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Factors Associated with the Risk of Type 2 Diabetes in Women of Childbearing Age in A Selected Community in Malaysia

Farah Yasmin Hasbullah[2], Barakatun Nisak Mohd Yusof[1,2,3] & Siti Nursyuhada Badrudin[2]
[1]Institute for Social Science Studies, Putra Infoport, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia, [2]Department of Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia, [3]Research Centre of Excellence for Nutrition and Non-Communicable Diseases, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia
Email: bnisak@upm.edu.my

Abstract
Women of childbearing age are at increased risk of type 2 diabetes (T2D), possibly due to metabolic alterations during pregnancy that contributes towards insulin resistance. However, limited studies assessed T2D risk specifically in Malaysian women of childbearing age. Hence, this study was conducted to determine factors associated with T2D risk in women of childbearing age at a selected public university in Malaysia. This cross-sectional study involved 83 childbearing-age women in Universiti Putra Malaysia (mean age: 37.7 ± 5.7 years; BMI: 26.6 ± 6.0 kg/m2). Weight, height and waist circumference were measured, and body mass index was calculated. Dietary intake and diabetes knowledge were assessed using a food frequency questionnaire and Diabetes Knowledge Questionnaire (DKQ-24), respectively. The Finnish Diabetes Risk Score (FINDRISC) tool predicted T2D risk within 10 years. A total of 66.3% (n = 55) respondents were at risk of T2D. The majority of the subjects (74%) had poor diabetes knowledge scores. Fibre intake was inadequate compared to the recommended range. Waist circumference, first- and second-degree family history of diabetes was significantly associated with increased T2D risk (p = 0.016, 0.001 and 0.009, respectively), whereas a daily consumption of fruits and vegetables was associated with reduced T2D risk (p = 0.024). The findings highlight the importance of public health action, including nutrition education, after delivery to prevent or delay their progression towards T2D.
Keywords: Childbearing-age Women, Type 2 Diabetes, Dietary Intake

Introduction

Type 2 diabetes (T2D) is a global public health issue that has reached epidemic proportions in several populations. International Diabetes Federation (IDF) estimated that about 463 million adults aged 20 – 79 were living with T2D in 2019, and this number was projected to increase to 700 million by 2045 (IDF, 2019). In Malaysia, the prevalence of T2D increased from 11.2% to 18.3% in less than 10 years (Institute for Public Health [IPH], 2019). Women were reported to have a slightly higher prevalence of T2D compared to men (18.4% vs 18.2%) (IPH, 2019). Globally, women also had a higher diabetes-related mortality incidence than men (IDF, 2019). The economic burden of T2D includes direct costs (health expenditures related to diabetes, including medical costs for diagnosis and treatment and transportation costs) and indirect costs (productivity loss, labour drop out and mortality) (IDF, 2019; Oh et al., 2021). Thus, early identification of high-risk individuals and prevention of T2D will help in reducing the financial burden of T2D in the community.

The average age for childbearing mothers in developing countries is between 15 to 49 years old (World Health Organization [WHO], 2020). The prevalence of T2D in women of childbearing age ranged from 1.4% to 67.5%, depending on country and age (Scavini et al., 2017; Gunderson et al., 2018; Vézina-Im et al., 2018; Chivese et al., 2019; Al-Rifai et al., 2019). Multiparity may attribute to increased T2D risk in women of childbearing age (Iversen et al., 2016). Metabolic alterations during a normal pregnancy may induce a prediabetic state and could contribute towards T2D if perturbations in glucose homeostasis are not corrected after delivery. Thus, multiple pregnancies may lead to persistent insulin resistance and eventual β-cell exhaustion (Iversen et al., 2016). However, associations between parity and T2D risk in Asian women have only been investigated in few studies (Mueller et al., 2013; Tian et al., 2014). Both studies focused on women of older age (≥45 years) instead of the broader age spectrum of childbearing-age women.

Besides multiparity, predictors of T2D in women of childbearing age included ethnicity; higher body mass index (BMI), waist circumference, fasting glucose, triglycerides, degree of insulin resistance, blood pressure; and lower high-density lipoprotein cholesterol (HDL-cholesterol), diet quality scores and physical activity (Gunderson et al., 2018). A previous history of gestational diabetes mellitus (GDM) is also an independent risk factor of T2D, increasing its risk by almost ten-fold (Vounzoulaki et al., 2020).

Predictors of T2D, which have been extensively studied in several adult populations, include adiposity, unhealthy dietary patterns characterized by high consumption of processed meat and sugar-sweetened beverages and lower intakes of whole grains; sedentary behaviour or low physical activity; and smoking (Bellou et al., 2018). The risk of T2D appeared to be highest in women presented with three risk factors, including obesity, previous history of GDM, and insulin resistance or B-cell dysfunction (Fan et al., 2020). Nevertheless, studies on predictors of T2D risk, specifically in women of childbearing age, particularly in the Asian context, have been limited, which warrants the current investigation.

Diabetes risk score tools have been developed to improve risk stratification, enhance early detection of T2D, identify individuals with undiagnosed diabetes, and raise awareness in the population to modify risk factors and practice a healthier lifestyle (Saleem et al., 2017; Dugee et al., 2015). Some of the diabetes risk score tools that have been used in the Malaysian population include the Australian T2D risk assessment tool (AUSDRISK) (Hasbullah et al., 2021), Finnish Diabetes Risk Score (FINDRISC) (Lim et al., 2020; Oo et al., 2020) and Indian Diabetes Risk Score (Abdullah et al., 2018). Nonetheless, none of these studies assessed T2D risk specifically in Malaysian women of childbearing age. Hence, this study was conducted to evaluate the risk of T2D in women of childbearing age in Malaysia using a diabetes risk score tool and determine factors associated with the development of T2D.

Materials and Methods

Study Design and Population

This cross-sectional study was conducted among women of childbearing age in Universiti Putra Malaysia (UPM) Serdang, Malaysia. Respondents were Malaysians aged between 18 – 49 years old and had previously given birth. The study excluded pregnant women and those who had a prior diagnosis of type 1 or type 2 diabetes. The Ethics Committee for Research Involving Human Subjects of Universiti Putra Malaysia (JKEUPM) approved the study (JKEUPM-2019-404). Data collection was conducted from January until February 2020.

Out of 16 faculties and two research centres in UPM, the study used simple random sampling to select half of the faculties (n = 8) and research centre (n = 1). Using a computerized randomizer software, the following faculties were selected: Faculties of Human Ecology; Economics and Management; Engineering; Food Science and Technology; Educational Studies; Sciences; Modern Languages and Communication; Environmental Studies. Meanwhile, the research centre randomly selected was the Family, Adolescent and Child Research Centre of Excellence. Name lists of staff of the chosen faculties and institute were obtained. Potential respondents were screened based on inclusion and exclusion criteria. Those who were eligible were invited to participate in this study.

Sample Size Calculation

The sample size was calculated using the formula for multiple regression (Milton, 1986). Based on the factors associated with T2D risk scores in a previous local study (Abdullah et al., 2018), a total of 70 respondents were required for the study. An additional 10% was required to account for missing data, non-response or refusal to participate, yielding a minimum of 78 respondents for the study.

Data Collection

Socio-demographic characteristics of respondents were obtained using questionnaires, including age, ethnicity, household income, education level, smoking habit, family history of diabetes and history of gestational diabetes mellitus (GDM). We measured respondents' height using a stadiometer (SECA model 206, Vogel & Halke GmbH & Co., Germany) and weight using a digital weighing scale (Tanita Health Equipment Ltd., Tokyo, Japan). BMI was calculated using the formula: Weight (kg) / height (m2); and classified according to the WHO cut-off values for adults (WHO, 2021). Waist circumference was measured according to the WHO protocol (WHO, 2008). The cut-off point of waist circumference to indicate abdominal obesity are ≥80 cm for women (WHO/IASO/IOTF, 2000).

The study used the FINDRISC tool to predict the risk of developing T2D within 10 years (Lindström & Tuomilehto, 2003). The risk score tool comprised of eight questions with a total score of 26: age, BMI, waist circumference, physical activity, fruit and vegetable intake, use of anti-hypertensive medication, history of hyperglycemia and family history of diabetes. T2D risk was classified into five categories based on the FINDRISC score: low risk (<7 points), slightly elevated risk (7-11 points), moderate risk (12-14 points), high risk (15-20 points) and very high risk (>20 points). Respondents were considered as having an increased risk of T2D if they scored ≥7 points. The FINDRISC tool was found to be reliable in the Malaysian population (Lim et al., 2020).

Dietary intake was assessed using a 165-item semi-quantitative food frequency questionnaire (FFQ) adapted from the Malaysian Adult Nutrition Survey (Institute for Public Health, 2014). The FFQ consisted of 14 food groups: cereal and cereal products; fast food; meat and meat products; fish and seafood; eggs; legumes and legume products; milk and dairy products; vegetables; fruits; beverages; alcoholic drinks; confectionaries; bread spreads; condiments. Respondents were asked about their frequency of food intake in the past one month (daily, weekly, monthly or not consumed) and the serving size of food. Food frequency was then converted to daily food intake using the formula: Amount of food (g/day) = Frequency of intake (the conversion factor) x serving size of food x total number of servings x weight of food per serving (Norimah et al., 2008). Adequacy of energy and macronutrient intakes were according to the Malaysian Recommended Nutrient Intakes (RNI) (National Coordinating Committee on Food and Nutrition [NCCFN], 2017).

Knowledge about diabetes was evaluated using the 24-item diabetes knowledge questionnaire (DKQ-24) (Garcia et al., 2001). The four domains in the DKQ-24 were causes of diabetes, complications of diabetes, treatment of diabetes and hyperglycemia/ hypoglycemia. Each correct answer was given "1" mark, while "0" mark was given for incorrect or unsure answers. Diabetes knowledge level was categorized as poor (<60%), acceptable (60-80%) or good (>80%). The DKQ-24 was a reliable tool to assess diabetes knowledge, as indicated by Cronbach's alpha value of 0.78 (Garcia et al., 2001). Content and construct validity of the items had also been established (Garcia et al., 2001). The Malay version of the DKQ-24 was used in a previous local study in Shah Alam, Selangor (Qamar et al., 2017).

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Descriptive data were presented as the mean and standard deviation for continuous variables and frequencies and percentages for categorical variables. Normality of the data was confirmed using the histogram, Kolmogorov-Smirnov test, skewness and kurtosis. Binary logistic regression was performed to determine the factors contributing to increased T2D risk. The variables with a significant association with T2D risk in bivariate analysis ($p<0.05$) were entered in a forward selection regression model. An odds ratio (OR) <1 indicated lower odds of T2D risk, whereas OR >1 indicated higher odds of T2D risk (Szumilas, 2010). A statistically significant level was set at $p<0.05$ for all tests.

Results

A total of 100 staff from the selected faculties and research centre were screened for eligibility. About 95 staffs were eligible based on inclusion and exclusion criteria and were invited to participate in the study. Only 83 of them completed the questionnaires and thus were included in the final analysis. The response rate was 87.4% (Figure 1).

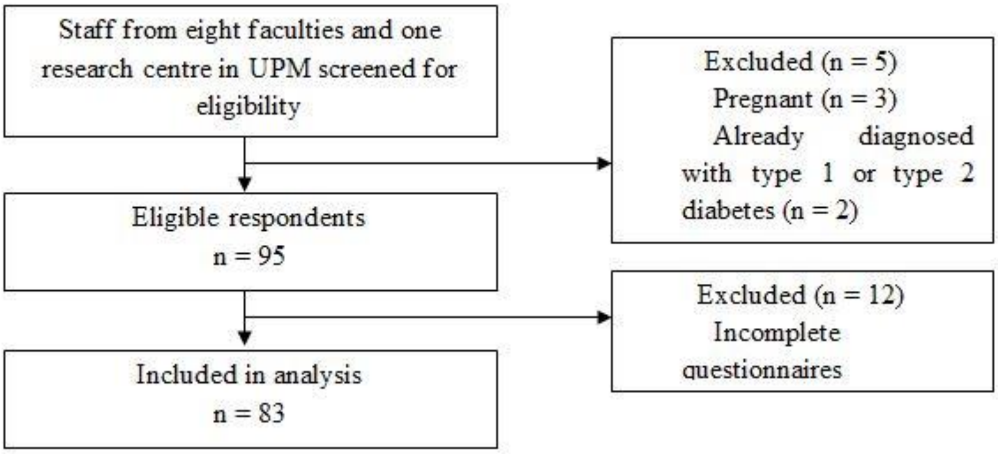

Figure 1. Screening and recruitment of respondents.

Respondents were generally in their late 30s (mean age 37.7 ± 5.7 years), were overweight (mean BMI 26.6 ± 6.0 kg/m2) and had abdominal obesity (mean waist circumference 82.5 ± 12.2 cm). The majority of the respondents were Malays (98.8%) (Table 1). More than half (54.2%) were in the M40 income category, and most of the respondents were college or university graduates (92.8%). More than half the respondents (60.2%) had a family history of diabetes, and 51.8% were overweight or obese (Figure 2).

Table 1: Socio-demographic characteristics and anthropometry measurements of respondents (n = 83)

Variable	N (%)	Mean ± SD
Age (years)		37.7 ± 5.7
Ethnicity		
Malay	82 (98.8%)	
Chinese	1 (1.2%)	
Monthly household income[a]		6515 ± 4145
RM <4850 / USD <1167 (B40)	28 (33.7)	
RM 4850 – 10,959 / USD 1167 - 2636 (M40)	45 (54.2)	
RM ≥10,960 / USD 2637 (T20)	10 (12.0)	
Highest education level		
Secondary education	6 (7.2)	
Tertiary education (college/university)	77 (92.8)	
Currently smoking	3 (3.6)	
Family history of diabetes[b]	50 (60.2)	
History of gestational diabetes mellitus	4 (4.8)	
Height (m)		1.57 ± 0.05
Weight (kg)		65.4 ± 15.4
Body mass index (kg/m^2)		26.6 ± 6.0
Underweight (<18.5 kg/m^2)	1 (1.2)	
Normal range (18.5 – 24.9 kg/m^2)	39 (47.0)	
Overweight (25.0 – 29.9 kg/m^2)	29 (34.9)	
Obese (≥30.0 kg/m^2)	14 (16.9)	
Waist circumference (cm)		82.5 ± 12.2
Within recommendation (<80 cm)	40 (48.2)	
Exceeded recommendation (≥80 cm)	43 (51.8)	

[a]Reference: Department of Statistics Malaysia (2020)
[b]Family history of diabetes includes both first-degree family (parents, siblings, own children) and second-degree family (grandparents, aunts, uncles, first cousins, nieces, nephews)

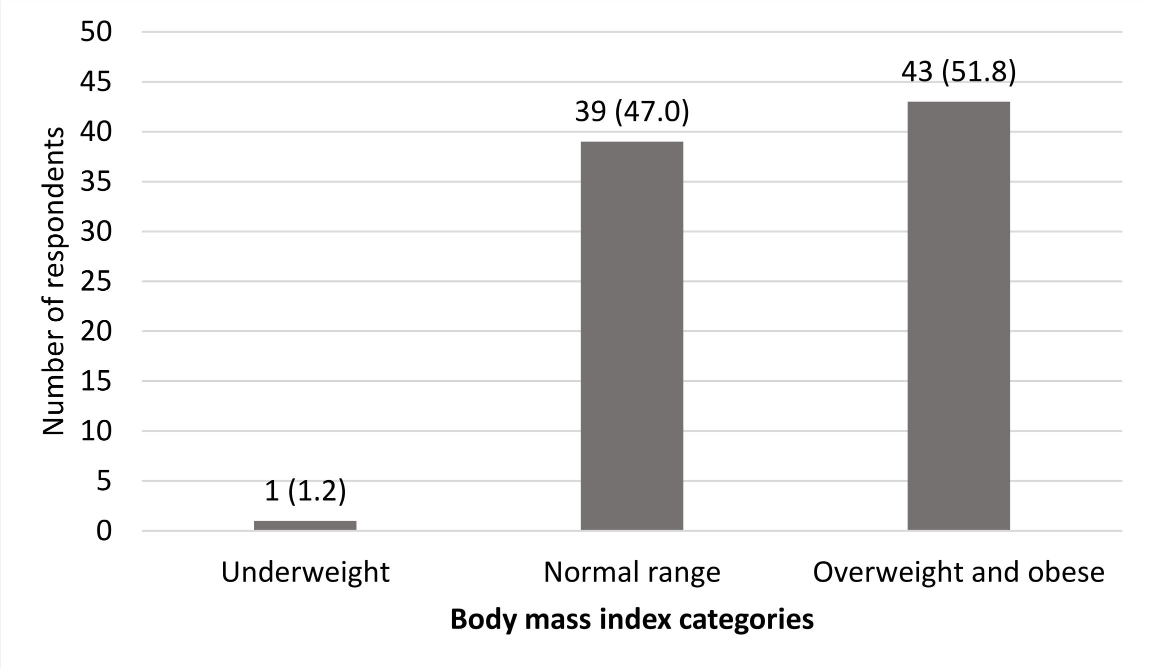

Figure 2: Body mass index categories of respondents (n = 83)

Respondents in the study had energy, carbohydrate, protein, fat, and sugar intake within the recommended range. However, total fiber intake was inadequate (Table 2).

Table 2: Dietary intake of respondents (n = 83)

Variable	Mean ± SD	Recommended intake[a]
Total energy intake (kcal/day)	2138 ± 510	1610 – 2370
Carbohydrate intake		
Total amount (g/day)	308.2 ± 94.9	-
As part of total energy (%TEI)	57 ± 10	50 – 65
Protein intake		
Total amount (g/day)	93.7 ± 30.4	52 – 53
As part of total energy (%TEI)	18 ± 4	10 – 20
Fat intake		
Total amount (g/day)	58.3 ± 22.1	-
As part of total energy (%TEI)	24 ± 6	25 – 30
Total fiber intake (g/day)	11.2 ± 9.5	20 – 30
Sugar intake		
Total amount (g/day)	47.0 ± 28.2	-
As part of total energy (%TEI)	9 ± 5	<10

[a]Reference: Malaysian RNI (NCCFN, 2017)

Most of the respondents (74.7%) had poor knowledge levels regarding causes, complications and treatment of diabetes. None of the subjects was reported to have a good level of diabetes knowledge. None of the respondents answered correctly whether overeating sugar and other sweet foods is a cause of diabetes (question 1). Other questions with the least number of correct responses were regarding wound dressing (question 17; 7.2% correct response) and symptoms of hyperglycemia (question 21; 13.3% correct response) (Table 3).

Table 3: Knowledge level of respondents and responses for the diabetes knowledge questionnaire (DKQ-24) (n = 83)

Variable	N (%)	Mean ± SD
Knowledge score		47 ± 15
Poor (<60%)	62 (74.7)	
Acceptable (60-80%)	21 (25.3)	
Good (>80%)	0 (0)	
Correct responses		
Q1 About sugar as a cause of diabetes	0 (0)	
Q2 About ineffective insulin as a cause of diabetes	71 (85.5)	
Q3 About the failure of kidney function as a cause of diabetes	15 (18.1)	
Q4 About kidney producing insulin	21 (25.3)	
Q5 About hyperglycemia if diabetes is untreated	75 (90.4)	
Q6 About the future risk of diabetes in offspring	69 (83.1)	
Q7 About diabetes being curable	20 (24.1)	
Q8 About high fasting plasma glucose level	28 (33.7)	
Q9 About diagnosing diabetes through a urine test	33 (39.8)	
Q10 About regular exercise increases the need for diabetes medication	19 (22.9)	
Q11 About types of diabetes	39 (47.0)	
Q12 About too much food causing an insulin response	17 (20.5)	
Q13 About medication being more important than diet/exercise	69 (83.1)	
Q14 About diabetes causing poor circulation	46 (55.4)	
Q15 About slow wound healing in diabetes	80 (96.4)	
Q16 About diabetic foot care	63 (75.9)	
Q17 About wound dressing in diabetes	6 (7.2)	
Q18 About food preparation	75 (90.4)	
Q19 About diabetic nephropathy	62 (74.7)	
Q20 About diabetic neuropathy	65 (78.3)	
Q21 About symptoms of hyperglycemia	11 (13.3)	
Q22 About symptoms of hypoglycemia	21 (25.3)	
Q23 About wearing tight hose or socks	21 (25.3)	
Q24 About diabetic diet	18 (21.7)	

More than half the subjects (66.3%) had an increased risk of developing T2D in the next 10 years (Figure 3). A portion of the respondents did not perform physical activity and did not consume fruits and vegetables daily (43.4% and 41.0%, respectively) (Table 4).

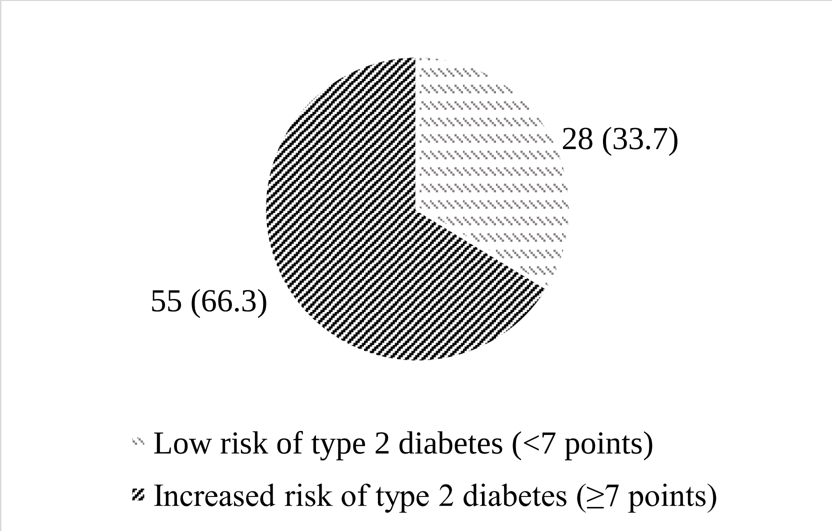

Figure 3: Risk of type 2 diabetes among respondents (n = 83)

Table 4: The diabetes risk score of respondents using the FINDRISC tool (n = 83)

Variable	N (%)	Mean ± SD
Type 2 diabetes risk score		9 ± 5
Low risk (<7 points)	28 (33.7)	
Slightly elevated risk (7 – 11 points)	34 (41.0)	
Moderate risk (12 – 14 points)	10 (12.0)	
High risk (15 – 20 points)	9 (10.8)	
Very high risk (>20 points)	2 (2.4)	
Components of FINDRISC		
Age group		
<35 years old	68 (81.9)	
45 – 54 years old	15 (18.1)	
Body mass index		
<25 kg/m^2	36 (43.4)	
25 – 30 kg/m^2	30 (36.1)	
>30 kg/m^2	17 (20.5)	
Waist circumference		
<80 cm	38 (45.8)	
80 – 88 cm	24 (28.9)	
>88 cm	21 (25.3)	
At least 30 minutes of daily physical activity		
Yes	47 (56.6)	
No	36 (43.4)	
Fruit and vegetable intake		
Everyday	49 (59.0)	
Not everyday	34 (41.0)	
Previous regular use of anti-hypertensive medication		
Yes	75 (90.4)	
No	8 (9.6)	
History of hyperglycemia		
Yes	18 (21.7)	
No	65 (78.3)	
Family history of diabetes		
No family history of diabetes	33 (39.8)	
First-degree family (parents, siblings, own children)	35 (42.2)	
Second-degree family (grandparents, aunts, uncles, first cousins, nieces, nephews)	15 (18.1)	

Logistic regression showed that waist circumference, first- and second-degree family history of diabetes were significantly associated with increased T2D risk (OR 1.809, p = 0.016; OR 1601.961, p = 0.001; and OR 218.621, p = 0.009, respectively). On the other hand, daily consumption of fruits and vegetables was significantly associated with decreased T2D risk (OR 0.019, p = 0.024). The model contributed towards an 82.6% variance in T2D risk (Table 5).

Table 5: Factors contributed towards increased risk of type 2 diabetes among respondents (n = 83)

Variable	Adjusted OR	95% CI	P-value
First-degree family history of diabetes	1601.961	17.069, 150343.883	0.001*
Second-degree family history of diabetes	218.621	3.803, 12567.532	0.009*
Body mass index (kg/m^2)	0.576	0.301, 1.102	0.095
Waist circumference (cm)	1.809	1.116, 2.934	0.016
Total energy intake (kcal/day)	0.999	0.992, 1.005	0.712
Carbohydrate intake (g/day)	1.006	0.980, 1.033	0.640
Protein intake (g/day)	1.023	0.950, 1.102	0.541
Daily intake of fruits and vegetables	0.019	0.001, 0.594	0.024*

OR: Odds ratio. Model R2 = 0.826. *p<0.05

Discussion

The present study investigated factors associated with T2D risk in women of childbearing age in a selected community in Malaysia. More than half (66.3%) of the respondents had an elevated risk of T2D with a risk score of ≥7 points. Factors significantly associated with increased T2D risk were family history of diabetes (both first- and second-degree) and waist circumference, whereas daily consumption of fruits and vegetables was significantly associated with decreased T2D risk.

An underlying genetic susceptibility towards diabetes is an established risk factor of T2D (Harrison et al., 2003). Family history reflects both genetic and environmental factors and thus serves as an independent predictor of T2D risk (Harrison et al., 2003). A previous study in Malaysia suggested using a family history of diabetes as a simple and quick screening tool to identify individuals at high risk of T2D (Hasbullah et al., 2021). A study involving Japanese women with a family history of diabetes in their early 20s found a correlation between family history of diabetes and postprandial hyperinsulinemia (Takeuchi et al., 2020). Their study findings suggested that reduced insulin sensitivity may lead to glucose and lipid dysmetabolism in women with a family history of diabetes although they were younger and had a normal BMI (Takeuchi et al., 2020).

On average, women in this study exceeded the waist circumference recommendation of ≥80 cm, which was comparable with a previous local study, in which the women had a mean waist circumference of 88.6 cm (Ambak et al., 2021). An increased waist circumference (>80 cm for women) could indicate abdominal obesity or visceral adiposity (Després, 2012). Visceral adiposity was associated with a multitude of metabolic abnormalities, including insulin resistance, metabolic syndrome and type 2 diabetes (Després, 2012). Abdominal adipocytes contain more glucocorticoid receptors than subcutaneous adipocytes, which promote fat deposition in the visceral adipose and induce insulin resistance in the skeletal muscle and liver (Després, 2012).

Daily consumption of fruits and vegetables was significantly associated with a reduce d risk of T2D. Findings from several prospective studies (n = 48) found that a "mainly healthy" dietary pattern characterized by high intakes of fruits, vegetables, fish, poultry and legumes were protective against T2D (relative risk, RR 0.84) (Jannasch et al., 2017). Several plausible mechanisms may explain the protective effects of fruits and vegetables against the risk of

T2D. Fruits and vegetables are high in phytochemicals, including antioxidants, which helps in reducing systemic oxidative stress (Carter et al., 2010). They are also high in fibre, which helps reduce postprandial glucose rise and improve insulin sensitivity by slowing the rate of glucose absorption (McRae et al., 2017). Subjects in this study may have inadequate consumption of fruits and vegetables, indicated by the inadequate fibre intake overall. Thus, nutritional education should emphasize a high-fibre diet, including a high intake of fruits and vegetables, in women of childbearing age to reduce their risk of T2D.

Findings from this study can contribute to the growing body of knowledge on the common risk factors associated with the risk of T2D in women of childbearing age. Nevertheless, the study had a few limitations. Firstly, the cross-sectional design of the study did not allow causal inferences to be made. Besides, the study was only limited to one university. Due to the study location, there was an unequal ethnicity distribution, with the respondents predominantly of Malay ethnicity. Thirdly, no biochemical assessments were performed in this study. Biochemical assessments such as glucose and HbA1c levels can provide a better indicator of T2D risk than diabetes risk score tools.

Another limitation of the study is the use of a subjective method of dietary assessment, i.e. FFQ. Although FFQs have been traditionally used in epidemiologic studies to assess long-term dietary intake, this self-reported method is subject to recall errors, health consciousness bias and errors in estimating nutrients from food composition databases (Guasch-Ferré et al., 2008). Guasch-Ferré et al (2018) has recommended the use of biomarkers, such as those identified from the metabolomics approach, to complement the use of validated FFQs and increase the accuracy of overall diet assessment.

Economic Impact of COVID-19 Pandemic on the Community

The economic impacts of the COVID-19 pandemic and the subsequent nationwide-imposed lockdown have been massive. Malaysia had recorded an accumulated loss of RM63 billion up to a month after the Movement Control Order (MCO) began on March 18, 2020 (Hashim et al., 2021). Approximately 81% of COVID-19 patients had comorbidities, including diabetes and cardiovascular diseases (Hashim et al., 2021). This has put a tremendous strain on the healthcare system in Malaysia, including daily demand for testing, increased hospitalization, and increased need for health care infrastructures such as ICU beds, ventilators and personal protective equipment (PPE) (Hashim et al., 2021).

During MCO, several economic activities either had to be closed down, or conducted under strict standard operating procedures (SOPs), causing widespread unemployment (Hashim et al., 2021). In an extensive online survey involving several countries, including Thailand, Italy, the United Kingdom, Slovenia and Malaysia (n = 5058), fewer individuals with a flexible income (such as contract or freelance workers) and other/no income were working during COVID-19 compared to those with a fixed income (Osterrieder et al., 2021). The majority of the women in this study were from the low- and average-income category (87.9%), which might mean that they were more financially affected by the COVID-19 pandemic. A previous online survey reported that 41.4% of respondents from low-income families in the USA had a decrease in fruits and vegetables due to COVID, and the majority of the respondents reported being food insecure (93.5%) (Sharma et al., 2020). The combination of stress (such as employment or financial hardship) and poor dietary habits can hinder efforts in disease prevention (Seligman & Schillinger, 2010). Thus, future studies should look into community health strategies such as food security and developing a rapid screening tool that include dietary patterns to prevent T2D among women of childbearing age.

Conclusions

Women of childbearing age with a family history of diabetes, increased waist circumference and low intake of fruits and vegetables increased T2D risk. Public health action, including nutrition education, after delivery, is highly needed to prevent or delay their progression towards T2D. Population-based studies with a larger sample size are recommended, focusing on developing a rapid screening tool to predict T2D risk.

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Conflict of Interest

The authors declare no conflict of interest.

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