BMJ Open

Cohort profile: the Singapore diabetic cohort study

Miyang Luo,[1] Linda Wei Lin Tan,[1] Xueling Sim,[1] Milly Khiam Hoon Ng,[1] Rob Van Dam,[1] E Shyong Tai,[1,2] Kee Seng Chia,[1] Wern Ee Tang,[3] Darren EJ Seah,[3] Kavita Venkataraman [1]

To cite: Luo M, Tan LWL, Sim X, *et al*. Cohort profile: the Singapore diabetic cohort study. *BMJ Open* 2020;**10**:e036443. doi:10.1136/bmjopen-2019-036443

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-036443).

Received 18 December 2019
Revised 21 March 2020
Accepted 17 April 2020

[1]Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore
[2]Division of Endocrinology, National University Hospital, Singapore
[3]National Healthcare Group Polyclinics, Singapore

Correspondence to
Dr Kavita Venkataraman; kavita_v@nus.edu.sg

ABSTRACT

Purpose The diabetic cohort (DC) was set up to study the determinants of complications in individuals with type 2 diabetes and examine the role of genetic, physiological and lifestyle factors in the development of complications in these individuals.

Participants A total of 14 033 adult participants with type 2 diabetes were recruited from multiple public sector polyclinics and hospital outpatient clinics in Singapore between November 2004 and November 2010. The first round of follow-up was conducted for 4131 participants between 2012 and 2016; the second round of follow-up started in 2016 and is expected to end in 2021. A questionnaire survey, physical assessments, blood and urine sample collection were conducted at recruitment and each follow-up visit. The data set also includes genetic data and linkage to medical and administrative records for recruited participants.

Findings to date Data from the cohort have been used to identify determinants of diabetes and related complications. The longitudinal data of medical records have been used to analyse diabetes control over time and its related outcomes. The cohort has also contributed to the identification of genetic loci associated with type 2 diabetes and diabetic kidney disease in collaboration with other large cohort studies. About 25 scientific papers based on the DC data have been published up to May 2019.

Future plans The rich data in DC can be used for various types of research to study disease-related complications in patients with type 2 diabetes. We plan to further investigate disease progression and new biomarkers for common diabetic complications, including diabetic kidney disease and diabetic neuropathy.

Strengths and limitations of this study

- The cohort focuses on diabetes, one of the biggest public health challenges in this century, with a relatively large pool of multiethnic participants comprising Chinese, Malay and Indians, and follow-up duration of more than a decade.
- This cohort has collected a variety of data on sociodemographics, lifestyle, health-related quality of life, anthropometric and other physical measurements, biochemical characteristics and genetic profiles through questionnaires, physical assessment, collection of biological samples and linkage to medical and administrative records.
- Diabetic cohort is a prevalence cohort, which recruited participants with varying durations of disease, and potentially at different stages of the natural history of disease.
- This cohort may be limited by the low rate of active follow-up of participants, which has been substantially overcome through the linkage with medical records and disease registries.

INTRODUCTION

Diabetes mellitus is a major public health problem that has reached epidemic proportions globally. The International Diabetes Federation has estimated that there were more than 400 million individuals with diabetes worldwide in 2017, which is projected to increase over 600 million by 2045,[1 2] with around 90% having type 2 diabetes. Diabetes also causes vascular damage in multiple organ systems, leading to increased risk of cardiovascular diseases, chronic kidney disease, retinopathy and lower limb amputations. The global burden of such complications is huge, with diabetes now a leading cause for end-stage renal disease, blindness and disability.[3–7] Therefore, diabetes and diabetes-related complications contribute substantially to the global burden of disease, in terms of morbidity,[8] mortality,[9] reduced quality of life[10 11] and economic cost.[12]

Rates of type 2 diabetes and related complications vary significantly across countries and regions. In particular, Asians are not only at higher risk for type 2 diabetes at lower levels of obesity and younger ages but also at increased risk of adverse outcomes.[13 14] In Singapore, the prevalence of diabetes has been rising, with prevalences of 8.3% and 8.6% being reported, using fasting plasma glucose measurements only, in the consecutive National Health Surveys in 2010 and 2017, respectively.[15] Incidence rates of serious diabetes-related complications like end-stage renal disease and lower extremity

amputations are much higher in Singapore as compared with other high-income countries.[6 16]

The diabetic cohort (DC), therefore, was set up to study the determinants of complications in individuals with type 2 diabetes and examine the role of genetic, physiological and lifestyle factors in the development of complications in these individuals. As a disease cohort in multiethnic Singapore, the DC provides the opportunity to examine intra-Asian variations in risk of complications and downstream outcomes and the role of the factors mentioned above in any differential risk.

Through the DC, we hope to provide a more complete understanding of the etiopathogenesis of type 2 diabetes and its related complications in Asia, with the long-term objective of improving care and outcomes in individuals with type 2 diabetes.

Cohort description

The DC is a part of the Singapore Population Health Studies in the Saw Swee Hock School of Public Health, National University of Singapore. It is a closed cohort with a total of 14 033 adults with diabetes enrolled during two recruitment phases in 2004–2006 and 2006–2010 from multiple public sector polyclinics and hospital outpatient clinics. In phase 1, 5324 participants were recruited from Clementi and Toa Payoh Polyclinics, Tan Tock Seng Hospital and National University Hospital in Singapore. An additional set of 8709 participants were recruited from Choa Chu Kang, Jurong, Yishun and Pasir Ris Polyclinics, as well as Changi General Hospital, and Alexandra Hospital in phase 2. Inclusion criteria for the DC were adult Singaporeans and permanent residents (aged 21 years and above) with physician-diagnosed type 2 diabetes. Subjects with mental illness, clinically obvious non-diabetic kidney disease (such as polycystic kidney disease), type 1 diabetes or diabetes mellitus resulting from endocrinopathies were excluded.

PATIENT RECRUITMENT

Recruitment was conducted in the following ways: (1) patients were identified by their attending physicians and referred to a research nurse or identified by a research nurse based on review of medical records and approached directly for recruitment at the clinic or (2) patients were approached by a trained researcher at the waiting area of the clinic for assessment of eligibility and recruitment. Written informed consent was obtained for (1) participation in the study, (2) extraction of information from case notes, (3) linkage to national disease registries and medical records, (4) storage of biospecimens for future research and (5) recontact. After informed consent, each participant completed an interviewer-administered questionnaire and underwent anthropometric assessments by a trained research nurse. Blood and spot urine specimens were collected at the time of recruitment and stored for future analysis. If the patient had already provided a blood specimen for the quarterly diabetes monitoring tests to the clinic prior to the providing consent, the blood specimen would be collected at the patients' next quarterly diabetes monitoring visit. Participants' medical record data of the past 5 years were extracted from the site of recruitment by the trained research nurses after enrolment.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

FOLLOW-UP INFORMATION

After the baseline recruitment in 2004 and 2010, 410 participants of the DC were selected for a pilot follow-up in 2010 to study the associations between the glycaemic index of their diet with glycaemic control and risk factors for cardiovascular disease. Following the pilot, the first wave of in-person follow-up with the cohort participants began in 2012 and ended in 2016. Of the 14 033 baseline participants, 4677 (33.3%) were not contactable (ie, contact details changed and no updated information available, frequently travelling, or access to household denied and unable to contact despite six attempts at household visitation) and 1058 (7.5%) were confirmed to have been lost to follow-up (ie, deceased, migrated, declined consent for follow-up at baseline, lost mental competence to give consent to continue the research, institutionalised or physically unfit to participate). Of the 8298 contactable participants, 4131 (29.4% of DC and 49.8% of contactable participants) agreed to participate in the follow-up survey. A second wave of in-person follow-up of the DC has been started in 2016 and is expected to be completed in 2021.

DATA COLLECTION

Table 1 summarises the information collected from DC participants at baseline and follow-up assessment. At recruitment, participants completed an interviewer-administered questionnaire, which took approximately 15–20 min. Questionnaires were available in English, and interviewers provided additional explanation and translation when necessary in other languages common to both the participant and the interviewer. Participants were interviewed about their demographic characteristics, smoking behaviour and personal and family medical history. Height and weight were based on the last recorded values in the medical record file of the participants which would have been measured on the same day or up to 3 months earlier. Waist circumference was measured at the level of the mid-point between the last rib and the iliac crest, with the participant in light expiration following WHO standards. Hip circumference was measured at the level of the greater trochanter of the femur.[17]

Follow-up of the DC was conducted in tandem with the follow-up of the Singapore Multiethnic Cohort using the same study protocol.[18] During the first follow-up

Table 1 Summary of variables collected or derived from the cohort

Variables	Baseline	First follow-up	Second follow-up
Questionnaire			
Demographics	✓	✓	✓
Tobacco use	✓	✓	✓
Environmental tobacco smoke		✓	
Alcohol consumption		✓	✓
Diet (FFQ)		✓	
Physical activity		✓	✓
Sleep quality (PSQI)			✓
Medication use		✓	✓
Medical history	✓	✓	✓
History of diabetes complications	✓		
Women's health		✓	✓
Skin health			✓
Family history	✓	✓	✓
Health-related quality of life (SF-12/SF-36/EQ-5D)		✓	✓
Stress		✓	
Kessler Psychological Distress Scale (K10)		✓	
Cognitive test (MMSE for age 40 years and older)		✓	✓
Workability			✓
ADL (for age 65 years and older)			✓
Instrumental ADL (for age 65 years and older)			✓
Physical examination			
Height	✓	✓	✓
Weight	✓	✓	✓
Waist circumference	✓	✓	✓
Hip circumference	✓	✓	✓
Blood pressure		✓	✓
Central aortic blood pressure		✓	
Ankle brachial index		✓	✓
Skinfold thickness		✓	
Resting ECG		✓	✓
Assessment of foot sensory function by monofilament and neurothesiometer		✓	✓
Hand grip strength		✓	✓
Visual acuity			✓
Timed-Up-and-Go (for age 40 years and older)			✓
Spirometry (for ages 35–80)			✓
Medical records			
Diabetes profile and treatment	✓	✓	
Blood pressure profile and treatment	✓	✓	
Lipid profile and treatment	✓	✓	
Complications of kidney, eye and macrovascular systems	✓	✓	
Laboratory tests (subset)			

Continued

Table 1 Continued

Variables	Baseline	First follow-up	Second follow-up
Urine protein, glucose, ketone and blood (semiquantitative)	✓		
Urine albumin (semiquantitative)		✓	✓
High sensitive C-reactive protein	✓	✓	
Cortisol	✓	✓	
Serum creatinine		✓	✓
Fasting glucose		✓	✓
Blood lipids		✓	✓
Haemoglobin A1c		✓	✓
Interleukin-6		✓	
Interleukin-1 receptor antagonist		✓	

ADL, activities of daily living; EQ-5D, EuroQol quality of life 5 dimensions; FFQ, food frequency questionnaire; MMSE, mini-mental state examination; PSQI, Pittsburgh sleep quality index; SF-12/SF-36, short form health survey - 12 items/ 36 items.

assessment, participants completed a more comprehensive questionnaire that included additional information on environmental tobacco smoke, alcohol consumption, diet, physical activity, medication use, women's health, health-related quality of life, stress, distress (Kessler Psychological Distress Scale (K10)) and cognition (mini-mental state examination). This was followed by a physical examination to measure height, weight, waist circumference, hip circumference, brachial and ankle blood pressure, central aortic blood pressure, skinfold thickness, resting ECG, hand grip strength and foot sensory function using monofilament and neurothesiometer. Systolic and diastolic blood pressures were measured using an automated digital monitor (Dinamap Carescape V100, General Electronic). A sphygmomanometer (Accoson, UK) was used for participants with blood pressures beyond the range of the digital monitor. Two readings were recorded for each participant, with a third reading if the difference between the first two readings exceeded 10 mm Hg for systolic or 5 mm Hg for diastolic blood pressure, respectively. Central aortic systolic pressure and arterial pulse waveform were measured on the left arm with the participant seated and the left arm resting on a table at chest level using A-PULSE CASPro Lite (HealthSTATS, Singapore). Skinfold thickness was measured by a Holtain/Tanner skinfold calliper at the left triceps, left biceps, subscapular, supra-iliac and calf regions with the participant in a standing position. A resting electrocardiogram (10 leads) was obtained using the ECG-1350K (Nihon Kohden, Japan). A hand dynamometer (TAKEI A5401, Japan) was used for assessing hand grip strength with three readings recorded for each arm. Foot sensory function was assessed with the participant in supine position with bare feet and closed eyes. A 10 g (5.07) monofilament (Sensory Testing System, USA) was used to test light touch on five least calloused plantar sites per foot—the distal great toe, third toe, fifth toe and the first and fifth metatarsal heads. The number of sites that the participants could feel was recorded for each foot. A neurothesiometer (Horwell, UK) was used to assess foot proprioception. A vibration-emitting probe with gradually increased voltage was applied to the apex of the big toe and medial malleolus of both feet, and the voltage reading was recorded when the participants indicated verbally that they could feel the vibration.

During the second follow-up, assessments of workability and activities of daily living were also included in the questionnaire, and measurements of visual acuity, Timed-Up-and-Go and spirometry have been added to the physical examination.

Medical records extraction and data linkage

After recruitment, relevant data were extracted from patients' medical case notes available at the site of recruitment. Extraction was restricted to a period of up to 5 years before recruitment and was performed by trained research nurses. Fields extracted included records of diagnosis of diabetes, haemoglobin A1c (HbA1c) levels, treatment regimens for diabetes, hypertension diagnosis, blood pressure levels, antihypertensive treatment, lipid values, usage of lipid-lowering agents, diagnosis of microalbuminuria, proteinuria and diabetic nephropathy; age at dialysis initiation, age at renal transplant, serum creatinine levels, urinalysis results, and diagnosis of diabetic retinopathy, cataract, ischaemic heart disease, stroke and limb amputation.

Additional comprehensive medical data on physical and laboratory investigations and medications for the period 2000–2015 were obtained by linkage with the electronic medical record system of the National Healthcare Group (NHG) Polyclinics for participants who ever visited the NHG polyclinics (n=11 721 participants). Extracted data included blood test results (ie, measurements of fasting or random glucose, HbA1c, lipids, creatinine, haemoglobin,

Table 2 Biosample availability for baseline and first follow-up

Biosamples	Baseline*	First follow-up *
Whole blood/whole blood plasma	7569	2255
DNA/buffy coat/buffy coat DNA	11901	2400
Plasma/plasma (sodium citrate)	9049	2414
Serum	8008	2040
Red blood cells	7123	372
Urine (buffered/normal)	5860	1787

*Number of participants with at least one aliquot of sample available. Sample availability was updated on 11 March 2020.

urea and uric acid), physical measurements (ie, blood pressure, height and weight), urine test results (ie, albumin, albumin creatinine ratio, protein, protein creatinine ratio, creatinine, cells and formed elements), medication records, clinic visits records and attendance at diabetic food screening and retinal photography. Cohort data have also been linked with the disease registers maintained by the National Registry of Diseases Office to identify the incidence of acute myocardial infarction, stroke, end-stage renal disease, cancer and death.

Biochemical analyses and biobanking

Blood and urine samples were collected from consenting participants at baseline and follow-up. In the first phase of recruitment, approximately 10 mL of blood (fasting or random) and 50 mL of urine were obtained from each consented participant; in the second phase, 15 mL of blood and 20 mL of urine were taken. During follow-up, participants were asked to fast 8–12 hour before their appointment, and up to 23 mL of blood and 6 mL of urine were stored. The samples were aliquoted and stored at −80°C. DNA, buffy coat, plasma, serum and red blood cells were extracted from blood samples and stored separately. The number of biosamples available is summarised in table 2.

Genome-wide array data are available for a subset of the DC cohort from a combination of Illumina genome-wide genotyping arrays (n=2010)[19] and imputed to 1000G Phase 3 reference panels. In addition, whole exome sequence data are also available for some of the participants as part of the T2D-GENES (Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples) Consortium.[20 21]

PARTICIPANT CHARACTERISTICS

The demographic profile of participants at recruitment is presented in table 3. The mean age of participants was 59.7±10.7 years and 50.8% were men. The ethnic composition was 59.3% Chinese, 22.7% Malay and 17.3% Indian.

Table 3 Participants characteristics at baseline (n=14 033)

	N (%)
Age at interview (in years), mean± SD	59.7 (10.7)
Duration of diabetes (years), median (IQR)	7.0 (3.0–14.0)
Gender	
Male	7134 (50.8)
Female	6899 (49.2)
Ethnicity	
Chinese	8327 (59.3)
Malay	3181 (22.7)
Indian	2423 (17.3)
Others	102 (0.7)
Marital status	
Never married	710 (5.1)
Currently married	10779 (76.9)
Separated/divorced	490 (3.5)
Widowed	2047 (14.6)
Education status*	
No formal qualification	3647 (26.0)
Primary	4614 (32.9)
Secondary	3832 (27.3)
Vocational training/postsecondary	1388 (9.9)
University and above	546 (3.9)
Occupation status	
Working	5909 (42.2)
Homemaker	4426 (31.6)
Retired	3101 (22.1)
Unemployed	574 (4.1)
Self-reported health conditions (%)†	
Hypertension	9608 (68.5)
Diabetic retinopathy	1534 (10.9)
Diabetic kidney disease	1268 (9.0)
Family history (%)‡	
Hypertension	6835 (48.7)
Diabetes	10755 (76.6)
Smoking status (%)	
Never smoker	10043 (71.6)
Ex-smoker	2370 (16.9)
Current smoker	1619 (11.5)

Numbers missing: duration of diabetes (n=927), marital status (n=7), educational status (n=6), occupation status (n=23) and smoking status (n=1).
*Educational status: secondary education ('O'/'N' level), vocational training (attended Institute of Technical Education or obtained National Technical Certificate) and postsecondary education ('A' level, polytechnic/diploma).
†Participants were asked whether they had been diagnosed with hypertension, diabetic retinopathy or diabetic kidney disease by Western doctors.
‡Family history was defined as having a history of the condition in parents or siblings.

Table 4 Disease profile of study participants at recruitment and the latest visit in medical records

	At recruitment* (n=14 033)	At latest visit† (n=12 242)	P value
Biomarkers, mean±SD			
HbA1c (%)	7.7 (1.5)	7.8 (1.6)	0.24
Total cholesterol (mmol/L)	4.9 (1.0)	4.4 (1.0)	<0.001
Triglycerides (mmol/L)	1.7 (1.1)	1.6 (0.9)	<0.001
HDL-C (mmol/L)	1.2 (0.3)	1.3 (0.4)	<0.001
LDL-C (mmol/l)	2.9 (0.9)	2.4 (0.8)	<0.001
eGFR (mL/min/1.73 m^2)‡	80.0 (21.8)	71.1 (24.8)	<0.001
Blood pressures (mm Hg), mean±SD			
Systolic	133.0 (15.6)	131.1 (16.3)	<0.001
Diastolic	77.0 (8.9)	70.3 (9.6)	<0.001
BMI category (kg/m^2), (%)			<0.001
<18.5	191 (1.4)	280 (3.1)	
18.5–23.0	2500 (18.1)	2184 (24.1)	
23.0–27.5	5850 (42.5)	3756 (41.5)	
≥27.5	5237 (38.0)	2831 (31.3)	
Follow-up duration, median, IQR	–	7.5 (4.0–9.8)	

Numbers missing at recruitment: HbA1c (n=1124), total cholesterol (n=6656), triglycerides (n=6659), HDL-C (n=6671), LDL-C (n=6753), eGFR (n=5426), blood pressure (n=440), BMI (n=255). Numbers missing at latest visit: total cholesterol (n=5042), triglycerides (n=5040), HDL-C (n=5040), LDL-C (n=5041), eGFR (n=5058), blood pressure (n=194), BMI (n=3191); most missing values are due to lack of records in extracted data.
*Variables measured within 1-year window from date of recruitment were used.
††date of the Latest Visit Was Defined Using the Date of the Last Hba1c Measurement for Each Subject, and Other Variables Measured Closest to This Date Within 1-year Window Were Used as the Latest Measurement.
‡eGFR was calculated based on the CKD-EPI formula.
BMI, body mass index; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

The median duration of diabetes in the cohort was 7 years with an IQR of 3 to 14. 68.5%, 10.9% and 9.0% of participants reported a prior diagnosis of hypertension, diabetic retinopathy and diabetic kidney disease, respectively. Approximately half of the participants reported a family history of hypertension (48.7%) and 76.6% reported a family history of diabetes. Participants who have been actively followed up were similar to the overall cohort at recruitment, except for slightly younger age and a greater proportion of those working (online supplementary table 1).

Disease characteristics of the study participants at recruitment and the latest visit in medical records are presented in table 4. Participants had a mean HbA1c of 7.7±1.5% at recruitment and similar levels were observed at their latest visit. There was a slight improvement in diastolic blood pressure (from 77±8.9 mm Hg to 70±9.6 mm Hg), and low-density lipoprotein cholesterol (from 2.9±0.9 mmol/L to 2.4±0.8 mmol/L) between recruitment and last visit. The prevalence of obesity, defined as body mass index ≥27.5 kg/m^2 using Asian-specific cut-offs,[22] decreased from 38.0% to 31.3% during this time. The median follow-up duration from recruitment to the last visit recorded was 7.5 years.

Findings to date

Data from the cohort have been used to identify determinants of diabetes and related complications. The longitudinal nature of the cohort and the linkage to a variety of records data have allowed the time trend analyses of diabetes control over time. An examination of determinants of poor glycaemic control in primary care over 5 years identified treatment with insulin at baseline, Malay or Indian ethnicity and presence of retinopathy to be associated with poor glycaemic control.[23] The availability of serial HbA1c values has been used to examine patterns of longitudinal HbA1c control. Four distinct patterns were identified, the largest being a low-stable pattern with mean HbA1c of 7.1% over time, followed by a moderate stable pattern with mean HbA1c of 8.5%, a pattern of deteriorating glycaemic control and one of improving glycaemic control. These patterns were associated with differential risks of late-stage complications and death.[24] The role of diabetes treatment in shaping the HbA1c patterns has also been examined, with findings revealing that treatment by and large matched the extent of dysglycemia, and that HbA1c deterioration occurred in spite of treatment intensification and not due to a lack of intensification.[25]

Using biological samples collected from the cohort participants, we have also focused on identifying correlates and markers for diabetes and diabetic kidney disease. As part of the Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, the DC has contributed to identification of T2D-associated genetic loci such as *KCNQ1*,[26] East Asian-specific *PAX4*[27 28] and trans-ethnic *SSR1-RREB1* and *ARL15* which have been implicated in regulation of fasting insulin and fasting glucose.[29] DC has also contributed cases to replication studies of novel T2D susceptibility loci identified first in European populations or other Asian populations[30 31] as well as to transancestral investigations into the genetic architecture of diabetes.[32 33] More recently, whole exome sequencing analyses across multiple ancestries have identified modest rare-variant associations with T2D.[20 21] In addition to diabetes meta-analyses, the DC has also contributed to large-scale meta-analysis of diabetic kidney disease.[34 35] Other analyses have demonstrated the significant associations of plasma tumor necrosis factor α and its receptors,[17] pentosidine[36] (an advanced glycation end product) and urinary excretion of nephrin[37] with reduced kidney function. Metabolomic analysis of urine samples from DC participants through liquid chromatography–mass spectrometry and gas chromatography–mass spectrometry has identified several metabolites that could potentially serve as markers of non-proteinuric diabetic kidney disease.[38]

The complete list of publications based on the DC data is available online (https://blog.nus.edu.sg/sphs/publications/).

Strengths and limitations

The main strengths of the DC are the focus on diabetes, which is one of the biggest public health challenges in this century, the relatively large pool of participants and a follow-up duration of more than a decade. The linkage of cohort data with medical records and disease registries is an important advantage for the cohort as this has allowed the in-depth and longitudinal tracking of several key clinical measures and outcomes in these patients. This linkage has also facilitated the capture of clinical data not only prospectively but also retrospectively before recruitment into the cohort. Another strength is the multiethnic composition of the cohort, representing three major ethnic groups in Asia, and thus allowing the evaluation of interethnic variation in diabetes progression, complication risk and outcomes. The stored biological samples are also an asset of the cohort, making it possible to examine novel and emerging biomarkers and genetic determinants in this population.

This study is not without its limitations. DC is a prevalence cohort, which recruited participants with varying durations of disease, and potentially at different stages of the natural history of disease. Another limitation is the low rate of active follow-up of participants, which has been substantially overcome through the linkage with medical records and disease registries. In spite of these limitations, the cohort continues to yield insights into diabetes and its complications in the Asian context.

Collaboration

We welcome potential collaboration with other researchers. Researchers can visit the Saw Swee Hock School of Public Health website (https://blog.nus.edu.sg/sphs/) for information on submitting a request for data and/or samples.

Contributors KV conceived the present manuscript and prepared the final version for the submission. ML drafted the manuscript. ML, LWLT and MKHN conducted the data analysis. RVD, EST, KSC, WET and DEJS established the cohort and provided intellectual inputs to the manuscript. XS critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Funding The study was funded by grants from the National Medical Research Council (NMRC/0850/2004), Biomedical Research Council of A Star (BMRC/05/1/21/19/425), Ministry of Health, Singapore, National University of Singapore and National University Health System.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethics approval for the DC was provided by the National University of Singapore Institutional Review Board (NUS IRB) and National Health Group Domain Specific Review Board (NHG DSRB).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Researchers can visit the Saw Swee Hock School of Public Health website (https://blog.nus.edu.sg/sphs/) for information on submitting a request for data and/or samples.

ORCID iD

Kavita Venkataraman http://orcid.org/0000-0002-3139-6998

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