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PREDICTORS OF PREDIABETES AND UNDIAGNOSED DIABETES MELLITUS BASED ON HBA1C LEVELS IN INDONESIA

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ABSTRACT

Prediabetes and Undiagnosed Diabetes Mellitus (UDDM) are associated with an increased risk of diabetes complications and other cardiovascular diseases. Early detection of both health problems is expected to reduce the burden of non-communicable diseases in the future. The purpose of this study is to investigate predictors of prediabetes and UDDM based on HbA1c levels among population ≥ 15 years old in Indonesia. This cross-sectional study involved 6,065 respondents of Indonesian Family Life Survey 5 (IFLS 5) who met the inclusion and exclusion criteria. Data associated with sociodemographic characteristics, lifestyle risk factors, hypertension, and obesity were obtained. Prediabetes was defined as HbA1c between 5.7-6.4%, while diabetes was defined as HbA1c ≥ 6.5%. Multinomial logistic regression analysis was performed to estimate adjusted Odds Ratio (aOR). The results showed that predictors of prediabetes were age, gender, marital status, and obesity, while predictors of UDDM were age, hypertension, and obesity. Identification of risk factors and early detection of prediabetes and UDDM is important, so that appropriate intervention can be given immediately to prevent complications.

Keywords: HbA1c, IFLS-5, prediabetes, predictors, undiagnosed diabetes mellitus

Introduction

Prediabetes is characterized by elevated blood glucose levels above the normal range but below Diabetes Mellitus (DM) threshold. Prediabetes can be defined by Impaired Fasting Glucose (IFG), Impaired Glucose Tolerance (IGT), or a combination of both. In addition to the use of fasting plasma glucose (FPG) and 2-hour plasma glucose during a 75-g Oral Glucose Tolerance Test (OGTT), American Diabetes Association (ADA) also recommends the use of glycated hemoglobin (HbA1C) as one of the methods of diagnosis of prediabetes and diabetes. A1c between 5.7-6.4% is considered prediabetes, while A1c ≥ 6.5% is classified as diabetes.[1]

The increased prevalence of prediabetes become a major public health concern. Basic Health Research (referred to *Riset Kesehatan Dasar* or Riskesdas) in Indonesia reported an increase in the prevalence of IGT in adults from 29.9% in 2013 to 30.8% in 2018.[2,3] Prediabetes needs special attention because it is a condition with a high risk of developing into diabetes and cardiovascular disease.[4] A prospective study in Bogor showed that 13.4% of respondents with prediabetes developed into type 2 DM during 2 years of observation.[5] Another follow-up study reported that 59% of respondents with IGT developed cardiovascular disease within 30 years, without proper intervention. Individuals with prediabetes are also at high risk of having microvascular complications such as retinopathy and nephropathy.[6]

However, prediabetes can be reversible by implementing a lifestyle modification program.[4] Various studies report that lifestyle changes (implementation of a healthy diet and physical activity, with or without pharmacotherapy) could prevent the progression of diabetes and its complications.[6–8] In the 30th-year follow-up, Daqing Study in China reported a delay of diabetes onset by 3.96 years and fewer incidences of microvascular complications in the intervention group compared to the control group.[6]

The time of the onset of diabetes cannot be specified, so it often results in a delay in diagnosis. About one in two adults with diabetes is reported to be unaware of their condition. Globally, an estimated 240 million people with diabetes remain undiagnosed. Undiagnosed Diabetes Mellitus (UDDM) is defined as an elevated glucose level that meets the criteria for diabetes but has never been diagnosed by a doctor. The longer diabetics are unaware of their status, the greater the risk of developing diabetes complications.[9] Diabetes-related complications could impose a greater burden on healthcare systems. In 2020, BPJS Kesehatan (*Badan Penyelenggara Jaminan Sosial Kesehatan*, Social Security Agency on Health) was reported to have spent 20 trillion rupiahs on healthcare services for catastrophic diseases, including diabetes management.[10]

Identification of risk factors and early detection of prediabetes and UDDM is important. Both allow the identification of high-risk groups that require implementing interventions as early as possible to prevent diabetes and its complications.[11] An asymptomatic preclinical phase can last more than a decade. When the disease is diagnosed later, microvascular complications have

developed in 20-30% of patients, so treatment of hyperglycemia as early as possible is considered more effective.[12]

In Indonesia, no nationwide studies assessing predictors of prediabetes and UDDM based on HbA1c. Therefore, this study aims to determine the predictors of prediabetes and UDDM based on HbA1c levels in the population aged ≥ 15 years.

Methods

We conducted a cross-sectional design using secondary data from the Indonesian Family Life Survey-5 (IFLS-5). IFLS-5 was an ongoing longitudinal survey conducted by RAND Corporation and Survey Meter. The first wave (IFLS-1) was conducted in 1993, while the fifth wave (IFLS-5) was held in 2014 - 2015 on the same households and their split-offs. The sample was estimated to represent about 83% of the Indonesian population living in 13 selected provinces. It collected wide-ranging socioeconomic and health status information at the community, household, and individual levels.[13]

Participants in this study were a total of IFLS-5 respondents who met the inclusion and exclusion criteria (6,065 respondents). The inclusion criteria were participants aged ≥ 15 years old and had HbA1c data. Participants with incomplete data and pregnant women were excluded from the study. Further analysis to determine the predictors of prediabetes and UDDM included only 5,914 respondents. A total of 151 respondents who had been diagnosed with diabetes by doctors/ paramedics/ nurses/ midwives (Diagnosed Diabetes Mellitus/DDM) were not included in the follow-up analysis.

The outcomes of the study were prediabetes and UDDM based on HbA1c. According to American Diabetes Association (ADA) criteria, diagnosis of prediabetes was defined as 5.7-6.4%, while diabetes was defined as HbA1c ≥ 6.5%. Dried Blood Spot (DBS) samples were collected to assess HbA1c. DBS sampling guideline for HbA1c testing is also available elsewhere.[14]

Independent variables in this study were socio-demographic characteristics, lifestyle risk factors, hypertension, and obesity. Socio-demographic characteristics (age, gender, level of education, marital status, residence, family history with cardiovascular diseases) and lifestyle factors (degree of smoking, physical activity, vegetables, and fruits intake, sweetened foods and beverages intake, depressive symptoms) were collected through interviews by trained personnel using structured questionnaires. The degree of smoking was analyzed using Brinkman Index (IB). BI was calculated based on the number of cigarettes smoked per day multiplied by the year of smoking. Respondents were classified as light (IB score < 200), medium (IB score 200-600), and heavy smokers (IB score > 600).[15]

Physical activity was assessed based on the Metabolic Equivalent of Tasks (METs). Respondents were asked a set of questions, modified from the International Physical Activity

Questionnaire (IPAQ), about the type and duration of activities carried out for one week. The total duration and intensity of the activities were transformed into METs-minutes. Furthermore, it was classified as low if METs score < 600. Food and beverage intake was assessed in the last 7 days. Vegetable and fruit intake was categorized as low if the total score < mean (< 15), while the intake of sweetened foods and beverages was categorized as high if the total score ≥ mean (mean=6). Depressive symptoms were measured through 10 Center for Epidemiological Studies Depression (CES-D) questions. It was defined as having depressive symptoms if the score ≥ 10.[16]

Anthropometric measurements were conducted using calibrated equipment and followed standard procedures. Blood pressure was measured three times by trained nurses. It is classified as hypertension if the average result of three times measurements of systolic blood pressure ≥ 140 mmHg or diastolic ≥ 90 mmHg and/or being under antihypertensive treatment. Respondents were classified as obese if the body mass index (weight in kg divided by height in m^2) ≥ 25 kg/m^2.[16]

Multinomial regression logistics analysis was performed to evaluate predictors of prediabetes and UDDM using STATA statistical software. The estimated risk was expressed in adjusted Odds Ratio (aOR) with 95% Confidence Intervals. IFLS-5 was approved by the Institutional Review Boards (IRBs) *RAND's Human Subjects Protection Committee* (No s0064-06-01-CR01), while this study has passed an ethical review from the Committee on Research Ethics and Public Health Service, Faculty of Public Health, University of Indonesia No. Ket-52 / UN2. F10. D11/PPM.00.02/2023. Informed consent was obtained from all recruited participants prior to data collection.

Results

A total of 6,065 respondents who met the inclusion and exclusion criteria were included in the analysis. Of the total respondents, 1,508 (24.86%) respondents were known to have prediabetes, 476 (7.85%) respondents had UDDM, and 151 (2.49%) respondents had DDM. The total number of respondents suffering from diabetes, both diagnosed and undiagnosed, was 627 respondents (10.34%) (Table 1).

Table 1. Characteristics of Respondents Based on Diabetes Diagnosis Criteria

Diagnosis Criteria	Total (n)	Prevalence (%)
Normoglycemic	3,930	64.80
Prediabetes	1,508	24.86
Undiagnosed Diabetes (UDDM)	476	7.85
Diagnosed Diabetes (DDM)	151	2.49
Total	**6,065**	**100.00**

Further analysis only included 5,914 respondents who had never been diagnosed with diabetes. Based on the results, it is known that the highest proportion of prediabetes was found in individuals aged ≥ 45 years, male, divorced, and having a family history of cardiovascular diseases. A higher prevalence was also observed in those with severe or moderate Brinkman index, low consumption of vegetables and fruits, high blood pressure, and obesity. Meanwhile, the highest proportion of UDDM was found in the low-educated group, divorced, having a family history of cardiovascular disease, heavy smoking, less physical activity, low consumption of vegetables and fruits, and suffering from hypertension and obesity (Table 2).

Table 2. Characteristics of Respondents Based on Risk Factors

Variable	Diagnosis Criteria			Total (N=5,914)
	Normoglikemi (%)	Prediabetes (%)	UDDM (%)	
Age group				
≥ 45 years	1,292 (55.47)	769 (33.02)	268 (11.51)	2,329
< 45 years	2,638 (73.58)	739 (20.61)	208 (5.80)	3,585
Gender				
Male	1,731 (63.55)	795 (29.19)	198 (7.27)	2,724
Female	2,199 (68.93)	713 (22.35)	278 (8.71)	3,190
Education Level				
Low	2,119 (63.46)	912 (27.31)	308 (9.22)	3,339
High	1,811 (70.33)	596 (23.15)	168 (6.52)	2,575
Marital Status				
Divorced	1,006 (78.35)	217 (16.90)	61 (4.75)	1,284
Married	2,527 (63.68)	1,094 (27.57)	347 (8.74)	3,968
Not married	397 (59.97)	197 (29.76)	68 (10.27)	662
Residence				
Rural	2,263 (65.98)	878 (25.60)	289 (8.43)	3,430
Urban	1,667 (67.11)	630 (25.36)	187 (7.53)	2,484
Family history of cardiovascular disease				
Yes	96 (56.80)	54 (31.95)	19 (11.24)	169
No	3,834 (66.74)	1,454 (25.31)	457 (7.95)	5,745
Brinkman Index				
Heavy	107 (51.69)	80 (38.65)	20 (9.66)	207
Moderate	447 (57.23)	269 (34.44)	65 (8.32)	781
Light	3,376 (68.53)	1,159 (23.53)	391 (7.94)	4,926
Physical Activity				
Inadequate	1,308 (66.67)	464 (23.65)	190 (9.68)	1,962
Adequate	2,622 (66.35)	1,044 (26.42)	286 (7.24)	3,952
Vegetable and fruit intake				
High	85 (59.86)	43 (30.28)	14 (9.86)	142
Low	3,845 (66.61)	1,465 (25.38)	462 (8.00)	5,772
Sweet snacks and beverages intake				
High	3,660 (66.06)	1,432 (25.85)	448 (8.09)	5,540
Low	270 (72.19)	76 (20.32)	28 (7.49)	374
Depressive Symptoms				
Yes	964 (68.61)	332 (23.63)	109 (7.76)	1,405
No	2,966 (65.78)	1,176 (26.08)	367 (8.14)	4,509
Hypertension				
Yes	1,599 (58.66)	805 (29.53)	322 (11.81)	2,726
No	2,331 (73.12)	703 (22.05)	154 (4.83)	3,188
Obesity				
Yes	970 (55.11)	545 (30.97)	245 (13.92)	1,760
No	2,960 (71.26)	963 (23.18)	231 (5.56)	4,154

Bivariate analysis showed factors associated with prediabetes were age, sex, education level, marital status, family history of cardiovascular disease, Brinkman index, intake of sweet snacks and beverages, hypertension, and obesity. Meanwhile, factors associated with UDDM were age, sex, education level, marital status, family history of cardiovascular disease, physical activity, hypertension, and obesity. Variables with p-value <0.25 were included in multivariate analysis (Table 3).

Table 3. Bivariate Analysis of Predictors of Prediabetes and UDDM based on HbA1c in the Population Aged ≥ 15 Years in Indonesia

Variable	Crude Odds Ratio/ cOR (95% CI)			
	Prediabetes	p-value	UDDM	p-value
Age group				
≥ 45 years	2.12 (1.88-2.12)	<0.001*	2.63 (2.17-3.12)	<0.001*
< 45 years	ref		ref	
Gender				
Male	1.42 (1.26-1.60)	<0.001*	0.91 (0.75-1.10)	<0.001*
Female	ref		ref	
Education Level				
Low	1.31 (1.16-1.48)	<0.001*	1.57 (1.29-1.91)	<0.001*
High	ref		ref	
Marital Status				
Divorced	2.00 (1.71-2.36)	<0.001*	2.26 (1.71-3.00)	<0.001*
Married	2.30 (1.84-2.88)	<0.001*	2.82 (1.96-4.07)	<0.001*
Not married	ref		ref	
Residence				
Rural	1.03 (0.91-1.16)	0.669	1.14 (0.94-1.38)	0.191
Urban	ref		ref	
Family history of cardiovascular disease				
Yes	1.48 (1.06-2.08)	0.023*	1.66 (1.01-2.74)	0.048*
No	ref		ref	
Brinkman Index				
Heavy	1.75 (1.49-2.07)	<0.001*	1.26 (0.95-1.66)	0.112
Moderate	2.18 (1.62-2.93)	<0.001*	1.61 (0.99-2.12)	0.055
Light	ref		ref	
Physical Activity				
Inadequate	0.89 (0.78-1.01)	0.077	1.33 (1.10-1.62)	0.004*
Adequate	ref		ref	
Vegetable and fruit intake				
High	1.33 (0.92-1.93)	0.135	1.37 (0.77-2.43)	0.281
Low	ref		ref	
Sweet snacks and beverages intake				
High	1.39 (1.07-1.81)	0.014*	1.18 (0.79-1.76)	0.418
Low	ref		ref	
Depressive Symptoms				
Yes	0.87 (0.75-1.00)	0.052	0.91 (0.73-1.15)	0.434
No	ref		ref	
Hypertension				
Yes	1.67 (1.48-1.88)	<0.001*	3.05 (2.49-3.73)	<0.001*
No	ref		ref	
Obesity				
Yes	1.73 (1.52-1.96)	<0.001*	3.24 (2.67-3.93)	<0.001*
No	ref		ref	

**) Significant at α= 0.05*

Based on the multivariable multinominal logistics final model in Table 4, it can be concluded that predictors of prediabetes based on HbA1c were age, gender, marital status, and obesity. People aged ≥ 45 years were 1,84 times more likely to have prediabetes than younger people. Male was 1,72 times more likely to have prediabetes than female. People who have been married, separated, or divorced had a higher risk of prediabetes, while obese people were 1,8 times more likely to have prediabetes than non-obese people.

Table 4. Final Model of Prediabetes and UDDM Predictors Based on HbA1c Levels in the Population Aged ≥ 15 Years in Indonesia

Variable	Adjusted OR/ aOR (95% CI)			
	Prediabetes	p-value	UDDM	p-value
Age group				
≥ 45 years	1.84 (1.59-2.13)	<0.001*	2.01 (1.60-2.53)	<0.001*
< 45 years	ref		ref	
Gender				
Male	1.72 (1.51-1.96)	<0.001*	1.18 (0.96-1.46)	0.119
Female	ref		ref	
Marital status				
Married	1.44 (1.20-1.72)	<0.001*	1.16 (0.85-1.59)	0.339
Divorced	1.52 (1.18-1.99)	0.002*	1.09 (0.71-1.67)	0.696
Not married	ref		ref	
Hypertension				
Yes	1.13 (0.99-1.29)	0.069	1.92 (1.54-2.40)	<0.001*
No	ref		ref	
Obesity				
Yes	1.80 (1.57-2.07)	<0.001*	2.89 (2.35-3.57)	<0.001*
No	ref		ref	

**) Significant at α= 0,05*

Predictors of UDDM based on HbA1c were age, hypertension, and obesity. People older than 45 years were 2,01 times more likely to have UDDM than younger people. People suffering from hypertension were 1,92 times more likely to have UDDM than people with normal tension, while obese people were 2,89 times more likely to have UDDM than non-obese people.

Discussion

Based on the results of this study, it is known that the proportion of prediabetes, UDDM, and DDM in the population aged ≥ 15 years in Indonesia was 24.86%, 7.85%, and 2.49%, respectively. This proportion is higher when compared to a study which reported the prevalence of TGT, UDDM, and DMM in Indonesia at 19.5%, 5.0%, and 1.9%, where the diagnosis was established based on the results of FPG and 2-hour plasma glucose.[17]

Nationwide surveys from different countries report a varying prevalence of prediabetes, UDDM, and DDM. A study in Korea reported a 38.3% prevalence of prediabetes in the population aged ≥ 30 years. In this study, prediabetes was diagnosed using FPG and/or HbA1c based on ADA criteria.[18] In New Zealand, the prevalence of prediabetes, UDDM, and DDM based on HbA1c

levels in the population aged ≥ 20 years was reported at 18.6%, 1.8%, and 4.9%.[19] Meanwhile, the prevalence of prediabetes of 33.1% and UDDM of 3.09% in the population aged ≥ 15 years was reported by a study in Canada.[12] Differences in results might be due to differences in age limits, methods and criteria of diagnosis, selection of reference groups, and socio-demographic conditions in each region.

In this study, it is known that the ratio of the proportion of UDDM and DDM is 1: 3. The present finding is similar to that of a study in Indonesia using secondary data from Riskesdas 2013.[17] Studies in the United States, Germany, and New Zealand also estimated that there was one case of UDDM for every 3 diagnosed diabetes.[19–21] At the global level, it is estimated that there are 240 million UDDM from a total of 537 million DDM. This means that almost one in two adults with diabetes is unaware of their condition.[9]

The use of HbA1c as a method of diagnosis of prediabetes and diabetes has several advantages and disadvantages. The test is not time-consuming, more convenient to do because fasting is not required, and is not affected by day-to-day variation in plasma glucose.[1] However, the test is more expensive and not readily available in all healthcare services, especially in low and middle-income countries.[22] In addition, other conditions such as anemia, hemodialysis, and pregnancy should be taken into consideration because those conditions can affect the test results. [1]

The HbA1c test can identify individuals with prediabetes who are missed by FPG test, and vice versa.[12,22,23] A study in Canada found that the use of HbA1c criteria resulted in a 3-fold increase in the prevalence of prediabetes and UDDM compared to the use of FPG.[12]Meanwhile, other studies reported lower prevalence using HbA1c criteria.[23] Since FPG is a measurement of plasma glucose at a certain point in time, while HbA1c reflects plasma glucose levels for the past 3 months, there might be a difference in results.[22]

Based on the multivariable multinominal logistics final model, it can be concluded that predictors of prediabetes based on HbA1c were age, gender, marital status, and obesity. People aged ≥ 45 years were 1.8 times more likely to have prediabetes compared to those aged < 45 years. Previous studies also reported that the risk of prediabetes increased with increasing age. Aging is considered a major risk factor for prediabetes due to the decrease in insulin sensitivity and beta cell function.[4] Similar to the current study, several studies report a higher prevalence rate of prediabetes in men.[18,19,24] On the contrary, few studies reported a higher prevalence rate of prediabetes in women.[17,25,26] In this study, marital status was significantly associated with prediabetes. It corresponds to the findings of a study conducted among productive-age women, which reported a significant association between marital status and prediabetes. The study stated that marital status might become a predisposing factor for obesity, which leads to the development of prediabetes.[27]

In the present study, we found that obesity was associated with an increased risk of prediabetes (aOR 1.8, 95% CI 1.57-2.07). This finding is consistent with previous studies that

showed an increased risk of prediabetes up to 1.2 – 2.54 times in obese individuals.[25,26,28] A prior study stated that 23% of prediabetes cases can be attributed to obesity.[25] An elevated amount of adipose tissue in individuals with obesity leads to insulin resistance, which results in homeostatic disruption of blood sugar levels.[4]

In addition, this study found that age, hypertension, and obesity were significant factors associated with UDDM. These results are in line with previous studies in Malaysia, which reported that older people and those with hypertension and obesity were at higher risk of developing UDDM.[29] Several previous studies also reported similar findings. However, those studies also found other predictors of UDDM, such as gender, family history of diabetes, abdominal obesity, and low physical activity.[17,26,30]

People with UDDM are unaware of their condition years before the disease is detected. They live with high blood glucose levels that can cause tissue damage before the appearance of classic signs of diabetes (polyuria, polydipsia, weight loss with or without polyphagia, and blurred vision). Such unawareness leads to delays in seeking treatment and the loss of opportunities to prevent complications as early as possible.[24,27,30] In the United States, diabetes awareness campaign alongside early detection and screening has resulted in a significant decline in the prevalence of UDDM in the last three decades.[31] Recognizing the risks and early symptoms of diabetes can help control the disease immediately. Therefore, health promotion is important to increase awareness of diabetes.

The results of this study emphasize the importance of early detection programs for prediabetes and diabetes that target high-risk groups such as older people, males, and those with obesity and hypertension. Early detection of prediabetes will provide an opportunity to implement lifestyle modifications as early as possible, while the identification of individuals with diabetes will ensure proper blood glucose control to prevent complications. The implementation of early detection programs needs to be accompanied by prompt diagnostic tests, diabetes awareness campaigns, and counseling.[11]

This research has several strengths and limitations. One of its strengths is the use of IFLS-5 data with a large enough sample which is estimated to represent 83% of Indonesia's population in 13 selected provinces. The IFLS study also provides various data on predictor factors of prediabetes and UDDM that can be assessed. However, this study could not assess the contribution of several important variables, such as abdominal obesity, consumption of high-calorie foods, and lipid profiles that could be closely related to prediabetes or UDDM. In addition, the nature of the cross-sectional study limits the ability to draw causal inferences between predictor variables and outcomes due to temporal ambiguity. This study is not free from recall bias and social desirability bias, which may affect the accuracy of the information given by respondents.

Conclusion

The results showed that people aged ≥ 45 years; male; married or divorced; and obese had a higher risk of developing prediabetes. In addition, older age, hypertension, and obesity were also identified as predictors of UDDM. Identifying the risk factors and conducting early detection of prediabetes and UDDM enables prompt treatment for high-risk groups to prevent diabetes progression and its complications.

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Conflict of Interest

The authors declare that there is no conflict of interest in writing this article.

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