

Association of Single Nucleotide Polymorphisms and Lifestyle Factors with Lipid and Glucose Profiles: A Preliminary Study in Indonesia

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease (CVD) emerged as a cause of high mortality rates in low-middle-income countries, including Indonesia. Understanding predictor variables to the commonly used biomarkers, including lipid profiles and blood glucose levels, can thus be beneficial in disease prevention strategies. To support that, this study aims to analyze the genetic, lifestyle, and disease history variables as predictor variables towards lipid and blood glucose profiles. A total of 106 respondent's data, including clinical data, food recall, health history, and genetic profiling, were collected. From the results, *APOA5* rs662799 is positively correlated with triglyceride (TG) levels. Sugar, fat, fiber, and calorie intake also significantly affect lipid and blood glucose profiles. Exercise conditions such as aerobic and flexibility exercise duration significantly correlated with low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) profiles. Disease history in individuals and families emerged as additional variables associated with the response variables. These findings can serve as a preliminary study for understanding the association between several health predictor variables and response variables, which can be used to predict the incidence of metabolic diseases in the Indonesian population.

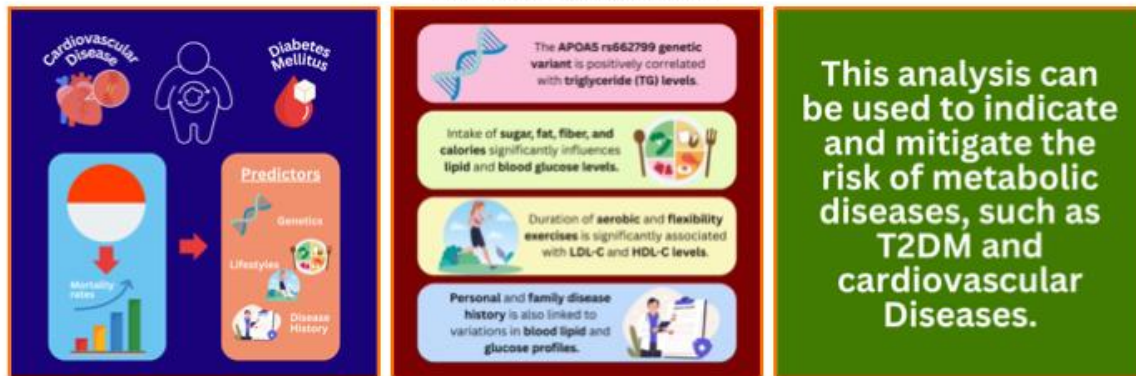
Key Messages:

- Key Genetic Finding: The *APOA5* rs662799 genetic variant is positively correlated with triglyceride (TG) levels.
- Dietary Influence: Intake of sugar, fat, fiber, and calories significantly influences lipid and blood glucose levels.
- Exercise Impact: Duration of aerobic and flexibility exercises is significantly associated with LDL-C and HDL-C levels.
- Disease History: Personal and family disease history is also linked to variations in blood lipid and glucose profiles.

GRAPHICAL ABSTRACT

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is one of the most prevalent metabolic diseases worldwide caused by the secretion and reaction of insulin issues (1). At least 90% of diabetes cases in the world, consisting of 537 million people as of 2021 according to the International Diabetes Federation, are T2DM (2). From a pathophysiological perspective, T2DM is closely related to cardiovascular disease (CDV) (3). CVD is the primary cause of death globally (4). An estimated 50% of patients with T2DM, which is linked to several CVD conditions such as ischemic heart disease, coronary artery disease, peripheral artery disease, and heart failure, may die (5).

CVD and T2DM usually do not experience any symptoms at first (6, 7). On the other hand, in the long term, these diseases may raise the risk of stroke, heart attacks, and other cardiac events as well as contribute to overall longevity (8, 9). Because of these conditions, these diseases are known as silent killers (10). The general quality of life, which is correlated with a patient's perspective of their place in life, including objectives, expectations, standards, and concerns, is also substantially affected by CVD and T2DM (11, 12). In another aspect, T2DM may lead to lower working-age productivity, associated with absenteeism and presenteeism (13). Additionally, a study by the World Health Organization (WHO) in 2010 said that around 75% of CVD deaths occur in low-middle-income countries, which results in a 7% decrease in Gross Domestic Product (GDP) in these nations (14).

T2DM is linked to blood glucose, whereas CVD is related to lipid profile or lipid ratio (15). Blood glucose has a positive correlation with lipid profiles such as triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) (15). Fasting blood glucose (FBG) and haemoglobin A_{1c} (HbA_{1c}) become a standard for diagnosing and monitoring glycemia in patients with diabetes (16, 17). A study by Hajian-Tilaki et al. showed that the high level of TG and the low level of high-density lipoprotein cholesterol (HDL-C) are associated with insulin resistance and T2DM. CVD may also be predicted by TG/HDL-C and LDL-C/HDL-C ratios (18). Moreover, high levels of homocysteine or C-reactive protein in the blood are commonly used as parameters for CVD (19). These studies may contribute to understanding several predictor variables for metabolic diseases. Predictor variables are important for mitigating risk, reducing the incidence of metabolic diseases, and are also commonly used to predict treatment outcomes. (20).

Lipid profile and blood glucose are primarily influenced by lifestyle and age (modified factors) and genetics (unmodified factors) (21, 22). Some modified factors such as weight loss and dietary intervention can achieve T2DM remission, in contrast to unmodified factors, which are difficult to intervene (23). While dietary and lifestyle factors are crucial, they are difficult to detect in busy clinical settings (24). When applied to risk assessment, genetic biomarkers are considered superior to lifestyle indicators since they

can diagnose patients more precisely and identify risk factors early on, allowing for lifestyle modifications and an earlier start to treatment (25). From research conducted by Lyssenko, Jonsson (26), 11 genes with Single Nucleotide Polymorphism (SNP) significantly correlated with T2DM. One of the correlated genes is uncoupling protein 2 (UCP2), especially polymorphism of UCP 2 promoter -866G/A (rs659366), which binds to insulin promoter factor 1 and the pancreatic transcription factor parried box-containing 6. It has been discovered that this SNP is linked to elevated levels of UCP2 mRNA, reduced insulin secretion, and an increased risk of T2DM (27). UCP2 is also associated with the regulation of glucose metabolism (28). On the other hand, the apolipoprotein 5 (APOA5) gene play a role in the metabolism of plasma TG, and is implicated in coronary artery disease (CAD) (29). In research by Jacob, Boczkowska (30), the rs662799 polymorphism in the APOA5 gene has been proven to be associated with the development of cardiovascular disease. These two genes are selected based on their important roles in lipid and glucose metabolism from previous researches.

In general, predictor variables such as lipid profile and blood glucose are known to be biomarkers in disease prevention strategies (31). However, genetic parameters are highly important, given that several studies indicate some genetic-lifestyle interaction (32). The use of genetic factors as predictor variables, and their association with lifestyle, is not commonly used in Indonesia. Also, only a few studies provide evidence linking genetic markers to the progression of metabolic diseases in specific populations, so research on these predictors is needed to improve early detection in Indonesia (33, 34). Therefore, this study aims to analyze the association between genetic, lifestyle, and disease history variables and lipid and blood glucose profiles in a small group in Indonesia.

METHODS

Research Respondents Recruitment

The respondents were employees of PT Nutrifood Indonesia from Pulo Gadung and Ciawi offices. Initially, the respondents collected their medical check-up results, joined briefing activity, and filled out lifestyle and food recall questionnaires. All respondents in this study also grasped informed consent and privacy policy. This research was approved by The Institution of Research and Community Services Atma Jaya Catholic University of Indonesia (001W/III/PPPE.PM.10.05/03/2023).

Body Composition and Clinical Parameter Data Collection

Respondent body composition was measured using the Body Composition Analyzer Inbody 230®. The measured parameters include Body Mass Index (BMI), Waist-Hip Ratio (WHR), and fat percentage. Before the measurement, respondents were required to fast for 2 hours. The respondents were also required to not consume caffeine for 24 hours before the measurement began. Clinical parameter data including blood sugar profiles (HbA_{1c} and fasting blood glucose (FBG)) and cholesterol profiles (total cholesterol, triglycerides, LDL-C, and HDL-C) were obtained from the respondents latest medical check-up results, carried out in the commercial medical laboratory company. The range for lipid profile concentration is adjusted to the American Heart Association (AHA) lipid profile chart, meanwhile for blood glucose and HbA_{1c} level is adjusted to the Centers for Disease Control and Prevention (CDC).

Food Recall & Risk Profiling

Respondents reported their daily dietary habits through an online questionnaire, followed by their integrity statement. They were asked to specify the quantity of their diet using grams or other measurements (plate, spoon, palm, etc.). Food recalls were completed over 3 days, consisting of 2 weekdays and 1 weekend day. The descriptions of the diet provided by the respondents were later converted into calories, sugar, salt, fat, protein, and fiber using the *Nutribase* application and *FatSecret*, which are linked to multiple food databases around the world. This macronutrient profile was then averaged per day. The risk profile of the respondents was tracked using a questionnaire, which was divided into lifestyle and family disease history profiles. The lifestyle profile included the type and duration of physical activity, work duration, and sleep duration. Family history included any history of disease in the immediate family, such as parents and grandparents.

DNA Isolation and Genetic Profiling

Saliva samples were taken from the respondents for genetic profiling, with sampling involving the collection of 1 mL of saliva into a microtube. DNA extraction from the saliva was performed using a standard DNA isolation method from PT. Nutrifood Indonesia, including cell lysis, extraction, and precipitation. The saliva was treated with Sodium Dodecyl Sulphate (SDS) and proteinase-K enzyme, followed by homogenization and incubation. Extract agent containing Phenol: Chloroform: Iso-Amyl-Alcohol was added, and the mixture was centrifuged. After supernatant removal and ethanol addition, the pellet was dried and resuspended in Nuclease Free Water (NFW). SNP polymorphism was detected using the PCR-Restriction Fragment Length Polymorphism (RFLP) method, where DNA templates from *APOA5* and *UCP2* genes were amplified. For the PCR method, DNA template from *APOA5* gene was amplified by forward primer 5'- GAT TGA TTC AAG ATG CAT TTA GGA C-3' and reverse primer 5' -CCC CAG GAA CTG GAG CGA AAT T-3'. For the *UCP2* gene, the DNA template was amplified with forward primer 5'-CACGCTGCTTCTGCCAGGAC-3' and reverse primer 5'-AGGCGTCAGGAGATGGACCG-3'. After PCR, samples were visualized via electrophoresis. Genetic profiling was performed using restriction enzymes to differentiate SNP variations. *APOA5* gene SNP was determined using MseI enzyme, while *UCP2* gene SNP was determined using MluI enzyme. Different SNP variations yielded distinct DNA fragment patterns upon enzymatic cleavage.

Statistical Analysis

This statistical analysis involves identifying associations between predictor variables and a response variable using stepwise linear regression. Several predictor variables used in this study are shown in Figure 1. Response variables are the observed variables or dependent variables. Predictor variables are other variables that influence the response variables. Respondent lifestyle, diet, and lipid profile characteristics were analyzed using descriptive analysis. SNP distribution was also analyzed using descriptive analysis. The predictor variable effect of the factors on lipid profile was analyzed by *Rstudio* Software using a linear regression method. For analysis for stepwise regression using *Rstudio*, all the predictor variables were measured towards response variables. The variable will be excluded from the model if the value does not acceptable fit the data based on the Akaike Information Criterion (AIC). The HbA_{1c} profile included the all-variable regression method and the stepwise regression method for FBG and all lipid profiles. The predictor variable effect and significance toward each lipid and blood glucose profile will be determined based on the reading of the $\text{pr}(> |t|)$ and the "estimate" value. Based on the $\text{pr}(> |t|)$ value, a predictor with values less than 0.05 or 95% confidence was determined to have a significant correlation.

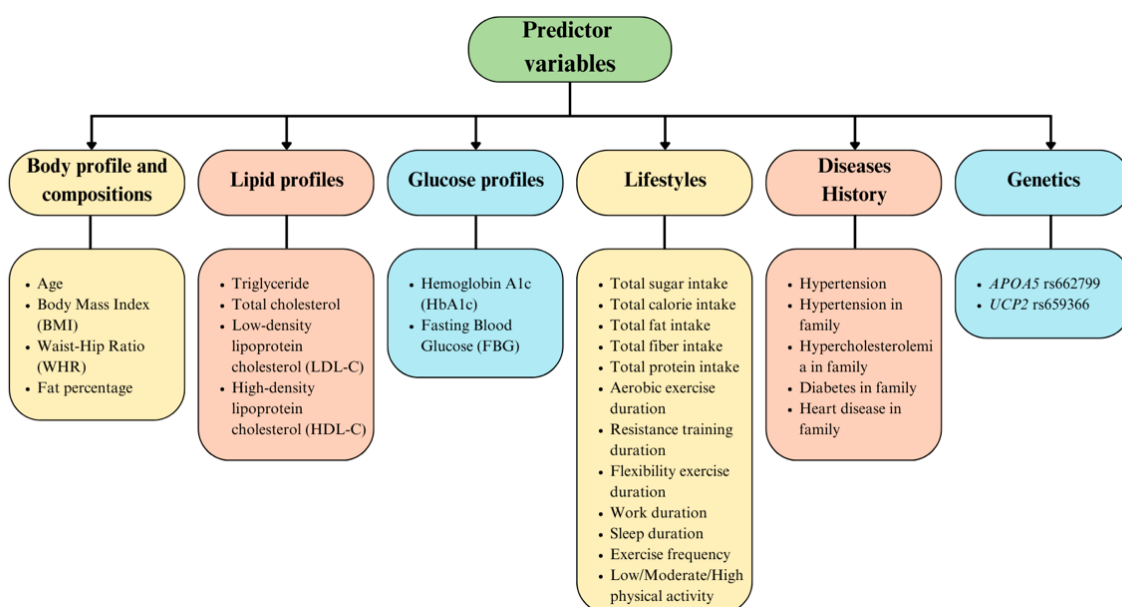


Figure 1, Several predictor variables related to metabolic diseases in this study

RESULTS

Research Respondents Profile and Body Composition

A total of 106 respondents registered and were willing to participate in the research procedure. The data obtained from respondents recruitment form which includes gender and age, for body composition measurements using the InBody 230® analyzer (**Table 1**). The average BMI of the respondents is 24.02 kg/m², the average body fat is 30.86%, and the average WHR is 0.87.

Table 1. Profile and Body Composition Characteristics of Respondents

Variables		
Respondents Profile	Male/Female Ratio (%)	44 (41.5%)/ 62(58.5%)
	Age (years old)	34.73 ± 7.2
Respondents Body	BMI (kg/m ²)	24.02 ± 3.7
Composition	Body Fat (%)	30.86 ± 8.6
Characteristics	WHR	0.87 ± 0.05

BMI: Body Mass Index; WHR: Waist-to-Hip Ratio. Values are expressed as mean ± SE.

Medical Check-up Result

The average fasting blood sugar and cholesterol profiles of the respondents can be seen in **Table 2**. Based on the latest medical check-up results, the average FBG is 87.33 mg/dL, HbA_{1c} is 5.37%, TG is 97.88 mg/dL, cholesterol is 197.26 mg/dL, LDL is 130.95 mg/dL, and HDL is 57.82 mg/dL. Meanwhile, the classification of risk of research respondents towards risk of these conditions is shown in Table 8. The range for lipid profile concentration is adjusted to the American Heart Association (AHA) lipid profile chart, meanwhile for blood glucose and HbA_{1c} level is adjusted to the Centers for Disease Control and Prevention (CDC).

Table 2. Respondents medical check-up result for blood glucose and lipid profile

Medical Check-up Result	Standard	Total Respondents
Triglyceride	Normal (< 150 mg/dl)	94
(97.88 ± 48.06 mg/dL)	Borderline High (150 - 499 mg/dl)	12
	High (> 499 mg/dl)	0
Total Cholesterol	Normal (< 200 mg/dl)	60
(197.26 ± 30.73 mg/dL)	Borderline High (200 – 239 mg/dl)	38
	High (> 239 mg/dl)	8
LDL-C	Normal (<100 mg/dl)	12
(130.95 ± 31.9 mg/dL)	Borderline High (100 – 159 mg/dl)	80
	High (> 159 mg/dl)	14
HDL-C	Normal (> 60 mg/dl)	28
(57.82 ± 11.93 mg/dL)	Borderline Low to Low (< 60 mg/dl)	78
HbA _{1c}	Normal (<5.7%)	79
(5.37 ± 0.37 %)	Borderline High (5.7 – 6.4%)	16
	High (>6.4%)	1
FBG	Normal (<100 mg/dL)	92
(87.33 ± 7.9 mg/dL)	Borderline High (100 – 125 mg/ dL)	5
	High (>125 mg/dL)	0

LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; HbA_{1c}: Haemoglobin A_{1c}; FBG: Fasting Blood Glucose. Values are expressed as mean ± SE.

3.3 Food Recall Analysis

The average consumption of sugar, salt, fat, calories, fiber, and protein obtained from the food recall form conducted over a total of 3 days can be seen in **Table 3**. The average sugar consumption of the respondents is 40.01 grams per day, salt consumption is 3.74 grams per day, fat consumption is 52.86 grams per day, fiber consumption is 11.02 grams per day, and protein consumption is 72.95 grams per day, with a total calorie intake of 1438.28 kcal.

Table 3. Respondent's food-recall analysis in three days

Variables	Average Daily Consumption (grams/day) $\pm$ SE
Sugar	40.01 $\pm$ 19.86
Salt	3.74 $\pm$ 2.0
Fat	52.86 $\pm$ 18.2
Fiber	11.02 $\pm$ 6.84
Calorie	1.438.24 $\pm$ 393.1
Protein	72.95 $\pm$ 24.7

Respondents' Lifestyle

The respondent's sleeping and working duration, as well as respondent exercise habits can be seen in **Table 4**. The average work duration is 8.38 hours per day and the sleep duration is 7.17 hours per day. On the other hand, the average exercise frequency per week is 2.44 times. Out of all 106 respondents, 88 respondents are shown to do aerobic exercise, while 37 are shown to do resistance training and 7 respondents are shown to do flexibility exercise. The respondents' physical activity duration was shown to be around 44 – 46 minutes. Based on the result, respondents who did aerobic exercises for around 45.56 minutes, respondents who did flexibility exercises for around 46.63 minutes, and respondents who did resistance training exercises for around 44.46 minutes. On the other hand, the records of the respondents' physical activity and family diseases history are shown in **Table 5**. From the survey, 79 respondents commonly did low physical activity, 24 did moderate physical activity, and 4 did high physical activity. Moreover, 10 respondents with hypertension, 38 respondents with a family history of high cholesterol, 53 respondents with a family history of diabetes, 68 respondents with a family history of hypertension, and 26 respondents with a family history of heart disease

Table 4. Survey of respondent's lifestyle

Lifestyle variables	
Work duration (hours/day)	8.38 $\pm$ 0.91
Sleep duration (hours/day)	7.17 $\pm$ 0.76
Exercise frequency (times/week)	2.44 $\pm$ 1.72
Aerobic exercise (minutes)	45.56 from 88 respondents
Resistance training (minutes)	44.46 from 37 respondents
Flexibility exercise (minutes)	46.63 from 7 respondents

Values are expressed as mean $\pm$ SE.

Table 5. Survey of respondent's physical activity and disease history

Variables	Number of respondents (%)	
Low physical activity	No	27 (25.47%)
	Yes	79 (74.53%)
Moderate physical activity	No	82 (77.36%)
	Yes	24 (22.64%)
High physical activity	No	102 (96.23%)
	Yes	4 (3.77%)
Hypertension	No	96 (90.6%)
	Yes	10 (9.4%)
Hypercholesterolemia in family	No	68 (64.2%)
	Yes	38 (35.8%)
Diabetes in family	No	53 (50%)
	Yes	53 (50%)
Hypertension in family	No	38 (35.8%)
	Yes	68 (64.2%)
Heart disease in family	No	80 (75.5%)
	Yes	26 (24.5%)

APOA5 and UCP2 Genetic Profile

Out of the total 106 respondents, in *UCP2* rs659366, 45 respondents (42.5%) have the GG genotype, which indicates a typical risk for diabetes, 44 respondents (41.5%) have the GA genotype, and 17 respondents (16%) have the AA genotype. Respondents with “A” allele are having a higher risk for diabetes. Meanwhile, *APOA5* rs662799 in the respondent are mostly TT allele with 56 respondents (52.8%), while 29 respondents (27.4%) are shown to be TC allele, lastly, 21 respondents (19.8%) are shown to be CC allele. Respondents with the “C” allele have a high risk of having higher triglyceride, total cholesterol, and LDL with lower HDL than those without it. The distribution of *UCP2* and *APOA5* gene SNP variations can be seen in **Table 6**.

Table 6. Genetic profile of respondents by SNP distribution

Genetic profile variables	Genotype distribution	Number of respondents (%)
<i>APOA5</i> rs662799	TT	56 (52.8%)
	TC	29 (27.4%)
	CC	21 (19.8%)
<i>UCP2</i> rs659366	GG	45 (42.5%)
	GA	44 (41.5%)
	AA	17 (16%)

Stepwise Regression Analysis

Stepwise regression analysis was conducted to determine the correlation between predictor and response variables (**Figure 2-7**). The estimated value shows the effect of the predictor variable on lipid and blood glucose profile. An estimate with a positive value shows the predictor variable to be linear toward the lipid and blood glucose profile, while an estimate with a negative value shows the predictor variable to be inverse toward the lipid and blood glucose profile. In the stepwise regression results, an increasing line from the lowest value of the predictor variable indicates a positive correlation, while a decreasing line indicates a negative correlation. The dots mean data distribution in both variables. The results of the regression analysis to determine the predictor variables that have a significant effect on the lipid and blood glucose profile are summarized in **Table 7**.

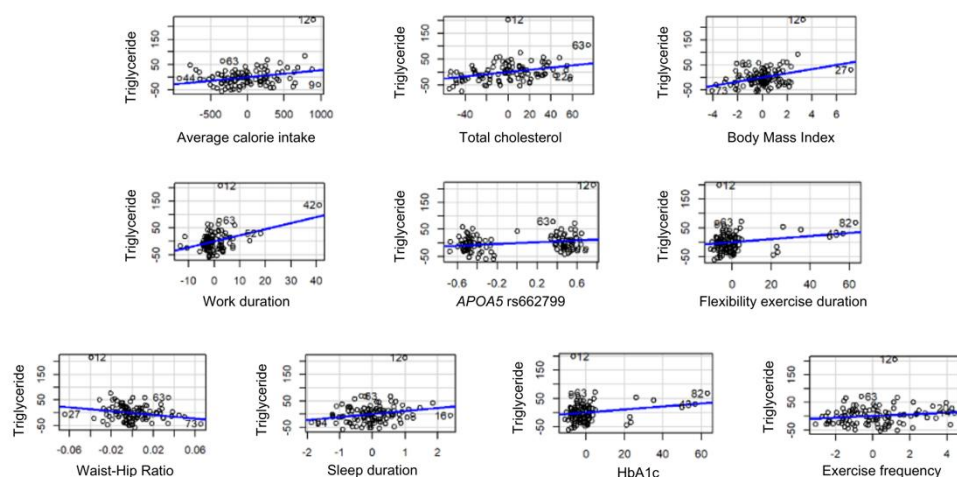


Figure 2. Stepwise regression analysis results on triglyceride response variables

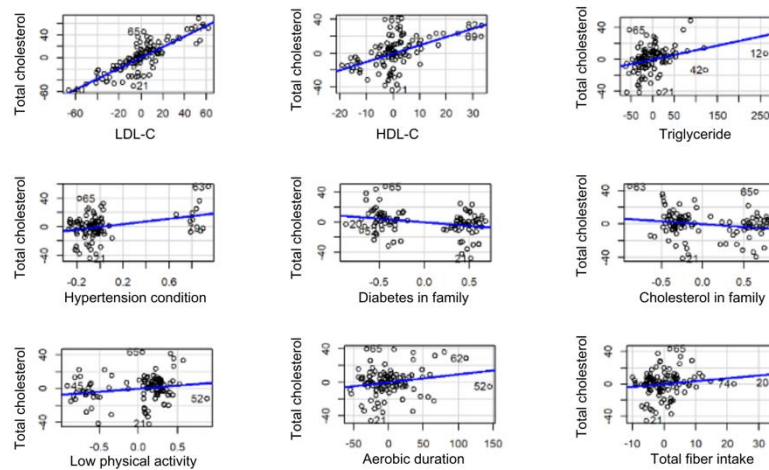


Figure 3. Stepwise regression analysis results on total cholesterol response variables

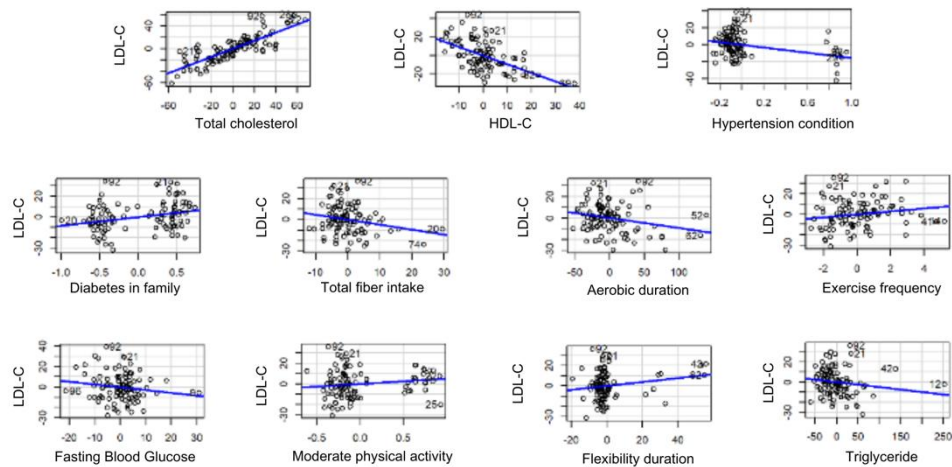


Figure 4. Stepwise regression analysis results on LDL-C response variables

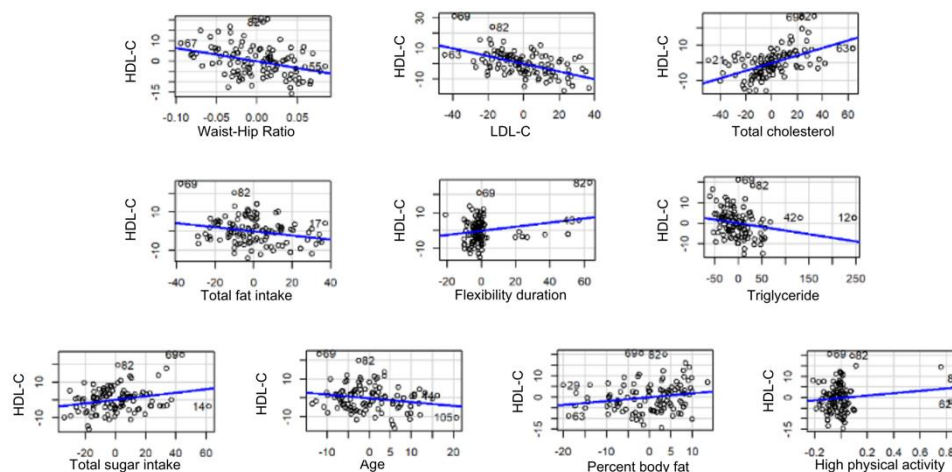


Figure 5. Stepwise regression analysis results on HDL-C response variables

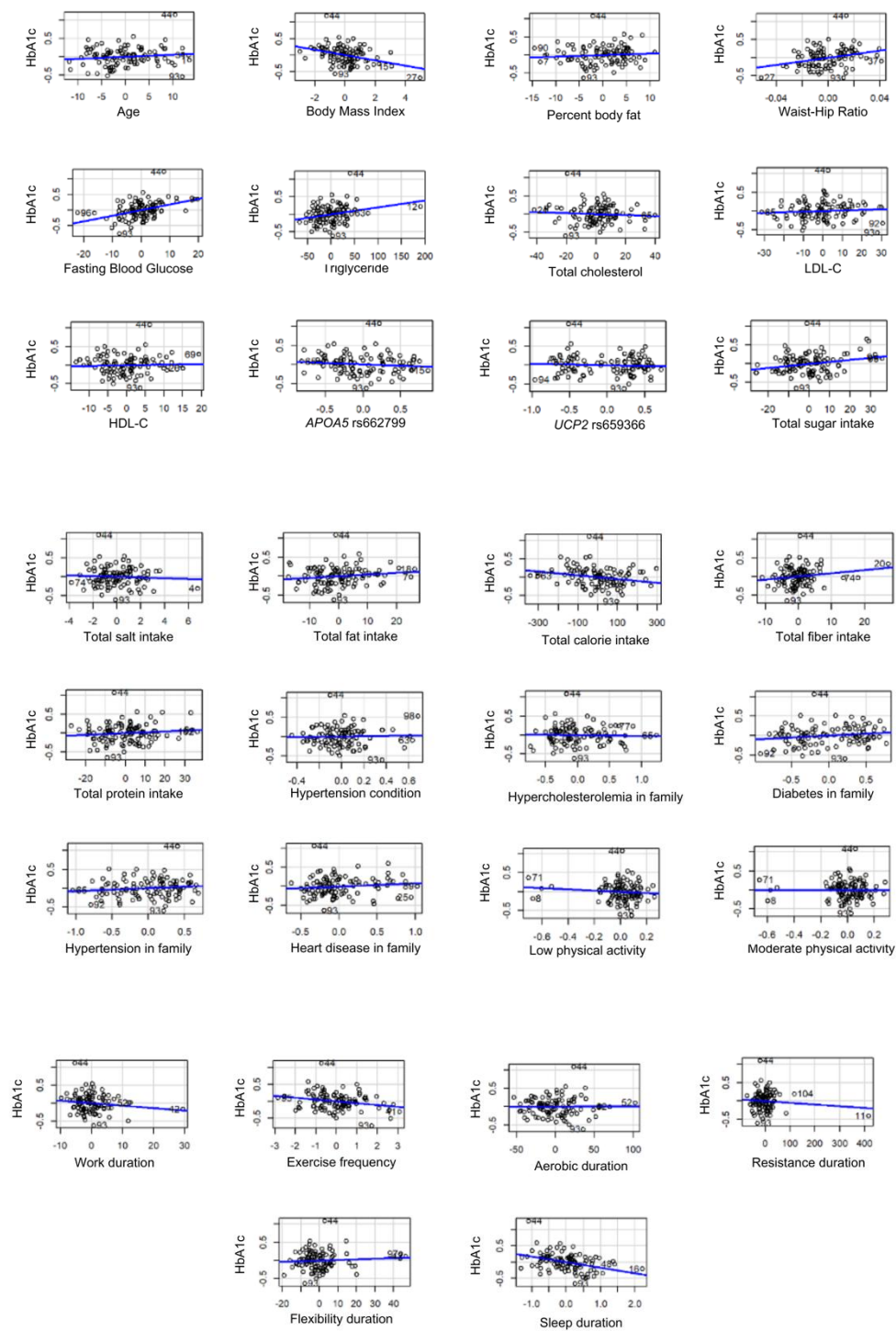


Figure 6. Stepwise regression analysis results on HbA_{1c} response variables

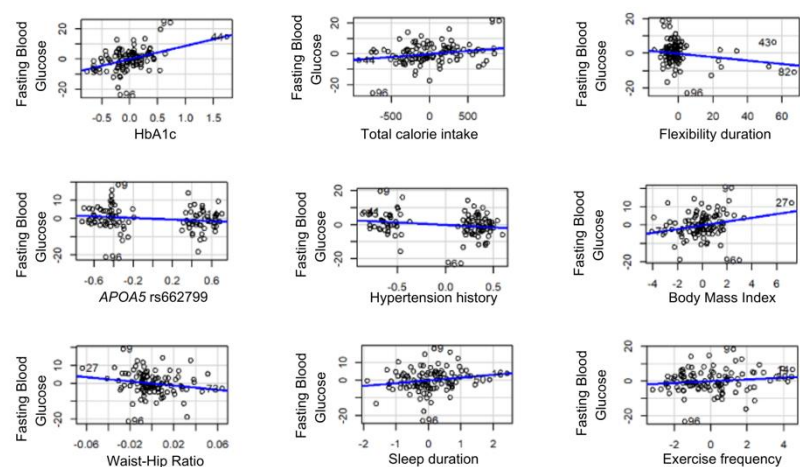


Figure 7. Stepwise regression analysis results on Fasting Blood Glucose response variables

Table 7. Summary of the effect of predictor variables on response variables

		Response Variable					
		TG	TC	LDL-C	HDL-C	HbA _{1c}	FBG
Predictor Variable	TG		+	0	-*	+	×
	TC	+		+	+	0	×
	LDL-C	×	+		-	0	×
	HDL-C	×	+	-		0	×
	HbA _{1c}	+	×	×	×		+
	FBG	×	×	0	×	+	
	Age	×	×	×	-*	0	×
	BMI	+	×	×	×	-	+
	Body fat	×	×	×	0	0	×
	WHR	-*	×	×	-	+	0
	Total sugar intake	×	×	×	+	+	×
	Total salt intake	×	×	×	×	0	×
	Total fat intake	×	×	×	-*	0	×
	Total fiber intake	×	0	-*	×	0	×
	Total calorie intake	+	×	×	×	-*	+
	Total protein intake	×	×	×	×	0	×
	Aerobic exercise duration	×	0	-*	×	0	×

	Response Variable					
	TG	TC	LDL-C	HDL-C	HbA _{1c}	FBG
Resistance training duration	×	×	×	×	0	×
Flexibility exercise duration	0	×	0	+ *	0	0
Work duration / week	+ ***	×	×	×	0	×
Sleep duration / week	+ *	×	×	×	- ***	0
Exercise frequency / week	0	×	0	×	- *	0
Low physical activity	×	0	×	×	0	×
Moderate physical activity	×	×	0	×	0	×
High physical activity	×	×	×	0	×	×
Hypertension history	×	+ ***	- **	×	0	×
Hypertension in family	×	×	×	×	0	- *
Hypercholesterolemia in family	×	- *	×	×	0	×
Diabetes in family	×	- **	+ **	×	0	×
Heart disease in family	×	×	×	×	0	×
“C” allele in <i>APOA5</i>	+ *	×	×	×	0	×
“A” allele in <i>UCP2</i>	×	×	×	×	0	0

Notes:

TG: Triglyceride; TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; HbA_{1c}: Haemoglobin A_{1c}; FBG: Fasting Blood Glucose; BMI: Body Mass Index; WHR: Waist-Hip Ratio

+: positive predictor; **-**: negative predictor, **0**: not significant, ×: not included in the stepwise regression model

*= p<0.05: statistically significant at the 5% level, **=p<0.01: statistically significant at the 1% level, ***=p<0.001: statistically significant at the 0.1% level.

DISCUSSION

Association of several predictor variables with triglyceride levels

In this study, the analysis of association by the stepwise regression analysis was used to identify the risk prediction and mitigate the prevalent and incidence risk. Based on the result, *APOA5* rs662799 has been proven to be a positive predictor of triglyceride (TG). Respondents with this kind of SNP showed higher TG levels. The same case with this SNP was also reported in end-stage kidney disease patients (30). A study in China, conducted by Jiang, Liu (35), *APOA5* rs662799 identified as a major determinant of plasma TG and may influence the susceptibility of the individual to cardiovascular disease. The rs662799 may modulate TG levels through defective transcriptional activity in the promoter region (36). As the positive predictor, *APOA5* gene regulates lipid profile, especially triglyceride by inducing an *APOA5* protein (37). This protein is associated with lipoprotein lipase to mediate the hydrolysis of Very Low-Density Lipoprotein (VLDL) and/or chylomicrons, which mainly carry TG (38, 39). The breakdown of VLDL and chylomicrons cause remnant-lipoprotein, smaller particles, and cholesterol-enriched, to be formed. *APOA5* protein mediates the remnant-lipoprotein uptake into the liver and generally accumulates in arterial walls (40).

Another positive predictor of TG in this study is BMI, whereas WHR has been shown to be a negative predictor. Past studies showed that high BMI and WHR were associated with an increase in

triglyceride levels (41, 42). BMI as a predictor may have varying results due to limitations in differentiating between fat, muscle, bone density, and water measurements (43). Moreover, BMI is just measuring based on an individual's height and weight (44). Based on systematic review by Darbandi, Pasdar (45), WHR is a better predictor for CVD occurrence. However, standard WHR for males and females are different. Males with a WHR ≥ 1.00 and females with a WHR ≥ 0.85 are classified as obese individuals (46). Generally, an estrogen-androgen ratio associated with lower WHR, sometimes causes fat accumulation in the abdominal area and will increase the probability of CVD and TD2M (47, 48). Testosterone in male also regulates fat distribution, so the WHR will be affected by testosterone levels (49). Moreover, ethnicity also influences how anthropometric factors predict obesity and cardiovascular disease (CVD). In Asia, waist circumference is a better predictor of CVD than BMI or WHR (50).

Triglycerides and total cholesterol are positively correlated and serve as predictors for each other. This result is in line with a study by Cui, Sun (51) which mentioned the strong positive association between elevated TG and total cholesterol level. In 2020, Cui et al. also continued their study and found an association between increased TG and total cholesterol with hyperuricemia. Furthermore, lifestyle emerged as a correlated cause of total cholesterol and triglyceride elevation (52, 53). For example, improper diets lead to the synthesis of cholesterol in the body by promoting high calories and saturated fatty acid, while high-glucose diets impact the expression of *APO C3* which can induce the hydrolysis of TG in chylomicrons (53). In addition, total cholesterol has been shown to be a positive predictor towards both HDL-C and LDL-C, while LDL and HDL also act as positive predictor toward total cholesterol. However, HDL-C and LDL-C seem to be a negative predictor toward each other. This occurs because total cholesterol is made up of both LDL and HDL, which are also forms of cholesterol. Consequently, an increase in total cholesterol is typically accompanied by an increase in LDL and HDL (54). In the mechanism, LDL-C supplies cholesterol to cells extracellularly (55). HDL-C is considered as a risk marker or diagnostic indicator for mortality calculation in the Chinese population (56).

Total calories showed to be a positive predictor for TG levels. Unused calories are usually stored as TG in adipose tissue (57). Moreover, calorie restriction has been approached to reduce triglyceride levels (58). Work duration and sleep duration are also a positive predictor for triglyceride and the reason is mainly due to the lack of physical activity during work and sleep. Out of 106 respondents, 76 of them claim to have low physical activity. This should also be considered along their average working duration of 8 hours. A study claimed that a low physical activity can lead to an increased triglyceride level (59). (60) also found that sleep duration has positive correlation with triglyceride.

Association of several predictor variables with total cholesterol

Hypertension condition seems to be a positive predictor for total cholesterol. This correlation may happen because cholesterol plaque and calcium lead to contracture arteries, also lead to the development of hypertension (61). In contrast, hypercholesterolemia and diabetes in families are shown as negative predictors for total cholesterol. Some studies show that high levels of total cholesterol were associated with metabolic condition and disease (62, 63). However, there is a lack of awareness about their health condition and family disease history in Indonesia, especially diabetes (64), which creates bias in this study result.

Association of several predictor variables with LDL-C levels

Another variable, average fiber intake has a negative effect on LDL-C. A study by Ghavami et al., 2023 showed that fiber supplementation significantly reduced LDL-C. Soluble fibers have been known to upregulate bile excretion, so total serum and LDL-C were decreased (65). Additionally, dietary fiber can help produce short chain fatty acid (SCFA) that lowered cholesterol synthesis (66). Aerobic exercise showed to be a negative predictor toward LDL-C, linear with a study from (67). Moreover, diabetes history in the family showed to be a positive predictor, may be related with poor glycemic control (68).

Association of several predictor variables with HDL-C levels

Fat intake in diet and WHR resulted in a negative predictor for HDL-C. Fat intake may be related with the effects of trans-fatty acid compounds which can reduce HDL-C (69). WHR is also significantly associated with HDL-C due to synthesis of VLDL and TG, also insulin resistance (70). Furthermore, flexibility exercise duration showed to be a positive predictor toward HDL-C. In another study, long-

duration exercise became the most effective trick to increase HDL-C (71). Duration of aerobic exercise is commonly associated with HDL-C as well (72). However in this study, flexibility exercise has emerged as a novel approach to examine with HDL-C.

Association of several predictor variables with HbA_{1c}

Increased levels of TG, FBG, WHR, and average sugar intake lead to positive effects on HbA_{1c}. In a recent study, TG has a significant correlation with HbA_{1c}, which may be related to the lipotoxic mechanism by TG (73). FBG also appeared as a positive predictor of HbA_{1c}. For T2DM patients, FBG can predict HbA_{1c} content. This mechanism occurs because of the relationship of haemoglobin and blood glucose which combine and form glycosylated haemoglobin (74). Additionally, WHR and sugar intake had a significant correlation with HbA_{1c}, possibly due to the mechanism of oxidative stress which leads to the glycation of haemoglobin. Commonly this oxidative stress occurs in individuals with obesity and have a higher chance of developing prediabetes (75).

In contrast, sleep duration was shown to be a negative predictor of HbA_{1c}, in line with the observation that patients with shorter sleep durations may experience lower glucose tolerance and postprandial insulin sensitivity, which can lead to higher HbA_{1c} levels (76). Exercise frequency related to WHR. If the exercise frequency is higher, it may lead to lower HbA_{1c} (77). On the average of calorie consumption, respondents consume 1438.25 kcal. From 1438.24 kcal, 670.75 kcal or 46.63% was obtained from carbohydrates, 475.7 kcal or 33.08 was obtained from total fat, and 291.8 kcal or 20.29% was obtained from protein. Lower intake of protein and fat may be associated with high HbA_{1c} levels (78). Interestingly, BMI showed negative effects on HbA_{1c} levels. BMI usually has a positive correlation with HbA_{1c} levels (79). However, it may be the same case with TG levels due to BMI limitations on muscle and bone mass measurement (43).

Association of several predictor variables with FBG

On the variable response FBG profile, it was found that the variables HbA_{1c}, body mass index, and average calorie consumption have positive effects toward FBG. The positive effect of the BMI predictor variable is associated with the positive effect of the calorie consumption predictor variable on FBG (80). According to the World Health Organization (WHO), individuals with a BMI categorized as overweight and obese are defined as having an excessive accumulation of fat that can be harmful to health (81). High BMI values are often associated with a habit of consuming daily calories in excess, leading to the accumulation of excess calories as stored energy over time, resulting in weight gain. This weight gain is associated with an increased risk of insulin resistance, which leads to an increase in FBG levels (82). Meanwhile, family history of hypertension has a negative effect on FBG, but commonly hypertension has positive correlation with FBG (83). FBG levels increase in circulatory fluid volume caused by regularly high blood glucose levels, correlates with the mechanism of hypertension (84). However, bias in the history of family diseases awareness and individual lifestyle might influence the result.

A lack of statistical significance does not imply the absence of an association

In this study, most predictor variables related to the risk of T2DM and CVD, but some of them did not show a significant effect on the response variable. *UCP2* rs659366 was usually used as one of the predictor factors because it showed an association with insulin secretion mechanism, which is associated with the risk of developing T2DM (27). However, this study showed that the genetic factor *UCP2* gene did not show significant effects when analyzed alongside other predictor variables. Sometimes, polymorphism in *UCP2* genes indicates an association with diseases only when considered together as haplotype parts (85). This also can be attributed to epigenetics, where changes in characteristics and environment can alter the way genes function. Epigenetics does not alter the genes themselves but affects gene expression (86).

Limitations and future studies

Overall, this study provides evidence of predictors between genetic factors, lifestyle, and disease history with glucose and lipid profiles. However, this study was still conducted on a small population, and therefore, its findings cannot yet be generalized to represent the broader population across Indonesia. The analysis may be useful for indicating potential risks and understanding the causes of future incidence. As a preliminary study, it can serve as a foundation for larger population studies in Indonesia, where there is a significant gap in health-related behaviors due to lifestyle and genetic variations (87). Future studies

should consider analyzing additional genetic variables to further enhance our understanding of genetic factors in metabolic diseases.

CONCLUSION

In conclusion, this study provides a comprehensive analysis of predictors for metabolic diseases, including Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease (CVD), based on genetic, lifestyle, and disease history factors related to blood and lipid profiles. *APOA5* is positively correlated with triglyceride (TG) levels. Several lifestyle factors such as total sugar intake and total calorie intake also significantly affect various lipid and glucose profiles. Work and sleep duration were found to influence the incidence of higher TG and lower HbA_{1c} levels, respectively. Hypertension in individuals, along with a family history of hypertension, diabetes, and hypercholesterolemia, emerged as additional predictor variables for future disease risk. For instance, a family history of diabetes significantly affects an individual's risk of having a higher LDL cholesterol (LDL-C) content. The analysis of the association between the predictor variable and the response variable considered as one approach for indicating and mitigating the risk of metabolic disease. Furthermore, the correlations between lipids and blood profiles should also be considered. These findings can serve as a preliminary study for understanding health predictors in the Indonesian population.

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CONFLICTS OF INTEREST

Declare conflicts of interest or state "The authors declare no conflict of interest."

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