Seremban Diabetes (SeDia) Cohort Study – A Study Proposal

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Diabetes is a major public health problem and involves a complex interplay of multiple factors. Being a non-communicable disease that has been described as "a pandemic of unprecedented magnitude spiralling out of control",[1] diabetes has been recognised as one of the fastest growing global health emergencies of the 21st century. In 2021, it was estimated that 537 million people have diabetes. Should there be no sufficient actions be taken to address the situation, this number is projected to reach 643 million by 2030, and 783 million by 2045.[1]

Diabetes has the highest rate of prevalence in Asia and one of the highest in the world. The prevalence of diabetes is steadily increasing everywhere. Worryingly, the prevalence of type-2 diabetes mellitus (T2DM) in Malaysia have almost doubled over the past 10 years and now includes rapidly rising numbers of children and adolescents.[2] At present, 1 in 5 adults (about 3.9 million people) aged 18 and above in Malaysia have diabetes,[3] the highest rate of incidence in Asia and gaining the title of "Sweetest Nation in Asia". It is projected that seven million Malaysian adults are to have diabetes by 2025, a worrying trend that will see diabetes prevalence of 31.3% for adults aged 18 years and above (1 in 3 adults).[4]

Diabetes imposes a substantial economic burden on countries, health systems, and patients with diabetes as well as their family members.[5-7] There has been considerable increase in global health expenditure due to diabetes, increasing from USD 232 billion in 2007 to USD 966 billion in 2021 for adults aged 20-79 years, representing a drastic 316% increase over a span of 15 years.[1] Nevertheless, the direct costs of diabetes are still anticipated to grow. It was estimated by the International Diabetes Federation (IDF) that total diabetes-related health expenditure will reach USD 1.03 trillion by 2030 and USD 1.05 trillion by 2045.[1] In Malaysia, the estimated total annual cost of diabetes was approximately USD 600 million in 2010 alone.[8, 9]

Among the Malaysian diabetes patients, almost 80% seek treatment at Ministry of Health (MOH) healthcare facilities.[10] Majority of the patients sought treatment at MOH health clinics (68.2%), followed by MOH hospitals (15.0%), private clinics (12.1%) and private hospitals (2.8%).[3] It was reported in 2017 that the annual direct healthcare costs from diabetes in Malaysia totalled about RM4.4 billion, 227 per cent higher than cancer (RM1.3 billion) and 11 per cent higher than cardiovascular disease (RM3.9 billion).[11] In addition, the proportion of Malaysians with risk factors for diabetes is still high.[3] This will indeed result in a substantial economic burden to the healthcare system and national economy. Certainly, this deserves attention and actions from all parties before the Malaysian healthcare system collapses.

Despite its name as being a disease of over sweetness, diabetes also entails with many disabling and life-threatening health complications which devastate the life of the sufferers. Diabetes causes vascular damage in multiple organ systems, leading to increased risk of cardiovascular diseases (CVD), nerve damage (neuropathy), chronic kidney disease (nephropathy), lower limb amputations, eye disease mainly affecting the retina (retinopathy) resulting in visual loss and even blindness.[1] The National Diabetes Registry 2019[12] audited 181,634 type 2 diabetes patients from 830 health clinics. The comorbidities reported for these patients were:

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(i) 80.4% hypertension;
(ii) 74.3% dyslipidemia;
(iii) 14.6% nephropathy;
(iv) 10.6% retinopathy; and
(v) 5.9% ischemic heart disease.

Moreover, incidence rates of serious diabetes-related complications like end-stage renal disease and lower extremity amputations are much higher in Malaysia as compared to other high-income countries.[13] Also based on the National Diabetes Registry 2019, there is a significant gap in the management of diabetes with more than 54.9-87.8% of the diabetes patients not achieving treatment targets.[12] Clearly, the global burden of such complications is huge, with diabetes now a leading cause for end stage renal disease, blindness and disability.[12, 14, 15] Rates of T2DM and related complications vary significantly across countries and regions. In particular, Asians are not only at higher risk for T2DM at lower levels of obesity and younger ages but also at increased risk of adverse outcomes.[16] Therefore, diabetes and diabetes-related complications contribute substantially to the global burden of disease, in terms of morbidity,[17] mortality,[18] reduced quality of life,[19, 20] and economic cost.[21]

Studies had reported that the risk of developing diabetes increased with the number of family members with diabetes, with the strongest risks being associated with children, where both parents had diabetes, as well as twins with a diabetic sibling.[22] It was remarked that offspring who have one parent with T2DM have an absolute risk of 20–40% of developing the condition.[23] Similarly, the risk also increased for individuals with a genetically unrelated family member with diabetes, such as a second-degree relatives and spouses.[22] Subgroup analysis of males versus females, and diabetic parents age below or above 60 years odds also portrayed similar results.[22] These findings are in line with a few studies conducted abroad[24-26] which found familial aggregation patterns of diabetes including half-siblings, first-degree relatives with type 1 and type 2 diabetes, as well as non-related family members. These findings strongly suggest that not only genetic dispositions, but also environmental factors would increase the risk of diabetes substantially.

The exponential increase in diabetes cases is significant as it does not only cause profound psychological and physical distress to both patients and carers, but also is becoming a major economic burden on the healthcare system and national economy. Nevertheless precision health promises a personalized intervention aimed at helping individuals achieve well-being and optimal health based on individual lifestyle, genetics, behaviours, and environment context. Unfortunately, the lack of longitudinal real-world data on T2DM management patterns and associated outcomes in a large number of Malaysian T2DM patients has hindered us to address this disease as a system problem, as opposed to a simple problem with a linear cause-and-effect relationship.

Besides, there is evidence for effective interventions to improve management of diabetes and to reduce its modifiable risk factors, but there are significant gaps in the knowledge base to translate these findings into action plans for the prevention, care and cure of diabetes in Malaysia. We hypothesize that genetics, individual lifestyle, environment and the socio-economy network dynamics, acting at different scales are contributing to T2DM. In addition to these, tertiary prevention of diabetes is also critical. Complications like end-stage renal failure (ESRF),

strokes and other major complications are common where diabetes hurts most, both financially and health wise (DALYs, QALYs, economic burden of disease). Therefore, it is important to aim, not only for glycaemic level targets but for A1C, blood pressure, and cholesterol (ABC) goals and manage therapeutic inertia (physician-, patient-, and system-related factors). From the big picture (especially in terms of policy) perspective, system factors must not be neglected. Health economic perspective is important. In addition, the Wagner Chronic Care Model includes six essential elements of a health care system that when integrated encourage high-quality chronic disease care:

(i) Community resources;
(ii) Health system;
(iii) Self-management support;
(iv) Delivery system design;
(v) Decision support;
(vi) Clinical information systems.

What may be needed is a system approach to understand and address T2DM.

Factors contributing to diabetes risk such as diet quality and quantity, little physical activity, short or disturbed sleep, smoking, and stress and depression have been identified by many studies.[27] These have led to the development of various T2DM risk stratification models to identify high-risk individual based on known risk factors and have been integrated into clinical guidelines to help guide decision making.[28] Although numerous cohort studies have included diabetes as part of the analyses, most of these studies suffer from major limitations. First, majority of the studies focus on western population with minimal involvement of Asian. Furthermore, the socio demographics and culture might be completely different to Malaysia and may not be directly interpretable into the Malaysian context. Second, most of these studies are considered "opportunistic" and focused on understanding limited factors in isolation and oversimplify complex relationships. Third, most studies used conventional methods and did not capitalize on the growing importance of capturing multi-dimensional data using state-of-the-art digital health technology and big data at community level to enhance diabetes prevention and its long-term effects on morbidity and mortality, which will be critical. Fourth, most studies did not include primary care-led health intervention to prevent diabetes, nor study the long-term effects of such interventions.

Therefore, the Seremban Diabetes (SeDia) Cohort was set up with an aim to use a combination of approach at population and individual levels to study the determinants of complications in individuals with T2DM and examine the role of genetic, physiological, environmental, lifestyle and psycho-social factors in the development of T2DM and its complications. The study will contribute tremendously to the understanding of complex interplay between lifestyle, environment, genetics and socioeconomic development in contributing to the increased prevalence of T2DM and how to address it.

As a disease cohort in multiethnic Malaysia, the SeDia cohort includes the following unique features:

1. Focusing on T2DM (n = 5000) and their family members (n = 5000) in Seremban with a minimal 12-year follow-up. Of note, Negeri Sembilan (Figure I) has the highest diabetes incidence

in the country (33.2%)[3] and the population demographic is closely resembling the Malaysian population (in terms of racial distribution, socio-economic status and etc).

2. Addressing the needs of the country in understanding the causal-effects relationship of T2DM in Malaysia.

3. Addressing the non-linear interactions among genetics/ physiology, lifestyle, environment, psycho-social, and healthcare delivery in the prevention, management and cure for diabetes.

4. Utilizing state-of-the-art mobile health, electronic health records and genomics technology to capture multidimensional data from the same individual in the most cost-effective manner, creating opportunities for innovations in achieving better diabetes outcomes.

5. Incorporating both observational and interventional elements in the same cohort for comparative effectiveness analyses.

Figure 1: Map of Peninsular Malaysia showing the study site (in red circle)

Through the SeDia Cohort, it is anticipated to provide a more complete understanding of the etiopathogenesis of T2DM and its related complications in Malaysia, with the long-term objective of improving care and outcomes of the patients. The data collected from this cohort will ideate new concepts in creating, enabling and sustaining better supportive policy, social and physical environments for healthy lifestyles with the ultimate long-term goal to prevent, care and create cure for diabetes.

With the collective rationales, the objectives for SeDia Cohort are:

1. To determine the incidence rate and the risk factors (sociodemographic, dietary, psychosocial, biological such as genomics/genetics, glycoproteomics, metabolomics, proteomics, lipidomics, cytokines and adipokines, hormonal, biochemical) and their interaction for:
   i) the development and progression of renal impairment and chronic renal failure
   ii) the development and progression of diabetic retinopathy
   iii) the development of angina pectoris and myocardial infarction
   iv) the development of transient ischaemic attack and stroke
   v) the development of limb gangrene
   vi) the development of diabetic neuropathy
   vii) hospitalisation and mortality

2. To determine the incidence rates and risk factors (sociodemographic, dietary, psychosocial, biological such as genomics/genetics, glycoproteomics, metabolomics, proteomics, lipidomics, cytokines and adipokines, hormonal, biochemical) and their interaction for:
   i) the development and progression of insulin resistance
   ii) the development and progression of impaired glucose tolerance
   iii) the development and progression of diabetes among patients with T2DM and their family members.

3. To develop:
   i) predictive biomarkers
   ii) statistical models and algorithms
   iii) diabetes complications risk score for patients with T2DM and their household family members

The establishment, maintenance and governance of SeDia Cohort is a collaborative public-private partnership between International Medical University (IMU), Kuala Lumpur and the Ministry of Health (MOH), Malaysia, represented by Negeri Sembilan Health Department and Seremban District Health Office. A Memorandum of Understanding was signed on 17th May 2022 between MOH and IMU. A Joint Steering Committee between Jabatan Kesihatan Negeri Negeri Sembilan (JKNNS) and IMU has been set up which is responsible for making all decisions related to policies and activities, supervising and monitoring the implementation of this MOU.

Aside from that, a Scientific Advisory Panel (SAP) has also been established with the aim to provide expert review, appraisal and guidance on the study protocol, implementation, analysis and evaluation of the progress of this SeDia cohort. SAP is anticipated to meet on an annual. The members of the SAP are:

1. Prof Dato' Dr Mafauzy Mohamed, Honorary Professor of Medicine and Senior Consultant Endocrinologist, Universiti Sains Malaysia.

2. Datuk Dr Zanariah Hussein, Consultant Endocrinologist Hospital Putrajaya and Head of Endocrinology Subspecialty Service, MOH.

3. Prof Datuk Dr Rahman Jamal, Founding Director of UKM Medical Molecular Biology Institute

(UMBI) and The Malaysian Cohort (TMC), Universiti Kebangsaan Malaysia.

4. Prof Edward Gregg, Professor and Chair in Diabetes and Cardiovascular Epidemiology, Royal Society Wolfson Fellow, School of Public Health, Imperial College London.

SeDia is a long-term observational cohort study on patients with diabetes and their household members. Seremban Health Clinic is chosen as study site as it is the main primary care health clinic which provides population-based prevention, management, and control of diabetes in Negeri Sembilan state. Patients with diabetes will be followed up for risk factors related to poor glycaemic control and the development of diabetic complications. The household family members will be followed up for risk factors for the development of diabetes.

It will be an open cohort with recruitment open to all patients with diabetes registered under the National Diabetes Registry (NDR) who are being followed up at Seremban Health Clinic. Household family members of these index patients with diabetes are to be invited to participate in the cohort. Each subject will be followed-up for at least 12 years after enrolment as the diabetes complications usually progress over the next 10 to 20 years from onset.[29] Recruitment will be started in 2023 and continued throughout the study.

Data will be collected from the subjects via face-to-face interviews through a series of questionnaires including socio-demographic information, 24-Hours Diet Recall, Global Physical Activity Questionnaire (GPAQ v2.0), Brief COPE Scale, Finnish Diabetes Risk Score, Summary of Diabetes Self-Care Activities (SDSCA), as well as Malaysia Medication Adherence Assessment Tool (MyMAAT). Clinical data of all patients will be retrieved from the medical records in the clinic. Besides that, blood samples will also be collected from the study subjects.

As part of this study, a questionnaire data entry tool will be designed as a means for data input of each participant. Having to ensure accuracy of data collection in mind, the tool will be designed by the scientific expertise in the study team and subsequently developed by a professional vendor with experience in mobile application and web development. The developed tool will also serve as a sophisticated, stable platform for data storage while allowing data to be entered with ease. The system will be able to create reports and queries to compile necessary output files for managing the day-to-day activities of the study (for example data files to allow linkage to external data sources and summary participation statistics).

In addition, another MOU has also been inked with the Pantai Medical Centre Sdn Bhd of IHH Healthcare on 2nd August 2022. As part of this agreement, the IHH Healthcare had agreed to sponsor a total of RM2million for the SeDia Cohort Study.

Being the first large-scale cohort study on diabetes of its kind to be conducted in Malaysia, SeDia cohort study marks the first important step towards obtaining data that is socio-culturally relevant to the local community. By understanding the complex connections between various factors encompassing genetics and family history of diabetes to lifestyle and environmental factors, SeDia Cohort Study will ultimately uncover optimal strategies for diabetes prevention and treatment. Subsequently,

this knowledge can be translated into implementing evidence-based public healthcare policies and programmes that are relevant to the local community, ensuring the efficacy of developed treatment and prevention initiatives in addressing the escalating burden of diabetes in Malaysia. On top of that, the SeDia Cohort study also provides an opportunity for researchers to gain a deeper understanding of the role of genetics and the environment within the local community which will help further improve diabetes management guidelines and public health policies towards better health outcomes.

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