

# Predictive Value of GAD Antibody for Diabetes in Normal Chinese Adults: A Retrospective Cohort Study in China

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**Purpose:** To investigate the prevalence of GAD antibody (GADA) in the general adult population and to evaluate its predictive value for diabetes in China.

**Patients and Methods:** We searched the PUMCH-HM database and identified 36,731 adult subjects with GADA test results from 2012 to 2015. We then established a retrospective cohort of 4835 nondiabetic subjects at baseline with complete annual health evaluation records through 2019. The median follow-up time was 4.8 (3.0–7.3) years.

**Results:** The overall prevalence of GADA was 0.53% and was higher in diabetic subjects (1.25%) than in nondiabetic subjects (0.47%). We found a decrease in baseline body mass index (BMI) from the GADA- to GADA<sub>high</sub> subgroups among baseline diabetic and pre-diabetic patients and also those who developed diabetes later in the cohort study. A total of 136 subjects (2.8%) developed diabetes after a median follow-up of 3.5 years. For GADA<sup>+</sup> participants, BMI was not associated with the risk for diabetes. In the Cox regression model, the GADA<sub>low</sub> and GADA<sub>high</sub> exhibited 2.63-fold and 4.16-fold increased risk for diabetes, respectively. This increased risk for diabetes by GADA-positivity is only found in male adults (HR 4.55, 95% CI 2.25–9.23).

**Conclusion:** GADA has a low prevalence in China but is associated with a 2.63–4.16-fold increased risk for diabetes.

**Keywords:** autoimmune diabetes, glutamic acid decarboxylase antibody, latent autoimmune diabetes in adults, obesity, prevention

## Introduction

The prevalence of diabetes in China has increased dramatically in the last three decades from 1% in 1980 to 12.8% in 2017.<sup>1,2</sup> China had the largest number of adults with diabetes in 2019 and is estimated to keep as rank 1 in 2030.<sup>3</sup> A better understanding of the factors contributing to the diabetes epidemic is crucial for prevention and intervention strategies. The etiology, epidemiology and prevention of type 2 diabetes have drawn enormous attention from Chinese clinicians, while little effort has been made regarding autoimmune diabetes in the adult Chinese population. A few studies have indicated that autoimmune diabetes in adults is much more common than originally thought in China. Most cases of new onset type 1 diabetes in China occurred among adults,<sup>4</sup> and 5.9% of newly diagnosed type 2 diabetes patients were actually latent autoimmune diabetes in adults (LADA) according to the LADA China Study.<sup>5</sup> Considering the large population, there are likely a large number of autoimmune diabetes patients among Chinese adults.

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It has been found that an increasing number of new autoimmune diabetes cases occur during adulthood.<sup>6</sup> With the destruction of pancreatic islet beta cells, autoimmune diabetes in adults follows a different clinical course and may quickly progress to insulin-dependent diabetes. Autoantibodies against beta cells include glutamic acid decarboxylase antibody (GADA), insulin autoantibody (IAA), insulinoma-associated antigen-2 autoantibody (IA-2A) and zinc transporter-8 autoantibody (ZnT8A). Among these antibodies, GADA is the most common marker in both adult-onset type 1 diabetes and LADA patients.<sup>7,8</sup>

It has been reported that autoimmune antibodies may be present years before disease onset,<sup>9,10</sup> indicating that there is a prediabetic period in which the disease could be identified before clinical onset through antibody screening in a healthy population. However, there are only a few studies regarding the prevalence of autoantibodies in the general adult population,<sup>11,12</sup> and the previous results of the predictive value of GADA in adults are not consistent.<sup>13,14</sup> In China, no data on the predictive role of GADA for diabetes are available because no cross-sectional or longitudinal study has been performed in nondiabetic people. Considering the previously reported ethnic differences in autoimmune diabetes prevalence,<sup>4,5,15</sup> such studies in China are necessary.

In this study, we investigated the prevalence of GADA in normal Chinese adults and established a 7-year retrospective cohort of baseline nondiabetic adults. We aimed to assess the necessity of screening GADA in normal adults and the impact of autoantibodies in the general population in China.

## Patients and Methods

### Data Source

The data were collected from the Peking Union Medical College Hospital-Health Management (PUMCH-HM) database. This database was established in 2008 mainly to keep records of annual health evaluations of urban residents in Beijing. By 31-12-2019, the database had collected 844,158 annual health evaluation records of 462,375 participants. These annual health evaluations were paid for by the participants themselves or by their employers since they were not covered by medical insurance in China. All clinical data were collected during a half-day clinic visit. Participants had their medical history reviewed by an internal physician, and previous diagnoses and medicines used were recorded. Blood

samples were drawn after the patient had been fasting for at least 8 hours. All the participants were invited to undergo their regular annual health evaluation at PUMCH every year. Clinical data were collected at each visit.

### Study Population

We searched the database from 2012 to 2015 and identified 36,731 adult subjects ( $\geq 18$  years old) with GADA test results and complete clinical records. For the 34,108 nondiabetic subjects, we further searched the database for their records from 2012 to 2019 and identified those who continued their sequential annual health evaluation in PUMCH and had complete medical records through 2019. Through this process, we assembled a retrospective cohort of 4835 nondiabetic participants at baseline. The date of incident diabetes development was defined as the date of their clinic visit at which they first met the definition of diabetes. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Peking Union Medical College Hospital Ethics Committee (No. S-K1368). Informed consent was obtained from all patients for being included in the study.

### Definition of Diabetes and Prediabetes

We used the 2020 American Diabetes Association (ADA) definition for diabetes and prediabetes.<sup>16</sup> The diabetes diagnostic criteria were defined as meeting any one or a combination of the following: fasting plasma glucose (FPG)  $\geq 7.0$  mmol/L, HbA1c  $\geq 6.5\%$ , or a self-reported previous diagnosis by health care professionals. The prediabetes diagnostic criteria were defined as FPG 5.6 mmol/L to 6.9 mmol/L, or HbA1C 5.7–6.4%, and no previous diagnosis of diabetes. Oral glucose tolerance test (OGTT) data were not available since it is not practical to conduct during a half-day clinic visit for normal participants.

### Test of GADA

GADA was analyzed in the PUMCH laboratory by Enzyme-Linked Immunosorbent Assay, ELISA (EUROIMMUN AG, Germany). The assay has a cut-off of 10 IU/mL according to the manufacturer's instructions (sensitivity of 92%, specificity of 98% for 150 Diabetes Autoantibody Standardization Program [DASP, 2003] serums from USA) and has a maximum value of 2000 IU/mL. Positive samples were reassessed to confirm their positivity.

## Anthropometric and Metabolic Measurements

The subjects' weight and height were measured by a body composition analyzer. BMI was calculated as weight (kg) divided by squared height ( $\text{m}^2$ ). Overweight and obesity were defined as  $\text{BMI} \geq 24 \text{ kg/m}^2$  and  $\text{BMI} \geq 28 \text{ kg/m}^2$  according to the 2016 Chinese consensus.<sup>17</sup> Central obesity (CO) was defined as waist circumference  $\geq 90 \text{ cm}$  for men and  $\geq 80 \text{ cm}$  for women. Blood pressure was measured twice by experienced nurses, and the mean value was recorded. Blood samples were drawn after the patient had been fasting for at least 8 hours for the measurement of FPG, serum total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and uric acid. Whole blood was collected for HbA1c measurement. All samples with abnormal results were measured in duplicate.

## Statistical Analysis

All statistical analyses were performed using IBM SPSS statistics software version 26 (IBM, Armonk, NY, USA). Data are given as numbers and percentages for categorical data and as the mean (standard deviation (SD)) for continuous data. Triglyceride was log10-transformed to account for the skewed distribution. The chi-square test (Pearson) was used to compare differences in categorical data. *t*-test and single-factor analysis of variance (ANOVA) was used to test the differences in continuous data between two groups or among more than two groups. Cox's proportional hazard regression was used to assess the cumulative risk for incident diabetes after proportional hazard assumption tested. Sex, age, BMI (as normal, overweight and obesity), prediabetes and GADA status were included in the multivariate model. A two-tailed *P* value of 0.05 was considered to be significant.

## Results

### GADA Prevalence at Baseline

The mean age of the 36,731 adult subjects identified was 44 (18–94) years, and 19,542 (53.2%) participants were male. A total of 2623 (7.1%) participants were diabetic at the baseline, 9886 (26.9%) participants met the criteria of prediabetes. GADA was positive in 195 (0.53%) participants, 94 male and 101 female,  $P=0.161$ . The frequency of GADA was significantly elevated in diabetic participants than in nondiabetic ones ( $n=33$ , 1.25% vs  $n=162$ , 0.47% respectively,  $P<0.001$ ).

For the  $\text{GADA}^+$  subjects, the median GADA titer was 51 IU/mL (lower quarter 21 IU/mL, higher quarter 199 IU/mL). We defined  $\text{GADA}_{\text{high}}$  as the highest quartile ( $\geq 199 \text{ IU/mL}$ ) and  $\text{GADA}_{\text{low}}$  as the lower three quartiles ( $<199 \text{ IU/mL}$ ).

## Clinical Parameter Differences According to GADA Status

Table 1 presents demographic and clinical characteristics of participants at baseline according to their GADA status in participants with normal glucose, prediabetes and diabetes. For the 2623 subjects with baseline diabetes, BMI, triglycerides and uric acid declined from the  $\text{GADA}^-$  to  $\text{GADA}_{\text{low}}$  to  $\text{GADA}_{\text{high}}$  subgroups (BMI  $26.83 \text{ kg/m}^2$ ,  $25.24 \text{ kg/m}^2$ ,  $24.11 \text{ kg/m}^2$  respectively,  $P=0.008$ ; triglycerides  $1.86 \text{ mmol/L}$ ,  $1.35 \text{ mmol/L}$ ,  $1.10 \text{ mmol/L}$ , respectively,  $P=0.009$ ; uric acid  $337 \text{ } \mu\text{mol/L}$ ,  $281 \text{ } \mu\text{mol/L}$ ,  $241 \text{ } \mu\text{mol/L}$ , respectively,  $P<0.001$ ). The trend of BMI decline was also found in prediabetic participants ( $25.82 \text{ kg/m}^2$ ,  $25.13 \text{ kg/m}^2$ ,  $23.74 \text{ kg/m}^2$  respectively,  $P=0.024$ ), but not in participants with normal glucose. For  $\text{GADA}^+$  subjects, no difference of BMI was found between diabetic and nondiabetic groups ( $24.13 [3.62] \text{ kg/m}^2$  vs  $25.03 [2.75] \text{ kg/m}^2$ ,  $P=0.180$ ).

## Incident Diabetes at Follow-Up

Of the 34,108 nondiabetic subjects, 4835 (94  $\text{GADA}^+$ ) continued their sequential annual health evaluation in PUMCH and had full medical records through 2019. The median follow-up time was 4.8 (3.0–7.3) years. A total of 136 subjects (92 male, 44 female) developed diabetes during a median follow-up of 3.5 (0.1–7.0) years after the baseline examination. Table 2 presents demographic and clinical characteristics at baseline of all the 4835 participants and of the 136 ones with incident diabetes according to their GADA status. For the 136 subjects who developed diabetes, baseline BMI decreased significantly from  $\text{GADA}^-$  to  $\text{GADA}_{\text{low}}$  to  $\text{GADA}_{\text{high}}$  ( $26.57 \text{ kg/m}^2$ ,  $26.36 \text{ kg/m}^2$ ,  $22.11 \text{ kg/m}^2$ , respectively,  $P=0.016$ ). The median age of diabetes diagnosis was reduced from  $\text{GADA}^-$  to  $\text{GADA}_{\text{low}}$  to  $\text{GADA}_{\text{high}}$  but not significantly (55 years old, 53 years old, and 45 years old, respectively,  $P=0.174$ ).

The incidence of diabetes development in the different GADA subgroups was 123 (2.6%) among  $\text{GADA}^-$  patients, 8 (12.1%) among  $\text{GADA}_{\text{low}}$  patients and 5 (17.9%) among  $\text{GADA}_{\text{high}}$  patients,  $P<0.001$ . More than one-third of the participants (5 of 14) with  $\text{GADA} \geq 669 \text{ IU/mL}$  developed diabetes. We contacted the 13 (9 male, 4 female) participants with incident diabetes in  $\text{GADA}^+$

**Table 1** Demographic and Clinical Characteristics of 36,731 Participants at Baseline According to Their GADA Status

GADA Status	Normal Glucose Metabolism (n=24,222)				Prediabetes (n=9886)				Diabetes (n=2623)			
	Negative	Low	High	P	Negative	Low	High	P	Negative	Low	High	P
n	24,117	79	26		9829	40	17		2590	27	6	
Age (years)	42 (12)	43 (10)	41 (10)	0.686	49 (12)	51 (11)	50 (11)	0.655	54 (11)	53 (17)	51 (12)	0.753
Male, n (%)	10,863 (45.0)	30 (38.0)	8 (30.8)	0.156	6632 (67.5)	27 (67.5)	10 (58.8)	0.749	1953 (75.4)	16 (59.3) <sup>a</sup>	3 (50.0) <sup>a</sup>	0.056
BMI (kg/m <sup>2</sup> )	23.68 (3.46)	23.82 (3.26)	23.77 (3.86)	0.930	25.82 (3.41)	25.13 (4.35)	23.74 (2.64)	0.024	26.83 (3.40)	25.24 (2.78)	24.11 (2.67)	0.008
CO <sub>2</sub> , n (%)	5122 (33.8)	15 (46.9)	1 (10.0) <sup>b</sup>	0.083	3350 (55.8)	8 (40.0)	5 (50.0)	0.342	1199 (70.2)	9 (52.9)	1 (50.0)	0.249
HT, n (%)	1562 (6.5)	6 (7.6)	0	0.375	1738 (17.7)	31 (22.5)	4 (23.5)	0.598	918 (35.4)	5 (18.5)	1 (16.7)	0.119
FPG (mmol/L)	5.0 (0.3)	5.0 (0.3)	4.9 (0.3)	0.252	5.8 (0.4)	5.7 (0.5)	5.6 (0.4)	0.281	8.5 (2.6)	8.9 (2.5)	8.5 (2.4)	0.666
HbA1c (%)	5.3 (0.3)	5.3 (0.3)	5.2 (0.3)	0.515	5.8 (0.4)	5.9 (0.2)	5.7 (0.3) <sup>b</sup>	0.268	7.3 (1.4)	7.7 (1.7)	8.2 (2.0)	0.262
LDL (mmol/L)	2.95 (0.77)	3.02 (0.79)	2.72 (0.48)	0.226	3.23 (0.83)	3.16 (0.81)	3.53 (0.51)	0.274	3.14 (0.92)	2.98 (0.72)	3.39 (0.95)	0.531
HDL (mmol/L)	1.40 (0.37)	1.40 (0.33)	1.53 (0.38)	0.197	1.26 (0.34)	1.29 (0.31)	1.31 (0.29)	0.753	1.14 (0.30)	1.31 (0.47) <sup>a</sup>	1.27 (0.25)	0.014
Lg TG	0.04 (0.24)	0.05 (0.20)	-0.02 (0.24)	0.447	0.18 (0.24)	0.22 (0.31)	0.16 (0.20)	0.493	0.27 (0.28)	0.13 (0.29) <sup>a</sup>	0.04 (0.16)	0.009
UA (μmol/L)	308 (86)	296 (74)	269 (86) <sup>a, b</sup>	0.030	350 (88)	350 (96)	333 (89)	0.729	337 (86)	281 (88) <sup>a</sup>	241 (69) <sup>a</sup>	<0.001
sBP (mmHg)	115.4 (15.5)	115.9 (13.6)	111.2 (13.0)	0.395	124.4 (17.0)	127.8 (17.6)	126.8 (16.6)	0.378	129.3 (17.2)	126.8 (22.6)	130.5 (29.7)	0.749

**Notes:** GADA high was defined as the highest quartile ( $\geq 199$  IU/mL), and GADA low was defined as the lower three quartiles ( $< 199$  IU/mL). Data are given as numbers and percentages for categorical data and as the mean (SD) for continuous data. <sup>a</sup> $p < 0.05$  comparing with GADA negative; <sup>b</sup> $p < 0.05$  comparing with GADA low.

**Abbreviations:** CO, central obesity; HT, hypertension; TG, triglycerides (mmol/L); UA, uric acid; sBP, systolic blood pressure.

**Table 2** Demographic and Clinical Characteristics of All the 4835 Participants in the Retrospective Cohort and 136 Ones with Incident Diabetes According to Their GADA Status

GADA Status	All (n=4835)				Incident Diabetes (n=136)			
	Negative	Low	High	P	Negative	Low	High	P
n	4741	66	28		123	8	5	
Age (years)	43 (12)	48 (11) <sup>a</sup>	45 (11)	0.007	51 (11)	50 (11)	42 (8)	0.194
Male, n (%)	2493 (52.6)	23 (34.8)	8 (28.6)	0.001	83 (67.5)	7 (87.5)	2 (40.0)	0.203
BMI (kg/m <sup>2</sup> )	23.84 (3.41)	24.27 (3.54)	23.61 (3.25)	0.560	26.57 (3.27)	26.36 (4.99)	22.11 (1.62) <sup>a</sup>	0.016
CO, n (%)	1018 (32.0)	12 (50.0)	4 (26.7)	0.154	60 (66.7)	3 (75.0)	1 (50.0)	0.829
HT, n (%)	376 (7.9)	8 (12.1)	1 (3.6)	0.317	34 (27.6)	0	0	0.091
Prediabetes, n (%)	1368 (28.9)	23 (34.8)	11 (39.3)	0.275	112 (91.1)	8 (100.0)	4 (80.0)	0.460
FPG (mmol/L)	5.2 (0.5)	5.3 (0.5)	5.2 (0.5)	0.859	6.1 (0.5)	5.9 (0.5)	5.3 (0.7) <sup>a</sup>	0.002
HbA1c (%)	5.4 (0.4)	5.6 (0.4) <sup>a</sup>	5.4 (0.5)	0.077	5.8 (0.3)	6.0 (0.2)	5.6 (0.4) <sup>b</sup>	0.178
LDL (mmol/L)	3.02 (0.78)	3.10 (0.82)	3.04 (0.60)	0.700	3.40 (0.77)	3.18 (0.79)	3.24 (0.42)	0.654
HDL (mmol/L)	1.41 (0.38)	1.34 (0.31)	1.47 (0.36)	0.225	1.24 (0.34)	1.16 (0.19)	1.38 (0.34)	0.527
Lg TG	0.06 (0.23)	0.10 (0.23)	0.06 (0.22)	0.354	0.23 (0.22)	0.22 (0.22)	0.04 (0.21)	0.163
UA (μmol/L)	322 (88)	310 (81)	274 (79) <sup>a, b</sup>	0.008	364 (78)	387 (79)	281 (29) <sup>a, b</sup>	0.042
sBP (mmHg)	116.6 (15.8)	121.3 (16.4) <sup>a</sup>	116.1 (17.1)	0.058	128.1 (17.5)	125 (17.0)	115 (11.0)	0.244

**Notes:** GADA high was defined as the highest quartile ( $\geq 199$  IU/mL), and GADA low was defined as the lower three quartiles ( $< 199$  IU/mL). Data are given as numbers and percentages for categorical data and as the mean (SD) for continuous data. <sup>a</sup> $P < 0.05$  comparing with GADA negative; <sup>b</sup> $P < 0.05$  comparing with GADA low.

**Abbreviations:** CO, central obesity; HT, hypertension; TG, triglycerides (mmol/L); UA, uric acid; sBP, systolic blood pressure.

group by phone calls to confirm their classification of diabetes and insulin uses. Three subjects with GADA<sub>high</sub> (GADA titer 669 IU/mL, 2000 IU/mL, 1224 IU/mL, respectively) were classified as having type 1 diabetes and started insulin therapy within six months. Only one subject was classified as LADA by his clinical physician and started insulin therapy one year after diagnosis.

Of the 1402 participants with prediabetes at baseline, 124 developed diabetes: 112 (8.2%) in GADA<sup>−</sup>, 8 (34.8%) in GADA<sub>low</sub> and 4 (36.4%) in GADA<sub>high</sub>,  $P < 0.001$ . Of the 3433 participants with normal glucose metabolism, 655 developed prediabetes (638 [18.9%] in GADA<sup>−</sup>, 12 [27.9%] in GADA<sub>low</sub>, 5 [29.4%] in GADA<sub>high</sub>,  $P = 0.157$ ), 12 developed diabetes (11 [0.3%] in GADA<sup>−</sup>, 1 [5.9%] in GADA<sub>high</sub> who diagnosed as type 1 diabetes).

## Clinical Parameter Differences According to Incident Diabetes

The comparison of clinical characteristics between participants with and without incident diabetes was presented in Table 3. For GADA<sup>−</sup> participants, those who developed

diabetes had significantly different clinical features in age, sex, BMI and all the metabolic parameters ( $P \leq 0.001$ ). For GADA<sup>+</sup> participants, we only found baseline prediabetes, male sex, and higher uric acid associated with incident diabetes.

## Cox Regression of Incident Diabetes

In the Cox's proportional hazard regression model, increased risk of incident diabetes was associated with GADA positivity (HR: GADA<sub>low</sub> 2.63 [95% CI 1.26–5.51], GADA<sub>high</sub> 4.16 [95% CI 1.69–10.25],  $P = 0.004$ ), higher baseline BMI (HR: overweight 1.77 [95% CI 1.17–2.70], obesity 2.42 [95% CI 1.50–3.90],  $P = 0.001$ ), prediabetes (HR: 18.35 [95% CI 9.99–33.70],  $P < 0.001$ ) and older age (HR: 1.02 [95% CI 1.00–1.03],  $P = 0.037$ ). We also found an interaction between GADA positivity and male sex ( $P < 0.001$ ) in the regression. So we further performed Cox's regression in male and female subgroups and found that GADA positivity increased the risk for incident diabetes only in male (HR: 4.55 [95% CI 2.25–9.23],  $P < 0.001$ ) but not in female ( $P = 0.368$ ), as presented in Figure 1.

**Table 3** Comparison of Demographic and Clinical Characteristics of Participants in the Retrospective Cohort According to with/without Incident Diabetes

Incident Diabetes	GADA Negative (n=4741)			GADA Positive (n=94)		
	No	Yes	P	No	Yes	P
n	4618	123		81	13	
Age (years)	43 (12)	51 (11)	<0.001	47 (11)	47 (11)	0.977
Male, n (%)	2410 (52.2)	83 (67.5)	0.001	22 (27.2)	9 (69.2)	0.003
BMI (kg/m <sup>2</sup> )	23.77 (3.38)	26.57 (3.27)	<0.001	23.97 (3.28)	24.73 (4.48)	0.464
CO, n (%)	958 (31.0)	60 (66.7)	<0.001	12 (36.4)	4 (66.7)	0.165
HT, n (%)	342 (7.4)	34 (27.6)	<0.001	9 (11.1)	0 (0)	0.206
Prediabetes, n (%)	1256 (27.2)	112 (91.1)	<0.001	22 (27.2)	12 (92.3)	<0.001
FPG (mmol/L)	5.2 (0.4)	6.1 (0.5)	<0.001	5.2 (0.5)	5.6 (0.6)	0.002
HbA1c (%)	5.4 (0.4)	5.8 (0.3)	<0.001	5.5 (0.4)	5.9 (0.3)	0.012
LDL (mmol/L)	3.01 (0.78)	3.40 (0.78)	<0.001	3.07 (0.77)	3.20 (0.65)	0.551
HDL (mmol/L)	1.42 (0.38)	1.24 (0.34)	<0.001	1.40 (0.33)	1.25 (0.27)	0.113
Lg TG	0.55 (0.23)	0.23 (0.22)	<0.001	0.08 (0.23)	0.15 (0.23)	0.312
UA (μmol/L)	321 (88)	364 (78)	<0.001	292 (79)	346 (83)	0.025
sBP (mmHg)	116.3 (15.6)	128.2 (17.5)	<0.001	119.5 (17.0)	121.2 (15.3)	0.732

**Note:** Data are given as numbers and percentages for categorical data and as the mean (SD) for continuous data.

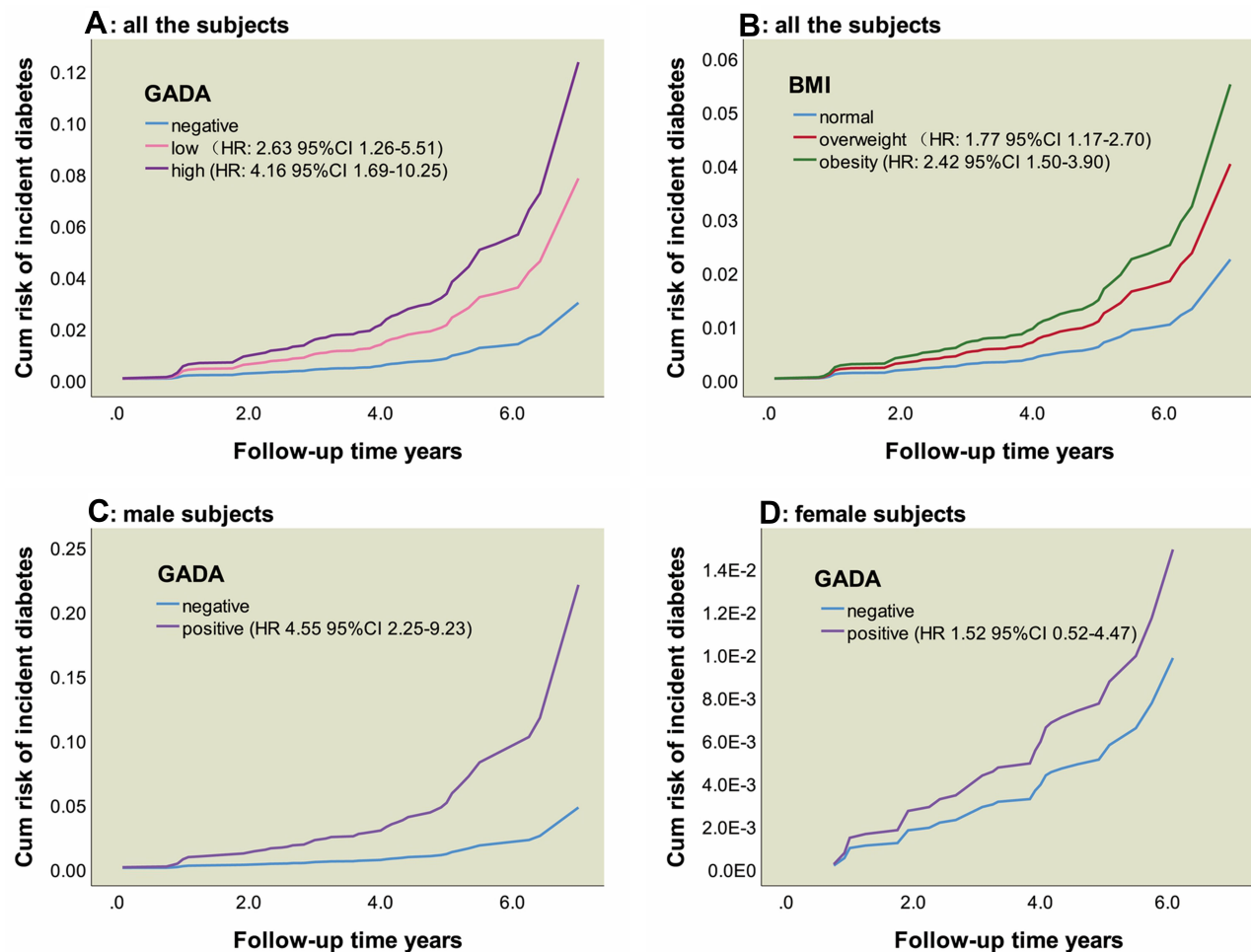
**Abbreviations:** CO, central obesity; HT, hypertension; TG, triglycerides (mmol/L); UA, uric acid; sBP, systolic blood pressure.

## Discussion

Our study is by far the largest GADA study in the general adult population worldwide and the first one conducted in China. We observed a low prevalence of GADA in Chinese adults (0.53%) compared with the findings of other reports from Norway,<sup>18</sup> Italy,<sup>19</sup> the Netherlands,<sup>20</sup> Finland,<sup>13,21</sup> the United States,<sup>11,12</sup> and Japan,<sup>22</sup> in which the frequencies range from 1% to 5.9% in the general adult population. The low prevalence in China is consistent with the fact that the incidence of type 1 diabetes in Chinese children was among the lowest; the incidence is 0.1/100,000/year in China compared to 40.9/100,000/year in Finland,<sup>4,15</sup> and the frequencies of autoantibodies in type 2 diabetes patients are generally lower in Asians than in Caucasians.<sup>23</sup> The reasons for this ethnic difference may be related to the distinct genetic background of Chinese individuals and differences in environmental factors. GADA was more frequently found in diabetic subjects than in nondiabetic ones, which was also reported in previous studies.<sup>11,19–21</sup>

Autoantibodies might be present 10–20 years before autoimmune diabetes diagnosis.<sup>9,10</sup> There is no doubt that

autoantibodies predict the incidence of type 1 diabetes in children.<sup>24</sup> However, inconsistent results have been found regarding the predictive ability of GADA for diabetes in adults, so its predictive value in the normal adult population is controversial. Previous studies in the general population were limited, and some of the studies had very small samples. In the American Diabetes Prevention Program, GADA was found to not be a predictive factor in 3050 individuals after 3.2 years of follow-up.<sup>12</sup> However, the participants in that study were actually at high risk for diabetes and were not normal adults. The other three studies with negative predictive results in northern Italy,<sup>19</sup> the USA<sup>25</sup> and Sweden<sup>26</sup> are limited by their small GADA<sup>+</sup> samples. The present study showed that GADA<sub>high</sub> was associated with a 4.16-fold increased risk, and GADA<sub>low</sub> was associated with a 2.63-fold increased risk of diabetes among Chinese adults. One-third of the subjects with GADA $\geq$ 669 IU/mL developed diabetes. Similar results were found in two previous longitudinal studies conducted in Finland and Sweden, in which GADA positivity conferred a 4.9- to 6-fold increased risk of diabetes.<sup>13,14</sup> Nevertheless, considering the low



**Figure 1** Cumulative (Cum) incidence of diabetes among all the subjects and male/female subgroups.

**Notes:** (A and B) Cumulative incidence of diabetes among all the subjects; (C) Cumulative incidence of diabetes among male subjects; (D) Cumulative incidence of diabetes among female subjects.

prevalence of GADA reported in this study, the economic benefit of screening may not be significant in China.

81% of the epidemiology investigations about type 1 diabetes reported that the incidence in male adults was larger than that in female adults (male-to-female ratio 1.47), even in low-incidence countries such as China.<sup>27,28</sup> However the frequency of GADA did not vary between genders, either in our study or previous studies.<sup>5,18</sup> We found that the increased risk of diabetes by GADA-positivity is only limited in male adults. This result implicated that there might be a different mechanism of GADA promoting diabetes in male adults but possible explanation of this difference needs further researches.

Reports have indicated that individuals with high levels of autoantibodies have more type 1 diabetes-like phenotypes and that individuals with low levels of autoantibody positivity have more type 2 diabetes-like phenotypes.<sup>8</sup> In

our study, the three subjects who developed type 1 diabetes were all in the GADA<sub>high</sub> subgroup. All the other 10 GADA<sup>+</sup> patients with incident diabetes met the diagnostic criteria of LADA (>30 years old, autoimmune antibody positive, not requiring insulin treatment in 6 months), while only one of them was recognized by his clinical physician. In China, even in a city such as Beijing, which has well-developed medical resources, the knowledge of LADA is still limited, and autoantibody screening has not become a standard process in the diagnosis of diabetes. More attention is needed for autoimmune diabetes in adults in clinical practice in China.

Excessive weight is associated with insulin resistance and is a risk factor for type 2 diabetes. The role of excess weight in the progression of autoimmune diabetes is not clear. In our study, we found that GADA status did not stratify subjects with normal glucose by BMI, as shown in

the HUNT study.<sup>18</sup> However, for patients with diabetes or prediabetes, GADA<sup>+</sup> patients were thinner. This finding is consistent with previous reports from the United States and China that showed that among diabetic participants, being GADA positive was associated with a lower BMI.<sup>5,11</sup> We also found that in the subjects who develop diabetes later, GADA<sup>+</sup> subjects had reduced baseline BMI, as reported before.<sup>13</sup> These findings indicate that although GADA status did not stratify the general population with normal glucose, in those who will develop diabetes later, insulin resistance played a less important role in GADA<sup>+</sup> individuals, especially in those with high GADA titers.

The first genome-wide association study (GWAS) of LADA in 2018 showed that both the genetic variants predisposing individuals to type 1 diabetes and the polygenic predisposition to type 2 diabetes contribute to the genetic background of LADA.<sup>29</sup> Previous reviews concluded that obesity was associated with an increased risk of LADA, especially in patients with low GADA titers, from the results of HUNT and ESTRID cross-sectional studies.<sup>30,31</sup> However, in this study, BMI is not associated with the risk of diabetes for GADA<sup>+</sup> participants either in the baseline investigation or in the retrospective cohort study. The small number of incident diabetes in GADA<sup>+</sup> participants and limited follow-up time may affect the result. Further prospective investigations exploring the role of obesity in the progression of autoimmune diabetes are needed in the future.

Our study is limited by its retrospective design. The GADA test was not repeated during follow-up, and we know that GADA-positive status may be transient and that the fluctuation of GADA levels is associated with disease progression.<sup>9</sup> For the 13 patients with incident diabetes in GADA<sup>+</sup> group, we were not able to recall them back to the hospital for further classification of diabetes diagnosis due to the COVID-19. Our study is also limited in the context of extrapolation to the general Chinese population since it is a one-center study, and the participants were mostly citizens with high socioeconomic status from North China.

## Conclusion

GADA has a low prevalence in China but is associated with a 2.63–4.16-fold increased risk for diabetes. This increased risk for diabetes is only found in male adults but not in females. Among the participants with diabetes or prediabetes, GADA<sup>+</sup> ones were thinner than GADA<sup>−</sup> ones. BMI was not associated with the risk of diabetes in GADA<sup>+</sup> participants either in the baseline cross-sectional investigation or in the cohort study. Further prospective investigations

exploring the role of gender and obesity in the progression of autoimmune diabetes are needed.

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## Disclosure

The authors report no conflicts of interest in this work.

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