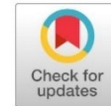




Association of vitamin D receptor and group-specific component gene polymorphisms with type 2 diabetes mellitus among Javanese in Jakarta

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a major public health problem with increasing prevalence globally and in Indonesia, particularly in Jakarta, which has one of the highest prevalence rates, with the Javanese as the predominant ethnic group. Vitamin D deficiency is highly prevalent in this population and has been associated with an increased risk of T2DM. Vitamin D plays an important role in glucose metabolism by enhancing insulin secretion and improving insulin sensitivity. Polymorphisms in the Vitamin D Receptor (VDR) and Group-Specific Component (GC) genes, which are involved in vitamin D metabolism and function, are hypothesized to influence T2DM risk.

Objective: This study aimed to analyze the association between VDR rs2228570 and GC rs7041 gene polymorphisms and T2DM among the Javanese population in Jakarta.

Materials and Methods: A comparative cross-sectional study was conducted among 101 Javanese adults (50 T2DM and 51 non-diabetic subjects). Gene polymorphisms were analyzed using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Associations were assessed using Chi-square tests.

Results: No significant association was found between VDR rs2228570 and GC rs7041 gene polymorphisms and T2DM.

Conclusion: No evidence of association was observed between VDR rs2228570 and GC rs7041 gene polymorphisms and T2DM in this population. These findings highlight the multifactorial nature of T2DM, suggesting that genetic factors related to vitamin D may play a limited role, while environmental and lifestyle factors remain important. Further studies with larger and multi-ethnic populations are needed to better understand the role of vitamin D-related genetic factors in T2DM.

Keywords: Type 2 diabetes mellitus; gene polymorphism; Vitamin D Receptor; group-specific component; javanese ethnicity

BACKGROUND

Type 2 diabetes mellitus (T2DM) is a major global health concern, contributing to reduced quality of life and increased morbidity and mortality.¹ The global prevalence of T2DM has increased rapidly, with an estimated 536.6 million people affected worldwide, and Indonesia ranking fifth globally with a prevalence of 10.6%.² At the national level, DKI Jakarta has one of the highest prevalence rates of T2DM (3.9%).³ Java Island contributes the largest number of cases, with the Javanese representing the largest ethnic group, including in Jakarta, where they account for 36.17% of the population.⁴⁻⁶

T2DM is a multifactorial disease involving complex interactions between genetic and environmental factors.⁷ Among these, vitamin D deficiency has emerged as an important modifiable risk factor.^{8,9} Vitamin D plays a crucial role in glucose metabolism by enhancing insulin secretion, improving insulin sensitivity, and modulating inflammation.^{9,10} However, vitamin D deficiency is highly prevalent in the Javanese population in Jakarta, with reported prevalence ranging from 49.7% to 73.3%, suggesting a potential role in T2DM risk in this population.¹¹⁻¹³

The biological effects of vitamin D are mediated through the vitamin D receptor (VDR) and vitamin D binding protein (VDBP), encoded by the VDR and group-specific component (GC) genes, respectively.⁹ Single-nucleotide polymorphisms (SNPs) such as rs2228570 in the VDR gene and rs7041 in the GC gene may alter protein function and influence vitamin D metabolism.¹⁴⁻¹⁶ Both SNPs are located in coding regions (exons) and result in amino acid substitutions that can affect protein activity.¹⁵ The rs2228570 variant produces a less active VDR protein, potentially reducing transcriptional activity of vitamin D target genes. Meanwhile,

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the rs7041 variant may decrease the binding affinity of VDBP, leading to reduced bioavailability of vitamin D.^{14,17–19} These polymorphisms were selected because they are key functional variants involved in vitamin D metabolism. Unlike other SNPs located in intronic regions that may not alter protein structure, rs2228570 and rs7041 are located in exonic regions and directly affect protein function. Therefore, these SNPs are considered to have greater biological relevance in influencing insulin secretion, insulin sensitivity, and inflammatory pathways associated with T2DM.^{18,20}

Despite increasing interest, findings regarding the association between these polymorphisms and T2DM remain inconsistent across different populations.²¹ In Indonesia, particularly among the Javanese population in Jakarta, where both T2DM and vitamin D deficiency are highly prevalent, research on this topic remains limited. Therefore, this study aimed to investigate the association between VDR rs2228570 and GC rs7041 polymorphisms and T2DM, providing insight into the potential role of vitamin D-related genetic factors in this population.

MATERIALS AND METHODS

Ethical Approval

This study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital (Approval No. KET-493/UN2.F1/ETIK/PPM. 00.02/2024) and received permission from the Jakarta Provincial Health Office (Approval No. 7/HM.10.02). Written informed consent was obtained from all participants prior to enrollment.

Study Design

This study employed a comparative cross-sectional design involving two groups: subjects with type 2 diabetes mellitus (T2DM) and non-diabetic controls. The aim was to analyze the association between genotypes and alleles of the VDR rs2228570 and GC rs7041 genes with T2DM status among individuals of Javanese ethnicity residing in Jakarta.

Population and Sample

The study population comprised adult individuals of Javanese descent living in Jakarta. Participants were recruited from three public health centers: Johar Baru, Cempaka Putih, and Senen, between January and April 2025. Inclusion criteria were: male or female aged 35–64 years; having two generations of Javanese ancestry without interethnic marriage; willingness to provide informed consent; and meeting HbA1c criteria ($\geq 6.5\%$ for the T2DM group, $< 5.7\%$ for the non-DM group). Exclusion criteria included: anemia, autoimmune disorders, chronic kidney disease, coronary heart disease, liver disease, cancer, tuberculosis, other types of diabetes, vitamin D supplementation in the previous month, and recent blood transfusion within the past 2–3 months. Participants were restricted to individuals of Javanese descent to reduce genetic heterogeneity; however, this approach may limit the generalizability of the findings to other populations.

Sample Size and Calculation

Sample size was calculated using the formula for comparing two independent proportions, resulting in a minimum of 45 subjects per group.^{22,23} However, in genetic association studies, an adequate sample size is required to capture allele variation within the population. Considering a minimum minor allele frequency of approximately 1%, at least 100 alleles are needed to ensure sufficient representation of genetic variation.²⁴ Therefore, the total sample size was set at 100 subjects (50 T2DM and 50 non-DM). In total, 101 participants were enrolled, comprising 50 T2DM and 51 non-DM subjects. The flow of participant recruitment and selection is presented in Figure 1.

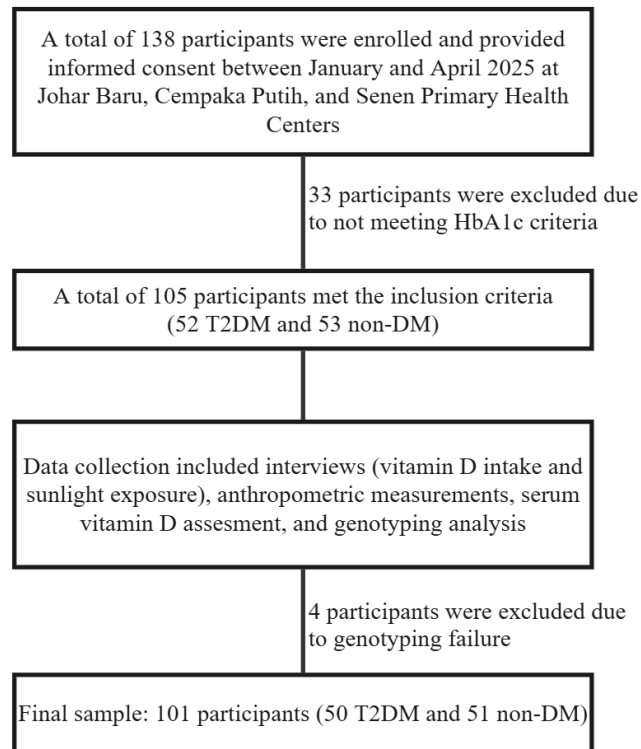


Figure 1. Flow Diagram of Participant Recruitment and Selection

Data Collection

Sociodemographic characteristics, family history of diabetes, comorbidities, history of vitamin D supplementation, and blood transfusions were collected via structured interviews using standardized questionnaires administered by trained enumerators.

Anthropometric Measurement

Body weight and height were measured using calibrated digital scales and stadiometers. Body Mass Index (BMI) was calculated as weight (kg) divided by height squared (m^2) and categorized based on the Asia-Pacific classification.

Vitamin D Intake Assessment

Vitamin D intake was assessed using a semi-quantitative food frequency questionnaire (SQ-FFQ), which estimated the frequency and portion size of vitamin D-rich foods consumed over the past month. Nutrient intake data were converted to grams and analyzed using Nutrisurvey 2007 software. Intake was categorized as inadequate if $<80\%$ of the recommended dietary allowance (RDA) and adequate if $\geq 80\%$ of the RDA ($15 \mu\text{g}/\text{day}$).

Sunlight Exposure Assessment

Sunlight exposure was assessed using a validated questionnaire adapted from Hanwell et al.²⁵ A score was obtained by multiplying the exposure duration (0 = <5 minutes; 1 = 5–30 minutes; 2 = ≥ 30 minutes) with the area of skin exposed (1 = face and hands only; 2 = face, hands, and arms; 3 = face, hands, and feet; 4 = nearly the entire body). Daily scores were summed over 7 days to yield a weekly score (range: 0–56).

Blood Sample Collection and Storage

Venous blood samples were collected by trained medical staff. EDTA tubes were used for genetic analysis, and plain tubes for vitamin D level analysis. Samples were kept at $2-8^\circ\text{C}$ during storage and transport to the Biochemistry and Biology Laboratory, Faculty of Medicine, Universitas Indonesia (FKUI), following standard biosafety procedures.

Vitamin D Level Analysis

Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured using a competitive enzyme-linked immunosorbent assay (ELISA). The assay quantified serum 25(OH)D by measuring the color intensity

at 450 nm, which was inversely proportional to 25(OH)D concentration. Values were interpreted using a standard calibration curve.

Genotyping and Polymorphism Analysis

Polymorphisms of the VDR rs2228570 and GC rs7041 genes were analyzed using the Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR-RFLP) technique. DNA was extracted from EDTA-preserved blood samples.

DNA concentration and purity were assessed using a Nanodrop spectrophotometer based on A260/A280 and A260/320 ratios. Samples not meeting quality criteria were re-evaluated prior to PCR amplification. To ensure genotyping reliability, a subset of samples was re-analyzed using the same PCR-RFLP procedure, yielding consistent results.

Table 1. Specific Primer for Amplification and PCR Conditions

	VDR rs2228570	GC rs7041
Forward	5'-CAC TGA CTC TGG CTC TGA CCG T-3'	5'-AAA TAA TGA GCA AAT GAA AGA AGA C-3'
Reverse	5'-AAC ACC TTG CTT CTT CTC CCT CC-3'	5'-AAA TAA TGA GCA AAT GAA AGA AGA C-3'
PCR Conditions	Initial denaturation at 95°C for 5 min 35 cycles of denaturation at 95°C for 30 s, annealing at 60°C for 30 s, extension at 72°C for 30 s Final extension at 72°C for 7 min	Initial denaturation at 95°C for 5 min 35 cycles of denaturation at 95°C for 30 s, annealing at 54°C for 30 s, extension at 72°C for 60 s Final extension at 72°C for 7 min

PCR products were digested with FokI (for VDR rs2228570) and HaeIII (for GC rs7041) enzymes at 37°C for 60–120 minutes.^{26,27} Digested products were separated by electrophoresis on 1% agarose gel stained with ethidium bromide and visualized using a UV transilluminator. Interpretation of VDR rs2228570 genotypes are 265 bp (CC/ homozygous wild type), 196+69 bp (TT/ homozygous mutant), 265+196+69 bp (CT/ heterozygous). Interpretation of GC rs7041 genotypes are 483 bp (TT/ homozygous *wild type*), 297+186 bp (GG/ homozygous mutant), 483+297+186 bp (TG/ heterozygous). Selected samples were further analyzed using DNA sequencing to validate genotyping results and confirm SNP identification.

Statistical Analysis

Data analysis was conducted using SPSS version 26. Descriptive statistics were used to summarize subject characteristics. Bivariate analysis using the Chi-square test was applied to evaluate associations between categorical variables, including genotypes/alleles and T2DM status. Fisher's exact test was used when the assumptions for the Chi-square test were not met. The strength of associations was presented as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant.

Chi-square analysis was selected as it is appropriate for assessing associations between categorical variables in genetic studies. Logistic regression was not performed because the primary objective of this study was to assess bivariate associations rather than to develop a multivariable model.

RESULTS

Characteristics of Study Subject

The characteristics of study subjects are summarized in Table 2. Significant differences were found in age ($p < 0.001$), family history of diabetes ($p = 0.022$), and sunlight exposure ($p = 0.016$) between the T2DM and non-DM groups. The T2DM group had a higher proportion of older individuals (55–64 years), a higher proportion with a positive family history of T2DM, and lower sunlight exposure. No significant differences were observed in sex, nutritional status, vitamin D intake, or vitamin D levels.

Table 2. Characteristics of Study Subject

Variable	T2DM	Non-DM	p
Age n (%)			<0.001
35-44 years	7 (14)	24 (47.1)	
45-54 years	17 (34)	12 (23.5)	
55-64 years	26 (52)	15 (29.4)	
Sex n (%)			0.862
Male	12 (24)	13(25.5)	
Female	38 (76)	38 (74.5)	
Family history of T2DM n (%)			0.022
Yes	28 (56)	17 (33.3)	
No	22 (44)	34 (66.7)	
Maternal history of gestational DM n (%)			0.495
Yes	0 (0)	2 (3.9)	
No	22 (44)	8 (15.7)	
Don't know	28 (56)	41 (80.4)	
Nutritional status n (%)			0.249
Obese (≥ 25 kg/m ²)	37 (74)	32 (62.7)	
Overweight (23-24,9 kg/m ²)	6 (12)	5 (9.8)	
Normal (18,5- 22,9 kg/m ²)	7 (14)	12 (23.)	
Underweight (<18,5 kg/m ²)	0 (0)	2 (3.9)	
Vitamin D intake n (%)			1.000
Inadequate (<80% RDA)	48 (96)	49 (96.1)	
Adequate ($\geq 80\%$ RDA)	2 (4)	2 (3.9)	
Sunlight exposure n (%)			0.016
Low (<33,6)	49 (98)	42 (82.4)	
Moderate (33,6-44,7)	1 (2)	3 (5.9)	
High ($\geq 44,8$)	0 (0)	6 (11.8)	
Vitamin D levels n (%)			0.107
Deficient (<20 ng/mL)	1 (2)	1 (2)	
Insufficient (20-29 ng/mL)	12 (24)	20 (39.2)	
Normal (30-100 ng/mL)	37 (74)	30 (58.8)	

Distribution of VDR Gene Polymorphism rs2228570

The PCR-RFLP product for the VDR gene rs2228570 is shown in Figure 2.

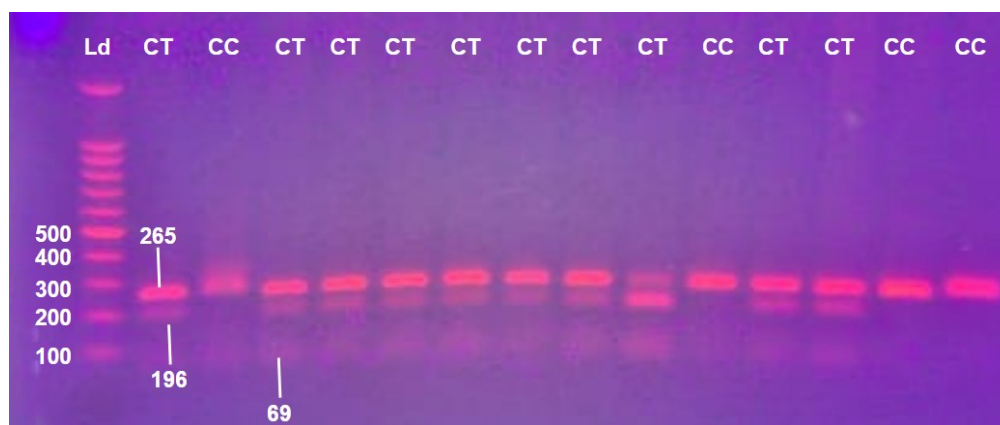


Figure 2. PCR-RFLP Product of VDR Gene rs2228570

For VDR rs2228570, genotypes CC and CT were observed in both groups, while genotype TT was absent. This finding indicates a low frequency of the T allele in this population, resulting in limited genotype

variability. The frequency distribution is shown in Table 3. There was no significant difference in the distribution of genotypes or alleles between the T2DM and non-DM groups.

Table 3. Frequency Distribution of VDR Gene Polymorphism rs2228570

Polymorphism	T2DM	Non-DM	Total
Genotype n (%)			
CC	28 (56)	29 (56.9)	57 (56.4)
CT	22 (44)	22 (43.1)	44 (43.6)
TT	0 (0)	0 (0)	0 (0)
Allele n (%)			
C	78 (78)	80 (78.4)	158 (78.2)
T	22 (22)	22 (21.6)	44 (21.8)

Distribution of GC Gene Polymorphism rs7041

The visualization result of the PCR-RFLP product for the GC gene rs7041 is presented in Figure 3.



Figure 3. PCR-RFLP Product of GC Gene rs7041

For GC rs7041, three genotypes (TT, TG, GG) were found in the T2DM group, while only TT and TG were observed in the non-DM group. The GG genotype was observed only in a small proportion of subjects and exclusively in the T2DM group, indicating a low frequency of this variant in the study population. The G allele was also less frequent in both groups. Details are provided in Table 4.

Table 4. Frequency Distribution of GC Gene Polymorphism rs7041

Polymorphism	T2DM	Non-DM	Total
Genotype n (%)			
TT	23 (46)	27 (52.9)	50 (49.5)
TG	23 (46)	24 (47.1)	47 (46.5)
GG	4 (8)	0 (0)	4 (4)
Allele n (%)			
T	69 (69)	78 (76.5)	147 (72.8)
G	31 (31)	24 (23.5)	55 (27.2)

Association Between VDR Gene Polymorphism rs2228570 and Type 2 Diabetes Mellitus

Bivariate analysis revealed no significant association between VDR rs2228570 polymorphism and T2DM (Table 5). Subjects with the CT genotype had a similar risk of T2DM compared to those with the CC genotype (OR: 1.036; 95% CI: 0.472–2.275; p=0.930), indicating no meaningful difference in risk between genotypes. The T allele also showed no significant association with T2DM (OR: 1.026; 95% CI: 0.526–2.001; p=0.941), with effect estimates close to unity.

Table 5. Association of VDR Gene Polymorphism rs2228570 with Type 2 Diabetes Mellitus

Polymorphism	T2DM	Non-DM	p	OR (95% CI)
Genotype n (%)				
CC	28 (56)	29 (56.9)	-	Reference
CT	22 (44)	22 (43.1)	0.930 ^{cs}	1.036 (0.472-2.275)
Allele n (%)				
C	78 (78)	80 (78.4)	-	Reference
T	22 (22)	22 (21.6)	0.941 ^{cs}	1.026(0.526-2.001)

cs) Chi-square test

Association Between GC Gene Polymorphism rs7041 and Type 2 Diabetes Mellitus

There was no significant association between GC rs7041 polymorphism and T2DM (Table 6). The TG+GG genotype did not significantly increase the risk of T2DM compared to the TT genotype (OR: 1.321; 95% CI: 0.604–2.887; p=0.485), indicating no clear association. Similarly, the G allele was not significantly associated with T2DM risk (OR: 1.460; 95% CI: 0.783–2.724; p=0.233), with confidence intervals crossing unity, suggesting statistical uncertainty.

Table 6. Association of GC Gene Polymorphism rs7041 with Type 2 Diabetes Mellitus

Polymorphism	T2DM	Non-DM	p	OR (95% CI)
Genotype n (%)				
TT	23 (46)	27 (52.9)	-	Reference
TG+GG	27 (54)	24 (47.1)	0.485 ^{cs}	1.321 (0.604-2.887)
Allele n (%)				
T	69 (69)	78 (76.5)	-	Reference
G	31 (31)	24 (23.5)	0.233 ^{cs}	1.460 (0.783-2.724)

cs) Chi-square test

DISCUSSION

This study found that age and family history of type 2 diabetes mellitus (T2DM) were significantly associated with T2DM. Older age is a well-established risk factor due to progressive beta-cell dysfunction and increased insulin resistance, which are further exacerbated by obesity, sarcopenia, or physical inactivity.^{28–31} A positive family history of T2DM was also more common in the T2DM group, reflecting the contribution of both genetic susceptibility and shared environmental and lifestyle factors.^{32,33}

Sun exposure was significantly lower in the T2DM group, potentially contributing to impaired glucose metabolism via reduced endogenous vitamin D synthesis.^{34,35} In addition to its role in calcium homeostasis, vitamin D is involved in insulin secretion, insulin sensitivity, and modulation of inflammation.^{9,10} These findings highlight the importance of modifiable factors, particularly sun exposure and vitamin D status, in the prevention and management of T2DM, especially in populations with a high prevalence of vitamin D deficiency.

The distribution of the VDR rs2228570 polymorphism showed that only the CC and CT genotypes were present, with no TT genotype observed, indicating a low frequency of the T allele and limited genetic variability in this population. Similarly, for GC rs7041, the TT and TG genotypes were predominant, while the GG genotype was rare, suggesting a low frequency of the G allele. These patterns are consistent with findings in Asian populations, where certain alleles are less prevalent, and genetic effects may differ across ethnic groups.^{36,37}

No significant associations were observed between VDR rs2228570 and GC rs7041 polymorphism and T2DM in this study. These findings are consistent with several studies conducted in Asian and European populations that reported no significant association between these polymorphisms and T2DM.^{36,38,39} However, studies in other populations, including East Asian and Middle Eastern cohorts, have reported significant associations, suggesting that the effects of these polymorphisms may vary depending on ethnic background, genetic structure, and environmental exposures.^{40,41}

The absence of the TT genotype in VDR rs2228570 and the low frequency of the G allele in GC rs7041 may have reduced the statistical power to detect significant associations. In addition, the predominance of wild-type alleles suggests a relatively lower genetic susceptibility related to these variants in this population. Furthermore, potential confounding factors such as vitamin D intake, sunlight exposure, and body mass index (BMI) may have influenced the observed associations, as these factors are known to affect both vitamin D status and glucose metabolism.

These findings support the concept that T2DM is a multifactorial disease influenced by complex interactions between genetic and environmental factors. Gene-environment interactions likely play a key role, where the effects of VDR and GC polymorphisms may depend on vitamin D availability, sun exposure, obesity, and dietary patterns. In addition, population stratification may have influenced the results, as this study focused on a relatively homogeneous Javanese population, which may limit genetic variability while improving internal consistency.

From a clinical and nutrigenetic perspective, these findings emphasize that modifiable factors remain central in T2DM prevention and management. Optimizing vitamin D intake, ensuring adequate sun exposure, and maintaining a healthy lifestyle are likely more impactful than single genetic variants in this population. This is particularly relevant in populations with a high prevalence of vitamin D deficiency, such as the Javanese population in Jakarta.

Although no significant association was identified, these polymorphisms may still play an indirect role in modulating vitamin D metabolism rather than acting as direct determinants of T2DM. Future studies should include larger, multi-ethnic populations and longitudinal designs to better assess causal relationships. In addition, further research exploring multiple polymorphisms within the VDR and GC genes, as well as other genes involved in vitamin D metabolism, is needed to provide a more comprehensive understanding of genetic contributions to T2DM.

This study has several strengths. It applied an integrated approach by combining genetic analysis, biochemical measurement of vitamin D, and environmental factors such as dietary intake and sun exposure, allowing a more comprehensive evaluation of T2DM risk. In addition, this study provides novel data on vitamin D-related genetic polymorphisms in the Javanese population in Jakarta, contributing to the development of nutrigenetic research in Indonesia.

However, several limitations should be considered. The inclusion of only Javanese participants may limit the generalizability of the findings to other ethnic groups, although this approach reduced genetic heterogeneity. The cross-sectional design precludes causal inference. The relatively small sample size and the low frequency of certain genotypes may have limited statistical power. In addition, the use of self-reported questionnaires for dietary intake and sun exposure may introduce recall bias, and potential confounding factors were not fully controlled.

CONCLUSIONS

No evidence of association was observed between VDR rs2228570 and GC rs7041 polymorphisms and type 2 diabetes mellitus (T2DM) in this study population. These findings suggest that these genetic variants may not play a major role as independent determinants of T2DM in the Javanese population in Jakarta. Environmental and modifiable factors, including age, family history, and sun exposure, appear to have a more prominent contribution to T2DM risk. This is particularly relevant in populations with a high prevalence of vitamin D deficiency. Further studies involving larger, multi-ethnic populations and longitudinal designs are warranted to better clarify causal relationships and explore broader genetic factors related to vitamin D metabolism.

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DECLARATIONS

Ethics Approval and Consent to Participate

This study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital (Approval No. KET-493/UN2.F1/ETIK/PPM. 00.02/2024) and received permission from the Jakarta Provincial Health Office (Approval No. 7/HM.10.02). Written informed consent was obtained from all participants prior to enrollment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest to disclose.

CONFLICT OF AI USE

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to improve the clarity, grammar, and readability of the manuscript. The authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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