DR VIVIAN YAWEI GUO (Orcid ID : 0000-0001-9399-1808)

DR CARLOS K H WONG (Orcid ID : 0000-0002-6895-6071)

Hypertriglyceridaemic–waist phenotype and risk of diabetes in people with impaired fasting glucose in primary care: a cohort study

V. Y-W. Guo[1], E. Y-T. Yu[1], C. K-H. Wong[1], R. W-S. Sit[2], J. H-L. Wang[3] and C. L-K. Lam[1]

[1]Department of Family Medicine and Primary Care, The University of Hong Kong, [2]The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, and [3]Department of Family Medicine and Health Care, Hong Kong West Cluster Hospital Authority, Hong Kong

Correspondence to: Esther Yee Tak Yu. Email: ytyu@hku.hk

What's new?

- Little is known about the prospective association between the hypertriglyceridaemic–waist phenotype and risk of Type 2 diabetes among individuals with impaired fasting glucose, who are often seen in primary care clinics.

- Individuals with the hypertriglyceridaemic–waist phenotype had an increased risk of developing Type 2 diabetes.

Abstract

Aim We aimed to determine the prospective association between baseline triglyceridaemic–waist phenotypes and diabetic mellitus incidence in individuals with impaired fasting glucose seen in primary care.

Methods A cohort of 1101 participants (84.4% of the recruited individuals) with impaired fasting glucose were recruited from three primary care clinics during regular follow-ups to monitor their chronic conditions. Baseline triglyceridaemic–waist phenotypes were divided into four groups: (1) normal waistline and triglyceride level ($n = 252$); (2) isolated central obesity ($n = 518$); (3) isolated high triglyceride level ($n = 80$); and (4) central obesity with high triglyceride level (i.e. hypertriglyceridaemic–waist phenotype) ($n = 251$). The presence of diabetes at follow-up was determined by fasting plasma glucose (≥ 7.0 mmol/l) and/or 2-h 75-g oral glucose tolerance test (≥ 11.1 mmol/l) and/or HbA$_{1c}$ (47.5 mmol/mol; $\geq 6.5\%$) according to American Diabetes Association diagnostic criteria. Multivariable Cox proportional hazards regressions were established to assess the impact of different triglyceridaemic–waist phenotypes on time to diabetes onset.

Results After a mean follow-up period of 6.5 months (SD 4.7 months), the number of diabetes cases was significantly higher in the group with hypertriglyceridaemic–waist phenotype (52.2%) compared with the other three phenotype groups (group 1: 28.2%; group 2: 34.6%; group 3: 30.0%). Only the hypertriglyceridaemic–waist phenotype showed an increased risk of developing diabetes (hazard ratio 1.581, 95% CI 1.172–2.134; *P* = 0.003) compared with the group with normal waistline and triglyceride level after controlling for confounders.

Conclusion The combination of central obesity and hypertriglyceridaemia is associated with > 50% risk of progression to diabetes within 6 months among individuals with impaired fasting glucose seen in primary care.

Introduction

With the development of modern society, lifestyle changes towards longer sedentary periods and over-nutrition, together with genetic susceptibility have led to increased body weight and waist circumference, and subsequently contributed to an epidemic of diabetes mellitus. It has been estimated that the prevalence of diabetes was 415 million in 2015, and this is expected to increase to 642 million by 2040 [1]. A major global non-communicable disease, diabetes accounted for an estimated 5 million deaths worldwide in 2015 [1].

Fasting plasma glucose (FPG) screening is the most popular method of testing for diabetes in primary care clinics in Hong Kong due to its convenience and low cost [2]. Therefore, impaired fasting glucose (IFG), a precursor of diabetes defined as a FPG level higher than normal but lower than that signifying diabetes [3], could be readily identified. It is important to treat people with IFG early to prevent or delay the development of diabetes, because people with IFG usually have a high risk of developing diabetes, with an annualized conversion rate to diabetes of 6%–9% [4,5]. However, it should be noted that the prevalence

of IFG is high. In a 2010 cross-sectional survey of a nationally representative sample of Chinese speakers, the prevalence of IFG among adults aged > 18 years was ~ 22.8% [6]. As a result, population interventions in all those with IFG are unlikely to be practical because of the cost and work involved, although current evidence suggests that diabetes can be prevented by changing behaviours or medication [7–10]. By contrast, targeted preventive interventions among those with a high probability of progressing to diabetes might be cost-effective.

The concept of a 'hypertriglyceridaemic–waist phenotype', i.e. central obesity and a high triglyceride level, was first used as a proxy to identify people at risk of developing cardiovascular disease [11]. Both central obesity and hypertriglyceridaemia are indicators of excess visceral adiposity, a well-establish risk factor for insulin resistance and disturbed glucose metabolism [12] that is independently associated with incident prediabetes and diabetes [13]. A systematic review of longitudinal studies showed that the incidence of diabetes increased 2.14 times (95% CI 1.70–2.71) in people with central obesity compared with those with a normal waist circumference [14]. In addition, previous studies have also demonstrated an association between elevated triglyceride levels and an increased risk of diabetes incidence [15,16]. Based on this evidence, the hypertriglyceridaemic–waist phenotype was found to be closely related to diabetes risk in the general population [17] and in those with impaired glucose tolerance [18]. However, whether it is associated with diabetes risk in people with IFG, a group that could be identified easily in primary care clinics, has been little studied. Here, we aimed to assess distribution of the triglyceridaemic–waist phenotypes among people diagnosed with IFG in primary care settings and the impact of different triglyceridaemic–waist phenotypes on the time to diabetes onset using multivariable Cox proportional hazards regressions.

Methods

Study design and participant recruitment

Participants in this cohort study were recruited from among individuals with chronic illness (except diabetes) that were managed at public primary care clinics in Hong Kong. Details of the study design and participant recruitment have been reported previously [9,19]. In brief, people attending public primary care clinics in Hong Kong undergo FPG testing if they are at risk of developing Type 2 diabetes, e.g. have hypertension, obesity or a positive family history of diabetes. Between May 2013 and February 2015, people attending three public primary care clinics in Hong Kong for routine chronic disease management were screened for eligibility. Individuals were included if they: were aged 18 years or above, without known history of diabetes, and had IFG defined by a plasma fasting glucose level between 5.6 and 6.9 mmol/l according to the American Diabetes Association (ADA) criteria [3].

Exclusion criteria were: (1) individuals with known diabetes or who were taking anti-diabetic medication; (2) being pregnant or breastfeeding; (3) on glucocorticoid therapy; (4) having active thyroid disease; (5) having anaemia or taking an iron supplement; (6) having a history of blood donation or blood transfusion within 3 months preceding the recruitment; (7) with an estimated GFR < 30 ml/min/1.73m^2 and (8) having missing clinical or laboratory information.

In total, 1304 individuals meeting the selection criteria were recruited with written consent at baseline. The follow-up assessment was conducted during routine visits to the participating clinics for management of participants' chronic conditions (except diabetes). We excluded 203 individuals from the analysis (3 had known diabetes, 41 had anaemia or were taking an iron supplement, 35 had active thyroid disease, 66 had missing clinical or laboratory data at either baseline or follow-up, and 58 people had a too short a follow-up period, i.e. < 30 days). Each included individual was observed from baseline until the incidence of diabetes, or the

date of last follow-up as censoring, or 15 February 2015, whichever came first. The current analysis included 1101 people (84.4%).

This study protocol was registered at the Hong Kong Clinical Trial Centre (Ref: HKCTR-1684) and ClinicalTrials.gov, the U.S. National Institutes of Health (Ref: NCT02439684). The study had received ethical approval by the institutional review board of the University of Hong Kong—the Hospital Authority Hong Kong West Cluster (Reference number: UW 13-299) and the institutional review board of Joint Chinese University of Hong Kong—New Territories East Cluster CRE (Reference number: 2013.585).

Outcome definition

Participants were asked to fast overnight for at least 8 h prior to the day of the laboratory assessment. On the day of the assessment, two blood samples were taken: one fasting blood sample to assess levels of FPG and HbA$_{1c}$, and a 2-h blood sampling after the 75-g oral glucose tolerance test (2h-OGTT). Blood samples were analysed at the Queen Mary Hospital or Prince of Wales Hospital laboratories, which have been accredited by the College of American Pathologists and are the providers of the usual laboratory service for the participating primary care clinics. Plasma glucose concentrations were measured using the Hexokinase method (Roche Cobas 8000), and HbA$_{1c}$ levels were measured using high-performance liquid chromatography (Bio-Rad Variant II Turbo).

Incident diabetes was the outcome of this study. Diabetes at follow-up was defined as FPG ≥ 7.0 mmol/l and/or 2h-OGTT ≥ 11.1 mmol/l and/or HbA$_{1c} \geq 47.5$ mmol/mol ($\geq 6.5\%$) according to ADA criteria [3].

Exposure definition

The triglyceridaemic–waist phenotypes were the exposures of this study. Waist circumference was measured while standing. Measurements were taken at a point midway between the iliac crest and the lower rib margin. Triglyceride level was determined from the fasting blood sample using enzymatic techniques.

Four groups were defined according to the waist circumference and level of triglyceride: (1) normal waist circumference and triglyceride level, i.e. waist circumference < 80 cm in women and < 90 cm in men, and triglyceride level < 1.7 mmol/l; (2) isolated central obesity, i.e. waist circumference ≥ 80 cm in women and ≥ 90 cm in men, and normal triglyceride level; (3) isolated high triglyceride level, i.e. triglyceride level ≥ 1.7 mmol/l with normal waist circumference; and (4) central obesity with high triglyceride level. In particular, the group with central obesity and high triglyceride level was also referred to as the hypertriglyceridaemic–waist phenotype.

Measurement of covariates

The sociodemographic and lifestyle information was collected using a standardized questionnaire. Smoking status was categorized as never, ex and current smoker. Physical activity level was measured using the short form International Physical Activity Questionnaire (IPAQ) in accordance with the user manual. Daily time spent on moderate-to-vigorous physical activity (MVPA) and sitting were collected [20]. BMI was calculated as weight divided by the square of height and categorized as normal weight (< 23.0 kg/m^2), overweight (23.0–24.9 kg/m^2) and obesity (≥ 25.0 kg/m^2) in these Asian participants. Systolic and diastolic BP were measured at the participating clinic using an automated blood pressure monitor after at least 10 min of resting. Total and HDL cholesterol were determined from a

fasting blood sample using enzymatic techniques. Levels of LDL cholesterol were calculated using the Friedewald equation for each individual [21].

Statistical analysis

The baseline characteristics in groups with normal waistline and triglyceride level, isolated central obesity, isolated high triglyceride level, and central obesity with high triglyceride level were compared using one-way analysis of variance (ANOVA) for continuous data and χ^2 test for categorical variables. Differences in diabetes incidence at follow-up among the four triglyceridaemic–waist phenotypes groups were compared using the χ^2 test. All data were expressed as means and standard deviation (SD) for continuous data and number (%) for categorical data.

Multivariable Cox proportional hazards regressions were established to measure the effect of triglyceridaemic–waist phenotypes on time to diabetes onset. A log-rank test was used to assess the significant difference in survival distributions between different triglyceridaemic–waist phenotypes. Age, sex and baseline FPG were adjusted in Model 1. In Model 2, family history of diabetes, smoking status and systolic BP were further adjusted; and daily time spent on MVPA and sitting were additionally included in Model 3.

All data analyses were performed with Stata/SE 13.0 (Stata-Corp, College Station, TX, USA). Statistical significance was set at $P < 0.05$.

Results

Of 1101 eligible participants, 252 (22.9%) had a normal waistline and triglyceride level, 518 (47.0%) had isolated central obesity, 80 (7.3%) had isolated high triglyceride level and 251 (22.8%) had central obesity and high triglyceride level. Table 1 shows a comparison of baseline demographic and clinical characteristics for the participants in each waistline and

triglyceride phenotype group. In general, compared with other triglyceridaemic–waist phenotypes, people with IFG and a hypertriglyceridaemic–waist phenotype, i.e. central obesity with high triglyceride level, were more likely to be male. They also spent less time on MVPA.

After a mean follow-up of 6.5 months (SD 4.7 months), 405 (36.8%) individuals with IFG had progressed to diabetes according to FPG, HbA_{1c} or 2h-OGTT criteria (Table 2). Compared with other triglyceridaemic–waist phenotypes, participants with central obesity and high triglyceride levels had the highest diabetes incidence under FPG, HbA_{1c} and 2h-OGTT definitions, respectively.

Table 3 shows the association between diabetes incidence and the triglyceridaemic–waist phenotypes. There was a significant difference in survival distributions between different triglyceridaemic–waist phenotypes assessed by log-rank test ($P < 0.001$). The results in Table 3 show that the hypertriglyceridaemic–waist phenotype group had a significantly greater diabetes incidence than the reference category in Model 1 [hazard ratio (HR) 1.630, 95% CI 1.210 – 2.196; $P = 0.001$]. After adjustment for other covariates and confounders, the trends were still significant (Model 2: HR 1.616, 95% CI 1.198–2.179; $P = 0.002$; Model 3: HR 1.581, 95% CI 1.172–2.134; $P = 0.003$). There were no significant associations between isolated central obesity or isolated high triglyceride level and diabetes incidence at follow-up in any of the models. A plot of the survival curves is shown in Fig. 1. Individuals with the hypertriglyceridaemic–waist phenotype had significantly earlier onset of diabetes than the other triglyceridaemic–waist groups.

Discussion

In this cohort study of Chinese people with IFG, the hypertriglyceridaemic–waist phenotype, i.e. central obesity with a high triglyceride level, was associated with a higher risk of diabetes incidence, independent of measured confounders and physical activity level. This association was significant when diabetes was defined by FPG, 2h-OGTT or HbA_{1c}. Our findings suggest that triglyceridaemic–waist phenotypes might be used as a simple tool to predict the risk of diabetes among people with IFG attending primary care clinics.

The association between hypertriglyceridaemic–waist phenotype and risk of diabetes is in accordance with several previous studies [17,18,22]. A cohort study among Chinese urban adults showed that hypertriglyceridaemic–waist phenotype increased the risk of diabetes in both men (HR 4.46, 95% CI 1.88–10.60) and women (HR 4.64, 95% CI 1.20–17.97) [17]. In another longitudinal study of elderly men aged > 70 years, the hypertriglyceridaemic–waist phenotype was also associated with a more than fourfold increased risk of incident diabetes [relative risk (RR) 4.64, 95% CI 1.61–13.4] [22]. Additionally, a similar study conducted in Asian–Indian men with impaired glucose tolerance revealed that the hypertriglyceridaemic–waist phenotype was independently associated with incident diabetes (HR 1.49, 95% CI 1.01–2.21) [18]. Our study and the one conducted on impaired glucose tolerance [18] had a smaller effect size than studies conducted in a relatively healthier population [17,22]. This may be because the populations with IFG or impaired glucose tolerance already had impaired glucose metabolism. Therefore, they might develop diabetes because of the impaired glucose metabolism, regardless of their hypertriglyceridaemic–waist phenotype.

There are several possible mechanisms underlying the association between hypertriglyceridaemic–waist phenotype and risk of diabetes. First, in our study, people with IFG and the hypertriglyceridaemic–waist phenotype tended to have less MVPA per day and

higher BMI, both of which are well-established modifiable risk factors for diabetes [9,23]. Second, the hypertriglyceridaemic–waist phenotype was found to be associated with increased insulin resistance and decreased insulin sensitivity [22], which could increase the risk of developing diabetes due to the dysfunction of β cell. In addition, inflammation markers, such as high-sensitive C-reactive protein (hs-CRP) and interleukin 6, could increase the risk of diabetes [24]. Although a previous study [25] has shown that both central obesity and elevated triglyceride levels are associated with increased levels of inflammation markers and decreased levels of adiponectin, an insulin-sensitizing and anti-inflammatory adipokine in adipose tissues, the association between hypertriglyceridaemic–waist phenotype and risk of diabetes is plausible.

In modern societies, unhealthy lifestyles, such as sedentary behaviours, limited physical activity and unhealthy eating habits dramatically increase the prevalence of central obesity and hypertriglyceridaemia [26,27]. Although several studies have demonstrated that the hypertriglyceridaemic–waist phenotype could identify individuals at high risk of developing diabetes in the general population [17], it is not feasible and cost-effective to screen waist circumference and triglyceride level for everyone. In addition, even though people with IFG represent a group with a high risk of developing diabetes and are usually encountered in primary care clinics, there are limited resources to intervene with every individual with IFG to prevent or delay the development of diabetes due to its high prevalence [6]. By contrast, our study highlighted the possibility of screening for the hypertriglyceridaemic–waist phenotype to identify individuals with IFG that were of increased risk of developing diabetes. This might serve as a potentially time- and cost-saving strategy to allocate resources to them to decrease the incident diabetes.

Our study exhibits several strengths, including the cohort design and relative large sample size of people with IFG, a group with high susceptibility to develop diabetes. We also used

standardized measures across different participating clinics, which minimized measurement errors. In addition, our results were validated under different methods of diagnosing diabetes, suggesting the robustness of the findings. Some potential limitations of our study merit discussion. First, our study included individuals with IFG from public primary care clinics. The generalizability to other populations or medical settings, such as those from private clinics or hospitals, deserved further discussion. Second, the follow-up period was short. However, the follow-up test for each participant was conducted during regular appointments to monitor their chronic conditions in primary care clinics. It reflected the true situation in primary care. Third, participants were recruited solely based on their FPG level, regardless of their HbA_{1c} and 2h-OGTT results at baseline, possibly leading to an overestimation of the incidence of diabetes at follow-up. Again, this was the true primary care situation in Hong Kong, where the FPG test is the most widely used method to screen for diabetes due to its low cost and convenience [2]. Fourth, a previous study has suggested that the association between hypertriglyceridaemic–waist phenotype and diabetes might be mediated through insulin resistance [18], something we were unable to confirm this study. In addition, follow-up assessments were conducted during participants' routine visits to the participating clinics to manage their chronic conditions. The time to diabetes onset is actually interval censored. Finally, several novel risk factors for diabetes, such as uric acid [28] and fetuin-A [29], have been recognized recently. Our study did not include measurements of these risk factors.

In conclusion, in a cohort study among people with IFG, we found that those with the hypertriglyceridaemic–waist phenotype were more likely to progress to diabetes than individuals with normal waist circumference and triglyceride, or people with isolated central obesity or isolated high triglyceride levels, indicating that simultaneous measurement of waist circumference and triglyceride could serve as a simple screening tool to identify individuals with IFG who are at high risk of developing diabetes in primary care clinics. Our study

underscored the importance of measuring waist circumference and triglyceride level in primary care clinics. However, the cost-effectiveness and generalizability of such a tool should be evaluated in future studies.

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FIGURE 1 Survival curve for the people with impaired fasting glucose who remained free of diabetes, stratified by triglyceridaemic–waist phenotypes.

Table 1. Comparison of baseline demographic and clinical characteristics by the triglyceridaemic-waist phenotypes

	Normal waist circumference and triglyceride level	Isolated central obesity	Isolated high triglyceride level	Central obesity with high triglyceride level	P-value†
n	252	518	80	251	−
Demographic and lifestyle factors					
Mean age (years)	65.5 (9.1)	63.7 (8.8)	64.7 (8.9)	63.6 (8.8)	0.035*
Male sex, *n* (%)	163 (64.7)	234 (45.2)	42 (52.5)	98 (39.0)	< 0.001*
Family history of diabetes, *n* (%)	80 (31.7)	173 (33.4)	29 (36.3)	82 (32.7)	0.894
Smoking status, *n* (%)					
Never smoker	186 (73.8)	422 (81.5)	64 (80.0)	207 (82.5)	0.146
Ex-smoker	43 (17.1)	71 (13.7)	12 (15.0)	30 (12.0)	
Current smoker	23 (9.1)	25 (4.8)	4 (5.0)	14 (5.6)	
Physical activity level					
MVPA (hours/day)	0.89 (0.93)	0.78 (0.79)	0.71 (0.77)	0.71 (0.76)	0.070
Sedentary time (hours/day)	5.09 (2.72)	5.07 (2.78)	5.15 (2.93)	5.16 (2.77)	0.982
Clinical/biochemical measures					
Mean BMI (kg/m^2)	22.5 (2.2)	27.2 (3.7)	22.7 (1.9)	27.7 (3.5)	< 0.001*
BMI group, *n* (%)					< 0.001*
Overweight	86 (34.1)	94 (18.1)	23 (28.8)	38 (15.1)	
Obesity	27 (10.7)	370 (71.4)	9 (11.3)	195 (77.7)	
Waist circumference (cm)					
Female	83.3 (4.8)	91.0 (8.0)	75.5 (3.0)	91.4 (7.9)	< 0.001*
Male	83.3 (4.8)	97.0 (6.1)	85.1 (3.9)	98.8 (7.5)	< 0.001*
Systolic BP (mmHg)	140.7 (16.1)	142.1 (15.8)	140.7 (15.0)	142.6 (15.4)	0.483
Diastolic BP (mmHg)	82.7 (9.2)	83.9 (9.7)	83.3 (9.5)	84.7 (9.3)	0.102
Mean FPG at recruitment (mmol/l)	6.0 (0.3)	6.1 (0.4)	6.0 (0.3)	6.1 (0.4)	0.003*

Total cholesterol (mmol/l)	4.9 (0.9)	4.9 (0.9)	5.3 (1.0)	5.3 (1.0)	< 0.001*
Triglycerides (mmol/l)	1.0 (0.3)	1.1 (0.3)	2.3 (0.6)	2.5 (0.9)	< 0.001*
HDL-cholesterol (mmol/l)	1.5 (0.4)	1.4 (0.3)	1.1 (0.3)	1.1 (0.3)	< 0.001*
LDL-cholesterol (mmol/l)	2.9 (0.8)	3.0 (0.8)	3.1 (0.9)	3.1 (0.9)	0.011*

MVPA, moderate-to-vigorous physical activity.

Normal waistline: < 80 cm in women; < 90 cm in men; central obesity: ≥ 80 cm in women, ≥ 90c m in men; normal triglyceride level: < 1.7 mmol/l; high triglyceride level: ≥ 1.7 mmol/l.

Between-group differences were compared using one-way ANOVA test for continuous data and χ^2 test for categorical variables.

*

†P-values were derived from either ANOVA test or χ^2 test, where appropriate.

Table 2. Comparison of the diabetes incidence rates by triglyceridaemic–waist phenotypes

Diabetes incidence	Normal waist circumference and triglyceride level	Isolated central obesity	Isolated high triglyceride level	Central obesity with high triglyceride level	P-value†
Any criteria, n (%)	71 (28.2)	179 (34.6)	24 (30.0)	131 (52.2)	< 0.001*
FPG criteria, n (%)	6 (2.4)	13 (2.5)	2 (2.5)	19 (7.6)	0.002*
HbA$_{1c}$ criteria, n (%)	19 (7.5)	64 (12.4)	9 (11.3)	48 (19.1)	0.001*
2h-OGTT criteria, n (%)	66 (26.2)	159 (30.7)	22 (27.5)	114 (45.4)	< 0.001*

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

Diabetes was defined according to the American Diabetes Association diagnostic criteria for diabetes [3] if the participant met any of the three definitions: FPG, ≥ 7.0 mmol/l; HbA$_{1c}$, 47.5 mmol/mol (≥ 6.5%); and 2h-OGTT, ≥ 11.1 mmol/l.

The incidence rates of diabetes in different triglyceridaemic–waist phenotypes were compared using χ^2 test.

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†P-values were derived from χ^2 test.

Table 3. Association of the triglyceridaemic–waist phenotypes with DM incidence

	Normal waist circumference and triglyceride level	Isolated central obesity	Isolated high triglyceride level	Central obesity with high triglyceride level
Model 1				
HR (95% CI)	Reference	1.185 (0.892, 1.573)	1.570 (0.984, 2.506)	1.630 (1.210, 2.196)
P-value	–	0.241	0.059	0.001*
Model 2				
HR (95% CI)	Reference	1.185 (0.891, 1.576)	1.585 (0.993, 2.530)	1.616 (1.198, 2.179)
P-value	–	0.242	0.054	0.002*
Model 3				
HR (95% CI)	Reference	1.176 (0.885, 1.563)	1.569 (0.982, 2.506)	1.581 (1.172, 2.134)
P-value	-	0.263	0.060	0.003*

HR, hazard ratio; CI, confidence interval

Diabetes was defined according to the American Diabetes Association diagnostic criteria for diabetes [3] if the participant met any of the three definitions: fasting plasma glucose, ≥ 7.0 mmol/l; HbA_{1c}, ≥ 47.5 mmol/mol ($\geq 6.5\%$); and 2 h-oral glucose tolerance test, ≥ 11.1 mmol/l.

Multivariable Cox proportional hazards regressions were established. Model 1 adjusted for age, sex and baseline FPG. Model 2 further adjusted for family history, smoking status and systolic BP. Model 3 further adjusted for MVPA and sedentary time.

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