without sunscreen for the subjects who wore short sleeves. For the subjects who wore long sleeves, sunbathing 30 min/ time are needed. The vitamin D group received 1000 IU of vitamin D3 daily for 17 wk. The control group only received routine ANC. Blood pressure measurements were done in all groups at before and every three weeks during the treatment. Serum Calcidiol measurements were done before the treatment started and at 37 wk of gestation. There was no dropout subject in all groups. All of the subjects in the vitamin D group consumed vitamin D every day and the sun exposed group also followed the instruction properly.

Data analysis was done in IBM SPSS ver. 21 (IBM Corp., Armonk, NY, USA) software with a Diponegoro University license (https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-21). Paired *t*-tests of version 21 IBM SPSS were used to compare the parameters before and after intervention in each group. ANOVA tests were also done by comparing the mean difference in systolic and diastolic blood pressure, Calcidiol level increments, and newborn anthropometric indices, between the groups. We used post hoc analysis of Tukey Test to find which groups were different. Multiple linear regressions were used to control the confounding variables.

Results

This study was conducted in Semarang, Central Java, Indonesia, during the dry season and the Covid-19 pandemic. All of the subjects finished the study. Subjects' characteristics can be seen in Table 1.

Table 1: Subjects' Characteristics

Variables	*Sun exposure*		*Vitamin D*		*Control*		P-values[a]
	Mean ± SD	Min-Max	Mean ± SD	Min-Max	Mean ± SD	Min-Max	
Age (yr)	28.9±4.90	18.0-39.0	29.9±5.10	21.0-38.0	29.1±5.09	21.0-39.0	0.666
BMI before pregnancy (kg/m²)	22.6±1.79	18.0-39.0	22.5±1.76	19.4-24.9	22.9±1.58	19.8-24.9	0.632
Weight gain during pregnancy (kg)	11.1±0.83	10.0-13.5	11.2±0.73	10.0-13.0	11.3±0.74	10.0-13.5	0.021
Monthly family income (in million rupiahs)	6.8±1.80	2.5-10.5	7.7±2.40	2.85-10.5	6.4±2.10	2.5-10.1	0.019

[a]*Anova*

The subjects were young women from 18 to 39 yr old, with normal BMI before pregnancies, and normal weight gains during their pregnancies. The family income ranges from 2.5 to 10.5 million Rupiahs per month, which shows a middle-income level in Indonesia. All subjects complied with the interventions, both in the sun exposure and the vitamin D group. In the control group, two subjects (5.6%) had sun exposure based on their awareness. There was no significant difference in age and BMI before pregnancy in all groups, but there were significant differences in weight gain during pregnancy and monthly family income among the groups.

Only 1 subject was less than 20 yr old in the sun exposure group, while 6 subjects were older than 35 yr old in the sun exposure and control groups. The parity of the subjects was mostly multipara. No subject had history of Type 2 Diabetes Mellitus and preeclampsia. Only one subject had monthly family income less than the regional standard salary. All of the variables were normally distributed.

Table 2 shows serum Calcidiol levels, systolic, and diastolic blood pressure in all groups before and after the intervention. Before the intervention, all of the subjects were in vitamin D deficiency (Calcidiol levels<30 ng/mL). No subject had high blood pressure. All of the variables were normally distributed.

Table 2: Serum Calcidiol Levels, Systolic and Diastolic Blood Pressures in All Groups before and After Intervention

Variables	*Groups*			*P-values*
	***Sun exposure* Mean ± SD**	***Vitamin D* Mean ± SD**	***Control* Mean ± SD**	
Serum Calcidiol (ng/mL)				
Before intervention	14.6 ± 3.91	16.5 ± 3.90	12.1 ± 2.52	0.000[a]
After intervention	29.8 ± 3.24	31.8 ± 3.24	14.9 ± 2.78	0.000[a]
p-values	0.000[b]	0.000[b]	0.000[b]	
Systolic blood pressure (mmHg)				
Before intervention	107.7 ± 2.06	105.8 ± 2.33	107.9 ± 1.55	0.000[a]
After intervention	106.9 ± 1.89	104.6 ± 2.12	107.5 ± 1.32	0.000[a]
p-values	0.104[b]	0.019[b]	0.245[b]	
Diastolic blood pressure (mmHg)				
Before intervention	70.8 ± 2.66	69.2 ± 2.48	71.5 ± 2.39	0.001[a]
After intervention	69.0 ± 2.43	68.8 ± 2.33	70.0 ± 2.47	0.071[a]
p-values	0.000[b]	0.089[b]	0.000[b]	

[a]Anova
[b] Paired *t* -test

Table 2 shows that the three groups had different Calcidiol levels, systolic, and diastolic blood pressures before intervention. Based on Tukey post hoc analysis, there were significant differences in Calcidiol levels between the sun exposure and control groups, and between vitamin D supplemented and control groups (P=0.000) before intervention. There was also a significant difference in systolic blood pressures between the sun exposure and vitamin D groups (P=0.000) before intervention. Therefore, the analysis of comparisons between before and after the intervention was also conducted using paired t-tests. The paired t -test results showed that Calcidiol levels increased significantly in all groups, the systolic blood pressure decreased significantly in the vitamin D group, and diastolic blood pressure significantly decreased in the sun exposure and control groups at P-values of <0.05.

Table 3 shows newborns' anthropometric indices in all groups. Data were normally distributed. This table shows significant differences in birth weight among the sun exposure, vitamin D supplementation, and control groups (P=0.000). The mean birth weight was the highest in the vitamin supplementation D group, the second was in the sun exposure group, and the lowest was in the control group. Most of the subjects had a normal birth weight for their newborns (2500-4000 g); only one baby in the sun exposure group and one baby in the control group had low birth weight.

The effect of sun exposure and vitamin D supplementation on Calcidiol levels of pregnant women can be seen in Table 4.

Table 3: Newborns' Anthropometric indices

Variables	***Groups***			**P-*values*** [a]
	Sun exposure Mean ± SD	Vitamin D Mean ± SD	Control Mean ± SD	
Birth weight (gram)	3,091 ± 362.50	3,172 ± 181.78	2,861 ± 207.97	0.000
Birth length (cm)	49.5 ± 1.29	49.5 ± 1.27	49.3 ± 1.19	0.834
Head circumference (cm)	33.1 ± 1.34	33.1 ± 1.39	33.1 ± 1.31	0.985

[a]Anova

Table 4: The Effect of Sun Exposure and Vitamin D Supplementation on Calcidiol Levels after Controlling for Calcium Adequacy Levels

Intervention	***B***	***Std. Error***	**P-*value***
Sun Exposure			
Calcium adequacy levels	0.003	0.012	0.826
Sun exposed	11.745	0.933	0.000
Vitamin D supplementation			
Calcium adequacy levels	0.003	0.010	0.782
Vitamin D supplemented	12.227	0.860	0.000

After controlling for calcium adequacy levels as the confounding variable, sun exposure alone and vitamin D supplementation alone still show significant effects, in comparison to the control group in the separate models. Table 4 shows that sun exposure increased Calcidiol levels by 11.745 ng/mL after controlling for calcium adequacy levels. Vitamin D supplementation increased Calcidiol levels by 12.227 ng/mL after controlling for calcium adequacy levels.

The effect of sun exposure and vitamin D on the newborn anthropometric indices after controlling for the confounding variables (protein and calcium adequacy levels) can be seen in Table 5.

Sun exposure has a significant effect on increasing birth weight by 222.9 g, and vitamin D supplementation increased birth weight by 302.26 g compared to the control group in the separate models. Sun exposure has no significant effect on birth length (*P*=0.051) and head circumference (*P*=0.147). The birth length and head circumference of newborns in the sun exposure group were in the normal category. Vitamin D supplementation has a significant effect on increasing birth length (*P*=0.011) by 1.1 cm. Vitamin D supplementation has no significant effect on increasing head circumference. The birth length and head circumference of newborns in the vitamin D supplemented group were in the normal category.

Table 5: The Effect of Sun Exposure and Vitamin D Supplementation on Newborn Anthropometric indices after Controlling for Protein and Calcium Adequacy Levels

Intervention	*B*	*Std. Error*	P-*values*
Sun exposure (on birth weight)			
Protein adequacy levels	6.024	3.540	0.093
Calcium adequacy levels	-0.547	1.023	0.595
Sun exposed	222.883	94.893	0.022
Vitamin D supplementation (on birth weight)			
Protein adequacy levels	1.715	2.712	0.529
Calcium adequacy levels	-0.225	0.686	0.744
Vitamin D supplemented	302.21	70.637	0.000
Sun exposure (on birth length)			
Protein adequacy levels	-0.025	0.015	0.092
Calcium adequacy levels	-0.009	0.005	0.040
Sun exposed	0.735	0.371	0.051
Vitamin D supplementation (on birth length)			
Protein adequacy levels	-0.036	0.016	0.032
Calcium adequacy levels	-0.010	0.004	0.015
Vitamin D supplemented	1.103	0.423	0.011
Sun exposure (on head circumference)			
Protein adequacy levels	-0.035	0.016	0.032
Calcium adequacy levels	-0.008	0.005	0.122
Sun exposed	0.582	0.396	0.147
Vitamin D supplementation (on head circumference)			
Protein adequacy levels	-0.032	0.018	0.087
Calcium adequacy levels	-0.005	0.005	0.285
Vitamin D supplemented	0.686	0.482	0.159

Discussion

The Calcidiol levels of the subjects were very low before the intervention (< 30 ng/mL) (18). Based on the observations and interviews, most of the subjects did not consume vitamin D supplements and rarely had sunbathing. The subjects did not know the benefits of vitamin D, especially for the health of pregnant women and fetal growth. In addition, the subjects had no information about the right time to sunbathe to prevent vitamin D deficiency. Vitamin D deficiency increased the risk of health problems such as preeclampsia, low birth weight, glucose intolerance, preterm birth, and cesarean delivery (3). Vitamin D deficiency in pregnant women may affect maternal health and fetal growth and development (14).

In this study, Calcidiol levels after the intervention increased in all the groups. The average Calcidiol levels increased by 15.2 ng/mL in the sun exposure group, 15.3 ng/mL in the vitamin D supplemented group, and 2.8 ng/mL in the control group. These results were higher compared to the results of the previous study in Bogor (West Java), which showed that 30 min sun exposure at 09.00-09.30 for 3 times/week in 12 wk increased Calcidiol levels by 2.5 ng/mL in women at childbearing age (15). In Palu (Central Sulawesi), sun exposure 3 times a week for 6 wk increased Calcidiol levels by 2.20 ng/mL. This study in Semarang (Central Java) showed the highest increase in Calcidiol levels among pregnant women. These results could be caused by the high compliance of the subjects who did not wear any sunblock cream, in the dry season. Sun exposure of 15-30 min 2-3 times/week can prevent vitamin D deficiency (17, 19).

The systolic blood pressure in the sun exposure group decreased by 0.8 mmHg, while the other group did not show a decrease. The results of this study were following the previous studies in Indonesia, which reported a decrease of 6 mmHg in systolic blood pressure among individuals who received sun exposure (20). Studies in Bogor (West

Java, Indonesia) reported a decrease of 11.2 mmHg in systolic blood pressure among the individuals who received sun exposure (15). Diastolic blood pressure in the sun exposure and control groups decreased between 0.8 to 1.5 mmHg. The results of this study are lower compared to those of the previous studies in Bogor (West Java) that reported a decrease of 6 mmHg in diastolic blood pressure among the childbearing women who got sun exposure (15).

Vitamin D can suppress the genes that encode renin so that it cannot be formed (21). This condition resulted in the inactivation of the angiotensin renin system, which prevents the increase in blood pressure. In addition, vitamin D also plays a role in suppressing cox-2 expression in macula densa cells of the kidney, which will stop the transformation of arachidonic acid into prostaglandin (22). It can also inhibit the transcription of the renin gene (23). Besides that, blood pressure is determined by cardiac output and the resistance of blood vessels. The resistance of blood vessels depends on blood viscosity, vessel length, and vessel radius (24). These may be the causes of the smaller decrease of blood pressure in this study compared to the previous studies. All of these mechanisms may explain the effect of vitamin D on lowering blood pressure in pregnant women.

Most of the newborns' weights in the three groups were in the normal category. The newborns' weights were influenced by mothers' nutritional status and environmental factors. The incidence of low birth weight was 2.8% in the sun exposure and control groups. These babies were born prematurely and the mothers' Calcidiol levels were less than 8 ng/mL before intervention. Vitamin D can be transferred through the placenta. Pregnant women who suffer from vitamin D deficiency will also have low vitamin D reserves. Babies born prematurely have low vitamin D reserves, so the risk of vitamin D deficiency is higher (25,26). Vitamin D influences the pathophysiology of preterm labor as it affects the processes of inflammation and immunomodulation (27). It is responsible for an adequate function of toll-like receptors which initiate the innate immune response. The susceptibility to infection is increased in the cases of vitamin D deficiency because of the impairment of toll-like mediated induction of antimicrobial peptide cathelicidin from macrophages (28).

This study also showed that 2.8% of the babies in the sun exposure group had a birth weight of > 4000 g (overweight). In this case, the mother's gestational age at delivery was more than 40 wk. The length and head circumference of the newborns in the three groups were normal. There was no difference in length and head circumference of the newborns among the groups.

The strength of the study was the use of a randomized controlled trial design. The limitations of the study were the differences in Calcidiol levels, systolic, and diastolic blood pressures among the groups at baseline. Furthermore, Calcidiol levels after intervention were still below normal for most of the subjects. Thus, a larger dose and longer vitamin D supplementation as well as sun exposure are recommended for a future study.

It is recommended, especially in the dry season and in the area near the equator, that pregnant women get sunlight exposure of 15-30 min between 10:00 a.m. to 02:00 p.m. 3 times a week starting from their first trimester to prevent vitamin D deficiency. Vitamin D supplementation for pregnant women is also recommended, but sunlight exposure is much cheaper and easier to get, especially in the tropics. In addition, sun exposure is safe for pregnant women.

Conclusion

Overall, 1000 IU vitamin D supplementation daily for 17 wk and sun exposure for 15-30 min, 3 times a week on the face, arms, and limbs started at 20 wk of gestations increased the Calcidiol levels of pregnant women and resulted in the higher birth weight of the newborns. Vitamin D supplementation could also maintain the systolic blood pressure of pregnant women. The effect of vitamin D supplementation on birth weight was higher than the sunlight exposure. Thus, pregnant women who could not have vitamin D supplementation get sunlight exposure for at least 15-30 min 3 times a week on the face, arms, and limbs starting from the 20 wk of gestation.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

There is no conflict of interest in this study.

References

1. Palacios C, Gonzales. L. (2014). Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol*, 144 Pt A:138-45.
2. Hossein Na, Holick MF (2013). Vitamin D for health: a global perspective. *Mayo Clin Proc*, 88(7): 720-755.
3. Song Hong-Bi, Xu Yin, Yang Xiaowu, et al (2018). High prevalence of vitamin D deficiency in pregnant women and its relationship with adverse pregnancy outcomes in Guizhou, China. *J Int Med Res,* 46 (11): 4500-4505.
4. Man RE, Li LJ, Cheng CY, et al (2017). Prevalence and Determinants of Suboptimal Vitamin D Levels in a Multiethnic Asian Population. *Nutrients*, 9(3):313.
5. Bardosono S. (2016). Maternal Micronutrient Deficiency during The First Trimester Among Indonesian Pregnant Women Living in Jakarta. *eJKI*; 4 (2): 76 – 81.
6. Aji AS, Yerizel E, Desmawati, Nur IP (2018). The association between lifestyle and maternal vitamin D during pregnancy in West Sumatra, Indonesia. *Asia Pac J Clin Nutr*, 27(6): 1286-93.
7. Aji AS, Erwinda E, Yusrawati Y, Malik SG, Lipoeto NI. (2019). Vitamin D deficiency status and its related risk factors during early pregnancy: a cross-sectional study of pregnant Minangkabau women, Indonesia. *BMC Pregnancy Childbirth*, 19: 183.
8. Putri NI, Lipoeto NI, Rita RS, Aji AS. (2019). Hubungan Kadar Vitamin D pada Ibu Hamil dengan Berat Bayi Lahir di Kabupaten Tanah Datar dan Kabupaten Solok. Jurnal Ilmiah Universitas Batanghari Jambi. 19 (1): 61 – 64.
9. Sathish P et al. (2016). Correlation Between Maternal and Neonatal Blood Vitamin D levels and its effect on the Newborn Anthropometry. *Int J Reprod Contracept Obstet Gynecol.* 5(9): 2983-2988.
10. Hashemipour Sh, Ziaee A, Javadi A, et al. (2014). Effect of Treatment of vitamin D deficiency and insufficiency during pregnancy on fetal growth indices and maternal weight gain: a randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol,* 172:15-9.
11. Vanchinathan V, Lim HW. (2012). A dermatologist's perspective on vitamin D. *Mayo Clin Proc*, 87 (4):372–80.
12. Pereira MU, Solé D (2015). Vitamin D deficiency in pregnancy and its impact on the fetus, the newborn, and in childhood. *Rev Paul Pediatr*, 33(1):104-113.
13. Moon RJ, Davies JH, Cooper C, Harvey NC. (2020). Vitamin D and Maternal and Child Health. *Calcif Tissue Int*, 106:30-46.
14. Holick MF. (2007). Vitamin D Deficiency. *N Engl J Med.* 357(3): 266-281.
15. Yosephin B, Khomsan A, Briawan D, Rimbawan. (2014). Peranan Ultraviolet B Sinar Matahari terhadap Status Vitamin D dan Tekanan Darah pada Wanita Usia Subur. *Jurnal Kesehatan Masyarakat Nasional.* 8(6): 256-260.
16. Van der Zande ISE, Van der Graaf R, Oudijk MA, et al (2017). Vulnerability of Pregnant Women in Clinical Research. *J Med Ethics.* 43: 657-63.
17. Samanek AJ, Croager EJ, Gies P, et al. (2006). Estimates of beneficial and harmful sun exposure times during the year for major Australian population centres. *Med J Aust,* 184(7): 338–341.
18. Pludowski P, Takacs I, Boyanov M, et al (2022). Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A

Central and Eastern European Expert Consensus Statement. *Nutrients,* 14:1483.

19. Setiati S, Oemardi M, Sutrisna B. (2007). The role of ultraviolet-B from sun exposure on vitamin D3 and parathyroid hormone level in elderly women in Indonesia. Jakarta: *Asian J Gerontol Geriatr*, 2(3): 126– 32.
20. Siagian, A. (2015). Peranan vitamin D pada pencegahan penyakit degeneratif. Medan: Departemen Gizi Kesehatan Masyarakat FKM USU Medan.
21. Christakos S, Ajibade DV, Dhawan P, et al (2010). Vitamin D: metabolism. *Endocrinol Metab Clin North Am,* 39(2):243-53.
22. Hermawan D, Kadarsih S, Sunarti Astuti I et al (2016). Pengaruh Vitamin D terhadap Ekspresi COX-2, Kadar cAMP, Kadar Renin Darah dan Tekanan Darah Sistolik dalam Sistem Renin Angiotensin Aldosteron. *Jurnal Kedokteran Brawijaya,* 29(2): 125-131.
23. Yuan W, Pan W, Kong J, et al (2007). 1,25-Dihydroxyvitamin D3 Suppresses Renin Gene Transcription by Blocking the Activity of the Cyclic AMP Response Element in the Renin Gene Promoter. *J Biol Chem,* 282(41):29821-30.
24. Lionakis N, Mendrinos, Dimitrios, et al. (2012). Hypertension in the elderly. *World J Cardiol*, 4(5):135-47.
25. Gernand AD, Schulze KJ, Stewart CP, et al (2016). Micronutrient deficiencies in pregnancy worldwide: Health effects and prevention. *Nat Rev Endocrinol*, 12:274-289.
26. Tsiaras WG, Weinstock MA. (2011). Factors influencing vitamin D status. *Acta Derm Venereol*, 91(2): 115-124.
27. Bodnar LM, Rouse DJ, Momirova V, et al. (2013). Maternal 25-Hydroxyvitamin D and preterm birth in twin gestations. *Obstet Gynecol,* 122:91-98.
28. Bodnar LM, Klebanoff MA, Gernand AD, et al (2014). Maternal vitamin D status and spontaneous preterm birth by placental histology in the US Collaborative Perinatal Project. *Am J Epidemiol*, 179:168–176.