diabetesresearchandclinicalpractice213(2024)111761

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

# Can the postload-fasting glucose gap be used to determine risk of developing diabetes in chinese adults: A prospective cohort study

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ARTICLE INFO

*Keywords:*
Type 2 Diabetes
OGTT
Normoglycemic
Prediabetes

ABSTRACT

*Objective:* To evaluate the relationship between fasting plasma glucose (FPG) and 2-hour postload plasma glucose (2hPG) measured during an oral glucose tolerance test, and the risk of developing diabetes in Chinese adults.
*Methods:* We followed 3,094 participants without diabetes, categorizing them based on their oral glucose tolerance test (OGTT) results into low post load (2hPG ≤ FPG) and high post load (2hPG > FPG) at baseline. We monitored the incidence of diabetes, incidence of prediabetes, disease progression from prediabetes to diabetes and disease reversal from prediabetes to normal glucose tolerance (NGT) over an average of 3.2 years of follow-up.
After the Schoenfeld residual test, Cox's time-varying covariate (Cox-TVC) models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) to compare the different clinical events between low and high post load groups.
*Results:* In the cohort study, of the 3,094 participants, 702 (22.7 %) had low post load (2hPG ≤ FPG, mean postload-fasting gap: −0.8 ± 0.7 mmol/L) and 2,392 (77.3 %) had high post load (2hPG > FPG, mean postload-fasting gap: 1.8 ± 1.2 mmol/L). Over 3.2 ± 0.2 years of follow-up, 282 (9.1 %) developed diabetes. In the low post load group, the incidence rates per 1,000 person-years were: diabetes was 7.9, prediabetes was 70.0, disease progression from prediabetes to diabetes was 23.4 and disease reversal to NGT was 327.2. For the high post load group, incidence rates for diabetes was 13.9, prediabetes was 124.3, disease progression was 59.5 and disease reversal was 238.6 per 1,000 person-years.
Participants with high post load showed higher incidence rates of diabetes, prediabetes, and progression from prediabetes to diabetes compared to those with low post load. HRs were significantly higher for incident diabetes and prediabetes, and disease progression from prediabetes to diabetes, whereas disease reversal was lower.
*Conclusion:* The risk of developing prediabetes/diabetes after 3.2 years of follow-up was higher in the participants with high post load. It suggested that postload-fasting gap may be a simple tool to predict the risk of developing prediabetes, diabetes or reversal to NGT.

## 1. Background

Diabetes mellitus is an important public health problem due to its rapidly increasing global prevalence, 90 % of which is type 2 diabetes mellitus (T2DM), and the disease has high levels of associated morbidity and mortality[1,2]. In China, population growth[3], urbanization[4],

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https://doi.org/10.1016/j.diabres.2024.111761
Received 19 March 2024; Received in revised form 14 June 2024; Accepted 25 June 2024
Available online 29 June 2024

ageing[5], obesity[6] and sedentary lifestyle[6] have led to a substantial increase in the number of people living with diabetes in recent decades, estimated at 140.9 million people with diabetes in 2021[7]. In 2015, the economic burden of diabetes in China was estimated at USD 222.3 billion, approximately 2.0 % of the country's gross domestic product (GDP), and is projected to reach USD 631.7 billion (approximately 2.9 % of GDP) in 2030[8]. People with prediabetes are at high risk of developing diabetes with up to two-thirds developing diabetes over their lifetime[9]. Early identification of people at risk of developing prediabetes or diabetes allows for early intervention to reduce the risk of developing disease or complications[10,11].

Fasting plasma glucose (FPG) and plasma glucose measured 2-hours following a 75 g glucose load (2hPG) measured during the oral glucose tolerance test (OGTT) are commonly used tests for the diagnosis of diabetes. It has been proposed that the value of the gap between 2hPG and FPG might be used as a measure of the risk of developing type 2 diabetes[12]. The Mexican-American San Antonio Heart Study found that among individuals with normal glucose tolerance (NGT), those with 2hPG levels higher than their FPG had a 2.33-fold higher odds of developing type 2 diabetes over 7–8 years follow-up period[13]. The Coronary Artery Risk Development in Young Adults (CARDIA) Study also suggested that normoglycemic adults with 2hPG higher than FPG during 20 years of follow-up were 1.56 times more likely to develop type 2 diabetes[14]. Although several studies examined the utility of OGTT measurements in risk stratification for developing type 2 diabetes, there is a lack of long-term follow-up data and little data from the Chinese population.

Hence, we hypothesize that the positive value or negative value of the postload-fasting gap might predict the risk of developing type 2 diabetes in individuals with NGT or prediabetes, and the probability that individuals with prediabetes may reverse to NGT. We describe the incidence of prediabetes/diabetes and disease progression/reversal based in a longitudinal cohort in China (the SENSIBLE-cohort study) [15,16].

## 2. Methods

### 2.1. Study population

SENSIBLE was a longitudinal study designed to determine the cut-off values of advanced glycation end-products and HbA1c for diagnosing diabetes in China[15,16]. Follow up began in November 2016, enrolling 7,600 participants aged from 20 to 70 years, who were re-visited between June 2018 to January 2019, and had a second re-visit between April 2020 to January 2021[17]. We excluded participants with missing data on glucose values (FPG, 2hPG and HbA1c), sociodemographic information (e.g. age, sex, ethnicities, family history of diabetes), and outliers (>99.9 percentile or < 0.1 percentile) of anthropometric examination characteristics, missing data on diet information, and excluded participants with self-reported diabetes or who were diagnosed with diabetes during the baseline OGTT, or people who did not attend either of the two re-visits (Fig. 1).

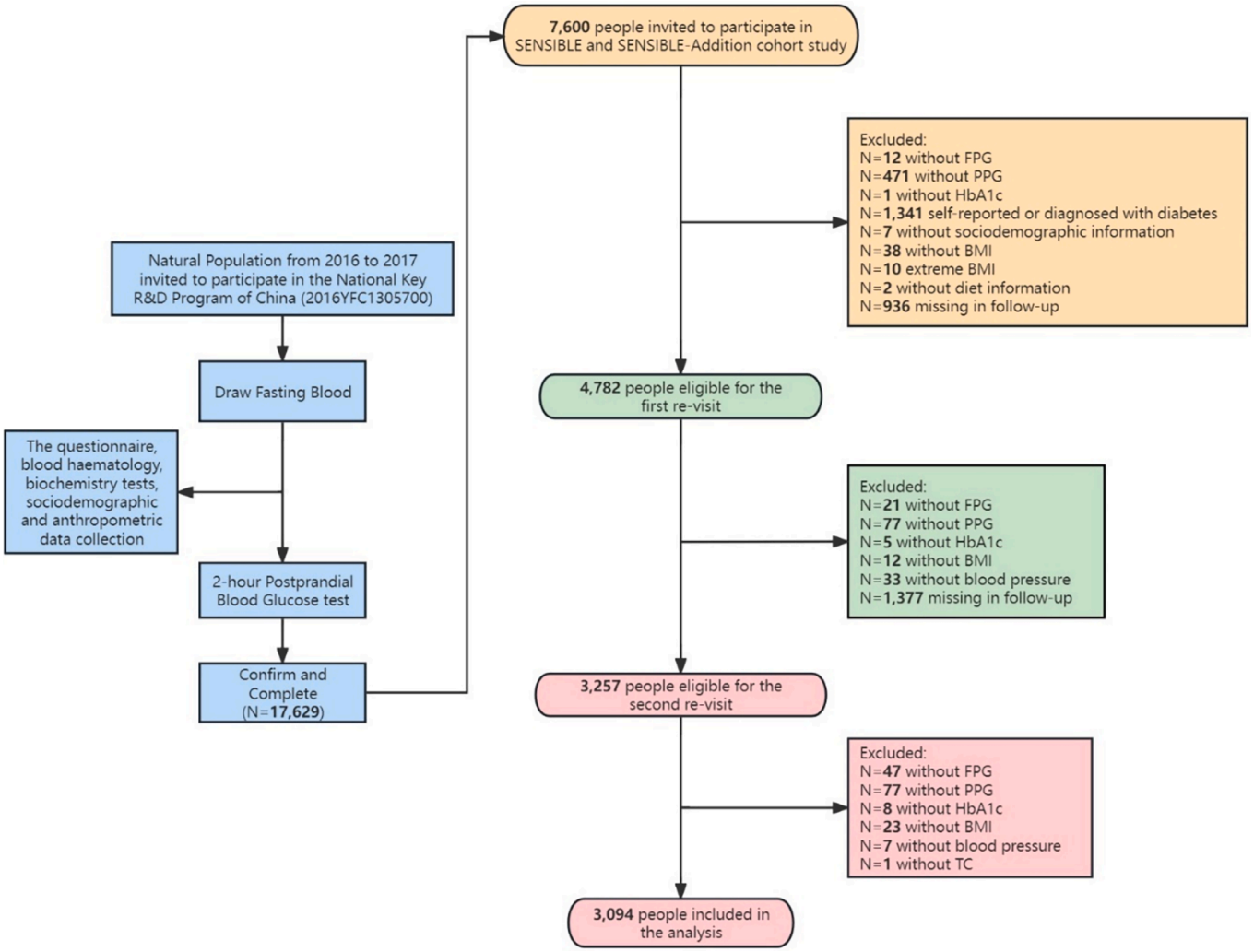


**Fig. 1.** Flowchart of this research.

### 2.2. Eth ical approval

The protocol of SENSIBLE-cohort study was approved by the Ethical Review Committees of Zhongda Hospital, Southeast University (approval number: 2016ZDSYLL092-P01). Informed consent was obtained from all participants before their participation[15].

### 2.3. Measurements

Demographic data, including age, sex, ethnicity, education, and occupation, as well as information on health behaviours such as smoking, drinking, eating habits, and exercise habits, along with medical and drug histories, were collected by trained interviewers using standardized questionnaires. Anthropometric parameters, including height, weight, waist circumference, and systolic and diastolic blood pressure (SBP and DBP), were measured according to standard protocols, and body mass index (BMI) was calculated.

After an overnight fast of at least 10 h, a venous blood sample was collected to measure FPG. This was followed by an OGTT, in which a standard 75-gram glucose solution was ingested within five minutes. A follow-up venous blood sample was collected 120 min later to measure the 2-hour post-load plasma glucose concentration. FPG and 2hPG were measured using an automatic chemistry analyzer (Synchron LX-20, Beckman Coulter Inc., CA, USA). HbA1c was measured with high-performance liquid chromatography (HPLC; D-10™ Haemoglobin Analyzer, Bio-Rad Inc., CA, USA)[16].

Definition of type 2 diabetes, prediabetes, disease progression and disease reversal groups.

Diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and normal glucose tolerance (NGT) were defined by WHO criteria[18]. For people without diabetes, the diagnostic criteria for hypoglycaemia were plasma glucose $< 2.8$ mmol/L, and for people with diabetes, plasma glucose $\leq 3.9$ mmol/L. NGT was defined as FPG less than 6.1 mmol/L, and the 2hPG was $\leq 7.8$ mmol/L. IFG was defined as FPG between 6.1 mmol/L and 7.0 mmol/L, and 2hPG $< 7.8$ mmol/L. IGT was defined as an FPG $< 7.0$ mmol/L, and 7.8 mmol/L $\leq$ 2hPG $<$ 11.1 mmol/L. People with typical symptoms of diabetes, such as polyuria, polydipsia, and unexplained weight loss, who had a random blood glucose level $\geq 11.1$ mmol/L, FPG $\geq 7.0$ mmol/L, or 2-hPG $\geq 11.1$ mmol/L, were considered to have diabetes[19].

We categorized participants into two groups based on their relationship between 2hPG and FPG at baseline. We defined them as low post load (2hPG $\leq$ FPG) and high post load (2hPG $>$ FPG) groups according to their postload-fasting gap[12]. OGTT was performed on three occasions (baseline and 2 follow-up re-visits) of the cohort study. We further divided participants into four groups based on their 2hPG and FPG values at the consecutive OGTTs. Stable low was defined as consecutive measures of low post load at baseline and 2 follow-up re-visits; stable high was defined as consecutive measures of high post load at baseline and 2 follow-up re-visits; fluctuating was defined as having varying measures of low post load or high post load during the follow up; and incomplete information was defined as people who had an OGTT at baseline and FPG tests at the first re-visit and the second re-visit. However, because the 2hPG test was not performed at the first and/or second re-visit, the postload-fasting gap could not be calculated.

### 2.4. Statistical analysis

In this study, the baseline demographic, socioeconomic and laboratory variables were described as mean (standard deviation) for normally distributed continuous variables and as percentages for categorical variables. For the difference in different groups, the Wilcoxon-rank sum test for continuous variables and Pearson's chi-square test for categorical variables.

We calculated the incidence rates of prediabetes and diabetes, and rates of disease progression and disease reversal in the low post load and high post load groups. Kaplan–Meier plots of time to incident prediabetes, incident diabetes, disease progression and disease reversal were generated to compare low post load and high post load categories, and stable low, stable high, fluctuating and incomplete information categories. The time to incident prediabetes/diabetes was defined as the time from NGT at admission to the study to prediabetes/diabetes diagnosis in any subsequent OGTT. The time of disease progression/reversal was defined as the time between the diagnosis of prediabetes to the diagnosis of diabetes/NGT. For participants who remained free of prediabetes/diabetes, the follow-up time was censored at their last available visit (Fig. 2).

We evaluated unadjusted Cox Proportional Hazard (Cox-PH) and Cox Proportional Hazards Models with time-varying covariates (Cox-TVC model 1 and Cox-TVC model 2). The Cox-PH model assumes that the HRs between different groups are constant over time, which might provide misleading results when the hazard function changes over time [20]. We considered that the risk of developing prediabetes/diabetes may change over time and used Cox-TVC models to account for this possibility[21,22]. To explore the relationship between outcomes and the postload-fasting gap, the Cox-PH and Gray's Survival models were used for each variable considered for analysis and when the residual tests suggested that variables ($p < 0.05$) violated the proportional hazard assumptions, these variables were used as time varying covariates in the Cox-TVC models.

To reduce the impact of baseline FPG value on the assessment of risk we added FPG as a covariate in the Cox-TVC models. In the Cox-TVC model 1, we controlled for age, sex, BMI and FPG. In the Cox-TVC model 2 we adjusted our survival analyses according to the baseline participants' characteristics which included the variables listed above as well as ethnicity, education levels, HbA1c, heart rate, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), smoking, drinking, regular diet. In addition, in the Cox-TVC model 2 for incident diabetes we added blood pressure (BP) and hypoglycaemic drugs use; the Cox-TVC model 2 for incident prediabetes added blood pressure (BP), total cholesterol (TC) and occupation types; the Cox-TVC model 2 for disease progression further added blood pressure (BP) and liver disease; the Cox-TVC model 2 for disease reversal further added blood pressure (BP), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). Global $\chi 2$ (likelihood ratio), Akaike's information criterion (AIC), and Bayesian information criterion (BIC) were used to assess the resulting goodness of fit in the models above.

All statistical tests were two-sided, and the P-value less than 0.05 was considered statistically significant. All statistical analyses used R version 4.2.1 (R Foundation for Statistical Computing, Viena, Austria).

## 3. Results

### 3.1. Population characteristics

The total number of participants included in this analysis was 3,094, 66.4 % (n = 2,053) of the participants were female, the average age of participants was 52.1 ± 9.2 years and the mean BMI was 25.3 ± 3.5 kg/$m^2$.

We divided the cohort into two groups based on the relationship between 2hPG and FPG values at baseline (Table 1). There were 702 (22.7 %) people who had low post load and 2,392 (77.3 %) who had high post load in the baseline survey. In the low post load group, 81.8 % (n = 574) had NGT compared with 60.4 % (n = 1,445) in the high post load group. There were no participants in the low post load group with IGT and 128 (18.2 %) participants had IFG. In the high post load group 175 (7.3 %) participants had IFG and 772 (32.3 %) participants had IGT ($p < 0.001$).

Compared with participants in high post load, participants in the low post load group were significantly younger, more likely to be male, had lower BMI, were educated, non-Han ethnicity, lower resting heart rate, as well as higher HDL-C level and lower TG level, all $P < 0.05$. The

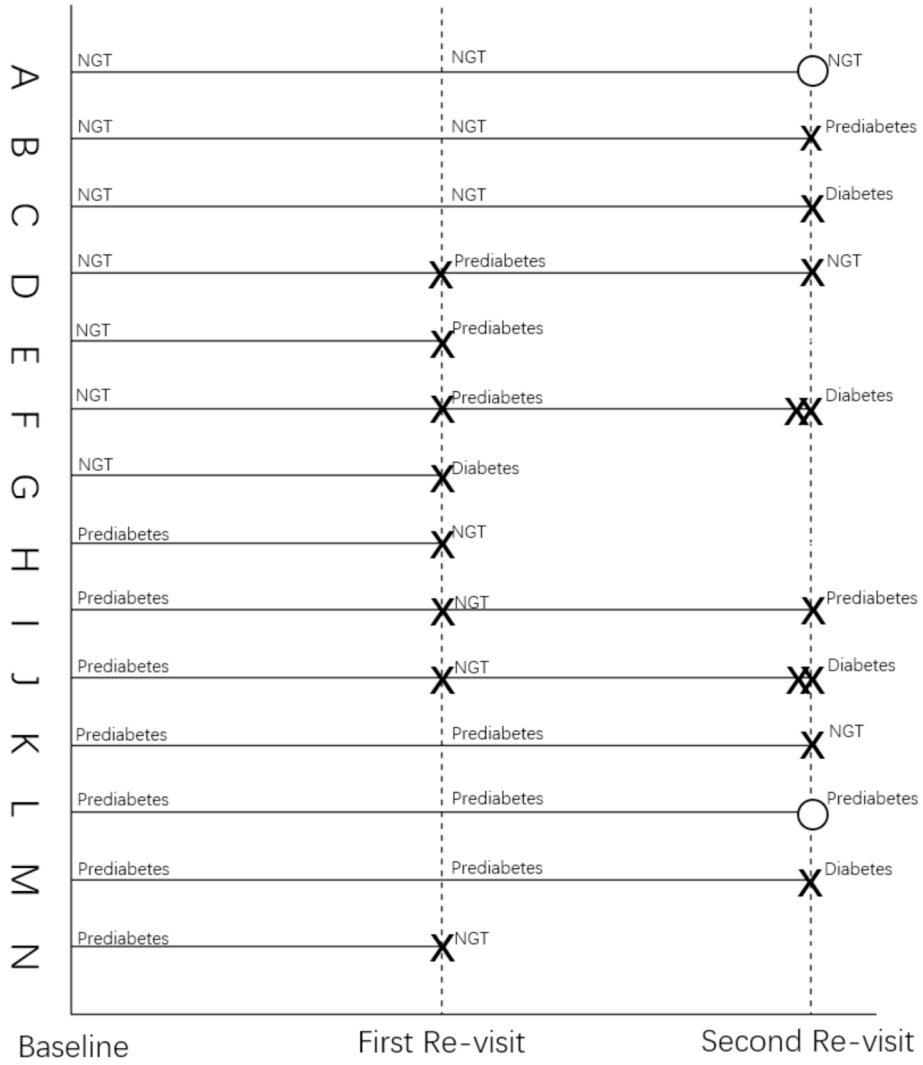


**Fig. 2.** Different events during follow-up. This chart tracks OGTT results of participants over three visits. ○ denotes no event; X marks an event occurrence (the change of OGTT results). Time is recorded as the time between the baseline to the event occurrence, and the time between two different event occurrences.

comparison of different groups in the first re-visit and the second re-visit are in Supplementary Table 1 and Supplementary Table 2.

### 3.2. Incidence of type 2 diabetes

Fig. 3(A) shows the Kaplan-Meier curves of cumulative proportion of diabetes events at different time points over time (in years) in low post load group and high post load group, and the high post load group had a higher cumulative incidence than the low post load group($p = 0.012$). As shown in Fig. 3(A), the risk ratios between different groups are not all constant in this cohort. Cox-PH and Gray's Survival models for each variable considered for analysis, and Schoenfeld residuals are included in Supplementary Table 3 (a).

During $3.2 \pm 0.2$ years of follow-up, 92 people with normal glucose tolerance developed diabetes, 16 in the low post load group and 76 in high post load group. The crude incidence rate of diabetes per 1,000 person-years of follow up was 12.3 for the whole cohort, 7.9 in the low post load group and 13.9 in the high post load group (Table 2). Participants in the high post load group were 1.98-fold (95 %CI: 1.15, 3.39, $p = 0.014$) more likely to develop diabetes from NGT during follow-up than those in the low post load group in unadjusted Cox-PH model. The Cox-TVC model 1 showed that the risk of developing type 2 diabetes was higher for participants in high post load group [HR: 2.79, 95 %CI (1.53, 5.07), $p < 0.001$], and this association remained high in Cox-TVC model 2 [HR: 1.89, 95 %CI (0.80, 4.47), $p = 0.144$].

### 3.3. Incidence of prediabetes

When considering the groups defined by the postload-fasting gap (Fig. 3(C)), the cumulative incidence of prediabetes in the high post load group was higher than the low post load group, and the difference was statistically significant($p < 0.001$).

We observed a higher incidence of prediabetes in participants with normal glucose tolerance in the high post load group (124.3 per 1,000 pyo) than the low post load group (70.0 per 1,000 pyo) and prediabetes incidence of 109.3 per 1000 pyo overall (Table 2). In comparison to participants in the low post load group, the risk of developing prediabetes was higher for participants in high post load' group [Cox-PH: 1.90, 95 % CI (1.58, 2.29), $P < 0.001$]. The hazard ratios remained significant after time-varying adjustment in Cox-TVC model 1 [HR: 2.00, 95 %CI (1.65, 2.43), $p < 0.001$ ] and after adjusting for additional variables in Cox-TVC model 2 [HR: 1.62, 95 %CI (1.26, 2.07), $p < 0.001$] (Supplementary Table 3(b)).

### 3.4. Disease progression

We also measured disease progression from prediabetes to diabetes, all variables considered for analysis in the models are in Supplementary

**Table 1**
Participant characteristics at study baseline.

| Characteristics | All N = 3,094 | Low post load N = 702 (22.69 %) | High post load N = 2,392 (77.31 %) | p-value[a] |
|---|---|---|---|---|
| **Age at baseline (years)** | 52.1 (9.2) | 51.2 (9.6) | 52.3 (9.0) | 0.004 |
| **Female (%)** | 2,053 (66.4 %) | 371 (52.9 %) | 1,682 (70.3 %) | <0.001 |
| **Ethnicity (Han)** | 2,507 (81.0 %) | 542 (77.2 %) | 1,965 (82.2 %) | 0.003 |
| **FPG (mmol/L)** | 5.6 (0.6) | 5.6 (0.5) | 5.6 (0.6) | 0.091 |
| **2hPG (mmol/L)** | 6.8 (1.7) | 4.8 (0.8) | 7.3 (1.4) | <0.001 |
| **Postload-Fasting Gap (mmol/L)** | 1.2 (1.6) | −0.8 (0.7) | 1.8 (1.2) | <0.001 |
| **HbA1c (%)** | 5.4 (0.4) | 5.3 (0.4) | 5.4 (0.4) | 0.016 |
| **Initial Glycaemic Status (WHO1999)** | | | | <0.001 |
| NGT | 2,019 (65.3 %) | 574 (81.8 %) | 1,445 (60.4 %) | |
| IFG | 303 (9.8 %) | 128 (18.2 %) | 175 (7.3 %) | |
| IGT | 772 (25.0 %) | 0 (0.0 %) | 772 (32.3 %) | |
| **BMI (kg/m$^2$)** | 25.3 (3.5) | 24.9 (3.3) | 25.5 (3.6) | <0.001 |
| **SBP (mmHg)** | 134 (19.3) | 134 (19.4) | 134 (19.2) | 0.807 |
| **DBP (mmHg)** | 82 (11.4) | 82 (11.8) | 82 (11.3) | 0.995 |
| **Heart rate (beats/min)** | 77 (11.0) | 75 (10.8) | 78 (11.0) | <0.001 |
| **TC (mmol/L)** | 5.0 (1.0) | 4.9 (1.0) | 5.0 (1.0) | 0.166 |
| **HDL-C (mmol/L)** | 1.5 (0.4) | 1.6 (0.4) | 1.5 (0.4) | <0.001 |
| **LDL-C (mmol/L)** | 2.7 (0.8) | 2.7 (0.7) | 2.8 (0.8) | 0.167 |
| **TG (mmol/L)** | 1.7 (1.8) | 1.4 (1.3) | 1.8 (1.9) | <0.001 |
| **Education levels (uneducated)** | 583 (18.8 %) | 104 (14.8 %) | 479 (20.0 %) | 0.002 |
| **Occupation type** | | | | 0.118 |
| Professional | 238 (7.7 %) | 53 (7.6 %) | 185 (7.7 %) | |
| Manual-worker | 2,846 (92.0 %) | 644 (91.7 %) | 2,202 (92.1 %) | |
| Student | 10 (0.3 %) | 5 (0.7 %) | 5 (0.2 %) | |
| **Smoking** | | | | <0.001 |
| Never | 2,466 (79.7 %) | 517 (73.7 %) | 1,949 (81.5 %) | |
| Former | 104 (3.4 %) | 31 (4.4 %) | 73 (3.1 %) | |
| Current | 524 (16.9 %) | 154 (21.9 %) | 370 (15.5 %) | |
| **Drinking** | | | | 0.010 |
| Never | 2,347 (75.9 %) | 503 (71.7 %) | 1,844 (77.1 %) | |
| Former | 109 (3.5 %) | 32 (4.6 %) | 77 (3.2 %) | |
| Current | 638 (20.6 %) | 167 (23.8 %) | 471 (19.7 %) | |
| **Vigorous exercise (yes)** | 983 (31.8 %) | 210 (29.9 %) | 773 (32.3 %) | 0.230 |
| **Regular diet (yes)** | 2,300 (74.3 %) | 485 (69.1 %) | 1,815 (75.9 %) | <0.001 |
| **Family history of diabetes (yes)** | 509 (16.5 %) | 107 (15.2 %) | 402 (16.8 %) | 0.326 |
| **Hypoglycaemic drugs use (yes)** | 7 (0.2 %) | 2 (0.3 %) | 5 (0.2 %) | 1.000 |
| **Self-report liver disease (yes)** | 109 (3.5 %) | 18 (2.6 %) | 91 (3.8 %) | 0.117 |
| **Self-report upper GI problems (yes)** | 15 (0.5 %) | 2 (0.3 %) | 13 (0.5 %) | 0.577 |

Abbreviations: FPG, fasting plasma glucose; 2hPG, 2-hour postload plasma glucose; HbA1c, glycated haemoglobin; NGT, normal glucose tolerance; IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; GI, gastrointestinal.

[a] All p values are two-sided.

Table 3 (c).There was a higher incidence of disease progression in the high post load group (59.5 per 1,000 pyo) than low post load group(23.4 per 1,000 pyo); 54.5 per 1000 pyo overall. This higher risk of disease progression was present in the unadjusted Cox-PH model and adjusted Cox-TVC models (all $p < 0.001$) (Fig. 3E).

### 3.5. Disease reversal

We also observed disease reversal from prediabetes to NGT in this cohort. When dividing participants according to their postload-fasting gap, Fig. 3(G) shows the probability of disease reversal in the low post load group was significantly higher than that in the high post load group ($p < 0.001$). The Table 2 shows similar results, there was a higher probability of disease reversal in the low post load group (327.4 per 1,000 pyo) than in the high post load group (238.6 per 1,000 pyo). Cox-PH model shows participants in the high post load group had lower probability of experiencing disease reversal from prediabetes to diabetes (HR: 0.72, 95 %CI (0.60, 0.87), $p < 0.001$). After adjusting for time-varying variables in Cox-TVC model 1 and model 2, variables selected according to Supplementary Table 3(d), the participants in the low post load group also showed a higher probability of disease reversal (all $p < 0.05$).

The resulting goodness of fit for Cox-PH, Cox-TVC model 1 and Cox-TVC model 2.

Supplementary Fig 1 shows the comparison of global chi-square values, AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion) of different models in incident diabetes, incident prediabetes, disease progression and disease reversal to evaluate the fit and complexity of these models. In all scenarios in this study, Cox-TVC model 2 shows the highest global chi-square values and lowest AIC and BIC values, except for the BIC in incident diabetes, and followed by Cox-TVC model 1, all p-values $< 0.001$.

Supplementary Table 4 further demonstrated the resulting goodness of fit for Cox-PH, Cox-TVC model 1 and Cox-TVC model 2. For different conditions in this study, Cox-TVC models have better prediction consistency and statistical significance than the Cox-PH model in most cases, capturing the dynamics of risk over time in these analyses.

### 3.6. Stability of the glucose load over the cohort study

Across the baseline and two follow-up re-visits of the cohort study, the distribution of participants based on the stability of the glucose load showed that 3.1 %(n = 95) were stable low post load (consecutive measures of 2hPG ≤ FPG), 63.0 % (n = 1,948) were stable high post load (consecutive measures of 2hPG > FPG) and 32.5 %(n = 1,006) fluctuating (vary between low or high post load). 1.5 %(n = 45) of participants underwent OGTT at baseline and FPG tests at the first re-visit and the second re-visit. However, because the 2hPG test was not performed at the second and/or first re-visit, the postload-fasting gap could not be calculated and was therefore defined as 'incomplete information'.

In the further definition of the stable low, fluctuating, stable high and 'incomplete information' groups, the incidence of diabetes, incidence of prediabetes and disease progression in the stable low group were always lower than that in other groups, and higher than other groups in disease reversal, all $p < 0.001$ as shown in Fig. 3 (B), Fig. 3 (D), Fig. 3 (F) and Fig. 3 (H).

Table 2 shows that there were no participants with NGT who developed diabetes in the stable low group (0.0 per 1,000 pyo), while 25 cases occurred in the fluctuating group (8.7 per 1,000 pyo), 55 cases in the stable high group (12.7 per 1,000 pyo) and 12 cases in the incomplete information group (504.8 per 1,000 pyo). More than this, participants in the stable low group (25.4 per 1,000 pyo) had the lowest incidence of prediabetes compared with other groups in Cox-PH models [fluctuating: 66.3 per 1,000 pyo, HR: 1.69, 95 %CI (1.16, 2.47), $p = 0.007$; stable high: 145.7 per 1,000 pyo, HR: 7.16, 95 %CI (3.39, 15.12), $p < 0.001$; incomplete information: 100.8, HR: 1.64, 95 %CI (1.04,

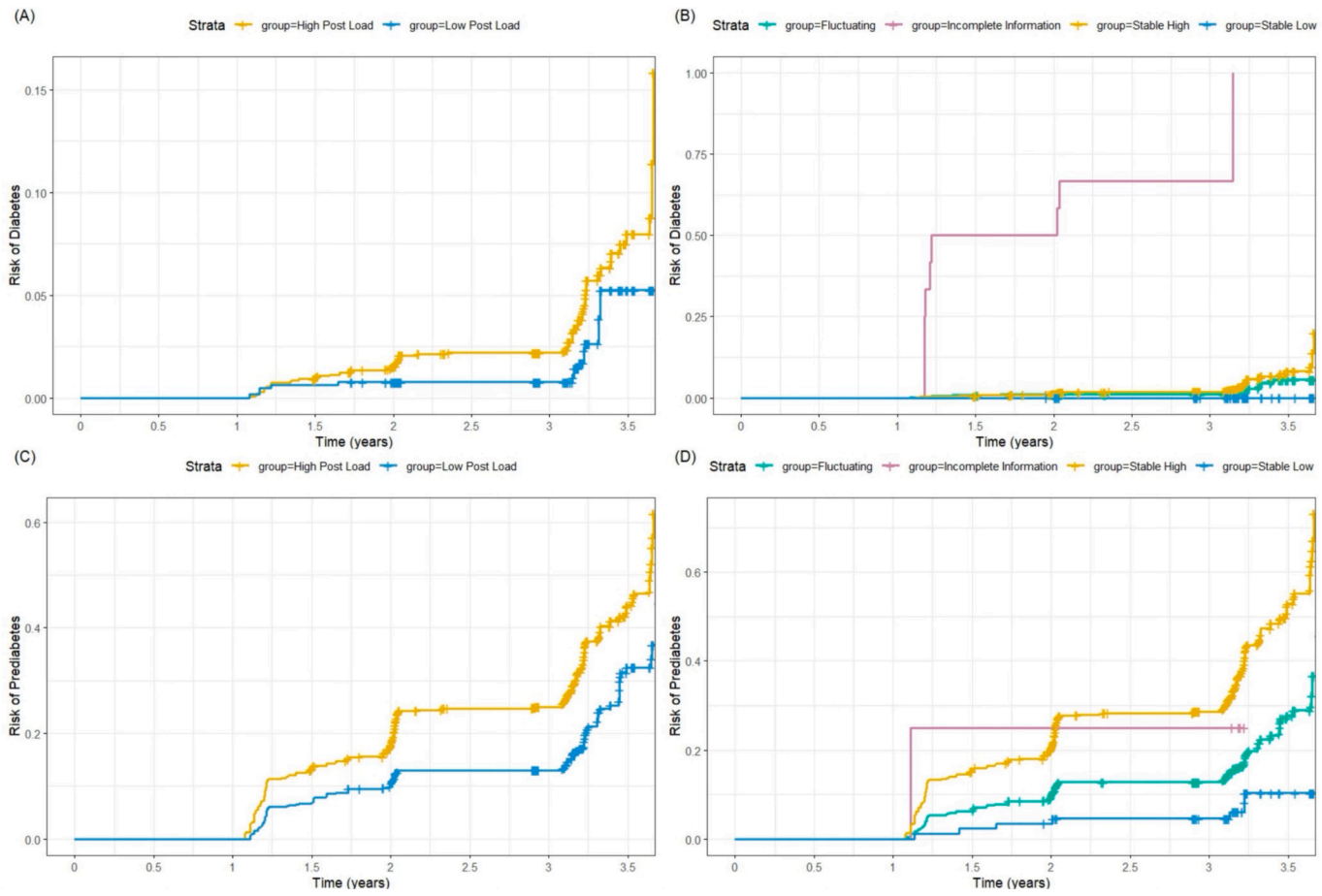


**Fig. 3.** (A) Kaplan–Meier plot of time to incident diabetes in low post load and high post load; Fig. 3 (B) Kaplan–Meier plot of time to incident diabetes stable low, stable high, fluctuating and incomplete Information; Fig. 3 (C) Kaplan–Meier plot of time to incident prediabetes in low post load and high post load; Fig. 3 (D) Kaplan–Meier plot of time to incident prediabetes in stable low, stable high, fluctuating and incomplete information; Fig. 3 (E) Kaplan–Meier plot of time to disease progression in low post load and high post load; Fig. 3 (F) Kaplan–Meier plot of time to disease progression in stable low, stable high, fluctuating and incomplete information; Fig. 3 (G) Kaplan–Meier plot of time to disease reversal in low post load and high post load; Fig. 3 (H) Kaplan–Meier plot of time to disease reversal in stable low, stable high, fluctuating and incomplete information.

2.59), p = 0.033]. When considered time-varying covariates in Cox-TVC model 1, the ratios were larger [fluctuating: 4.51, 95 %CI (1.73, 11.76), p = 0.002; stable high: 10.53, 95 %CI (4.31, 25.75), p < 0.001; incomplete information: 49.99, 95 %CI (3.89, 643.180), p = 0.003], and Cox-TVC model 2 shows similar results (all p < 0.05).

For participants with prediabetes, the disease progression from prediabetes to diabetes was 1 case in stable low group (19.0 per 1,000 pyo), while 18 cases in fluctuating group (19.9 per 1,000 pyo), 177 cases in stable high group (53.9 per 1,000 pyo) and 38 in incomplete information group (669.8 per 1,000 pyo). But due to the small sample size in stable low group, there was no statistical significance when compared with other groups, except the incomplete information group in both Cox-PH model and Cox-TVC models (p < 0.001 in Cox-PH and Cox-TVC Model 1).

The disease reversal from prediabetes to NGT were 13 cases in stable low group (346.5 per 1,000 pyo). There was no statistical significance compared with the fluctuating group (210 cases, 357.3 per 1,000 pyo) and stable high group (599 cases, 234.0 per 1,000 pyo), and significant in incomplete information group (2 cases, 16.9 per 1,000 pyo) in both Cox-PH model and Cox-TVC models (all p < 0.05).

Table 3 demonstrates that stable low was associated with a lower risk of diabetes at the end of the study when compared with stable high and fluctuating groups both in the crude and adjusted models. We further explored the factors which were positively associated with the stable low group, including younger age, males, non-Han population, educated, lower BMI, and lower triglycerides were found as shown in Table 3.

## 4. Discussion

In this large Chinese population-based study, we demonstrate that the risk of progression to prediabetes and diabetes is higher in people who have a 2hPG that greater than their FPG value (high post load). For people with prediabetes, those with low post load have a lower probability of disease progression from prediabetes to diabetes and were more likely to have disease reversal to NGT. Our study results suggested that people with high post load should be considered to be at greater risk for developing diabetes and that this risk increases over time.

In an analysis of the full SENSIBLE cohort, we found a quarter (26.04 %) of participants had 2hPG that was equal to or less than their FPG value, which is similar to the findings in the baseline data of this cohort [12]. FPG reflects the net effect of basal insulin and glucagon on endogenous glucose production and glucose disposal[23,24]. After the OGTT, blood glucose levels will rise due to the carbohydrates absorbed in the proximal small intestine[25]. The time that is required for the 2hPG level to return to, or drop below, the FPG level following glucose ingestion is dependent on the insulin response during the OGTT and peripheral and hepatic insulin sensitivity. The faster the 2hPG level

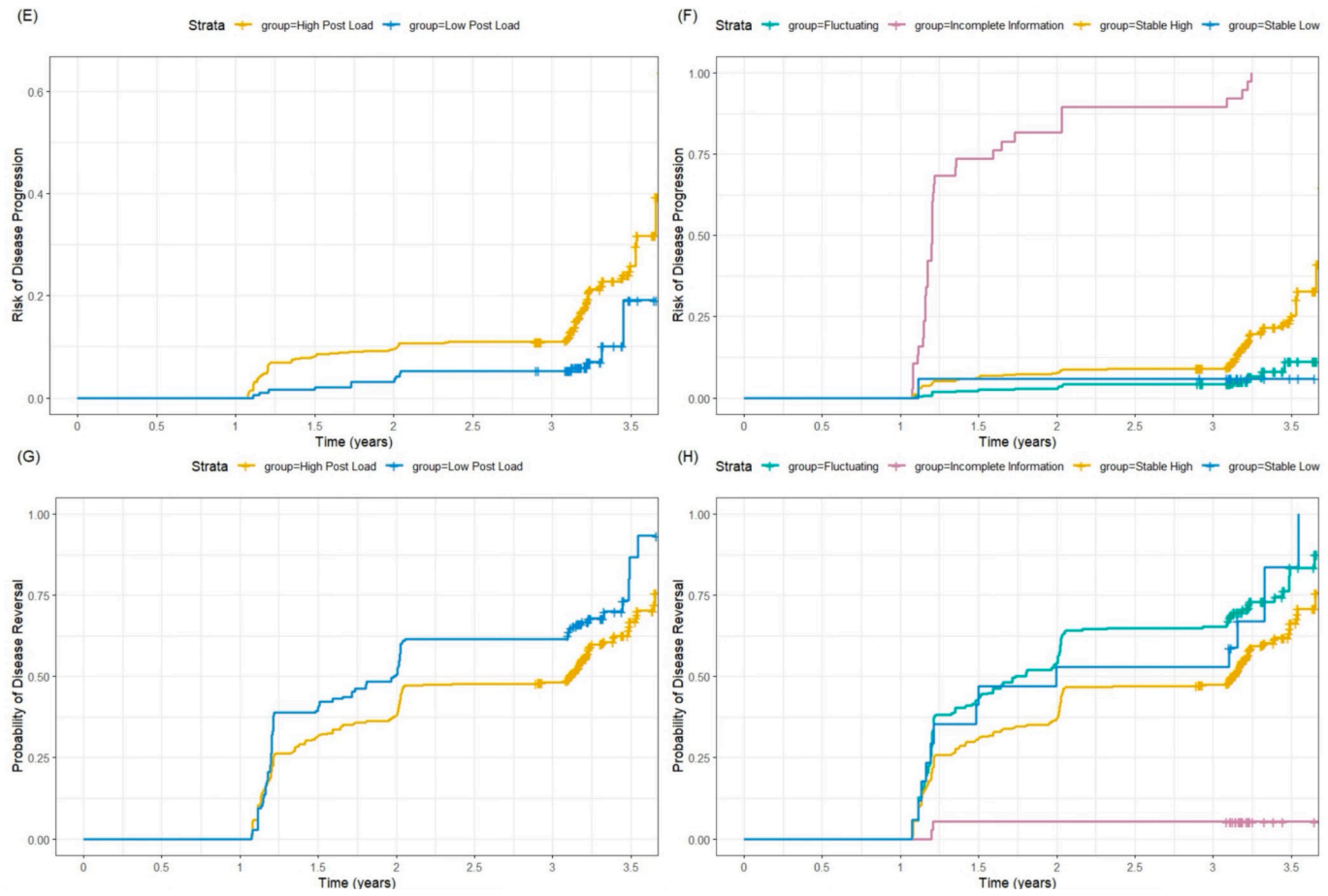


**Fig. 3.** (*continued*).

declines to the FPG level, the more efficient is the person in disposing of the glucose load[26] although whether this is due to the size of insulin response or the response of tissues to insulin is not clear[27]. Therefore, low post load may be caused by excessive insulin production, insulin sensitivity, or both; and a high post load reflects either insulin insensitivity or reduced insulin production.

Prediabetes is an intermediate stage on the continuum between normal glucose regulation and diabetes[28], which includes IFG (insulin resistant) and IGT (insulin insufficient)[28]. People with prediabetes have an increased risk of progression to type 2 diabetes at an annual rate of 10 %[29], and also experience associated microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular complications (myocardial infarction, stroke, or cardiovascular diseases)[30,31]. In our study, incidence of prediabetes in people with NGT at baseline was higher for participants with high post load compared with low post load. Similarly, the participants with prediabetes in high post load group were more like to develop to diabetes and less likely to experience disease reversal, relationships that persisted in adjusted time-varying analyses.

According to the latest IDF Diabetes Atlas, the global prevalence of diabetes among adults aged 20–79 years was estimated to be 10.5 % in 2021, equating to 536.6 million individuals[1]. Due to the size of the population in China, although the prevalence rate is in the middle range worldwide, China had the highest number of adults aged 20–79 years with diabetes, amounting to 140.9 million people in 2021[1]. While prevalence data indicates the current burden of the disease in the population, accurate health policy responses and monitoring of the impact of interventions require estimates of incidence. Our study presents one of the few sources of directly measured type 2 diabetes incidence in China. In this study, we estimated diabetes incidence at 12.3 per 1,000 pyo and the rate of disease progression from prediabetes to diabetes was 54.5 per 1,000 pyo, similar to that reported in a study of middle-aged and older adults who self-reported diabetes status[32], and higher than that reported in a study that used a population-based diabetes registry system of 281.7 / 100,000 person-years[33]. The difference in the estimates is likely due to different study designs, population characteristics, study periods and statistical methods[32,33]. In general, our study and previous studies found that the incidence of diabetes was on the rise[32–34], consistent with the increasing prevalence among adults in China, rising from 10.9 % in 2013 to 12.8 % in 2017[35,36].

The increasing incidence of diabetes emphasizes the need for prevention and early identification of people at risk of developing diabetes. In this cohort, we found that regardless of the initial glycaemic status, i.e. NGT or prediabetes, people with high/stable high post load have a higher risk of developing diabetes. The effect persisted after adjusting for the baseline level of FPG and time-varying covariates. This indicates that high post load may be an independent indicator of diabetes risk, independent of the level of FPG and initial glycaemic status. Likewise, in the CARDIA study, they found that the risk of type 2 diabetes was higher in participants with high post load compared with low post load during 20 years of follow-up[14].

We have determined factors influencing the stability of the postload-fasting gap based on two follow-up visits and baseline measurements. We demonstrated that younger people, males, those with lower BMI, lower TG; factors associated with a favourable metabolic profile were positively associated with the long-term stability of the stable low post load group, and positively associated with the lower probability of developing diabetes. Interestingly, we found that compared with low post load group, the proportion of females in the stable low group decreased rapidly over time (52.85 % vs 29.47 %, $p < 0.001$). This could be because the average age of participants in the baseline survey was

**Table 2**
Association of the postload-fasting gap at baseline with incidence and hazard ratios for developing diabetes after adjusting for covariates.

| Clinical events | Total | Low post load N = 702 (22.69 %) | High post load N = 2,392 (77.31 %) | Stable low N = 95 (3.07 %) | Fluctuating N = 1,006 (32.51 %) | Stable high N = 1,948 (62.96 %) | Incomplete information N = 45 (1.45 %) |
|---|---|---|---|---|---|---|---|
| **Incident Diabetes** | | | | | | | |
| No. of Events / Person-years | 92 / 7,508.2 | 16 / 2024.1 | 76 / 5484.1 | 0 / 280.7 | 25 / 2,861.7 | 55 / 4,342.1 | 12 / 23.8 |
| Incidence rate $ | 12.3 | 7.9 | 13.9 | 0.0 | 8.7 | 12.7 | 504.8 |
| Cox-PH | – | 1.00 | 1.98 (1.15, 3.39); p = 0.014 | 1.00 | – | – | – |
| Cox-TVC Model 1 | – | 1.00 | 2.79 (1.53, 5.07); p < 0.001 | 1.00 | – | – | – |
| Cox-TVC Model 2 | – | 1.00 | 1.89 (0.80, 4.47); p = 0.144 | 1.00 | – | – | – |
| **Incident Prediabetes** | | | | | | | |
| No: Events / Person-years | 753 / 6,893.1 | 134 / 1,914.1 | 619 / 4,979.0 | 7 / 275.2 | 181 / 2,729.8 | 562 / 3,858.3 | 3 / 29.8 |
| Incidence rate $ | 109.3 | 70.0 | 124.3 | 25.4 | 66.3 | 145.7 | 100.8 |
| Cox-PH | – | 1.00 | 1.90 (1.58, 2.29); p < 0.001 | 1.00 | 1.69 (1.16, 2.47); p = 0.007 | 7.16 (3.39, 15.12); p < 0.001 | 1.64 (1.04, 2.59); p = 0.033 |
| Cox-TVC Model 1 | – | 1.00 | 2.00 (1.65, 2.43); p < 0.001 | 1.00 | 4.51 (1.73, 11.76); p = 0.002 | 10.53 (4.31, 25.75); p < 0.001 | 49.99 (3.89, 643.180); p = 0.003 |
| Cox-TVC Model 2 | – | 1.00 | 1.62 (1.26, 2.07); p < 0.001 | 1.00 | 4.38 (1.28, 14.95); p = 0.018 | 9.10 (3.01, 27.55); p < 0.001 | 1.62e + 04 (3.00e + 03, 8.70e + 04); p < 0.001 |
| **Disease Progression** | | | | | | | |
| No: Events / Person-years | 234 / 4,293.5 | 14 / 597.7 | 220 / 3,695.9 | 1 / 52.6 | 18 / 903.4 | 177 / 3,280.8 | 38 / 56.7 |
| Incidence rate | 54.5 | 23.4 | 59.5 | 19.0 | 19.9 | 53.9 | 669.8 |
| Cox-PH | – | 1.00 | 2.63 (1.53, 4.51); p < 0.001 | 1.00 | 1.02 (0.14, 7.67); p = 0.984 | 2.88 (0.40, 20.57); p = 0.292 | 45.35 (6.14, 335.00); p < 0.001 |
| Cox-TVC Model 1 | – | 1.00 | 3.60 (2.08, 6.24); p < 0.001 | 1.00 | 1.58 (0.20, 12.31); p = 0.665 | 4.47 (0.62, 32.24); p = 0.137 | 44.82 (5.84, 343.85); p < 0.001 |
| Cox-TVC Model 2 | – | 1.00 | 3.23 (1.86, 5.63); p < 0.001 | 1.00 | 1.06 (0.13, 8.71); p = 0.957 | 3.66 (0.51, 26.48); p = 0.199 | 3.31e + 09 (0.00, Inf); p = 0.997 |
| **Disease Reversal** | | | | | | | |
| No: Events / Person-years | 824 / 3,303.3 | 132 / 403.5 | 692 / 2899.8 | 13/ 37.5 | 210 / 587.8 | 599 / 2559.5 | 2 / 118.5 |
| Incidence rate $ | 249.6 | 327.2 | 238.6 | 346.5 | 357.3 | 234.0 | 16.9 |
| Cox-PH | – | 1.00 | 0.72 (0.60, 0.87); p < 0.001 | 1.00 | 1.01 (0.76, 1.33); p = 0.965 | 0.64 (0.37, 1.12); p = 0.116 | 0.37 (0.22, 0.60); p < 0.001 |
| Cox-TVC Model 1 | – | 1.00 | 0.65 (0.51, 0.83); p < 0.001 | 1.00 | 0.81 (0.40, 1.66); p = 0.569 | 0.51 (0.25, 1.06); p = 0.073 | 0.06 (0.00, 0.69); p = 0.025 |
| Cox-TVC Model 2 | – | 1.00 | 0.68 (0.53, 0.87); p = 0.002 | 1.00 | 0.77 (0.36, 1.65); p = 0.502 | 0.50 (0.23, 1.07); p = 0.074 | 2.04e-17 (1.47e-30, 2.84e-04); p = 0.013 |

Cox-TVC Model 1: Age, sex, BMI and FBG.
Cox-TVC Model 2: Age, sex, BMI, FPG, ethnicity, education levels, HbA1c, heart rate, HDL-C, TG, smoking, drinking and regular diet. Incident diabetes further added BP and hypoglycaemic drugs use; Incident prediabetes further added BP, TC and occupation types; Disease progression further added BP and liver disease; Disease reversal further added BP, TC and LDL-C.
$ Incidence rate is expressed as the number of events per 1000 person-years.

51.18 ± 9.56 years old, which is when women enter the perimenopause or are already menopausal.

One of the strengths of our study is the use of longitudinal design rather than cross-sectional design, which provides insights into the natural history of the disease over 3.2 years without intervention. We also captured time-varying covariates, included them in the Cox-TVC models and calculated the goodness of fit of each model, which provided a more accurate risk assessment. This study also has the following limitations. In this study, HbA1c was not used for the diagnosis of diabetes or prediabetes, and using FPG and 2hPG alone may have led to a misdiagnosis. However, in guidelines currently in use in China HbA1c is recommended to be used as a supplementary diagnostic criterion for diabetes as level B evidence as the optimal cut-off point of HbA1c for diagnosing diabetes in Chinese adults is still unclear[18]. Second, as our data points were limited to the baseline survey and two follow-up visits, our estimate of the timing of disease progression or reversal is impacted by the timing of the tests rather than estimates of the actual time at which someone developed the disease. Third, due to fluctuation in the glycaemic status of participants, we may have overestimated the incidence rates. Fourth, in this cohort study, we do not have insulin values, and cannot therefore describe the relative contribution of insulin production or insulin sensitivity to the described phenomena. Finally, in the group we labelled as incomplete information, likely, these people did not have a complete OGTT as there was a reason identified which made it inappropriate to complete it and this group may be more likely to be diabetic.

In summary, we found 282 (9.11 %) new cases of diabetes, the incidence of diabetes was 12.3 per 1,000 pyo and the disease progression from prediabetes to diabetes was 54.5 per 1,000 pyo. High/stable high post load was associated with a higher risk of incident diabetes, prediabetes and disease progression from prediabetes to diabetes. Compared with participants in high post load, factors associated with having low post load were younger age, being male, lower BMI, and a favourable metabolic profile, and they are the same factors that related to low probability of developing diabetes. In conclusion, the postload-fasting gap may be an indicator of risk of progression to diabetes. Additional prospective follow-up trials could help identify the level of risk associated with varying sizes of the postload-fasting gap and FPG values to help guide clinical monitoring and interventions.

**Table 3**
Distribution of the baseline characteristics by the stability of the postload-fasting gap among the 3,094 study participants who had three OGTT measures over 3.24 years of follow-up.

| Characteristics | Stable low N = 95 (3.07 %) | Fluctuating N = 1,006 (32.51 %) | Stable high N = 1,948 (62.96 %) | Incomplete information N = 45 (1.45 %) | p-value[a] | p-value[b] | p-value[c] |
|---|---|---|---|---|---|---|---|
| **Age at baseline (years)** | 49.5 (9.6) | 50.7 (9.9) | 52.9 (8.6) | 52.9 (8.0) | 0.279 | <0.001 | 0.042 |
| **Female (%)** | 28 (29.5 %) | 607 (60.3 %) | 1,390 (71.4 %) | 28 (62.2 %) | <0.001 | <0.001 | <0.001 |
| **Ethnicity (Han)** | 66 (69.5 %) | 750 (74.6 %) | 1,650 (84.7 %) | 41 (91.1 %) | 0.280 | <0.001 | 0.009 |
| **FPG (mmol/L)** | 5.5 (0.6) | 5.6 (0.6) | 5.6 (0.5) | 6.1 (0.6) | 0.342 | 0.113 | 0.427 |
| **2hPG (mmol/L)** | 4.4 (0.9) | 5.6 (1.4) | 7.4 (1.4) | 8.4 (2.0) | <0.001 | <0.001 | <0.001 |
| **Postload-Fasting Gap (mmol/L)** | −1.1 (0.9) | 0.0 (1.3) | 1.8 (1.2) | 2.2 (1.8) | <0.001 | <0.001 | <0.001 |
| **HbA1c (%)** | 5.3 (0.4) | 5.3 (0.4) | 5.4 (0.4) | 5.8 (0.5) | 0.552 | 0.103 | <0.001 |
| **Glycaemic status (WHO1999)** | | | | | 0.031 | <0.001 | <0.001 |
| NGT | 81 (85.3 %) | 799 (79.4 %) | 1,129 (58.0 %) | 10 (22.2 %) | | | |
| IFG | 14 (14.7 %) | 138 (13.7 %) | 142 (7.3 %) | 9 (20.0 %) | | | |
| IGT | 0 (0.0 %) | 69 (6.86 %) | 677 (34.75 %) | 26 (57.78 %) | | | |
| **BMI (kg/m$^2$)** | 24.4 (3.2) | 24.9 (3.5) | 25.6 (3.5) | 26.7 (3.2) | 0.114 | 0.001 | <0.001 |
| **SBP (mmHg)** | 131 (19.2) | 132 (19.6) | 135 (19.0) | 143 (19.9) | 0.688 | 0.090 | <0.001 |
| **DBP (mmHg)** | 81 (10.9) | 81 (11.7) | 82 (11.3) | 87 (11.1) | 0.535 | 0.168 | 0.002 |
| **Heart rate (beats/min)** | 76 (11.7) | 77 (11.0) | 78 (11.1) | 76 (8.0) | 0.742 | 0.283 | 0.737 |
| **TC (mmol/L)** | 4.8 (0.9) | 4.9 (1.0) | 5.0 (1.1) | 4.9 (0.8) | 0.509 | 0.070 | 0.658 |
| **HDL-C (mmol/L)** | 1.6 (0.3) | 1.6 (0.4) | 1.5 (0.4) | 1.4 (0.3) | 0.917 | 0.150 | 0.001 |
| **LDL-C (mmol/L)** | 2.7 (0.7) | 2.7 (0.7) | 2.8 (0.8) | 2.7 (0.8) | 0.998 | 0.412 | 0.751 |
| **TG (mmol/L)** | 1.3 (0.8) | 1.4 (1.3) | 1.8 (2.0) | 2.3 (2.2) | 0.071 | <0.001 | 0.004 |
| **Education (uneducated)** | 11 (11.6 %) | 151 (15.0 %) | 412 (21.2 %) | 9 (20.0 %) | 0.367 | 0.010 | 0.184 |
| **Occupation Type** | | | | | 0.274 | 0.607 | 0.654 |
| Professional | 5 (5.3 %) | 87 (8.7 %) | 142 (7.3 %) | 4 (8.9 %) | | | |
| Manual-worker | 90 (94.7 %) | 913 (90.8 %) | 1,802 (92.5 %) | 41 (91.1 %) | | | |
| Student | 0 (0.00 %) | 6 (0.6 %) | 4 (0.2 %) | 0 (0.0 %) | | | |
| **Smoking** | | | | | 0.025 | <0.001 | 0.167 |
| Never | 62 (65.3 %) | 780 (77.5 %) | 1,588 (81.5 %) | 36 (80.0 %) | | | |
| Former | 6 (6.3 %) | 36 (3.6 %) | 61 (3.1 %) | 1 (2.2 %) | | | |
| Current | 27 (28.4 %) | 190 (18.9 %) | 299 (15.4 %) | 8 (17.8 %) | | | |
| **Drinking** | | | | | 0.033 | 0.001 | 0.384 |
| Never | 59 (62.1 %) | 742 (73.8 %) | 1,515 (77.8 %) | 31 (68.9 %) | | | |
| Former | 7 (7.4 %) | 38 (3.8 %) | 63 (3.2 %) | 1 (2.2 %) | | | |
| Current | 29 (30.5 %) | 226 (22.5 %) | 370 (19.0 %) | 13 (28.9 %) | | | |
| **Vigorous Exercise (yes)** | 18 (19.0 %) | 313 (31.1 %) | 632 (32.4 %) | 14 (31.1 %) | 0.013 | 0.006 | 0.109 |
| **Regular diet (yes)** | 75 (79.0 %) | 718 (71.4 %) | 1,476 (75.8 %) | 31 (68.9 %) | 0.116 | 0.479 | 0.195 |
| **Family History of Diabetes (yes)** | 18 (19.0 %) | 154 (15.3 %) | 330 (16.9 %) | 7 (15.6 %) | 0.350 | 0.611 | 0.625 |
| **Hypoglycaemic drugs use (yes)** | 1 (1.1 %) | 1 (0.1 %) | 3 (0.2 %) | 2 (4.4 %) | 0.409 | 0.455 | 0.503 |
| **Self-report liver disease (yes)** | 5 (5.3 %) | 28 (2.8 %) | 75 (3.9 %) | 1 (2.2 %) | 0.175 | 0.488 | 0.702 |
| **Self-report upper GI problems (yes)** | 0 (0.0 %) | 4 (0.4 %) | 11 (0.6 %) | 0 (0.0 %) | 1.000 | 1.000 | 1.000 |

Abbreviations: FPG, fasting plasma glucose; 2hPG, 2-hour postload plasma glucose; HbA1c, glycated haemoglobin; NGT, normal glucose tolerance; IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; GI, gastrointestinal.

[a] P-value represents the comparison between stable low group and fluctuating group, all p values are two-sided.

[b] P-value represents the comparison between stable low group and stable high group, all p values are two-sided.

[c] P-value represents the comparison between stable low group and incomplete information group, all p values are two-sided.

## CRediT authorship contribution statement

**Xiaohan Xu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation. **Duolao Wang:** Writing – review & editing, Supervision, Data curation. **Shabbar Jaffar:** Writing – review & editing, Supervision. **Uazman Alam:** Writing – review & editing. **Shanhu Qiu:** Writing – review & editing, Resources, Project administration, Data curation. **Bo Xie:** Writing – review & editing, Data curation. **Xiaoying Zhou:** Writing – review & editing, Data curation. **Zilin Sun:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation. **Anupam Garrib:** Writing – review & editing, Supervision, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

This research was funded by the Key Research and Development Program in Jiangsu Province (grant number BE2022828) and the National Key R&D Program of China (grant number 2016YFC1305700). X. XU. is supported by China Scholarship Council (CSC).

**Informed Consent.**

Written informed consent was been obtained from people participating in this study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111761.

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