BMI AND GENDER AS MEDIATORS IN THE ASSOCIATION BETWEEN ETHNICITY AND GLYCEMIC CONTROL IN PRIMARY HEALTHCARE SETTINGS: MALAYSIA NATIONAL DIABETES REGISTRY COHORT

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ABSTRACT

Background: The prevalence of type 2 diabetes continues to escalate across all ethnic groups in Malaysia. Evidence on ethnic differences among Asian population mostly focused on the incidence and prevalence of diabetes, rather than on glycaemic control. Poor glycemic control leads to development of diabetes-related complications. The association between ethnicity and glycemic control was investigated. The roles of sex and body mass index (BMI) as mediators were assessed. We also determined the association between ethnicity and diabetes-related complications. **Methods:** A retrospective cohort study involving 338,349 primary care patients registered in the Malaysian National Diabetes Registry (NDR) between 2011 and 2015 was conducted. All major ethnic groups were included (Malays, Chinese, Indian, Indigenous Sabah [consisted of Kadazan, Dusun, Bajau and Other Sabah] and Indigenous Sarawak [consisted of Iban, Bidayuh, Melanau and Other Sarawak]). Linear mixed effect model with random intercept and logistic random intercept models were used to analyze cross-sectional associations (defined as glycemic control at five years of diabetes) and longitudinal associations (defined as glycemic control for every five years of diabetes). Generalized structural equation modeling (GSEM) was used to conduct mediation analysis, and discrete-time survival analysis was used to determine the hazard of diabetes-related complications. **Results:** Ethnicity was significantly associated with HbA1c level. Cross-sectionally, all ethnicities were significantly associated with lower HbA1c level compared to the Malays. In the longitudinal associations, the HbA1c levels changed by 0.1% among Chinese and Indian, 0.24% among Dusun and 0.12% among Indigenous Sarawak, compared to the Malays [Chinese and Indian: β= -0.10 (95%CI -0.13, -0.07), Dusun: β= 0.24 (95%CI 0.07, 0.41), Indigenous Sarawak: β= 0.12 (95%CI 0.01, 0.22)]. Compared to Malays, the odds of good glycemic control increased by 20% among the Indians and 7% among the Chinese [Indian: OR 1.20 (95%CI 1.13, 1.28),

Chinese: OR 1.07 (95%CI 1.01, 1.12)], while among the Indigenous Sabah and Indigenous Sarawak, the odds decreased by 14% and 20% [Indigenous Sabah: OR 0.86 (95%CI 0.75, 0.99), Indigenous Sarawak OR 0.80 (95%CI 0.65, 0.98)]. Sex mediated the association between Chinese, Indian and Iban ethnicities and HbA1c level [Indirect associations: Chinese (0.7%), Indian (1.1%) and Iban (0.1%)]. BMI mediated the association between Chinese, Indian, Bajau, Iban and Melanau and HbA1c level (Indirect associations ranged from 0.1% to 7.0%). Compared to Malays, Indian ethnicity was associated with significantly increased hazard of diabetic retinopathy and peripheral vascular disease (PVD) [Retinopathy: HR 1.18 (95%CI 1.13, 1.23), PVD: HR 1.11 (95%CI 1.00, 1.22)]. Chinese, Bajau, and Other Sabah had an increased hazard of diabetic retinopathy [Chinese: 23%, Bajau: 93%, Other Sabah: 115%] and a decreased hazard of diabetic nephropathy [Chinese: 5%, Bajau: 51%, Other Sabah: 32%] and PVD [Chinese: 33%, Bajau: 67%, Other Sabah: 63%]. The Ibans had significantly decreased hazard for all three diabetes-related complications [Retinopathy: HR 0.62 (95%CI 0.52, 0.75), Nephropathy: HR 0.68 (95%CI 0.58, 0.79), PVD: HR 0.58 (95%CI 0.36, 0.92)]. **Conclusion:** Ethnicity appears to be a significant predictor of glycemic control, and diabetes-related complications. These associations are mediated by sex, and BMI. In multi-ethnic settings like Malaysia, health programs aiming for early detection of diabetes, improvement of health literacy in diabetes for better glycemic control, prevention of diabetes-related complications, and provision of supportive care should be tailored according to ethnic groups. Future studies should examine the potential mediating role of other lifestyle factors in the control of diabetes.

Keywords: ethnicity, HbA1c, glycemic control, diabetes-related complications, mediator.

ABSTRAK

Latar belakang Perkaitan di antara kumpulan etnik dan kawalan glukosa belum pernah dibincangkan dengan jelas terutama bagi negara-negara Asia yang terdiri daripada pelbagai kumpulan etnik termasuk Malaysia yang mempunyai prevalen pesakit diabetes yang tinggi. Melalui kajian ini, kami ingin membuktikan kaitan di antara kumpulan etnik, kawalan glukosa dan komplikasi diabetes serta membuktikan BMI dan jantina adalah pengantara kepada kaitan tersebut dalam kalangan pesakit diabetes di klinik-klinik kesihatan, KKM Malaysia. **Metodologi** Satu kajian retrospektif kohort telah dijalankan menggunakan data daripada *National Diabetes Registry*, KKM Malaysia (bagi tahun 2011 hingga 2015) untuk menganalisa kawalan glukosa (didefinisikan sebagai paras HbA1c ≤6.5% dan perubahan paras HbA1c) dan komplikasi diabetes, serta 2 pengantara gaya hidup iaitu BMI dan jantina dalam kalangan 27 kumpulan etnik yang telah dikategorikan semula kepada 11 kumpulan etnik utama iaitu Melayu, Cina, India, Kadazan, Dusun, Bajau, Lain-lain Sabah, Iban, Bidayuh, Melanau dan Lain-lain Sarawak, n=338,349 yang telah menerima rawatan penjagaan kesihatan diabetes di 622 klinik-klinik kesihatan kerajaan seluruh Malaysia. *Linear Mixed Effect Model with random intercept* dan *Logistic Random Intercept Model* digunakan untuk menentukan kaitan di antara kumpulan etnik dan kawalan glukosa. *Generalized Structural Equation Modeling* (GSEM) digunakan untuk menetukan peranan pengantara dalam kaitan tersebut dan *Discrete-time Survival Analysis* digunakan bagi menentukan kaitan di antara kumpulan etnik dan komplikasi diabetes. **Keputusan** Kawalan glukosa (didefinisikan sebagai perubahan paras HbA1c bagi setiap 5 tahun diabetes dan paras HbA1c ≤6.5% untuk kawalan glukosa yang baik) mempunyai kaitan yang signifikan dengan semua kumpulan etnik. Analisa awal menunjukkan semua kumpulan etnik dikaitkan dengan perubahan paras HbA1c yang rendah berbanding Melayu. Analisa akhir menunjukkan Dusun mempunyai perubahan

paras HbA1c lebih rendah sebanyak 0.2% dan 0.1% bagi Cina dan India bagi setiap 5 tahun diabetes, berbanding Melayu. Lain-lain Sarawak menunjukkan perubahan paras HbA1c lebih tinggi sebanyak 0.4% berbanding Melayu. Kumpulan etnik utama iaitu Cina, India, Indigenous Sabah dan Indigenous Sarawak telah menunjukkan kaitan dengan paras HbA1c ≤6.5% [India; OR 1.20 (95%CI 1.13, 1.28), p-value <0.001)] manakala nisbah odds bagi Cina, Indigenous Sabah dan Indigenous Sarawak ialah 1.07, 0.86 dan 0.80. BMI merupakan pengantara bagi Cina, India, Bajau, Iban dan Melanau kepada kaitan dengan perubahan paras HbA1c (% *indirect effect* dari *total effect* untuk menerangkan kaitan tersebut berada dalam lingkungan 0.1% ke 7.0%). Jantina merupakan pengantara bagi Cina, India dan Iban dalam kaitan tersebut. Kumpulan etnik mempunyai kaitan dengan kejadian komplikasi diabetes. India dikaitkan dengan peningkatan bahaya *Diabetic Retinopathy* serta PVD tetapi tidak dikaitkan dengan bahaya *Diabetic Nephropathy*. Kumpulan etnik Cina, Bajau dan Lain-lain Sabah dikaitkan dengan peningkatan bahaya *Diabetic Retinopathy* tetapi mempunyai kaitan dengan bahaya *Diabetic Nephropathy* dan PVD yang lebih rendah berbanding Melayu. Iban dikaitkan dengan bahaya yang lebih rendah berbanding Melayu bagi ketiga-tiga komplikasi diabetes dalam kajian ini. **Rumusan** Bukti kajian ini dapat dijadikan panduan supaya fokus dalam penjagaan kesihatan diabetes melalui *personalized care* (pengesanan awal, pendidikan kesihatan serta sokongan kepada pesakit diabetes) dapat dilaraskan berdasarkan keperluan kumpulan etnik demi memastikan pesakit diabetes di Malaysia mencapai kawalan glukosa yang baik.

Kata kunci: etnik, HbA1c, kawalan glukosa, komplikasi diabetes, pengantara.

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CHAPTER 1: INTRODUCTION

1.1 Chapter Introduction

This chapter introduces the topic of the thesis. It includes an overview of the burden of diabetes around the world and in Malaysia, the conceptual framework for the causal relation between ethnicity and glycaemic control, the rationale of the study, the research questions and the objectives of the study.

1.2 Background on Burden of Diabetes Mellitus in Malaysia

Diabetes is a growing pandemic. The International Diabetes Federation (IDF) estimates that as of 2017, there are 425 million people living with diabetes around the world. This in turn means that 8.8% of the world population aged 20–79 years old have diabetes. The above figure represents an increase of about 10 million cases within just a 2-year period from 2015, and this number is projected to rise further to 629 million in 2045 (IDF, 2017).

The Western Pacific Region (WPR) is currently home to 37% of the global population with diabetes. In this region, there are 159 million people who have diabetes, which is the highest number of diabetes patients among all the regions (IDF, 2017). As of 2017, Malaysia has the highest prevalence of diabetes in the WPR at 16.9% (not including the Pacific Island countries), surpassing all its neighbours including Singapore (13.7%), Thailand (8.3%), the Philippines (6.3%), Brunei Darussalam (13.8%), and Indonesia (6.7%) (IDF, 2017).

Indeed, the prevalence of Type 2 Diabetes in Malaysia continues to escalate and cuts across all ethnicities. In Malaysia at present, 3.5 million adults aged 18 years and above have diabetes. The National Health and Morbidity Survey (NHMS) 2015 found the prevalence of diabetes in Malaysia to be 17.5%, with the highest prevalence among the Indian population at 22.1%, followed by the Malays at 14.6% and the Chinese at 12.0%

(NHMS, 2015). The survey also projected that the prevalence of diabetes will rise to around 31.3% in 2025. Furthermore, this survey indicated that Sabah, Sarawak and Wilayah Persekutuan Labuan which are the three Malaysian states with the most multi-ethnic populations have also started to show an increasing trend in the prevalence of diabetes in recent years (NHMS, 2015).

The rising prevalence of diabetes globally, which is occurring in concordance with decreasing mortality, has led to an increase in overall mean years lived with diabetes. This further contributes to the occurrence of diabetes-related complications (Gregg, Sattar, & Ali, 2016). Regrettably, data on the global trends and the changes in the characteristics of diabetes-related complications are reprehensibly scarce in low- and middle-income countries (Gregg et al., 2016).

Nevertheless, premature mortality in diabetes is definitely a concern. Although mortality estimates are decreasing, diabetes still accounted for 10.7% of all-cause deaths worldwide among those aged 20 to 79 years old in 2017 (IDF, 2017). Four million people in the above age group were estimated to have died from diabetes and diabetes-related complications in 2017 (IDF, 2017). In 2012, diabetes accounted for 3% of all-cause deaths in Malaysia, and 73% of total deaths due to non-communicable diseases (NCDs) (WHO, 2014).

1.3 Conceptual Framework

In this study on diabetes patients, ethnicity is defined by differences in cultural beliefs, religious beliefs, and socioeconomic status. Due to these differences, different ethnic groups could possess dissimilarities in psychosocial beliefs and perceptions towards the disease, or in their health beliefs in general (Nazroo, 1998). Ethnic differences in health beliefs could also predispose people towards unhealthy behaviours

such as smoking, poor diet, and physical inactivity. All the above may eventually result in health disparities between different ethnic groups (Chida & Hamer, 2008).

Health disparities in this sense would mean that the importance of the early detection of diabetes might not be understood among some population groups. This could lead to delay in diagnosis and treatment, self-denial especially on diagnosis, and perceived difficulty when already diagnosed with diabetes and consequently poor self-management, as well as differences in perceived risk and fatalism (L. R. M. Hausmann, D. Ren, & M. A. Sevick, 2010).

Hence, an undesirable impact on diabetes management could be seen when these issues are not addressed accordingly. Patients could present at a late age for diagnosis, and already have diabetes-related complications and co-morbidities at diagnosis of diabetes as well as have poor adherence to medications. Disparities in glycaemic control among diabetes patients could also occur as a result of differences in health beliefs, as explained by the prognostic factor of ethnicity.

These issues are summarized in Figure 1.1 below, which illustrates the conceptual framework for a causal relation between ethnicity and glycaemic control.

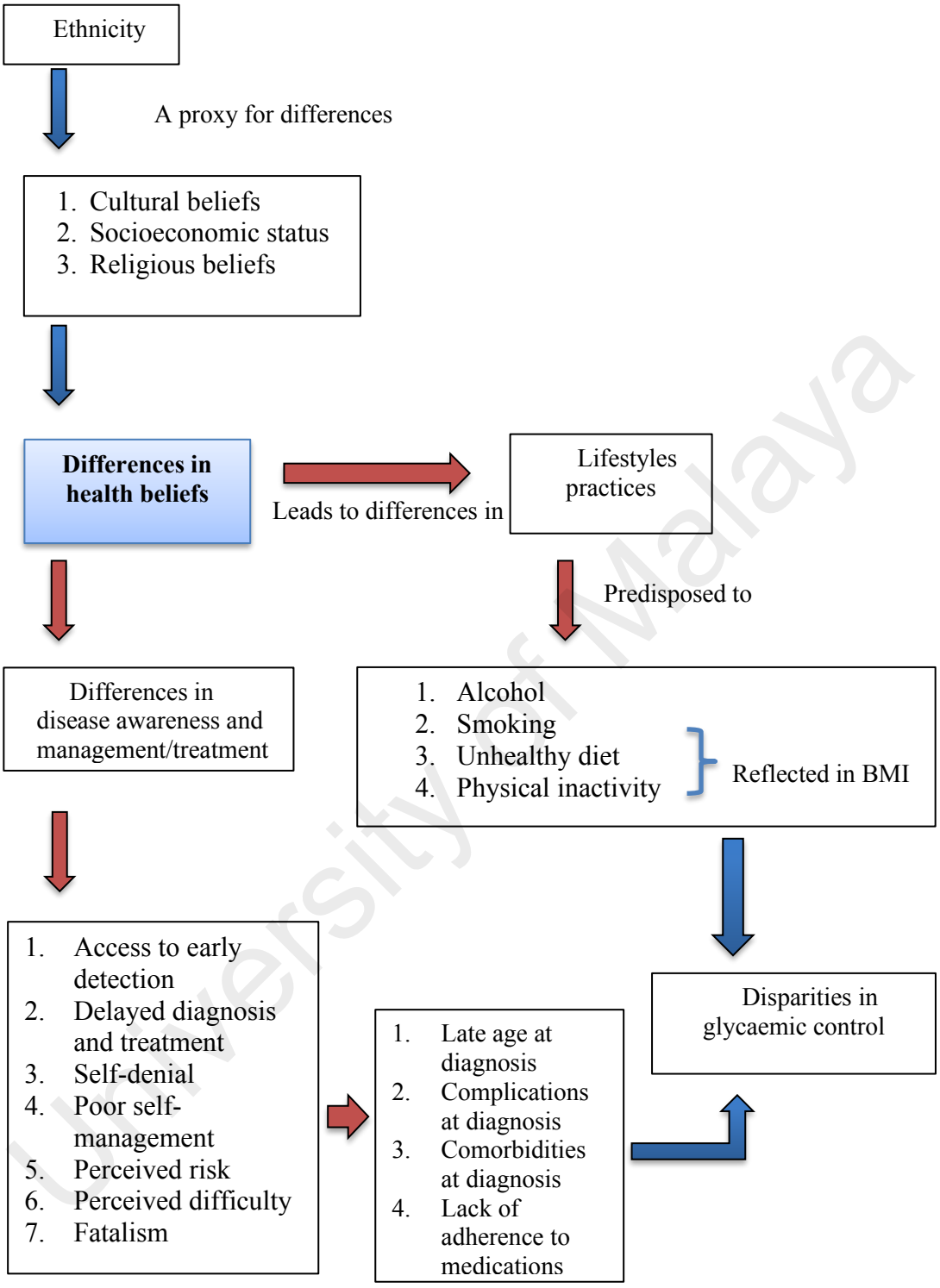

Figure 1.1: Conceptual framework for a causal relation between ethnicity and glycemic control

1.4 Rationale for Study

Most of the previous studies that have examined ethnic differences among the Asian population have focused on the incidence and prevalence of diabetes, rather than on glycaemic control. Only a handful of studies have investigated the association between ethnicity and glycaemic control among Asians, and these were conducted primarily in Singapore and Malaysia (Boon How Chew et al., 2011; Low et al., 2016; Luo et al., 2017; Ng et al., 2005; Rampal et al., 2010; Shankar et al., 2009; N. C. Tan, Barbier, Lim, & Chia, 2015; Yeo et al., 2006).

Some of these studies employed a prospective cohort design, which is a methodologically sound approach for this area of research. However, these studies only focused mainly on the Malay, Chinese and Indian ethnic groups and did not consider the potential variation in other ethnic groups. Nevertheless, it is particularly important to do so in a multi-ethnic country such as Malaysia. Also, apart from these studies, most of the other studies are cross-sectional and descriptive in nature, which hence limits the temporal and causal inferences that can be drawn from the results.

In contrast, a myriad of American- and European-based studies have looked into differences in glycaemic control among a wide range of different ethnicities; for instance, comparing South Asian Indians and Native Americans to Non-Hispanic Whites within the United States. (Kanaya et al., 2014; Menke, Casagrande, Geiss, & Cowie, 2015; Mukhopadhyay, Forouhi, Fisher, Kesson, & Sattar, 2006; Wolffenbuttel et al., 2013). A number of studies have also compared the South Asians and Chinese living in the United States and European countries to those residing in their country of origin due to the high prevalence of diabetes among Indians and Chinese (Unjali P. Gujral, Pradeepa, Weber, Narayan, & Mohan, 2013; O'Keefe, DiNicolantonio, Patil, Helzberg, & Lavie, 2016; L. Wang et al., 2017). However, these studies discussed

mainly the associated factors of diabetes, including pathophysiology (biological and genetic) and environmental factors (behaviour and lifestyle changes)

Yet, due to the increasing burden of diabetes among Asians, there is a need to look beyond merely the etiologic factors. It is important that the role of ethnicity as a prognostic factor in diabetes is explored further particularly in the context of Malaysia, a multi-ethnic country with different cultural beliefs and lifestyles as well as a high prevalence of diabetes.

However, to date there is no direct evidence to prove that non-glycaemic factors, including genetic make-up and cultural, behavioural, and lifestyle factors, can act as proxy for ethnicity and thereby help in explaining the role of ethnicity in glycaemic control. Despite that, to entirely disregard the absence of evidence due to the inexistence of a statistically significant explanation would be wrong. Also, disagreeing with the suggestion that ethnicity should be considered as a fundamental component for effective diabetes management might lead to disparities in the HbA1c level and poorer diabetes outcomes (Herman, 2016; Selvin, 2016).

Although currently there is some evidence that contradicts and does not exclusively support the hypothesis that ethnicity modifies the HbA1c level independent of glycaemia, this does not disprove the possibility. It is thus crucial to explore in detail whether there are disparities in glycaemic control in different populations, not least because poor glycaemic control is a risk factor for diabetes-related complications.

Therefore, it is vital to understand the pathway that may lead ethnicity to act as a prognostic factor in causing a differing level of glycaemic control. In this regard, it is envisaged that an assessment of body mass index (BMI) as a lifestyle-related mediator and gender that could potentially mediate the pathway would be of benefit especially in designing interventions to achieve good glycaemic control. These interventions could be strategized and personalized to target the mediating variable that is causally related to the outcome, and could be implemented in a culturally sensitive way that meets the needs of each patient according to their ethnic group.

1.5 Research Question

In light of the foregoing, this study seeks to answer the following research question: What is the association between ethnicity and glycaemic control as well as diabetes-related complications in patients with Type 2 Diabetes Mellitus managed in primary healthcare settings in Malaysia?

1.6 Objectives

To answer the above question, the following objectives were set:

1. To determine the association between ethnicity and glycemic control in patients with Type 2 Diabetes Mellitus.
2. To determine the role of BMI as lifestyle-related mediator and gender as mediator that will explain the association between ethnicity and glycemic control in patients with Type 2 Diabetes Mellitus.
3. To determine the association between ethnicity and risk of diabetes-related complications in patients with Type 2 Diabetes Mellitus.

1.7 Chapter Summary

This chapter highlighted the importance of looking into the association between ethnicity and glycemic control and the role of BMI and gender as mediators. With the increasing prevalence of diabetes in Malaysia that has also cut across all ethnicities, it is vital that the role of ethnicity as an independent prognostic factor for glycemic control is further explored especially given the state of this nation with multi-ethnicities and possess different cultural beliefs and lifestyles. Although to date there is contradicting evidence that does not support the postulation of ethnicity modifies HbA1c level independent of glycaemia, this does not disprove the possibility. It is therefore crucial to explore in detail whether there are disparities in glycaemic control among different ethnic groups.

CHAPTER 2: LITERATURE REVIEW

2.1 Chapter Introduction

This chapter discusses the associations between ethnicity and glycaemic control and diabetes-related complications. The first part addresses the emerging evidence for a relationship between ethnicity and glycaemic control based on global and Asian findings as well as the Malaysian evidence that is available thus far. Then, the influence of body mass index and sex as mediators in the association between ethnicity and glycaemic control is considered. Lastly, the association between ethnicity and diabetes-related complications including diabetes-related mortality is discussed in depth.

2.2 Evidence for an Association between Ethnicity and Glycaemic Control

Evidence is emerging to support an association between ethnicity and glycaemic control (Campbell, Walker, Smalls, & Egede, 2012; Egede, Mueller, Echols, & Gebregziabher, 2010; Kirk et al., 2008; Lynch et al., 2014; Saydah, Cowie, Eberhardt, De Rekeneire, & Narayan, 2007). Several studies conducted in the United Kingdom (UK), the United States (US), Australia, Sweden, Singapore and Malaysia have shown a positive association between ethnicity and glycaemic control (Alharbi et al., 2015; Boon How Chew et al., 2011; Ng et al., 2005; Rawshani et al., 2015; Wolffenbuttel et al., 2013). For instance, studies conducted in the US and the UK have mainly suggested that South Asians, especially Indians, have the poorest level of glycaemic control. (Abate & Chandalia, 2001, 2003; Mostafa et al., 2012).

It has long been suggested that factors such as biological makeup, socioeconomic status, medical and insurance coverage and quality of care contribute to the differences in glycaemic control (Diabetes & Complications Trial Research, 1993; Group, 1998; Karter et al., 2002; Kirk et al., 2008). The ethnic differences in glycaemic control that have been recognized for many years has also in general been attributed to differences

in the access to health care for different ethnic groups (Herman & Cohen, 2012). However, thus far, there is no direct evidence to show whether non-glycaemic factors such as genetic makeup and cultural, behavioural and lifestyle factors can help to fully explain the ethnic differences in glycaemic control (Selvin, 2016).

Despite arguments on glycaemia and non-glycaemia factors contributing to the ethnic differences in glycemic control, there is also evidence that support independent effect of ethnicity on glycemic control (Cavagnolli, Pimentel, Freitas, Gross, & Camargo, 2017). A systematic review and meta-analysis conducted in the UK investigated the effect of ethnicity on HbA1c levels among individuals without diabetes. This meta-analysis consisted of 12 studies with 49,236 individuals above 18 years without diabetes. Participants without diabetes were selected to exclude possible variability of HbA1c due to glucose fluctuations. It was found that there were significant differences between HbA1c levels in Blacks [0.26% (95% CI 0.18, 0.33), p <0.001; I^2=90%, p <0.001], Asians [0.24% (95% CI 0.16, 0.33), p <0.001; I^2=80%, p=0.0006] and Latinos [0.08% (95% CI 0.06, 0.10), p <0.001; I^2=0%; p=0.72] when compared to Whites. This study presumed the ethnic differences observed are most likely to be independent of diabetes status and other factors related to health care as the study populations involved healthy individuals and that their glucose levels were below the cut off point for the diagnosis of diabetes.

The review also discussed on the differences in HbA1c values in Blacks, Asians and Latinos compared to Whites could also possibly be due to physiological characteristics that are explained as biological factors including variations in the glycation gap, differences in erythrocytes survival, variances in hemoglobin glycation, heterogeneity in the glucose concentration gradient across the erythrocyte membranes and differences in the passage of glucose mediated by GLUT1 transporter into the erythrocyte. Therefore,

the authors postulated that, Blacks, Asians and Latinos populations could possibly have specific physiological characteristics that differentiate them from the White populations. These distinct characteristics could have contributed to the ethnic differences in HbA1c levels in this study among individuals without diabetes and supported the hypotheses on independent effect of ethnicity on glycemic control.

However, in recent debates, the question that has been posed is not why there are differences in the HbA1c level, which is widely considered the gold standard for monitoring glycaemic control, because differences do exist. The question that needs to be asked is why the HbA1c levels are higher in specific ethnic groups, for example, in Blacks compared with Whites, and are these differences clinically meaningful for the management of type 2 diabetes? A better understanding on the mechanisms involved in HbA1c variability among ethnic groups are crucial in order to improve its clinical applicability (Cavagnolli et al., 2017).

2.3 Global Findings on Ethnic Differences in Glycemic Control

The meta-analyses, systematic reviews, prospective and retrospective cohort studies, cross-sectional studies and observational studies that have been conducted mainly in the US, the UK, and Sweden in previous years have identified a positive association between ethnicity and glycaemic control.

In the US, an analysis of data from the National Health and Nutrition Examination Surveys (NHANES) for the period from 1988 to 2010 was conducted in order to observe the changes in the proportions of participants achieving targeted HbA1c level of less than 7% (Casagrande, Fradkin, Saydah, Rust, & Cowie, 2013). With age and sex standardized to the 2007–2010 NHANES population with diabetes, the prevalence of diabetes patients achieving a HbA1c of < 7% among the Mexican American population is lower than that among non-Hispanic Whites and non-Hispanic Blacks (P< 0.03).

Nonetheless, it should be noted that the analysis also found that, over time, all ethnic groups showed an increase in the prevalence of diabetes patients with a HbA1c of < 7%.

On the other hand, a meta-analysis conducted in the US in 2006 that looked into the differences in the HbA1c level among African American and non-Hispanic White adults with diabetes found that 10 out of 11 studies reported a significantly higher HbA1c level among African Americans compared to non-Hispanic Whites. Specifically, there is a 0.65% difference in the HbA1c level between these two ethnic groups (effect size = -0.32, p-value < 0.001), indicating that African Americans have HbA1c values at average of 0.32 SD above those of non-Hispanic Whites (Kirk et al., 2006). Also, the 0.65% higher HbA1c level among African Americans was put forward as an explanation for the high prevalence of microvascular complications among this population nationally (Kirk et al., 2006).

Then, in 2008, a further meta-analysis was conducted to investigate the differences in the HbA1c level, in which a comparison was made between Hispanic and non-Hispanic White adults with diabetes (Kirk et al., 2008). Similar to the difference observed between African Americans and non-Hispanic Whites in the above-mentioned study, the 2008 meta-analysis yielded a statistically significant mean difference of -0.46 (95% CI -0.63 to -0.33, [$P > 0.0001$]), correlating to a 0.5% higher HbA1c among Hispanics. Moreover, this difference persists regardless of the body mass index (BMI) and age of the diabetes patients. In addition, Hispanics were found to have the most considerable differences in the HbA1c level, especially among the non-managed care groups (Kirk et al., 2008).

The differences in the HbA1c level identified by the above two studies are clinically significant. However, the findings of both of these studies are limited in terms of the ability of the results to explain the reasons behind the observed disparities in the HbA1c

level. However, the authors hypothesized that differences in genetic makeup, healthcare access, insurance coverage and adherence in regards to medication, dietary intake and self-management could be plausible explanations for the observed disparities. Therefore, it was suggested that such differences in glycaemic control may contribute to the dissimilar diabetes care received by these ethnic groups. Furthermore, the authors expressed the opinion that it would be crucial to undertake further work in order to determine the causes of the disparity in glycaemic control, and to what extent the disparity may be due to biology, lifestyle, healthcare access and utilization, and socioeconomic factors. The authors also argued that further evaluation of these factors would be crucial for the improvement of diabetes management in this population (Kirk et al., 2006; Kirk et al., 2008).

It has also been argued that differences in health beliefs with regards to diabetes are common among Hispanics compared to other ethnic groups and might result in differences in perceived risk that could lead to disparities in glycaemic control (Arcury, Skelly, Gesler, & Dougherty, 2004; Coronado, Thompson, Tejeda, & Godina, 2004; Hunt, Valenzuela, & Pugh, 1998).

A systematic review conducted in 2012 investigated the impact of racial differences on self-monitoring and glycaemic control among adults with diabetes (Campbell et al., 2012). This systematic review revealed that the differences in glycaemic control (defined as average in HbA1c for statistically significant point estimates) as compared to non-Hispanic Whites ranged from 0.2 to 0.9 for African Americans, 0.28 to 0.76 for Hispanics and 0.4 to 0.5 for Asian Americans. As the clinically significant difference in HbA1c was set at 0.5, the differences in the HbA1c level between these ethnic groups can be regarded as clinically significant. The authors hypothesized that significant barriers exist in diabetes management as racial differences in self-monitoring were also

reported to be significantly different between non-Hispanic Whites and the other ethnic groups studied (Campbell et al., 2012). Hence, the authors suggested that further work would be needed to define the pathways and possible mediators that could explain these differences, which could then inform the development of strategies to reduce the racial gaps in diabetes care.

Retrospective cohort studies have also been conducted to address this research question in the US: using a national cohort (Egede et al., 2011) and a cohort confined to a Veteran Affairs facility (Egede et al., 2010). These two studies looked at the impact of ethnicity on glycaemic control among the well-functioning elderly population. In the national cohort, the study showed that the adjusted means of HbA1c were statistically significantly higher among non-Hispanic Blacks over time (0.25%, 0.54% [$P < 0.001$]) (Egede et al., 2011). Non--Hispanic Blacks were also one to two times more likely to exhibit poor control compared to non-Hispanic Whites as seen in the study confined to Veterans Affair facility (Egede et al., 2010). Given the age of the population and the longer duration of diabetes, these findings indicate that ethnic differences are present, as evidenced by the effect size of the results.

Another retrospective cohort study in the US, which was published a few years later in 2016, sought to clarify whether ethnicity is an independent risk factor for glycaemic control among diabetes patients by adjusting for the effect of economic status in a large primary care diabetes patient population (N = 25,123) (Heidemann, Joseph, Kuchipudi, Perkins, & Drake, 2016). The results of this study revealed that ethnicity is an independent risk factor for glycaemic control as evidenced by White patients having a significantly lower average level of HbA1c compared to Black patients in all income quartiles ($P < 0.001$). However, within Whites, the prevalence of uncontrolled diabetes (defined as HbA1c > 9%) and the average HbA1c level ($P = 0.14$) is inversely

proportional to income level, a finding that could possibly be explained by the presence of other underlying factors. Meanwhile, among Blacks, there is no significant differences in income level that were related to uncontrolled diabetes (*P*= 0.94) and the average HbA1c level (p = 0.282). Insurance status and economic status, which previous studies (LaVeist, Thorpe, Galarraga, Bower, & Gary-Webb, 2009; Levesque, Harris, & Russell, 2013; Osborn, De Groot, & Wagner, 2013) had identified as factors contributing to ethnic disparities in glycaemic control were proved to be misleading as the study by Heidemann et al. (2016) controlled for economic status and almost all patients had insurance coverage.

Therefore, in addition to the glycaemic and non-glycaemic factors postulated to be the underlying causes of the ethnic differences in glycaemic control, the study by Heidemann et al. (2016) provides evidence to support the idea that ethnicity plays an independent role in glycaemic control. Moreover, the authors argued that further exploration of the impacts of patient–provider communication, diabetes education, medication adherence and self-monitoring on diabetes management were warranted in order to identify whether these factors may be responsible for the disparity in glycaemic control (Heidemann et al., 2016).

Further evidence also comes from other studies conducted in the US that supporting ethnic differences in glycaemic control among non-Hispanic Whites in comparison to other ethnic minorities including Hispanics, African Americans and Asian Americans (Casagrande et al., 2013; Goonesekera et al., 2015; Lopez, Bailey, Rupnow, & Annunziata, 2014; Parrinello et al., 2015; Saydah et al., 2007; Rebekah J. Walker, Neelon, Davis, & Egede, 2018; Wolffenbuttel et al., 2013). However, the majority of these studies were cross-sectional in nature.

Among the above-mentioned studies, a global study whose primary objective was to compare the efficacy, safety, and durability of insulin regimens among type 2 diabetes patients in five different continents also examined the ethnic differences in the glycaemic markers among 1,879 diabetes patients, who comprised a subgroup of the total study population. The study revealed that the level of HbA1c is 0.2%–0.5% (2–6 mmol/mol) higher in Asian Americans, Hispanics, and African Americans compared to that of Caucasians, based on the clinically relevant HbA1c range of 7.0%–9.0% (Wolffenbuttel et al., 2013). These findings support a previous cross-sectional study that also looked into ethnic differences among diabetic adults in which it was found that Mexican Americans (32.7%) and non-Hispanic Blacks (35.8%) are less likely to have A1C levels < 7% compared to non-Hispanic Whites (48.7%) (Saydah et al., 2007).

Similarly, in a cross-sectional study that examined the prevalence and control of risk factors among older diabetic adults, Blacks were shown to have a marginally significant association in meeting the HbA1c target of < 8% as compared to Whites (PR 1.07 [95% CI 1.00, 1.15]) (Parrinello et al., 2015).

Also, a study that looked into the contribution of spatial patterns to the association between ethnicity and poor glycaemic control conducted in the south-eastern US and involved 64,022 non-Hispanic Blacks and non-Hispanic White veterans found a higher percentage of poor glycaemic control (defined as HbA1c ≥ 8%) among Blacks (40.8% in non-Hispanic Blacks vs 33.4% in non-Hispanic Whites). Moreover, the study also found that although the odds of non-Hispanic Blacks having poor glycaemic control attenuate after incorporating spatial effects, the effect of ethnicity remains statistically significant (OR: 1.07, 95% CI 1.03, 1.11) (Rebekah J. Walker et al., 2018). The findings of the above study showed that there are differences in the spatial patterns of glycaemic control between these ethnic groups. The authors therefore suggested that future work

should consider adjusting variables such as healthcare location, community resources, and individual household income and also employ spatiotemporal analysis to investigate racial differences in the changes in spatial patterns of glycaemic control over time.

Another study looked into ethnic differences in diabetes treatment and glycaemic control among highly insured, community-based diabetes patients by using data from the third wave of the Boston Area Community Health Survey (2010–2012). The survey results suggested that there is poorer glycaemic control among African Americans prescribed with alternative or miscellaneous regimens of diabetes medications compared to non-Hispanic Caucasians prescribed with similar regimes. In contrast to other studies, the study found no ethnic differences in glycaemic control including those prescribed with alternative or miscellaneous treatment regimens, following adjustment for other factors including age, gender, BMI, education, adequate health literacy, private insurance, income, physical activity, diet and caloric intake and duration of diabetes (Goonesekera et al., 2015). The authors suggested that the absence of a disparity in their results was because their population had universal health coverage whereas the populations in other studies did not, and also, among the insured patients in the other studies, the underlying reasons for the disparity included non-adherence, lack of self-monitoring and treatment differences.

However, a study that was carried out in the previous year to characterize the type 2 diabetes burden by age and ethnicity based on the results of a nationwide survey reported a contradictory result (Lopez et al., 2014). The study observed that there is a significant association between glycaemic control and medication adherence by ethnicity, where American Indians have a significantly higher percentage of good glycaemic control (defined as HbA1c level < 7%) at 43% compared to Asian Americans (30.4%), African Americans (26.1%) and Hispanic Americans (24.4%; $P = 0.04$).

However, the association between glycaemic control and medication adherence is not significant among Whites (38%; $P = 0.276$) (Lopez et al., 2014).

The Swedish National Diabetes Registry recently published a paper on impact of ethnicity on the progress of glycaemic control among patients with newly diagnosed type 2 diabetes (Rawshani et al., 2015). The paper was based on a nationwide prospective observational study involving 131,935 patients, making it the most extensive study by far to look into ethnic differences in glycaemic control. The study involved 10 years follow-up of patients representing all major ethnic groups in the world from different socioeconomic, cultural and religious backgrounds including South Asian. However, it should be noted that the representation of major ethnic groups was discussed according to countries of origin rather than specific ethnic groups, thus limiting the understanding of the role of ethnicity per se.

The findings of the above study supported a positive association between ethnicity and glycaemic control as disparities were observed in all major ethnic groups. For instance, South Asians were predicted to have a HbA1c level of between 1.9–4.2 mmol/L among persons on diet, lifestyle modifications and oral hypoglycaemic agents, and had higher odds of not achieving good glycaemic control or experiencing therapy failure during the second year after diagnosis of diabetes (OR = 2.11 [95% CI 1.35, 3.29]) compared to natives Swedes (Rawshani et al., 2015). These findings indicate that ethnicity is a strong predictor for glycaemic control, a keystone of diabetes care. Moreover, the presence of albuminuria, which is an indicator for the risk of complications, was observed among the South Asians in the study and further highlighted the disparities in glycaemic control (South Asia [OR = 1.92 (95% CI 1.5-2.45)]) (Rawshani et al., 2015).

One possible explanation for the observed differences is that the effectiveness of the glucose-lowering therapy prescribed to patients varied as the study's finding showed an effect modification between ethnicity and glucose-lowering therapy. The predictions also revealed that South Asians on a diet and lifestyle modification have a higher HbA1c compared to those on OHA alone (South Asian β coefficients [95% CI]: diet and lifestyle modification 4.21 [2.85 to 5.56] and OHA 1.93 [0.6 to 3.25]) (Rawshani et al., 2015). However, this finding was not discussed further by the authors.

The study by Rawshani et al. (2015) emphasized the importance of investigating the issue of glycaemic control, not only for a better prognosis for those who have the disease but especially for the prevention of future complications. The study results imply that there is an urgent need for a country such as Malaysia that has multi-ethnic and cultural diversity to look into disparities in glycaemic control given that evidence for this context is currently very limited. Evidence-based studies are essential in helping to direct diabetes management so as to achieve better glycaemic control and prevent complications that very much depend on multiple underlying factors in multi-ethnicities.

Numerous studies have been conducted that compare South Asians with Europeans and with Americans. For instance, two prospective cohort studies that compared glycaemic control between South Asian and European type 2 diabetes patients in primary care settings in the UK have been conducted (McElduff et al., 2005; Mukhopadhyay et al., 2006). Both of these studies reported similar findings concerning the association between ethnicity and glycaemic control, where the mean HbA1c worsens with time among South Asians compared to Europeans. The more recent of the two studies found an average deterioration in HbA1c of 1.31% among South Asians compared to 0.82% among Europeans (P = 0.003) (Mukhopadhyay et al., 2006).

Moreover, these findings persisted after adjusting for age, sex, baseline HbA1c, changes in weight, time to referral and duration of diabetes.

Furthermore, in the US and European contexts, South Asian Indians are recognized to have higher diabetes prevalence that is diagnosed at an earlier age and to have poorer glycaemic control for a given BMI compared to Europeans and US citizens (Menke et al., 2015; Mostafa et al., 2012; Mukhopadhyay et al., 2006). Excessive insulin resistance among South Asian Indians compared to Caucasians has been thought to explain these variations, which might be affected by environmental factors (including behavioural factors and socioeconomic status) and genetic factors or by a combination of both (Abate & Chandalia, 2001, 2003; Kanaya et al., 2014).

While genetic factors may play a role in the presence of diabetes, the study by Abate & Chandalia (2001, 2003) and Kanaya et al (2014) observed that cultural and language barriers lead to poor adherence to treatment and follow-up among Asian Indian migrants. Factors such as acculturation and adoption of a Westernized lifestyle, which might contribute to these outcomes, have not been explored thus far as a possible explanation for the association.

However, Asian Indians in India were also found to have a higher age-specific prevalence of diabetes compared to Whites, Blacks, and Hispanics in the US, even with lower adiposity measurements (U. P. Gujral et al., 2016). The authors suggested that a non-obesity-driven factor, namely an impaired beta cell function contributes to disparities in glycaemic control among Asian Indians from India.

In addition, it has been argued that attitudes and cultural and religious beliefs, as well as social factors lead to the presence of barriers to the effective prevention and management of diabetes among South Asians (Misra, Ramchandran, Jayawardena, Shrivastava, & Snehalatha, 2014). Coupled with biological susceptibility, this could also go some way to explain the role of ethnicity in the differences in glycaemic control, especially among South Asian Indians (Unjali P. Gujral et al., 2013).

Similarly, among Chinese and East Asians, the increased prevalence of diabetes during recent decades has been speculated to be due to a lower beta cell function that leads to a vulnerability in insulin resistance (Kodama et al., 2013). In 2013, the prevalence of diabetes among Chinese adults in China was 11.6% (95% CI 11.3%–11.8%), and among those with diabetes only slightly more than one-third had adequate glycaemic control (39.7% [95% CI 37.6%–41.8%]) (Y. Xu et al., 2013).

Chinese in China were also found to have a higher prevalence of diabetes when overweight compared to the US population (L. Wang et al., 2017), which is consistent with the findings that Asians may have a higher risk of developing diabetes at a given BMI (Mukhopadhyay et al., 2006). However, it should be noted that among the Chinese population, there are almost 56 different ethnic groups that have been described as having extensively distinct genetic backgrounds, socioeconomic levels, cultures and lifestyles that may contribute to the differences in diabetes prevalence among the Chinese population, in addition to the biological susceptibility that has been identified (L. Wang et al., 2017).

2.4 Findings on Glycaemic Control among Different Ethnic Groups in Asia

Asia-based studies have primarily been confined to Singaporean ethnic groups, which are similar to those of the Malaysian population in West Malaysia. Therefore, the

currently available studies are limited in terms of their findings, arguments, and justifications for the association between ethnicity and glycaemic control among Asians.

Among the earliest study done in Singapore has established that the prevalence of diabetes was high across three major ethnic groups, namely Malay, Chinese and Indians, with ethnic differences present for NCD risk factors (obesity, hypertension, dyslipidemia and smoking) (C. E. Tan, Emmanuel, Tan, & Jacob, 1999). This in return was predicted to explain the different coronary heart disease rates in those ethnic groups in Singapore with Asian Indians having the highest rates. This could be explained by the highest prevalence of diabetes, significantly higher insulin resistant among non diabetes, highest prevalence of hypertension, significantly lower HDL level (1.03 ± 0.14 in men and 1.24 ± 0.17 in women, P=0.0001) and statistically significantly higher BMI (23.59 ± 2.82 kg/m^2 in men and 23.68 ± 2.84 kg/m^2 in women) and waist hip ratio (0.85 ± 0.04 in men and 0.73 ± 0.04 in women) among Asian Indians compared to Malays and Chinese that was found from this study (C. E. Tan et al., 1999).

In addition, studies in Singapore also identified Malays as having worse glycaemic control than Chinese and regarded Malay ethnicity as a significant predictor for glycaemic control due to the social and cultural attributes of this group (Chiang et al., 2011; Ng et al., 2005; Shankar et al., 2009). Also, an earlier study in Singapore reported that while the Chinese have better glycaemic control, they suffer more diabetes-related complications compared to Indians (Prevalence rate ratio (PRR) 0.64, 95% CI 0.41–0.99) (Hong, Chia, Hughes, & Ling, 2004). Moreover, Indian ethnicity is also associated with a higher risk of ischaemic heart disease (IHD) (adjusted HR Indian = 2.29 [1.40–3.73]) compared to the Malays (adjusted HR = 1.40 [0.73–2.69]) and Chinese (adjusted HR = 0.74 [0.42–1.3]) ethnicities (Yeo et al., 2006).

Recently, a longitudinal study that examined the trends in glycaemic control as well as the associations with comorbidity and all-cause mortality revealed that Malays and Indians have poorer glycaemic control (moderate-increased group, defined as having a moderately high HbA1c level in the beginning that increases over time to an average HbA1c level of 10.6%) (Luo et al., 2017) compared to Chinese. The study also reported that Malays have the highest risk of developing both acute myocardial infarction (AMI) (HR 1.76 95% CI [1.30–2.37]), and death (HR 1.25 95% CI [1.02–1.54]), while the Indians are at a higher risk of developing AMI (HR 2.37 95% CI [1.80–3.13]) compared to the Chinese (Luo et al., 2017).

Both the Malay and Indian ethnicities have also been reported to be associated with a higher HbA1c level compared to the Chinese ethnicity because the HbA1c level was found to increase by 0.3% after 3 years in a 5-year longitudinal study of the determinants of glycaemic control conducted in Singapore (N. C. Tan et al., 2015). However, the authors did not quantify the mean HbA1c for Chinese as a reference and the mean HbA1c at recruitment for each ethnic group.

Many of the above-mentioned studies have suggested that psychosocial factors including personal beliefs, attitudes, and behaviour as well as cultural beliefs might explain the observed differences. Nevertheless, the combination of genetic, modern and urban environmental factors in Singapore could also predispose the population to disparities. Also, some studies have disputed that level of education and income are plausible explanations for the differences; On one hand, the educational score is high among Malays with the lowest socioeconomic status, and on the other, the majority of patients seek treatment in highly subsidized primary care settings (Ng et al., 2005). However, one particular study showed that a lower level of education is inversely associated with the incidence and control of diabetes, while a higher level of education

is associated with higher diabetes knowledge, a healthy lifestyle and dietary choices that could lead to better glycaemic control (Shankar et al., 2009).

2.5 Malaysian Studies on the Level of Glycaemic Control Among Different Ethnic Groups.

In Malaysia, the study of ethnic differences in glycaemic control is not as established as in the US or European countries. The few studies that have been conducted have focused on mainly three major ethnic groups (Malay, Chinese and Indian), thus the multi-ethnic groups in Sabah and Sarawak are under-represented. Nevertheless, the studies that do exist for the Malaysian context (Blebil, Hassan, & Dujaili, 2011; Boon How Chew et al., 2011; Ismail et al., 2001; Ismail, Nazaimoon, et al., 2000; Rampal et al., 2010; Wong & Rahimah, 2004) showed a weak association between ethnicity and glycaemic control even though they do not clearly portray the burden of diabetes in different ethnic groups. Not only did they not cover all the ethnic groups in Malaysia, they were cross-sectional and descriptive in design. Therefore the findings only suggested ethnicity as a predictor that precedes glycaemic control. Younger patients in these studies represent patient who were recently diagnosed with diabetes and yet to achieve good glycaemic control and patients with longer duration of diabetes had more severe disease with poorer glycaemic control as expected. None that has presented longitudinal changes in HbA1c level among different ethnic groups to explain the consistent dynamic of relationship between ethnicity and glycaemic control with time.

In Malaysia, one of the first large cross-sectional studies that was carried out involved 929 type 2 diabetes patients receiving diabetes care at nine public and private healthcare facilities, with and without specialist care (Ahmad, Khalid, Zaini, Hussain, & Quek, 2011). The study sought to examine the factors influencing glycaemic control in diabetes patients attending urban healthcare settings. The authors found that there is a

positive association between the glycaemic control level and the following factors: age more than 50 years, lowest level of education, low-income group, insulin use and ethnicity. They also found that Chinese and Indian patients have better glycaemic control compared to Malays; Chinese: OR (95% CI) = 0.283 (0.153–0.522); Indian: OR (95% CI) = 0.564 (0.343–0.927) (Ahmad et al., 2011). This study had shown evidence of ethnicity as a significant predictor for glycemic control. Besides, this study was conducted on patients who seek treatment from both public as well as private healthcare facilities, and, education and income groups have been found to be associated with glycemic control. However, due to cross-sectional design of this study, it has limit the temporality of this link. Nonetheless, it still has provided vital information on the predictors for glycemic control in Malaysia, including ethnicity.

Another study, which was conducted in seven different hospitals in Peninsular Malaysia involving 597 type 2 diabetes patients who were representative of the general Malaysian population, looked into the socio-demographic determinants of glycaemic control among young diabetes patients aged below 40 years old (Ismail, Wan Nazaimoon, et al., 2000). The study reported that glycaemic control is significantly different between ethnicities (F = 7.82, P <0.001) with a geometric mean (95% CI) of HbA1c among Chinese of 8.0 (5.6–10.4), among Malays of 8.8 (6.3–11.3) and among Indians of 8.5 (6.0–11.0). Ethnicity was also shown to have an independent effect on glycaemic control (F = 3.74, p = 0.02). The participants of this study represents diabetes patients who seek care in tertiary centre, with possible established diabetes complications and on insulin treatment where the glycemic control likely to be uncontrolled. Although, to the authors defence, insulin is initiated in patients due to poor glycemic control, and being the cause. The explanation by the authors that ethnicity was an independent risk factor for glycemic control because Chinese were proportionately more in some particular hospitals, with additional culture and genetic

factors contributing to it, as compared to Indians whom likely to be insulin resistance, hence having poor glycemic control, was not justifiable and warrant further studies.

Similarly, a cross-sectional study conducted in Penang, a state in the northern region of Malaysia, investigated the demographic and clinical characteristics of type 2 diabetes patients according to gender and race (Blebil et al., 2011). The study found that Malays and Indians have a higher mean HbA1c as compared to Chinese (mean HbA1c: Malay 8.4 ± 1.9, Indian 8.8 ± 2.0, Chinese 8.1 ± 1.8). However, the differences between these ethnic groups are not statistically significant. Also, the participants of this study do not represent the population as they all were diabetes patients attending a specialist (endocrine) clinic in only one tertiary hospital in Penang.

A study that was published in the same year analysed data from the National Diabetes Registry (NDR; formerly known as the Adult Diabetes Control and Management [ADCM] Registry) to determine whether there was a relationship between glycaemic control and diabetes-related complications and whether there were any associations with any particular ethnicities. However, its finding are limited to a certain extent because it was conducted as a nested cross-sectional study involving 53 health centres and 20,330 patients and it only considered the three major ethnic groups (Boon How Chew et al., 2011). Nevertheless, the findings of the study showed that the Chinese had better glycaemic control (mean HbA1c of 7.8% [$x^2 = 71.64$ ($P < 0.001$)]) compared to the Malays and Indians, and also suffered from diabetes complications as much as those Indians with the poorest glycaemic control (Chinese had the highest prevalence of retinopathy [$x^2 = 12.83$ ($P < 0.015$)] while Indians suffered more nephropathy [$x^2 = 168.76$ ($P < 0.001$)]). However, the strength of the association between ethnicity and glycaemic control was low as the results presented in terms of Chi-squared and the effect size was not reported.

Meanwhile, a descriptive study was performed in Sarawak where native groups are assumed together to be the predominant group. However, this diverse group was under-represented as the majority of the study population of 1,031 type 2 diabetes patients was Chinese and Malay (Wong & Rahimah, 2004). The study reported a mean HbA1c of 7.4 ± 1.6 with 28% of the patients achieving optimal glucose control (HbA1c < 6.5%). Nonetheless, no findings were reporting based on ethnic distribution.

The most recent study conducted in Malaysia was published in 2010 and covered a large adult (30 years and above) population (n = 7,683). The study was cross-sectional in design and sought to examine the association between different ethnic groups (Malay, Chinese, Indian, Indigenous Sarawak and Others) and the prevalence, awareness, and control of diabetes in Malaysia (Rampal et al., 2010). The findings of that study are consistent with those in the NHMS 2011 in terms of prevalence of diabetes (15.2% [95% CI 14.1–16.4]) and suggested that Indians are more likely to have diabetes (adjusted OR 1.54; 95% CI = 1.20, 1.98) compared to Malays and Chinese (adjusted OR 0.71; 95% CI = 0.56, 0.91). The study also showed that there is a significant association between the prevalence of diabetes and different ethnic groups with 25.1% among those treated for diabetes having good glycaemic control as defined by a fasting blood sugar level of < 5.6 mmol/L (Rampal et al., 2010). Therefore, the findings of in the study could serve as basis upon which to further investigate the relationship between ethnicity and glycaemic control. However, plausible explanations of the associations and temporality could not be ascertained from this study given the cross-sectional nature of its design.

The current study conducted for the purpose of this thesis will therefore add value due to its use of an established prospective database from the NDR that will allow better data collection and analysis of patients' clinical status. Furthermore, all the patients

received similar diabetes care from government health clinics, which permitted the researcher to control for confounding factors such as standard of care and socioeconomic status that might otherwise have affected glycaemic control.

2.6 The Role of BMI and Sex as Mediators in the Association between Ethnicity and Glycemic Control Among Type 2 Diabetes Patients.

There is, as yet, an absence of direct evidence on whether BMI or sex have a mediating effect on the association between ethnicity and glycaemic control. Many of the studies that have been carried out so far in this area have focused on the association between BMI, overweight and obesity and the incidence as well as the risk of diabetes. Also, the increasing volume of evidence on the link between sex or gender differences and the risk of complications in diabetes patients has not also considered the factor of ethnicity and rarely has the association between sex and glycaemic control been explored (Asnawi Abdullah, Peeters, de Courten, & Stoelwinder, 2010; Hsu, Araneta, Kanaya, Chiang, & Fujimoto, 2015; Huxley, Barzi, & Woodward, 2006; Kautzky-Willer, Harreiter, & Pacini, 2016; Menke, Casagrande, & Cowie, 2017; Staimez, Weber, Narayan, & Oza-Frank, 2013; C. Wang et al., 2015). Therefore, perhaps, given the mounting evidence that shows that the risk of diabetes-related complications is associated with gender differences, researchers may wish to consider incorporating a clear distribution of ethnicities and the issue of the association between sex and glycaemic control into future studies, the results of which would then contribute to finding a plausible explanation regarding the role or otherwise of BMI and sex as mediators in the progression of diabetes.

In this regard, a prospective cohort study was carried out in the UK to examine the association between ethnicity-specific obesity cut-off points and the incidence of diabetes among 1,356 Europeans, 842 South Asians and 335 African Caribbeans (Tillin et al., 2015). The study reported that South Asians and African Caribbeans, at a lower BMI cut-off point (25.2 kg/m^2 [23.4, 26.6] for South Asians and 27.2 kg/m^2 [25.2, 28.6] for African Caribbeans) face the equivalent risk of becoming diabetic as Europeans with a BMI of 30 kg/m^2. This study was correct in explaining the temporal relationship between BMI and the incidence of diabetes. Hence, the findings of the study could also imply that BMI potentially plays a role in mediating the association between ethnicity and glycaemic control.

A study conducted in the US among non-Hispanic White, non-Hispanic Black and Mexican American adults with type 2 diabetes by using data from National Health and Nutritional Examination Surveys for the period 2005-2010 (N = 2,910) looked into the association between the clustering of cardiometabolic risk factors and the risk of an elevated HbA1c level (Okosun, Annor, Dawodu, & Eriksen, 2014). The results of the multivariable analysis for that study showed that abdominal obesity is independently associated with increased odds of elevated HbA1c (non-Hispanic Whites: OR 1.9 [95% CI: 1.5–2.6]; Mexican Americans: OR 2.4 [95% CI: 1.4–4.2]; non-Hispanic Blacks: OR 2.7 [1.7–4.1]). The study also showed that the clustering of abdominal obesity, high blood pressure, and elevated triglycerides are positively associated with elevated HbA1c among non-Hispanic Blacks and Mexican Americans (Okosun et al., 2014). The authors recognized the limitations of this study, including the fact that it was cross-sectional in design, and that hence it was not able to establish a temporal relationship between abdominal obesity and elevated HbA1c, or the actual impact on glycaemic control.

The study by Okosun et al. (2014) supported the results of an earlier cross-sectional study on the different levels of HbA1c in identifying more cardiovascular and metabolic risk profiles among the Chinese population in China with normal OGTT (Peng et al., 2013) that revealed that subjects with normal OGTT but with an elevated HbA1c level of ≥ 6.5% have more cardiovascular risk factors including obesity and abdominal obesity. However, similarly, this previous study was also not able to explain whether there is a temporal link between obesity and abdominal obesity with elevated HbA1c.

Although the two studies discussed above did not specifically focus on obesity, their results suggest that BMI might play a role in determining glycaemic control and that there could be a possible relation with ethnicity. Hence, a more in-depth exploration on the association between ethnicity, BMI, and glycaemic control is needed, given the beneficial outcome of a reduced BMI in targeted interventions for the prevention of complications.

A more recent study in the US that used data from the US Physician Health Records for the period 2009–2011 looked into the issue of obesity and glycaemic control in diabetic adults in the US (Bae, Lage, Mo, Nelson, & Hoogwerf, 2016). The study revealed that there is an association between being overweight and being obese (across all classes) and having higher odds of poor glycaemic control, as defined by a HbA1c of ≤ 7%, than those with a normal BMI. The study also showed that African Americans have higher odds of poor glycaemic control as compared to Caucasians (Bae et al., 2016). However, this study did not discuss the association between BMI and glycaemic control according to ethnic distribution, so the role of ethnicity as a contributing factor in the association remains unclear.

Turning to the role of sex as a mediator, to date, a limited number of studies have investigated the association between gender differences and glycaemic control including the mediating effect of sex on glycaemic control among different ethnicities. However, among the few that do exist, a very recent retrospective cohort study that was conducted in Korea looked into gender differences in glycaemic control among newly diagnosed diabetes patients (n = 2,253) who were being treated in primary care clinics and who had completed 1 year of OHA treatment (Choe, Kim, Ro, & Cho, 2018). The study reported that, compared to men, women have a significantly lower baseline mean HbA1c at 8.2 ± 1.6 (baseline mean HbA1c for men = 8.3 ± 1.7, p-value 0.041), lower odds of achieving the targeted HbA1c of < 6.5% (OR 0.70 [95% CI 0.55, 0.90]) and a significantly lower proportion of them achieved the targeted HbA1c after 1 year of diabetes management (38.9% vs. 40.6%). There were no significant differences between men and women concerning diabetes management reported in the study. In light of their results, the authors suggested the need for sex-specific diabetes management, further exploration of socio-behavioural determinants and changes in diabetes medication regimes given that women are also more likely to suffer worse complications than men. Therefore, the study highlighted the importance of sex in diabetes management and its role in mediating the effect of glycaemic control.

Another recent study, this time in the US, that looked into the socioeconomic status and glycaemic control among type 2 diabetes patients, also found evidence in support of the association between sex and glycaemic control (Assari, Moghani Lankarani, Piette, & Aikens, 2017). The study found that being female is associated with changes in HbA1c (β = -0.44 [95% CI -3.00, 0.32], p-value 0.016). Meanwhile, age, socioeconomic status, and national insurance are the contributing factors associated with changes in HbA1c among Black men (Assari et al., 2017). The authors suggested tailoring diabetes interventions according to sex and race due to the consistency

between the findings of their study and those of previous studies (Assari et al., 2017). However, their study was cross-sectional and involved a small sample of 112 diabetes patients whose treatment was limited to only insulin. Hence, the results of cannot be generalized to the whole population.

A larger cross-sectional study conducted in Spain that looked into sex and age differences in the achievement of glycaemic control among 32,638 diabetes patients in primary care settings (Cambra et al., 2016) found that, compared to men, a significantly lower proportion of women (59% vs. 61%) meet the targeted HbA1c of less than 7%. Women also have higher odds of poor glycaemic control (OR 1.13 [95% CI 1.04, 1.24]). In addition, a significantly lower proportion of women compared to men (14% vs. 18%) meet composite triple targets (HbA1c < 7%, blood pressure < 140/90 mmHg, LDL < 100 mg/dl). The authors hypothesized that the inequalities of glycaemic control between men and women are due to higher diabetes-related cardiovascular risks among women, as suggested in previous studies (Huxley et al., 2006; Peters, Huxley, Sattar, & Woodward, 2015). Sex is proved to have a role in predicting glycaemic control. Therefore, the authors suggested reducing sex inequalities to achieve improved glycaemic control.

Nevertheless, an earlier study that examined gender differences in glycaemic control by analysing patient-level pooled data from six randomized controlled studies revealed that, compared to men, women experienced a lesser reduction in HbA1c over time (-1.22 vs. -1.36, p-value = 0.002) (Kautzky‐Willer, Kosi, Lin, & Mihaljevic, 2015). Also, the proportion of men who achieved the targeted HbA1c of less than 7% was significantly higher than that of women (33% vs. 26.5%, p-value <0.001). Moreover, regardless of BMI level, women still had a significantly higher HbA1c at the end of the study, thereby emphasizing the effect of gender (Kautzky‐Willer et al., 2015). The

authors hypothesized that women do not respond in the same way as men to diabetes treatment, specifically insulin, because the analysed studies also investigated the efficacy of insulin treatment. Hence, the review study suggested that gender plays an essential role in glycaemic control and therefore treatment needs to be carefully monitored and individualized, especially among women in order to prevent diabetes complications.

However, the role of sex in mediating the effect of diabetes treatment among different ethnicities remains unclear as the review study did not discuss changes in the HbA1c level over time according to ethnicity.

2.7 Ethnicity, Diabetes-related Complications, All-Cause Mortality and Diabetes-Related Mortality.

The increasing burden of diabetes in the past decades has led to a 9% increase in the mortality rate from Year 1990 to 2013(Abubakar, Tillmann, & Banerjee, 2015). Moreover, diabetes-related mortality is projected to continue to increase to become the seventh leading cause of death globally by 2030 when it is expected to account for 3% of total deaths compared to 2.7% in 2012 (Mathers & Loncar, 2006; WHO, 2015).

A systematic review and meta-analysis of 35 studies with 220,689 patients and mean follow up of 10.7 years, showed that diabetes increases mortality twofold, with macrovascular complications as the predominant cause (RR = 1.76 [95% CI 1.66–1.88] for cardiovascular mortality and RR = 2.26 [95% CI 1.7–3.02] for stroke) (Chukwuemeka Nwaneri, 2013). This review proved that type 2 diabetes is associated with an indisputible increase in mortality risk regardless of the age at diagnosis comparing to the general population. This study had also portray the varying independent predictors including gender, smoking, hypertension, peripheral vascular disease and duration of diabetes, as well as cause-specific mortalities that includes

cardiovascular disease, cerebrovascular accident, stroke, diabetes retinopathy and diabetes nephropathy. Hence, the authors suggested for further primary research to take place as to appreciate the clinical benefits of pro-active management of these micro- and macrovascular complications given the mounting evidence on control of complications with appropriate interventions could reduce mortality among diabetes patients.

The UK Prospective Diabetes Study (UKPDS) 83 showed that, compared to White Caucasians, Asian Indians are at higher risk (RR = 1.18, 95% CI 1.07–1.29) for any diabetes-related end point including death, but are at lower risk for all-cause mortality (RR = 0.89, 95% CI 0.80–0.97), while African Caribbeans are at lower risk for all-cause mortality (RR = 0.84, 95% CI 0.76–0.93) and diabetes-related death (RR = 0.75, 95% CI 0.64–0.88) (Davis, Coleman, & Holman, 2014). Evidence that supports an association between differences in the risk of coronary heart disease and the HbA1c level among African American and White diabetes patients has also been published (Zhao et al., 2013). The study revealed that, in contrast to African Americans, in low socioeconomic settings Whites had a prominent graded positive association between the risk of developing coronary heart disease and their HbA1c at baseline and their mean level of HbA1c in all of the six years of follow-ups.

A study that was conducted to examine the survival of 12,466 diabetes patients from seven ethnic groups in Australia over 25 years found that ethnicity is a significant determinant for survival of diabetes patients (Alharbi et al., 2015). The Chinese have the lowest hazard ratio for death (HR = 0.4, 95% CI: 0.4–0.5) compared to Indigenous Australians who have the highest (HR = 2.3, 95% CI 1.7–3.0). The reason given for the differences is the different CVD risk factors among these ethnic groups. Indigenous Australians have a higher prevalence of albuminuria and poor glycaemic control compared to Chinese (Alharbi et al., 2015). Therefore, the authors suggested that the

risk of complications is different according to ethnic group and that this might be explained by disparities in glycaemic control.

Previous studies have also indicated that there may be some evidence of a relation between increased risk of complications and poor glycaemic control. For instance, UKPDS 35 provided evidence of a direct relationship between the risk of diabetes-related complications and glycaemic control over time and that the rate of increased risk of microvascular complications is more considerable than that of macrovascular diseases (Stratton et al., 2000). Furthermore, a meta-analysis of 102 prospective studies showed that even diabetes alone leads to a twofold increased risk of developing macrovascular complications, with an interaction of age and sex as the hazard of developing coronary heart disease were higher in women than in men, at 40–59 years than at 70 years and older [Adjusted HRs with diabetes: 2.00 (95% CI 1.83, 2.19) for coronary heart disease; 2.27 (95% CI 1.95, 2.65) for ischaemic stroke; 1.56 (95% CI 1.19, 2.05) for haemorrhagic stroke; 1.84 (95% CI 1.59, 2.13) for unclassified stroke; and 1.73 (95% CI 1.51, 1.98) for the aggregate of other vascular deaths] (Emerging Risk Factors, 2010). However, the justification for whether ethnicity modifies the association between glycaemic control and risk of complications is unclear in these studies.

In Malaysia, a study using 2009 data from the NDR looked into diabetes-related complications profiles and the associated factors among adults with type 2 diabetes (B. H. Chew et al., 2015). The authors found that Chinese have a higher proportion of microvascular and macrovascular complications compared to the other population groups. However, the multivariablee analysis conducted for that study revealed that Malays have higher odds of microvascular complications (OR, 95% CI, 1.21 [1.07–1.38], p = 0.003) while Chinese have 28% lower odds of having macrovascular complications (OR, 95% CI, 0.72 [0.54–0.97], p = 0.03) compared to Indians. In

addition, a HbA1c level of > 6.5% is also associated with microvascular complications (OR, 95% CI, 1.14 [1.01–1.28], p = 0.03) (B. H. Chew et al., 2015). The study employed a cross-sectional design, which limits the temporal aspect of its analysis. However, it is the only study in Malaysia that has considered ethnicity as one of the associated factors. The information it provides is thus notable. Nevertheless, currently, there is continued evidence on different rates of diabetes-related complications between Asian populations and ethnicities from other different continents.

A systematic review consisted of 51 studies conducted mainly in the US and the UK that examined the prevalence of complications and mortality among different ethnic groups with diabetes revealed that ethnic minorities experience a higher risk of complications and mortality rates (Lanting, Joung, Mackenbach, Lamberts, & Bootsma, 2005). Moreover, the study found that the US Blacks and Hispanics have an increased risk of end stage renal disease (ESRD) and retinopathy, while the UK Asians have a higher risk of ESRD alone (Lanting et al., 2005) after adjustment for risk factors that include smoking, socioeconomic status, income, years of education, and BMI where in most occasions, ethnic differences disappear. Intermediate outcomes of care or process care were seen to be worse amongst Blacks, and outcomes among Hispanics were also leaning to the worse side. This review suggested ethnic differences were due to diabetes quality of care as some diabetes complications persisted after adjustment of risk factors other than diabetes care. This could contribute to worse diabetes outcome among ethnic minorities and the results do implicate the importance of quality of care in striving for equal health outcomes among ethnic minorities, although generalizations could not be made for all complications among all ethnic groups in all regions due to the diversity in risks of the several diabetes complications in ethnic groups, combined with the different results for the US and the UK.

Another recent systematic review of randomized controlled trials (RCTs) on lowering blood glucose sought to examine the differences in the incidence of vascular complications and mortality between Western and Asian patients with type 2 diabetes (Li, Dong, Wu, & Tong, 2016). The systematic review included two large multicentre RCTs with 19,439 patients with advanced diabetes that were eligible for analysis. This review aimed to compare the effects of intensive and standard glycaemic control on CVD outcomes (namely, The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study and The Action in Diabetes and Vascular Disease: Pretext and Diamicron MR Controlled Evaluation (ADVANCE) trial). Patients were divided into those of Western (including Australia and New Zealand) and Asian ethnicities.

The study reported that Westerners (including Australians and New Zealanders) have significantly higher rates of all-cause mortality, cardiovascular death, and major coronary events (defined as death due to coronary heart disease and non-fatal myocardial infarction), whereas the incidence of major cerebrovascular events (defined as death due to cerebrovascular disease or non-fatal stroke and not including peripheral neuropathy) and microvascular events (including new or worsening nephropathy and retinopathy) is significantly higher among Asians (Li et al., 2016). The authors suggested that glycaemic control is more important among Asians as there is significantly higher incidence of microvascular complications after excluding differences in treatment strategy and glucose control in the RCTs included in this analysis. This study also emphasized on Asians should be monitored and managed more closely for cerebrovascular and microvascular events as Asians patients might be more susceptible to hyperglycemia impairment.

However, a prospective cohort study on 64,211 diabetes patients conducted to examine the heterogeneity of diabetes outcomes among Asians and Pacific Islanders in the US revealed different findings (Kanaya et al., 2011). The study suggested that the incidence of complications varied considerably among the Asian subgroups (Kanaya et al., 2011). For instance, Pacific Islander women have the highest incidence of myocardial infarction (MI), while the rest of the other ethnic groups have lower rates of MI than Whites. However, most non-white groups have higher rates of end stage renal disease (ESRD). On the other hand, Asians have a 60% lower incidence of lower extremity amputation compared to Whites, African Americans and Pacific Islanders and the incidence rates for most of the other complications are similar among Chinese, Japanese and Filipinos.

A longitudinal cohort study that examined the prevalence of diabetes-related complications in regards to CVD and diabetic nephropathy, and the subsequent risk of mortality in 429,918 members of the elderly population in the national healthcare system of the US, and who were from various ethnic groups, showed that there are statistically significant racial differences (Young, Maynard, & Boyko, 2003). For example, Asians are more likely to develop diabetes-related ESRD (adjusted OR = 1.8 [95% CI 1.5–2.1]) compared to Caucasians, but have lower odds of developing CVD (adjusted OR = 0.67 [95% CI 0.61–0.74]). However, the relative risk of 18-month mortality among Asians is similar to that of Caucasians (RR = 0.88 [95% CI 0.72–1.09]) (Young et al., 2003). These findings suggest that ethnic differences and age have an impact on the incidence of macrovascular and microvascular complications as well as on mortality that might be partially explained by glycaemic control.

In addition, a small retrospective cohort study of 1,684 diabetes patients in the UK, which included 45 patients already diagnosed with renal impairment or diabetic nephropathy, found that the decline in renal function is greater in Indo-Asians (Indian, Pakistani, and Bangladeshi) based on an estimated rate of increase in creatinine, with a two to threefold increase in the mean compared to African Caribbeans and Caucasians (β mean [95% CI]; Indo-Asian: 5.36 [2.21–8.52]; African Caribbean 3.14 [0.82–5.46]; Caucasian 2.22 [1.31–3.14], p = 0.035) (Earle, Porter, Ostberg, & Yudkin, 2001). These findings imply that there is not only an association between ethnicity and diabetes-related complications, but also the progress of the disease as this varied between ethnic groups, hence this aspect warrants further attention.

A cross-sectional study that investigated whether ethnicity modifies the association between diabetes and IHD and that involved 5,707 Chinese, Indian, and Malay adults in Singapore showed that the diabetes-related population-attributable risk of IHD is highest among Indians (40.9%), followed by Malays (27.9%) and then Chinese (11%) (Yeo et al., 2006). Also, a study entitled 'Diabetic Retinopathy in Various Ethnic groups in the UK' (DRIVE UK) found that South Asian type 2 diabetes patients have a significantly higher prevalence of diabetic retinopathy at 42.3% and sight-threatening diabetic retinopathy at 10.3% compared to White Europeans (38% and 5.5%, respectively) (Sivaprasad et al., 2012).

However, these studies were cross-sectional in design, and there was an absence of discussion on the association between the HbA1c level or glycaemic control and the incidence of diabetes-related complications. Nonetheless, the findings of these studies demonstrate the possibility of ethnic variation in the risk of developing diabetes-related complications.

At the time of writing, the most recent cross-sectional study on the influence of ethnicity on cardiovascular outcomes and complications among type 2 diabetes patients was conducted in Australia (Kou et al., 2017). The study found that South Asians have higher rates of non-ST elevation MI compared to Caucasians (STEMI, 21.7%, p = 0.05), while East-Southeast Asians have higher rates of nephropathy (59%, p = 0.05), but male East-Southeast Asians have fewer CVDs compared to Caucasians. In addition, the study showed that peripheral vascular disease is common among Caucasians (20%, p = 0.05). However, the study also showed that South Asians experience more cardiovascular complications than Caucasians. Consequently, the authors hypothesized that ethnicity independently predicts NSTEMI among East-Southeast Asians and retinopathy in South Asians and Pacific Islanders. The authors also suggested that consideration should be given to these differences during clinical decisions about investigation and management.

A much earlier study in Singapore showed that, compared to Malays and Chinese, Indians have the highest rate of coronary heart disease (C. E. Tan et al., 1999). The study posited that the different rates are due to Indians having the highest prevalence of diabetes. Moreover, the study stated that Indians also have the highest prevalence of hypertension, a significantly lower level of high-density lipoprotein (1.03 ± 0.14 in men and 1.24 ± 0.17 in women, $P = 0.0001$), significantly higher BMI (23.59 ± 2.82 kg/m^2 in men and 23.68 ± 2.84 kg/m^2 in women) and a higherwaist-hip ratio (0.85 ± 0.04 in men and 0.73 ± 0.04 in women) compared to Malay and Chinese (C. E. Tan et al., 1999). Also, the risk factors of obesity, hypertension, dyslipidemia, and smoking for non-communicable diseases were more predominant in Indians compared to the other ethnic groups.

The most recently published cohort study in Singapore looked into the longitudinal trend of HbA1c and its association with long-term diabetes outcomes, including co-morbidities and all-cause mortality, in multi-ethnic Asians living in the country (Low et al., 2016). The findings revealed that there is a significant association between AMI and diabetes among Malays and Indians with HRs of 2.81 (95% CI 1.81–4.37) and 2.03 (95% CI, 1.15–3.59), respectively. In addition, Malays and Indians made up the majority of the moderate-increase group (2.9%) for the HbA1c pattern, where the risk of co-morbidities and death was significantly higher and the hazard ratios for stroke, ESRD and death were 3.22 (95% CI, 1.27–8.15), 4.76 (95% CI, 1.92–11.83) and 1.88 (95%CI, 1.15–3.07), respectively.

Table 2.1: Evidence Of Association Between Ethnicity, Glycemic Control, Diabetes-Related Complications, BMI and Sex

Country	Author (Year)	Study Design	Main Objective	Sample Size (N)	Setting	Main Outcome
Malaysia	Ahmad et al. (2011)	Cross-sectional	To elucidate influencing factors of HbA1C in various health care settings	929 diabetes patients	Primary care, hospital outpatient departments and specialist diabetes clinics from public and private healthcare facilities	Factors significantly associated with HbA1C include age group (p = 0.000), household income (p = 0.045), education level (p = 0.001) and insulin user (p = 0.000). The multivariate analysis showed three factors namely insulin usage (OR = 3.856; 95% CI 2.445–6.083), medication (OR = 2.013; 95% CI: 1.021–3.968) and ethnicity (Chinese: OR = 0.283; 95% CI: 0.153–0.522; Indians: OR = 0.564; 95% CI: 0.343–0.927 and others: OR = 0.413, 95% CI: 0.052–3.266 as compared to Malays) are significantly predictive of HbA1C control.
Singapore	Tan et al. (2015)	Retrospective Cohort Study	To determine the risk factors associated with glycaemic control of ambulatory patients with type 2 diabetes mellitus (T2DM) who are managed in primary care	1256 diabetes patients	Data was retrieved from a primary care site within the Singapore Consortium of Cohort Studies-Diabetes Cohort (SCCS-DC)	Mean HbA1c decreased by <0.1% in the initial 3 years, but increased thereafter. Compared with Chinese patients, Malays had higher HbA1c (+0.3%), Indians (+0.3%), and others (+0.2%), (all p < 0.01). Patients with retinopathy had higher HbA1c (+0.2%) and those with cataract had lower mean HbA1c (0.2%) (p < 0.01).
US	Egede et al. (2010)	Retrospective Cohort Study	To examine longitudinal differences in glycemic control between non-Hispanic white and non-Hispanic black veterans with type 2 diabetes	8813 veterans with type 2 diabetes	Veteran Affairs Facility in Southeastern United States	The final model adjusted for time, and relevant confounders showed Non Hispanic Blacks have poor glycemic control compared with Non Hispanic Whites (OR: 1.8, 95% CI, 1.7; 2.0, *P* 0.0001).

Table 2.2: Cont, Evidence Of Association Between Ethnicity, Glycemic Control, Diabetes-Related Complications, BMI and Sex

Country	Author (Year)	Study Design	Main Objective	Sample Size (N)	Setting	Main Outcome
US	Heidemann et al. (2016)	Retrospective Cohort Study	To determine race as an independent risk factor for glycemic control among diabetic patients in a large primary care patient population.	25,123 diabetes patients	264,000 primary care patients at large, urban academic medical center to identify patients with a diagnosis of diabetes	Race had an independent association with diabetes prevalence and glycemic control. White patients had a lower average A1c level and a lower prevalence of diabetes than Black patients in all income quartiles (P<.001). Among White patients, the prevalence of uncontrolled diabetes (P<.001), and A1c level (P=.014) were inversely proportional to income level. No significant difference in the prevalence of diabetes (P=.214), A1c level (P=.282), or uncontrolled diabetes related to income was seen in Black patients (P=.094).
Sweden	Rawshani et al. (2015)	Retrospective Cohort Study	To study the effect of ethnicity on glycemic control in a large cohort of patients with type 2 diabetes.	131 935 patients (with 713 495 appointments), representing 10 ethnic groups, who were followed up to 10 years.	Nationwide data (mainly from primary care) from the Swedish National Diabetes Register (2002–2011) to identify patients with newly diagnosed (within 12 months) type 2 diabetes.	South Asians were predicted to have a HbA1c level of between 1.9–4.2 mmol/L among persons on diet, lifestyle modifications and oral hypoglycaemic agents, and had higher odds of not achieving good glycaemic control or experiencing therapy failure during the second year after diagnosis of diabetes (OR = 2.11 [95% CI 1.35, 3.29]) compared to natives Swedes.
UK	Tillin et al. (2015)	Prospective Cohort Study	To identify equivalent ethnicity-specific obesity cut-points for the estimation of diabetes risk	1356 Europeans, 842 South Asians, 335 African-Caribbeans	Population-based cohort from London, UK	South Asians and African Caribbeans, at a lower BMI cut-off point (25.2 kg/m^2 [23.4, 26.6] for South Asians and 27.2 kg/m^2 [25.2, 28.6] for African Caribbeans) face the equivalent risk of becoming diabetic as Europeans with a BMI of 30 kg/m^2.

Table 2.3: Cont, Evidence Of Association Between Ethnicity, Glycemic Control, Diabetes-Related Complications, BMI and Sex

Country	Author (Year)	Study Design	Main Objective	Sample Size (N)	Setting	Main Outcome
US	Lopez et al. (2014)	Cross-sectional design	To characterize Type 2 Diabetes burden, from a patient perspective, with respect to age and race/ethnicity.	682 patients	Internet-based, nationwide survey	The study observed significant association between glycaemic control and medication adherence by ethnicity, where American Indians have a significantly higher percentage of good glycaemic control (defined as HbA1c level < 7%) at 43% compared to Asian Americans (30.4%), African Americans (26.1%) and Hispanic Americans (24.4%; $P = 0.04$). The association between glycemic control and medication adherence is not significant among Whites (38%; $P = 0.276$)
Spain	Cambra et al. (2016)	Cross-sectional design	To determine the degree to which control targets of glycaemia and cardiovascular risk factors were achieved among patients with type 2 diabetes and to investigate sex- and age-related differences in this population.	32,638 cases	Electronic clinical primary care records	Compared to men, a significantly lower proportion of women (59% vs. 61%) meet the targeted HbA1c of less than 7%. Women have higher odds of poor glycaemic control (OR 1.13 [95% CI 1.04, 1.24]). A significantly lower proportion of women compared to men (14% vs. 18%) meet composite triple targets (HbA1c < 7%, blood pressure < 140/90 mmHg, LDL < 100 mg/dl).
Korea	Choe et al. (2018)	Retrospective cohort study	To examine differences in the achievement of glycemic control among newly diagnosed type 2 diabetes patients according to gender	2,253 patients	36 primary care clinics	Women have a significantly lower baseline mean HbA1c at 8.2 ± 1.6 (baseline mean HbA1c for men = 8.3 ± 1.7, p-value 0.041), lower odds of achieving the targeted HbA1c of < 6.5% (OR 0.70 [95% CI 0.55, 0.90]) and a significantly lower proportion achieving the targeted HbA1c after 1 year of diabetes management (38.9% vs. 40.6%). There were no significant differences between men and women concerning diabetes management reported in the study.

Table 2.4: Cont, Evidence Of Association Between Ethnicity, Glycemic Control, Diabetes-Related Complications, BMI and Sex

Country	Author (Year)	Study Design	Main Objective	Sample Size (N)	Setting	Main Outcome
US	Okosun et al. (2014)	Cross-sectional	To determine which cardiometabolic risk factors and clusters of cardiometabolic risk factors that are mostly associated with elevated HbA1c in non-Hispanic White (NHW), non-Hispanic Black (NHB) and Mexican-American (MA) adults who have type 2 diabetes.	2910, from the United States National Health and Nutritional Examination Surveys	Adults 18 years and older who have diagnosed and undiagnosed diabetes, without cardiovascular, periodontal and kidney disease	Abdominal obesity is independently associated with increased odds of elevated HbA1c (non-Hispanic Whites: OR 1.9 [95% CI: 1.5–2.6]; Mexican Americans: OR 2.4 [95% CI: 1.4–4.2]; non-Hispanic Blacks: OR 2.7 [1.7–4.1]).
Austria	Kautzky et al. (2015)	Patient-level pooled data of six Randomized Controlled Trials	To determine the impact of gender on glycaemic control and hypoglycaemia in insulin-naive patients with type 2 diabetes (T2DM)	Female= 1251 Male=1349	Data were pooled from six randomized clinical trials of insulin glargine or NPH insulin in insulin-naïve, inadequately controlled patients.	Women experienced a lesser reduction in HbA1c over time (-1.22 vs. -1.36, p-value = 0.002). The proportion of men who achieved the targeted HbA1c of less than 7% was significantly higher than that of women (33% vs. 26.5%, p-value <0.001). Regardless of BMI level, women had a significantly higher HbA1c at the end of the study, emphasizing the effect of gender.

Table 2.5: Cont, Evidence Of Association Between Ethnicity, Glycemic Control, Diabetes-Related Complications, BMI and Sex

Country	Author (Year)	Study Design	Main Objective	Sample Size (N)	Setting	Main Outcome
Singapore	Low et al. (2017)	Retrospective Cohort Study	To examine longitudinal trends in HbA1c in a multi-ethnic Asian cohort of diabetes patients, and the associations of these trends with future risk of acute myocardial infarction (AMI), stroke, end stage renal failure (ESRD) and all-cause mortality	6079 type 2 diabetes patients	National Disease Registry Singapore	There is a significant association between AMI and diabetes among Malays and Indians with HRs of 2.81 (95% CI 1.81–4.37) and 2.03 (95% CI, 1.15–3.59), respectively. In addition, Malays and Indians made up the majority of the moderate-increase group (2.9%) for the HbA1c pattern, where the risk of co-morbidities and death was significantly higher and the hazard ratios for stroke, ESRD and death were 3.22 (95% CI, 1.27–8.15), 4.76 (95% CI, 1.92–11.83) and 1.88 (95%CI, 1.15–3.07), respectively.
Australia	Kou et al. (2017)	Cross-sectional	To determine whether cardiovascular outcomes in type 2 diabetes (T2D) differ according to ethnicity, and whether ethnicity influences the effect of gender on these outcomes in Caucasians, East-Southeast-Asians, Middle-Easterners, South-Asians and Pacific-Islanders.	204 diabetes patients	Patients attending diabetes clinic at Westmead Hospital between from April to October 2015.	South Asians have higher rates of non-ST elevation MI compared to Caucasians (STEMI, 21.7%, p = 0.05), while East-Southeast Asians have higher rates of nephropathy (59%, p = 0.05), but male East-Southeast Asians have fewer CVDs compared to Caucasians. Peripheral vascular disease is common among Caucasians (20%, p = 0.05). South Asians experience more cardiovascular complications than Caucasians. Ethnicity independently predicts NSTEMI among East-Southeast Asians and retinopathy in South Asians and Pacific Islanders.

Table 2.6: Cont, Evidence Of Association Between Ethnicity, Glycemic Control, Diabetes-Related Complications, BMI and Sex

Country	Author (Year)	Study Design	Main Objective	Sample Size (N)	Setting	Main Outcome
US	Bae et al. (2016)	Retrospective cohort study	To examine the association between obesity and glycemic control among patients with type 2 diabetes mellitus	248,567 type 2 diabetes patients	US Physician Electronic Health Records 2009-2011	There is an association between being overweight and being obese (across all classes) and having higher odds of poor glycaemic control, as defined by a HbA1c of ≤ 7%, than those with a normal BMI. The study showed African Americans have higher odds of poor glycaemic control as compared to Caucasians.
China	Peng et al. (2013)	Cross-sectional survey	To investigate the significance of hemoglobin A1c (HbA1c) in cardiovascular and metabolic risk stratification among diabetes and non-diabetes in southern Chinese	6,540 participants	General population from 17 villages in Southern China	Patients with HbA1c ≥ 6.5% had higher body weight, waist circumference, waist-hip ratio, and higher concentration of total cholesterol, triglyceride, fasting plasma glucose, 2-hour post prandial and HbA1c.

CHAPTER 3: METHODOLOGY

3.1 Chapter Introduction

This chapter describes the methodology of the study. The first section focuses on the study design. The second section focuses on the data source, which is the National Diabetes Registry (NDR), the study population, the sampling method, and the study variables. The third section encompasses the data collection and data management procedures. The last section describes the statistical analyses used for this study.

3.2 Study design

A registry-based retrospective cohort study of type 2 diabetes patients managed in government primary healthcare clinics between the year 2011 and 2015.

3.3 Data Sources

The data used for this study was obtained from the NDR of the Ministry of Health (MOH) Malaysia.

In Malaysia, the primary healthcare is divided into public and private sectors. The public primary healthcare is a two-tier system that consists of health clinics (lead by either a Family Medicine Specialist or a Senior Medical Officer) and community clinics (lead by a community nurse) (WHO, 2013). The public sectors are a government-led and funded by the government of Malaysia while the private sector is regulated under the Private Health Care Facilities and Services Act 1998 where the Act requires the private practitioners to apply for a license from the MOH to practice and operate the medical clinics as to meet the basic standards (WHO, 2013). Out-of-pocket payments account for a majority of the financing source for the private sector besides employers through private insurers or group managed care scheme (World Health, 2014).

As of 2015, there were 1,061 health clinics in the public or government primary healthcare and 7,146 medical clinics in the private sector all over Malaysia (Malaysia, 2016). In Malaysia, only diabetes patients who are followed up in government health clinics under the MOH are registered with the NDR (the health clinics participating in the NDR are listed in Appendix A). From January 2011 to December 2015, there were 717 registered health clinics (refer to Appendix A) in the NDR (67.6% of all health clinics under the MOH) (Malaysia, 2011-2015).

Hence, the NDR only consist of diabetes patients who seek treatment in the public primary healthcare. Some of the government health clinics are still not registered with the NDR and NDR does not include patients attending follow up in private healthcare facilities and majority of hospitals in Malaysia (Feisul, 2013). This will explain the level of extensiveness of the data on diabetes patients in Malaysia. However, the National Health and Morbidity Survey in 2011 reported around 80% of all diabetic patients seek treatment in MOH healthcare facilities that include both MOH health clinics (56%) and MOH hospitals (24%), whereas the rests had chose private clinics and hospitals as the usual place for treatment (NHMS, 2011). Hospital admissions and diagnosis related to in-patient treatment would tend to be missing unless the information is recorded in the patients' profile in the health clinic. The variables on diagnosis of ischemic heart disease and cerebrovascular disease during hospital admissions are available in the NDR and is expected to be updated during patients' follow up.

The NDR was initiated in 2009, and it became a web-based registry in 2011. It was developed for the primary purpose of monitoring the achievement of targets and the clinical outcomes of diabetes patients registered in the NDR. Patient data is regularly updated at least annually in terms of clinical investigation results (HbA1c level, random blood sugar, fasting blood sugar, 2-hour post-prandial, serum creatinine, and fasting

serum lipid), clinical examinations (screening for complications of diabetes and cardiovascular risk factors i.e. blood pressure, BMI, smoking status, ECG, funduscopic examination, foot examination and erectile dysfunction screening), treatments, complications and comorbidities. The registration of diabetes patients is performed by the healthcare staff in the specified health clinic that the patients are attending for follow-up.

The NDR consists of two components: a Diabetes Registry Section and a Diabetes Clinical Audit Section. The Diabetes Registry Section contains records on, for example, smoking status, complications, and patient outcomes such as transfer out to other facilities, loss to follow-up, and death. These records are available and updated throughout the year.

Meanwhile, the Clinical Audit Section, which is a subset of the Diabetes Registry Section, contains full sets of clinical variables including demographics, clinical investigation results, treatments for diabetes and comorbidities, comorbidities at diagnosis and incidence of comorbidities as well as diabetes-related complications at diagnosis and incidence of complications. These records are updated accordingly when the patients randomly sampled for the diabetes clinical audit, are audited. A diabetes clinical audit is conducted at least once a year.

The study population for this study was the dataset from the Clinical Audit Section. Table 3.1 provides the overview on the variables that are available in the patient registry section and patient clinical audit section.

Table 3.1: Variables in the Diabetes Registry Section and Diabetes Clinical Audit Section

No.	Section of National Diabetes Registry	Variables
1.	Diabetes Registry Section	i. Health facility, name of patient and identification number ii. Demographics i.e. date of birth, age group, sex and ethnic group iii. Diabetes characteristics including age at diagnosis, date of diagnosis and duration iv. Concomitant comorbidities at diagnosis of diabetes (hypertension and dyslipidaemia) v. Complications at diagnosis of diabetes and incidence (i.e. diabetic foot ulcer, diabetic retinopathy, diabetic nephropathy, amputation, ischaemic heart disease and cerebrovascular disease) vi. Smoking status vii. Follow-up status (i.e. active follow-up, lost to follow-up, date of last visit, date of death, cause of death)
2.	Diabetes Clinical Audit Section	As above and: i. Clinical results with date of each blood investigation performed (i.e. random blood sugar, fasting blood sugar, 2-hour post-prandial, HbA1c, height, weight, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, lipid profile, creatinine level). ii. Screening for complications with date of each examination performed (i.e. foot examination, funduscopic examination, ECG, proteinuria, microalbuminuria, erectile dysfunction Screening). iii. Medications for diabetes (OHA and Insulin), hypertension (ACE inhibitors, beta blockers, calcium channel blockers, diuretics and others), dyslipidaemia (statins and fibrates) and antiplatelet medications (aspirin and ticlopidine). iv. Incidence of comorbidities and date of diagnosis.

3.3.1 Diabetes clinical audit at Ministry of Health (MOH) healthcare facilities

3.3.1.1 Scope of the diabetes clinical audit

A diabetes clinical audit is conducted every year between 1 and 31 August in all districts in Malaysia at all MOH health clinics that provide diabetes treatment and management services. To date, all health clinics registered in the NDR (refer to Appendix A) have been involved in this auditing process.

The diabetes clinical audit involves auditing the diabetes management records that are stored in the NDR for each diabetes patient. A number of patients are randomly selected for a diabetes clinical audit in a particular year and their records are then audited. Therefore, the diabetes treatment and management records of these selected patients are updated for that particular year.

The accuracy, quality and completeness of data in the NDR are still of concerns. The audits of the NDR itself also act as a quality check. In the efforts to ensure the quality and accuracy of data, some states have started to see how accurate the data extraction and entry has been during the audit process through cross-auditing where staff from other clinics go through the diabetes green book and do data entry for other clinics. However, this is yet to be done systematically, and to date, there is no formal documentation for this process.

3.3.1.2 Diabetes clinical audit process

The diabetes clinical audit follows a standard procedure as detailed in the *User Manual for Diabetes Clinical Audit at MOH Healthcare Facilities* (Malaysia, 2008a). The audit process involves data extraction from the *Diabetes Green Book* before the data entry into the NDR by the auditors. The audit process focuses on two components: (i) the completeness, accuracy, and quality of the data entered into the NDR regarding

the management and treatment of diabetes patients and (ii) the achievement of targets set in relation to diabetes control, which contributes to the quality assurance and shortfall in quality (QA SIQ) assessment process for diabetes care at MOH healthcare facilities (Malaysia, 2008b).

The diabetes clinical audit looks at data that includes the latest clinical variables for every patient (available data within 1 year from the last audit date of the previous year).

The lists of variables that are audited are as follows (from the clinical audit dataset, as also detailed in the figures in Appendix D):

a. Age
b. Sex
c. Ethnic group
d. Age at diagnosis of diabetes
e. Clinical results (glucose profile including HbA1c, fasting blood glucose, random blood glucose and 2-hour post-prandial, height, weight, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, lipid profile, creatinine level)
f. Screening for complications (foot examination, funduscopic examination, ECG, proteinuria, microalbuminuria, erectile dysfunction screening)
g. Treatment including medication for diabetes, medication for hypertension, medication for dyslipidaemia, and antiplatelet medications
h. Comorbidities at diagnosis of diabetes and incidence of comorbidities
i. Diabetes-related complications at diagnosis of diabetes and incidence of complications.

3.3.1.3 Criteria for selection of patients for diabetes clinical audit

Only the patients who are classed as 'active' type 2 diabetes patients are selected for a diabetes clinical audit. In this context, the term 'active patients' refers to those patients at every health clinic registered in the NDR who have been registered for at least for 1 year and who have had follow-ups recorded at least once within 1 year from the audit date.

Level 3 users of the NDR (i.e., at the State Health Department level) are responsible for the selection of patients for the diabetes clinical audit at the beginning of each year. Their role is to determine the total number of active patients for each district in a particular state before generating the number of patients needed for audit in each district.

The number needed for audit is calculated either manually or based on a calculation table in the *Diabetes Clinical Audit Manual* (refer to Appendix B) (Malaysia, 2008a). After generating the number of patients needed from the pool of active patients for each district, this total number is divided equally according to the number of registered health clinics in the NDR in that district. The number is then entered into the NDR so that the NDR can select the patients randomly and generate a list of the patients who will be involved in the diabetes clinical audit. (Refer to Appendix C for the flowchart of the procedure for the selection of patients for diabetes clinical audits at MOH healthcare facilities.)

Therefore, not all registered diabetes patients are audited annually. It is only those who are selected for audit who have their data updated. Also, some patients are selected for audit more than once, and these patients have their data updated and audited every time they participate in a diabetes clinical audit.

3.3.1.4 Terms of reference for diabetes clinical audit

The diabetes clinical audit in each district of Malaysia is led by the most Senior Family Medicine Specialist for that district. In the absence of a Family Medicine Specialist, the Medical Officer of Health has the authority to appoint any Senior Medical and Health Officer to act as the coordinator.

The Diabetes Clinical Audit Coordinator is responsible for selecting, appointing, and training auditors for the audit process and for determining the number of auditors for each health clinic. These auditors can be Medical Officers, Assistant Medical Officers, Staff Nurses or those who have experience in providing diabetes services in healthcare facilities.

3.4 Study Population

The study population for this study complied with the following inclusion and exclusion criteria:

Inclusion criteria:

1. Type 2 diabetes patients enrolled in the NDR.
2. Being followed up in health clinics.
3. Aged 18 years and above.
4. Selected for diabetes clinical audit at a MOH healthcare facility between 2011 and 2015. This includes subjects who pay multiple visits even to different health clinics.

Exclusion criteria:

1. Hospital-based patients registered in the NDR; this study focused on diabetes management in primary healthcare settings.
2. Patients with unknown or undefined ethnicities and non-citizens.

3. Patients with diabetes-related complications at diagnosis of diabetes (prevalence of complications).

3.4.1 Entry and Exit Time For Study Participants

The entry time for every participant of this study is when the registered patient in NDR is selected for diabetes clinical audit for the first time between years 2011 and 2015, as every patient is possible to be selected again for diabetes clinical audit the following year. The exit time for the participant is when the participant is not selected for diabetes clinical audit again between years 2011 and 2015.

3.5 Sampling Method

All patients who fulfilled the inclusion and exclusion criteria were included in this study. Therefore, the final study population consisted of 338,349 patients. Figure 3.1 explains the process in selecting the participants for this study.

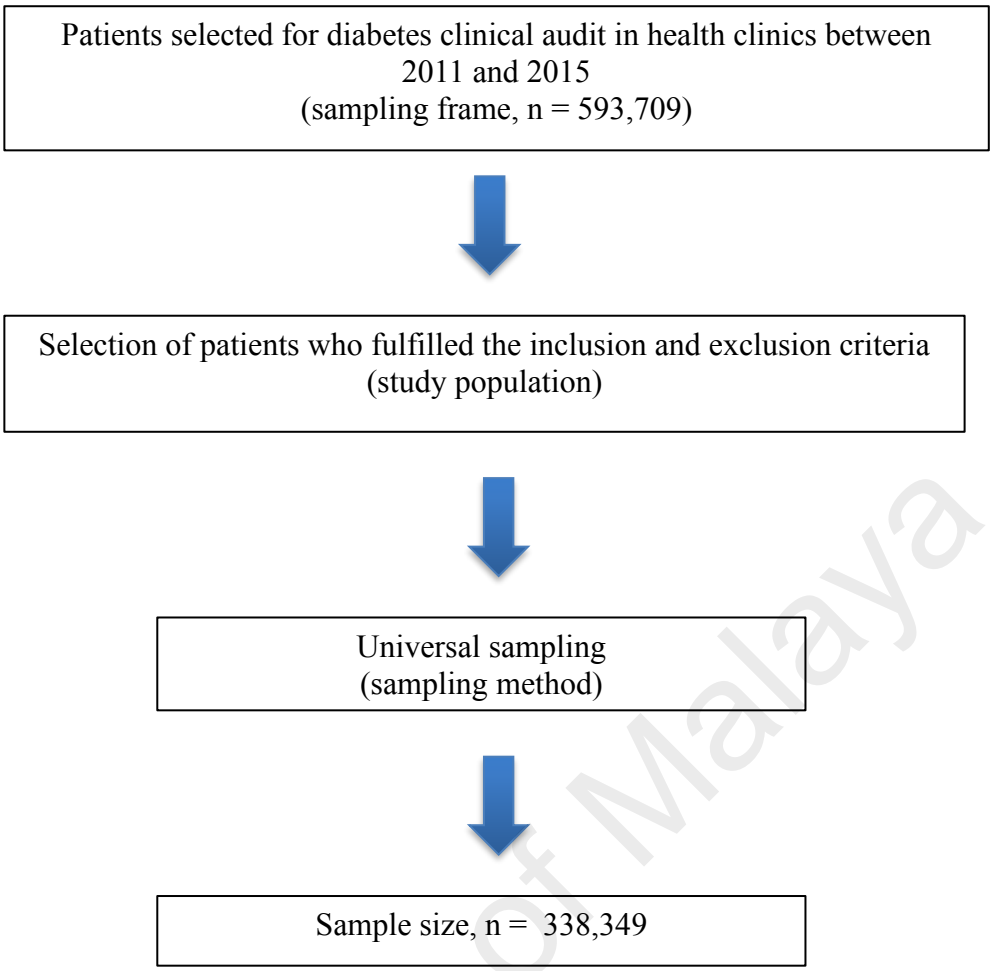

Figure 3.1: Flowchart of process to select study participants

3.6 Study Variables

3.6.1 Patients and diabetes characteristics and cardiovascular risk factors

i. Patients characteristics:

a. Age

b. Sex

c. Ethnic group.

ii. Diabetes characteristics:

a. Age at diagnosis

b. Duration of diabetes

c. HbA1c level

d. Type of diabetes medication, i.e., insulin or oral hypoglycaemic agents or both

e. Incidence of any diabetes-related complications.

iii. Cardiovascular risk factors:

a. BMI

b. Smoking status

c. Presence of comorbidities, i.e., dyslipidaemia or hypertension or both at diagnosis of diabetes

d. Anti-hypertensive treatments

e. Lipid-lowering treatments.

3.6.2 Independent variable

The independent variable in this study was ethnicity. Ethnicity was categorized into the following major ethnicities (Malay, Chinese, Indian, Indigenous Sabahan and Indigenous Sarawakian) and was stratified into further ethnicities for Sabah and Sarawak, which gave rise to another eight subgroups: Kadazan, Dusun, Bajau, Other Sabah, Iban, Bidayuh, Melanau, and Other Sarawak.

In the NDR, data on ethnicity is self-reported. There are 27 ethnic groups registered in the NDR. These ethnic groups have been further categorized into five major ethnicities:

i. Malay
ii. Chinese
iii. Indian
iv. Indigenous Sabahan (further categorized into four ethnic groups):
    a. Kadazan
    b. Dusun
    c. Bajau
    d. Other Sabah (consisting of Murut and Bumiputera Sabah)
v. Indigenous Sarawakian (further categorized into four ethnic groups):
    a. Iban
    b. Bidayuh
    c. Melanau
    d. Other Sarawak (consisting of Bumiputra Sarawak Kelabit, Bumiputra Sarawak Kayan, Kedayan, Bumiputra Sarawak Lun Bawang, Bumiputra Sarawak Kenyah, Bumiputra Sarawak Punan, Bumiputra Sarawak Sabans, Bumiputra Sarawak Penan, Bumiputra Sarawak Ukit, Bumiputra Sarawak Bukitan and Bumiputra Sarawak (Others)).

3.6.3 Dependent variables

The outcomes of interest to this study were (i) glycaemic control (HbA1c level) and (ii) incidence of diabetes-related complications.

i. Glycaemic control

The measurement of glycaemic control was made using both continuous (change in HbA1c levels) and categorical (HbA1c ≤6.5%) variables for the HbA1c level. According to the *National Clinical Practice Guideline on Management of Type 2 Diabetes Mellitus 2015*, well-controlled diabetes is defined as a HbA1c level of less than or equal to 6.5% (MOH, 2015). In all health clinics that provide diabetes management services, the HbA1c level should be measured at least every 6 months.

ii. Incidence of diabetes-related complications

The diabetes-related complications that were measured for each different ethnic group were diabetic nephropathy, diabetic retinopathy and peripheral vascular disease developed in the course of the disease. These were also the only complications available in the NDR. The NDR does not collect complications involving other systems, hence these were not measured. The definitions and criteria of diagnosis followed the descriptions provided in the *National Diabetes Registry User Guide Version 1.0* (Malaysia, 2010).

In this guide, diabetic nephropathy and diabetic retinopathy are referred to as diabetes-related complications diagnosed by a medical practitioner and recorded in the case notes. Peripheral vascular disease is defined as including either a diabetic foot ulcer or amputation or both. A diabetic foot ulcer is defined as a current ulcer or history of previous ulcers caused by diabetes as diagnosed by a medical practitioner and recorded in the case notes. Amputation is described as a non-traumatic lower limb amputation (toe, forefoot or leg (above or below knee)) as recorded in the case notes. These complications are updated in the Diabetic Registry Section of the NDR throughout the year.

3.6.4 Lifestyle mediator

Body mass index (BMI) was considered as a lifestyle mediator in this study. The BMI variable was calculated as weight (kg) divided by height (m) square. BMI is measured by the health staffs in the health clinics using validated and calibrated weighing scales and stadiometers.

3.6.5 Other covariates

The other covariates that were investigated in this study were age, age at diagnosis, duration of diabetes, comorbidities including hypertension and dyslipidaemia, and medications (glucose-lowering agents, anti-hypertensives, and lipid-lowering agents). These factors were adjusted for during the data analysis.

Hypertension was defined as systolic blood pressure of ≥140 mmHg, and/or a diastolic blood pressure of ≥90 mmHg, and/or on antihypertensive medication .

The presence of dyslipidaemia was recorded where there were any abnormal measurements of total cholesterol (more than 5.2 mmol/l), triglyceride (1.7 mmol/l and above), Low-density Lipoprotein (LDL) cholesterol (2.6 mmol/l and above) and High-density Lipoprotein (HDL) cholesterol (1.0 mmol/l and below), with or without medication.

The current age of every patient was calculated using the date of birth to the date of every diabetes clinical audit in which they had been involved. The age at diagnosis was calculated based on the date of diagnosis of diabetes from the date of birth. The date of diagnosis of diabetes was the date of a clinical diagnosis made by a medical practitioner and recorded in the case notes. The duration of diabetes was calculated from the date of diagnosis of diabetes to the current clinical audit date for every patient.

The glucose-lowering agents that were considered in this study were oral hypoglycaemic agents and insulin. The oral hypoglycaemic agents were metformin, sulphonylureas, alpha-glucosidase inhibitors, meglitinides, and glitazones. No specification was made for insulin types. A single variable was used to represent all the oral hypoglycaemic agents, which was denoted as OHA, and another variable was created to represent the usage of both an OHA and insulin.

The anti-hypertensives that were included in this study were angiotensin-converting enzyme inhibitors (ACE-I), the angiotensin receptor blocker (ARB), beta-blockers, calcium channel blockers (CCB), diuretics and others (alpha-blockers and centrally acting blockers). The lipid-lowering agents were fibrates and statins. Medical practitioners prescribe these medications for each patient and record them in the case notes for reference.

3.7 Data Collection and Data Management

3.7.1 Data collection

Data collection was carried out by extracting clinical audit data from the *Diabetes Clinical Audit Report* and smoking status data from the *Diabetes Registry Report* in the NDR. The *Diabetes Clinical Audit Report* is stored in the NDR according to state and year. For each year, there are a total of 16 states (the Federal Territory of Kuala Lumpur, Labuan, and Putrajaya are considered as three different states). Therefore, data was extracted separately for each year from 2011 to 2015, and data for each state was extracted separately according to the year.

The smoking status data is stored in the Diabetic Registry Section of the NDR according to state and covers all years. Data extraction was conducted separately for each state for the years 2011 to 2015.

The clinical audit data and smoking status data were then saved into Excel files as raw data. These files of raw data were saved as separate datasets, according to year for the clinical audit data and according to state for the smoking status data. The raw data was backed up on three external hard discs and in the cloud (Dropbox) before transferring it to statistical software for data management and data analysis.

Data management and data analysis were carried out using the statistical software package STATA IC for Mac version 14. Data management involved data preparation and data cleaning.

3.7.2 Data management: data preparation

3.7.2.1 Data preparation of clinical audit data

The first step in the preparation of the clinical audit data involved importing the raw data of the *Diabetes Clinical Audit Report* from the Excel files into STATA. For each year, the Excel files for every state were imported into STATA one by one, saved as temporary data files and then these temporary data files for every state were appended to become a single data file for each year. In total, there were five data files, one for each year from 2011 to 2015. These data files were then appended to become one general file.

The subsequent steps performed in the data preparation were the renaming of the variables and the inspection of the data for duplicates. Duplicates were detected through the following identifiers: identification number (ID), audit dates, and dates of every blood investigation and clinical examination performed (weight, waist circumference, BMI, blood pressure, glucose profiles, lipid profiles, renal profiles and screening for complications). The ID and audit and examination dates were selected as the identifiers as they were unique to each patient. The duplicates that were identified were inspected

by browsing through the data randomly and confirming those instances where there were two or more observations with identical values for the specified variables. Following confirmation these duplicates were dropped from the dataset. The remaining clinical audit data was then saved in a general data file.

3.7.2.2 Data preparation for smoking status data

The first step in preparing the smoking status data for data cleaning involved importing the raw data on smoking status from the Excel files into STATA. Similar to the process for the clinical audit data, the raw data files on smoking status for every state were imported into STATA one by one, then saved as temporary data files before appending these data files to become a single data file on smoking status. An inspection for duplicates was also carried out. The ID was not available for this dataset. Therefore the process of identifying duplicates was quite challenging as there was a need to search for some other unique identifiers.

Several variables were selected in order to identify duplicates. These variables were state, district, health facility, date of birth, sex, ethnic group and date of diagnosis of diabetes. These variables were selected after running duplicate reports many times using several different variables as they were the best available identifiers for identifying each patient uniquely. The duplicates that were identified were inspected by browsing the data and when they were confirmed to be duplicates they were dropped from the dataset. The remaining smoking status data was then saved in one smoking data file.

3.7.3 Data management: data cleaning

3.7.3.1 Merging of datasets

Before data cleaning, both the general clinical audit data file and the smoking data file were merged. The general clinical data file was designated as the master file and the smoking data file was the working file. As IDs were not available for the smoking data file, this precluded perfect matching between the two files. Therefore, matching proceeded by identifying patients with identical values on a set of variables that was specified for both datasets. The two datasets were matched through the 'many to one' command and by using the variables health facility, date of birth, sex, ethnic group and date of diagnosis of diabetes as the matching variables. These variables were selected as they were present in both datasets and were the best available in terms of their capability to uniquely match the two datasets. The files that were selected for the data analysis were the merged file and the master file that did not match. The working file that had no matches was dropped from the dataset. The remaining files were then merged and backed up on external discs and in the cloud. Data cleaning was carried out on this merged data file.

3.7.3.2 Data cleaning

Data cleaning was performed to prepare the data for analysis and consisted of several steps. The merged data consisted of 593,709 observations that included patients with repeated follow-ups and 129 variables. The first step involved generating a new ID for each patient using the original ID. The purpose of the new ID was to enable the sorting of the data according to each individual patient.

The data cleaning process was quite extensive as all the continuous variables were in the form of a string or a word, so an analysis could not be carried out on these forms of variables. Hence, the subsequent data cleaning step involved de-stringing the continuous variables into integer variables to allow for analysis to take place. Observations that did not meet the study criteria were dropped from the dataset. The following steps then consisted of generating new variables to fit the analysis plan, defining new value labels for all the categorical variables, creating variable labels, and renaming the variables. Data cleaning gave rise to 338,349 observations with 540,801 registered follow-ups and 284 variables, including the original variables.

3.7.4 Creation of longitudinal dataset for longitudinal data analysis

A longitudinal dataset was prepared for the analysis in this study. There were participants enrolled in this study who had been selected for a diabetes clinical audit more than once and therefore had repeated measurements of their HbA1c level. Therefore, the data became prospective as data collection occurred on several occasions or follow-ups.

These occasions or follow-ups were nested in the subjects or the patients. Hence the subjects became clusters, and these subjects were followed up over a period at a subject-specific time. Hence, the changes in the measurements over the period could be observed for every individual patient.

3.7.5 Missing data analysis

Missing data analysis was carried out for core variables in the analysis (as listed in Table 3.2, Table 3.3 and Table 3.4). Core variables included the main exposure, outcomes, confounders, and mediators related to the three main objectives. The missingness of each variable was categorized as 0 "Present" and 1 "Missing". The

missingness of HbA1c was then cross-tabulated with the missingness of the other core variables. Logistic regression was used to model the association between HbA1C missingness and the other core variables.

Variable HbA1c is the primary outcome, and it had 21.6% missing values. Iban, Bidayuh, Melanau and Other Sarawak had 50%-60% of missing HbA1c. Statistical analysis in this study was carried out on all observations including those with missing HbA1c due to several factors. Firstly, observations of Iban, Bidayuh, Melanau and Other Sarawak whom half of them had missing HbA1c had the final total number of observations of more than 500 for each of these ethnic groups. The lowest was n=568 among the Bidayuh, and the highest was amongst the Iban (n=7,742). Also, the total number of observations of other core variables with non-missing HbA1c was adequate. Hence, with an adequate number of observations, reliable results could be estimated due to the presence of precision and power. Secondly, the rest of the other core variables had 25% or less of missing HbA1c. Lastly, the odds of missingness for core categorical variables showed lower odds of missing HbA1c, and there was no significant difference in the values for continuous core variables amongst missing HbA1c compared to those with non-missing HbA1c. Therefore, the missing data analysis showed the data were missing at random.

HbA1c as an outcome was measured in the linear mixed model using random coefficient analysis. Linear mixed model is one of the approaches in handling missing data using maximum likelihood estimation model and was able to reduce bias by controlling for confounding at the individual level in a clustered data such as in this dataset and was able to retain consistency. It involved intraclass correlation (ICC) in the modeling process, which enables a more realistic model of the clustered data.

Tables 3.2, 3.3 and 3.4 explained the associations between missing values of HbA1c and values of all core variables measured in the analysis in this study. The pattern of missing data is missing at random. There were lower odds of missing HbA1c for core categorical variables, and no significant difference in the values for continuous core variables with missing HbA1c compared to those with non-missing HbA1c.

Table 3.2: Association between missing value of HbA1c and values for core variables (Sociodemography and Cardiovascular Risk factors)

Variables	HbA1c Present, n (%) or mean ± SD	HbA1c Missing, n (%) or mean ± SD	OR for Missingness (95% CI)	P-value
Overall	423,913 (78.4)	116,888 (21.6)		
Sociodemographics				
Age				
mean ± SD	59.8 ± 11.0	59.7 ± 12.0	1.00 (0.99, 1.00)	0.101
Sex				
Female	263,054 (79.4)	68,160 (20.6)	1.00 (ref)	
Male	160,859 (76.7)	48,728 (23.3)	1.17 (1.15, 1.18)	<0.001
Ethnicity				
Malay	285,301 (79.2)	74,853 (20.8)	1.0 (ref)	
Chinese	73,868 (78.6)	20,111 (21.4)	1.04 (1.02, 1.06)	<0.001
Indian	49,201 (79.9)	12,390 (20.1)	0.96 (0.94, 0.98)	<0.001
Kadazan	2,185 (85.1)	382 (14.9)	0.67 (0.60, 0.74)	<0.001
Dusun	2,200 (94.0)	141 (6.0)	0.24 (0.21, 0.29)	<0.001
Bajau	2,781 (81.6)	627 (18.4)	0.86 (0.79, 0.94)	0.001
Iban	4,176 (40.3)	6,199 (59.8)	5.66 (5.44, 5.89)	<0.001
Bidayuh	341 (46.5)	392 (53.5)	4.38 (3.79, 5.07)	<0.001
Melanau	365 (41.7)	510 (58.3)	5.33 (4.65, 6.09)	<0.001
Other Sabah	3,132 (84.7)	567 (15.3)	0.69 (0.63, 0.75)	<0.001
Other Sarawak	363 (33.6)	716 (66.4)	7.52 (6.62, 8.53)	<0.001
Cardiovascular risk factors				
Smoking status				
No	261,841 (79.8)	66,504 (20.3)	1.00 (ref)	
Yes	16,425 (77.4)	4,786 (22.6)	1.15 (1.11, 1.19)	<0.001
Hypertension				
No	65,005 (82.4)	13,935 (17.7)	1.00 (ref)	
Yes	355,999 (84.4)	65,749 (15.6)	0.86 (0.84, 0.88)	<0.001
Dyslipidaemia				
No	36,681 (29.0)	89,917 (71.0)	1.00 (ref)	
Yes	387,232 (93.5)	26,971 (6.5)	0.03 (0.03, 0.03)	<0.001
BMI				
mean ± SD	27.6 ± 6.3	27.3 ± 6.0	1.00 (0.99, 1.00)	<0.001
SBP				
mean ± SD	135.2 ± 17.6	135.5 ± 18.5	1.00 (0.99, 1.00)	<0.001
DBP				
mean ± SD	77.6 ± 10.0	78.8 ± 10.2	1.00 (0.99, 1.00)	<0.001
TC				
mean ± SD	5.1 ± 1.2	5.2 ± 1.3	1.04 (1.03, 1.05)	<0.001
TG				
mean ± SD	1.8 ± 1.1	1.9 ± 1.2	1.07 (1.06, 1.08)	<0.001
LDL				
mean ± SD	3.1 ± 1.1	3.1 ± 1.2	1.01 (0.99, 1.02)	0.291
HDL				
mean ± SD	1.3 ± 0.5	1.3 ± 0.5	0.92 (0.89, 0.95)	<0.001
Serum creatinine				
mean ± SD	89.6 ± 51.0	96.7 ± 65.1	1.00 (1.00, 1.00)	<0.001

***** The number of participants with incomplete data were 116,888 (21.6%) for HbA1c, 121,498 (22.5%) for smoking status, 60,663 (11.2%) for BMI, 116,842 (21.6%) for TC, 119,838 (22.2) for TG, 216,754 (40.1%) for HDL, 219,049 (40.5%) for LDL, 40,113 (7.4%) for Hypertension, 39,932 (7.4%) for SBP, 40,009 (7.4%) for DBP, 123 (0.02%) for Diabetic Nephropathy, 114 (0.02%) for Diabetic Retinopathy, 127 (0.02) for Amputation and 128 (0.02%) for Diabetes Foot Ulcer.

Table 3.3: Association between missing value of HbA1c and values for core variables (Diabetes Characteristics and Diabetes-related Complications)

Variables	HbA1c Present, n (%) or mean ± SD	HbA1c Missing, n (%) or mean ± SD	OR for Missingness (95% CI)	P-value
Diabetes Characteristics				
Age at diagnosis				
mean ± SD	52.8 ± 10.9	52.8 ± 11.7	1.00 (0.99, 1.00)	0.065
Duration of diabetes				
mean ± SD	6.9 ± 5.1	6.9 ± 5.2	1.00 (0.99, 1.00)	0.951
Diabetes-related Complications				
Diabetic foot ulcer				
No	381,057 (79.4)	98,758 (20.6)	1.00 (ref)	
Yes	4,653 (76.0)	1,465 (24.0)	1.21 (1.15, 1.29)	<0.001
Amputation				
No	383,600 (79.4)	99,738 (20.6)	1.00 (ref)	
Yes	2,281 (77.1)	679 (22.9)	1.14 (1.05, 1.25)	0.002
Nephropathy				
No	343,378 (79.1)	90,520 (20.9)	1.00 (ref)	
Yes	37,682 (84.0)	7,191 (16.0)	0.70 (0.68, 0.72)	<0.001
Retinopathy				
No	338,3507 (79.5)	87,390 (20.5)	1.00 (ref)	
Yes	32,624 (84.7)	5,915 (15.4)	0.70 (0.68, 0.72)	<0.001
IHD				
No	361,605 (79.6)	92,809 (20.4)	1.00 (ref)	
Yes	17,709 (82.0)	3,899 (18.0)	0.86 (0.83, 0.89)	<0.001
Cerebrovascular disease				
No	376,182 (79.5)	96,893 (20.5)	1.00 (ref)	
Yes	4,134 (77.2)	1,221 (22.8)	1.15 (1.08, 1.22)	<0.001

Table 3.4: Association between missing values of HbA1c and values of core variables (Treatment)

Variables	HbA1c Present, n (%) or mean ± SD	HbA1c Missing, n (%) or mean ± SD	OR for Missingness (95% CI)	P-value
Diabetes Medications				
No medication	13,065 (31.1)	28,947 (68.9)	1.00 (ref)	
OHA	303,065 (81.5)	69,165 (18.6)	0.23 (0.23, 0.24)	<0.001
Insulin	24,240 (81.6)	5,473 (18.4)	0.57 (0.56, 0.57)	<0.001
OHA and insulin	82,998 (86.2)	13,303 (13.8)		
Anti-hypertensives				
ACE Inhibitors				
No	200,516 (73.0)	74,337 (27.0)	1.00 (ref)	
Yes	223,397 (84.0)	42,551 (16.0)	0.51 (0.51, 0.52)	<0.001
ARB				
No	402,087 (78.1)	112,983 (21.9)	1.00 (ref)	
Yes	21,286 (84.8)	3,905 (15.2)	0.64 (0.62, 0.66)	<0.001
Beta blocker				
No	319,860 (77.0)	95,328 (23.0)	1.00 (ref)	
Yes	104,053 (82.8)	21,560 (17.2)	0.70 (0.68, 0.71)	<0.001
CCB				
No	237,590 (74.6)	81,011 (25.4)	1.00 (ref)	
Yes	186,323 (83.9)	35,877 (16.1)	0.56 (0.56, 0.57)	<0.001
Diuretics				
No	333,769 (77.1)	99,149 (22.9)	1.00 (ref)	
Yes	90,144 (83.6)	17,739 (16.4)	0.66 (0.65, 0.67)	<0.001
Lipid-lowering Agents				
Fibrates				
No	409,149 (78.2)	114,115 (21.8)	1.00 (ref)	
Yes	14,764 (84.2)	2,773 (15.8)	0.67 (0.65, 0.70)	<0.001
Statins				
No	126,411 (67.4)	61,145 (32.6)	1.00 (ref)	
Yes	297,502 (84.2)	55,743 (15.8)	0.39 (0.38, 0.39)	<0.001

3.7.6 Documentation of audit trail in do-files

Documentation of all the processes involved in data collection, data management, and data analysis was carried out in well-defined steps in different do-files. Each do-file contained commands and notes on every step taken. Documentation on data collection, data management, missing data analysis, descriptive analysis, and analysis of the three different objectives was written in separate do-files. Any modification made to the dataset was also documented as part of the audit trail. All saved data was password-locked so that only the researchers had access to the data. Backups for every change made were carried out on a daily to weekly basis.

3.8 Data Analysis

3.8.1 Descriptive analysis

Continuous variables were summarized using the mean ± standard deviation (SD). The crude differences between the means by ethnicity for overall and for newly diagnosed diabetes were statistically tested using analysis of variance (ANOVA) and pairwise differences were tested using the post-hoc Bonferroni test. Categorical variables were tabulated using proportions and the differences between the proportions were tested using the chi square test.

The primary outcome of this analysis was glycaemic control. The mean values of HbA1c were measured for all ethnic groups to determine the glycaemic control of each ethnicity. A comparison between the means was tested for statistical significance using ANOVA and pairwise differences were tested using the post-hoc Bonferroni test.

3.8.2 Mixed effect random intercept models

The association between ethnic group (independent variable) and glycaemic control in terms of changes in the HbA1c level (continuous level and categorical level as defined by ≤6.5 and >6.5 (dependent variable), respectively) was examined using analysis that employed the linear mixed effect model with random intercept (for the continuous outcome) and the logistic random intercept model (for the categorical outcome).

The linear mixed effect model was used for this longitudinal dataset. Participants were followed up more than once at subject-specific time of follow-up. Therefore, we would expect to see unobserved between-subject heterogeneity and within-subject correlations and the effect of time in the analysis (Rabe-Hesketh & Skrondal, 2008). Random intercept was used to allow the intercepts to vary between subjects and to allow the overall levels of response to vary over the clusters, which were the subjects after controlling for covariates. Random intercept also explained the remaining unexplained variance from the total variance of the outcome (Twisk, 2013). The linear mixed model was also able to model unbalanced data accounts for missing values through maximum likelihood estimation. Exposure was lagged for this longitudinal data to ensure temporality.

The association between glycaemic control and ethnicity was adjusted for confounders via four linear mixed effect models. Model 1 adjusted for ethnicity and duration of diabetes in order to explain the cross-sectional association between ethnicity and HbA1c level. Cross-sectional association referred to the prevalent associations at time of first presentation to the registry. The constant was set at 5-years (N. C. Tan et al., 2015). The duration of diabetes was modelled as changes in HbA1c for every 5 years of diabetes duration. The beta coefficients for this model were interpreted as the

changes in HbA1c level (percentage in HbA1c) at time of first presentation to the registry, which is at 5 year of having diabetes.

Model 2 was an extension of Model 1 to control for additional covariates. The included covariates were (i) continuous variables: age at recruitment and (ii) categorical variables: sex, comorbidities (hypertension or dyslipidaemia or both), type of glucose-lowering agent (insulin or oral hypoglycaemic agent or both), anti-hypertensive (yes or no) and lipid-lowering agents (yes or no). The model also represented cross-sectional association that referred to the prevalent associations at time of first presentation to the registry. The constant was set at 5-years and the beta coefficients for this model were also interpreted as the changes in HbA1c level at time of first presentation to the registry, which is at 5 year of having diabetes.

Model 3 was an extension of Model 1 in which the interaction between ethnicity and duration of diabetes was included in order to explain both the cross-sectional and longitudinal association between ethnicity and change in HbA1c level. The cross-sectional association similarly to Model 1, referred to the prevalent associations at time of first presentation to the registry where the constant was set at 5-years and the beta coefficients were also interpreted as the changes in HbA1c level at time of first presentation to the registry, which is at 5 year of having diabetes. Longitudinal association referred to associations that change with time and in the analysis, a 5-year time change was used for the coefficients for the longitudinal associations. Hence, the beta coefficients were interpreted as the changes in HbA1c level for every five years of having diabetes.

Model 4, the final model, was an extension of Model 3 with the addition of covariates as in Model 2. The cross-sectional association similarly to Model 2, referred to the prevalent associations at time of first presentation to the registry where the

constant was set at 5-years and the beta coefficients were also interpreted as the changes in HbA1c level at time of first presentation to the registry, which is at 5 year of having diabetes. Longitudinal association referred to associations that change with time and in the analysis, the beta coefficients were interpreted as the changes in HbA1c level for every five years of having diabetes, as a 5-year time change was used for the coefficients for the longitudinal associations.

Two models were used in the logistic random intercept model. Model 1 adjusted for ethnicity and duration of diabetes in order to explain the cross-sectional association between ethnicity and glycaemic control. The cross-sectional association also referred to the prevalent associations at time of first presentation to the registry, with the constant was set at 5-years and the duration of diabetes was modelled as changes in HbA1c for every 5 years of diabetes duration. The odds ratio for this model were interpreted as the odds of good glycemic control at time of first presentation to the registry, which is at 5 year of having diabetes.

Model 2 additionally adjusted for age at recruitment, sex, hypertension or dyslipidaemia or both, insulin or oral hypoglycaemic agent or both, anti-hypertensive (yes or no) and lipid-lowering agents (yes or no). The odds ratio for this model were interpreted similar to Model 1 as the odds of good glycemic control at time of first presentation to the registry, which is at 5 year of having diabetes.

3.8.3 Generalized structural equation modelling for mediation analysis

Generalized structural equation modelling (GSEM) was used in the mediation analysis between each ethnic group and glycaemic control to investigate the indirect effect, direct effect, and total effect of the associations. The total percentage of the

indirect effect from the total effect was also calculated to summarize the mediation of pair-wise ethnic comparisons.

A mediator is a variable in the causal sequence between two variables. In classical mediation, the independent variable have statistically significantly associated with the potential mediators; the potential mediators have a significant individual effect on the dependent variable when controlling for the independent variable; and the magnitude of the effect of the independent variable on the dependent variable is statistically significant changed with the adjustment of the mediator in the model (Richiardi, Bellocco, & Zugna, 2013).

In this analysis, ethnicity was the independent (exogenous) variable and glycaemic control was the dependent (endogenous) variable. Glycaemic control was analysed continuously as change in the HbA1c level and categorically as good glycaemic control (HbA1c ≤6.5%). The mediators that were assessed were (i) BMI, which was measured as a continuous variable and as a categorical variable (categorized into overweight and obese) and (ii) sex, which was measured as a categorical variable. The analysis was adjusted for age, sex, and treatment for diabetes. The analysis was conducted using baseline data, n = 338,349.

3.8.4 Discrete-time survival analysis

Discrete-time survival analysis was used to evaluate the association between ethnicity and the hazard of diabetes-related complications. Complications were captured at follow-up visits. Before the discrete-time survival analysis was performed, a descriptive analysis was carried out to describe the proportions of diabetes-related complications among the overall sample, among each of the major ethnicities, and among the ethnicities of Sabah and Sarawak in the stratified analysis.

Three models were employed in the discrete-time survival analysis in order to analyse diabetic retinopathy, diabetic nephropathy, and peripheral vascular disease as diabetes-related complications. Model 1 was an extension of the crude model and adjusted for age and sex. Model 2 was an extension of Model 1 with the addition of HbA1c and treatment for diabetes. Model 3, which was the final model, adjusted for Model 2 with the addition of comorbidities (hypertension and dyslipidaemia), BMI, and smoking status. The hazard ratio of diabetes-related complications was then ascertained for each ethnicity in order to explain the association between ethnicity and the hazard of diabetes-related complications.

Two-tailed p-values <0.05 were considered statistically significant. All statistical analysis was performed using STATA IC for Mac version 14.0.

3.9 Chapter Summary

This was a historical cohort study using data from Clinical Audit Datasets of the Malaysia National Diabetes Registry (NDR). The study populations include Type 2 Diabetes patients enrolled in NDR attending follow-ups in government primary care clinics, and had been selected for Diabetes Clinical Audit at MOH Healthcare Facilities between years 2011 and 2015. The study populations also include patients who pay multiple visits in same and different clinics. The total sample size was 338,349 patients who fulfilled the study criteria. The independent variable for this study was ethnicity. There were five major ethnic groups including Malay, Chinese, Indian, Indigenous Sabah and Indigenous Sarawak. Indigenous Sabah and Indigenous Sarawak were further categorized into Kadazan, Dusun, Bajau and Other Sabah, Iban, Bidayuh, Melanau and Other Sarawak. The mediators measured were BMI and gender. The dependent variables in this study were HbA1c and diabetes-related complications, namely diabetic retinopathy, diabetic nephropathy and peripheral vascular disease. Mean and

proportions were used for descriptive analysis, linear and logistic mixed effect model with random intercept were used in the analysis for association between ethnicity and glycemic control, generalized structural equation modeling was used for mediation analysis and discrete-time survival analysis was used in the analysis for the association between ethnicity and hazard of developing diabetes-related complications.

CHAPTER 4: RESULTS

4.1 Chapter Introduction

This chapter presents the results of this study. The sections are divided into findings on the descriptive analysis, results on the associations between ethnicity and glycaemic control, the results on the mediation analysis and the results on the associations between ethnicity and diabetes-related complications. The last section summarizes the main findings of this study.

4.2 Baseline Characteristics of Multi Ethnic Diabetes Cohort

There was a total of 338,349 diabetes patients in this study. 540,801 appointments were registered in the NDR in which 202,452 had two or more follow-ups. Negeri Sembilan had the highest number of patients in this study (13%), followed by Pahang (11%) and Melaka (9%). 53% of all diabetes patients in this study followed up in health clinics without a Family Medicine Specialist. Majority of the diabetes patients represented by Malay (65%), Chinese (19%) and Indian (12%) and multi-ethnic from Sabah and Sarawak represented 4.8% of all diabetes patients in this study.

Table 4.1: Distribution of diabetes patients according to states and type of facility providing diabetes services.

	Overall, (n, column %)	Facility Type, (n, row %)	
States		No FMS	FMS
Overall (n,%)	338,349	177,577 (52.5)	160,772 (47.5)
Johor	28,436 (8.4)	21,651 (76.1)	6,785 (23.9)
Melaka	31,468 (9.3)	19,056 (60.6)	12,412 (39.4)
Negeri Sembilan	44,142 (13.1)	19,808 (44.9)	24,334 (55.1)
Selangor	25,587 (7.6)	14,199 (55.5)	11,388 (44.5)
Perak	26,540 (7.8)	20,552 (77.4)	5,988 (22.6)
Pulau Pinang	12,631 (3.7)	5,991 (47.4)	6,640 (52.3)
Kedah	28,495 (8.4)	16,597 (58.3)	11,898 (41.8)
Perlis	4,724 (1.4)	2,543 (53.8)	2,181 (46.2)
Kelantan	23,538 (7.0)	13,122 (55.8)	10,416 (44.3)
Terengganu	18,573 (5.5)	7,170 (38.6)	11,403 (61.4)
Pahang	36,242 (10.7)	21,338 (58.9)	14,904 (41.1)
Sabah	9,396 (2.8)	2,726 (29.0)	6,670 (71.0)
Sarawak	21,496 (6.4)	5,822 (27.1)	15,674 (72.9)
WP Kuala Lumpur	24,434 (7.2)	6,655 (27.2)	17,779 (72.8)
WP Putrajaya	2,097 (0.6)	275 (13.1)	1,822 (86.9)
WP Labuan	550 (0.2)	72 (13.1)	478 (86.9)

- FMS, Family Medicine Specialist

Table 4.2: Sociodemographic and baseline diabetes characteristics for overall and major ethnicities of multi ethnic diabetes cohort

	Overall	Malay	Chinese	Indian	Indigenous Sabah	Indigenous Sarawak	P-value
	Mean ± SD or n, %						
N, (%)	338,349	219,478 (64.9)	62,427 (18.5)	40,287 (11.9)	6,329 (1.9)	9,828 (2.9)	
Male	134,043 (39.6)	82,463 (37.6)	29,223 (46.8)	16,364 (40.6)	2,521 (39.8)	3,472 (35.3)	<0.001
Age	59.2 ± 11.3	58.5 ± 11.1	63.8 ± 11.0	57.5 ± 11.0	56.0 ± 10.9	55.9 ± 11.5	<0.001
Age at diagnosis of diabetes	52.9 ± 11.2	52.5 ± 11.0	56.6 ± 11.4	50.3 ± 10.9	51.4 ± 10.8	50.2 ± 11.4	<0.001
Duration of diabetes	6.3 ± 5.1	5.9 ± 4.7	7.2 ± 6.0	7.1 ± 5.6	4.6 ± 4.1	5.6 ± 4.6	<0.001
BMI, kg/m2	27.5 ± 6.3	27.9 ± 6.7	26.2 ± 5.3	27.4 ± 5.8	28.0 ± 5.3	27.7 ± 5.4	<0.001
Waist circumference, cm	91.9 ± 12.2	91.9 ± 12.4	90.9 ± 11.4	93.6 ± 11.8	91.8 ± 11.5	91.4 ± 11.8	<0.001
SBP, mmHg	135 ± 17.8	136 ± 18.2	135 ± 17.0	133 ± 17.5	132 ± 15.5	132 ± 15.0	<0.001
DBP, mmHg	78 ± 10.0	79 ± 10.1	77 ± 9.9	78 ± 10.0	79 ± 8.8	81 ± 9.2	<0.001
Current smoking status	12,599 (3.7)	8,629 (3.9)	2,200 (3.5)	1,314 (3.3)	241 (3.8)	215 (2.2)	<0.001
Co-morbidities							
Hypertension only	46,419 (13.7)	27,359 (12.5)	9,735 (15.6)	5,027 (12.5)	923 (14.6)	3,375 (34.3)	<0.001
Dyslipidaemia only	41,278 (12.2)	27,283 (12.4)	5,986 (9.6)	6,690 (16.6)	737 (11.6)	582 (5.9)	<0.001
Both comorbidities	213,814 (63.2)	139,924 (63.8)	41,184 (66.0)	23,845 (59.2)	4,133 (65.3)	4,728 (48.1)	<0.001
Diabetes Medications							
OHA only	244,986 (72.4)	156,655 (71.4)	47,685 (76.4)	27,765 (68.9)	5,071 (80.1)	7,810 (79.5)	<0.001
Insulin only	15,567 (4.6)	11,160 (5.1)	2,385 (3.8)	1,543 (3.8)	169 (2.7)	310 (3.2)	<0.001
Both OHA and Insulin	52,166 (15.4)	33,654 (15.3)	8,143 (13.0)	8,265 (20.5)	793 (12.5)	1,311 (13.3)	<0.001
Anti-hypertensive							
Ace Inhibitors	161,431 (47.7)	104,912 (47.8)	30,010 (48.1)	18,595 (46.2)	3,163 (50.0)	4,751 (48.3)	<0.001
Angiotensin Receptor Blocker	15,269 (4.5)	9,074 (4.1)	3,619 (5.8)	1,331 (3.3)	628 (9.9)	617 (6.3)	<0.001
Beta Blocker	77,361 (22.9)	48,598 (22.1)	17,579 (28.2)	7,430 (18.4)	1,228 (19.4)	2,526 (2.7)	<0.001
Calcium Channel Blocker	132,256 (39.1)	83,960 (38.3)	27,010 (43.3)	13,484 (33.5)	3,033 (47.9)	4,769 (48.5)	<0.001
Diuretics	65,116 (19.3)	42,593 (19.4)	13,023 (20.9)	6,870 (17.1)	853 (13.5)	1,777 (18.1)	<0.001
Others	12,030 (3.6)	7,471 (3.4)	2,777 (4.5)	1,343 (3.3)	76 (1.2)	363 (3.7)	<0.001
Lipid-lowering agents							
Statins	215,357 (63.7)	139,411 (63.5)	40,674 (65.2)	24,608 (61.1)	3,964 (62.6)	6,700 (68.2)	<0.001
Fibrates	10,539 (3.1)	6,290 (2.9)	2,408 (3.9)	1,516 (3.8)	158 (2.5)	167 (1.7)	<0.001

Table 4.3: Sociodemographic and baseline diabetes characteristics of multi ethnic diabetes cohort from Sabah and Sarawak

	Indigenous Sabah					Indigenous Sarawak			
	Kadazan	Dusun	Bajau	Other Sabah	Iban	Bidayuh	Melanau	Other Sarawak	P value
	Mean ± SD or n, %								
N, (%)	1,461 (0.4)	1,100 (0.3)	1,847 (0.6)	1,921 (0.6)]	7,742 (2.3)]	568 (0.2)]	731 (0.2)]	787 (0.2)]	
Male	623 (42.6)	453 (41.2)	681 (36.9)	764 (39.8)	2,666 (34.4)	219 (38.6)	279 (38.2)	308 (39.1)	<0.001
Age	57.6 ± 11.5	55.8 ± 11.0	55.5 ± 10.5	55.6 ± 10.6	55.6 ± 11.5	56.4 ± 10.6	58.5 ± 10.6	56.0 ± 12.5	<0.001
Age at diagnosis of diabetes	52.5 ± 11.0	52.1 ± 11.1	51.1 ± 10.4	50.7 ± 12.3	50.0 ± 11.4	50.5 ± 10.6	52.0 ± 10.5	50.8 ± 12.3	<0.001
Duration of diabetes	5.2 ± 4.7	3.7 ± 3.5	4.4 ± 3.8	4.8 ± 4.3	5.5 ± 4.5	5.9 ± 4.9	6.4 ± 4.9	5.3 ± 4.4	<0.001
BMI, kg/m2	28.2 ± 5.0	27.8 ± 4.9	27.9 ± 5.6	27.9 ± 5.4	27.7 ± 5.4	27.8 ± 5.2	27.1 ± 4.9	28.3 ± 5.4	<0.001
Waist circumference, cm	91.3 ± 11.5	91.7 ± 11.6	91.8 ± 11.7	92.0 ± 11.1	91.5 ± 11.8	90.0 ± 12.2	90.2 ± 11.3	93.6 ± 12.5	<0.001
SBP, mmHg	132 ± 14.4	131 ± 15.3	133 ± 15.5	132 ± 16.3	132 ± 15.0	132 ± 14.0	133 ± 15.0	131 ± 14.7	<0.001
DBP, mmHg	78 ± 8.2	79 ± 8.9	79 ± 8.4	80 ± 9.6	81 ± 9.2	81 ± 9.2	81 ± 9.4	80 ± 9.6	<0.001
Current smoking status	45 (3.1)	62 (5.6)	43 (2.3)	91 (4.7)	148 (1.9)	16 (2.8)	21 (2.9)	30 (3.8)	<0.001
Co-morbidities									
Hypertension only	212 (14.5)	105 (9.6)	316 (17.1)	290 (15.1)	2,768 (35.8)	134 (23.6)	232 (31.7)	241 (30.6)	<0.001
Dyslipidaemia only	122 (8.4)	140 (12.7)	226 (12.2)	249 (13.0)	428 (5.5)	61 (10.7)	36 (4.9)	57 (7.2)	<0.001
Both comorbidities	1,010 (69.1)	817 (74.3)	1,093 (59.2)	1,213 (63.1)	3,693 (47.7)	324 (57.0)	367 (50.2)	344 (43.7)	<0.001
Diabetes Medications									
OHA only	1,209 (82.8)	936 (85.1)	1,428 (77.3)	1,498 (78.0)	6,169 (79.7)	466 (82.0)	582 (79.6)	593 (75.4)	<0.001
Insulin only	33 (2.3)	25 (2.3)	43 (2.3)	68 (3.5)	220 (2.8)	10 (1.8)	28 (3.8)	52 (6.6)	<0.001
Both medications	174 (11.9)	110 (10.0)	259 (14.0)	250 (13.0)	1,054 (13.6)	76 (13.4)	92 (12.6)	89 (11.3)	<0.001
Anti-hypertensive									
Ace Inhibitors	723 (49.5)	549 (49.9)	941 (51.0)	950 (49.5)	3,796 (49.0)	250 (44.0)	367 (50.2)	338 (43.0)	<0.001
Angiotensin Receptor Blocker	219 (15.0)	90 (8.2)	151 (8.2)	168 (8.8)	488 (6.3)	35 (6.2)	30 (4.1)	64 (8.1)	<0.001
Beta Blocker	350 (24.0)	184 (16.7)	317 (17.2)	377 (19.6)	2,073 (26.8)	111 (19.5)	177 (24.2)	165 (21.0)	<0.001
Calcium Channel Blocker	826 (56.5)	576 (52.4)	772 (41.8)	859 (44.7)	3,862 (50.0)	218 (38.4)	359 (49.1)	330 (41.9)	<0.001
Diuretics	208 (14.2)	174 (15.8)	219 (11.9)	252 (13.1)	1,426 (18.4)	97 (17.1)	117 (16.0)	137 (17.4)	<0.001
Others	30 (2.1)	10 (0.9)	15 (0.8)	21 (1.1)	309 (4.0)	11 (1.9)	30 (4.1)	13 (1.7)	<0.001
Lipid lowering agents									
Statins	905 (61.9)	684 (62.2)	1,129 (61.1)	1,246 (64.9)	5,260 (67.9)	435 (76.6)	492 (67.3)	513 (65.2)	<0.001
Fibrates	54 (3.7)	29 (2.6)	25 (1.4)	50 (2.6)	136 (1.8)	12 (2.1)	5 (0.7)	14 (1.8)	<0.001

Table 4.2 and table 4.3 above described the sociodemographic characteristics and baseline diabetes characteristics of multi ethnic diabetes cohort for major ethnicities and ethnicities from Sabah and Sarawak.

At baseline, the proportions of males varied from 34% amongst the Iban to 47% amongst the Chinese. Overall mean age was 59 years old. Dusun, Bajau, Other Sabah, and Iban ethnic groups were among the youngest patients with mean age of 55 years and the Chinese ethnic group had the highest mean age at 64 years.

Malay, Indian and the multi ethnic from Sabah and Sarawak were diagnosed with diabetes at an earlier age, with the mean ranged from 50 years amongst the Iban to 53 years amongst the Kadazan ethnic group. Compared to Chinese ethnic group, the patients of this ethnic group were diagnosed at later age at 57 years.

Overall mean BMI at baseline was 27.5 kg/m^2. According to the classification of weight by BMI in the *Malaysian Clinical Practice Guideline on Management of Obesity 2004* (MOH, 2004), only the Chinese and Melanau ethnic groups were overweight at baseline while the other ethnic groups were obese. Kadazan and Other Sarawak had the highest BMI at 28.2 kg/m^2 and 28.3 kg/m^2, respectively.

Overall mean for systolic blood pressure was 135 mmHg and diastolic blood pressure was 78 mmHg. Majority of all diabetes patients in this study had both hypertension and dyslipidemia at baseline (63%), while 14% had only hypertension and 12% had only dyslipidemia. Dusun ethnic group had the highest proportions of patients with hypertension and dyslipidemia. 74% of Dusun's patients already diagnosed with both co-morbidities at baseline.

Majority of diabetes patients in this study were prescribed with oral hypoglycemic agents (OHAs) (83% of all diabetes patients were on OHAs). The proportions ranged from 69% among the Indian to 85% among the Dusun. OHAs were more common between Indigenous Sabah and Indigenous Sarawak as 75% to 85% of the patients were prescribed with OHAs, compared to the three major ethnic groups (Malay, Chinese and Indian) where the proportions ranged lower from 68% to 71%. Malay and Indian had higher proportions of patients being prescribed with both OHA and insulin (20% among the Indian and 15% among the Malay).

Majority of diabetic hypertensive patients were prescribed with Angiotensin Inhibitors (ACE-i) and Calcium Channel Blockers (CCB) for the treatment of hypertension. Angiotensin Receptor Blocker (ARB) was common amongst the Indigenous Sabah especially Kadazan. Statin was the preferred choice for lipid-lowering agents as more than 60% of all diabetic dyslipidemic patients were prescribed with this medication at baseline.

Table 4.4: Baseline biomarkers for overall and major ethnicities of multi ethnic diabetes cohort

	Overall	Malay	Chinese	Indian	Indigenous Sabah	Indigenous Sarawak	P-value
	Mean ± SD or n, %						
Glycemic Profile							
Fasting Blood Glucose, mmol/l	8.0 ± 3.1	8.2 ± 3.3	7.4 ± 2.6	8.1 ± 3.2	7.3 ± 2.6	7.4 ± 2.4	<0.001
Post prandial, mmol	11.2 ± 4.5	11.3 ± 4.6	10.9 ± 4.1	11.4 ± 4.4	10.3 ± 3.8	10.1 ± 4.7	<0.001
HbA1c, %	8.0 ± 2.1	8.2 ± 2.2	7.5 ± 1.7	8.2 ± 2.1	7.4 ± 1.8	7.3 ± 1.8	<0.001
Lipid Profile							
Total Cholesterol, mmol/l	5.2 ± 1.2	5.3 ± 1.3	4.9 ± 1.1	4.9 ± 1.1	5.0 ± 1.1	5.0 ± 1.1	<0.001
Triglyceride, mmol/l	1.8 ± 1.1	1.8 ± 1.2	1.7 ± 1.1	1.7 ± 1.0	1.7 ± 1.1	1.9 ± 1.2	<0.001
HDL, mmol/l	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	<0.001
LDL,mmol/l	3.1 ± 1.1	3.2 ± 1.2	2.8 ± 1.0	2.9 ± 1.0	3.1 ± 1.1	2.8 ± 1.1	<0.001
Renal Profile							
Serum Creatinine, mmol/l	89.5 ± 52.3	90.4 ± 53.0	89.9 ± 53.5	84.5 ± 50.3	80.1 ± 39.1	95.3 ± 36.9	<0.001
Urine Microalbumin, positive	50,453 (14.9)	35,346 (16.1)	8,441 (13.5)	5,346 (13.3)	763 (12.1)	557 (5.7)	<0.001
Urine Protein, positive	49,957 (14.8)	35,141 (16.0)	7,959 (12.8)	5,036 (12.5)	999 (15.8)	822 (8.4)	<0.001

Table 4.5: Baseline biomarkers of multi ethnic diabetes cohort from Sabah and Sarawak

	Indigenous Sabah				Indigenous Sarawak				
	Kadazan	Dusun	Bajau	Other Sabah	Iban	Bidayuh	Melanau	Other Sarawak	P-value
	Mean ± SD or n, %								
Glycemic Profile									
Fasting Blood Glucose, mmol/l	7.1 ± 2.3	7.0 ± 2.3	7.7 ± 2.7	7.5 ± 2.7	7.4 ± 2.4	7.5 ± 2.4	7.4 ± 2.5	7.2 ± 2.6	<0.001
Post prandial, mmol/L	10.0 ± 3.8	10.4 ± 3.5	10.5 ± 3.9	10.2 ± 3.9	10.3 ± 4.8	9.2 ± 5.1	7.9 ± 2.7	10.7 ± 3.6	<0.001
HbA1c, %	7.2 ± 1.7	7.3 ± 1.7	7.4 ± 1.9	7.5 ± 1.9	7.3 ± 1.8	7.1 ± 1.6	7.0 ± 1.6	7.3 ± 1.9	<0.001
Lipid Profile									
Total Cholesterol, mmol/l	5.0 ± 1.1	4.9 ± 1.1	5.1 ± 1.1	5.0 ± 1.1	4.9 ± 1.2	5.0 ± 1.1	5.1 ± 1.1	5.0 ± 1.1	<0.001
Triglyceride, mmol/l	1.9 ± 1.4	1.9 ± 1.2	1.6 ± 0.9	1.7 ± 1.0	1.9 ± 1.2	1.9 ± 1.4	1.6 ± 0.9	1.8 ± 1.1	<0.001
HDL, mmol/l	1.3 ± 0.5	1.3 ± 0.4	1.2 ± 0.4	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.5	1.3 ± 0.5	1.3 ± 0.4	<0.001
LDL,mmol/l	3.1 ± 1.0	3.0 ± 1.0	3.2 ± 1.0	3.0 ± 1.1	2.8 ± 1.1	2.9 ± 1.0	2.8 ± 1.0	3.0 ± 1.1	<0.001
Renal Profile									
Serum Creatinine, mmol/l	80.4 ± 44.8	79.2 ± 38.3	77.4 ± 31.4	82.6 ± 40.4	96.0 ± 37.1	96.2 ± 43.5	88.9 ± 25.3	94.2 ± 37.3	<0.001
Urine Microalbumin, positive	226 (15.5)	157 (14.3)	182 (9.9)	198 (10.3)	441 (5.7)	42 (7.4)	22 (3.0)	52 (6.6)	<0.001
Urine Protein, positive	237 (16.2)	214 (19.5)	240 (13.0)	308 (16.0)	647 (8.4)	48 (8.5)	57 (7.8)	70 (8.9)	<0.001

Table 4.4 and table 4.5 above described the baseline level for biomarkers of multi ethnic diabetes cohort for major ethnicities and the indigenous populations from Sabah and Sarawak. The glycemic profile (HbA1c level, fasting blood glucose and post-prandial glucose level) and lipid profile (triglyceride, HDL, and LDL) are the biomarkers that are being monitored in the management of type 2 diabetes patients treated in Malaysia (MOH, 2015).

At baseline, glycemic control defined by HbA1c level showed the overall mean of 8.0%. Malay and Indian had the highest level of HbA1c with a mean of 8.2%, followed by Chinese at 7.5%, Indigenous Sabah at 7.4% and Indigenous Sarawak at 7.3%. HbA1c level among ethnicities from Sabah and Sarawak ranged from 7.0% to 7.5%. All ethnicities had exceeded the target level for control of type 2 diabetes, which is less than or equal to 6.5%. However, these targets were set for newly diagnosed diabetes patients, patients at younger age and had shown no evidence of having significant cardiovascular complications. A less robust target of 7.1% to 8.0% had been set for patients with diabetes-related complications.

The overall mean for fasting blood glucose (FBG) level was 8.0 mmol/L. Malay had the highest FBG level at 8.2 mmol/L, followed by Indian (8.1 mmol/L), Bajau (7.7 mmol/L) and Other Sabah and Bidayuh at 7.5 mmol/L. Post-prandial glucose (PPG) level ranged higher at 9.0 mmol/L to 11 mmol/L. At baseline, FBG and PPG for all ethnic groups were above the normal values.

Malay and Melanau ethnic groups had abnormal total cholesterol level at baseline that ranged between 5.2 and 5.3 mmol/L. In contrast to Triglyceride (TG), only Bajau and Melanau ethnic groups had a normal level of TG at baseline (1.6 mmol/L). All diabetes patients from all ethnic groups had a normal level of HDL, but with an abnormal level of LDL at baseline (ranged from 2.8-3.2 mmol/L for LDL). However,

looking at the differences in means, the standardized mean differences of HDL and LDL that expressed the size of the differences were relatively small between all ethnicities.

Urine microalbumin and urine protein described in the renal profile acted as indicators for renal complications among diabetes patients. 15% to 16% among Malay and Kadazan ethnic groups had positive urine microalbumin at baseline while 16% to 19% among Malay, Kadazan, Dusun and Other Sabah ethnic groups had positive urine protein at baseline.

Table 4.6: Proportions of abnormal baseline biomarkers for overall and major ethnicities of multi ethnic diabetes cohort

	Overall	Malay	Chinese	Indian	Indigenous Sabah	Indigenous Sarawak	P-value
	N, (%)						
Glycemic Profile							
Fasting Blood Glucose, <4.4 mmol or > 7.0 mmol/l	114,641 (55.6)	74,105 (58.4)	20,106 (48.7)	14,396 (57.8)	2,402 (45.7)	3,632 (46.1)	<0.001
Post prandial, <4.4 mmol/L or > 8.5 mmol/L	12,937 (68.6)	8,421 (69.0)	2,327 (68.0)	1,512 (69.5)	551 (63.3)	126 (67.7)	<0.001
HbA1c, >6.5%	178,998 (69.4)	121,744 (71.4)	29,395 (62.1)	22,880 (72.9)	2,936 (55.4)	2,043 (56.4)	<0.001
Lipid Profile							
Total Cholesterol, >5.2mmol/l	111,287 (42.5)	81,600 (47.7)	15,376 (31.4)	10,587 (33.5)	1,790 (36.5)	1,934 (35.2)	<0.001
Triglyceride, ≥1.7mmol/l	113,282 (43.5)	77,615 (45.6)	19,413 (40.0)	11,830 (37.6)	1,913 (40.9)	2,511 (46.9)	<0.001
HDL, ≤1.0mmol/l	51,992 (25.9)	32,701 (24.7)	8,025 (22.0)	9,332 (36.9)	427 (23.5)	1,507 (30.6)	<0.001
LDL, ≥2.6mmol/l	133,057 (66.6)	92,688 (70.5)	20,363 (56.0)	15,985 (63.7)	1,192 (66.9)	2,829 (56.7)	<0.001
Renal Profile							
Serum Creatinine,>100mmol/l	62,230 (24.1)	42,589 (25.2)	11,648 (24.1)	5,582 (17.8)	785 (17.0)	1,626 (30.8)	<0.001

Table 4.7: Proportions of abnormal baseline biomarkers among multi ethnic diabetes cohort from Sabah and Sarawak

	Indigenous Sabah				Indigenous Sarawak				
	Kadazan	Dusun	Bajau	Other Sabah	Iban	Bidayuh	Melanau	Other Sarawak	P-value
	N, (%)								
Glycemic Profile									
Fasting Blood Glucose, <4.4 mmol or > 7.0 mmol/l	467 (39.6)	363 (38.4)	776 (51.7)	796 (48.7)	2,932 (46.5)	176 (48.5)	267 (43.9)	257 (42.6)	<0.001
Post prandial, <4.4 mmol/L or > 8.5 mmol/L	50 (64.1)	60 (72.3)	146 (63.2)	295 (61.6)	109 (69.9)	6 (54.6)	5 (50.0)	6 (66.7)	<0.001
HbA1c, >6.5%	596 (50.2)	554 (55.4)	823 (54.7)	963 (59.9)	1,623 (57.2)	134 (53.8)	164 (53.6)	122 (52.8)	<0.001
Lipid Profile									
Total Cholesterol, >5.2mmol/l	426 (37.3)	307 (31.9)	510 (38.8)	547 (37.0)	1,446 (34.0)	149 (37.9)	168 (39.0)	171 (40.9)	<0.001
Triglyceride, ≥1.7mmol/l	466 (42.4)	453 (49.7)	422 (33.7)	572 (40.4)	2,050 (49.1)	158 (42.6)	130 (33.3)	173 (41.5)	<0.001
HDL, ≤1.0mmol/l	92 (18.0)	55 (21.0)	106 (29.4)	174 (25.4)	1,237 (32.0)	105 (32.0)	83 (23.7)	82 (21.9)	<0.001
LDL, ≥2.6mmol/l	341 (67.9)	161 (65.5)	249 (71.1)	441 (64.5)	2,215 (56.6)	197 (61.2)	183 (48.3)	234 (61.9)	<0.001
Renal Profile									
Serum Creatinine,>100mmol/l	181 (16.5)	128 (14.0)	174 (15.1)	302 (20.7)	1,296 (31.7)	118 (32.0)	96 (23.4)	116 (28.4)	<0.001

Table 4.6 and table 4.7 above explained the proportions of multi ethnic diabetes cohort with abnormal baseline biomarkers for major ethnicities and ethnicities from Sabah and Sarawak.

69% of all diabetes patients had an abnormal HbA1c level at baseline that is defined as HbA1c level of more than 6.5%. The highest proportions were among the Indian ethnic group where 73% of the Indian patients had an abnormal level of HbA1c at baseline. This is followed by Malay at 71% and Chinese at 62%. 50%-60% of patients of ethnicities from Sabah and Sarawak had their HbA1c level of more than 6.5%.

56% of all diabetes patients had abnormal FBG level. 50% of patients of Malay, Indian and Bajau ethnic groups had abnormal FBG. More than 50% of all ethnicities had their PPG level out from the normal range, which is between 4.4 mmol/L and 8.5 mmol/L.

Malay ethnic group had the highest proportions of patients with abnormal total cholesterol (54%), while Dusun ethnic group had the highest proportions with abnormal TG. The highest proportions of patients with abnormal LDL were among the Indian (41%). Malay, Kadazan, Dusun, and Bajau ethnic groups had more than 70% of the diabetes patients to have abnormal LDL level at baseline.

23% to 32% of patients of Indigenous Sarawak ethnic group had abnormal serum creatinine level at baseline (more than 100 mmol/L). Ethnic groups from Sabah had 14% to 20% with abnormal serum creatinine level, while Malay, Chinese, and Indian had 25%, 24% and 18% of the diabetes patients with abnormal serum creatinine level, respectively.

Table 4.8: Baseline characteristics of multi ethnic diabetes cohort duration < 1 year and duration ≥ 1 year

	Duration < 1 year, N=15,326 (4.5)	Duration ≥ 1 year, N=323,023 (95.5)	P-value
	Mean ± SD or n, %		
Male	6,684 (43.6)	127,359 (39.4)	<0.001
Age	55.2 ± 11.9	59.4 ± 11.2	<0.001
Age at diagnosis of diabetes	54.5 ± 11.9	52.8 ± 11.2	<0.001
BMI, kg/m2	28.3 ± 8.3	27.5 ± 6.2	<0.001
Waist circumference, cm	92.6 ± 12.5	91.9 ± 12.1	<0.001
SBP, mmHg	135 ± 17.6	135 ± 17.8	0.9835
DBP, mmHg	80 ± 10	78 ± 10.0	<0.001
Current smoking status	744 (4.9)	11,855 (3.4)	<0.001
Co-morbidities			
Hypertension only	1,755 (11.5)	44,664 (13.8)	<0.001
Dyslipidemia only	2,963 (19.3)	38,315 (11.9)	<0.001
Both comorbidities	9,425 (61.5)	204,389 (63.3)	<0.001
Type of Diabetes Medications			
OHA only	13,123 (85.6)	231,863 (71.8)	<0.001
Insulin only	370 (2.4)	15,197 (4.7)	<0.001
Both OHA and Insulin	803 (5.2)	51,363 (15.9)	<0.001
Antihypertensive			
Ace Inhibitors	5,457 (35.6)	155,974 (48.3)	<0.001
Angiotensin Receptor Blocker	382 (2.5)	14,887 (4.6)	<0.001
Beta Blocker	2,658 (17.3)	74,703 (23.1)	<0.001
Calcium Channel Blocker	6,097 (39.8)	126,159 (39.1)	<0.001
Diuretics	2,244 (14.6)	62,872 (19.5)	<0.001
Others	277 (1.8)	11,753 (3.6)	<0.001
Lipid-lowering agents			<0.001
Statins	8,762 (57.2)	206,595 (64.0)	<0.001
Fibrates	354 (2.3)	10,185 (3.2)	<0.001

Table 4.8 above explained the baseline sociodemography and diabetes characteristics of multi ethnic diabetes cohort among newly diagnosed diabetes, compared to patients who have been diagnosed with diabetes for more than a year. Newly diagnosed is defined as the duration of diabetes of less than a year between the date of diagnosis of diabetes and the first date enrolled in this study. 4.5% or 15,326 patients were newly diagnosed diabetes patients in this study.

Among the newly diagnosed diabetes, the proportion of male was 44%, compared to 39% of those with longer duration of diabetes. Mean age of the newly diagnosed diabetes patients was 55 years. Newly diagnosed diabetes patients were diagnosed at an older age of 55 years compared to patients with longer duration of diabetes. These patients were diagnosed at a comparatively younger age of 53 years.

At baseline, the mean BMI among the newly diagnosed diabetes patients was significantly higher compared to patients with longer duration of diabetes. This observed difference in BMI between the two groups of diabetes patients is expected as BMI of diabetes patients could reduce with time due to several contributing factors including diabetes medications, lifestyle changes or even the progression of the disease.

There was no clinically significant difference in mean for systolic blood pressure and diastolic blood pressure observed among newly diagnosed diabetes patients compared to patients with longer duration of diabetes.

A significant difference was observed between newly diagnosed diabetes patients and patients with longer duration of diabetes in the proportions of having hypertension, dyslipidemia and both co-morbidities. Majority of the diabetes patients had both hypertension and dyslipidemia at baseline (62% among newly diagnosed diabetes patients and 63% among patients with longer duration of diabetes). Hypertension alone

is more common among patients with longer duration of diabetes (14%, p-value<0.001), while dyslipidemia is more common among newly diagnosed with diabetes patients (19%, p-value<0.001).

Duration of diabetes explained changes in diabetes medication prescribed to the patients. With longer duration of diabetes, OHA usage was seen to reduce and was either replaced with insulin or used in combination with OHA. 86% of newly diagnosed diabetes patients were on OHA, 2.4% were on insulin and 5.2% were on both OHA and insulin. Compared to patients with longer duration of diabetes, 72% were on OHA, 5% were on insulin and 16% were on both OHA and insulin. The differences explained the progression of disease with time that required more intensified therapeutic management.

Diabetic hypertensive patients were prescribed with ACE-i and calcium channel blockers (CCB), regardless of the duration of diabetes. 60% of all diabetic dyslipidemic patients from both groups of diabetes patients were on statins.

Table 4.9 below described the baseline biomarkers of newly diagnosed diabetes patients compared to patients with longer duration of diabetes in the multi ethnic diabetes cohort.

Standardized mean differences for all biomarkers, regardless of the duration of diabetes, were not pronounced. Mean HbA1c for newly diagnosed diabetes patients was 7.8 mmol/L, compared to 8.1 mmol/L among patients with longer duration of diabetes. Similarly, with FBG, it was 7.9 mmol/L among newly diagnosed diabetes patients compared to 8.0 mmol/L among patients with longer duration of diabetes. Post-prandial glucose level was higher among newly diagnosed diabetes patients at 12.7 mmol/L, compared to patients with longer duration of diabetes that had a lower level at 11.1 mmol/L.

Total cholesterol, triglyceride and LDL level were higher at baseline even among newly diagnosed diabetes patients. HDL level remained within the normal range for all patients. There was an increased serum creatinine level among patients with longer duration of diabetes at 89.9 mmol/L, compared to 81.8 mmol/L among newly diagnosed diabetes patients. However, the differences in mean were not distinct.

Table 4.9: Baseline biomarkers of multi ethnic diabetes cohort diagnosed < 1 year and diagnosed ≥ 1 year

	Diagnosed < 1 year	Diagnosed ≥ 1 year	P-value
	Mean ± SD or n, %		
Glycemic Profile			
Fasting Blood Glucose, mmol/l	7.9 ± 2.9	8.0 ± 3.1	<0.001
Post prandial, mmol/L	12.7 ± 5.1	11.1 ± 4.4	<0.001
HbA1c, %	7.8 ± 2.1	8.1 ± 2.1	<0.001
Lipid Profile			
Total Cholesterol, mmol/l	5.4 ± 1.3	5.2 ± 1.2	<0.001
Triglyceride, mmol/l	1.8 ± 1.2	1.8 ± 1.1	<0.001
HDL, mmol/l	1.3 ± 0.5	1.3 ± 0.5	<0.001
LDL,mmol/l	3.3 ± 1.2	3.1 ± 1.1	<0.001
Renal Profile			
Serum Creatinine, mmol/l	81.8 ± 40.5	89.9 ± 52.8	<0.001

4.3 Association between ethnicity and glycemic control

Table 4.10 below explained the cross-sectional association between ethnicity and the changes in HbA1c levels. There was a total of 166,550 diabetes patients in this analysis. As previously mentioned, cross-sectional association referred to prevalent associations at time of first presentation to the registry. The constant was set at 5-years.

Model 1 described the association between HbA1c levels and ethnicity, adjusted for all other ethnicities and duration of diabetes. In Model 1, there was a significant cross-sectional association between all other ethnicities, compared to Malay. Malay, as the reference group had HbA1c level of 8.2% at presentation. At presentation, all ethnic groups were associated with lower HbA1c levels, compared to Malay [Chinese 0.9%, Indian 0.1%, Indigenous Sabah 0.8% and Indigenous Sarawak 0.8%]. Kadazan contributed most to the significant association amongst Indigenous Sabah while Bidayuh and Melanau contributed most to the significant association amongst the Indigenous Sarawak. These ethnic groups had 1.0% lower HbA1c level, compared to Malay at presentation.

Model 2 was adjusted for Model 1, age, sex and treatment of diabetes. Malay, as reference group had HbA1c level of 7.1% at presentation. Though the changes seen in the associations between all other ethnic groups and HbA1c level were small, the cross-sectional association remained significant. Compared to Malay, all other ethnic groups had significantly lower HbA1c levels at presentation, controlling for other covariates [Chinese 0.6%, Indian 0.2%, Indigenous Sabah 0.8% and Indigenous Sarawak 0.9%]. Among the Indigenous Sabah, Kadazan was associated with 1.0% lower HbA1c level, Bajau with 0.8% lower and Dusun and Other Sabah with 0.7% lower HbA1c level at presentation. Among the Indigenous Sarawak, Iban, Bidayuh and Melanau were

associated with 0.9% lower HbA1c level, and Other Sarawak was associated with 0.6% lower HbA1c level at presentation, compared to Malay.

Table 4.10: Association between ethnicity and HbA1c levels in multi ethnic diabetes cohort

Difference in HbA1c levels for every 5 years of diabetes				
Ethnicity N=166,550	Model 1 β (95%CI)	P-value	Model 2 β (95%CI)	P-value
Duration of diabetes	0.34	<0.001	0.25	<0.001
Ethnicity				
Malay	0 (ref)		0 (ref)	
Chinese	-0.89 (-0.92, -0.86)	<0.001	-0.58 (-0.61, -0.55)	<0.001
Indian	-0.09 (-0.13, -0.06)	<0.001	-0.18 (-0.21, -0.14)	<0.001
Indigenous Sabah	-0.78 (-0.85, -0.71)	<0.001	-0.77 (-0.84, -0.71)	<0.001
Kadazan	-1.03 (-1.19, -0.88)	<0.001	-0.95 (-1.09, -0.80)	<0.001
Dusun	-0.75 (-0.90, -0.60)	<0.001	-0.70 (-0.83, -0.56)	<0.001
Bajau	-0.71 (-0.85, -0.58)	<0.001	-0.77 (-0.89, -0.64)	<0.001
Other Sabah	-0.68 (-0.81, -0.55)	<0.001	-0.72 (-0.83, -0.61)	<0.001
Indigenous Sarawak	-0.82 (-0.93, -0.71)	<0.001	-0.89 (-0.99, -0.80)	<0.001
Iban	-0.83 (-0.95, -0.71)	<0.001	-0.92 (-1.03, -0.81)	<0.001
Bidayuh	-1.00 (-1.45, -0.55)	<0.001	-0.92 (-1.32, -0.51)	<0.001
Melanau	-0.96 (-1.51, -0.42)	0.001	-0.92 (-1.41, -0.42)	<0.001
Other Sarawak	-0.54 (-0.94, -0.15)	0.007	-0.62 (-0.98, -0.27)	0.001

** Model 1 adjusted for all other ethnicities and duration of diabetes.*
*** Model 2 adjusted for Model 1, age, sex, and treatment for diabetes.*
****Using Linear Mixed Effect Model with random intercept.*

Table 4.11: Longitudinal analysis of the association between ethnicity and HbA1c levels

Difference in HbA1c levels for every 5 years of diabetes				
Ethnicity N=166,550	Model 3 β (95%CI)	P-value	Model 4 β (95%CI)	P-value
Duration of diabetes	0.39	<0.001	0.28	<0.001
Ethnicity				
Malay	0 (ref)		0 (ref)	
Chinese				
Cross-sectional[1]	-0.80 (-0.84, -0.76)	<0.001	-0.51 (-0.55, -0.48)	<0.001
Longitudinal[2]	-0.13 (-0.16, -0.10)	<0.001	-0.10 (-0.13, -0.07)	<0.001
Indian				
Cross-sectional	-0.02 (-0.05, 0.04)	0.930	-0.11 (-0.15, -0.07)	<0.001
Longitudinal	-0.13 (-0.17, -0.10)	<0.001	-0.10 (-0.13, -0.07)	<0.001
Indigenous Sabah				
Cross-sectional	-0.78 (-0.85, -0.70)	<0.001	-0.78 (-0.85, -0.71)	<0.001
Longitudinal	0.05 (-0.04, 0.13)	0.286	0.06 (-0.01, 0.14)	0.116
Kadazan				
Cross-sectional	-1.01 (-1.18, -0.85)	<0.001	-0.95 (-1.10, -0.80)	<0.001
Longitudinal	-0.03 (-0.20, 0.14)	0.724	0.03 (-0.13, 0.18)	0.746
Dusun				
Cross-sectional	-0.76 (-0.91, -0.61)	<0.001	-0.71 (-0.85, -0.58)	<0.001
Longitudinal	0.29 (0.10, 0.48)	0.003	0.24 (0.07, 0.41)	0.005
Bajau				
Cross-sectional	-0.71 (-0.85, -0.57)	<0.001	-0.76 (-0.89, -0.63)	<0.001
Longitudinal	0.05 (-0.12, 0.21)	0.588	0.02 (-0.12, 0.17)	0.747
Other Sabah				
Cross-sectional	-0.66 (-0.80, -0.53)	<0.001	-0.72 (-0.84, -0.60)	<0.001
Longitudinal	-0.01 (-0.16, 0.14)	0.912	0.04 (-0.10, 0.17)	0.588
Indigenous Sarawak				
Cross-sectional	-0.88 (-1.00, -0.75)	<0.001	-0.96 (-1.07, -0.84)	<0.001
Longitudinal	0.10 (-0.01, 0.22)	0.072	0.12 (0.01, 0.22)	0.025
Iban				
Cross-sectional	-0.86 (-1.00, -0.72)	<0.001	-0.96 (-1.09, -0.83)	<0.001
Longitudinal	0.06 (-0.06, 0.19)	0.327	0.08 (-0.03, 0.20)	0.164
Bidayuh				
Cross-sectional	-1.18 (-1.67, -0.68)	<0.001	-1.08 (-1.53, -0.64)	<0.001
Longitudinal	0.39 (-0.04, 0.81)	0.073	0.34 (-0.02, 0.74)	0.067
Melanau				
Cross-sectional	-1.07 (-1.77, -0.38)	0.003	-0.99 (-1.62, -0.36)	0.002
Longitudinal	0.10 (-0.35, 0.54)	0.677	0.06 (-0.34, 0.47)	0.763
Other Sarawak				
Cross-sectional	-0.68 (-1.11, -0.26)	0.002	-0.77 (-1.16, -0.39)	<0.001
Longitudinal	0.42 (-0.03, 0.86)	0.068	0.44 (0.04, 0.85)	0.033

** P-value for ethnicity-time interaction <0.001.*

*** Model 3 adjusted for all other ethnicities, duration of diabetes and interaction between all other ethnicities and duration of diabetes.*

*** Model 4 adjusted for Model 3, age, sex and treatment for diabetes.*

****Using Linear Mixed Effect Model with random intercept.*

[1]Cross-sectional associations are prevalent associations at time of first presentation to the registry.

[2]Longitudinal associations are associations for every 5-years of diabetes duration.

Table 4.11 above described the cross-sectional associations and the longitudinal associations between ethnicity and HbA1c levels. Time in this study was the duration of diabetes for every patient. Cross-sectional association in these models referred to prevalent associations at time of first presentation to the registry. Longitudinal association referred to HbA1c levels that change with every five years of diabetes duration.

Model 3 adjusted for all other ethnicities, duration of diabetes and included interaction between all other ethnicities and duration of diabetes. Only Chinese and Dusun ethnicity that showed significant cross-sectional association and significant longitudinal association in this model. The HbA1c level among the Chinese at presentation was 0.8% lower compared to Malay (mean HbA1c of 8.1%), and 0.1% lower for every 5-year of diabetes duration. Amongst the Dusun, the HbA1c level was 0.8% lower at presentation, compared to Malay and increases by 0.3% for every 5-year of diabetes duration [Longitudinal associations: Chinese: β= -0.13 (-0.16, -0.10), p-value <0.001, Dusun: β= 0.29 (0.10, 0.48), p-value at 0.003]. The HbA1c level was similar between Indian and Malay at presentation, but the HbA1c level decreases by 0.1% for every 5-year of diabetes duration [Cross-sectional: β= -0.02 (-0.05, 0.04), p-value at 0.930, Longitudinal: β= -0.13 (-0.17, -0.10), p-value <0.001].

Model 4 was the full model, adjusted for Model 3, age, sex and treatment for diabetes. All other ethnicities showed significant cross-sectional associations and are associated with lower HbA1c level at presentation, compared to Malay (mean HbA1c of 7.5%). Only Chinese, Indian, Dusun and Indigenous Sarawak including Other Sarawak that remained to be significant in the longitudinal associations.

Compared to Malay, Chinese was associated with 0.5% lower HbA1c level at presentation and the HbA1c level among Chinese decreases by 0.1% for every 5-year of diabetes duration [Chinese: Cross sectional association: β= -0.51 (-0.55, -0.48), p-value <0.001, Longitudinal association: β= -0.10 (-0.13, -0.07), p-value <0.001]. The Indian was associated with 0.1% lower HbA1c at presentation, compared to Malay and the HbA1c level decreases by 0.1% for every 5-year of diabetes duration [Indian: Cross sectional association: β= -0.11 (-0.15, -0.07), p-value <0.001, Longitudinal association: β= -0.10 (-0.13, -0.07), p-value <0.001].

Among the Indigenous Sabah, Dusun was significantly associated with 0.7% lower HbA1c level at presentation. For every 5-year of diabetes duration, the HbA1c level among Dusun increases by 0.2% for every 5-year of diabetes duration, compared to Malay. Kadazan was associated with 1.0% lower HbA1c level, compared to Malay. Bajau was associated with 0.8% lower, and Other Sabah with 0.7% lower HbA1c level compared to Malay. However, the HbA1c level was similar between Kadazan, Bajau, Other Sabah and Malay for every 5-year of diabetes duration. There were no significant longitudinal associations among these ethnic groups with changes in HbA1c level.

Indigenous Sarawak was associated with 1.0% lower HbA1c level at presentation, compared to Malay and for every 5-year of diabetes duration, the HbA1c level decreases by 0.1%. Other Sarawak contributed to the significant longitudinal association amongst the Indigenous Sarawak. At presentation, Other Sarawak was associated with 0.8% lower HbA1c level and the level increases by 0.4% for every 5-year of diabetes durationt, compared to the Malay.

Amongst the other Indigenous Sarawak, Bidayuh was associated with 1.1% lower HbA1c level compared to Malay and Iban and Melanau with 1.0% lower HbA1c level compared to Malay. These ethnic groups showed no significant longitudinal associations. The HbA1c level was similar between Bidayuh, Iban , Melanau and Malay for every 5-year of diabetes duration.

Table 4.12 below described the association between ethnicity and good glycemic control in multi ethnic diabetes cohort. Good glycemic control was defined as the level of HbA1c of less than or equals to 6.5%. In these models, the cross-sectional association also referred to prevalent associations at time of first presentation to the registry.

Model 1 adjusted for all other ethnicities and duration of diabetes. In model 1, all other ethnicities showed significant cross-sectional associations with good glycemic control, except amongst the Indian. Chinese, Indigenous Sabah, and Indigenous Sarawak had a positive association with good glycemic control compared to Malay. Amongst the Indigenous Sabah and Indigenous Sarawak, Bidayuh, Kadazan, Melanau, and Bajau had the highest odds of good glycemic control, compared to Malay. The odds of having good glycemic control among Bidayuh were 3.9 times higher compared to Malay, while Kadazan, Melanau, and Bajau had the odds of having good glycemic control at 4.5, 4.1 and 3.6 times of those Malay. Chinese had the odds of having good glycemic control at 2.4 times compared to Malay.

In model 2, adjusted for age, sex, and diabetes treatment, the odds of having good glycemic control attenuated and the significance level changed. Malay was the reference group. Indian had its odds of having good glycemic control increased and significant in this adjusted model [OR 1.13 (95%CI 1.05, 1.20)] while Chinese had its odds of having good glycemic control hovering at a higher level than Indian [OR 1.67 (95%CI 1.58, 1.76)] compared to Malay. All ethnicities from Sabah and Sarawak had increased odds of having good glycemic control than Malay in this model. Bidayuh, Kadazan, Melanau, and Dusun had their odds attenuated but remained significantly associated with good glycemic control after adjustment for covariates [Bidayuh: OR 4.41 (95%CI 2.15, 9.05), Kadazan: OR 4.03 (95%CI 3.18, 5.10), Melanau: OR 3.80 (95%CI 1.57, 9.22) and Dusun OR 2.93 (95%CI 2.33, 3.68)].

Table 4.12: Association between ethnicity and good glycemic control in multi ethnic diabetes cohort

Good glycemic control (HbA1c ≤6.5%)				
Ethnicity N=166,551	Model 1 OR (95%CI)	P-value	Model 2 OR (95%CI)	P-value
Duration of diabetes	0.60 (0.59, 0.62)	<0.001	0.67 (0.91, 0.99)	<0.001
Ethnicity				
Malay	0 (ref)		0 (ref)	
Chinese	2.44 (2.30, 2.59)	<0.001	1.67 (1.58, 1.76)	<0.001
Indian	0.99 (0.92, 1.06)	0.765	1.13 (1.05, 1.20)	<0.001
Indigenous Sabah	3.37 (2.99, 3.81)	<0.001	3.36 (3.00, 3.75)	<0.001
Kadazan	4.51 (3.48, 5.84)	<0.001	4.03 (3.18, 5.10)	<0.001
Dusun	3.11 (2.42, 4.00)	<0.001	2.93 (2.33, 3.68)	<0.001
Bajau	3.62 (2.87, 4.56)	<0.001	3.84 (3.11, 4.74)	<0.001
Other Sabah	2.75 (2.22, 3.42)	<0.001	2.91 (2.39, 3.55)	<0.001
Indigenous Sarawak	3.09 (2.55-3.74)	<0.001	3.37 (2.82, 4.02)	<0.001
Iban	2.95 (2.39, 3.64)	<0.001	3.29 (2.71, 4.00)	<0.001
Bidayuh	4.89 (2.25, 10.63)	<0.001	4.41 (2.15, 9.05)	<0.001
Melanau	4.10 (1.58, 10.62)	0.004	3.80 (1.57, 9.22)	0.003
Other Sarawak	3.03 (1.54, 5.97)	0.001	3.31 (1.77, 6.19)	<0.001

** P-value for ethnicity-time interaction <0.001.*
*** Model 1 adjusted for all other ethnicities and duration of diabetes.*
*** Model 2 adjusted for Model 1, age, sex and treatment for diabetes.*
****Using random intercept logistic regression models.*

Table 4.13: Association between ethnicity and good glycemic control in multi ethnic diabetes cohort with time interaction

Good glycemic control (HbA1c ≤6.5%)				
Ethnicity N=166,551	Model 3 OR (95%CI)	P-value	Model 4 OR (95%CI)	P-value
Ethnicity				
Malay	0 (ref)		0 (ref)	
Chinese				
Cross-sectional[1]	2.33 (2.18, 2.50)	<0.001	1.61 (1.52, 1.71)	<0.001
Longitudinal[2]	1.08 (1.02, 1.15)	0.005	1.07 (1.01, 1.12)	0.014
Indian				
Cross-sectional	0.86 (0.79, 0.94)	0.001	1.01 (0.93, 1.09)	0.835
Longitudinal	1.25 (1.17, 1.34)	<0.001	1.20 (1.13, 1.28)	<0.001
Indigenous Sabah				
Cross-sectional	3.44 (3.03, 3.91)	<0.001	3.43 (3.06, 3.85)	<0.001
Longitudinal	0.86 (0.73, 1.00)	0.053	0.86 (0.75, 0.99)	0.037
Kadazan				
Cross-sectional	4.54 (3.44, 6.01)	<0.001	4.15 (3.21, 5.35)	<0.001
Longitudinal	0.96 (0.71, 1.30)	0.784	0.90 (0.68, 1.19)	0.470
Dusun				
Cross-sectional	3.14 (2.44, 4.05)	<0.001	2.95 (2.34, 3.71)	<0.001
Longitudinal	0.70 (0.49, 0.99)	0.046	0.73 (0.53, 1.02)	0.064
Bajau				
Cross-sectional	3.74 (2.94, 4.75)	<0.001	3.92 (3.15, 4.88)	<0.001
Longitudinal	0.82 (0.61, 1.10)	0.191	0.87 (0.67, 1.14)	0.320
Other Sabah				
Cross-sectional	2.80 (2.24, 3.51)	<0.001	2.99 (2.43, 3.67)	<0.001
Longitudinal	0.87 (0.65, 1.16)	0.347	0.85 (0.65, 1.10)	0.219
Indigenous Sarawak				
Cross-sectional	3.46 (2.79, 4.30)	<0.001	3.72 (3.05, 4.54)	<0.001
Longitudinal	0.77 (0.61, 0.96)	0.022	0.80 (0.65, 0.98)	0.031
Iban				
Cross-sectional	3.19 (2.51, 4.05)	<0.001	3.51 (2.82, 4.37)	<0.001
Longitudinal	0.84 (0.66, 1.07)	0.162	0.86 (0.69, 1.08)	0.203
Bidayuh				
Cross-sectional	6.74 (2.88, 15.78)	<0.001	5.64 (2.57, 12.38)	<0.001
Longitudinal	0.35 (0.11, 1.13)	0.079	0.45 (0.16, 1.28)	0.135
Melanau				
Cross-sectional	5.68 (1.72, 18.71)	0.004	5.07 (1.68, 15.27)	<0.001
Longitudinal	0.68 (0.28, 1.67)	0.403	0.71 (0.31, 1.63)	0.417
Other Sarawak				
Cross-sectional	3.67 (1.79, 7.53)	<0.001	4.00 (2.06, 7.77)	<0.001
Longitudinal	0.44 (0.17, 1.16)	0.098	0.43 (0.17, 1.08)	0.071

** P-value for ethnicity-time interaction <0.001.*

*** Model 3 adjusted for all other ethnicities and duration of diabetes.*

*** Model 4 adjusted for Model 3, age, sex and treatment for diabetes.*

****Using random intercept logistic regression models.*

[1]Cross-sectional associations are prevalent associations at time of first presentation to the registry.

[2]Longitudinal associations are associations that change with time and for these results, a 5-year time change was used for the coefficients of the associations.

Table 4.13 above described the association between ethnicity and good glycemic control in multi ethnic diabetes cohort with time interaction. Time was defined similarly to the previous models, which was the duration of diabetes. Cross-sectional association in these models also referred to prevalent associations at time of first presentation to the registry. Longitudinal association referred to changes in the HbA1c level for every 5-year of diabetes duration.

Model 4 was the final model adjusted for Model 3, age, sex, treatment for diabetes and included interaction between ethnicity and duration of diabetes. All other ethnicities showed significant cross-sectional associations with good glycemic control. With time interaction within the same model, the significant longitudinal association remained for Chinese, Indian, Indigenous Sabah and Indigenous Sarawak.

Indian had similar odds of good glycemic control with Malay at presentation but [OR 1.01 (95%CI 0.93, 1.09) p-value 0.835] increases by 20% for every 5-year of diabetes duration. Chinese had the odds of having good glycemic control at 1.6 times, compared to Malay and for every 5-year duration of diabetes, the odds of good glycemic control increases by 7% for Chinese.

Indigenous Sabah had the odds of good glycemic control at 3.4 times at presentation, compared to Malay and the odds reduces by 14% for every 5-year of diabetes duration. Kadazan had the highest odds of having good glycemic control at presentation at 4.1 times, followed by Bajau [OR 3.92 (95%CI 3.15, 4.88)] and Dusun and Other Sabah at 3.0 times at presentation, compared to Malay. The odds of good glycemic control were similar between these ethnic groups and Malay for every 5-year of diabetes duration.

The odds of good glycemic control among Indigenous Sarawak was 3.7 times than Malay at presentation and reduces by 20% for every 5-year of diabetes duration. Bidayuh had shown the highest odds of having good glycemic control at 5.6 times higher compared to Malay, followed by Melanau at 5.1 times higher, Other Sarawak at 4.0 times higher and Iban had the odds of having good glycemic control at 3.5 times higher compared to Malay. The odds of good glycemic control among these ethnic groups were similar with Malay for every 5-year of diabetes duration.

4.4 Role of BMI and Sex as mediators in the association between ethnicity and glycemic control

Table 4.14, table 4.15, table 4.16 and table 4.17 below explained BMI and sex as lifestyle mediators in the association between ethnicity and HbA1c level. BMI, as a mediator was measured as continuous variable and categorical variable (overweight and obese). Glycemic control as the outcome was also measured as continuous outcome and categorical outcome (defined as good glycemic control when HbA1c ≤6.5%).

Overall, Chinese, Indian and Melanau had BMI and Sex mediated the association with glycemic control.

Table 4.14 explained the role of BMI as a mediator (continuous mediator) in the association between ethnicity and HbA1c level (continuous outcome). Chinese and Indian showed significant indirect effects and direct effects in the association with changes in HbA1c level. The significance of both direct and indirect effects in these particular ethnic groups explained BMI as a partial mediator in the association with changes in HbA1c level. The percentage of indirect effect from the total effect explained the indirect associations or the magnitude of effect of the mediation. Comparing Chinese to Malays and HbA1c levels, 1.7% of the Total Effect [aβ= -0.52 (95%CI -0.55, -0.50), p<0.001] was mediated by BMI. Comparing Indian to Malays and

HbA1c levels, 4.1% of the Total Effect [aβ= -0.12 (95%CI -0.15, -0.10), p<0.001] was mediated by BMI. The indirect associations for the other ethnic groups were less than 1%.

Table 4.14: BMI level as lifestyle mediator in the association between ethnicity and HbA1c level

Ethnicity	Indirect Effect β (95%CI)	P-value	Direct Effect β (95%CI)	P-value	Total Effect β (95%CI)	P-value	% Indirect effect of Total effect
BMI							
Malay	0 (reference)		0 (reference)		0 (reference)		
Chinese	0.01 (0.01, 0.01)	<0.001	-0.53 (-0.55, -0.51)	<0.001	-0.52 (-0.55, -0.50)	<0.001	1.7%
Indian	0.01 (0.01, 0.01)	<0.001	-0.13 (-0.15, -0.11)	<0.001	-0.12 (-0.15, -0.10)	<0.001	4.1%
Indigenous Sabah	0.01 (0.01, 0.01)	0.013	-0.80 (-0.86, -0.75)	<0.001	-0.80 (-0.86, -0.75)	<0.001	0.2%
Kadazan	-0.01 (-0.01, 0.01)	0.206	-0.93 (-1.04, -0.82)	<0.001	-0.93 (-1.04, -0.82)	<0.001	0.2%
Dusun	0.01 (-0.01, 0.01)	0.084	-0.82 (-0.95, -0.70)	<0.001	-0.82 (-0.94, -0.70)	<0.001	0.4%
Bajau	0.01 (0.01, 0.01)	0.011	-0.81 (-0.91, -0.71)	<0.001	-0.81 (-0.91, -0.70)	<0.001	0.4%
Other Sabah	-0.01 (-0.01, 0.01)	0.592	-0.69 (-0.79, -0.59)	<0.001	-0.69 (-0.79, -0.59)	<0.001	0.1%
Indigenous Sarawak	0.01 (0.01, 0.01)	<0.001	-0.94 (-1.00, -0.87)	<0.001	-0.93 (-1.00, -0.87)	<0.001	0.5%
Iban	0.01 (0.01, 0.01)	<0.001	-0.92 (-0.99, -0.85)	<0.001	-0.92 (-0.99, -0.84)	<0.001	0.6%
Bidayuh	0.01 (-0.01, 0.01)	0.283	-1.01 (-1.25, -0.76)	<0.001	-1.00 (-1.25, -0.76)	<0.001	0.3%
Melanau	0.01 (0.01, 0.01)	0.002	-1.08 (-1.30, -0.86)	<0.001	-1.07 (-1.29, -0.85)	<0.001	0.7%
Other Sarawak	-0.01 (-0.01, 0.01)	0.154	-0.92 (-1.18, -0.66)	<0.001	-0.92 (-1.18, -0.66)	<0.001	0.4%

**Model adjusted for age, sex and treatment for diabetes.*
***Using Generalized Structural Equation Modeling (GSEM).*

Table 4.15 below summarizes the effect of overweight and obese as mediators in the association between ethnicity and changes in HbA1c level.

Comparing Chinese to Malays and HbA1c levels, 1.6% of the Total Effect [aβ= -0.53 (95%CI -0.55, -0.51), p<0.001) was mediated by being overweight and 3.5% of the Total Effect [aβ= -0.52 (95%CI -0.54, -0.50), p<0.001] was mediated by being obese. Comparing Indian to Malays and HbA1c levels, 3.3% of the Total Effect [aβ= -0.13 (95%CI -0.15, -0.10), p<0.001] was mediated by being overweight and 7.5% of the Total Effect [aβ= -0.12 (95%CI -0.15, -0.10), p<0.001] was mediated by being obese. Comparing Melanau to Malays and HbA1c levels, 1.2% of the Total Effect [aβ= -1.08 (95%CI -1.30, -0.85), p<0.001] was mediated by being obese. The indirect associations for the other ethnic groups were less than 1%.

Table 4.16 below summarizes the effect of overweight and obese as mediators in the association between ethnicity and good glycemic control.

Comparing Chinese to Malays and good glycemic control, 3.7% of the Total Effect [aβ= 0.27 (95%CI 0.25, 0.29), p<0.001) was mediated by being overweight and 6.4% of the Total Effect [aβ= -0.52 (95%CI -0.54, -0.50), p<0.001] was mediated by being obese. Comparing Melanau to Malays and good glycemic control, 1.5% of the Total Effect [aβ= 0.85 (95%CI 0.61, 1.08), p<0.001] was mediated by being obese. The indirect associations for the other ethnic groups were less than 1%. The total effect of the association between Indian and good glycemic control was not significant, likely contributed by the small effect size.

In Table 4.17 below, it summarizes the effect of sex as a mediator in the association between ethnicity and glycemic control. HbA1c was measured as both continuous outcome and categorical outcome defined at a cut off point of HbA1c ≤6.5% for good glycemic control.

Comparing Indian to Malays and HbA1c levels, 1.1% of the Total Effect [aβ= -0.12 (95%CI -0.14, -0.10), p<0.001] was mediated by sex. The indirect associations were less than 1% for other ethnic groups with significant indirect effects.

Table 4.15: Overweight and Obese as lifestyle mediators in the association between ethnicity and HbA1c level

Ethnicity	Indirect Effect β (95%CI)	P-value	Direct Effect β (95%CI)	P-value	Total Effect β (95%CI)	P-value	% Indirect effect of Total effect
Overweight							
Malay, normal weight	0 (reference)		0 (reference)		0 (reference)		
Chinese	0.01 (0.01, 0.01)	<0.001	-0.54 (-0.56, -0.52)	<0.001	-0.53 (-0.55, -0.51)	<0.001	1.6%
Indian	0.01 (0.01 (0.01)	<0.001	-0.13 (-0.15, -0.11)	<0.001	-0.13 (-0.15, -0.10)	<0.001	3.3%
Indigenous Sabah	0.01 (-0.01, 0.01)	0.505	-0.80 (-0.86, -0.75)	<0.001	-0.80 (-0.86, -0.75)	<0.001	0.1%
Kadazan	-0.01 (-0.01, 0.01)	0.139	-0.93 (-1.04, -0.81)	<0.001	-0.93 (-1.04, -0.81)	<0.001	0.3%
Dusun	-0.01 (-0.01, 0.01)	0.964	-0.82 (-0.94, -0.70)	<0.001	-0.82 (-0.94, -0.70)	<0.001	0.1%
Bajau	0.01 (-0.01, 0.01)	0.156	-0.81 (-0.91, -0.71)	<0.001	-0.81 (-0.91, -0.71)	<0.001	0.3%
Other Sabah	0.01 (-0.01, 0.01)	0.256	-0.69 (-0.79, -0.59)	<0.001	-0.69 (-0.79, -0.59)	<0.001	0.3%
Indigenous Sarawak	0.01 (0.01, 0.01)	0.016	-0.94 (-1.00, -0.87)	<0.001	-0.94 (-1.00, -0.87)	<0.001	0.2%
Iban	0.01 (0.01, 0.01)	0.033	-0.92 (-0.99, -0.85)	<0.001	-0.92 (-0.99, -0.84)	<0.001	0.2%
Bidayuh	0.01 (-0.01, 0.01)	0.524	-1.00 (-1.30, -0.76)	<0.001	-1.00 (-1.25, -0.76)	<0.001	0.2%
Melanau	0.01 (0.01, 0.01)	0.037	-1.08 (-1.30, -0.76)	<0.001	-1.08 (-1.30, -0.85)	<0.001	0.6%
Other Sarawak	-0.01 (-0.01, 0.01)	0.571	-0.92 (-1.18, -0.66)	<0.001	-0.92 (-1.18, -0.67)	<0.001	0.2%
Obese							
Malay, normal weight	0 (reference)		0 (reference)		0 (reference)		
Chinese	0.02 (0.02, 0.02)	<0.001	-0.54 (-0.56, -0.52)	<0.001	-0.52 (-0.54, -0.50)	<0.001	3.5%
Indian	0.01 (0.01, 0.01)	<0.001	-0.13 (-0.15, -0.11)	<0.001	-0.12 (-0.15, -0.10)	<0.001	7.5%
Indigenous Sabah	0.01 (-0.01, 0.01)	0.504	-0.80 (-0.86, -0.75)	<0.001	-0.80 (-0.86, -0.75)	<0.001	0.2%
Kadazan	-0.01 (-0.01, 0.01)	0.131	-0.93 (-1.04, -0.81)	<0.001	-0.93 (-1.04, -0.82)	<0.001	0.6%
Dusun	-0.01 (-0.01, 0.01)	0.964	-0.82 (-0.94, -0.70)	<0.001	-0.82 (-0.94, -0.70)	<0.001	0.1%
Bajau	0.01 (-0.01, 0.01)	0.148	-0.81 (-0.91, -0.71)	<0.001	-0.81 (-0.91, -0.70)	<0.001	0.6%
Other Sabah	0.01 (-0.01, 0.01)	0.250	-0.69 (-0.79, -0.59)	<0.001	-0.69 (-0.79, -0.59)	<0.001	0.6%
Indigenous Sarawak	0.01 (0.01, 0.01)	0.011	-0.94 (-1.00, -0.87)	<0.001	-0.94 (-1.00, -0.87)	<0.001	0.4%
Iban	0.01 (0.01,0.01)	0.026	-0.92 (-0.99, -0.85)	<0.001	-0.92 (-0.99, -0.84)	<0.001	0.4%
Bidayuh	0.01 (-0.01, 0.01)	0.523	-1.00 (-1.30, -0.76)	<0.001	-1.00 (-1.25, -0.76)	<0.001	0.4%
Melanau	0.01 (0.01, 0.02)	0.030	-1.08 (-1.30, -0.76)	<0.001	-1.08 (-1.30, -0.85)	<0.001	1.2%
Other Sarawak	-0.01 (-0.01, 0.01)	0.570	-0.92 (-1.18, -0.66)	<0.001	-0.92 (-1.18, -0.66)	<0.001	0.3%

**Model adjusted for age, sex and treatment for diabetes.*

***Using Generalized Structural Equation Modeling (GSEM). Comparing overweight to normal weight and obese to normal weight*

Table 4.16: Overweight and Obese as lifestyle mediators in the association between ethnicity and good glycemic control

Ethnicity	Indirect Effect β (95%CI)	P-value	Direct Effect β (95%CI)	P-value	Total Effect β (95%CI)	P-value	% Indirect effect of Total effect
Overweight							
Malay, normal weight	0 (reference)		0 (reference)		0 (reference)		
Chinese	0.01 (0.01, 0.01)	<0.001	0.26 (0.24, 0.28)	<0.001	0.27 (0.25, 0.29)	<0.001	3.7%
Indian	0.01 (0.01, 0.01)	<0.001	-0.03 (-0.06, 0.01)	0.077	-0.02 (-0.05, 0.01)	0.150	23.1%
Indigenous Sabah	0.01 (-0.01, 0.01)	0.505	0.66 (0.60, 0.72)	<0.001	0.66 (0.60, 0.72)	<0.001	0.1%
Kadazan	-0.01 (-0.01, 0.01)	0.138	0.79 (0.67, 0.92)	<0.001	0.79 (0.67, 0.91)	<0.001	0.4%
Dusun	-0.01 (-0.01, 0.01)	0.964	0.74 (0.60, 0.87)	<0.001	0.74 (0.60, 0.87)	<0.001	0.1%
Bajau	0.01 (-0.01, 0.01)	0.155	0.68 (0.57, 0.79)	<0.001	0.68 (0.57, 0.79)	<0.001	0.4%
Other Sabah	0.01 (-0.01, 0.01)	0.255	0.50 (0.39, 0.61)	<0.001	0.50 (0.39, 0.61)	<0.001	0.4%
Indigenous Sarawak	0.01 (0.01, 0.01)	0.016	0.79 (0.72, 0.86)	<0.001	0.79 (0.72, 0.86)	<0.001	0.3%
Iban	0.01 (0.01, 0.01)	0.032	0.77 (0.69, 0.85)	<0.001	0.77 (0.69, 0.85)	<0.001	0.3%
Bidayuh	0.01 (-0.01, 0.01)	0.524	0.82 (0.56, 1.08)	<0.001	0.83 (0.57, 1.09)	<0.001	0.3%
Melanau	0.01 (0.01, 0.01)	0.036	0.83 (0.60, 1.07)	<0.001	0.84 (0.61, 1.08)	<0.001	0.9%
Other Sarawak	-0.01 (-0.01, 0.01)	0.571	0.96 (0.69, 1.23)	<0.001	0.96 (0.69, 1.23)	<0.001	0.2%
Obese							
Malay, normal weight	0 (reference)		0 (reference)		0 (reference)		
Chinese	0.02 (0.02, 0.02)	<0.001	0.26 (0.24, 0.28)	<0.001	0.28 (0.25, 0.30)	<0.001	6.4%
Indian	0.01 (0.01, 0.01)	<0.001	-0.03 (-0.06, 0.01)	0.077	-0.02 (-0.05, 0.01)	0.236	50.2%
Indigenous Sabah	0.01 (-0.01, 0.01)	0.504	0.66 (0.60, 0.72)	<0.001	0.66 (0.60, 0.72)	<0.001	0.2%
Kadazan	-0.01 (-0.01, 0.01)	0.132	0.79 (0.67, 0.92)	<0.001	0.79 (0.66, 0.91)	<0.001	0.8%
Dusun	-0.01 (-0.01, 0.01)	0.964	0.74 (0.60, 0.87)	<0.001	0.73 (0.60, 0.87)	<0.001	0.1%
Bajau	0.01 (-0.01, 0.01)	0.149	0.68 (0.57, 0.79)	<0.001	0.68 (0.57, 0.80)	<0.001	0.8%
Other Sabah	0.01 (-0.01, 0.01)	0.255	0.50 (0.39, 0.61)	<0.001	0.50 (0.40, 0.61)	<0.001	0.8%
Indigenous Sarawak	0.01 (0.01, 0.01)	0.012	0.79 (0.72, 0.86)	<0.001	0.79 (0.72, 0.86)	<0.001	0.5%
Iban	0.01 (0.01, 0.01)	0.026	0.77 (0.69, 0.85)	<0.001	0.77 (0.69, 0.85)	<0.001	0.5%
Bidayuh	0.01 (-0.01, 0.01)	0.523	0.82 (0.56, 1.08)	<0.001	0.83 (0.57, 1.09)	<0.001	0.5%
Melanau	0.01 (0.01, 0.02)	0.031	0.83 (0.60, 1.07)	<0.001	0.85 (0.61, 1.08)	<0.001	1.5%
Other Sarawak	-0.01 (-0.01, 0.01)	0.570	0.96 (0.69, 1.23)	<0.001	0.96 (0.68, 1.23)	<0.001	0.3%

**Model adjusted for age, sex and treatment for diabetes.*

***Using Generalized Structural Equation Modeling (GSEM). Comparing overweight to normal weight and obese to normal weight*

Table 4.17: Sex as mediator in the association between ethnicity, HbA1c level and good glycemic control

Ethnicity	Indirect Effect β (95%CI)	P-value	Direct Effect β (95%CI)	P-value	Total Effect β (95%CI)	P-value	% Indirect effect of Total effect
HbA1c Level							
Malay	0 (reference)		0 (reference)		0 (reference)		
Chinese	-0.01 (-0.01, -0.01)	<0.001	-0.52 (-0.54, -0.50)	<0.001	-0.52 (-0.54, -0.50)	<0.001	0.7%
Indian	-0.01 (-0.01, -0.01)	<0.001	-0.12 (-0.14, -0.09)	<0.001	-0.12 (-0.14, -0.10)	<0.001	1.1%
Indigenous Sabah	-0.01 (-0.01, 0.01)	0.126	-0.80 (-0.85, -0.74)	<0.001	-0.80 (-0.85, -0.74)	<0.001	0.1%
Kadazan	-0.01 (-0.01, 0.01)	0.110	-0.93 (-1.04, -0.81)	<0.001	-0.93 (-1.04, -0.82)	<0.001	0.2%
Dusun	-0.01 (-0.01, 0.01)	0.306	-0.82 (-0.94, -0.70)	<0.001	-0.82 (-0.94, -0.70)	<0.001	0.2%
Bajau	0.01 (-0.01, 0.01)	0.836	-0.81 (-0.90, -0.71)	<0.001	-0.80 (-0.90, -0.71)	<0.001	0.1%
Other Sabah	-0.01 (-0.01, 0.01)	0.390	-0.68 (-0.78, -0.59)	<0.001	-0.68 (-0.78, -0.59)	<0.001	0.1%
Indigenous Sarawak	0.01 (-0.01, 0.01)	0.090	-0.94 (-1.00, -0.88)	<0.001	-0.94 (-1.00, -0.88)	<0.001	0.1%
Iban	0.01 (0.01, 0.01)	0.036	-0.92 (-0.99, -0.85)	<0.001	-0.92 (-0.99, -0.84)	<0.001	0.1%
Bidayuh	-0.01 (-0.01, 0.01)	0.826	-1.01 (-1.26, -0.77)	<0.001	-1.01 (-1.26, -0.77)	<0.001	0.1%
Melanau	-0.01 (-0.01, 0.01)	0.897	-1.08 (-1.30, -0.86)	<0.001	-1.08 (-1.30, -0.86)	<0.001	0.1%
Other Sarawak	-0.01 (-0.01, 0.01)	0.695	-0.95 (-1.20, -0.69)	<0.001	-0.95 (-1.20, -0.69)	<0.001	0.1%
Good Glycemic Control							
Malay	0 (reference)		0 (reference)		0 (reference)		
Chinese	0.01 (0.01, 0.01)	0.013	0.27 (0.25, 0.30)	<0.001	0.28 (0.25, 0.30)	<0.001	0.5%
Indian	0.01 (0.01, 0.01)	0.025	-0.02 (-0.05, 0.01)	0.122	-0.02 (-0.05, 0.01)	0.132	2.5%
Indigenous Sabah	0.01 (-0.01, 0.01)	0.184	0.66 (0.61, 0.72)	<0.001	0.66 (0.61, 0.72)	<0.001	0.1%
Kadazan	0.01 (-0.01, 0.01)	0.170	0.78 (0.66, 0.90)	<0.001	0.78 (0.66, 0.90)	<0.001	0.1%
Dusun	0.01 (-0.01, 0.01)	0.340	0.74 (0.61, 0.87)	<0.001	0.74 (0.61, 0.87)	<0.001	0.1%
Bajau	-0.01 (-0.01, 0.01)	0.836	0.69 (0.58, 0.80)	<0.001	0.69 (0.58, 0.80)	<0.001	0.1%
Other Sabah	0.01 (-0.01, 0.01)	0.413	0.50 (0.39, 0.61)	<0.001	0.50 (0.39, 0.61)	<0.001	0.1%
Indigenous Sarawak	-0.01 (-0.01, 0.01)	0.152	0.79 (0.72, 0.86)	<0.001	0.79 (0.72, 0.86)	<0.001	0.5%
Iban	-0.01 (-0.01, 0.01)	0.100	0.77 (0.70, 0.85)	<0.001	0.77 (0.69, 0.85)	<0.001	0.1%
Bidayuh	0.01 (-0.01, 0.01)	0.827	0.82 (0.56, 1.08)	<0.001	0.82 (0.56, 1.08)	<0.001	0.1%
Melanau	0.01 (-0.01, 0.01)	0.897	0.86 (0.63, 1.09)	<0.001	0.86 (0.63, 1.09)	<0.001	0.1%
Other Sarawak	0.01 (-0.01, 0.01)	0.699	0.92 (0.65, 1.19)	<0.001	0.92 (0.65, 1.19)	<0.001	0.1%

**Model adjusted for age and treatment for diabetes.*

***Using Generalized Structural Equation Modeling (GSEM).*

4.5 Association between ethnicity and diabetes-related complications

Table 4.18 and table 4.19 below described the proportions of diabetes-related complications among major ethnicities and ethnicities from Sabah and Sarawak from the multi ethnic diabetes cohort.

Overall, there were 281,204 or 83% of all diabetes patients in this study with known status on the presence and absence of diabetes-related complications. 44,238 or 16% of all diabetes patients with a known status of diabetes-related complications were diagnosed with at least one complication. The majority was diagnosed with diabetic nephropathy (51%, n=19,285), whereas 42% (n=15,959) were diagnosed with diabetic retinopathy and 7% were diagnosed with peripheral vascular disease (PVD).

Overall

Among the major ethnicities, 16% of Malay, Chinese, Indian and Indigenous Sabah and 8% of Indigenous Sarawak diabetes patients were diagnosed with diabetes-related complications. Kadazan showed the highest proportion of diabetes patients diagnosed with diabetes-related complications at 19%, followed by Other Sabah at 18% and Bajau (16%). The proportions of diabetes-related complications among Melanau, Bidayuh, Dusun, Iban and Other Sarawak varied from 6% to 10%.

Diabetic Nephropathy

In the distribution for each complication, the highest proportions of diabetic nephropathy were amongst the Indigenous Sarawak at 56%, followed by Malay at 53%, Chinese and Indian at 48% and Indigenous Sabah at 25%. Among the Indigenous Sarawak, Other Sarawak, Iban and Melanau had the highest proportions of diabetes patients diagnosed with diabetic nephropathy. Dusun and Kadazan contributed to the high proportions of patients with nephropathy amongst the Indigenous Sabah.

Diabetic Retinopathy

Indigenous Sabah had the highest proportions of diabetes patients diagnosed with diabetic retinopathy at 74%, followed by Chinese (47%) and Indian (44%). Malay and Indigenous Sarawak had 38%-39% of the diabetes patients diagnosed with diabetic retinopathy. Amongst the Indigenous Sabah diabetes patients, Bajau had the highest proportions of diabetes patients diagnosed with diabetic retinopathy at 81%, followed by Other Sabah at 75%, and 64%-66% from Kadazan and Dusun ethnic groups. Bidayuh ethnic group had the highest proportions of diabetes patients diagnosed with diabetic retinopathy at 77% amongst the Indigenous Sarawak.

Peripheral Vascular Disease

Diagnosis of PVD as diabetes-related complications ranged from 2%-8% among the major ethnic groups as well as amongst ethnic groups from Sabah and Sarawak. The highest proportions were amongst Melanau (9%), followed by Indian and Malay at 8%, while Iban and Other Sarawak ranged between 6% and 7%.

Table 4.18: Distribution of diabetes-related complications for overall and major ethnicities of multi ethnic diabetes cohort

Ethnicities	Overall	Malay	Chinese	Indian	Indigenous Sabah	Indigenous Sarawak	P-value
				N(%)			
Complications	338,349	219,478	62,427	40,287	6,329	9,828	
Unknown	57,145 (16.9)	38,968 (17.8)	9,496 (15.2)	6,066 (15.1)	1,000 (15.8)	1,615 (16.4)	
Known	281,204 (83.1)	180,510 (82.2)	52,931 (84.8)	34,221 (84.9)	5,329 (84.2)	8,213 (83.6)	
No	236,966 (84.3)	151,866 (84.1)	44,374 (83.8)	28,718 (83.9)	4,487 (84.2)	7,521 (91.6)	<0.001
Yes	44,238 (15.7)	28,644 (15.9)	8,557 (16.2)	5,503 (16.1)	842 (15.8)	692 (8.4)	<0.001
Nephropathy	19,285 (50.9)	12,954 (53.0)	3,545 (48.0)	2,246 (47.9)	183 (24.5)	357 (55.8)	<0.001
Retinopathy	15,959 (42.1)	9,620 (39.4)	3,486 (47.2)	2,059 (44.0)	551 (73.7)	243 (38.0)	<0.001
PVD	2,658 (7.0)	1,870 (7.7)	354 (4.8)	380 (8.1)	14 (1.9)	40 (6.3)	<0.001

Table 4.19: Distribution of diabetes-related complications of multi ethnic diabetes cohort from Sabah and Sarawak

Ethnicities	Kadazan	Dusun	Bajau	Other Sabah	Iban	Bidayuh	Melanau	Other Sarawak	P-value
Complications	1,461	1,100	1,847	1,921	7,742	568	731	787	
Unknown	175 (12.0)	149 (13.6)	342 (18.5)	334 (17.4)	1,324 (17.1)	45 (7.9)	96 (13.1)	150 (19.1)	
Known	1,286 (88.0)	951 (86.4)	1,505 (81.5)	1,587 (82.6)	6,418 (82.9)	523 (92.1)	635 (86.9)	637 (80.9)	
No	1,040 (80.9)	880 (92.5)	1,269 (84.3)	1,298 (81.8)	5,862 (91.3)	487 (93.1)	599 (94.3)	573 (90.0)	<0.001
Yes	246 (19.1)	71 (7.5)	236 (15.7)	289 (18.2)	556 (8.7)	36 (6.7)	36 (5.7)	64 (10.1)	<0.001
Nephropathy	64 (30.8)	20 (33.9)	41 (18.7)	58 (22.1)	299 (57.8)	7 (20.6)	16 (47.1)	35 (63.6)	<0.001
Retinopathy	138 (66.4)	38 (64.4)	178 (81.3)	197 (75.2)	186 (36.0)	26 (76.5)	15 (44.1)	16 (29.1)	<0.001
PVD	6 (2.9)	1 (1.7)	0 (0.0)	7 (2.7)	32 (6.2)	1 (2.9)	3 (8.8)	4 (7.3)	<0.001

Ψ PVD: Peripheral vascular disease

Table 4.20, table 4.21 and table 4.22 below explained the association between ethnicity and the hazard of developing diabetes-related complications, namely diabetic retinopathy, diabetic nephropathy and peripheral vascular disease. There were three models included in this analysis. Model 1 adjusted for age and sex, and Model 2 adjusted for Model 1, HbA1c level and treatment for diabetes. In the final model, Model 3 adjusted for Model 2, BMI, smoking status and comorbidities.

Table 4.20 below described the association between ethnicity and hazard of developing diabetic retinopathy. In overall, there were ethnic differences in the hazard of developing diabetic retinopathy. Major ethnic groups including Chinese, Indian and Indigenous Sabah showed increased hazard in developing diabetic retinopathy, compared to Malay. This association persisted in the final multivariable-adjusted model.

Indian and Chinese showed 18%, and 23% increased hazard of diabetic retinopathy while Indigenous Sabah showed a hazard ratio of 1.91, compared to Malay. Amongst the Indigenous Sabah, Kadazan showed the highest hazard ratio amongst all other ethnicities with HR 2.72 (95%CI 2.39, 3.09), followed by Other Sabah [HR 2.15 (95%CI 1.90, 2.42)] and Bajau [HR 1.93 (95%CI 1.69, 2.20)].

Indigenous Sarawak showed decreased hazard in developing diabetic retinopathy in the final multivariable-adjusted model compared to Malay [HR 0.63 (95%CI 0.54, 0.75)]. Among Indigenous Sarawak, Iban, Melanau and Other Sarawak were associated with diabetic retinopathy in the earlier model. However, the significant association persisted for only Iban and Melanau in the final adjusted model. Iban showed 38% decreased hazard in developing Diabetic Retinopathy, while Melanau showed 53% decreased hazard, compared to Malay.

Table 4.21 below explained the association between ethnicity and hazard of developing diabetic nephropathy. Overall, Indian, Kadazan, and Other Sarawak showed no significant association with the hazard of developing diabetic nephropathy.

Chinese, in the earlier model, showed an increased hazard of diabetic nephropathy [HR 1.03 (95%CI 1.00, 1.07), p-value 0.027]. The association attenuated but remained significant in the final multivariable-adjusted model and showed decreased hazard of diabetic nephropathy at HR 0.95 [(95%CI 0.91, 0.98), p-value 0.001].

Indigenous Sabah and Indigenous Sarawak showed 30% and 37% lower hazard of diabetic nephropathy in the final multivariable-adjusted model compared to Malay. Among the Indigenous Sabah, Dusun, Bajau and Other Sabah contributed to the significant association with a decreased hazard of diabetic nephropathy. Dusun and Bajau had 50% to 60% decreased hazard of developing diabetic nephropathy, compared to Malay while Other Sabah showed 32% decreased hazard in the final multivariable-adjusted model.

Among Indigenous Sarawak, the association in Bidayuh and Melanau attenuated, but remained to have the lowest hazard of developing diabetic nephropathy at HR 0.24 [(95%CI 0.09, 0.65), p-value 0.005)] and HR 0.26 [(95%CI 0.11, 0.63), p-value 0.003)], respectively.

Table 4.20: Association between ethnicity and Diabetic Retinopathy for diabetes-related complications

Ethnicity	Crude Model HR (95%CI)	P-value	Model 1 HR (95%CI)	P-value	Model 2 HR (95%CI)	P-value	Model 3 HR (95%CI)	P-value
Diabetic Retinopathy								
Malay	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Chinese	1.30 (1.26, 1.34)	<0.001	1.16 (1.12, 1.20)	<0.001	1.24 (1.20, 1.28)	<0.001	1.23 (1.18, 1.27)	<0.001
Indian	1.17 (1.13, 1.22)	<0.001	1.20 (1.16, 1.25)	<0.001	1.18 (1.13, 1.23)	<0.001	1.18 (1.13, 1.23)	<0.001
Indigenous Sabah	1.66 (1.56, 1.78)	<0.001	1.75 (1.64, 1.87)	<0.001	1.92 (1.79, 2.06)	<0.001	1.91 (1.78, 2.05)	<0.001
Kadazan	2.39 (2.12, 2.70)	<0.001	2.43 (2.16, 2.74)	<0.001	2.74 (2.42, 3.11)	<0.001	2.72 (2.39, 3.09)	<0.001
Dusun	0.73 (0.59, 0.91)	0.004	0.77 (0.62, 0.95)	0.017	0.83 (0.66, 1.03)	0.096	0.81 (0.64, 1.01)	0.060
Bajau	1.66 (1.46, 1.87)	<0.001	1.77 (1.56, 2.00)	<0.001	1.92 (1.68, 2.19)	<0.001	1.93 (1.69, 2.20)	<0.001
Other Sabah	1.81 (1.61, 2.02)	<0.001	1.92 (1.71, 2.15)	<0.001	2.14 (1.90, 2.40)	<0.001	2.15 (1.90, 2.42)	<0.001
Indigenous Sarawak	0.60 (0.54,0.67)	<0.001	0.64 (0.57, 0.71)	<0.001	0.68 (0.57, 0.80)	<0.001	0.63 (0.54, 0.75)	<0.001
Iban	0.58 (0.51, 0.65)	<0.001	0.61 (0.54, 0.69)	<0.001	0.67 (0.56, 0.81)	<0.001	0.62 (0.52, 0.75)	<0.001
Bidayuh	0.97 (0.68, 1.39)	0.867	1.02 (0.71, 1.45)	0.934	1.08 (0.64, 1.82)	0.781	1.02 (0.59, 1.76)	0.936
Melanau	0.61 (0.40, 0.92)	0.019	0.61 (0.40, 0.93)	0.021	0.48 (0.23, 1.00)	0.052	0.47 (0.23, 0.99)	0.048
Other Sarawak	0.58 (0.39, 0.84)	0.004	0.60 (0.41, 0.88)	0.009	0.57 (0.28, 1.14)	0.111	0.58 (0.29, 1.16)	0.123

** Crude model included ethnicity as a predictor.*
*** Model 1 adjusted for age and sex.*
*** Model 2 adjusted for Model 1, HbA1c level and treatment for diabetes.*
*** Model 3 adjusted for Model 2, comorbidities, BMI and smoking.*
****Using Discrete-time survival analysis*

Table 4.21: Association between ethnicity and Diabetic Nephropathy for diabetes-related complications

Ethnicity	Crude Model HR (95%CI)	P-value	Model 1 HR (95%CI)	P-value	Model 2 HR (95%CI)	P-value	Model 3 HR (95%CI)	P-value
Diabetic Nephropathy								
Malay	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Chinese	1.03 (1.00, 1.07)	0.027	0.89 (0.87, 0.92)	<0.001	0.94 (0.91, 0.97)	<0.001	0.95 (0.91, 0.98)	0.001
Indian	1.00 (0.97, 1.04)	0.828	1.02 (0.99, 1.06)	0.198	1.00 (0.97, 1.04)	0.811	1.00 (0.96, 1.04)	0.908
Indigenous Sabah	0.60 (0.55, 0.66)	<0.001	0.63 (0.58, 0.70)	<0.001	0.69 (0.62, 0.76)	<0.001	0.70 (0.63, 0.77)	<0.001
Kadazan	1.06 (0.91, 1.24)	0.430	1.07 (0.92, 1.25)	0.382	1.17 (0.99, 1.37)	0.067	1.17 (0.99, 1.39)	0.062
Dusun	0.45 (0.36, 0.58)	<0.001	0.48 (0.38, 0.61)	<0.001	0.51 (0.40, 0.65)	<0.001	0.50 (0.39, 0.64)	<0.001
Bajau	0.41 (0.33, 0.51)	<0.001	0.45 (0.36, 0.55)	<0.001	0.49 (0.39, 0.62)	<0.001	0.49 (0.39, 0.62)	<0.001
Other Sabah	0.56 (0.47, 0.67)	<0.001	0.60 (0.51, 0.72)	<0.001	0.65 (0.54, 0.78)	<0.001	0.68 (0.57, 0.82)	<0.001
Indigenous Sarawak	0.64 (0.58, 0.70)	<0.001	0.69 (0.63, 0.75)	<0.001	0.68 (0.58, 0.78)	<0.001	0.63 (0.54, 0.73)	<0.001
Iban	0.67 (0.60, 0.74)	<0.001	0.72 (0.65, 0.80)	<0.001	0.74 (0.63, 0.86)	<0.001	0.68 (0.58, 0.79)	<0.001
Bidayuh	0.25 (0.13, 0.46)	<0.001	0.26 (0.14, 0.49)	<0.001	0.29 (0.12, 0.69)	0.005	0.24 (0.09, 0.65)	0.005
Melanau	0.41 (0.26, 0.64)	<0.001	0.41 (0.26, 0.65)	<0.001	0.26 (0.11, 0.63)	0.003	0.26 (0.11, 0.63)	0.003
Other Sarawak	0.82 (0.62, 1.09)	0.176	0.86 (0.65, 1.14)	0.296	0.77 (0.46, 1.30)	0.335	0.78 (0.46, 1.33)	0.364

** Crude model included ethnicity as a predictor*
*** Model 1 adjusted for age and sex.*
*** Model 2 adjusted for Model 1, HbA1c level and treatment for diabetes.*
*** Model 3 adjusted for Model 2, comorbidities, BMI and smoking.*
****Using Discrete-time survival analysis*

Table 4.22 below explained the association between ethnicity and hazard of developing peripheral vascular disease (PVD). Bidayuh, Melanau and Other Sarawak showed no significant association in the hazard of PVD.

The Indians were the only ethnic group that had increased hazard of developing PVD. The association although attenuated, remained significantly associated with increased hazard of PVD in the final multivariable-adjusted model [HR 1.11 (95%CI 1.00, 1.22), p-value 0.040].

The other major ethnicities i.e. Chinese, Indigenous Sabah, and Indigenous Sarawak were associated with decreased hazard of developing PVD. Indigenous Sabah had the lowest hazard of developing PVD at HR 0.44 (95%CI 0.31, 0.61), followed by Indigenous Sarawak at HR 0.52 (95%CI 0.34, 0.81), and Chinese with a hazard ratio of 0.67 (95%CI 0.60, 0.75), compared to Malay.

Dusun, Bajau, Other Sabah and Iban were the ethnic groups that remained to be significantly associated with decreased hazard of developing PVD in the final multivariable-adjusted model. Each Dusun and Iban diabetes patients had 49%, and 42% decreased hazard of developing PVD, compared to Malay. Amongst Bajau and Other Sabah, the hazard of developing PVD was 57% and 53% lower compared to Malay in the final model.

Table 4.22: Association between ethnicity and Peripheral Vascular Disease for diabetes-related complications

Ethnicity	Crude Model HR (95%CI)	P-value	Model 1 HR (95%CI)	P-value	Model 2 HR (95%CI)	P-value	Model 3 HR (95%CI)	P-value
Peripheral Vascular Disease								
Malay	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Chinese	0.70 (0.65, 0.76)	<0.001	0.64 (0.59, 0.69)	<0.001	0.70 (0.64, 0.77)	<0.001	0.67 (0.60, 0.75)	<0.001
Indian	1.16 (1.07, 1.26)	<0.001	1.16 (1.07, 1.26)	<0.001	1.14 (1.04, 1.25)	0.005	1.11 (1.00, 1.22)	0.040
Indigenous Sabah	0.36 (0.27, 0.48)	<0.001	0.36 (0.27, 0.49)	<0.001	0.42 (0.30, 0.58)	<0.001	0.44 (0.31, 0.61)	<0.001
Kadazan	0.52 (0.31, 0.88)	0.016	0.52 (0.31, 0.88)	0.014	0.64 (0.36, 1.13)	0.124	0.61 (0.33, 1.14)	0.119
Dusun	0.34 (0.18, 0.66)	0.001	0.35 (0.18, 0.67)	0.002	0.47 (0.25, 0.91)	0.026	0.51 (0.27, 0.99)	0.046
Bajau	0.19 (0.09, 0.41)	<0.001	0.20 (0.10, 0.42)	<0.001	0.30 (0.14, 0.62)	0.001	0.33 (0.16, 0.69)	0.003
Other Sabah	0.40 (0.25, 0.65)	<0.001	0.41 (0.25, 0.67)	<0.001	0.33 (0.17, 0.64)	0.001	0.37 (0.19, 0.71)	0.003
Indigenous Sarawak	0.47 (0.36, 0.61)	<0.001	0.49 (0.38, 0.64)	<0.001	0.54 (0.35, 0.82)	0.004	0.52 (0.34, 0.81)	0.004
Iban	0.45 (0.34, 0.61)	<0.001	0.47 (0.35, 0.64)	<0.001	0.58 (0.37, 0.91)	0.017	0.58 (0.36, 0.92)	0.022
Bidayuh	0.43 (0.14, 1.34)	0.146	0.44 (0.14, 1.36)	0.154	0.80 (0.20, 3.19)	0.749	0.45 (0.06, 3.21)	0.428
Melanau	0.49 (0.19, 1.32)	0.158	0.50 (0.19, 1.32)	0.161	0.36 (0.05, 2.58)	0.312	0.40 (0.06, 2.85)	0.361
Other Sarawak	0.67 (0.32, 1.40)	0.287	0.68 (0.32, 1.42)	0.300	1.00		1.00	-

* *Crude model included ethnicity as a predictor*
** *Model 1 adjusted for age and sex.*
** *Model 2 adjusted for Model 1, HbA1c level and treatment for diabetes.*
** *Model 3 adjusted for Model 2, comorbidities, BMI and smoking.*
****Using Discrete-time survival analysis*

4.6 Chapter Summary

4.6.1 Sociodemographic of Multi Ethnic Diabetes Cohort

The sociodemographic of multi ethnic diabetes cohort of this study showed 40% of the study participants were male and the proportions varied from 34% among the Iban to 47% among the Chinese. Mean age of the patients was at 59 ± 11 years. Patients of Dusun, Bajau, Other Sabah and Iban ethnic groups were among the young patients with mean age at 55 years and Chinese had the highest mean age at 64 years. Mean age at diagnosis was at 53 ± 11 years. Patients of Malay, Indian and multi ethnics from Sabah and Sarawak were diagnosed at an earlier age with the mean age at diagnosis ranged between 50 years among the Iban to 53 years among the Kadazan. Chinese were diagnosed at later age at 57 years. Mean BMI at baseline was 27.5 ± 6.3 kg/m^2. Chinese and Melanau were the only patients who were overweight at baseline (26 to 27 kg/m^2). Kadazan and Other Sarawak had the highest BMI at 28.3 kg/m^2 at baseline. Mean HbA1c at baseline was 8.0%. Malay and Indian had the highest mean HbA1c at baseline at 8.2%, followed by Chinese at 7.5%, Indigenous Sabah (7.4%) and Indigenous Sarawak (7.3%). The other multi ethnics from Sabah and Sarawak had mean HbA1c that ranged between 7.0% to 7.5%.

4.6.2 Association between ethnicity and glycemic control

The final adjusted model showed significant cross-sectional associations between all other ethnic groups and HbA1c level, compared to Malays. However, only the Chinese, Indian, Dusun and Indigenous Sarawak including Other Sarawak ethnic group remained to have significant longitudinal associations with HbA1c level.

Compared to Malays, Chinese ethnic group is associated with 0.5% lower HbA1c at presentation [aβ= -0.51 (95%CI -0.55, -0.48), p<0.001], and for every 5-year of diabetes duration, the HbA1c decreases by 0.1% [aβ= -0.10 (95%CI -0.13, -0.07), p<0.001]. Indians were associated with 0.1% lower HbA1c level at presentation [aβ= -0.11 (95%CI -0.15, -0.07), p<0.001], compared to Malays and the level decreases by 0.1% for every 5-year of diabetes duration [aβ= -0.10 (95%CI -0.13, -0.07), p<0.001]. Dusun ethnic group is associated with 0.7% lower HbA1c level at presentation compared to Malays [aβ= -0.71 (95%CI -0.85, -0.58), p<0.001]. However, with every 5-year of diabetes duration, the HbA1c level increases by 0.2% [aβ= 0.24 (95%CI 0.07, 0.41), p=0.005].

Indigenous Sarawak ethnic group is associated with 1.0% lower HbA1c level at presentation, compared to Malays [aβ= -0.96 (95%CI -1.07, -0.84), p<0.001], and with every 5-year of diabetes duration the HbA1c level increases by 0.1% [aβ= 0.12 (95%CI 0.01, 0.22), p<0.001]. Bidayuh and Other Sarawak contributed to the significant longitudinal associations amongst the Indigenous Sarawak. At presentation, Bidayuh is associated with 1.1% lower HbA1c level compared to Malays [aβ= -1.08 (95%CI -1.53, -0.64), p<0.001] and the HbA1c level increases by 0.3% for every 5-year of diabetes duration [aβ= 0.34 (95%CI -0.02, 0.74), p=0.067]. For Other Sarawak ethnic group, at presentation the HbA1c level is 0.8% lower compared to Malay [aβ= -0.77 (95%CI -1.16, -0.39), p<0.001]. The HbA1c level increases by.0.4% for every 5-year of diabetes duration [aβ= 0.44 (95%CI 0.04, 0.85), p=0.033].

Compared to Malays, the Chinese were associated with 61% increased odds of good glycemic control at presentation [aOR 1.61 (95%CI 1.52, 1.71), p<0.001], and the odds increases by 7% [aOR 1.07 (95%CI 1.01, 1.12), p=0.014] for every 5 years of diabetes duration. The odds of good glycemic control was similar between the Malays and

Indians at presentation, but with every 5-years of diabetes duration, the odds increases by 20% in the Indians [aOR 1.20 (95%CI 1.13, 1.28), p<0.001]. The odds of good glycemic control among the Indigenous Sabah was 3.43 times, compared to Malays [aOR 3.43 (95%CI 3.06, 3.85), p<0.001] and reduces by 14% with every 5-year of diabetes duration [aOR 0.86 (95%CI 0.75, 0.99), p=0.037]. Among the Indigenous Sarawak ethnic group, the odds of good glycemic control was 3.72 times compared to Malays [aOR 3.72 (95%CI 3.05, 4.54), p<0.001] and reduces by 20% with every 5-year of diabetes duration [aOR 0.80 (95%CI 0.65, 0.98), p=0.031].

4.6.3 BMI and sex as mediators in the association between ethnicity and glycemic control

Comparing Chinese to Malays and HbA1c levels, 1.7% of the Total Effect [aβ= -0.52 (95%CI -0.55, -0.50), p<0.001] was mediated by BMI. Comparing Indian to Malays and HbA1c levels, 4.1% of the Total Effect [aβ= -0.12 (95%CI -0.15, -0.10), p<0.001] was mediated by BMI. The indirect associations for the other ethnic groups were less than 1%.

Comparing Chinese to Malays and HbA1c levels, 1.6% of the Total Effect [aβ= -0.53 (95%CI -0.55, -0.51), p<0.001) was mediated by being overweight and 3.5% of the Total Effect [aβ= -0.52 (95%CI -0.54, -0.50), p<0.001] was mediated by being obese. Comparing Indian to Malays and HbA1c levels, 3.3% of the Total Effect [aβ= -0.13 (95%CI -0.15, -0.10), p<0.001] was mediated by being overweight and 7.5% of the Total Effect [aβ= -0.12 (95%CI -0.15, -0.10), p<0.001] was mediated by being obese. Comparing Melanau to Malays and HbA1c levels, 1.2% of the Total Effect [aβ= -1.08 (95%CI -1.30, -0.85), p<0.001] was mediated by being obese. The indirect associations for the other ethnic groups were less than 1%.

Comparing Chinese to Malays and good glycemic control, 3.7% of the Total Effect [aβ= 0.27 (95%CI 0.25, 0.29), p<0.001) was mediated by being overweight and 6.4% of the Total Effect [aβ= -0.52 (95%CI -0.54, -0.50), p<0.001] was mediated by being obese. Comparing Melanau to Malays and good glycemic control, 1.5% of the Total Effect [aβ= 0.85 (95%CI 0.61, 1.08), p<0.001] was mediated by being obese. The indirect associations for the other ethnic groups were less than 1%.

Comparing Indian to Malays and HbA1c levels, 1.1% of the Total Effect [aβ= -0.12 (95%CI -0.14, -0.10), p<0.001] was mediated by sex. The indirect associations were less than 1% for other ethnic groups with significant indirect effects.

4.6.4 Association between ethnicity and diabetes-related complications

The hazard of diabetic retinopathy and peripheral vascular disease (PVD), was 18% and 11% higher in Indians compared to Malays [(Retinopathy: HR 1.18 (95%CI 1.13, 1.23), p-value <0.001), (PVD: HR 1.11 (95%CI 1.00, 1.22), p-value 0.040)]. The hazard of diabetic nephropathy was similar between the Indians and Malays.

Chinese and Indigenous Sabah was associated with 23% and 91% higher hazard of diabetic retinopathy [Chinese: HR 1.23 (95%CI 1.18, 1.27), p-value <0.001, Indigenous Sabah: HR 1.91 (95%CI 1.78, 2.05), p-value <0.001], compared to Malay. The hazard of diabetic nephropathy and PVD was lower, compared to Malay [(Nehropathy; Chinese: HR 0.95 (95%CI 0.91, 0.98), p-value 0.001, Indigenous Sabah: HR 0.70 (95%CI 0.63, 0.77), p-value <0.001]. Bajau and Other Sabah contributed to the significant association amongst the Indigenous Sabah.

Indigenous Sarawak was associated with significantly lower hazard in all three diabetes-related complications measured in this study and Iban was the only ethnic group contributed to the associations. The hazard of diabetic retinopathy, diabetic

nephropathy and PVD was 38%, 32% and 42% lower in Iban, compared to Malay [Iban: (Retinopathy: HR 0.62 (95%CI 0.52, 0.75), p-value <0.001), (Nephropathy: HR 0.68 (95%CI 0.58, 0.79), p-value <0.001), (PVD: HR 0.58 (95%CI 0.36, 0.92), p-value 0.022)].

CHAPTER 5: DISCUSSION

5.1 Chapter Introduction

This chapter discusses the public health significance of the results of this study in relation to diabetes management in Malaysia. In particular, it covers the clinical significance of the ethnic differences in glycaemic control, the role of the mediators and the hazard of complications among different ethnic groups. It also discusses on the plausible mediators that were not assessed in this study, as these variables are not available from the registry due to the limitation of the registry. Following that, some suggestions for improving diabetes management in terms of the early detection of diabetes, enhancing health literacy in regards to diabetes and providing supportive care that is tailored according to the needs of the various ethnic groups have been made. The chapter ends by highlighting the strengths and limitations of this study.

5.2 Ethnicity and Glycemic Control

This study has provided evidence on the role of ethnicity as a prognostic factor for glycaemic control in a multi-ethnic Asian setting. Ethnicity appears to be associated with glycaemic control and longitudinal changes in the HbA1c level, and in the hazard of diabetes-related complications. Furthermore, the study showed that BMI and sex were mediators in the association between ethnicity and glycaemic control.

This study employed data from the NDR. The NDR is currently the most extensive database on diabetes patients treated in government primary healthcare clinics and some government hospitals in Malaysia. Almost 68% of all government health clinics and approximately 900,000 diabetes patients are currently registered in the NDR. Currently, the NDR is the only method of diabetes surveillance in Malaysia that can not only register, but also follow up the progress of each diabetes patient.

Based on a review and analysis of the data obtained from the NDR, this study revealed the overall picture of diabetes in Malaysia by ethnic groups. Unlike all the other previous studies conducted in Malaysia, this study is, to the best of the author's knowledge, the first study in Malaysia that has investigated ethnic differences in glycaemic control by including all the major ethnic groups as well as all the ethnic groups of Sabah and Sarawak to ensure that the diversity of the Malaysian population was well represented. Sabah and Sarawak are home to a multitude of ethnic groups that at present include high numbers of diabetes patients.

The present study observed that there were ethnic differences in glycaemic control where glycaemic control is defined by a HbA1c level ≤6.5%. All ethnicities showed a significantly lower HbA1c level and better glycaemic control compared to the Malay in the cross-sectional associations that is defined as prevalent association at time of first presentation to the registry. This is in line with previous different studies conducted that consistently found the Chinese and Indian populations in Malaysia to have better glycaemic control compared to the Malay ethnic group (Boon How Chew et al., 2011; Ismail, Nazaimoon, et al., 2000). Similar evidence from Singapore also showed the Malay ethnic group were persistently found to have poor glycaemic control (Hong et al., 2004).

The present study also observed ethnic differences in changes in the HbA1c level for every 5 years of diabetes duration in the longitudinal analysis. The HbA1c level among the Chinese and Indian decreases by 0.1% while among the Indigenous Sarawak ethnic groups including Other Sarawak and Indigenous Sabah ethnic groups including Dusun, the HbA1c level increases by 0.44% and 0.24%, respectively for every 5 years of diabetes duration compared to the Malay ethnic group. Singapore has previously published several studies that showed ethnic differences in changes in HbA1c level in

the longitudinal analysis. It has been reported in these previous studies from Singapore that the HbA1c level among Malays and Indians increases by 0.3% at 3 years following diagnosis of diabetes (Ng et al., 2005; N. C. Tan et al., 2015). This is in contrast to the results of this study, which found a 0.1% lower HbA1c level among the Chinese and Indian ethnic groups at every 5-year following diagnosis of diabetes. However, the authors of these previous studies postulated, with longer follow up, the differences in HbA1c level between Chinese and Indians and Malays could narrow down.

The current study had also found that the Dusun and Other Sarawak ethnic groups had 0.24% and 0.44% higher HbA1c level for every 5 years of duration of diabetes than the Malays, whereas the Bidayuh ethnic group was marginally associated with a higher HbA1c level at 0.34% for every 5 years of duration of diabetes. These findings are an added value to the current evidence on the ethnic differences in glycemic control, in terms of findings in Malaysia, as it has never been reported previously. Other Sarawak ethnic group in this study consisted of 11 different ethnic minorities from Sarawak. Majority of these ethnic minorities live in the rural or remote areas, where access to the healthcare services could be constrained by several factors including availability of transportation as well as distance and time taken to travel to attend appointments in health clinics. Besides, the socioeconomic status including income level, occupational status and even the educational level, which can be fairly explained to be in the lowest side, could also possibly contribute to reduce in access to primary care, not attending the scheduled follow ups, measurement of biomarkers for glycemic control level and complications assessment could not be conducted regularly leading to inadequate treatment and poorly controlled diabetes. Dusun is an ethnic group from Sabah, also a state in the Borneo Island other than Sarawak. The poor glycemic control compared to Malay could also be postulated as inadequate utilization of healthcare due to geographical barriers, socioeconomic status and education level. However, these

findings deserve further explanation through other research looking into the unmeasured components that define the different ethnic groups.

It is suggested in previous studies that poor glycaemic control among the Malays are probably due to their unique attitude, health behaviour, education level, culture and genetic attributes that deserve further investigations (Ng et al., 2005; N. C. Tan et al., 2015). The differences in these characteristics for instance could lower their propensity to insulin usage compared to other ethnic groups, given that insulin therapy may be withheld if patients have poor education and health literacy, have poor social support, or are fearful to any form of long-term injection treatment, but unexplained differences between ethnic groups persisted (Ng et al., 2005). Poor glycemic control among the Indians was believed to be attributed by lower education level as Indian patients with lowest level of education comprised the largest proportion of very poor control of diabetes (Ahmad et al., 2011). However, it had also been discussed that genetic and cultural factors has provide protection to the Chinese ethnic group and contributed to better glycaemic control (Ismail, Wan Nazaimoon, et al., 2000).

This study also produced new evidence on the influence of ethnicity on glycaemic control as the impact of ethnic group on the HbA1c level was found to differ for each ethnic group. Ethnicity acts as a proxy for heterogeneous phenotypes in a multiracial and multicultural country such as Malaysia. Also, given the longitudinal design of this study, it was possible to establish temporality and causality. The duration of diabetes and glycaemic level are the two main factors in the pathophysiology of diabetes. The duration of diabetes plays a substantial role in explaining the change in the HbA1c level in the pathway between ethnicity and glycaemic control throughout the course of the disease. Previous studies that have investigated the factors contributing to glycaemic control have shown that earlier age at diagnosis and duration of diabetes have explicit,

individual associations with increased HbA1c level (Hsieh et al., 2014; Khattab, Khader, Al-Khawaldeh, & Ajlouni, 2010; Kuo, Lin, Yu, Chang, & Kuo, 2010; Otiniano et al., 2012; Rosilio et al., 1998). Therefore, the effect of time, or in this study the duration of diabetes, which was explained explicitly in the longitudinal association, supported the causality and temporality of ethnicity in relation to the change in the HbA1c level among diabetes patients, especially among the Dusun, Other Sarawak, Chinese and Indian ethnic groups who showed significant associations.

As stated above, the previous studies have focused mainly on the three major ethnic groups and none have reported specific findings for the many ethnicities in the Malaysian states on the island of Borneo, states that have a substantial number of patients with diabetes. In this study, all the major ethnic groups of Sabah and Sarawak were well represented and it was found that there was a positive association between ethnicity and glycaemic control at least at the 5-year diagnosis of diabetes. In previous studies, the ethnic groups of these states were classified as Others, which often created difficulties when attempting to explain the association when the findings were in favour with this ethnic group. It has also probably contributed to the difficulties to convince the policy makers in taking into account the ethnicity of patients as one of the approaches in diabetes management. However, in this study, the findings for the Indigenous Sabah and Indigenous Sarawak, especially that were grouped into Other Sabah and Other Sarawak, could be used to explain the association as it represented different and distinct ethnic minorities of Bumiputera Sabah and Sarawak.

5.3 BMI and Sex as Mediators in the Association Between Ethnicity and Glycemic Control

The association between ethnicity and glycaemic control seems to be mediated by BMI as in this study BMI was proven to be a mediator, although the indirect effects were small and the percentage of indirect effect from the total effect that explained the association varied between 0.1% and 7.0% only. Changes in BMI that explained the changes in glycaemic control that were seen more among the Chinese, Indian and Melanau ethnic groups could possibly contributed to the hazard of developing macrovascular complications, the unmeasured complications in this study as this study focused in diabetes-related complications mainly microvascular components. Previous studies did not overtly investigate BMI as a mediator and analysed through mediation analysis, but more towards the causal effect of BMI on glycaemic control and incidence of diabetes as well as through interactions, effect modifications and stratum-specific associations (Bae et al., 2016; Koshizaka et al., 2017; Lu et al., 2014; L. Xu, Borges, Hemani, & Lawlor, 2017). Hence, this study provided new evidence on the role of BMI in glycemic control, which is an added value on diabetes progression knowledge as this study proved that changes in BMI resulted in changes in glycemic control.

The findings of this study also suggest that the role of BMI as a mediator, although it was found to be small, is highly likely to be ethnicity dependent as a significant mediating effect was observed among the Chinese, Indian, and Melanau ethnic groups. Given the high prevalence of diabetes, high prevalence of overweight and obesity in Malaysia, and findings from this study that showed only Chinese and Melanau were in the overweight category at baseline, the role of BMI in the course of diabetes among these ethnic groups needs to be reiterated especially with regards to the management of diabetes in primary care settings.

Emphasis could be placed on secondary prevention as this approach can takes care of the mediating effect of BMI on glycaemic control and thereby help to prevent diabetes-related complications, particularly macrovascular complications that also urgently warrant further investigations and research on the relation with ethnicity in Malaysia. In addition, this study found evidence of gender differences among the Indian ethnic group for the association with changes in the HbA1c level. Therefore, incorporating secondary prevention into diabetes management would mean managing diabetes patients according to ethnic group, targeting specified BMI levels, and also probably making those levels gender-specific.

5.4 Ethnicity and Diabetes-related Complications

The role of ethnicity was also found in this study to be a significant predictor for the hazard of diabetes-related complications. Chinese, Bajau, Other Sabah and Iban showed a significant association with the hazards of all three diabetes-related complications measured in this study, namely, diabetic retinopathy, diabetic nephropathy, and peripheral vascular disease (PVD). Chinese, Bajau and Other Sabah had an increased hazard of developing diabetic retinopathy but had lower hazards for diabetic nephropathy and PVD. What was more interesting was that the Indian ethnicity had an increased hazard for diabetic retinopathy and PVD, but showed no association with diabetic nephropathy. Also, the Iban ethnicity contributed to the significant association for the Indigenous Sarawak ethnic group, showing a lower hazard for developing all three diabetes-related complications. The Indigenous Sarawak ethnic group had a lower glycaemic level compared to the Malay, but the ethnicities within this group had the hazard of developing microvascular complications at different rates. Therefore, these detailed findings may help to explain the findings reported in previous studies that frequently supported the association between poor glycaemic control and the

development of microvascular complications (Nanayakkara et al., 2017; Zoungas et al., 2014).

Furthermore, at baseline, there were already ethnic differences with deranged values seen in the HbA1c level and the mean of the BMI. With a mean duration of having diabetes for 6 years, at baseline, all ethnicities were at least overweight and had a mean HbA1c of at least 7.0%. The Malay ethnicity, as the reference group, had a mean BMI of 27.9 kg/m^2 and had the highest mean HbA1c at 8.2%. The Indigenous Sabah, Kadazan and Other Sarawak groups were obese at baseline, but these ethnic groups were among those with the lowest mean HbA1c at baseline, ranging from 7.2%–7.4%. On the other hand, the Chinese, Indian, Dusun, Bajau, Other Sabah, Iban, Bidayuh and Melanau groups were all overweight at baseline. Except for the Indian ethnic group, which had a mean HbA1c of 8.2%, the mean HbA1c for the other ethnic groups was lower than that of the Malay ethnic group, ranging between 7.0% and 7.5%. Although overall mean age at diagnosis of diabetes was 53 years old, it is possible that these diabetes patients were actually diagnosed late where additional risk factors such as overweight and obese had already started to set in and compromised the HbA1c level. The increased hazard of diabetes-related complications, especially diabetic retinopathy, among the Chinese, Indian, Bajau and Other Sabah groups could be the result of microvascular complications that are directly related to glycaemic exposure over time (Klein, Klein, & Moss, 1996; Stratton et al., 2000). At least 60% of the Indigenous Sabah diabetes patients were diagnosed with both hypertension and dyslipidaemia at baseline. These particular ethnic groups could also have increased hazard of macrovascular complications, an area that needs to be explored in the future. Macrovascular complications were not measured in this study as this study focused on diabetes-specific complications.

The management of diabetes in primary healthcare in Malaysia includes screening for diabetes-related complications, which is standardized throughout the country. In Sabah, there are 49 government primary health clinics and a relatively lower number of diabetes patients throughout the state, compared to Selangor, Johor, Perak, Melaka, and Negeri Sembilan which have an unusually high number of diabetes patients but a relatively lower number of health clinics. Inequalities in screening activities for complications could be assumed due to the different burden in managing diabetes patients in the health clinics of these particular states. In the context of Sabah, 16% of the diabetes patients in the Malay, Chinese, Indian and Indigenous Sabah ethnic groups were diagnosed with at least one complication, whereas among the Indigenous Sarawak diabetes patients, only 8% had known diabetes complications. Hence differences in screening activities could be presumed given that the total number of diabetes patients in the Indigenous Sarawak ethnic group was higher than that in the Indigenous Sabah ethnic group. It could also possibly due to the participants in this study were from the audit samples, thus individual compliance to annual screening was not able to be determined (Malaysian Healthcare Performance Unit, 2017).

Another explanation for the above could be related to the registration of health clinics on the NDR system. For instance, in Sarawak, not all health clinics are registered on the NDR system. The few health clinics that are registered are located in urban areas and their total number of diabetes patients is high with most of the patients having poor glycaemic control and diabetes-related complications that require close monitoring. Patients with good control are usually discharged back to their hometown and continue follow-ups at a local or nearby health clinic. Most of these clinics are in rural areas and these clinics are not registered in the NDR. This means that the progress and updates for these patients cannot continue to be captured in the NDR after they have been transferred out to a rural clinic. Therefore, this scenario could contribute to the low

percentage of diabetes-related complications observed among the Indigenous Sarawak group.

5.5 Education level, Socioeconomic Status and Access to Healthcare as Plausible Mediators of the Association Between Ethnicity and Glycemic Control

Besides BMI and sex, there are other substantial factors that could possibly act as mediators but were not measured in this study as these variables are not available from the registry. Although these factors were not measured due to the limitation of the registry, they are worth to be discussed, as the findings could possibly be an added value to the observed outcomes of this study. Education level and socioeconomic status including income level, occupation and employment are among the substantial factors that have been postulated to mediate the association between ethnicity and glycemic control (A. F. Brown et al., 2004). Moreover, lower education level and lower income status are often associated with more frequent diabetes-related complications and mortality, which is closely related to having poor glycemic control (Dupre, Silberberg, Willis, & Feinglos, 2015; Saydah & Lochner, 2010). Access to healthcare is another important non-glycemic factor that has long been discussed to have influence over ethnic differences in prevalence of diabetes and glycemic control (A. F. Brown et al., 2004; Paduch et al., 2017).

Education is certainly an important component that could explain ethnic differences in glycemic control. The role of education in the association between ethnicity and glycemic control needs to be acknowledged as different level of education within and between ethnicity could lead to different level of knowledge in diabetes management. Education could be mediating the effect, or it could also possible to moderate the association and modify the role of observed mediators namely BMI and sex in the

association between ethnicity and glycemic control. Different ethnic groups will come from different background of education level. Patients with higher education level will have the advantages in understanding the disease, will have the ability to manage the disease, follow and read instructions, advocate themselves and families, and most importantly these patients will be able to communicate effectively with the healthcare providers (Zimmerman, Woolf, & Haley, 2015). Education level has also been seen to be associated with risk of mortality where mortality among uncontrolled diabetes patients are greater among those with lower education level (Dupre et al., 2015). As with any chronic disease, one of the vital components in the management of diabetes would be health education and this requires effective communication between healthcare providers and the patients. Therefore, with different education background, each ethnic group will have different level of understanding of the disease and this could be further complicate with different language used between healthcare providers and patients or present of language barriers.

Education level is also strongly associated with health literacy, and has also been described to be a mediating factor of the association between education and health outcomes (Van der Heide et al., 2013; Zimmerman et al., 2015). Hence, ethnicity, education level and health literacy are all in a causal relation with glycemic control. Limited health literacy will impact the ability of an individual to manage their health and to decide appropriately for their health as health literacy is directly related to knowledge, motivation and capability to access, understand, and apply health information before making decisions on healthcare, disease prevention and health promotion to improve the quality of life (Sørensen et al., 2012). It is also understood with limited health literacy, an individual will have less health-related knowledge and subsequently to bear with poorer health status (Berkman, Sheridan, Donahue, Halpern, & Crotty, 2011). Similarly with diabetes patients, lower level of education and limited

health literacy will make these patients vulnerable to non-adherence to medication, difficult to understand the importance of follow-up care, will have different perceived risk of the disease, and eventually leads to discontinuation of treatment (Bailey et al., 2014). This will be the turning point where glycemic control could have been improved through ethnic-specific diabetes management by tackling the factor contributing to the differences in glycemic control.

Regrettably, healthcare providers will not be able to choose or improve patients' education level and so does ethnicity. It has been suggested that healthcare providers should provide the opportunity for the patients to get all the support they need in order for them to understand, appraise and apply health information in the process of managing their health condition, and that include management of diabetes (Adina Abdullah, Liew, Salim, Ng, & Chinna, 2019). This is an important area to acknowledge especially in a multiethnic and multicultural country like Malaysia as some states still have very rural and remote areas where the educational level and health literacy of the people varied significantly. In Sarawak for instance, some of the patients understand only their native language or local dialect that if the healthcare providers or the educators could not converse in the similar language, the education that is supposed to be conveyed will not reach the patients. Hence, both the educators and the education materials should fit with the ethnic groups and this is the area where ethnic-specific diabetes management should play a role to yield the desirable health outcome, which is good glycemic control and prevention of complications.

It might not be much of an issue in peninsular Malaysia as the three ethnic groups namely Malay, Chinese and Indian are the majority and communication, lifestyle and cultures are almost coherent between the healthcare providers and the patients. It is in the east part of Malaysia, the island of Borneo, where there are many ethnic groups with

distinct language and dialects, lifestyle and cultures that warrant the healthcare providers to have deeper understanding before they could engage with patients, establish a rapport and empower the patients with self-care diabetes management. Self-care in diabetes is crucial as almost all diabetes care are provided by the patients themselves and diabetes patients are expected to make decisions on healthcare and to undertake multifaceted self-management on daily basis in order to achieve good glycemic control (Adina Abdullah et al., 2019; Krichbaum, Aarestad, & Buethe, 2003). This process requires the patients to be educated by healthcare providers and for the health education to better take place, the process of educating must be accustomed according to the level of education of the patients that is plausible to mediate the association between ethnicity and glycemic control.

Due to the limitation of the registry, education was not measured as a mediator in the mediation analysis. Although if it was measured, it will not change the outcome of this study but instead it will be an added value to BMI and sex as mediators of the association between ethnicity and glycemic control. Education is a mediator as education is a mean through which ethnicity influences glycemic control. Education could also possibly become a moderator if the effect of ethnicity on glycemic control differs according to the level of education. Besides, it could also provide an avenue for the improvement of the registry in adding a pivotal variable into the registry such as education.

Access to healthcare is another crucial variable that is not available from the registry but has been postulated to play a role in mediating the association between ethnicity and glycemic control. Access to healthcare comprises of either the availability of the healthcare services or the utilization of the services. Availability of healthcare services in Malaysia might not contribute much to the disparities in diabetes outcome as the

government primary healthcare settings in Malaysia are well distributed throughout the country. The public primary healthcare in Malaysia offers a comprehensive range of services that include health promotion, disease prevention, curative and rehabilitative care. The coverage goes beyond general population including both urban and rural population to ensure universal coverage. The private health sector on the other hand provides mainly curative care that also includes traditional and alternative care. The distribution of private health clinics is more populous in the urban settings limiting the coverage to those who can afford and those who have access to the facilities (WHO, 2013). Somehow, utilization of healthcare can still be constrained by the financial and organizational barriers to the use of the patients such as lack of proximity to the healthcare services even though in a healthcare system that provide universal coverage, like Malaysia (Gold, 1998). In Malaysia, majority of the chronic disease patients including diabetes patients seek care from the government health facility especially the primary care clinics. These clinics are highly subsidized as to ensure universal health coverage, which is an environment that facilitate equal health outcomes independent of the background of the patients, socioeconomic status and health profile.

However, some parts in Malaysia still experience barriers to the utilization of the healthcare. In Sabah and Sarawak for instance, distance to health clinics and remoteness of the areas contribute to the logistical barriers in accessing the healthcare. Lack of transportation, road conditions and access through watercourse further add up to longer travelling time to appointments and possibility of reducing access to care. How does this condition related to ethnicity is a pathway that require greater understanding. Some ethnic groups, especially the ethnic minorities live in these remote areas not because of poverty but these specific ethnic groups originated from these areas and have never leave the place. Some ethnic groups are still nomad and it is possible for them to go further into the rural areas. Therefore, this a population characteristics that is explained

through ethnic composition with underlying geographical barriers due to the location and distance to healthcare services in addition to lack of transportation, that contributed to the under utilization of healthcare services.

Nevertheless, ethnic minorities themselves have shown to be one of the barrier in healthcare use due to the differences in language as well as cultural, religious and social beliefs (A. F. Brown et al., 2004). The differences describe the specific ethnic group, and these differences also have lead the different ethnic groups to have differences in access to healthcare services. It would be interesting additional information to the observed findings of this study if access to healthcare services in Malaysia could be assessed as mediator to better explain the association between ethnicity and glycemic control. Access to healthcare with no doubt is a necessity to the registry to further elevate its role as a disease registry and to delineate the impact of ethnicity.

Ministry of Health Malaysia has taken the initiative in reaching very rural areas with difficult access through programs such as Rural Clinic Visiting Doctors, Village Health Teams and Flying Doctor Services. These programs aim at delivering the similar healthcare services being provided in the primary care clinics to the community in far-to-reach areas as well as rural health clinics without medical officers. Hence, the target of these programs is also to ensure all the populations in a particular district, division or area receive an equal healthcare services and to reduce the barriers to utilization of healthcare services.

Socioeconomic status is certainly a vital component in explaining poorer health outcome, specifically glycemic control (A. F. Brown et al., 2004). Lower socioeconomic status as measured by income status, occupation, employment and living in the underprivileged areas has long been associated with poorer glycemic control (Roper, Bilous, Kelly, Unwin, & Connolly, 2001; Weng, Coppini, & Sönksen, 2000)

and increased risk of microvascular complications (Chaturvedi, Stephenson, & Fuller, 1996; Unwin, Binns, Elliott, & Kelly, 1996). Furthermore, it is indispensable to recognize the role of socioeconomic status in the causal pathway between ethnicity and poor glycemic control as different ethnic groups are reflected by the differences in socioeconomic status. It has been hypothesized that lower socioeconomic status could lead to poorer access to care resulting in inadequate treatment and increased risk of complications, poorer quality of care such as reduce measurements of HbA1c and worse self-care behavior that includes improper dietary habits and physical inactivity (Kington & Smith, 1997). Therefore, different level of socioeconomic status could explain the differing level of ethnicity impact on glycemic control. Socioeconomic status is an important variable that should not be adjusted for in the analysis, but need to be analyzed as a potential mediator or a plausible moderator when assessing effect of ethnicity on diabetes outcome.

Socioeconomic status is very much closely related to access to healthcare services. In Malaysia, there are still very remote and rural areas where the populations are of lower socioeconomic status with lower education level. As mentioned, some ethnic groups are very specific to be living in some specified areas probably due to their origins or because they have never had the chance to migrate to more urbanized areas to pursue for example in higher level of education or to find a job as to earn a living, as this would be the most common way for people to leave their place of origin. Due to the limited opportunities coming into their way, it has made these specific ethnic groups to have never left their settlements. These multi factors have synergistically contributed to having limited access to healthcare services for certain population groups and causing poor diabetes outcome.

5.6 Public Health Significance on Role of Ethnicity in Diabetes Management

However, prior to making changes to the diabetes management approach, it is vital to have a proper understanding of the influences that ethnicity has on glycaemic control. Ethnic differences in glycaemic control cannot be entirely attributed to genetic predisposition or biological variables; rather, as indicated in this study, they should be defined as a combination of social determinants of health that can cause modification in the evolution of disease, as discussed by many schools of thought (S. A. Brown et al., 2016; Hu, 2011; J Oldroyd, 2005; Nabila Dahodwala et al., 2010; R. J. Walker, Strom Williams, & Egede, 2016). Social determinants are comprised of cultural beliefs, socioeconomic status, religious beliefs and political influences, which, in this study, were represented to a certain extent by ethnicity. The variations within these determinants could result in differences in their choices in regards to a healthy lifestyle as well as disease management and affect their dietary habits, physical activity level, confidence and willingness to self-manage, medication adherence and probably also have an impact on the communication process with their healthcare providers. It could also leads to adverse psychosocial factors including self-efficacy, social support, and perceived risk that were not measured in this study, but which it is highly possible and distinct to each ethnic group. Although the role of the social determinants of health on health outcomes and their possible role in glycaemic disparities have essentially in some ways been ignored, a previous study has provided evidence on the consistent association between these psychosocial factors and glycaemic control (R. J. Walker et al., 2016). Hence, the glycaemic disparities seen among the different ethnic groups in this study could be explained by differences in the social determinants and psychosocial factors possessed by these different ethnic groups and perhaps support the hypothesis that ethnicity plays a prognostic role in the presence of glycaemic disparities.

On the other hand, social determinants alone, which includes psychosocial factors (self-efficacy, perceived stress and social support) and neighbourhood factors (social cohesion and neighbourhood aesthetics) have been shown to have a consistent association with glycaemic control, yet the specific roles that these determinants could potentially play has largely been ignored (R. J. Walker et al., 2016).

A previous systematic review and meta-analysis found evidence of an association between psychosocial factors (low social support, stressful events and coping mechanism) and glycaemic control (Chida & Hamer, 2008). Also, it has been hypothesized that high-risk behaviours could mediate this relationship, besides the direct physiological pathway (Pollard, 1997). For instance, where different psychosocial factors are possessed by type 2 diabetes patients, this could promote unhealthy dietary practices, physical inactivity, and smoking that would lead to disparities in glycaemic control (Lloyd, Smith, & Weinger, 2005). Hence, the findings from this study support the previous evidence that ethnicity does play a role in determining glycaemic control and that BMI plays a role as a lifestyle mediator in explaining glycaemic disparities among different ethnic groups. An in-depth understanding of this relationship and the influence of the related mediator is of crucial importance especially in a country such as Malaysia with its diverse ethnicities, cultural practices and high prevalence of diabetes as well as NCD risk factors as this will enable the betterment of diabetes management, which urgently needs to be tailored according to ethnicity.

Besides, evidence from the US shows that several psychosocial factors contribute to the disparities in glycaemic control among different ethnic groups (L. R. Hausmann, D. Ren, & M. A. Sevick, 2010), where perceived interference of diabetes with daily life activities, perceived severity of diabetes, emotional distress, social support, and access to healthcare and access to diabetes resources were significantly different between

ethnic groups and the level of glycaemic control. Therefore, it is fundamental that diabetes management and clinical outcomes are viewed from the perspective of ethnicity in order to design and implement ethnic-specific interventions to reduce the defaulter rate by focusing on the preferences and cultural differences among the various ethnic groups.

The findings of this present study is also consistent with findings from published studies in European countries and the US as well as with more recent studies from South Asian countries and China in terms of ethnic differences in glycaemic control and the emphasis on the importance of intervening diabetes patients according to ethnicity. The multiracial population with diabetes in Malaysia is in need of culturally specific diabetes management to suit the multicultural nature of the nation.

Yet, intervening in each ethnicity according to its specific cultural practices and designing a programme for each parameter that requires intervention is not feasible. For instance, the Indigenous Sabah and Indigenous Sarawak groups considered in this study consist of various ethnic groups whose culture, lifestyle and perception of disease are distinct from one ethnic group to another. Thus, an intervention should be designed in such a way that it incorporates multiple perspectives that are appealing to the broad spectrum of the target population. In other words, through segmentation of the audience, materials that are designed for a single or specific ethnic group can also be multiracial (Resnicow, Baranowski, Ahluwalia, & Braithwaite, 1999).

However, is it possible to implement this type of diabetes management in health clinics in Malaysia? The situation in health clinics differs by district and by state. Some of them are overly burdened with patients, but many are not. An adequate knowledge of the importance of the impact of ethnicity and the role of BMI in glycaemic control accompanied by a suitable plan for executing an intervention are two important factors

that need to be instilled in primary care teams. It might be difficult to convince the primary care teams on the ground involve directly with diabetes management in health clinics on the implementation of ethnic-specific diabetes management without a prior policy or guidelines being in place. However, the evidence of this study could serve as a platform for innovation in the management of diabetes especially in health clinics with a lower number of diabetes patients who have better glycaemic control.

5.7 Ethnic-Specific Diabetes Management

Diabetes management does not encompass clinical management alone, which indeed will be the same across patients from various ethnic groups. The management also includes control of disease and prevention of complications, which should be culturally-specific through various methods including patients' education.

Based on the findings of this study, the two vital components to consider in managing diabetes would seem to be glycaemic control and the prevention of diabetes-related complications. Tight glycaemic control is often associated with reducing the risk of microvascular complications (Hemmingsen et al., 2013), while monitoring of the BMI level and co-morbidities including hypertension and dyslipidemia through pharmacological treatment and behavioural change are crucial in the prevention of macrovascular complications and in reducing the risk of mortality. Every diabetes patient should adopt and adhere to self-care behaviours that include practising a healthy lifestyle (healthy eating and being physically active), ensuring medication adherence and developing independent problem-solving skills in order to achieve good glycaemic control and reduce the future risk of complications.

These are the bases for the type of diabetes management that is currently being practised in Malaysia. However, whether this practice is consistent and effective is an open question. Currently, approaches for supporting behavioural change range from

diabetes self-management education (which is still lacking in Malaysian primary care practice) to support for clinical, behavioural, psychosocial and educational elements as well as lifestyle programmes. All of these approaches are crucial and should be more patient-centred, interactive and behaviour-specific so as to allow more problem-solving activities that are culturally specific to take place.

However, at the moment it remains unclear as to which combination of programme components and delivery mechanisms would be the most effective for each ethnic group (Chodosh et al., 2005; Ellis et al., 2004; Fan & Sidani, 2009; Glazier, Bajcar, Kennie, & Willson, 2006; Norris, Lau, Smith, Schmid, & Engelgau, 2002). The programme components in culturally specific diabetes management, which involves a combination of diabetes self-management and additional support from healthcare providers in terms of clinical, psychosocial, educational and behavioural components as well as lifestyle programmes that focus on diabetes dietary habit intervention and the physical activity element, could help to individualize diabetes management according to the needs of every ethnic group (Pillay et al., 2015). There are many ways of delivering these components according to need. For instance, interpersonal communication, without the use of technology, has been shown to benefit the diabetes patients and involvement of multidisciplinary teams should be able to outweigh the benefit (Pillay et al., 2015). Using a mixture of group and individual activities for delivering the programme contents could also help in engaging patients to practice diabetes self-care management. Group activities could allow interaction with peers while individual activities could be more focused by basing them on the individual needs assessment conducted a priori. In addition, the level of community engagement must also be taken into account as appropriate usage of existing resources within the community would be able to elevate adherence towards peer support and programmes conducted.

In designing culturally sensitive diabetes programmes, it is also important to consider both the surface and deep structures of such programmes (Resnicow et al., 1999). Surface structures are concerned with acceptance of the intervention materials among the target population and how well the intervention design fits the observable characteristics of the specific culture of the particular target population. On the other hand, deep structures incorporate the elements of the culture, social, environment and psychological forces that could influence the target population (Resnicow et al., 1999). Focus group discussions (FGDs) or exploratory focus groups and pretesting are two key techniques that have long been discussed in achieving culturally sensitive diabetes management. A FGD can be utilized to clarify the elements of both the surface and deep structures as the purpose of the FGD is to delineate the cultural differences as well as the perceived benefits and barriers of a particular intervention. Pretesting, on the other hand, is crucial to follow through the results of the FGD in order to obtain feedback on the content and format of the intervention as well as to test the adequacy of the materials that have been designed for the intervention.

To date, there are substantial numbers of studies especially in the US and the UK that includes systematic reviews and meta analyses that discussed on not only culturally specific and ethnicity specific interventions in improving diabetes outcomes but also the effectiveness of those interventions as observed in the measured treatment outcomes (Nam, Janson, Stotts, Chesla, & Kroon, 2012; Ricci-Cabello et al., 2014). Majority of the interventions discussed focused on ethnic minorities because as to current knowledge on ethnic differences in glycemic control, ethnic minorities in the US and in the UK have shown worse glycemic control compared to Whites and it seems that the usual care does not produce similar outcomes compared to those of Whites. The characteristics of effective interventions include diabetes educations through individual counseling with ethnically matched educators as well as having a peer educator for

every patient, delivered face to face and focused on diabetes self-management and diabetes knowledge. Delivery of intervention through individual counseling with peer and ethnically matched educators was seen to be more effective as it could address patients' individual characteristics and needs, hence producing better patient engagement and glycemic control, although group discussion is more appealing as it is low in cost and promotes better patient-patient interactions. Face-to-face somehow has won efficacy over telecommunication programs even though telecommunication program has higher potential to improve attrition rates with its capability in overcoming barriers such as distance to the service. Compared to face-to-face, these type of programs can become an additional barrier to patients from ethnic minority groups, who are more likely to have reduced access to information technologies and lower digital literacy (Ricci-Cabello et al., 2014).

Among the components of culturally tailored intervention or ethnic-specific diabetes management include teaching on dietary change through modifying ethnic foods and change in physical activity using culturally appropriate activities, delivery of intervention in the preferred language, contents of educational materials that are also in the preferred language, accompanying family members to elicit home-based support and use of visual aids to tailor to low-literacy needs (Nam et al., 2012).

In the US, there is a proven diabetes lifestyle intervention program that was developed for and evaluated with Native Americans, and was successfully adapted for and effective among African Americans and the Latinos (Two Feathers et al., 2005). The curricula of the intervention were designed with the objective to reduce risk factors associated with diabetes complications by increasing participants' diabetes self-management understanding, self-efficacy, and autonomous motivation. In making it culturally specific to African Americans and Latinos, the Family Health Advocates,

who were the locals among the community members, contributed to the local and cultural knowledge in the curricula intervention during adaptation process. The interventions were community-based, delivered by the trained Family Health Advocates with the aim to help participants to gain knowledge and skills related to healthy eating, physical activity, and stress reduction through a five sessions of 2-hour group meetings conducted in two community locations. The interventions were delivered in their native language and participants were encouraged to bring family members and friends.

These intervention programs have all the characteristics of an effective culturally specific diabetes management. There were significant improvements seen from these five months intervention programs. Among the positive post-intervention outcomes include better understanding of the relationship between healthy eating and blood sugar control compared to at baseline, significant improvement on knowledge of exercise could improve blood sugar levels, significant increased in vegetable consumption, increased in numbers of participants who reported pouring fat off of meats after cooking fatty foods, a significant decreased in consumption of regular soda or fruit-flavored beverages, an increase in number of days of participants reporting that they follow a healthy eating plan, significant increased in the number of days for blood sugar monitoring as recommended by doctors and a significant improvement in HbA1c values compared to the health system comparison group, pre and post interventions. These significant improvements seen post-intervention were also associated with gender.

The above mentioned study and the findings suggested that a culturally tailored, community-based healthy lifestyle intervention delivered by community residents or peers who are ethnically matched, in the preferred native language and conducted in the local community can significantly improve glycemic control, knowledge and behavior towards diabetes self-care management and ultimately to prevent diabetes-related

complications. This is a show of an example where diabetes management does not refer to only clinical management, but it comprises of a holistic management to tackle all the components that need to be managed throughout the course of the disease including continuous education on disease control and prevention of complications, healthy eating and nutrition, reading food labels and exercise, medications and food-drug interactions, and problem solving and communication skills with a primary care physician that is proven to be more effective if it is delivered through ethnically specific approach (Kim et al., 2009). Looking from the Malaysia context, it is possible to adapt Western intervention programs but adopting the interventions is the area that requires interest, support and expertise from the healthcare providers. We should seek to determine on how best to design and implement culturally tailored and community-based behavior change interventions in greater depth. The question on what elements of interventions is the most effective for what outcomes and in what context should be answered.

There was also another example in looking at effectiveness of culturally specific interventions amongst the Korean Americans in the US (Kim et al., 2009). This ethnic group that also represented Asians were seen to have significant reduction in HbA1c level and achieving HbA1c level of less than 7% after 30 weeks of intervention programs. The interventions were self-help interventions that include 6-week structured psychobehavioral education, home glucose monitoring with teletransmission, and bilingual nurse telephone counseling for 24 weeks.

Both the above mentioned studies have shown evidence on knowledge and behavior change are the two keys in the design of culturally specific diabetes interventions. It is also important to have a strategy in maintaining the retention rates through proper planning of execution such as considering the location for intervention that preferably should be near to the target population to avoid traffic, travelling cost and longer

absence from work and engaging the community organizations. This is especially true in planning for culturally specific intervention in Sabah and Sarawak.

With regards to this current study, a major area in the clinical component intervention that would need to be acknowledged is that BMI acts a fundamental mediator of glycaemic control and that it affects the ethnicity and gender differences in glycaemic control that exist especially among the Chinese, Indian and Melanau ethnic groups. With regards to the implementation of interventions and diabetes management in primary health clinics, these should first be personalized, where personalized in this context refers to making them ethnicity-specific. It would probably not be particularly difficult to gain an understanding of the culture and lifestyle of the Malay, Chinese and Indian populations in Malaysia as these are the major ethnic groups in the country. On the other hand, it would perhaps be more challenging to do so for the Indigenous Sabah and Indigenous Sarawak ethnicities that are comprised of various ethnic groups with significant differences in terms of culture and lifestyle.

Personalized diabetes care and Focus Group Discussion that are ethnicity-specific could be incorporated into and leveraged through the existing family doctor concept (FDC) in primary health clinics. Although the family doctor concept is currently implemented only in selected clinics, as this concept is still early in its implementation, the family doctor concept could be adopted and adapted for ethnic-specific diabetes management. Under the family doctor concept, the whole family is treated and managed by the same healthcare provider, namely, the family doctor throughout their life course as the family doctor concept applies the idea that household areas act as a determinant for the allocation of families to a family doctor. Although the family doctor concept holds to the integrated management concept as the family doctor treats the whole family from the newborn to the elderly, the personalized care of ethnicity-specific diabetes

management could be unified and intensified under the family doctor concept as the family doctors would already know the family's ethnic background, including their culture and lifestyle.

It may be challenging to implement the above in all health clinics and especially in those clinics that have a high number of diabetes patients and that do not apply the family doctor concept. However, it would still be possible to introduce the concept of personalized diabetes care that is ethnic-specific to health clinics with a lower number of patients who have better glycaemic control. The healthcare providers would still be in control of the clinic situation and better patient plans could then be made.

While it is considered that it would not be particularly difficult to incorporate the clinical components into an intervention programme, the psychosocial component, which has the most impact on behavioural change, is an area that would require more study in order to further explore the underlying reasons for ethnic differences in glycaemic control and diabetes-related complications. Hence, further qualitative and quantitative studies are essential for determining the psychosocial factors that could possibly lead to the requisite behavioural changes in order to address issues such as access to early detection that leads to delay in diagnosis and treatment, self-denial, poor self-management, perceived risk, perceived difficulty, and fatalism.

5.8 Strengths

This study, which used a population-based registry to examine ethnic differences in glycaemic control disparities and risk of complications, is, to the best of the author's knowledge, the most extensive that has been conducted in Malaysia to date. This study is also the first to assess whether a lifestyle mediator, namely, BMI, could explain the association between ethnicity and glycaemic control.

All the major ethnic groups, including those from Sabah and Sarawak, which have a substantial number of diabetes patients, were well represented in this cohort study. Moreover, in addition to cross-sectional associations, the longitudinal associations were also established as this study used longitudinal data that allowed for reliable estimates of the effect of ethnicity, time and change in HbA1c levels to be measured.

5.9 Limitations

The use of secondary data in research naturally invites various limitations. The validity, accuracy, and completeness of the data as well as conducting an analysis of available variables and surrogate markers for other variables were among the issues faced in this study.

The extent of the validity and accuracy of the NDR data needs to be acknowledged as one of the limitations of this study. Accuracy relies on the completeness of the data in the diabetes green book and the quality of the data entry done by the staff. To reduce and prevent instances of missing data in the diabetes green book, many clinics have now started doing cross-auditing, where staff from other clinics go through the diabetes green book and do data entry for other clinics. Audits of the NDR itself also act as a quality check, where some states have started to see how accurate the data extraction and entry has been during the audit process, also through cross auditing. However, this is yet to be done systematically, and to date, there is no formal documentation for this process.

In relation to the completeness of the data, the amount of missing data identified by the study analysis also needs to be acknowledged as a limitation. The missing data analysis was conducted to ascertain differences in the odds according to the missingness of the HbA1c level. The key concern in this respect was the missingness of the HbA1c level among the ethnic groups of Sarawak. Altogether, the ethnic groups of Sarawak

had 50%–60% missingness of the HbA1c level. One of the factors that may explain this is that the NDR only obtains data from the health clinics that are registered with it. Some patients may have been transferred out of these registered health clinics to other health facilities that may not be registered in the NDR. In such cases, these patients' names remain in the system and continue to belong to the previous health clinic. Consequently, these patients' details are not updated in the NDR and their progress cannot be followed. Furthermore, these patients could still be selected for a diabetes clinical audit. Hence, without updates on their progress, there is a possibility that they will have missing clinical variables, including the HbA1c level and diabetes-related complications. However, these patients were not excluded from the dataset used for this study because the precision and power of the data was assured with reliable estimates because the analysis showed that the missing data was missing at random.

In addition, the accuracy of the data on diabetes-related complications in the NDR still needs further work. The percentages of diabetes patients with complications were very low and this is likely due to poor documentation. Indeed, this could possibly be an accurate assumption given the high proportion of patients with an unknown complication status.

Another limitation to note is that the data sources for this study were limited to the parameters included in the current NDR dataset. There was therefore a lack of data on dietary intake and physical activity. Hence these two parameters were reflected in the body weight that was measured through the BMI. Education level, socioeconomic status, namely income status and occupation and access to healthcare are not captured in the registry, hence were not adjusted for in the analysis. Nevertheless, in this study, education level, income status, occupation and access to healthcare are not confounders, but instead these are the plausible mediators that were not measured and could possibly

modify the outcome (A. F. Brown et al., 2004). Confounder is a variable that is not in the causal relation but causes both independent and dependent variables where if the variable is not adjusted for in the analysis, the confounding variable will confound or lead to incorrect conclusions on the relation between independent and dependent variables (Mackinnon, 2011). Therefore, education level, income status, occupational status and access to healthcare are not confounders because these variables are not related to both ethnicity and glycemic control, but instead these variables are in the causal pathway between ethnicity and glycemic control (mediating variables). Education level, income status, occupational status and access to healthcare could also be potential moderators because the association between ethnicity and glycemic control may differ across different level of these variables (education, income status, occupation and access to healthcare). Besides, by being moderators, these mentioned variables could also modify the role of mediators (BMI and sex) and influence the outcome. The relation between independent variable and dependent variable may not differ across values of confounding variables (Mackinnon, 2011).

5.10 Way Forward

This study suggested a new evidence for diabetes prevention and control programmes that should be tailored according to ethnicity-specific needs. Furthermore, the results of this study could act as a stepping-stone in the planning and development of new policy initiatives in this area. However, it could be very challenging to move forward in diabetes management in the way suggested above because the importance of the factors of ethnicity and specified BMI level is not yet well known and they are not the subject of current debate and discussion. The doubts on looking into ethnicity as a prognostic factor and the raised fundamental question on how the presence of an association between ethnicity and glycaemic control among type 2 diabetes patients

could help in giving suggestions for intervention because ethnicity cannot be changed or modified, has made us think otherwise following the findings from this study.

The ethnic group of a particular person is, of course, fixed and can never be changed. It is more crucial to understand that it is the underlying cultures, religious beliefs and lifestyles that lie behind every ethnic group that need to be considered. BMI as the mediating factor could be modified and made as the object of intervention in order to improve glycaemic control and diabetes outcomes overall.

It is foreseen that the public health significance of the findings of this study may have an impact on or be able to facilitate the development of suggestions for planning and policy changes and the development of new public health programmes, or at least contribute to the nurturing of a stronger connection with other organizations, particularly the non-governmental organizations or NGOs or civil societies, that are working on diabetes as the findings show that there is a need to create ethnic-specific interventions. Health programmes that are designed to improve the early detection of diabetes and health literacy in relation to diabetes as well as the provision of supportive care should be tailored according to the needs of the various ethnic groups. Lastly, the evidence presented in this study could serve as a foundation for future research in this and other health conditions, as well as for actions that could be taken in the future to include the issue of ethnicity in approaches to diabetes management.

5.11 Chapter Summary

Ethnicity, including multi ethnics from Sabah and Sarawak, in this study was seen as a predictor for glycemic control and diabetes-related complications. This study has also shown evidence on BMI and sex as mediators to explain ethnic differences in glycemic control, which is a new knowledge in the practice, management as well as prevention and control of diabetes. This study revealed the importance of some other variables that

was inevitably not measured in this study, as these variables are not available from the registry due to the limitation of the registry itself. Education, socioeconomic status and access to healthcare are essential factors that could possibly mediate the association and to explain the ethnic differences in glycemic control. These variables also have been proven for many years to be causally related to diabetes outcome and conceptually possible to become mediators for ethnicity and diabetes outcome including glycemic control. These variables could possibly become added values to the observed outcome of this study, alongside restating on the imperative roles of these variables and that it is mandatory to include them into the registry for the betterment of future analysis of the data of the NDR. Findings from this study could serve as a platform to propose on ethnic-specific management, with the aim to increase access to care, to increase quality of care and to improve self-care behavior. Therefore, diabetes outcome could be improved and to reduce the risk of complications, that is also proven to be associated with ethnicity. Intervention should focus on ethnic-specific treatment, targeted specified BMI and to be gender-specific. Health education should be tailored to ethnicity needs with focus on self-care including dietary habit and physical activity, whereas content of the education materials and visual aids needs to be designed to also suit the low-literacy needs.

CHAPTER 6: CONCLUSION

Diabetes is a global issue that is on the rise and burdening not only low- and middle-income countries, but also high-income nations. Malaysia is no exception; the country is facing its worst ever epidemic of diabetes, which is projected to worsen even further by 2025. In addition to planning programmes for the prevention and control of diabetes, it is essential to pay urgent attention to the implementation methods employed in such programmes, as well as the monitoring and sustainability of said programmes because they are supposed to be personalized according to each person's culture and lifestyle.

Evidence on the association between ethnicity and glycemic control was established in this study. Compared to the Malays, all other ethnic groups in this study were associated with lower level of HbA1c at 5 years of having diabetes. Indigenous Sarawak had 1.0% significantly lower HbA1c level; the lowest among other ethnic groups followed by Indigenous Sabah with 0.8% lower HbA1c level. The other ethnic groups of Sabah and Sarawak also showed significantly lower HbA1c level. Chinese and Indian had HbA1c level of 0.5% and 0.1% lower at 5 years of having diabetes.

Chinese, Indian, Dusun and Indigenous Sarawak including Bidayuh and Other Sarawak even showed significant association with changes in HbA1c level for every 5 years of having diabetes. Chinese and Indian continued to have lower HbA1c level compared to Malay as the HbA1c decreases by 0.1% for every 5 years of having diabetes. However, the level of HbA1c amongst the Dusun and Indigenous Sarawak increases by 0.2% and 0.1% (Bidayuh increase by 0.3% and Other Sarawak increase by 0.4%) for every 5 years of diabetes.

Therefore, the Chinese were associated with 61% increased odds of good glycemic control at 5-year of having diabetes and the odds increases by 7% for every 5 years of diabetes. The odds of good glycemic control was similar between the Malays and Indians at 5-year of having diabetes, but with every 5-years of diabetes duration, the odds increases by 20% in the Indians. The odds of good glycemic control amongst the Indigenous Sabah was 3.43 times, and reduces by 14% with every 5-year of diabetes duration. Among the Indigenous Sarawak ethnic group, the odds of good glycemic control was 3.72 times and reduces by 20% with every 5-year of diabetes duration.

Body mass index and sex were found to be partial mediators of the association between Chinese, Indian and Melanau and HbA1c level in this study. Chinese and Indian had 1.7% and 4.1% of the Total Effect mediated by BMI. Chinese also had 1.6% and 3.5% respectively of the Total Effect mediated by being overweight and obese. Indian had higher percentage at 3.3% and 7.5% of the Total Effect mediated by being overweight and obese. Melanau, the ethnic group of the Indigenous Sarawak had 1.2% of the Total Effect mediated by being obese. The indirect associations for the other ethnic groups were less than 1%. Sex was found to be partial mediator of the association between Indian and HbA1c level.

This study has also found ethnicity as a significant predictor for diabetes-related complications. The hazard of diabetic retinopathy and peripheral vascular disease (PVD) was among the Indian compared to Malay. The hazard of diabetic nephropathy was similar between the Indian and Malay. Chinese and Indigenous Sabah was associated with higher hazard of diabetic retinopathy and lower hazard of diabetic nephropathy and PVD. Bajau and Other Sabah contributed to the significant association amongst the Indigenous Sabah. Indigenous Sarawak was associated with significantly

lower hazard in all three diabetes-related complications measured in this study and Iban was the only ethnic group contributed to the associations.

In brief, ethnicity is associated with HbA1c level and longitudinal changes in HbA1c level. BMI including being overweight and obese, and sex act as partial mediators in the association between ethnicity and HbA1c level. Lastly, ethnicity also act as predictor for diabetes related-complications.

This study could be considered critical in guiding future diabetes management in Malaysia using evidence-based findings. Diabetes management does not refer solely to clinical management, where clinical management usually reflects the treatment for the patient. The management also includes control of the disease and prevention of complications, which should be culturally-specific through various methods including patients' education. Hence, the evidence form this study could act as a guide in the design for ethnic-specific interventions to improve glycemic control by focusing on the preferences and cultural differences among the various ethnic groups. BMI was proved to be a significant mediator in this study and is ethnicity-dependent. This new knowledge provides added value for those involved in diabetes management as it indicates a way to apply interventions among the various ethnic groups based on personalized care and treatment targeted at specific groups that could become more meaningful in the future. As the results of this study show, chronic disease management clearly requires personalized care that should be based on evidence in order to achieve excellent clinical outcomes among diabetes patients.

Innovation in primary care is one way in developing culturally specific approach in diabetes management such as incorporating secondary prevention into diabetes management by managing according to ethnic group, targeting specified BMI levels, and to be gender-specific. Moreover, the early detection of diabetes and related

complications through screening, health literacy, and supportive care should be focused on vulnerable groups in order to reduce the plethora of problems that arise from the incidence of diabetes-related complications that, as this study has also shown, are associated with ethnicity. The findings from this study could also serve as a stepping-stone in the planning and development of new policy initiatives that include the issue of ethnicity in approaches to diabetes management. Besides, it could also be an opportunity in engaging other multi agencies and to nurture stronger connection with NGOs or civil societies working on diabetes. Lastly, this study serves as a foundation for future research, for instance qualitative research looking into unmeasured components of implications from different health beliefs.

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LIST OF PUBLICATIONS AND PAPERS PRESENTED

No.	Title of Papers Presented	Name of Conferences
1.	Body Mass Index As Mediators In The Association Between Ethnicity and Glycemic Control Among Type 2 Diabetes Patients	Diabetes Asia Conference 2018, Borneo Convention Centre, Kuching, Sarawak
2.	Association Between Ethnicity And Longitudinal Changes In HbA1c Among Type 2 Diabetes Patients	12th International Diabetes Federation (IDF) Western Pacific Region (WPR) Congress, Kuala Lumpur Convention Centre, Kuala Lumpur