Title: Incidence and variation in progression to Type 2 Diabetes Mellitus among Singaporeans with impaired fasting glycaemia – a retrospective cohort study

Abstract:

Objective: Asians have a greater risk of progression from intermediate hyperglycaemia to Type 2 Diabetes Mellitus (T2DM). We investigated variation in progression from impaired fasting glycaemia (IFG) among Singapore's three major ethnic groups over 8 years, testing the hypothesis that Malays and Indians have higher risk than Chinese.

Methods: : In this retrospective cohort study, 2,350 Chinese, Malay and Indian adults newly diagnosed with IFG between September 2011 and August 2014 at five public primary care polyclinics in Singapore were followed until August 2023. We calculated T2DM incidence per 1,000 person-years and compared progression hazards using Cox regression, adjusting for variables including age, sex, smoking, Aspartate Aminotransferase/Alanine Aminotransferase (AST/ALT) ratio, and percent weight change.

Results: Over a median 95-month follow-up (IQR 53–138), 50.3% developed T2DM (incidence 81.6 per 1,000 person-years). After multivariable adjustment, Malays had significantly higher odds of progression compared to Chinese (OR 1.36 [95% CI 1.00–1.85] p = 0.048), though progression rates were similar (HR 1.14 [95% CI 0.94–1.37] p = 0.156). Female sex, smoking, lower AST/ALT ratio and percentage weight gain independently increased progression risk and accelerated rate.

Conclusion: Clinical and demographic variables appear to influence progression from IFG to T2DM among Singaporeans. Tailored preventive strategies targeting high-risk groups—particularly Malays, smokers, women and those with weight gain—could optimise resource allocation and reduce T2DM burden.

Research – Main report

1. Introduction:

Intermediate hyperglycaemia is an at-risk state for the development of diabetes mellitus (DM). Individuals in this state have an increased risk of developing retinopathy, neuropathy, nephropathy, and macrovascular complications.[1]

Various organizations have defined intermediate hyperglycaemia with criteria that are not uniform. The World Health Organization (WHO) defines IFG as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dL) and impaired glucose tolerance (IGT) as 2 hour plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 g of oral glucose load or a combination of the two based on a 2 hour oral glucose tolerance test (OGTT).[2] Singapore uses the WHO definitions of intermediate hyperglycaemia.

In 2021, an estimated 537 million people worldwide were living with diabetes. This number is expected to rise to 643 million by 2030 and 783 million by 2045. The Western Pacific (WP) Region, which includes Singapore, accounts for 38% of the global diabetic population.[3] According to the International Diabetes Federation (IDF), the region's diabetic population is projected to reach 260 million by 2045, with prevalence increasing from 11.9% to 14.4%. Additionally, the proportion of undiagnosed diabetes in the WP Region stands at 52.9%, the second highest among all IDF Regions.[4]

In a systematic review evaluating the progression of prediabetes to diabetes in global cohort settings, the annual incidence rate of diabetes was found to be 4%-6% for isolated IGT, 6%-9% for isolated IFG and 15%-19% for both IGT and IFG.[5] Compared to Caucasians, Asians had a significantly increased rate of progression from prediabetes to T2DM in a recent meta-analysis.[6]

The Singapore National Health Survey showed an increase in prevalence of obesity from 10.5% in 2019–2020 to 11.6% in 2021–2022, but prevalence of diabetes dropped. However, it is estimated that the number of Singaporeans with diabetes will rise to 1 million by 2050, much higher than an earlier projection that was based on aging alone.[7] A prospective study on a multi-ethnic cohort without prediabetes found that different ethnicities had unique biological risk factor profiles related to T2DM development.[8] However, recent data on the risk of progression among those newly confirmed to have IFG is lacking.

The primary aim of this study is to evaluate if there are ethnic differences in the risk and rate of progression from newly confirmed IFG to T2DM among Singaporean adults seen in primary care. Our hypothesis is that Indian and Malay Singaporeans have an increased risk of progression from IFG to T2DM compared to their Chinese counterparts.

2. METHODS

2.1 Study design and setting

This retrospective study is based on de-identified patient records, including demographics and relevant clinical data, extracted from electronic medical records of the National Healthcare Group Polyclinics (NHGP) in Singapore. The study was submitted to the National Healthcare Group (NHG) Domain Specific Review Board (DSRB) for ethics review and was deemed to have met the criteria for DSRB 'review not required'.

Participants who were found to have IFG on laboratory testing between 01 Sep 2011 and 31 Aug 2014 were identified. Selected individuals (see Figure 1, Participant flow chart) were then followed-up until 31 August 2023.

The study followed the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) reporting guideline.

2.2 Study population

All Chinese, Malay and Indian patients (citizens or permanent residents) who attended five primary care clinics of NHGP, Singapore and who were found to have IFG between 01 September 2011 and 31 August 2014 were included in the study population. (see Figure 1)

2.2.1 Patient selection

Inclusion criteria:

- Singaporean or Permanent Resident of SIngapore
- Ethnicity: Chinese, Malay or Indian (as reflected in the records)
- Patients registered in public primary care polyclinics managed by NHGP
- Patients who newly developed IFG between 01 Sep 2011 and 31 Aug 2014, as defined by laboratory confirmation of IFG, preceded by at least two consecutive normal fasting plasma glucose (FPG) readings.

Exclusion criteria:

- Pre-existing diagnosis of diabetes
- Ethnicities other than Chinese, Malay or Indian
- No confirmed date of "newly diagnosed impaired fasting glucose (IFG)".

The electronic medical records (EMR) of NHGP contained all the above information, as well as demographic and clinical parameters. Each Singaporean has a unique identification

number which is used as the primary identifier of each patient's health records across the nation, as standard protocol in all healthcare institutions.

2.3 Variables

2.3.1 Exposures

Impaired fasting glucose status and ethnicity were the exposures of interest in this study.

Other predictor variables were various demographic characteristics and clinical parameters (as listed in table S1 in the appendix) which were available in the EMR.

Gender and ethnicity were based on the participant's National Registration Identity Card, the official identification document in Singapore. Age and marital status were taken at time of inclusion into the study. Latest smoking (currently, ever and never smoking) status as recorded in electronic medical records was taken at reaching one of the endpoints of the study.

The address indicates subsidized flats built by the government Housing Development Board (HDB) or private housing. Housing type was grouped into two categories: ≤ 3-room HDB and ≥ 4-room HDB (which included private housing), serving as a rough gauge of financial standing, with those in private housing or larger apartments considered to belong to a higher socioeconomic tier.

All information was obtained from previous medical records. No patient interviews were conducted.

2.3.2 Definition of impaired fasting glycaemia

Throughout the study, we used the World Health Organization (WHO) definition of impaired fasting glucose defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dL).[2] This is the definition of IFG used in Singaporean routine clinical care and guidelines.

2.3.3 Other clinical parameters

All laboratory tests were performed by National Healthcare Group Diagnostics. Results flow from the diagnostic database into the electronic medical records used by the polyclinic. Information on comorbidities was extracted from the patients' medical records.

2.3.4 Outcomes

The primary outcome of interest was the time to onset of T2DM. The incident date was determined based on blood test results, while the detect date was the first recorded diagnosis of T2DM in the medical records. In polyclinics, all blood test results are reviewed by a physician by the next working day. For significant findings - such as newly diagnosed T2DM - patients

are contacted and scheduled to see a doctor within a few days, if their upcoming appointment is more than two weeks away.

2.4 Sample size

Overseas studies on white Europeans estimate rate of progression from prediabetes to Type 2 DM variably: from 4% in some studies, up to 21.6% in others.[9] [10], [11], [12], [13] These studies found a higher rate of progression in South Asians and Southeast Asians. An Asian Indian cohort reported a 30% incidence of DM after 9 years of follow-up.[11] According to WHO criteria, up to 50% of untreated prediabetic individuals may develop diabetes within five years.[14]

Due to the wide variation in risk, a whole population sampling approach was taken in this study.

2.5 Data collection

The NHG Polyclinics Information Management and Analytics (IMA) Department acted as the Trusted Third Party (TTP), extracting and securely transferring de-identified data to the study team in compliance with institutional policy. The data, free of identifiable information, was stored and analysed on password-protected devices, with secure eDoc transfer for analysis. Data analysis was carried out using a password protected laptop or computer.

2.6 Follow-up period:

Follow-up was from the date of “newly diagnosed IFG” until one of the following end points:

a) Development of DM

b) Death

c) Loss to follow-up

d) Study end date (31 August 2023)

Death and date of diagnosis of DM is recorded in registries from which information was extracted by the trusted third party (NHGP IMA).

Participants were considered lost to follow-up if they had no documented clinical encounters or relevant laboratory data beyond a pre-defined period of 12 months from their last recorded visit, and none of the study endpoints – development of DM, death, or study completion – had occurred.

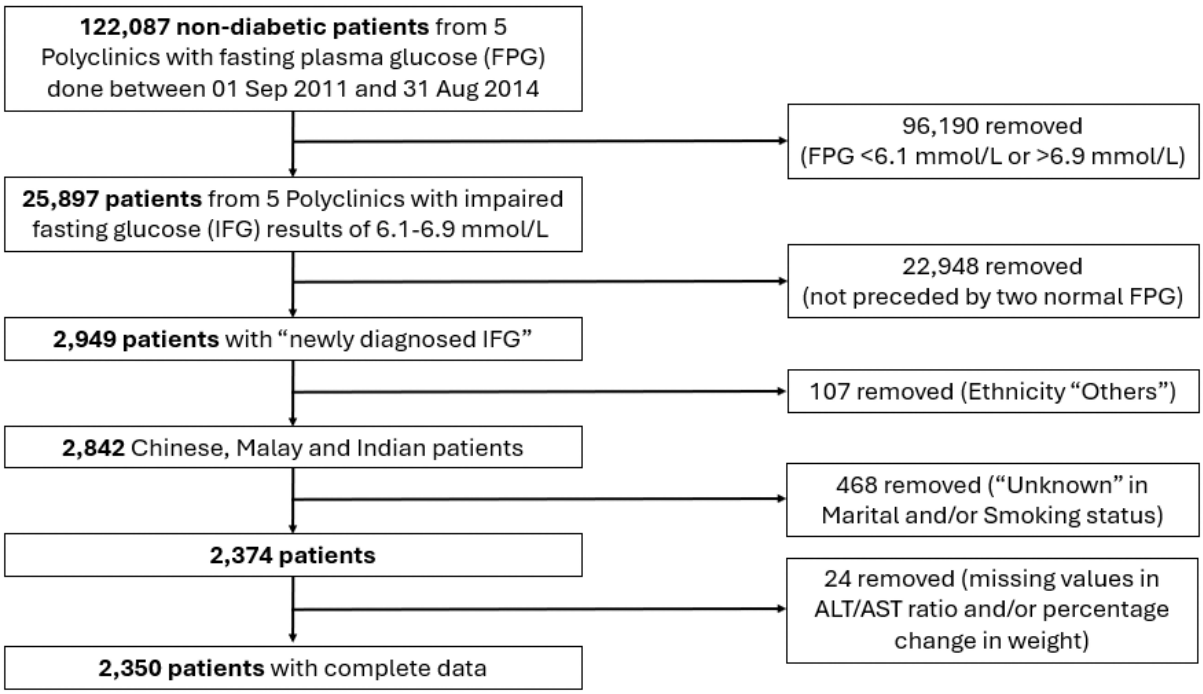

Figure 1: Participant flowchart

Total Study period:

01 Sep 2011 to 31 Aug 2023.

There were no documented losses to follow-up. Among the 2,350 participants with newly diagnosed IFG, 1,182 progressed to T2DM, while 1,168 remained non-diabetic. Within this non-diabetic group, 169 participants passed away before the study's end date.

2.7 STATISTICAL ANALYSIS

Person-years of follow-up were calculated from the date of "newly diagnosed IFG" until the occurrence of an endpoint. A total of 468 patients with missing information for smoking and/or marital status, and 24 participants with missing ALT/AST ratio and/or percentage change in weight were excluded, leaving 2,350 patients with complete data for statistical analysis.

2.7.1 Covariates

Known predictors of progression from prediabetes to T2DM include lifestyle factors: physical inactivity[15] smoking and diet[16]; psychosocial factors: anxiety and depression[15]; sociodemographic factors: age, sex, family history,[15] ethnicity, socioeconomic status[17]; clinical factors: body mass index, waist circumference and waist-to-hip ratio, hypertension, high triglyceride and low high-density lipoprotein, fatty liver index, higher baseline fasting plasma glucose and higher baseline glycated haemoglobin (HbA1c). [15, 16, 18]

In the analysis of the exposure of interest (ethnicity), the following were included as covariates in the model: age, gender, marital status[19], housing type, latest smoking status, percentage change in weight[20], AST/ALT ratio[21] and medication use (User/Non-user of Propranolol/Atenolol[22, 23] ; Hydrochlorothiazide/Indapamide[24, 25, 26] and Statins [27]).

Multiple large cohort studies in Chinese and Japanese populations found that a lower AST/ALT ratio increased risk of developing T2DM. First- and second-generation beta blockers, thiazide and loop diuretics, and several statins are associated with a modestly increased risk of developing T2DM.

2.7.2 Analyses

Descriptive statistics were used to summarize the data. Continuous variables were abnormally distributed and hence expressed as median and interquartile range (IQR), while categorical variables were reported as proportions. Chi-square tests were conducted for categorical variables, including race, gender, marital status, housing type, smoking status, and medication use (Propranolol/Atenolol, Hydrochlorothiazide/Indapamide, and Statins). Binary Regression was performed for continuous variables - age, AST/ALT ratio, and percentage change in weight - all of which were abnormally distributed (Shapiro-Wilk $p < 0.05$).

Adjusted relative risk (RR) and relative risk reduction (RRR) were analysed to improve interpretability and was possible in this study as the temporal sequence was clear with good follow-up duration. We adjusted for confounding using Poisson regression with log link and robust standard errors.

The rate of progression from impaired fasting glycaemia to T2DM was calculated as *x* per 1,000 patient-years.

Odds ratio (OR) was calculated with binary logistic regression and Hazard ratio was calculated using Cox Regression, adjusting for age, gender, marital status, housing type, smoking status, AST/ALT ratio, percentage change in weight, and medication use.

3. RESULTS

The median duration of follow-up was 95 months (IQR 53 – 138). Incidence rate of T2DM was 81.6 new cases per 1,000 patient-years. Characteristics of participants who progressed to diabetes (“progressors”) versus those who did not progress (“non-progressors”) are reported in Table 1.

Median age of participants was 63.1 (56.5 – 70.6). Individuals who developed diabetes had a median age of 62.2 years (IQR: 55.3–69.1), two years younger than those who did not (64.3 years, IQR: 57.1–71.5), ($p < 0.001$).

Females comprised 54.1% of the population with IFG, while males made up 45.9%. Diabetes progression was slightly higher in females (52.1%, 663 of 1,272 females) than males (48.1%, 519 of 1,078). This difference was not significant (p = 0.055).

Ethnic distribution in Singapore in 2014 was 74.2% Chinese, 13.3% Malay and 9.1% Indian, with approximately 3.1% 'others' (Eurasians and other ethnic groups). Among the study population with IFG, 84.7% were Chinese, 9.3% Malay, and 6.0% Indian. Malays had the highest percentage progressing to T2DM (60.1%, 131/218), followed by Indians (53.5%, 76/142) and Chinese (49.0%, 975/1,990), (p = 0.006).

Most individuals were non-smokers (2,220), with only 5.5% smokers (130). Progression to DM was higher in smokers (57.6%, 75/130) than non-smokers (49.8%, 1,107/2,220), but the difference was not significant (p = 0.083).

Participants who progressed to T2DM had a median weight gain of +1.62% (IQR: -1.33% to 4.58%), while those who did not progress showed a median weight loss of -2.63% (IQR: -7.41% to 2.16%), (p < 0.001). Individuals who progressed to T2DM had a median AST/ALT ratio of 1.00 (IQR: 0.78–1.22), slightly lower than those who did not progress (1.05, IQR: 0.85–1.27), (p < 0.001).

No significant differences were observed in gender, marital status, housing type, smoking status, or medication use.

3.2 Relative Risk (RR) and Relative Risk Reduction (RRR) (Table 2)

Table 2 shows adjusted relative risk and relative risk reduction. Given the mix of categorical and continuous variables, we used Poisson Regression with log link and robust standard errors. We used RR even though this was an observational study since the temporal sequence is clear, we followed participants over a prolonged period and we adjusted for confounding using Poisson-robust.

Males had a lower risk of progression to diabetes than females (RR: 0.90, 95% CI: 0.83–0.98, p = 0.012). It was noted that Malays (RR: 1.12, 95% CI: 0.99–1.26) and Indians (RR: 1.03, 95% CI: 0.88–1.21) had a slightly higher risk than Chinese, but the difference was not significant (p = 0.078).

Smokers had a significantly higher risk of developing diabetes (RR: 1.19, 95% CI: 1.02–1.39, p = 0.028). Weight gain was linked to increased diabetes risk (RR: 1.04, 95% CI: 1.04–1.05, p < 0.001), with a narrow confidence interval reinforcing the association. A higher AST/ALT ratio correlated with reduced diabetes risk (RR: 0.83, 95% CI: 0.73–0.95, p = 0.005).

Marital status, housing type, and medication use did not impact RR or RRR.

Characteristics	Pre-DM (n = 1168)	T2DM (n = 1182)	P
Age, Median (IQR)			
	64.3 (57.1 – 71.5)	62.2 (55.3 – 69.1)	<0.001
Gender, n (%)			0.055
Female	609 (52.1%)	663 (56.1%)	
Male	559 (47.9%)	519 (43.9%)	
Race, n (%)			0.006
Chinese	1015 (86.9%)	975 (82.5%)	
Malay	87 (7.4%)	131 (11.1%)	
Indian	66 (5.7%)	76 (6.4%)	
Marital Status, n (%)			0.636
Married	1006 (86.1%)	1010 (85.4%)	
Single/Divorced/Widowed	162 (13.9%)	172 (14.6%)	
Housing Type, n (%)			0.237
≤ 3-room HDB	285 (24.4%)	264 (22.3%)	
≥ 4-room HDB / Others	883 (75.6%)	918 (77.7%)	
Smoking Status, n (%)			0.083
Non-Smoker	1113 (95.3%)	1107 (93.7%)	
Smoker	55 (4.7%)	75 (6.3%)	
% Change in Weight, Median (IQR)	-2.63 (-7.41 – 2.16)	1.62 (-1.33 – 4.58)	<0.001
AST/ALT Ratio, Median (IQR)	1.05 (0.83 – 1.27)	1.00 (0.78 – 1.22)	<0.001
Medication Use, n (%)			
Statins	954 (81.7%)	955 (80.8%)	0.584
Propranolol/Atenolol	463 (39.6%)	484 (40.9%)	0.518
Hydrochlorothiazide/Indapamide	21 (1.8%)	16 (1.4%)	0.387

Table 1: Characteristics of non-progressors versus progressors to T2DM

3.3 Odds Ratio (OR) and Hazard Ratio (HR) (Table 3)

Multivariate logistic regression identified independent associations between several covariates and the progression from IFG to diabetes.

Age had no independent effect on progression to diabetes (OR: 1.00, 95% CI: 0.99–1.01; HR: 1.00, 95% CI: 1.00–1.01). Males had a lower risk (OR: 0.80, 95% CI: 0.67–0.96, p = 0.017) and slower progression rate (HR: 0.87, 95% CI: 0.76–0.97, p = 0.016) than females. Malays had a significantly higher risk of progression to diabetes than Chinese (OR: 1.36, 95% CI: 1.00–1.85, p = 0.048), though progression rates across ethnicities were similar (HR: 1.14, 95% CI: 0.94–1.37).

Smokers had an increased risk of developing diabetes (OR: 1.55, 95% CI: 1.05–2.30, p = 0.027), and faster progression rate (HR: 1.32, 95% CI: 1.04–1.69, p = 0.023). Percentage change in weight showed a significant impact: each 1% weight gain raised risk by 10% (OR: 1.10, 95% CI: 1.08–1.11, p < 0.001) and progression rate by 5% (HR: 1.05, 95% CI: 1.04–1.06, p < 0.001). A higher AST/ALT ratio lowered risk (OR: 0.70, 95% CI: 0.54–0.92, p = 0.011) and slowed progression (HR: 0.77, 95% CI: 0.63–0.92, p = 0.004), suggesting a protective effect.

Age, marital status, housing type, and medication use had no impact on risk or rate of progression.

In summary, females, smokers, participants who gained weight and those with lower AST/ALT ratios had both significantly increased risk and rate of progression to diabetes from IFG. Malays had an increased risk of progression to T2DM, but not at an increased rate.

Variable	Progression from IFG to DM		
	RR (95% CI)	P	RRR (95% CI)
Age (years)	1.00 (1.00 – 1.01)	0.778	0% (-1% – 0%)
Gender			
Female	REF		
Male	0.90 (0.83 – 0.98)	0.012	10% (2% – 17%)
Race			
Chinese	REF		
Malay	1.12 (0.99 – 1.26)	0.078	-12% (-26% – 1%)
Indian	1.03 (0.88 – 1.21)	0.685	-3% (-21% – 12%)
Marital Status			
Single/Divorced/Widowed	REF		
Married	0.90 (0.70 – 1.15)	0.480	10% (-15% – 30%)
Housing Type			
≤ 3-room HDB	REF		
≥ 4-room HDB / Others	1.06 (0.96 – 1.16)	0.265	-6% (-16% – 4%)
Smoking Status			
Non-smoker	REF		
Smoker	1.19 (1.02 – 1.39)	0.028	-19% (-39% – -2%)
% Change in Weight	1.04 (1.04 – 1.05)	<0.001	-4% (-5% – -4%)
AST/ALT Ratio	0.83 (0.73 – 0.95)	0.005	17% (5% – 27%)
Medication Use			
Statins			
Non-user	REF		
User	0.99 (0.90 – 1.10)	0.887	1% (-10% – 10%)
Propranolol/Atenolol			
Non-User	REF		
User	1.07 (0.98 – 1.15)	0.119	-7% (-15% – 2%)
Hydrochlorothiazide/Indapamide			
Non-user	REF		
User	0.88 (0.63 – 1.24)	0.462	12% (-24% – 37%)

Table 2: Relative Risk and Relative Risk Reduction

Variables	Progression from IFG to DM		Rate of Progression from IFG to DM	
	OR (95% CI)	P	HR (95% CI)	P
Age (years)	1.00 (0.99 – 1.01)	0.736	1.00 (1.00 – 1.01)	0.225
Gender				
Female	REF			
Male	0.80 (0.67 – 0.96)	0.017	0.86 (0.76 – 0.97)	0.016
Race				
Chinese	REF			
Malay	1.36 (1.00 – 1.85)	0.048	1.14 (0.95 – 1.38)	0.156
Indian	1.12 (0.78 – 1.62)	0.543	1.05 (0.83 – 1.33)	0.677
Marital Status				
Single/Divorced/Widowed	REF			
Married	0.90 (0.70 – 1.15)	0.382	0.96 (0.82 – 1.13)	0.622
Housing Type				
≤ 3-room HDB	REF			
≥ 4-room HDB / Others	1.12 (0.91 – 1.37)	0.283	1.08 (0.94 – 1.24)	0.296
Smoking Status				
Non-smoker	REF			
Smoker	1.55 (1.05 – 2.30)	0.027	1.32 (1.04 – 1.69)	0.023
% Change in Weight	1.10 (1.08 – 1.11)	<0.001	1.05 (1.04 – 1.06)	<0.001
AST/ALT Ratio	0.70 (0.54 – 0.92)	0.011	0.76 (0.63 – 0.92)	0.004
Medication Use				
Statins				
Non-user	REF			
User	0.97 (0.78 – 1.22)	0.817	0.98 (0.84 – 1.13)	0.733
Propranolol/Atenolol				
Non-User	REF			
User	1.17 (0.98 – 1.40)	0.079	1.08 (0.96 – 1.21)	0.224
Hydrochlorothiazide/Indapamide				
Non-user	REF			
User	0.77 (0.38 – 1.54)	0.456	0.75 (0.46 – 1.23)	0.260

Table 3: Odds ratio and Hazard ratio

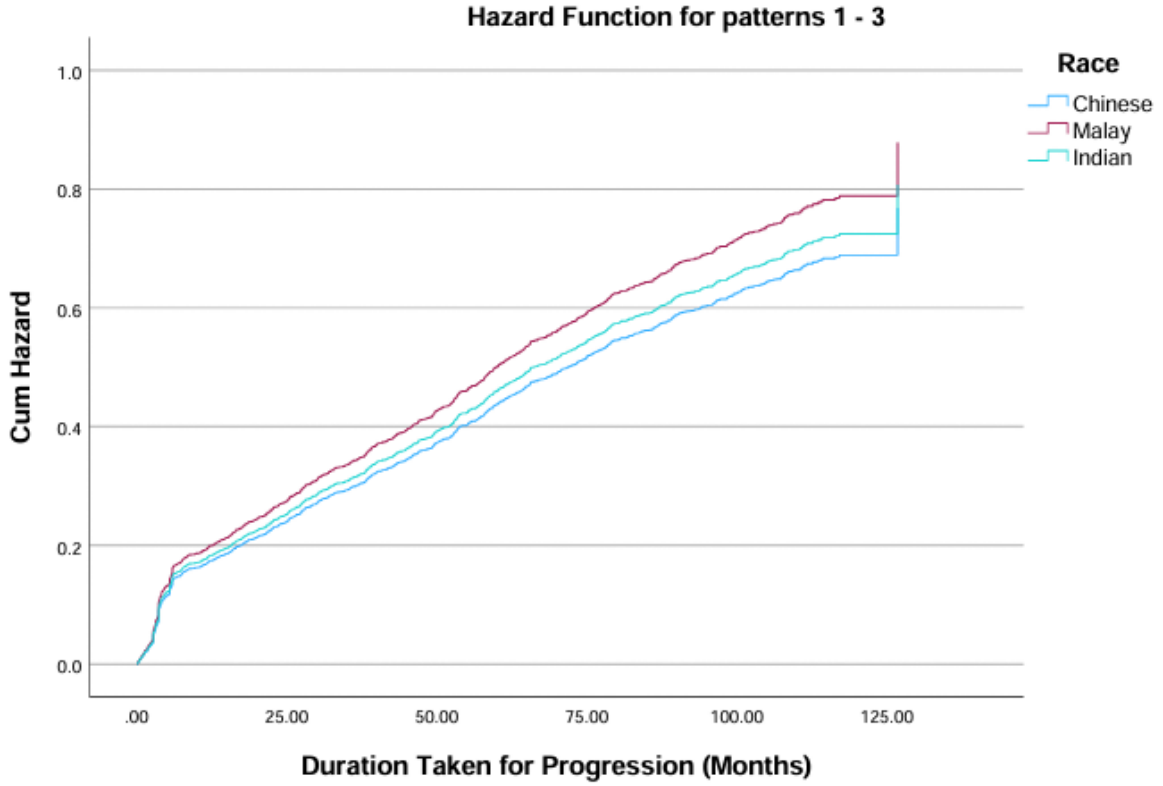

Figure 2. Hazard function for ethnic variation in progression from IFG to T2DM

4. Discussion

In this retrospective cohort study of 2,350 Singaporean adults with impaired fasting glycaemia (IFG), we found a high progression rate to type 2 diabetes mellitus (T2DM), with over half (50.3%) developing the condition over a median follow-up of 95 months, and a median duration of progression of 29 months [IQR 1 - 57]. The overall incidence rate was 81.6 per 1,000 patient-years, underscoring the substantial risk associated with IFG in this multi-ethnic urban population in Southeast Asia.

A systematic review and meta-analysis by Akhtar et al. found that the prevalence of T2DM among Malays in Malaysia was 15.25%, compared to 12.87% among Chinese.[28] Lifestyle factors such as obesity, advancing age, and family history of diabetes increase the prevalence of T2DM among Malays as compared to Chinese living in Malaysia.[29] Whilst all ethnic groups are affected by T2DM, South Asians have a greater susceptibility. South Asian individuals develop T2DM at a younger age than white European individuals, are more insulin resistant and experience earlier decline in beta cell function.[30] Our findings confirm that, compared to Chinese, Malays had significantly higher odds of developing T2DM (OR 1.36, 95% CI 1.00–1.85, p = 0.048). While the confidence interval touches unity, the finding remains statistically significant and highlights the need for tailored preventive strategies in this subgroup.

The American Heart Association has found no specific indication that Asian females are at a higher risk compared to Asian males when considering the progression from prediabetes to T2DM.[31] Men are often reported to have a higher T2DM risk globally. A meta-analysis by Hu et al. identified male sex as a significant risk factor for the progression from prediabetes to T2DM, with an odds ratio of 1.13.[15]

The findings in our study indicate a lower risk and slower progression rate in males as compared to females, which matches findings from other studies in the region. Research in Asia suggests that Asian females with a history of gestational diabetes mellitus may have an elevated risk of developing T2DM.[32] Genetic, lifestyle, and metabolic factors contribute to rising diabetes rates in Asia, and factors such as higher body fat percentage despite lower body mass index (BMI), insulin resistance, and dietary patterns may play a role in increased risk among Asian females.[33]

Smoking emerged as a strong predictor of progression to T2DM, with both increased odds (OR 1.55) and hazard ratios (HR 1.32). This risk was almost the same as another study in Japan, which found that current smokers had a significantly higher risk of developing T2DM compared to never smokers, with a hazard ratio (HR) of 1.34.[34] Korean studies found a dose response relationship, with increased risk of T2DM incidence and mortality.[35, 36]

Patients with a lower AST/ALT ratio were more likely to develop T2DM (OR 1.30, HR 1.24). This concurs with findings in Chinese populations that a lower AST/ALT ratio was associated with a higher risk of diabetes, indicating that individuals with a lower ratio had a higher cumulative incidence of diabetes.[37] A low AST/ALT ratio results from increased ALT activity, which is a marker of hepatocellular dysfunction and metabolic dysfunction. Wang et al. found that a higher AST/ALT ratio was negatively associated with the risk of diabetes progression in prediabetic patients, with higher quartiles of the AST/ALT ratio presenting a lower risk compared to the lowest quartile.[21]

One of the most striking associations was the impact of weight change. A greater percentage increase in body weight was strongly linked to both increased odds (OR 1.10 per unit increase) and hazard (HR 1.05) of progression. Japanese individuals who progressed to diabetes had a larger increase in mean BMI compared to those who remained with prediabetes or returned to normoglycemia.[38] A Singaporean study showed that weight loss was associated with regression from prediabetes to normoglycaemia.[39] This reinforces the critical role of weight management in diabetes prevention, particularly among individuals already identified as high-risk due to impaired fasting glucose.

Taken together, these findings highlight the heterogeneous nature of diabetes risk in a population with IFG. Not all individuals progress uniformly; certain subgroups - particularly

Malays, women, smokers, those with metabolic liver markers, and those with weight gain - are at higher risk. This supports a more nuanced, personalised approach to prediabetes management, including closer monitoring and early intervention for high-risk individuals.

This study has several limitations. Firstly, 2842 Chinese, Malay and Indian patients (our population of interest) with “first abnormal glucose” reading within the study period reduced to 2350, after the removal of 492 patients with missing data in smoking status, marital status, ALT/AST Ratio and/or percentage change in weight. Secondly, information on variables known to increase the risk of progression - such as physical activity levels, dietary choices, family history, psychosocial factors like anxiety and depression, educational background, and socioeconomic status - was either unavailable or of limited quality. Third, data on certain clinical factors that increase risk - such as waist circumference and waist-to-hip ratio - was not available.

The advantages are the relatively large sample, despite the removal of patients with missing data, and the long duration of follow up (95 months [IQR 53 - 138]). Determining the true onset of impaired fasting glycaemia is a challenge with a retrospective design. Using the first IFG reading after two consecutive normal fasting plasma glucose readings enabled the researchers to more accurately identify individuals with incident IFG in this records-based study.

5. Conclusion

This study found that Malays had a higher risk of progression from IFG to T2DM. Similar to other studies, smokers, individuals with low AST/ALT ratios, and Asian females appear to have an increased risk and rate of progression. We found that percentage change in weight significantly influenced both risk and progression rate, with each 1% weight gain increasing risk by 10% and progression rate by 5%. Further studies may be necessary to determine whether this effect is independent of other variables.

In conclusion, progression from IFG to T2DM is common and influenced by a range of demographic and clinical factors. These findings can inform risk stratification and targeted prevention strategies, moving us closer to personalised diabetes care for at-risk populations.

3.2.C. Research – References

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3.2.C. Supplement 1: List of extracted variables

- Demographics
    - Age (at diagnosis of IFG) [numeral, years]
    - Gender (male/female)
    - Ethnicity [Chinese / Malay / Indian]
    - Marital status (Single / Married / Separated / Divorced)
    - Housing type (during study period) [HDB / private housing]
    - Smoking status (currently, ever and never smoking)
    - Alcohol consumption (currently, ever and never alcohol consumption)
- Clinical parameters
    - Baseline BMI (measurement prior to diagnosis of impaired fasting glycaemia) [numeral, kg/m^2]
    - Change in BMI (at baseline and at reaching one of the endpoints* of the study) [numeral, kg/m^2]
    - %Change in BMI (from baseline to reaching one of the endpoints of the study) [% change]
    - Baseline Weight (earliest recorded weight in the study period) [numeral, kg]
    - Change in Weight (at baseline and at reaching one of the endpoints of the study) [numeral, kg]
    - %Change in weight (from baseline to reaching one of the endpoints of the study) [% change]
    - Systolic blood pressure (SBP)/diastolic blood pressure (DBP) [numeral, mmHg]
    - Metformin use during the study period (total duration of prescription since diagnosis of impaired fasting glycaemia) [numeral, years]
    - Diabetogenic drugs (prescribed during the study period)
        a) Hydrochlorothiazide/Indapamide - YES/NO
        b) Propranolol/Atenolol - YES/NO
        c) Prednisolone - YES/NO
        d) Antipsychotics: Haloperidol/Quetiapine - YES/NO
        e) Statins: Simvastatin/ Atorvastatin/Rosuvastatin/Lovastatin - YES/NO [categorical data for these criteria]
        - If YES to one or more: (total duration of prescription since diagnosis of impaired fasting glycaemia) [numeral, years]
    - Fasting plasma glucose values (at baseline and at reaching one of the endpoints of the study) [numeral, mmol/l]

- Earliest recorded HbA1c [numeral, %]
- Change in HbA1c (at baseline and at reaching one of the endpoints of the study) [numeral, %]
- %Change in HbA1c (from baseline to reaching one of the endpoints of the study) [% change]
- Lipid profile (at baseline and at reaching one of the endpoints of the study)
    a) Triglyceride (TG) levels [numeral, mmol/l]
    b) High density lipoprotein cholesterol (HDL-c) [numeral, mmol/l]
    c) Low density lipoprotein cholesterol (LDL-c) [numeral, mmol/l]
    d) Total cholesterol [numeral, mmol/l]
    e) Ratios: TG:HDL-c ratio [numeral]
- Aspartate aminotransferase (AST) (at baseline and at reaching one of the endpoints of the study) [numeral, mmol/l]
- Alanine aminotransferase (ALT) (at baseline and at reaching one of the endpoints of the study) [numeral, mmol/l]
- Comorbidities and/or complications:
    a) Hypertension - YES/NO
    b) Hyperlipidaemia - YES/NO
    c) Chronic kidney disease - YES/NO
    d) Ischaemic heart disease - YES/NO
    e) Stroke - YES/NO
    f) Peripheral arterial disease - YES/NO

    [categorical data for these criteria]
    - If YES to one or more: (duration of diagnosis during the study period) [numeral, years]
- Duration of IFG: [numeral, years]