Journal of Medicinal and Chemical Sciences 7 (2024) 383-391

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Cross Sectional Study

# Determinant Factors of Vitamin D Levels in Down Syndrome of Indonesian Children

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**ARTICLE INFO**

**Article history**

Receive: 2023-08-30
Received in revised: 2023-10-19
Accepted: 2023-10-29
Manuscript ID: JMCS-2308-2199
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatima Ramezani
Editor who approved publication:
Dr. Asghar Mesbahi

**DOI:10.26655/JMCHEMSCI.2024.2.10**

**KEYWORDS**

Vitamin D
Determinant factor
Down's syndrome
Children

**ABSTRACT**

**Background:** Down's syndrome (DS) is a prevalent autosomal disorder that is widely observed on a global scale. Children diagnosed with DS have several environmental and hormonal factors that impact their development. Vitamin D (VD) plays a crucial role in conferring a protective effect to the human body. However, there is a scarcity of study on VD and the factors that influence its level in Indonesian Down's syndrome children. The primary purpose of this research was to examine the levels of VD and the factors that influence them among children in Indonesia diagnosed with DS.
**Methods:** Using a cross-sectional method of Indonesian DS and control children (aged 1 month to18 years), the subjects' VD concentration was evaluated using Elisa and classified into sufficient and non-sufficient groups based on the results. The determinant factors consisted of the subjects' characteristics: demographic characteristics, milk intake, sun exposure, and meat consumption. Kruskal-Wallis, Chi-Squared, Spearman's correlation, and regression tests were used for statistical analysis; outcome was considered significant if *p*-values <0.05.
**Results:** Thirty children with DS and 30 healthy controls were recruited as participants. The mean VD levels in the DS and control groups were 38.74 ng/mL and 70.109 ng/mL, respectively. The rate of VD insufficiency was 33.3% and 26.7% in the DS children and healthy controls, respectively. A significant difference in age, milk intake, body mass index, sun exposure, and meat consumption was observed (*p*-values lower than 0.05).
**Conclusions:** The VD concentration in the DS was below the control group. The key determining factors were the level of milk consumption and exposure to sunlight.

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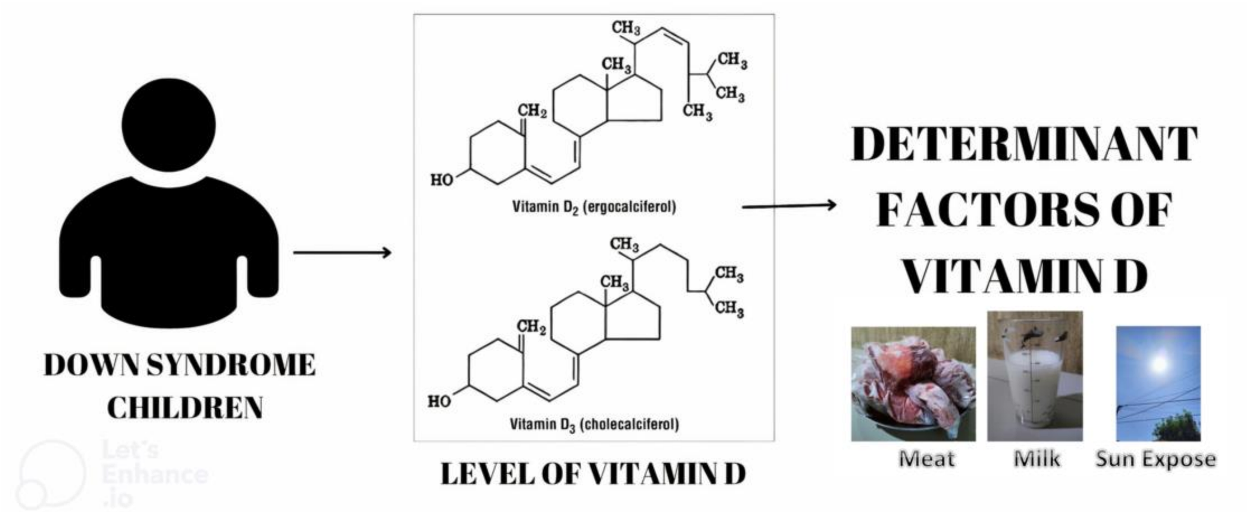
**G R A P H I C A L A B S T R A C**




## Introduction

Down's syndrome (DS) is a common condition with a global prevalence of roughly 1 in 1000 live births [1]. The disorder is generally attributable to autosomal duplication, which results in an extra chromosome twenty-one [2]. Incidence of DS in Indonesia shown a notable rise, with the number of new cases escalating from 1,657 in 2015 to 4,130 in 2017 [3]. This autosomal abnormality has a wide spectrum of clinical symptoms that impact multiple organ systems. These characteristics include, but are not limited to, a protruding tongue, a flat nasal bridge, short stature, hypotonia, and developmental delay [4]. Multiple comorbidities such as thyroid disease, epilepsy, and osteoporosis were more prevalent in Down's syndrome [5].

The 25(OH) D or Vitamin D (VD) is a type of sercosteroid prohormone that had solubility in lipids and is formed in the epidermis when exposed to sunlight. The conversion of calcidiol into calcitriol hormone is facilitated by a series of metabolic processes. This hormone serves a vital function in regulating calcium and phosphate metabolisms [6]. Vitamin D has a number of roles in the body and is linked to a number of disorders, including type 1 diabetes, hypertension, and cancer development [7-9]. Furthermore, vitamin D supplementation has potential to lowering anti-thyroid antibody levels, enhancing thyroid function, and improving other autoimmune markers such as cytokines such as IP10, TNF-, and IL-10, as well as the ratio of T-cell subsets such as Th17 and Tr1 [10]. As a result, VD insufficiency has the potential to cause musculoskeletal symptoms such as muscular weakness, gait abnormalities, and bone deformities. Furthermore, it has the potential to induce other non-skeletal manifestations, including immunological, cardiovascular, and neuropsychiatric conditions [11].

Various environmental and hormonal factors have been identified as potential contributors to the observed decline in bone quality and density in individuals with Down's syndrome (DS). These factors include hypotonia, insufficient physical exercise, and poor consumption of calcium and VD [12, 13]. The remarkable potential impact of VD on the health of children diagnosed with DS deserves special consideration. The phenomenon is further impacted by many elements, including solar exposure, nutritional intake, and the utilization of supplements [14, 15]. A certain study has provided evidence indicating elevated levels of parathyroid hormone (PTH) and insufficient VD in children diagnosed with DS [16, 17].

There was insufficient scientific research addressing VD levels and the factors influencing them in children with Down syndrome (DS) in Indonesia. Therefore, the study's purpose became to investigate VD concentration and the factors that influence it in Indonesian children with DS.

## Materials and Methods

*Study participants*

Our project was held in the pediatric clinic Dr. Soetomo Hospital, East Java, Indonesia, using the cross-sectional method. Ethical approval was done by the ethics council of the hospital (approval no. 0397/KEPK/III/2022). Subject's families had agreed with the informed consent. The inclusion criteria were DS patients aged 1 month to 18 years with positive karyotyping examination. Participants who exhibited acute medical conditions, severe malnutrition, other micronutrient deficiencies, or had received VD supplementation were excluded from the research.

For comparison, 30 healthy subjects with the same age who also visited the pediatric endocrinology clinic in Dr. Soetomo Hospital, Surabaya, Indonesia, were included to the group of control. The determinant factors for VD levels were the subjects' characteristics, such as demographic characteristics, milk intake, sun exposure, and meat consumption. The subject's characteristics were obtained from their parents' recall method and questionnaire.

*Vitamin D (VD) level's measurement*

The subjects' VD level was examined from the venous blood samples obtained from the patients. The categories of 25-hydroxy-D or VD was Table 1 summarizes the characteristics of DS children and healthy controls stratified by VD categories. The significant variations were seen in age, milk intake, BMI, sun exposure, and meat consumption at the four groups ($P < 0.05$). The connection between VD level and its determinant factors for this study was listed as Table 2.

determined using the [25(OH) D] Elisa Kit from DBC Canada (Cat.No.CAN-VD 510) in accordance to the Pediatric Endocrine Society (2011) [18]. The subjects were characterized with deficiency (lower or equal than 21 ng/ mL), inadequate amount (from 22 to 31 ng/ mL), and sufficient (more than or equal 32 ng/ mL) VD.

*Statistical analysis*

VD level was divided into sufficient and non-sufficient group. The non-sufficient group consisted of subjects with deficiency and also VD insufficiency. Univariate analysis was conducted on the subjects' characteristics. The Kolmogorov-Smirnov test was used to calculate whether the numerical outcome had a normal distribution. The DS and control group's differences in terms of whether they are sufficient of VD or not were measured using the Kruskal-Wallis test for the numeric data and chi-squared test for the nominal or categorical data. The correlation between the VD level and its determinant factor was tested using Spearman's correlation test. Results of the multivariate analysis based on the VD level were examined using the regression Test. The SPSS version 22 was used to analyse all the data; p-values less than 0.05 were interpreted to indicate statistically significant and also CI (confidence interval) as 95%.

## Results and Discussion

This study included 30 children with DS (12 females, 18 males) and 30 healthy children for controls (13 females, 17 males). The subjects' characteristics and the determinant factors are presented as Table 3. The mean VD levels in DS children were below the healthy controls (38.74 ±18.435; 70.109 ± 55.7). It was discovered that the percentages of subjects with a non-sufficient VD level were 33.3% in the DS children and 26.7% in the healthy controls.

The amount of milk intake, sun exposure, and meat consumption indicated a strong correlation that was positive (r = 0.612, r = 0.326, and r = 0.352). This indicates that the high amount of milk intake, sun exposure, and meat consumption is associated with an increased VD level. The bivariate analysis indicated in Table 4 reveals that age, milk intake, sun exposure, and meat consumption are significant determinant factor that affect the VD levels in DS children and healthy controls. Conversely, in the multivariate

**Table 1:** Group difference between the DS group and control

| Variables | Down Syndrome group | | Control group | | P-value |
|---|---|---|---|---|---|
| | Non-sufficient | Sufficient | Non-sufficient | Sufficient | |
| Age | 22.2 ± 28.17 | 19.2 ± 14.17 | 58.5 ± 20.72 | 58.90 ± 16.93 | 0.000KW* |
| Sex<br>Male<br>Female | <br>4 (40)<br>6 (60) | <br>14 (70)<br>6 (30) | <br>4 (50)<br>4 (50) | <br>13 (59.1)<br>9 (40.9) | 0.793CS |
| Milk intake | 254 ±170.762 | 522 ± 183.090 | 165 ± 72.30 | 790 ± 150.899 | 0.000KW* |
| Type of milk<br>Formula milk<br>Breast milk | <br>7 (70)<br>3 (30) | <br>20 (100)<br>0 (0) | <br>6 (75)<br>2 (25) | <br>16 (72.7)<br>6 (27.3) | 0.095CS |
| BMI SD-S | -1.719 ± 2.204 | -0.469 ± 6.335 | -0.361 ± 1.361 | 0.007 ± 1.404 | 0.006KW* |
| Sun exposure | 20 ± 7.071 | 32.75 ± 32.866 | 97.5 ± 86.97 | 209.09 ± 121.377 | 0.000KW* |
| Meat consumption | 0.9 ± 1.911 | 2.75 ± 2.844 | 3.125 ± 2.9 | 5.409 ± 2.630 | 0.000KW* |

**CS: Chi-Squared test; KW: Kruskal-Wallis; and SD-S: Standard Deviation-Score.*

**Table 2:** The correlation at the VD levels and its determinant factors

| Variables | P-value | Coefficient correlation |
|---|---|---|
| Age | 0.498 | 0.089 |
| Sex | 0.548 | -0.079 |
| Milk intake | 0.000* | 0.612 |
| Body Mass Index SD-S | 0.075 | 0.231 |
| Sun exposure | 0.011* | 0.326 |
| Meat consumption | 0.006* | 0.352 |

**Statistically significant and SD-S: Standard Deviation-Score.*

analysis, the primary determinant factors affecting the VD levels are the amount of milk intake and sun exposure.

According to the preliminary results of our VD study, the DS group had a higher level of VD insufficient amounts compared to the controls. This result is consistent with a prior investigation that revealed a substantial prevalence of VD deficiency in Down syndrome children [16, 17, 19, 20]. According to study by Stagi *et al.*, there is a very high frequency of VD insufficiency in DS children, with a mean VD level of 14.34 ± 8.31 [21]. The DS group's lower VD levels can be linked to a higher vulnerability to genetically influenced VD metabolism and intake [22]. The increasing neuro-inflammation in DS [23] could result in a higher need for the immune-modulating effects of VD [23]. This result is different from study by Hisbiyah *et al.*, which found that VD sufficiency was more dominant in DS children in Indonesia, with a mean level of 36.85 ± 20,322 ng/mL [24].

This study demonstrated a significant difference in age, BMI, milk intake, sun exposure, and meat consumption between the DS and control groups stratified by VD categories. A study in Turkey demonstrated that the VD levels significantly down from infancy until preschool in DS children [19]. Meat consumption status in children with Down syndrome is also linked to numerous nutritional issues. Given the major worry about the underlying condition, micronutrient deficits including those in folate, iron, magnesium, and vitamin D are commonly disregarded but are essential for achieving the children's optimal growth and development. However, resolving these issues lessens the child's neurological deficiencies and improves his or her chances of achieving the best potential level of growth, lifespan, and quality of life. Patients with neurodevelopmental problems frequently have difficulties such as malnutrition, excessive nutritional intake, and micronutrient deficiencies, which have an impact on their general health and quality of life.

**Table 3:** Down syndrome group and control group's characteristics

| No. | Variables | Down syndrome group | Control group |
|---|---|---|---|
| 1 | Age (years) | 20.20 ± 19.49 | 58.5 ± 17.64 |
| 2 | Sex | | |
| | Female | 12 (40) | 13 (43.3) |
| | Male | 18 (60) | 17 (56.7) |
| 3 | Parent's profession | | |
| | Private companies | 24 (80) | 29 (96.7) |
| | Teacher | 2 (6.7) | 1 (3.3) |
| | Civil servants | 3 (10) | 0 (0) |
| | Fisherman | 1 (3.3) | 0 (0) |
| 4 | Parent's education | | |
| | Elementary school | - | 2 (6.7) |
| | Junior high-school | 3 (10) | 6 (20) |
| | High-school | 16 (53.3) | 19 (63.4) |
| | Bachelor | 11 (36.7) | 3 (10) |
| 5 | VD level (ng/mL) | 38.74 ±18.435 | 70.109 ± 55.7 |
| 6 | VD categories | | |
| | Non-sufficient | 10 (33.3) | 8 (26.7) |
| | Sufficient | 20 (66.7) | 22 (73.3) |
| 7 | Milk intake (cc/day) | 432.667 ± 217.999 | 624 ± 311.454 |
| 8 | Types of milk | | |
| | Formula milk | 27 (90) | 22 (73.3) |
| | Breast milk | 3 (10) | 8 (26.7) |
| 9 | Body Mass Index (BMI) SD-S | -0.886 ± 5.307 | -0.091 ± 1.379 |
| 10 | BMI categories | | |
| | Underweight | 14 (46.7) | 3 (10) |
| | Normal | 15 (50) | 24 (80) |
| | Overweight | 1 (3.3) | 3 (10) |
| 11 | Sun Exposure (minute/day) | 28.5 ± 27.57 | 179.333 ± 122.528 |
| 12 | Meat consumption (slice/week) | 2.133 ± 2.687 | 4.8 ± 2.845 |

**SD-S: Standard Deviation-Score.*

**Table 4:** Analysis of bivariate and multivariate for VD levels and their determinant factors

| Variables | Bivariate | | Multivariate | |
|---|---|---|---|---|
| | P-value | OR 95% CI | P-value | OR 95% CI |
| Age | 0.000* | 1.1 (1.049 – 1.152) | 0.176 | 1.216 (0.916 – 1.615) |
| Sex | 0.432 | 0.619 (0.172 – 2.225) | - | - |
| Milk intake | 0.000* | 1.010 (1.004 – 1.016) | 0.000* | 0.991(0.984 – 0.998) |
| Body Mass Index SD-S | 0.393 | 0.737 (0.485 – 1.120) | - | - |
| Sun exposure | 0.000* | 1.050 (1.023 -1.077) | 0.001* | 1.048 (1.009 – 1.089) |
| Meat consumption | 0.000* | 1.408 (1.102 -1.800) | 0.108 | 0.924 (0.570 – 1.496) |

**CI: Confidence Interval; OR: Odd Ratio; and SD-S: Standard Deviation-Score.*

The deterioration of motor skills and cognitive abilities typically makes nutrition-related problems worse [33, 36]. Study by Hisbiyah *et al.* found that daily milk consumption, as well as meat and fish consumption were risk factors for VD levels in VD sufficiency [24]. The findings of this study are in contrast to those of another study which indicated that there were no notable disparities in VD categories among adolescents and children diagnosed with Down's syndrome (DS) [16]. The significant difference in the BMI SDS in this study was similar to that in another study, even when the children and adolescents were individually analysed [16].

This study analysis results in group differences of milk intake was consistent with another study [16], with a high prevalence of DS subjects consuming less milk and VD deficiency or its severe deficiency. Meanwhile, the differences in sun exposure between the groups are contrary to those in another study [25] that demonstrated no differences in the DS than control groups. The low sun exposure in DS children could be due to hypotonia and developmental delay [19].

Poor VD consumption, sun-exposure insufficient, and malabsorption or rapid VD breakdown as a result of anticonvulsant medication are risk factors that related to VD deficiency in DS patients [26]. Limited sun exposure was identified as VD insufficiency's risk factor at the age of 6 months. Consequently, more sun exposure helps shield children from VD insufficiency [27]. Numerous variables, including genetics, environment, and lifestyle, have an impact for the currency of VD deficiency [28]. It is also known that children who had vitamin D injections have a lower risk of acquiring diabetes type I. It inhibits hypertension and reduces arterial wall stiffness and affects reducing triglyceride and cholesterol levels in the body, preventing cardiac problems as a result [34, 37]. The technique of giving VD supplements, medication distribution, and pharmaceutical applications are other factors that must be taken into account. Using soft medicines is one effective method of administration [38, 39].

Sunlight exposure along with milk consumption both significantly increased VD levels. This study found a similar relationship between milk consumption and VD levels as previous study did [16, 29]. Although it is acknowledged in several journals that exposure to sunlight is not the only factor affecting an individual's vitamin D status and levels, UVB sunlight exposure is still necessary for the production of vitamin D, which is regarded as the main source of vitamin D for the majority of the population rather than dietary sources. In addition, a number of variables like air pollution and a number of candidate genes like cytochrome P450 may be involved in the variation in serum vitamin D levels between people [35, 40]. Another study on Indonesian children found that the VD deficient group received less sun exposure than the group of VD sufficient, and this finding is consistent with that study's findings [30]. In this study, there was a strong link between VD levels and meat consumption. According to a UK's study, meat eaters had higher VD levels than vegans and vegetarians [31]. In the context of children with Down syndrome in Indonesia, the consumption of meat and milk, as well as exposure to sunlight are significant factors that influence vitamin D (VD) levels. Our study aligns with previous research that has demonstrated a correlation between consistent milk consumption and a decreased likelihood of autoimmune illness in children diagnosed with Down syndrome [32].

The limitation of this study is single-centre and cross-sectional study which might lead to a study bias, even though a multiple recall method and questionnaire was already used to minimalize it. Despite its limitations, this study's strength lay in its analysis of VD level and its determinant factor of DS children in developing country, Indonesia, where the study was still limited. The result of this study may encourage further study into nutritional assessment or intervention in DS patients.

## Conclusion

Children with DS from Indonesia were found to have reduced VD levels. Age, BMI, milk intake, sun exposure, and meat consumption were all significantly different between the DS and control groups when divided into different VD categories. The primary determinant factors were the amount of milk intake and sun exposure. Therefore, VD examination and supplementation are needed in children with DS.


## Acknowledgments

The authors would like to thank the endocrinology of Dr. Soetomo Hospital, East Java, Indonesia.


## Disclosure Statement

No potential conflict of interest was reported by the authors.


## Funding

The present study was supported by Universitas Airlangga, Indonesia no. 1312/UN3.1.1/HK/2022.


## Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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**HOW TO CITE THIS ARTICLE**

Nur Rochmah, Muhammad Faizi, Yuni Hisbiyah, Rayi Kurnia Perwitasari, Tyas Maslakhatien Nuzula, Ema Qurnianingsih*, Zakiyatul Faizah. Determinant Factors of Vitamin D Levels in Down Syndrome of Indonesian Children. *J. Med. Chem. Sci.*, 2024, 7(2) 383-391.

DOI: https://doi.org/10.26655/JMCHEMSCI.2024.2.10

URL: https://www.jmchemsci.com/article_183240.html