

# Relationship between statin use and depression among diabetic patients in Seremban: a cross-sectional study

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## ABSTRACT

**Introduction:** Statins are one of the most commonly used drugs in primary care. Both hyperlipidaemia and diabetes have independently shown statistically significant association with depression. Conversely, patients with depression have also been shown to have increased comorbidity with and poorer control of both diabetes and hyperlipidaemia.

**Materials and Methods:** A retrospective cross-sectional study was conducted for about 7 months (from 23 January 2024 to 9 August 2024) among adult Type 2 diabetic patients in the non-communicable disease section of Seremban Health Clinic to determine the association between statin use and depression. The data was collected via interviewer-guided questionnaire that consisted of 5 sections: Section A (Participant Information), Section B (Depression, Anxiety and Stress Scale 21 [DASS-21]), Section C (Beliefs about Medicines Questionnaire [BMQ]), Section D (Malaysia Medication Adherence Assessment Tool [MyMAAT]) and Section E (Patient Health Questionnaire-9 [PHQ-9]). Consecutive patients that met inclusion and exclusion criteria who consent to be involved in the study were sampled. Although the ideal sample size that was required is 242, only 82 participants were enrolled in this study. These participants were also part of the Seremban Diabetes cohort study.

**Results:** Since only 82 participants consented to be part of this study, the response rate was 33.9%. About 25% of patients had depression. As the statin dosage intensity increased, the prevalence of depression also increased but this was not statistically significant. Based on Pearson's chi square test, only stress ( $p < 0.001$ ), anxiety ( $p = 0.002$ ), beliefs about medicines ( $p = 0.010$ ) and marital status ( $p = 0.039$ ) had a statistically significant association with depression. Upon adjusted logistic regression of the 4 factors (marital status, stress, anxiety and belief about medicines), only stress (OR 14.000, 95% CI 2.682 - 73.076,  $p = 0.002$ ) was statistically significant.

**Conclusion:** The association between depression and statin use among patients with Type 2 diabetes mellitus is not statistically significant. Further studies are needed to confirm the cause of depression in this group of patients.

## KEYWORDS:

Cross-sectional studies, Diabetes mellitus, Depression, Hydroxymethylglutaryl-CoA reductase inhibitors, Sociodemographic factors

## INTRODUCTION

Statins are one of the most common medications in primary care.<sup>1</sup> In 2018, about 145.8 million people worldwide are taking statins.<sup>2</sup> In Malaysia, statins are used for primary prevention of cardiovascular diseases among high-risk individuals as well as for secondary prevention of cardiovascular diseases.<sup>3</sup> Despite its benefits, some studies have associated statin use with depression.<sup>4,7</sup> For example, a prospective cohort study in the Swedish population revealed that simvastatin was associated with reduced risk of depression while atorvastatin was associated with increased risk of depression.<sup>4</sup> However, there is less research regarding this association in the Malaysian population. This data could be clinically important because it can help clinicians to decide if further interventions are needed to screen for depression in the Malaysian population who are on statins.

Thus, since there is a high prevalence of cardiovascular diseases, depression and Type 2 diabetes mellitus among the Malaysian population along with less research regarding the association between statin use and depression in Malaysia.<sup>8-10</sup> This study was conducted to verify the association between statin use and depression among diabetic patients in Seremban, Malaysia. The other objectives of this research were to: 1) determine the prevalence of depression among diabetic patients taking statins and 2) identify sociodemographic factors that could be contributing to depression among diabetic patients.

## MATERIALS AND METHODS

The inclusion criteria for study participants were adult patients aged at least 18 years at time of interview who were diagnosed with Type 2 diabetes mellitus and are taking statin therapy. On the other hand, the exclusion criteria were: 1) Patients with limited ability to understand Malay or English, 2) Patients aged 65 and above at the time of interview and 3) Patients with Type 1 diabetes mellitus. The study design was retrospective cross-sectional as patients were not followed up after they were sampled to observe for possible changes.

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This study was conducted for about 7 months (from 23 January 2024 to 9 August 2024) at the non-communicable disease section of Seremban Health Clinic, Negeri Sembilan. During the clinic's operating hours, data collection was done by members of the research team based on their availability. The method used was interviewer-guided questionnaire where a member of the research team sits with the patient as they answer the questionnaire to help provide clarification if the patient is unsure of any part of that questionnaire. This questionnaire was bilingual (Malay and English) and it consisted of five parts which were Section A (Participant Information), Section B (Depression, Anxiety and Stress Scale 21 [DASS-21]), Section C (Beliefs about Medicines Questionnaire [BMQ]), Section D (Malaysia Medication Adherence Assessment Tool [MyMAAT]) and Section E (Patient Health Questionnaire-9 [PHQ-9]). Section A was for collection of sociodemographic data on the patients (e.g. age, gender, financial status, highest education level). Section B to E were included with written permission from the authors via email.<sup>11-14</sup> Therefore, this questionnaire was designed to facilitate collection of necessary data related to the study's three objectives which were mentioned in the introduction paragraph.

The questionnaire was pilot tested at the study site on 7 July 2023. During this test, seven patients were interviewed: five out of seven met the inclusion criteria, the other two did not meet the inclusion criteria and none met the exclusion criteria. This test prompted revision of the questionnaire to allow for more straightforward answers by the study participants for some questions (e.g. financial status was revised to T20, M40 and B40).

Depression was assessed using DASS-21. For the reliability of the Malay version of DASS-21, a study revealed that this version had a good Cronbach's alpha value of 0.75, 0.74 and 0.79 for depression, anxiety and stress respectively.<sup>11</sup> On the other hand, for validity, the same study also revealed that all questions in the Malay version of DASS-21 had factor loading of more than 0.3 which is good except for 4 questions which are: D21 (0.18), A15 (0.21), A20 (0.11) and S18 (0.04).<sup>11</sup> The score on DASS-21 was multiplied by 2 to calculate the final score for each category. The score ranges of depression in DASS-21 was as follows: Normal (0 to 9), Mild (10 to 13), Moderate (14 to 20), Severe (21 to 27) and Extremely Severe (28 to 42). Patients who scored at least 10 in DASS-21 would be further assessed using PHQ-9. The Malay version of PHQ-9 had good internal reliability among adult female patients in a primary care clinic with Cronbach's alpha value of 0.70.<sup>12</sup> For Malaysia Medication Adherence Assessment Tool, the internal reliability among Type 2 diabetic patients in Malaysia was good with Cronbach's alpha value of 0.910.<sup>13</sup> For Beliefs on Medicine Questionnaire, the internal reliability among Type 2 diabetes patients in primary care clinics in Malaysia was good with Cronbach's alpha value of 0.74 to 0.75.<sup>14</sup>

Consecutive patients that met inclusion and exclusion criteria who consent to be involved in the study were sampled. Sample size,  $n$  was calculated using the following formula:  $n = [z^2 \times p(1-p)] / e^2$  where  $z$  was  $z$  score,  $p$  was population proportion and  $e$  was margin of error. Our study was using a confidence level of 95% and margin of error of

5%. Thus, the  $z$  score was 1.96. Based on data from a systematic review and meta-analysis on the prevalence of depression among Type 2 diabetic patients in Malaysia, this study found that the overall pooled prevalence was 17%.<sup>15</sup> One of the papers cited in this study also covered Negeri Sembilan via DASS-21 questionnaire and the prevalence in that study was 16.25% which was close to the overall pooled prevalence.<sup>15</sup> Therefore,  $p$  in our study was set at 17%. After taking these values into consideration, the proposed sample size was 217. However, after assuming a non-response rate of 10%, the final sample size was 242.

Ethical approval from the Medical Research & Ethics Committee (MREC) was needed prior to the start of any study related activities at the study site. MREC approval was necessary to ensure that this research will be conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines. Before applying for MREC approval via the National Medical Research Register (NMRR), this research received the necessary internal, ethical approval first from the IMU University Joint Committee on Research and Ethics (IMU-JC) on 2 October 2023 with reference number of 4.6/JCM-274/2023 Bachelor of Medicine & Bachelor of Surgery (MBBS). Once IMU-JC approved this study, MREC approval was obtained via the NMRR system (dated 21 December 2023 with reference number 23-03149-QPX). After MREC approval, this study also received permission from the study site's District Health Officer which was dated as 12 January 2024 with reference number of PKS.51/671 Jld.5 (6). There was minimal involvement of potentially vulnerable subjects in this study. Children aged below 18 were excluded as they were below minimum age of consent in Malaysia. Adults aged 65 and above were also excluded as they might have cognitive impairment. Since pregnant and lactating women were not recommended to take statins due to treatment guidelines, this population might not be in our study sample. If subjects were critically ill, they were allowed to go for needed treatment first. Prisoners were also excluded from this study. On the other hand, if a patient's score indicated poorer than normal adherence to statins or higher than normal depression, anxiety or stress, the relevant person-in-charge at the Seremban Health Clinic (e.g. medical officer) would be notified to discuss if further action needed to be taken (e.g. referring patient for further assessment).

After reading and understanding the given patient information sheet and informed consent form, all participants provided verbal and written informed consent before participating in this research. If patients insisted on consulting their family members first, they were allowed to take a copy of the information sheet home. Then, if the patient was interested to join this study, the patient could contact the investigators from details given in the patient information sheet to arrange an appointment at the study site.

#### *Dependent variable*

The primary outcome for this study was depression, measured using the DASS-21. Participants were classified as having depression if their DASS-21 depression subscale score was greater than 9.

### *Independent variable*

The primary independent variable in this study was the intensity of statin use, which was categorised based on both the type and dosage of the statin prescribed. Statin intensity was classified into three levels: low intensity, which included simvastatin 10 mg ON; moderate intensity, which encompassed simvastatin 20-40 mg ON and atorvastatin 10-20 mg ON; and high intensity, which included atorvastatin 40-80 mg ON. This categorization was based on the 2018 American Heart Association guideline on Management of Blood Cholesterol. Lipid control was assessed with LDL level using a cut-off value of 2.6mmol/L. Diabetes control was evaluated using latest HbA1c levels, with the following categories: HbA1c less than 6.5% was classified as good control, HbA1c between 6.5% and 7.9% as fairly good control, and HbA1c greater than 8% as poor control. Anxiety and stress were diagnosed using the DASS-21. For anxiety, a score greater than 7 was used to classify participants as having anxiety. For stress, a score greater than 14 was used to classify participants as experiencing stress. Beliefs about medicines were evaluated using the Beliefs on Medicine Questionnaire. Participants were categorised into four groups based on their responses: Accepting (specific necessity score  $\geq 15$ , specific concerns score  $< 15$ ); Ambivalent (specific necessity score  $\geq 15$ , specific concerns score  $\geq 15$ ); Sceptical (specific necessity score  $< 15$ , specific concerns score  $\geq 15$ ); and Indifferent (specific necessity score  $< 15$ , specific concerns score  $< 15$ ). Adherence to medication was assessed using the Malaysia Medication Adherence Assessment Tool questionnaire. Participants' adherence levels were categorised based on their scores from the questionnaire, with a score of 54 or higher indicating good adherence, and anything below indicating poor adherence.

### *Statistical analysis*

The data was anonymously keyed into a Microsoft Excel sheet before being transferred to the Statistical Package for the Social Sciences (SPSS) software for further analysis. Data analysis was conducted using SPSS version 30.0. Descriptive statistics were used to summarise the demographic and clinical characteristics (e.g. age, financial status, marital status etc.) of the study sample. Frequencies, percentages, means, and range were calculated as appropriate. Then, frequency was used to describe prevalence of depression among patients with Type 2 diabetes mellitus who are taking statins. The frequency observed via DASS-21 and PHQ-9 was also compared to determine validity of DASS-21, as PHQ-9 incorporates the DSM-IV diagnostic criteria of depression. On the other hand, Pearson's chi-square test was used to compare the association between statin use and depression based on the intensity of statin dosage. Lastly, for sociodemographic factors that could be contributing to depression, Pearson's chi-square test was also used to identify variables that had a statistically significant association with depression. Statistical significance was set at  $p < 0.05$ . To further refine the analysis and account for potential confounding factors, an adjusted logistic regression model was conducted. This model included all significant variables from the chi square test to estimate adjusted odds ratios (AORs) and 95% confidence intervals (CIs). This approach controlled for the influence of other variables, providing a clearer picture of each variable's independent effect on depression.

## **RESULTS**

### *Response rate and subject recruitment*

Of the 242 people who were approached, only 82 of them consented, giving a response rate of 33.9%. The response rate was low because of two factors: 1) patients met the exclusion criteria (e.g. age of 65 and above) and 2) patients were not keen to participate in this study.

### *Socio-demographic characteristics of the respondents*

The demographic and clinical data of all participants were shown in Table I. A total of 82 patients were recruited for this study. The predominant categories by type were: females (gender), Indians (ethnicity), married (marital status), B40 (financial background), secondary school (highest education level) and 3 or more comorbidities (number of long-term illnesses). Most participants were on at least 3 or more medications and about 75% of participants were also taking antihypertensives. More than 50% of participants were on atorvastatin and the statin dosage was mostly of moderate intensity. On the other hand, regarding diabetes control, about 66% of participants had good or fairly good control while 34% had poor control. Only 25% of participants were on insulin therapy. Most participants also had no family history of depression and never smoked or drank alcohol. The mean age was 55 years and the age range was from 36 years to 64 years.

More than 50% of participants had a poorly controlled lipid profile. However, 54% had good adherence to their medication but only 11% had an 'accepting' belief about medicines. Anxiety was present in 33 out of 82 participants (11 had mild anxiety, 9 had moderate anxiety, 4 had severe anxiety and 9 had extremely severe anxiety). Stress was present in 25% of participants (10 had mild stress, 6 had moderate stress, 2 had severe stress and 3 had extremely severe stress).

### *Prevalence of depression among Type 2 diabetic patients taking statins*

According to PHQ-9 results, 20 patients had depression among the 82 subjects recruited (24.4%). In contrast, DASS-21 results showed 22 patients (26.8%) had depression. The minimal discrepancy in frequency (2.4%) showed that the results of PHQ-9 and DASS-21 were aligned to each other. The number of patients with depression, anxiety and stress is shown in Table II.

In Table III, validity of DASS-21 was shown by comparing its depression and non-depression rate with those of PHQ-9. It was shown that DASS-21 was highly specific (specificity 89%), and moderately sensitive (sensitivity 75%) as a tool in assessing depression. The accuracy was able to reach 85% and the positive and negative predictive values were 68% and 92% respectively. Therefore, DASS-21 was considered as a good tool for determining depression among the subjects in this study. It also provided a view of the correlation between depression and anxiety as well as stress.

### *Association between statin use and depression among Type 2 diabetic patients*

There was an increasing trend for prevalence of depression with increasing dosage intensity. For example, the prevalence of depression was 21.4% in the low-intensity group, 24.4% in the moderate intensity group and 34.8% in the high intensity

Table I: Demographic and clinical data

		Number	Percentage (%)	Mean	Range
Gender	Male	27	32.9	55	36-64
	Female	55	67.1		
Age					
Ethnicity	Malay	21	25.6		
	Chinese	18	22.0		
	Indian	41	50.0		
	Others	2	2.4		
Marital status	Married	73	89.0		
	Divorced	2	2.4		
	Widowed	2	2.4		
	Unmarried	5	6.2		
Financial background	B40	65	79.3		
	M40	16	19.5		
	T20	1	1.2		
Highest educational level	No formal education	4	4.8		
	Primary school	10	12.2		
	Secondary school	55	67.1		
	University	13	15.9		
Occupational status	Unemployed	32	39.0		
	Working	32	39.0		
	Retired	18	22.0		
Number of long term illnesses	1	1	1.2		
	2	19	23.2		
	≥3	62	75.6		
Number of medications	<3	9	11.0		
	>3	73	89.0		
On antihypertensive	No	21	25.6		
	Yes	61	74.4		
Beta blocker	No	62	75.6		
	Yes	20	24.4		
Diuretics	No	73	89.0		
	Yes	9	11.0		
Types of statin	Simvastatin	38	46.3		
	Atorvastatin	44	53.7		
Intensity of statin	Low	14	17.1		
	Moderate	45	54.9		
	High	23	28.0		
Family history of depression	No	64	78.0		
	Yes	18	22.0		
Smoking	No	73	89.0		
	Yes	9	11.0		
Drinking alcohol	No	77	93.9		
	Yes	5	6.1		
Lipid control	Poorly controlled	42	51.2		
	Well controlled	40	48.8		
Insulin	No	61	74.4		
	Yes	21	25.6		
Diabetes control	Poor	28	34.2		
	Fairly good	33	40.2		
	Good	21	25.6		
Depression (DASS-21)	No	60	73.2		
	Yes	22	26.8		
Severity of depression (DASS-21)	Normal	60	73.2		
	Mild	10	12.2		
	Moderate	8	9.8		
	Severe	1	1.1		
	Extremely severe	3	3.7		
Anxiety	No	49	59.8		
	Yes	33	40.2		
Severity of anxiety	Normal	49	59.8		
	Mild	11	13.4		
	Moderate	9	11.0		
	Severe	4	4.8		
	Extremely severe	9	11.0		
Stress	No	61	74.4		
	Yes	21	25.6		

		Number	Percentage (%)	Mean	Range
Severity of stress	Normal	61	74.4		
	Mild	10	12.2		
	Moderate	6	7.3		
	Severe	2	2.4		
	Extremely severe	3	3.7		
Beliefs about medicines (BMQ)	Accepting	9	11.0		
	Ambivalent	27	32.9		
	Sceptical	30	36.6		
	Indifferent	16	19.5		
Adherence to medication (MyMAAT)	Poor adherence	37	45.1		
	Good adherence	45	54.9		
Depression (PHQ-9)	No	62	75.6		
	Yes	20	24.4		

More than 50% of participants were on atorvastatin and the statin dosage was mostly of moderate intensity. On the other hand, regarding diabetes control, about 66% of participants had good or fairly good control while 34% had poor control. Only 25% of participants were on insulin therapy. Most participants also had no family history of depression and never smoked or drank alcohol.

**Table II: Number of patients with depression, anxiety and stress based on PHQ-9 and DASS-21**

	Number	Frequency
Depression (PHQ-9)	20	24.4%
Depression (DASS-21)	22	26.8%
Anxiety	33	40.2%
Stress	21	25.6%

The minimal discrepancy in frequency (2.4%) showed that the results of PHQ-9 and DASS-21 were aligned to each other.

**Table III: Validity of DASS-21**

	Depression (PHQ-9)	Not depressed (PHQ-9)	
Depression (DASS-21)	15	7	22
Not depressed (DASS-21)	5	55	60
	20	62	82

DASS-21 was highly specific (specificity 89%), and moderately sensitive (sensitivity 75%) as a tool in assessing depression.

**Table IV: Correlation analysis of multiple variables with depression (DASS-21)**

	Pearson chi square	P value
Gender	0.435	0.509
Ethnicity	4.149	0.246
Marital status	4.25	0.039
Financial background	0.541	0.763
Highest educational level	0.214	0.975
Occupational status	1.930	0.381
Number of long-term illnesses	1.556	0.459
Beta-blocker	1.885	0.170
Diuretics	0.109	0.741
Family history of depression	0.497	0.481
Smoking	1.598	0.206
Alcohol	0.127	0.722
Lipid control	0.018	0.894
Insulin	0.044	0.835
Diabetes control	4.053	0.132
Anxiety	9.759	0.002
Stress	22.821	<0.001
Beliefs about medicines (BMQ)	11.305	0.010
Adherence to medication (MyMAAT)	2.369	0.124

Based on Pearson's chi square test, the only sociodemographic factors that had a statistically significant association with depression were stress ( $\chi^2=22.821$ ;  $p < 0.001$ ), anxiety ( $\chi^2=9.759$ ;  $p = 0.002$ ), beliefs about medicines ( $\chi^2: 11.305$ ;  $p = 0.010$ ) and marital status ( $\chi^2=4.25$ ;  $p = 0.039$ ).

**Table V: Adjusted Logistic Regression Analysis of depression and its association with marital status, stress, anxiety and belief about medicines**

	Adjusted OR	p-value	95% Confidence interval
Marital status	6.178	0.050	0.998 - 38.259
Stress	14.000	0.002	2.682 - 73.076
Anxiety	1.113	0.892	0.237 - 5.224
Belief about medicines	ref	ref	ref
Indifferent	0.480	0.360	0.100 - 2.312
Sceptical	0.295	0.145	0.057 - 1.524
Ambivalent	0.000	0.999	0.000
Accepting			

\* OR=Odd ratio

Upon adjusted logistic regression of the 4 factors (marital status, stress, anxiety and belief about medicines), only stress was statistically significant. Beliefs about medicines were not showing statistically significant results due to its low variability of data.

group. However, this result was not statistically significant ( $p=0.583$ ).

#### *Sociodemographic factors contributing to depression among Type 2 diabetic patients*

Based on Pearson's chi square test, the only sociodemographic factors that had a statistically significant association with depression were stress ( $\chi^2=22.821$ ;  $p < 0.001$ ), anxiety ( $\chi^2=9.759$ ;  $p=0.002$ ), beliefs about medicines ( $\chi^2: 11.305$ ;  $p=0.010$ ) and marital status ( $\chi^2=4.25$ ;  $p=0.039$ ). The findings from other sociodemographic factors were summarised in Table IV.

Therefore, the four statistically significant factors above were analysed further. The odds ratio of stress was 13.25 (95% CI 4.1 - 42.82), beliefs about medicines was 0.461 (95% CI 0.218 - 0.976), and anxiety was 5.00 (95% CI 1.744 - 14.34). For marital status, the odds ratio was 4.118 (95% CI 0.993 - 17.076), and its confidence interval included 1. Hence, this indicated that the result was not statistically significant. Upon adjusted logistic regression of the 4 factors (marital status, stress, anxiety and belief about medicines), only stress was statistically significant. Anxiety and marital status were not statistically significant as the 95% confidence interval of odds ratios included 1. Beliefs about medicines were not showing statistically significant results due to its low variability of data. The adjusted logistic regression was shown in Table V.

## DISCUSSION

Based on the study's objective, this study had three major findings. Firstly, about 25% of the study population had depression. While this finding was higher than the overall prevalence of depression among patients with Type 2 diabetes mellitus in Malaysia, it was still within the normal range if locality-based prevalence was used.<sup>15</sup> This was because the prevalence ranged from 4.3% in Hulu Selangor to 36.8% in Perak.<sup>15</sup> This was an important negative finding as an increased rate of depression among patients with Type 2 diabetes mellitus in Malaysia would warrant further studies to determine the need for early mental health intervention in these patients.

The second major finding was the lack of a statistically significant association between statin use and depression. While this was different from other studies that have associated statin use with reduced risk of depression, it was important to note that a study in Denmark explained that

the association could be due to residual confounding bias such as coming for more follow-up visits due to statin therapy.<sup>7</sup> This was another significant negative finding as it would not make clinicians hesitate to prescribe statins for patients with depression when there was a clinical indication such as prevention and treatment of cardiovascular diseases.

The third major finding was the presence of one sociodemographic factor (stress) that had a statistically significant association with depression. The association with stress and increased risk for depression was also similar to what was reported in other studies. For example, in a study in Germany, 3 domains of chronic stress (Pressure to Perform, Social Isolation and Chronic Worrying) had a statistically significant association for increased risk of depression.<sup>16</sup> These sociodemographic factors are important positive findings as they might represent modifiable risk factors that could be tackled via effective health policies.

Although cholesterol had important normal functions in the central nervous system, this was an important contribution to cardiovascular disease prevention because high cholesterol levels were a risk factor for cardiovascular diseases especially in diabetic patients.<sup>17-18</sup> Statins helped to reduce cholesterol levels by competitively inhibiting the rate-limiting enzyme of the cholesterol synthesis pathway which is HMG-CoA reductase.<sup>19</sup> While statin use did not have a statistically significant association with depression among this study's participants, other studies had reported that the use of statins was associated with a reduction in risk of depression in people under the age of 40 years.<sup>4</sup>

Lipid control was also not shown to have a statistically significant association with depression in this study. However, other studies have reported otherwise. For example, hyperlipidaemia was linked with increased rates of depression.<sup>20</sup> This tied in with the fact that both hyperlipidaemia and diabetes had independently shown statistically significant association with depression.<sup>21</sup> Conversely, patients with depression had also been shown to have increased comorbidity with and poorer control of both diabetes and hyperlipidaemia.<sup>22</sup>

It was also important to note that all of the participants in this study were also part of the Seremban Diabetes (SeDia) cohort study and this could affect the study results. SeDia cohort study was officially launched by Duli Yang Maha Mulia Yang Di Pertuan Besar Negeri Sembilan, Tuanku Muhriz ibni Almarhum Tuanku Munawir on 10 July 2023.<sup>23</sup>

This initiative involved the Ministry of Health of Malaysia and IMU University.<sup>23</sup> SeDia cohort study was the first large-scale cohort study on diabetes in Malaysia as it involved a 12-year longitudinal open observational cohort study of previously diagnosed and newly diagnosed diabetes patients, who registered with the National Diabetes Registry at Seremban Health Clinic, along with their household family members.<sup>24</sup> An example of a factor which could be affected was medication adherence. For example, participants would have been counselled about this matter leading to better lipid control and diabetes control. This could lead to lack of statistically significant findings in regards to medication adherence.

On the other hand, this study had some limitations. Firstly, the target sample size of 242 patients for an ideal data analysis was not achieved. This might affect the internal validity of the study due to possible selection bias. Secondly, this study only involved 1 location. Hence, the results might not give an accurate general view of the association between statin use and depression among all patients with Type 2 diabetes mellitus. Thirdly, duration of statin therapy, duration of diabetes, complications of diabetes, quality of sleep and presence of cognitive impairment were not obtained and these could be confounders in the association between statin and depression among patients with diabetes mellitus. Fourthly, while our study could pick up possible undiagnosed cases of depression, we were unable to determine if the depression was due to statin use. This was because a retrospective study was done instead of a prospective study. Fifthly, this study did not involve any hydrophilic statins. Thus, a comparison could not be made between the association of depression with hydrophilic statin use or lipophilic statin use. This is important as other research had found that lipophilic statins (e.g. simvastatin) not hydrophobic statins were associated with a statistically significant reduction in risk of depression.<sup>4</sup>

The recommendations for further research are as follows: 1) conduct follow-up for patients that were involved in this study to identify possible causal links between statin use and depression, 2) carry out similar research but in areas with different population demographics (e.g. race, socioeconomic status, country) to verify if the observations are similar to what was seen in this study and 3) include hydrophilic and lipophilic statins in the study to determine if there is any difference in their association with depression.

## CONCLUSION

This study showed that the association between depression and statin use among patients with Type 2 diabetes mellitus was not statistically significant. Hence, the null hypothesis was accepted. However, further studies are needed to confirm if the depression that was seen in this group of patients was due to statin use. Most importantly, patients with long-term illnesses should be compliant to the medical and lifestyle interventions for their respective conditions. Through good control of these long-term illnesses, the psychiatric morbidity can be reduced.

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