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Research Article

Genetic *CYP2A6* Polymorphism May Worsen Glycohemoglobin Levels: Study among Javanese Indonesian Smokers

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Abstract

We have examined the inactive *CYP2A6* alleles gene, including CYP2A6*4, CYP2A6*7, and CYP2A6*9, associated with glycohemoglobin levels among Javanese Indonesian smokers. There are 106 smokers participating in this study. Due to the number of cigarettes smoked per day, there are three groups of smokers: light, intermediate, and heavy smokers, with 98.7% being light and intermediated smokers while the rest are heavy smokers. All participants had smoked for more than 10 years, indicating they had been exposed to nicotine for a long time. Based on their genotype, there were four groups of smokers, including fast, intermediate, slow, and poor metabolizers. Most fast and intermediate metabolizers have HbA1c levels in the normal range (<5.7). On the other hand, most slow metabolizers have Hb1c levels >5.7, and all fast metabolizers have HbA1c levels >5.7, indicating that they the prediabetes and diabetes. The chi-square test showed a relationship between CYP2A6 polymorphism and HbA1c levels among the participants (P-value 0.000 <0.005 and χ^2=54.6, df=1). The presence of an inactive allele will worsen the HbA1c levels in smokers.

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INTRODUCTION

Diabetes mellitus (DM), a chronic disease, was the third leading cause of death in Indonesia, with a percentage of 6.7% after stroke (21.1%) and coronary heart disease (12.9%). The DM prevalence in Indonesia has increased substantially from 6.9% in 2013 to 8.5% in 2018[1]. Other data has estimated that approximately 30% of Indonesia's population (30 million people) with diabetes remains undiagnosed. The diabetics in Indonesia were estimated could reach 30 million people in 2030 if lifestyles including unhealthy diet, obesity, lack of physical activity, alcohol consumption, and smoking are not a concern[2]. In line with this report, The International Diabetes Federation (IDF) found that people with diabetes in Indonesia have increased precipitously in the last ten years from 2021. Without proper management, people with diabetes will jump to a staggering 28.57 million in 2045, or 47% greater than 19.47 million in 2021[3].

Type 2 diabetes mellitus (T2DM) is the most common in adults and accounts for 90% of all diabetes cases. In past years, T2DM typically develops in adulthood. However, in recent years, it has been increasingly seen in children and adolescents partially due to lifestyle, including rising obesity rates, unhealthy diet, lack of physical inactivity, alcohol consumption, and smoking[4]. The Basic Health Research of Indonesia (*Riset Kesehatan Dasar, RISKESDAS*) 2018 reports that T2DM prevalence in the Daerah Istimewa Yogyakarta (DIY) Province was second among provinces in Indonesia[5]. About 74,668 DIY people have been diagnosed with diabetes, but only 55,190 patients have received standard health services or the equivalent of 73.9%[6].

Several studies have suggested that poor smoking behavior is associated with chronic complications of T2DM compared to non-smokers[7,8]. Another study has reported that smoking can increase glycohemoglobin (HbA1c) blood levels[9]. This HbA1c value can accurately reflect glucose control 2-3 months ago. HbA1c levels are normal if <5.7%, prediabetes 5.7 to 6.4%, and

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diabetes ≥6.5%[10]. Nicotine, the main compound in cigarettes, was considered most responsible for increasing blood sugar levels due to insulin resistance[11].

Nicotine is primarily metabolized by the CYP2A6 enzyme to cotinine and excreted in the urine[12]. The CYP2A6 enzyme encoded by the *CYP2A6* gene is a polymorphic gene. The active allele gene is *CYP2A6*1*, and the inactive is CYP2A6*4, CYP2A6*7, and CYP2A6*9. Due to their genotype, a person with having CYP2A6*4, CYP2A6*7, and CYP2A6*9 allele genes is associated with a slow metabolizer or poor metabolizer[13]. Furthermore, according to Liu *et al.*[14], reduced metabolism function *CYP2A6* in smokers appears to be associated with a higher risk of T2DM.

Our preliminary study[15] revealed a high-frequency CYP2A6*4 allele gene among smokers and non-smokers in Javanese Indonesian. We have also reported that smoking can increase diabetes risk factors. Prediabetes was developing in smokers who had smoked for at least 25 years with 25 cigarettes per day[16]. Furthermore, in our recent study on diabetic patients, both smokers and non-smokers, high-frequency CYP2A6*4, the inactive allele gene of *CYP2A6*, was detected[17]. In high frequency, the other inactive alleles, CYP2A6*7 and CY2A6*9, have also been found among Javanese Indonesian smokers[13]. So, in this research, we study the association of the CYP2A6*4, CYP2A6*7, and CYP2A6*9 on glycohemoglobin levels in Indonesian Javanese smokers.

MATERIALS AND METHODS

Materials

A Norudia® N HbA1c Immunoassay Method using the Architect 600 instrument, calibrated using Diabetes Control and Complications Trial (DCCT) standards with a coefficient of variation <2.5% was used to analyze total HbA1c in the Clinical Pathology Laboratory, Bethesda Hospital, Yogyakarta. Genomic DNA was extracted using a DNA Mini Kit from Bioron GmbH (Germany). The CYP2A6*4, *7, and *9 allele genes were analyzed using the Polymerase Chain Reaction (PCR) method. The forward and reverse primers used in this study were 5' CCT CAT CAC ACA CAA CTT CCT C 3' and 5' TGC AGG TAC TGG GTG CTT GGT AG 3' for CYP2A6*4; 5′-CTC CCA GTC ACC TAA GGA CAC-3' and 5′-AAA ATG GGC ATG AAC GCC C-3' for CYP2A6*7; as well as 5′-GAT TCC TCT CCC CTG GAA C-3' and 5′-GGC TGG GGT GGT TTG CCT TTC-3' for CYP2A6*9.

The PCR mixture contained 12.5 µL Promega Go Taq Green Master Mix, 1.25 µL forward primer, 1.25 µL reverse primer, 5.0 µL genomic DNA, and 5.0 µL nuclease-free water in a final volume of 25 µL. This mixture was run using a PCR machine (Thermal cycler Perkin Elmer 2400) to amplify the genomic DNA. The PCR conditions used are shown in **Table I**.

Table I. PCR condition used.

PCR Condition	Allele gene		
	CYP2A6*4	**CYP2A6*7**	**CYP2A6*9**
Initial denaturation	95°C (5′)	95°C (5′)	94°C (3′)
Denaturation	98°C (20″)	95°C (20″)	94°C (30″)
Annealing	64°C (15″)	56.5°C (30″)	60°C (30″)
Extention	72°C (30″)	72°C (30″)	70°C (25″)
Cycle	30	35	35
Final extention	72°C (5′)	72°C (5′)	72°C (5′)

Methods

Research subject

It is an observational study using a cross-sectional design to analyze the *CYP2A6* polymorphism among Javanese Indonesian Smokers associated with glycohemoglobin blood levels, the main predictor for diabetes disease. Participants were enrolled between July and August 2022. They live in Yogyakarta, as indicated by their identity card. A preliminary survey was conducted to find respondents who smoked using a self-reported smoking questionnaire adopted from the Fagerström Test for Nicotine Dependence (FTND) questionnaire[18]. The participants had to meet the study's inclusion criteria: active smokers who had smoked for at least ten years, Javanese Indonesians with at least three grandparents of Javanese descent due to their self-reported, male, aged 20-50 years, weight between 46 to 75 kg, with a varying height between 150-170 cm. This study excluded the participant who had an infection at the blood sampling and was taking an

anticoagulant. All participants had agreed to participate in this study indicated by signing the informed consent. The study was approved by the Ethics Commission for General Medicine Research, Universitas Duta Wacana, Yogyakarta (No. 1413/C.16/FK/2022).

Blood sample collection

Three mL of blood was sampled from a cubital vein in all participants who had met the inclusion and exclusion criteria. Blood samples were collected in a vacutainer containing EDTA (1.8 mg/mL blood) and immediately stored in the refrigerator at 4°C.

PCR analysis

The PCR products were analyzed using electrophoresis with 1.5% agarose and evaluated using a UV transilluminator. Expressed PCR products are documented using a Polaroid camera.

Data analysis

To describe the study population and evaluate data, we used Microsoft Excel 2019. All values are displayed as the mean ±SD or number (%). We assumed $p < 0.05$ indicated significant differences. Using a box plot diagram, we also described the distribution of HbA1c levels among the subjects based on their *CYP2A6* allele gene. The chi-square test was used to analyze the relationship between *CYP2A6* polymorphism and HbA1c levels.

RESULTS AND DISCUSSION

A total of 106 participants were participating in this study. There are three groups of test subjects, based on the number of cigarettes per day (CPD) they smoked: light smokers (CPD: 1-10), intermediate smokers (CPD: 11-20), and heavy smokers (CPD: 21-30)[19]. All the respondents were smoking a white filter cigarette containing 12 mg of nicotine/cigarette. **Table II** below shows the respondent characteristics participating in this study. Based on **Table II**, 88.7% of the respondents are light and intermediate smokers, while 11.3% are heavy smokers. The Ministry of Health of the Republic of Indonesia has reported that the average CPD by Indonesian adults was 13 cigarettes or the equivalent of one pack[6]. Some of the respondents started smoking at the age of under ten years. Several factors influence smoking behavior among children and adolescents, including easy access to cigarettes, family and peer environment, and cigarette promotion/advertising[20]. All respondents had smoked for at least ten years, indicating that they had been exposed to nicotine for a long time.

Table II. Respondent characteristics.

Characteristics	Smoking Status			Total
	Light	Intermediate	Heavy	
Number (%)	43 (40.6)	51 (48.1)	12 (11.3)	106
Age				
Mean ± SD	44.4 ± 9.5	43.6 ± 11.7	45.0 ± 8.2	47.2 ± 12.9
Range	32 - 71	29 - 78	37 - 62	29 -78
First age smoking				
Mean ± SD	18.5 ± 3.8	17.2 ± 3.0	14.1 ± 6.2	17.3 ± 3.4
Range	13 - 30	13 - 27	10 - 16	10 - 27
Smoking duration				
Mean ± SD	26.3 ± 9.8	26.5 ± 11.7	29.8 ± 7.1	30.1 ± 12.5
Range	14 - 51	13 - 63	24 - 46	13 - 63
CPD				
Mean ± SD	8 ± 2	14 ± 2	24 ± 3	13 ± 5
Range	3 - 10	11 - 20	21 - 30	3 - 30

Several studies have proven that cigarette dependence can trigger the occurrence of T2DM[21,22]. Compared to non-smokers, active smokers have a 76% higher risk of developing T2DM[23,24]. Nicotine in cigarette smoke was responsible for the development of T2DM in smokers[25-27]. Nicotine in cigarettes has caused insulin resistance and reduced insulin secretion[28]. Xie *et al.*[29] has revealed that nicotine exposure in the long term will decrease insulin secretion through the activation of nAChRs present in pancreatic cells. Furthermore, Xie *et al.*[29] also mentioned that nicotine exposure for a short period (24

Indonesian Journal of Pharmacy, Vol 1 Issue 1, February 2024, Pages 29 – 39 eISSN: 2621-4814

hours) will inhibit insulin release from the pancreas. Other studies have shown that nicotine exposure can cause pancreatic cell dysfunction and increased cell apoptosis[30,31]. Eventually, it will cause an increase in blood glucose levels and the T2DM risk factor in smokers[7].

Our study assesses the T2DM risk factor in smokers using the HbA1c blood level. Several studies have used the HbA1c parameter to control blood glucose levels[8,16,23,32]. Indonesian Endocrinology Society (*Perkumpulan Endokrinologi Indonesia, PERKENI*) stated that people with HbA1c levels <6.5 have a normal glucose level. People with HbA1c levels between 5.7% and 6.4% have prediabetes and a higher chance of getting diabetes. The diabetes condition is established if the HbA1c levels are higher than 6.5%[33]. Akkuzulu *et al.*[23] has reported a positive correlation between nicotine dependence and HbA1c levels in smokers. Several other previous studies have also revealed that compared to non-smokers, smokers have higher HbA1c levels and a 30-40% higher risk of T2DM[8,34]. Somm *et al.*[31] has revealed that nicotine administration in low doses will increase HbA1c levels by 8.8%, and at high doses, after being given nicotine for two days, increase HbA1c levels by 34.5%.

Figure 1 describes the distribution of HbA1c levels among the respondents. According to **Figure 1**, 16.04% of the respondents participating in this study had diabetes, and 13.16% were pre-diabetic. They are mainly distributed among intermediate and heavy smokers with smoking for more than 20 years. It is in line with our previous study that prediabetes among Javanese smokers will occur at a minimum CPD of 20 cigarettes with a minimum smoking duration of 25 years. Meanwhile, diabetes will occur at a minimum CPD of 20 cigarettes with a minimum smoking duration of 29 years[16]. Therefore, it is possible for respondents whose HbA1c levels <5.7 will still develop T2DM if they continue to smoke. Diabetes was an underdiagnosed disease. Approximately 30% of diabetics are often unaware of their condition, resulting in 25% of people with diabetes being diagnosed with microvascular complications. The average delay from onset to diagnosis is about seven years[35]. This study has also supported the report issued by *RISKESDAS* 2018, that only about 25% of diabetics in Indonesia know that they have diabetes[36].

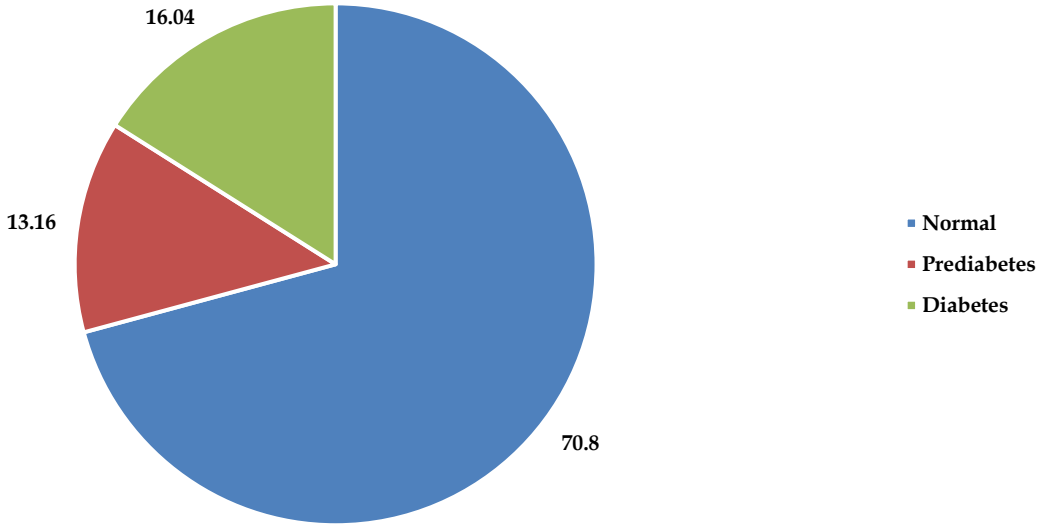

Figure 1. The HbA1c distribution among participants.

In addition, another factor that can increase the T2DM risk in a smoker is the *CYP2A6* polymorphism. The three *CYP2A6* inactive allele genes have been identified in this study: CYP2A6*4, *7, and *9. The CYP2A6*4, a whole gene deletion, due to the unequal crossover junction with CYP2A7. CYP2A6*7 occurred due to the Single Nucleotide Polymorphism (SNPs) in the 8454th nucleotide base sequence (T>C). The CYP2A6*9 allele formed due to the SNPs in the TATA box in the *CYP2A6* promoter region at the -48T>G point[37]. These three allele genes will decrease the CYP2A6 enzyme activity, either intermediate, slow, or poor metabolizer. Smokers with slow or poor metabolizers are more susceptible to suffering T2DM than fast metabolizers[38].

Table III shows that the CYP2A6*4, CYP2A6*7, and CYP2A6*9 allele frequency were 50.9%, 4.3%, and 3.8%, respectively. It is consistent with our previous studies[15,16], where the CYP2A6*4 allele frequency in Javanese was high. These allele genes will decrease the CYP2A6 enzyme activity. Several studies[39-41] have revealed that smokers with the inactive allele would slowly metabolize the nicotine compared to the active allele. Consequently, the nicotine blood level becomes higher, and the

CPD and nicotine dependence become lower. Based on the three allele genes, Peamkrasatam *et al.*[42] and Malaiyandi *et al.*[43] classified the *CYP2A6* phenotype into four groups: fast metabolizer (CYP2A6*1/*1), intermediate metabolizer (CYP2A6*1/*4; CYP2A6*1/*7, CYP2A6*1/*9), slow metabolizer (CYP2A6*4/*7; CYP2A6*4/*9, CYP2A6*7/*9), and poor metabolizer (CYP2A6*4/*4). As shown in **Table III**, only four (3.8%) smokers are fast metabolizers, and most smokers are intermediate metabolizers (74.5%), while the rest are slow and poor metabolizers (21.7%).

Table III. *CYP2A6* genotype and allele frequency among respondents.

Allele	Frequency (n = 212)	Genotype	Frequency (n = 106)
*CYP2A6*1*	41% (87)	*CYP2A6*1/*1*	3.8% (4)
*CYP2A6*4*	50.9% (108)	*CYP2A6*1/*4*	74.5% (79)
*CYP2A6*7*	4.3% (9)	*CYP2A6*4/*7*	8.5% (9)
*CYP2A6*9*	3.8% (8)	*CYP2A6*4/*9*	7.5% (8)
		*CYP2A6*4/*4*	5.7% (6)
Total	**100%**	**Total**	**100%**

Figure 2 describes the distribution of HbA1c levels among the respondent based on their phenotype. **Figure 2** shows that all participants with fast metabolizers and most intermediate metabolizers had HbA1c levels <5.7. There are only 10 participants with intermediate metabolizers had HbA1c >5.7. In the slow metabolizer, two people have HbA1c values <5.7, and the rest have >5.7. On the other hand, all participants with poor metabolizers have HbA1c levels >5.7, indicating that they have diabetes condition. It is in line with another study[44] that heavy smokers with slow and poor metabolizers would have a high risk of developing T2DM compared to light smokers with fast and intermediate metabolizers. Furthermore, we used a chi-square test to analyze the effect of the inactive alleles on the HbA1c levels among the participants.

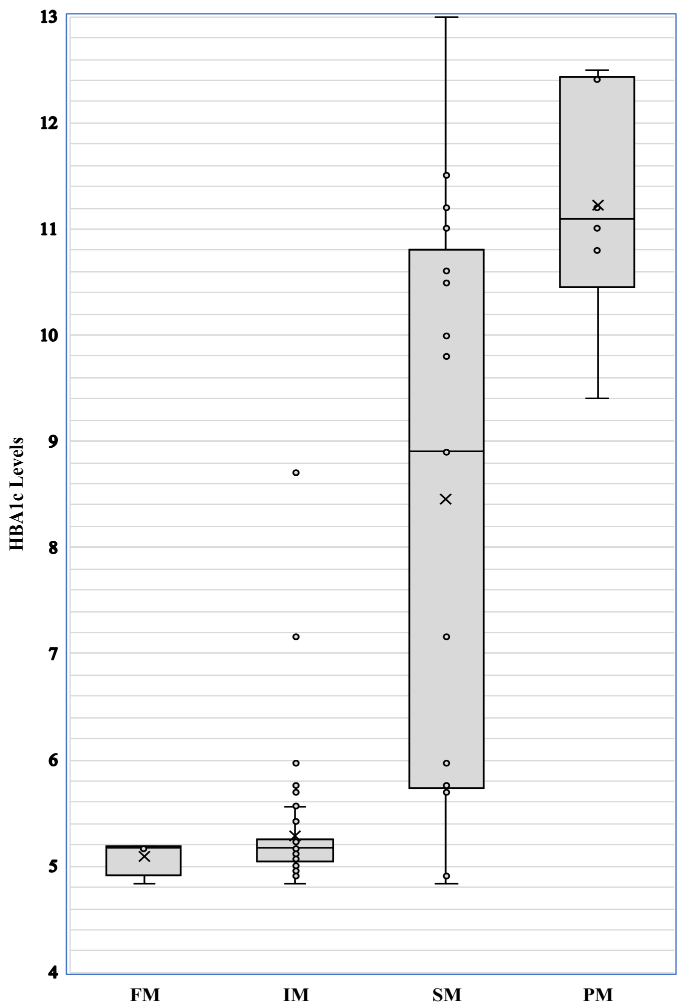

Figure 2. HbA1c levels distribution among the test subjects according to their genotype. **FM**: fast metabolizers; **SM**: slow metabolizers; **IM**: intermediate metabolizers; **PM**: poor metabolizers.

Indonesian Journal of Pharmacy, Vol 1 Issue 1, February 2024, Pages 29 – 39 eISSN: 2621-4814

As shown in **Table IV**, due to its p-value (0.000 <0.005) and χ^2 (54.6) with df=1, it is known that *CYP2A6* polymorphism could have affected the HbA1c levels among the participants. The homozygous and heterozygous *4, *7, and *9 among smokers would increase the risk of HbA1c levels in smokers. CYP2A6 enzyme encoded by *CYP2A6* is the enzyme corresponding to nicotine inactivation. The inactive metabolites of nicotine excreted in the urine are cotinine and trans-3-hydroxycotinine[45]. Therefore, heavy smokers with slow or poor metabolizers tend to have higher nicotine plasma levels than light smokers with fast or intermediate metabolizers. Several studies have revealed that smokers may increase the risk of T2DM, indicated by an increase in HbA1c levels. It is due to pancreatic β cell dysfunction and insulin resistance[34,46].

Table IV. The relationship between *CYP2A6* polymorphism to HbA1c values among participants.

***CYP2A6* polymorphism**	**HbA1c levels (n, %)**		**Total**	**p-value (*V*)**	χ^2 **(df)**
	<5.7	**>5.7**			
Homozigote **1/*1* and heterozigote **1/*4*	73 (88%)	10 (12%)	83 (100%)	0.000 (0.718)	54.6 (1)
Homozigote and heterozigote **4, *7, *9*	2 (8.7%)	21 (91.3%)	23 (100%)		
Total	**75 (70.8%)**	**31 (29.2%)**	**106 (100%)**		

CYP2A6 is also known as the enzyme responsible for nitrosamine metabolic activation, the pre-carcinogen compound in tobacco smoke, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N*'-nitrosonornicotine (NNN), *N*'-nitrosoanabasine (NAB), and *N*'-nitrosoanatabine (NAT)[47]. Therefore, smokers with slow or poor metabolizers could reduce the hepatic first-pass clearance of tobacco nitrosamines, resulting in greater exposure to other organs, such as the pancreas, due to its higher systemic levels[48]. The increased exposure of nitrosamine in pancreatic islet cells could lead it's the metabolic activation by other cytochrome P450 enzymes (CYPs), including CYP2E1[47], resulting in inflammation and apoptosis of pancreatic cells, which is furthermore might decrease insulin secretion and the increased risk of developing T2DM[49].

According to Bergman *et al.*[50], insulin sensitivity will recover in a smoker who has quit smoking; therefore, to prevent diabetes, a smoker must stop smoking. It is also supported by other studies[51-53] on preventing T2DM among smokers through smoking cessation strategies. Several studies[54-56] have also shown that smokers who have inactive alleles tend to quit smoking more easily. Therefore, to increase efforts to reduce the prevalence of diabetes in Indonesia, cooperation from various parties is needed to reduce cigarette consumption in Indonesia. *RISKESDAS* in Indonesia has reported that the number of smokers over 15 years of age was 33.8%, of which 62.9% were male and 4.8% were female[57]. In addition, The Southeast Asia Tobacco Control Alliance (SEATCA) in The Tobacco Control Atlas has reported that the number of smokers in Indonesia was 65.19 million, placing Indonesia as the highest number in Southeast Asia[58]. Therefore, based on our study, we suggest promoting smoking cessation campaigns is the best effort to reduce cigarette consumption and diseases related to cigarettes, such as T2DM, stroke, and coronary heart disease.

Quite a few limitations of our study are: this was a cross-sectional study, the causal association between *CYA2A6* polymorphism and HbA1c levels should be interpreted carefully; we used self-report surveys to collect the data regarding smoking behavior, thus it might have been caused bias data; the other inactive allele of *CYP2A6* might be reduced *CYP2A6* activity resulting in the alteration of phenotype, primarily on fast and intermediate metabolizers; and some confounding factor, including obesity, physical activity, and dietary factors have not fully accounted in our analysis.

CONCLUSION

In conclusion, this study reveals that the heterozygote CYP2A6 alleles, including *4, *7, and *9, corresponding to slow and poor metabolizers, may worsen HbA1c levels among Javanese Indonesian smokers. Furthermore, due to our result, it may be crucial for the government to encourage smoking cessation programs in Indonesia, which are trusted to prevent various health problems, especially diseases related to smoking behavior, including T2DM, stroke, and coronary heart disease.

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AUTHORS' CONTRIBUTION

Conceptualization: Christine Patramurti
Data curation: Christine Patramurti
Formal analysis: Christine Patramurti
Funding acquisition: Christine Patramurti
Investigation: Dita Maria Virginia
Methodology: Dita Maria Virginia
Project administration: Dita Maria Virginia
Resources: Christine Patramurti
Software: -
Supervision: Christine Patramurti
Validation: Christine Patramurti
Visualization: Dita Maria Virginia
Writing - original draft: Christine Patramurti
Writing - review & editing: Dita Maria Virginia

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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