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Title Page

Association of Apolipoprotein B to A-I ratio with diabetes and prediabetes in Chinese subjects: a stratified random sampling based cross-sectional study

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Abstract

Objectives Apolipoprotein (Apo)B/ApoA-I ratio is a useful predictor of cardiovascular risk. However, the association between the ApoB/ApoA-I ratio and the risk of type 2 diabetes mellitus (T2DM) was still obscure. The aim of the study was to investigate the associations between the value of ApoB/ApoA-I ratio and the risk of T2DM, prediabetes in Chinese population and also assess the role of gender in these associations.

Participants and Methods A stratified random sampling design was used in this cross-sectional study including 264 men and 465 women with either normal glucose tolerance (NGT), prediabetes or T2DM. Serum Apo B, Apo A-I and other lipid and glycaemic traits were measured. Pearson's partial correlation and multivariable logistic analysis were used to evaluate the association between ApoB/ApoA-I ratio and the risk of T2DM, prediabetes.

Results The levels of ApoB/ApoA-I ratio were significantly increased across the stage of NGT, prediabetes and T2DM. Women showed higher levels of ApoB/ApoA-I ratio and ApoB than men in prediabetic and T2DM group, but not in NGT group. ApoB/ApoA-I ratio was closely related with TG, TC, HDL-C, LDL-C and other glycemic traits. Moreover, in women, the risk of diabetes and prediabetes in the top tertile of ApoB/ApoA-I ratio were 5.34- (95%CIs: 1.834-15.525) and 4.12-fold (95%CIs: 1.167-10.512) higher than in the bottom tertile respectively, after adjusting for potential confounding factors. However, the association was disappeared in men after adjusting for other factors.

Conclusions The level of ApoB/ApoA-I ratio showed a positive association with the risk of diabetes and prediabetes in Chinese women.

Strengths and limitations of this study

- This is an in-depth investigation of the association between ApoB/ApoA-I ratio and diabetes or prediabetes in Chinese population.
- Stratified random sampling ensured the equal chance for participant enrolment and the validity of results.
- Data collection and analysis were supported by trained survey team, which included researchers with differing areas of expertise and backgrounds.
- The cross-sectional design may not confirm the causality between ApoB/ApoA-I ratio and diabetes risk.
- Potential bias might be existed due to the single-centre design.

Keywords: apolipoprotein B; apolipoprotein A-I; type 2 diabetes; prediabetes; dyslipidemia

Introduction

Atherogenic dyslipidemia is a typical lipoprotein abnormality that including high levels of triglyceride (TG) -rich lipoproteins (mainly very low-density lipoprotein[VLDL]), low levels of high-density lipoprotein (HDL) as well as an elevated proportion of small dense low-density lipoprotein (sd-LDL) particles [1]. To

date, the evaluation of clinical relevance of atherogenic dyslipidemia has been focused on its role as an effective predictor of cardiovascular disease (CVD) rather than conventional lipid examinations. Apolipoproteins are important structural and functional proteins in lipoprotein particles, which take part in the transportation of lipids. Considering the circulating levels of apolipoproteins indicate the number of lipoprotein particles, the level of Apo-B may reflect the total number of potentially atherogenic particles, as it is contained in each LDL. Besides, the level of ApoA-I may present the number of HDL particles [2]. Thus, the ratio of apolipoproteins B and A-I (ApoB/ApoA-I) would be, theoretically, an ideal indicator for the atherogenic lipid disturbances and cardiovascular risk [3 4].

It is well established that atherogenic dyslipidemia is associated with T2DM and high risk of CVD in T2DM patients [5 6]. Moreover, the mortality rate of CVD in women with diabetes is higher than men [7]. However, the traditional lipid indices (e.g. elevated TG and decreased HDL) do not show gender difference in patients with diabetes. Since ApoB/ApoA-I ratio is an outstanding indicator of atherogenic dyslipidemia and CVD, the role of it in predicting diabetic risk was expected, particularly its gender effects. Previous studies demonstrated that ApoB/ApoA-I ratio may be a strong indicator of metabolic syndrome and insulin resistance in certain population [8-10]. Nevertheless, the associations of ApoB/ApoA-I ratio with T2DM and prediabetes as well as its gender effects are still poorly clarified, especially in Chinese population. Additionally, the association between ApoB/ApoA-I ratio and

other lipid or glycaemic traits, such as TG, TC, glucose, insulin sensitivity and secretion, remains partially characterized.

Therefore, in this observational study, we aimed to evaluate the association between the level of ApoB/ApoA-I ratio and the risk of T2DM, prediabetes in both men and women and also investigate the correlations between the ratio and other lipid and glycaemic traits.

Subjects and Methods

Subjects

Stratified random sampling was performed to select participants from the database of Renji hospital from January 2010 to December 2014. A total of 1538 subjects aged from 18 to 80 years were included. All of them had visited the department of Endocrinology, Renji Hospital, School of Medicine, Shanghai Jiaotong University for a relative health checkup.

The exclusion criteria were regular diabetic and/or lipid-lowing medication use, a history of cardiovascular disease, cerebrovascular disease, chronic renal or hepatic failure, cancer, pregnant, hyperthyroidism and hypothyroidism. Subjects with incomplete data were also excluded.

Finally, 729 subjects (264 men and 465 women) were involved in the present study. The study was carried out in accordance with the declaration of Helsinki and the study protocol was approved by the Ethical Committee of Renji Hospital, School of Medicine, Shanghai Jiaotong University. Written informed consents were obtained

from all subjects included in the study.

Anthropometry measurements

Body height, weight, waist circumference (WC), hip circumference and blood pressure (BP) were measured by trained survey personnel. Body height was measured once with a portable height scale to the nearest 0.1 cm. Weight was measured using a platform digital scale to the nearest 0.1kg. Both height and weight measurements were taken in light clothing without shoes. Waist circumference was recorded as the midpoint circumference between the iliac crest and the lowest rib. Hip circumference was recorded as the largest gluteal circumference. Circumference measurements were taken twice by a single observer and the mean value was reported. Blood pressure was measured twice in each subject on the right arm after five minutes resting in a sitting position, and the mean of two measurements was considered.

Laboratory analysis

All subjects underwent a standard 75g glucose oral glucose tolerance test (OGTT) after an 8-hour overnight fast. Glucose and lipid levels were measured using fully automatic biochemistry analyzer (Hitachi 7600–110 and Hitachi 7020, respectively, Hitachi Co. Tokyo, Japan); Insulin concentration was determined by immunoradiometric assay kit (Dainabot, Tokyo, Japan); Glycated hemoglobin A1c (HbA1c) level was measured by a high-performance liquid chromatography.

Definition of T2DM and prediabetes

According to the 1999 World Health Organization criteria [11], diabetes was defined as fasting plasma glucose (FPG) ≥7.0 mmol/L and/or 2-h postload plasma glucose (2hPG) ≥11.1 mmol/L, prediabetes was defined as FPG between 6.1mmol/L and 7.0mmol/L and/or 2hPG between 7.8mmol/L and 11.1mmol/L.

Calculation

Body mass index (BMI) was defined as the body weight (kg) divided by the square of body height (m^2). Waist to hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm). Indices of insulin resistance and insulin secretion were calculated from the OGTT data: homeostasis model assessment for insulin resistance (HOMA-IR) = fasting insulin (μU/ml) × fasting glucose (mmol/L) /22.5; homeostasis model assessment for β cell function index (HOMA-β) = 20×fasting insulin in μU/ml / (fasting glucose in mmol/L -3.5).

Statistical analysis

All statistical analyses were performed using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as median (Interquartile range 25-75%) due to the skewed distribution and compared by Kruskal-Wallis H test or Mann–Whitney U test. Adjusted means were calculated and compared with general linear models. Categorical variables were shown as percentages and compared with Chi-square test. A Pearson's partial correlation analysis was carried out to identify the

correlativity between ApoB/ApoA-I ratio and other variables after adjusting for several covariates. Data with skewed distribution were log-transformed before analysis. A multivariable logistic regression model was conducted to test the associations between ApoB/ApoA-I ratio and the risk of prediabetes and diabetes after controlling for potential confounding factors. The odds ratios (OR) and 95% confidence intervals (CIs) of tertiles 2 to 3 were calculated and compared by using tertile 1 as the reference. Statistical significance was considered at $p<0.05$.

Results

Clinical and laboratory characteristics

In the present study, among the 729 eligible participants, 36.2% were men and 63.8% were women, with a mean age of 51.2 years. There were 222 subjects (75 men and 147 women) diagnosed as T2DM, 240 (90 men and 150 women) as prediabetes, and 267 (99 men and 168 women) as NGT.

The anthropometric and metabolic characteristics of them were presented in Table 1. After comparison, it was notable that subjects with T2DM had much higher levels of ApoB/ApoA-I ratio than those with prediabetes and NGT, accompanied by worse glucose and lipid profiles. Moreover, those subjects showed higher levels of blood pressure, BMI and WHR. Besides, subjects with prediabetes had higher levels of ApoB/ApoA-I ratio than those with NGT. The levels of blood pressure, BMI and WHR in prediabetes group were also higher than those with NGT.

When men and women were analyzed separately, we found the levels of

ApoB/ApoA-I ratio in women were higher than in men both in T2DM and prediabetic group. However, the gender difference in NGT group was not significant. Additionally, the level of ApoB in women were also higher than in men in T2DM and prediabetes group. But other lipid indices including TG, TC and LDL-C showed little difference between men and women.

Correlations between ApoB/ApoA-I ratio and other variables

After adjusting for age, systolic blood pressure and diastolic blood pressure, the results of Pearson's partial correlation analysis showed that ApoB/ApoA-I ratio was positively correlated with TG, TC, LDL-C and negatively correlated with HDL-C, no matter in NGT, prediabetic and diabetic group (Table 2). Moreover, gender difference was also insignificant. Besides, ApoB/ApoA-I ratio was strongly associated with FPG, HbA1C and HOMA-IR both in men and women. However, the correlations between ApoB/ApoA-I ratio and HOMA-β, insulin levels were not significant.

Risk of prediabetes and diabetes according to ApoB/ApoA-I ratio

The level of ApoB/ApoA-I ratio was further devided into tertiles and the first tertile of it was regarded as the reference group. In men, univariate logistic regression analysis showed that the risk of prediabetes in tertile 2 was 2.21-fold higher than in the bottom tertile (OR=2.210, 95%CIs:1.121-4.356, p<0.05). However, this association was disappeared after adjusting for age, SBP, DBP and TC. In parallel with prediabetes, the association of ApoB/ApoA-I ratio with diabetes was also

disappeared after adjusting for the aforementioned confounding factors in men (Table 3).

Nevertheless, the associations between ApoB/ApoA-I ratio and prediabetes or diabetes risk in women were much obvious than in men (Table 4). In women, univariate logistic regression analysis showed that the risk of prediabetes was increased across the tertile of ApoB/ApoA-I ratio (T2: OR=2.204, 95%CIs: 1.174-3.487, $p<0.01$; T3: OR=4.300, 95%CIs: 2.428-7.615, $p<0.001$). After adjusting for age, SBP, DBP and BMI, the association between ApoB/ApoA-I ratio and prediabetes was attenuated but still significant in T3 group (OR=4.123, 95%CIs: 1.167-10.512, $p<0.01$). Moreover, the crude ORs and 95%CIs of diabetes in tertile 2 to 3 were 6.071 (95%CIs: 3.110-11.849, $p<0.001$) and 14.426 (95%CIs: 7.247-28.716, $p<0.001$), respectively. After further adjusting for TG, TC, HDL-C and LDL-C, the risk of diabetes in the top tertile of ApoB/ApoA-I ratio was still 5.34-fold higher than in the bottom tertile (OR=5.335, 95%CIs: 1.834-15.525, $p<0.01$).

Prevalence of prediabetes and diabetes according to tertile of ApoB/ApoA-I ratio

As shown in **Fig 1**, the prevalence of prediabetes and T2DM in women were increased in sequence from the bottom to the top tertile of ApoB/ApoA-I ratio (for prediabetes: T1:16.5%, T2:19.8%, T3:25.5%, $p=0.014$; for diabetes, T1:6.2%, T2:22.2%, T3:32.1%, $p<0.001$). However, the prevalence of prediabetes and diabetes in men was higher in T2 than in T1 and T3(for prediabetes: T1:13.2%, T2:14.0%, T3:9.9%, p>0.05; for diabetes, T1:7.4%, T2:12.8%, T3:10.7%, $p>0.05$).

Discussion

In the current cross-sectional study, we observed a strong positive association between the level of ApoB/ApoA-I ratio and the risk of prediabetes and diabetes in women, independent of traditional metabolic risk factors. However, the association in men was insignificant after adjusting for potential compounding factors.

It is well known that ApoB/ApoA-I ratio is a better predictor of cardiovascular risk than other conventional lipid indices [3 4]. Moreover, emerging evidence indicated that the ratio may be a powerful indictor of metabolic syndrome [10 12] as well as insulin resistance in certain populations [13 14]. However, only a few studies have shown the associations between atherogenic lipoprotein and apolipoprotein levels and the risk of diabetes. Hwang et al.[15] indicated that ApoB/ApoA-I ratio is an effective predictor of T2DM in Korea population. Moreover, the ApoB/LDL-C ratio has been associated with T2DM in a population-based study of Turkish adults [16] and ApoB in the Aboriginal Canadian population [17]. In our study, the results consistently suggested that ApoB/ApoA-I ratio was associated with diabetes and prediabetes in Chinese women.

Apolipoproteins regulate the synthesis and metabolism of lipoprotein particles and stabilize their structures additionally. Apolipoprotein B and A-I are the major parts of the protein moieties of LDL-C and HDL-C, respectively. The total level of ApoB reflects the total number of potentially atherogenic particles, as it is present in VLDL, intermediate density lipoprotein, large buoyant LDL, and sd-LDL. Meanwhile,

ApoA-I plays an important role on removing excess cholesterol from tissues and incorporating it into HDL for reverse transport to the liver, which was act as atheroprotective particles [18]. Thus, Apo B/Apo A-I ratio reflects the balance of atherogenic and atheroprotective particles, so the higher the level, the higher the tendency of cholesterol deposition, and consequently the higher the risk of CVD[19].

Development of hyperglycermia is closely associated with lipid disturbances [20 21]. In diabetic dyslipidemia, ApoB-containing lipoprotein particles endure compositional changes, including the formation of sd-LDL and the predominance of large VLDL (l-VLDL) particles [22-24]. These features were present in up to 50% of T2DM patients [25 26] and even occurred in prediabetic patients with insulin resistance but with normal glucose tolerance [27]. Moreover, this relationship has been demonstrated by several prospective studies, which indicated that increased levels of TG, sd-LDL, l-VLDL and small HDL particles are closely associated with incident diabetes, whereas elevated levels of large HDL particles and Apo A-I are protective of diabetes [28-30]. In addition, some lipoprotein ratios, which reflect the proportion of atherogenic and antiatherogenic lipoproteins particles, have also been suggested as powerful markers of diabetes [15]. In our study, we found the level of ApoB was significantly increased in subjects with diabetes and prediabetes. However, the level of ApoA-I showed the opposite trends across the stage of NGT, prediabetes and diabetes. As a consequence, the ratio of ApoB/ApoA-I was positively associated with prediabetes and diabetes.

The mechanisms leading to the accumulation of triglyceride-rich lipoproteins (TRLs) in patients with T2DM have not been fully elucidated. Hogue et al. [31] demonstrated that the elevated apoB-48 containing TRLs of intestinal origin and apoB-100 containing TRLs of hepatic origin in diabetic subjects are due to the increased production rates and decreased catabolism of these particles. Furthermore, Duez et al.[32] showed that intestinal secretion of apoB-48 containing TRLs is increased in insulin-resistant subjects with hyperinsulinmia. They found that hyperinsulinmia might enhance the production rate of apoB-48 containing TRLs of intestinal origin in insulin-resistant people.

HDL takes part in the process of reverse cholesterol transportation. Since Apo A-I is the major protein component of HDL, both HDL and ApoA-I were considered as protective factors for diabetes. However, one study found that the increased level of ApoA-I may also enhance the risk of diabetes [33]. This paradoxical result might be explained by the fact that beneficial HDL can be degenerated to dysfunctional particles with pro-inflammatory or pro-atherosclerotic property with the help of glycation and oxidation [34 35]. The lipid and apolipoprotein composition of HDL was obviously changed and the level of ApoA-I was increased. Thus, the role of ApoA-I may have two sides in the pathogenesis of diabetes.

The effects of gender on lipid and apolipoprotein metabolism have been studied in several research, but the results were still under discussion. Anahnostis et al. [36] conducted a cross-sectional study in the population of Caucasian premenopausal and

postmenopausal women and men, and they indicated that ApoB concentrations are highest in men but in women rise with age while Apo A-I concentrations are highest in postmenopausal women and lowest in men. Moreover, Li et al. [37] observed that male gender confers decreases in HDL subspecies due to lower levels of ApoA-I; while postmenopausal status results in higher levels of all ApoB-containing lipoproteins. Hence, the risk of CVD was increased in women after menopause. The mechanisms of the gender effects on lipoprotein and apolipoprotein metabolism were not fully elucidated, but may be related to sex hormone changes. Some authors have reported that serum estrone or estradiol levels were positively correlated with HDL-C and TG and inversely associated with TC and LDL-C [38 39]. Moreover, androgen excess in premenopausal women, as is the case in polycystic ovary syndrome (PCOS), has been associated with increased TG and sd-LDL particles, as well as reduced HDL-C [40]. In addition, hyperandrogenemic women demonstrate increased insulin resistance and incidence of CVD [41]. However, there is no denying that the effects of sex hormone on lipid metabolism were still controversial, since some other studies reported conflicting results about the effects of estrone or androgen [42 43]. In our study, it is noticeable that in prediabetic and diabetic group, the levels of ApoB were increased remarkably in women, so was the level of ApoB/ApoA-I ratio. While the concentration of ApoA-I didn't show significant difference between men and women. Additionally, the association between ApoB/ApoA-I ratio and the risk of diabetes was more significant in women than in men, independent of other conventional factors. Unfortunately, in the current study, women were not further divided into

premenopausal and postmenopausal groups due to the lack of related information. However, from the median age of women in prediabetic and diabetic groups (56.0 years old), we may make an inference that a great number of these women were in the postmenopausal status, which may, to some extent, explain the higher levels of ApoB in women groups and also the higher risk of prediabetes and diabetes in women than men.

There were some limitations in our study. First, it was performed using a cross-sectional design and did not control for potential biases from diet, physical activity, smoking and drinking history. Second, women were not further divided according to menopausal statue because of the missing information. Thus, a prospective and well- controlled study will be needed to elucidate the association of apoB/ApoA-I ratio with diabetes and prediabetes.

In conclusion, our findings indicated a positive association between ApoB/ApoA-I ratio and the risk of prediabetes and diabetes in Chinese women, independent of traditional metabolic risk factors. However, the association in men was insignificant after adjusting for potential compounding factors. Collectively, the results of this study may provide valuable evidence for a better understanding of the role of ApoB/ApoA-I ratio in detecting prediabetes and diabetes in Chinese population, especially in female gender.

Competing interests

We declare that we have no conflict of interest.

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Author contributions

SZ, TH and HX attended the statistical analysis, data interpretation, manuscript writing and revision. HZ, XR, PW, YZ and LW contributed to data interpretation. ME, YJ, YC, HQ and WL contributed to data collection. YH contributed to acquisition of funding, study design, and revision of the paper. All authors revised and approved the final manuscript.

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Data sharing statement Additional research data will be made available to the scientific community with as few restrictions as possible.

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Figure legend

Fig 1 Prevalence of prediabetes and diabetes according to tertiles of ApoB/ApoA-I ratio

The numbers above the bars mean the prevalence of each outcome, respectively.

T1: tertile 1; T2: tertile 2; T3: tertile 3

1

2

1

Table 1 Characteristics of participants according to glucose status and gender

	NGT			Prediabetes			Diabetes					
	Total	Men	Women	Total	Men	Women	Total	Men	Women	*P*1	*P*2	*P*3
Number	267	99	168	240	90	150	222	75	147	NS	NS	NS
Age (years)	51.0 (41.0,57.0)	51.0 (41.5,57.5)	51.0 (40.0,57.0)	56.0 (45.0.61.0)	56.0 (44.0,59.0)	56.0 (47.0,62.0)	56.0 (46.0,60.0)	58.0 (46.0, 61.5)	56.0 (46.0,59.5)	<0.001	<0.001	NS
SBP (mmHg)	114.0 (113.0,116.0)	114.0 (102.0,127.0)	110.0 (102.0,120.5)	121.0 (119.0,123.0)	116.0 (110.0,131.0)	121.0* (114.0,132.0)	121.0 (119.0,123.0)	119.0 (113.0,129.5)	120.0 (110.0,130.5)	<0.001	<0.001	NS
DBP (mmHg)	74.0 (73.0,75.0)	72.0 (68.0,79.0)	74.0 (69.0,80.0)	77.0 (76.0,78.0)	78.0 (72.0,83.0)	78.0 (74.0,82.0)	80.0 (78.0,81.0)	79.0 (73.5,82.0)	79.0 (75.5,85.5)	<0.001	<0.001	0.005
BMI	23.03 (22.60,23.46)	23.11 (21.32,25.15)	23.06 (19.78,24.92)	23.92 (23.47,24.37)	24.12 (21.21,27.46)	23.64 (21.79,26.33)	25.09 (24.61,25.55)	27.67 (24.23,29.45)	23.37** (21.94,26.38)	0.005	<0.001	<0.001
WHR	0.86 (0.85,0.87)	0.88 (0.82,0.91)	0.85* (0.81,0.90)	0.89 (0.88,0.89)	0.89 (0.84.0.93)	0.89 (0.86,0.92)	0.90 (0.90,0.91)	0.91 (0.89,0.94)	0.90* (0.87,0.93)	<0.001	<0.001	0.001
FPG (mmol/L)	4.98 (4.87,5.09)	4.98 (4.65,5.25)	5.01 (4.75,5.35)	5.57 (5.46,5.69)	5.44 (4.92,5.97)	5.60 (5.04,6.11)	7.31 (7.19,7.43)	7.33 (7.16,8.06)	7.15** (5.73,7.87)	<0.001	<0.001	<0.001
2hPG (mmol/L)	6.01 (5.77,6.26)	5.88 (5.30,6.55)	6.05 (5.19,6.83)	9.29 (9.03,9.54)	9.19 (8.51,9.85)	9.36 (8.58,10.19)	13.95 (13.68,14.21)	12.99 (12.23,14.76)	13.07 (11.92,14.73)	<0.001	<0.001	<0.001

FINS (μIU/L)	13.73 (12.85,14.61)	12.27 (9.51,16.90)	11.98 (8.76,20.11)	14.70 (13.78,15.61)	11.75 (10.59,17.71)	12.06 (10.74,18.71)	15.38 (14.42,16.33)	14.77 (10.80,20.03)	14.19 (9.82,18.29)	NS	0.014	NS
2hINS (μIU/L)	64.18 (57.49,70.87)	42.98 (24.02,87.40)	55.13 (35.57,71.38)	80.05 (73.08,87.02)	75.27 (41.60,119.56)	71.97 (48.35,103.81)	71.23 (63.97,78.49)	65.53 (24.57,90.22)	63.75* (34.21,110.37)	0.001	NS	NS
HbA1c （%）	5.5 (5.4,5.6)	5.5 (5.2,5.7)	5.6 (5.3,5.8)	5.8 (5.7,5.9)	5.8 (5.5,6.0)	5.9* (5.6,6.1)	6.9 (6.8,7.0)	6.9 (6.6,7.3)	6.7 (6.0,7.4)	<0.001	<0.001	<0.001
HOMA-IR	3.07 (2.81,3.33)	2.63 (2.01,3.86)	2.67 (1.95,4.60)	3.72 (3.46,3.99)	2.93 (2.27,4.18)	3.28 (2.58,4.58)	5.04 (4.76,5.32)	4.82 (3.46,7.29)	4.18 (3.15,5.85)	0.001	<0.001	<0.001
HOMA-β	218.63 (203.73,233.53)	185.08 (136.51,246.24)	161.87 (124.18,257.26)	154.67 (139.14,170.19)	123.17 (94.47,185.50)	122.29 (87.07,186.75)	93.41 (77.24,109.58)	77.45 (58.17,88.08)	74.54 (55.07,112.40)	<0.001	<0.001	<0.001
TG (mmol/L)	1.50 (1.36,1.65)	1.23 (0.77,1.70)	1.15 (0.77,1.77)	1.77 (1.62,1.92)	1.50 (1.06,1.99)	1.68 (1.09,2.24)	2.72 (2.56,2.88)	2.55 (1.73,4.14)	2.44 (1.69,3.50)	0.012	<0.001	<0.001
TC (mmol/L)	5.02 (4.92,5.12)	4.94 (4.67,5.20)	5.02* (4.67,5.40)	5.13 (5.03,5.23)	5.15 (4.31,5.78)	5.27 (4.66,5.55)	5.64 (5.53,5.75)	5.47 (5.13,6.18)	5.90 (4.93,6.29)	NS	<0.001	<0.001
HDL-C (mmol/L)	1.48 (1.44,1.51)	1.43 (1.19,1.69)	1.45 (1.24,1.68)	1.34 (1.31,1.38)	1.30 (1.14,1.48)	1.29 (1.15,1.46)	1.23 (1.19,1.27)	1.12 (1.09,1.28)	1.28* (1.07,1.38)	<0.001	<0.001	<0.001
LDL-C (mmol/L)	3.03 (2.95,3.12)	2.84 (2.58,3.29)	3.12 (2.58,3.45)	3.05 (2.96,3.14)	2.83 (2.60,3.78)	3.08 (2.76,3.54)	3.37 (3.28,3.47)	3.50 (2.88,3.69)	3.36 (3.02,4.18)	NS	<0.001	<0.001
ApoA-I	1.48	1.43	1.45	1.39	1.40	1.34	1.33	1.36	1.31	<0.001	<0.001	0.005

(g/L)	(1.45,1.51)	(1.31,1.68)	(1.28,1.63)	(1.36,1.43)	(1.26,1.56)	(1.25,1.52)	(1.29,1.36)	(1.22,1.38)	(1.17,1.42)			
ApoB	0.84	0.80	0.84	0.91	0.90	0.97**	0.97	0.97	1.05**	<0.001	<0.001	0.001
(g/L)	(0.81,0.86)	(0.68,0.97)	(0.68,0.97)	(0.88,0.93)	(0.70,0.98)	(0.84,1.03)	(0.94,1.00)	(0.80,1.03)	(0.87,1.17)			
ApoB/Apo	0.60	0.55	0.56	0.67	0.66	0.74**	0.76	0.71	0.78**	<0.001	<0.001	<0.001
A-I ratio	(0.57,0.62)	(0.42,0.72)	(0.44,0.72)	(0.64,0.70)	(0.48,0.77)	(0.56,0.81)	(0.73,0.78)	(0.60,0.82)	(0.68,0.94)			

Data were expresses as medians (interquartile ranges 25-75%).

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; WHR: waist to hip ratio; FPG: fasting plasma glucose; 2hPG: 2 hour postload plasma glucose; FINS: fasting serum insulin; 2hINS:2 hour postload serum insulin; HbA1c: glycated hemoglobin A1c; HOMA-IR: homeostatic model assessment of insulin resistance; HOMA-β: homeostatic model assessment of β-cell function; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA-I: apolipoprotein A-I; ApoB: apolipoprotein B.

*P*1: NGT versus prediabetic group, *P*2: NGT versus diabetic group, *P*3: prediabetic versus diabetic group

Comparisons among NGT, prediabetic and diabetic groups were performed after adjusting for age.

Table 2 Partial correlation coefficients of ApoB/ApoA-I ratio with lipid profiles and glycometabolism-related traits

	NGT		Prediabetes		Diabetes	
	Men	Women	Men	Women	Men	Women
TG (mmol/L)	0.500***	0.474***	0.560***	0.570***	0.503***	0.654***
TC (mmol/L)	0.410***	0.350***	0.331**	0.271**	0.292*	0.648***
HDL (mmol/L)	-0.835***	-0.727***	-0.614***	-0.563***	-0.337**	-0.721***
LDL (mmol/L)	0.652***	0.597***	0.433***	0.228**	0.427***	0.767***
FPG (mmol/L)	0.340**	0.261**	0.432***	0.296***	0.675***	0.471***
2hPG (mmol/L)	0.550***	0.277***	0.198	0.287***	0.300*	0.162
FINS (μIU/mL)	0.281**	0.195*	0.370***	0.122	0.581***	0.463***
2hINS (μIU/mL)	0.279**	0.286***	0.696***	0.182*	0.109	0.172*
HbA1C (%)	0.253*	0.254**	0.274*	0.213*	0.265*	0.278**
HOMA-IR	0.326**	0.225**	0.427***	0.175*	0.677***	0.584***
HOMA-β	-0.007	-0.016	0.014	-0.084	0.208	-0.007

Data were analyzed after adjusting for age, SBP and DBP. Variables with skewed distributions were log-transformed before statistical analysis.

*P<0.05, **P<0.01, ***P<0.001

Table 3 The risk of prediabetes and Type 2 diabetes according to tertiles of ApoB/ApoA-I ratio in men

		T1 (0-0.5703)	T2 (0.5704-0.7723)	T3 (≥0.7724)
Prediabetes	n,cases/participants	32/102	34/90	24/72
	Model 1	1	2.210 (1.121, 4.356)*	1.773 (0.857, 3.668)
	Model 2	1	1.673 (0.819, 3.415)	1.251 (0.582, 2.689)
	Model 3	1	1.560 (0.749, 3.251)	1.174 (0.506, 2.727)
Type 2 Diabetes	n,cases/participants	18/102	31/90	26/72
	Model 1	1	3.582 (1.689, 7.596)**	3.414 (1.564, 7.454)**
	Model 2	1	2.615 (1.191, 5.744)*	2.356 (1.041, 5.332)*
	Model 3	1	1.905 (0.841, 4.316)	1.091 (0.433,2.747)

Data are odds ratios (OR), 95% confidential intervals (CI).

Model 1: unadjusted

Model 2: adjusted for age, SBP, DBP

Model 3: adjusted for Model 2+ TC

*P<0.05, **P<0.01, ***P<0.001

Table 4 The risk of prediabetes and Type 2 diabetes according to tertiles of ApoB/ApoA-I ratio in women

		T1 (0-0.5703)	T2 (0.5704-0.7723)	T3 (≥0.7724)
Prediabetes	n,cases/participants	40/141	48/153	62/171
	Model 1	1	2.024 (1.174, 3.487)**	4.300 (2.428, 7.615)***
	Model 2	1	1.506 (0.835, 2.715)	3.347 (1.810, 6.187)***
	Model 3	1	1.824 (0.863, 3.859)	4.123 (1.617, 10.512)**
Type 2 Diabetes	n,cases/participants	15/141	54/153	78/171
	Model 1	1	6.071 (3.110, 11.849)***	14.426 (7.247, 28.716)***
	Model 2	1	4.772 (2.384, 9.550)***	11.537 (5.619, 23.690)***
	Model 3	1	4.164 (1.720, 10.078)**	5.335 (1.834, 15.525)**

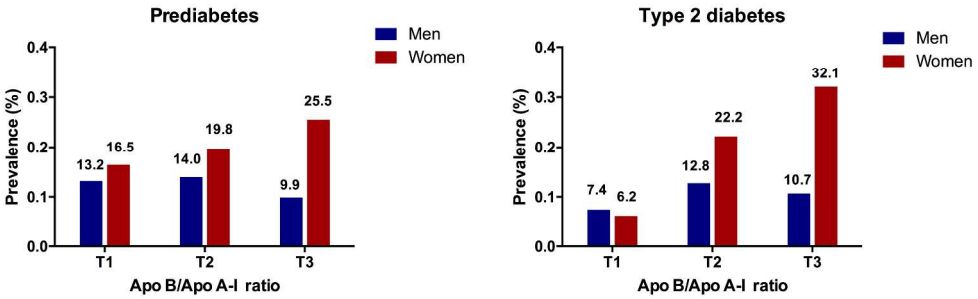
1 Data are odds ratios (OR), 95% confidential intervals (CI).

2 Model 1: unadjusted

3 Model 2: adjusted for age, SBP, DBP, BMI

4 Model 3: adjusted for Model 2+TC, TG, HDL-C, LDL-C

5 $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$



Prevalence of prediabetes and diabetes according to tertiles of ApoB/ApoA-I ratio
The numbers above the bars mean the prevalence of each outcome, respectively.
T1: tertile 1; T2: tertile 2; T3: tertile 3

Fig. 1
270x87mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			7
Key results	18	Summarise key results with reference to study objectives	7-8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Associations of Apolipoprotein B to A-I ratio with diabetes and prediabetes in Chinese subjects: a stratified random sampling based cross-sectional study

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Title Page

Associations of Apolipoprotein B to A-I ratio with diabetes and prediabetes in Chinese subjects: a stratified random sampling based cross-sectional study

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Abstract

Objectives Apolipoprotein (Apo)B/ApoA-I ratio is a useful predictor of cardiovascular risk. However, the association between the ApoB/ApoA-I ratio and the risk of type 2 diabetes mellitus (T2DM) was still obscure. The aims of the study were to investigate the associations between the value of ApoB/ApoA-I ratio and the risk of T2DM, prediabetes in Chinese population and also assess the role of gender in these associations.

Participants and Methods A stratified random sampling design was used in this cross-sectional study including 264 men and 465 women with either normal glucose tolerance (NGT), prediabetes or T2DM. Serum Apo B, Apo A-I and other lipid and glycaemic traits were measured. Pearson's partial correlation and multivariable logistic analysis were used to evaluate the associations between ApoB/ApoA-I ratio and the risk of T2DM, prediabetes.

Results The levels of ApoB/ApoA-I ratio were significantly increased across the stage of NGT, prediabetes and T2DM. Women showed higher levels of ApoB/ApoA-I ratio and ApoB than men in prediabetic and T2DM groups, but not in NGT group. ApoB/ApoA-I ratio was closely related with TG, TC, HDL-C, LDL-C and other glycemic traits. Moreover, in women, the risk of diabetes and prediabetes in the top tertile of ApoB/ApoA-I ratio were 3.65- (95%CIs: 1.69-6.10) and 2.19-fold (95%CIs: 1.38-2.84) higher than in the bottom tertile respectively, after adjusting for potential confounding factors. However, the associations were disappeared in men after adjusting for other factors.

Conclusions The level of ApoB/ApoA-I ratio showed positive associations with the risk of diabetes and prediabetes in Chinese women.

Strengths and limitations of this study

- This is an in-depth investigation of the associations between ApoB/ApoA-I ratio and diabetes or prediabetes in Chinese population.
- Stratified random sampling ensured the equal chance for participant enrolment and the validity of results.
- Data collection and analysis were supported by trained survey team, which included researchers with differing areas of expertise and backgrounds.
- The cross-sectional design may not confirm the causality between ApoB/ApoA-I ratio and diabetes risk.
- Potential bias might be existed due to the single-centre design.

Keywords: apolipoprotein B; apolipoprotein A-I; type 2 diabetes; prediabetes; dyslipidemia

Introduction

Atherogenic dyslipidemia is a typical lipoprotein abnormality that including high levels of triglyceride (TG)-rich lipoproteins (mainly very low-density lipoprotein [VLDL]), low levels of high-density lipoprotein (HDL) as well as an elevated proportion of small dense low-density lipoprotein (sd-LDL) particles [1]. To date, the evaluation of clinical relevance of atherogenic dyslipidemia has been focused on its role as an effective predictor of cardiovascular disease (CVD) rather than conventional lipid examinations. Apolipoproteins are important structural and functional proteins in lipoprotein particles, which take part in the transportation of lipids. Given that the circulating levels of apolipoproteins indicate the number of lipoprotein particles, the level of Apo-B may reflect the total number of potentially atherogenic particles, as it is present in VLDL, intermediate density lipoprotein, large buoyant LDL, and sd-LDL. Besides, the level of ApoA-I may present the number of HDL particles [2]. Thus, the ratio of apolipoproteins B and A-I (ApoB/ApoA-I) would be, theoretically, an ideal indicator of atherogenic lipid disturbances and cardiovascular risk [3 4].

It is well established that atherogenic dyslipidemia is associated with T2DM and high risk of CVD in T2DM patients [5 6]. Moreover, the mortality rate of CVD in diabetic patients varies with gender [7]. Considering the outstanding performance of ApoB/ApoA-I ratio in indicating atherogenic dyslipidemia and CVD, the role of it in predicting diabetes risk was expected, particularly its gender effects. Previous studies

have demonstrated that ApoB/ApoA-I ratio may be a strong marker of metabolic syndrome and insulin resistance in certain population [8-10], but the associations of it with T2DM and prediabetes as well as its gender effects in Chinese population are still poorly clarified. Additionally, the correlations between ApoB/ApoA-I ratio and other lipid or glycaemic traits, such as TG, TC, glucose, insulin sensitivity and secretion, need further investigation.

Therefore, in this observational study, we aimed to evaluate the associations between the level of ApoB/ApoA-I ratio and the risk of T2DM, prediabetes in both Chinese men and women and also investigate the correlations between the ratio and other lipid and glycaemic traits.

Subjects and Methods

Subjects

Stratified random sampling was performed to select participants from the database of Renji hospital from January 2010 to December 2014. A total of 1538 subjects aged from 18 to 80 years were included. All of them had visited the department of Endocrinology, Renji Hospital, School of Medicine, Shanghai Jiaotong University for a relative health checkup.

The exclusion criteria were regular diabetic and/or lipid-lowing medication use, a history of cardiovascular disease, cerebrovascular disease, chronic renal or hepatic failure, cancer, pregnant, hyperthyroidism and hypothyroidism. Subjects with incomplete data were also excluded.

Finally, 729 subjects (264 men and 465 women) were involved in the present study. The study was carried out in accordance with the declaration of Helsinki and the study protocol was approved by the Ethical Committee of Renji Hospital, School of Medicine, Shanghai Jiaotong University. Written informed consents were obtained from all subjects included in the study.

Anthropometry measurements

Body height, weight, waist circumference (WC), hip circumference and blood pressure (BP) were measured by trained survey personnel. Body height was measured once with a portable height scale to the nearest 0.1 cm. Weight was measured using a platform digital scale to the nearest 0.1kg. Both height and weight measurements were taken in light clothing without shoes. Waist circumference was recorded as the midpoint circumference between the iliac crest and the lowest rib. Hip circumference was recorded as the largest gluteal circumference. Circumference measurements were taken twice by a single observer and the mean value was reported. Blood pressure was measured twice in each subject on the right arm after five minutes resting in a sitting position, and the mean of two measurements was considered.

Laboratory analysis

All subjects underwent the standard 75g glucose oral glucose tolerance test (OGTT) after an 8-hour overnight fast. Serum ApoB (predominantly ApoB-100) and ApoA-I concentrations were determined by immunoturbidimetric methods using

automatic immunoassay analyzer (Roche E-170, Roche, Basel, Switzerland).Glucose and other lipid levels were measured using fully automatic biochemistry analyzer (Hitachi 7600–110 and Hitachi 7020, respectively, Hitachi Co. Tokyo, Japan); Insulin concentration was determined by immunoradiometric assay kit (Dainabot, Tokyo, Japan); Glycated hemoglobin A1c (HbA1c) level was measured by a high-performance liquid chromatography.

Definition of T2DM and prediabetes

According to the 2006 World Health Organization criteria [11], diabetes was defined as fasting plasma glucose (FPG) ≥7.0 mmol/L and/or 2-h postload plasma glucose (2hPG) ≥11.1 mmol/L, prediabetes was defined as FPG between 6.1mmol/L and 7.0mmol/L and/or 2hPG between 7.8mmol/L and 11.1mmol/L.

Calculation

Body mass index (BMI) was defined as the body weight (kg) divided by the square of body height (m^2). Waist to hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm). Indices of insulin resistance and insulin secretion were calculated from the OGTT data: homeostasis model assessment for insulin resistance (HOMA-IR) = fasting insulin (μU/ml) × fasting glucose (mmol/L) /22.5; homeostasis model assessment for β cell function index (HOMA-β) = 20×fasting insulin in μU/ml / (fasting glucose in mmol/L -3.5).

Statistical analysis

All statistical analyses were performed using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as median (Interquartile range 25-75%) due to the skewed distribution and compared by Kruskal-Wallis H test or Mann–Whitney U test. Adjusted means were calculated and compared with general linear models. Categorical variables were shown as percentages and compared with Chi-square test. A Pearson's partial correlation analysis was carried out to identify the correlativity between ApoB/ApoA-I ratio and other variables after adjusting for several covariates. Data with skewed distribution were log-transformed before analysis. A multivariable logistic regression model was conducted to test the associations between ApoB/ApoA-I ratio and the risk of prediabetes and diabetes after controlling for potential confounding factors. The relative ratios (RR) and 95% confidence intervals (CIs) of tertiles 2 to 3 were calculated and compared by using tertile 1 as reference. RR was calculated based on the formula: RR=OR/(1-P0+P0*OR), where OR was odds ratio and P0 was the disease incidence in non-exposed group. Statistical significance was considered at $p<0.05$.

Results

Clinical and laboratory characteristics

In the present study, among the 729 eligible participants, 36.2% were men and 63.8% were women, with a mean age of 51.2 years. There were 30.5% subjects (10.3%

men and 20.2% women) diagnosed as T2DM, 32.9% (12.3% men and 20.6% women) as prediabetes, and 36.6% (13.6% men and 23.0%women) as NGT.

The anthropometric and metabolic characteristics of them were presented in Table 1. After comparison, it was notable that subjects with T2DM had much higher levels of ApoB/ApoA-I ratio than those with prediabetes and NGT, accompanied by worse glucose and lipid profiles. Moreover, those subjects showed higher levels of blood pressure, BMI and WHR. Besides, subjects with prediabetes had higher levels of ApoB/ApoA-I ratio than those with NGT. The levels of blood pressure, BMI and WHR in prediabetic group were also higher than those with NGT.

When men and women were analysed separately, we found the levels of ApoB/ApoA-I ratio in women were higher than in men both in T2DM and prediabetic groups. However, the gender difference in NGT group was not significant. Additionally, the levels of ApoB in women were also higher than in men in both T2DM and prediabetic groups. But other lipid indices including TG, TC and LDL-C showed little difference between men and women.

Correlations between ApoB/ApoA-I ratio and other variables

After adjusting for age, systolic blood pressure and diastolic blood pressure, the results of Pearson's partial correlation analysis showed that ApoB/ApoA-I ratio was positively correlated with TG, TC, LDL-C and negatively correlated with HDL-C, no matter in NGT, prediabetic and diabetic groups (Table 2). Moreover, gender difference was also insignificant. Besides, ApoB/ApoA-I ratio was strongly associated

with FPG, HbA1C and HOMA-IR both in men and women. However, the correlations between ApoB/ApoA-I ratio and HOMA-β, insulin levels were not significant.

Risk of prediabetes and diabetes according to ApoB/ApoA-I ratio

The level of ApoB/ApoA-I ratio was further devided into tertiles and the first tertile of it was regarded as the reference group. In men, the risk of prediabetes in tertile 2 was 1.60-fold higher than in the bottom tertile (RR=1.602, 95%CIs:1.080-2.122 $p<0.05$). However, this association was disappeared after adjusting for age, SBP, DBP and TC. In parallel with prediabetes, the association of ApoB/ApoA-I ratio with diabetes was also disappeared after adjusting for the aforementioned confounding factors in men (Table 3).

Nevertheless, the associations between ApoB/ApoA-I ratio and prediabetes or diabetes risk in women were much obvious than in men (Table 4). In women, the risk of prediabetes was increased across the tertile of ApoB/ApoA-I ratio (T2: RR=1.568, 95%CIs: 1.119-2.044, $p<0.01$; T3: RR=2.221, 95%CIs: 1.728-2.647, $p<0.001$). After adjusting for age, SBP, DBP, BMI and other lipid profiles, the association between ApoB/ApoA-I ratio and prediabetes was attenuated but still significant in T3 group (RR=2.186, 95%CIs: 1.376-2.842, $p<0.01$). Moreover, the crude RRs and 95%CIs of diabetes in tertile 2 to 3 were 3.943 (95%CIs: 2.540-5.500, $p<0.001$) and 5.940 (95%CIs: 4.353-7.272, $p<0.001$), respectively. After further adjusting for confounding factors, the risk of diabetes in the top tertile of ApoB/ApoA-I ratio was still 3.65-fold higher than in the bottom tertile (RR=3.651, 95%CIs: 1.685-6.099, $p<0.01$).

Prevalence of prediabetes and diabetes according to tertile of ApoB/ApoA-I ratio

As shown in **Fig 1**, the prevalence of prediabetes and T2DM in women were increased in sequence from the bottom to the top tertile of ApoB/ApoA-I ratio (for prediabetes: T1:16.5%, T2:19.8%, T3:25.5%, p=0.014; for diabetes, T1:6.2%, T2:22.2%, T3:32.1%, p<0.001). However, the prevalence of prediabetes and diabetes in men were higher in T2 than in T1 and T3 (for prediabetes: T1:13.2%, T2:14.0%, T3:9.9%, p>0.05; for diabetes, T1:7.4%, T2:12.8%, T3:10.7%, p>0.05).

Discussion

In the current cross-sectional study, we observed strong positive associations between the level of ApoB/ApoA-I ratio and the risk of prediabetes and diabetes in women, independent of traditional metabolic risk factors. However, the associations in men were insignificant after adjusting for potential compounding factors. Moreover, ApoB/ApoA-I ratio was closely related with other lipid profiles and insulin resistance both in men and women.

It is well known that ApoB/ApoA-I ratio is a better predictor of cardiovascular risk than other conventional lipid indices [12]. However, only a few studies have shown the associations between apolipoprotein levels and the risk of diabetes. Hwang et al. [13] indicated that ApoB/ApoA-I ratio is an effective predictor of T2DM in Korea population. Moreover, the ApoB/LDL-C ratio has been associated with T2DM in a population-based study of Turkish adults [14] and ApoB in the Aboriginal

Canadian population [15]. Our results consistently suggested that ApoB/ApoA-I ratio was associated with diabetes and prediabetes in Chinese women. Furthermore, ApoB/ApoA-I ratio was closely related with TG, TC, HDL-C, LDL-C, FPG, HbA1C and HOMA-IR, which was in accordance with previous studies [10 16].

Apolipoproteins regulate the synthesis and metabolism of lipoprotein particles and stabilize their structures additionally. Hence, there is no doubt that ApoB/ApoA-I ratio was closely related with TG, TC, HDL-C and LDL-C. Apolipoprotein B and A-I are the major parts of the protein moieties of LDL and HDL, respectively. The value of ApoB reflects the number of potentially atherogenic particles [17]. Meanwhile, ApoA-I plays an important role in removing excess cholesterol from tissues and incorporating it into HDL for reverse transport to the liver, which is supposed to stand for atheroprotective particles [18 19]. Thus, ApoB/Apo A-I ratio reflects the balance of atherogenic and atheroprotective particles, so the higher the level, the higher the tendency of cholesterol deposition, and consequently the higher the risk of CVD [20].

Development of hyperglycermia is closely associated with lipid disturbances [21 22]. In diabetic dyslipidemia, ApoB-containing lipoprotein particles endure compositional changes, including the formation of sd-LDL and the predominance of large VLDL (l-VLDL) particles [23-25]. These features were present in up to 50% of T2DM patients [26 27] and even occurred in prediabetic patients with insulin resistance but normal glucose tolerance [28]. Moreover, this relationship has been demonstrated by several prospective studies, which indicated that increased levels of

TG, sd-LDL, l-VLDL and small HDL particles are closely associated with incident diabetes, whereas elevated levels of large HDL particles and Apo A-I are protective of diabetes [29-31]. In our study, we found the levels of ApoB were significantly increased in subjects with diabetes and prediabetes. However, the levels of ApoA-I showed the opposite trends across the stage of NGT, prediabetes and diabetes. As a consequence, the ratio of ApoB/ApoA-I was positively associated with prediabetes and diabetes. Moreover, this ratio was significantly correlated with insulin resistance. Previous studies have demonstrated that the ApoB/ApoA-I ratio is an independent predictor of insulin resistance in both US non-diabetic subjects [32] and Chinese obesity population [33]. A possible explanation for the positive association between the ApoB/ApoA-I ratio and insulin resistance could be that both ApoB and insulin resistance are linked to an inflammatory state [34]. However, detailed mechanisms interpreting this association need further exploration.

The mechanisms leading to the accumulation of triglyceride-rich lipoproteins (TRLs) in patients with T2DM have not been fully elucidated. Hogue et al. [35] demonstrated that the elevated apoB-48 containing TRLs of intestinal origin and apoB-100 containing TRLs of hepatic origin in diabetic subjects are due to the increased production rates and decreased catabolism of these particles. Furthermore, Duez et al. [36] showed that intestinal secretion of apoB-48 containing TRLs is increased in insulin-resistant subjects with hyperinsulinmia.

HDL takes part in the process of reverse cholesterol transportation. Since Apo A-I is the major protein component of HDL, both HDL and ApoA-I were considered as protective factors for diabetes. However, one study found that the increased level of ApoA-I may also enhance the risk of diabetes [37]. This paradoxical result might be explained by the fact that beneficial HDL can be degenerated to dysfunctional particles with pro-inflammatory or pro-atherosclerotic property with the help of glycation and oxidation [38-40]. The lipid and apolipoprotein composition of HDL was obviously changed and the level of ApoA-I was increased. Thus, the role of ApoA-I may have two sides in the pathogenesis of diabetes.

The effects of gender on lipid and apolipoprotein metabolism have been studied in several research, but the results were still under discussion. Anahnostis et al. [41] conducted a cross-sectional study in the population of Caucasian premenopausal and postmenopausal women and men, and they indicated that ApoB concentrations are highest in men but in women rise with age, while Apo A-I concentrations are highest in postmenopausal women and lowest in men. Moreover, Li et al. [42] observed that postmenopausal status results in higher levels of all ApoB-containing lipoproteins. Hence, the risk of CVD was increased in women after menopause. The mechanisms of the gender effects on lipoprotein and apolipoprotein metabolism were not fully revealed, but may be related to sex hormone changes. Some authors have reported that serum estrone or estradiol levels are positively correlated with HDL-C and TG and inversely associated with TC and LDL-C [43 44]. Moreover, androgen excess in

premenopausal women, as is the case of polycystic ovary syndrome (PCOS), has been associated with increased TG and sd-LDL particles, as well as reduced HDL-C [45]. In addition, hyperandrogenemic women demonstrate increased insulin resistance and incidence of CVD [46]. However, there is no denying that the effects of sex hormone on lipid metabolism were still controversial, since some other studies reported conflicting results about the effects of estrone or androgen [47 48].

In our study, it is noticeable that the gender difference was not significant in NGT groups, but in prediabetic and diabetic groups, the levels of ApoB were increased remarkably in women, so were the levels of ApoB/ApoA-I ratio. The results might be interpreted by that age, gender, hormone levels, glucose and lipid metabolism exist in a complicated relative network and the cooperative effects of hormone and glucose status may strengthen the gender difference and worsen the lipid metabolism among prediabetic and diabetic groups. Fortunately, we found the association between ApoB/ApoA-I ratio and the risk of diabetes was still significant in women after adjusting for conventional factors. But it was regret that women were not further divided into premenopausal and postmenopausal groups due to the lack of related information. However, from the median age of women in prediabetic and diabetic groups (56.0 years old), we may make an inference that a great number of these women were in the postmenopausal status, which may, to some extent, explain the higher levels of ApoB in women groups and also the higher risk of prediabetes and diabetes in women. Regarding men, the hormone changes in andropause presented

progressivity and obvious individual difference, which is not as recognizable as in menopause [49 50]. Moreover, the risk of diabetes in men derived from various influence factors, such as high working stress, smoking and drinking problems and lacking of physical exercise. In addition, the number of male participants included in this study was relatively small. Thus, to a certain extent, the aforementioned factors may explicate the loss of significant association between ApoB/ApoA-I ratio and diabetes risk in men.

There were some limitations in our study. First, it was performed using a cross-sectional design and did not control for potential biases from diet, physical activity, smoking and drinking history. Second, women were not further divided according to menopausal statue because of the missing information. Therefore, a prospective and well- controlled study would be needed to elucidate the associations of apoB/ApoA-I ratio with diabetes and prediabetes risk.

In conclusion, our findings indicated positive associations between ApoB/ApoA-I ratio and the risk of prediabetes and diabetes in Chinese women, independent of traditional metabolic risk factors. However, the associations in men were insignificant after adjusting for potential compounding factors. Collectively, the results of this study may provide valuable evidence for a better understanding of ApoB/ApoA-I ratio in detecting prediabetes and diabetes risk in Chinese population, especially in female gender.

Competing interests

We declare that we have no conflict of interest.

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Author contributions

SZ, TH and HX attended the statistical analysis, data interpretation, manuscript writing and revision. HZ, XR, PW, YZ and LW contributed to data interpretation. ME, YJ, YC, HQ and WL contributed to data collection. YH contributed to acquisition of funding, study design, and revision of the paper. All authors revised and approved the final manuscript.

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Figure legend

Fig 1 Prevalence of prediabetes and diabetes according to tertiles of ApoB/ApoA-I ratio

The numbers above the bars mean the prevalence of each outcome, respectively.

T1: tertile 1; T2: tertile 2; T3: tertile 3

1

2

1

Table 1 Characteristics of participants according to glucose status and gender

	NGT			Prediabetes			Diabetes					
	Total	Men	Women	Total	Men	Women	Total	Men	Women	*P*1	*P*2	*P*3
Number	267	99	168	240	90	150	222	75	147	NS	NS	NS
Age (years)	51.0 (41.0,57.0)	51.0 (41.5,57.5)	51.0 (40.0,57.0)	56.0 (45.0.61.0)	56.0 (44.0,59.0)	56.0 (47.0,62.0)	56.0 (46.0,60.0)	58.0 (46.0, 61.5)	56.0 (46.0,59.5)	<0.001	<0.001	NS
SBP (mmHg)	114.0 (113.0,116.0)	114.0 (102.0,127.0)	110.0 (102.0,120.5)	121.0 (119.0,123.0)	116.0 (110.0,131.0)	121.0* (114.0,132.0)	121.0 (119.0,123.0)	119.0 (113.0,129.5)	120.0 (110.0,130.5)	<0.001	<0.001	NS
DBP (mmHg)	74.0 (73.0,75.0)	72.0 (68.0,79.0)	74.0 (69.0,80.0)	77.0 (76.0,78.0)	78.0 (72.0,83.0)	78.0 (74.0,82.0)	80.0 (78.0,81.0)	79.0 (73.5,82.0)	79.0 (75.5,85.5)	<0.001	<0.001	0.005
BMI	23.03	23.11	23.06	23.92	24.12	23.64	25.09	27.67	23.37**	0.005	<0.001	<0.001

	(22.60,23.46)	(21.32,25.15)	(19.78,24.92)	(23.47,24.37)	(21.21,27.46)	(21.79,26.33)	(24.61,25.55)	(24.23,29.45)	(21.94,26.38)			
WHR	0.86 (0.85,0.87)	0.88 (0.82,0.91)	0.85* (0.81,0.90)	0.89 (0.88,0.89)	0.89 (0.84.0.93)	0.89 (0.86,0.92)	0.90 (0.90,0.91)	0.91 (0.89,0.94)	0.90* (0.87,0.93)	<0.001	<0.001	0.001
FPG (mmol/L)	4.98 (4.87,5.09)	4.98 (4.65,5.25)	5.01 (4.75,5.35)	5.57 (5.46,5.69)	5.44 (4.92,5.97)	5.60 (5.04,6.11)	7.31 (7.19,7.43)	7.33 (7.16,8.06)	7.15** (5.73,7.87)	<0.001	<0.001	<0.001
2hPG (mmol/L)	6.01 (5.77,6.26)	5.88 (5.30,6.55)	6.05 (5.19,6.83)	9.29 (9.03,9.54)	9.19 (8.51,9.85)	9.36 (8.58,10.19)	13.95 (13.68,14.21)	12.99 (12.23,14.76)	13.07 (11.92,14.73)	<0.001	<0.001	<0.001
FINS (μIU/L)	13.73 (12.85,14.61)	12.27 (9.51,16.90)	11.98 (8.76,20.11)	14.70 (13.78,15.61)	11.75 (10.59,17.71)	12.06 (10.74,18.71)	15.38 (14.42,16.33)	14.77 (10.80,20.03)	14.19 (9.82,18.29)	NS	0.014	NS
2hINS (μIU/L)	64.18 (57.49,70.87)	42.98 (24.02,87.40)	55.13 (35.57,71.38)	80.05 (73.08,87.02)	75.27 (41.60,119.56)	71.97 (48.35,103.81)	71.23 (63.97,78.49)	65.53 (24.57,90.22)	63.75* (34.21,110.37)	0.001	NS	NS
HbA1c （%）	5.5 (5.4,5.6)	5.5 (5.2,5.7)	5.6 (5.3,5.8)	5.8 (5.7,5.9)	5.8 (5.5,6.0)	5.9* (5.6,6.1)	6.9 (6.8,7.0)	6.9 (6.6,7.3)	6.7 (6.0,7.4)	<0.001	<0.001	<0.001

HOMA-IR	3.07 (2.81,3.33)	2.63 (2.01,3.86)	2.67 (1.95,4.60)	3.72 (3.46,3.99)	2.93 (2.27,4.18)	3.28 (2.58,4.58)	5.04 (4.76,5.32)	4.82 (3.46,7.29)	4.18 (3.15,5.85)	0.001	<0.001	<0.001
HOMA-β	218.63 (203.73,233.53)	185.08 (136.51,246.24)	161.87 (124.18,257.26)	154.67 (139.14,170.19)	123.17 (94.47,185.50)	122.29 (87.07,186.75)	93.41 (77.24,109.58)	77.45 (58.17,88.08)	74.54 (55.07,112.40)	<0.001	<0.001	<0.001
TG (mmol/L)	1.50 (1.36,1.65)	1.23 (0.77,1.70)	1.15 (0.77,1.77)	1.77 (1.62,1.92)	1.50 (1.06,1.99)	1.68 (1.09,2.24)	2.72 (2.56,2.88)	2.55 (1.73,4.14)	2.44 (1.69,3.50)	0.012	<0.001	<0.001
TC (mmol/L)	5.02 (4.92,5.12)	4.94 (4.67,5.20)	5.02* (4.67,5.40)	5.13 (5.03,5.23)	5.15 (4.31,5.78)	5.27 (4.66,5.55)	5.64 (5.53,5.75)	5.47 (5.13,6.18)	5.90 (4.93,6.29)	NS	<0.001	<0.001
HDL-C (mmol/L)	1.48 (1.44,1.51)	1.43 (1.19,1.69)	1.45 (1.24,1.68)	1.34 (1.31,1.38)	1.30 (1.14,1.48)	1.29 (1.15,1.46)	1.23 (1.19,1.27)	1.12 (1.09,1.28)	1.28* (1.07,1.38)	<0.001	<0.001	<0.001
LDL-C (mmol/L)	3.03 (2.95,3.12)	2.84 (2.58,3.29)	3.12 (2.58,3.45)	3.05 (2.96,3.14)	2.83 (2.60,3.78)	3.08 (2.76,3.54)	3.37 (3.28,3.47)	3.50 (2.88,3.69)	3.36 (3.02,4.18)	NS	<0.001	<0.001
ApoA-I	1.48	1.43	1.45	1.39	1.40	1.34	1.33	1.36	1.31	<0.001	<0.001	0.005

(g/L)	(1.45,1.51)	(1.31,1.68)	(1.28,1.63)	(1.36,1.43)	(1.26,1.56)	(1.25,1.52)	(1.29,1.36)	(1.22,1.38)	(1.17,1.42)			
ApoB	0.84	0.80	0.84	0.91	0.90	0.97**	0.97	0.97	1.05**	<0.001	<0.001	0.001
(g/L)	(0.81,0.86)	(0.68,0.97)	(0.68,0.97)	(0.88,0.93)	(0.70,0.98)	(0.84,1.03)	(0.94,1.00)	(0.80,1.03)	(0.87,1.17)			
ApoB/Apo	0.60	0.55	0.56	0.67	0.66	0.74**	0.76	0.71	0.78**	<0.001	<0.001	<0.001
A-I ratio	(0.57,0.62)	(0.42,0.72)	(0.44,0.72)	(0.64,0.70)	(0.48,0.77)	(0.56,0.81)	(0.73,0.78)	(0.60,0.82)	(0.68,0.94)			

1 Data were expresses as medians (interquartile ranges 25-75%).

2 SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; WHR: waist to hip ratio; FPG: fasting plasma glucose;

3 2hPG: 2 hour postload plasma glucose; FINS: fasting serum insulin; 2hINS:2 hour postload serum insulin; HbA1c: glycated hemoglobin A1c;

4 HOMA-IR: homeostatic model assessment of insulin resistance; HOMA-β: homeostatic model assessment of β-cell function; TG: triglyceride;

5 TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA-I: apolipoprotein A-I;

6 ApoB: apolipoprotein B.

7 *P*1: NGT versus prediabetic group, *P*2: NGT versus diabetic group, *P*3: prediabetic versus diabetic group

8 *P<0.05, **P<0.01 means the gender difference in each group

1 Comparisons among NGT, prediabetic and diabetic groups were performed after adjusting for age

Table 2 Partial correlation coefficients of ApoB/ApoA-I ratio with lipid profiles and glycometabolism-related traits

	NGT		Prediabetes		Diabetes	
	Men	Women	Men	Women	Men	Women
TG (mmol/L)	0.500***	0.474***	0.560***	0.570***	0.503***	0.654***
TC (mmol/L)	0.410***	0.350***	0.331**	0.271**	0.292*	0.648***
HDL (mmol/L)	-0.835***	-0.727***	-0.614***	-0.563***	-0.337**	-0.721***
LDL (mmol/L)	0.652***	0.597***	0.433***	0.228**	0.427***	0.767***
FPG (mmol/L)	0.340**	0.261**	0.432***	0.296***	0.675***	0.471***
2hPG (mmol/L)	0.550***	0.277***	0.198	0.287***	0.300*	0.162
FINS (μIU/mL)	0.281**	0.195*	0.370***	0.122	0.581***	0.463***
2hINS (μIU/mL)	0.279**	0.286***	0.696***	0.182*	0.109	0.172*
HbA1C (%)	0.253*	0.254**	0.274*	0.213*	0.265*	0.278**
HOMA-IR	0.326**	0.225**	0.427***	0.175*	0.677***	0.584***
HOMA-β	-0.007	-0.016	0.014	-0.084	0.208	-0.007

Data were analyzed after adjusting for age, SBP and DBP. Variables with skewed distributions were log-transformed before statistical analysis.

*P<0.05, **P<0.01, ***P<0.001

Table 3. The risk of prediabetes and Type 2 diabetes according to tertiles of ApoB/ApoA-I ratio in men

		T1 (0-0.5703)	T2 (0.5704-0.7723)	T3 (≥0.7724)
Prediabetes	n, cases/participants	32/102	34/90	24/72
	Model 1	1	1.602 (1.080, 2.122)*	1.427 (0.897, 1.997)
	Model 2	1	1.381 (0.868, 1.943)	1.160 (0.670, 1.758)
	Model 3	1	1.327 (0.813, 1.905)	1.113 (0.599, 1.769)
Type 2 Diabetes	n, cases/participants	18/102	31/90	26/72
	Model 1	1	2.461 (1.506, 3.510)**	2.394 (1.422, 3.485)**
	Model 2	1	2.035 (1.152, 3.126)*	1.901 (1.034, 3.022)*
	Model 3	1	1.643 (0.865, 2.723)	1.074 (0.481, 2.100)

Data are relative ratios (RR), 95% confidential intervals (CI).

Model 1: unadjusted

Model 2: adjusted for age, SBP, DBP

Model 3: adjusted for Model 2+ TC

*$P<0.05$, **$P<0.01$, ***$P<0.001$

Table 4. The risk of prediabetes and Type 2 diabetes according to tertiles of ApoB/ApoA-I ratio in women

		T1 (0-0.5703)	T2 (0.5704-0.7723)	T3 (≥0.7724)
Prediabetes	n, cases/participants	40/141	48/153	62/171
	Model 1	1	1.568 (1.119, 2.044)**	2.221 (1.728, 2.647)***
	Model 2	1	1.317 (0.876, 1.826)	2.009 (1.472, 2.503)***
	Model 3	1	1.478 (0.898, 2.131)	2.186 (1.376, 2.842)**
Type 2 Diabetes	n, cases/participants	15/141	54/153	78/171
	Model 1	1	3.943 (2.540, 5.500)***	5.940 (4.353, 7.272)***
	Model 2	1	3.405 (2.078, 5.001)***	5.439 (3.767, 6.939)***
	Model 3	1	3.115 (1.598, 5.126)**	3.651 (1.685, 6.099)**

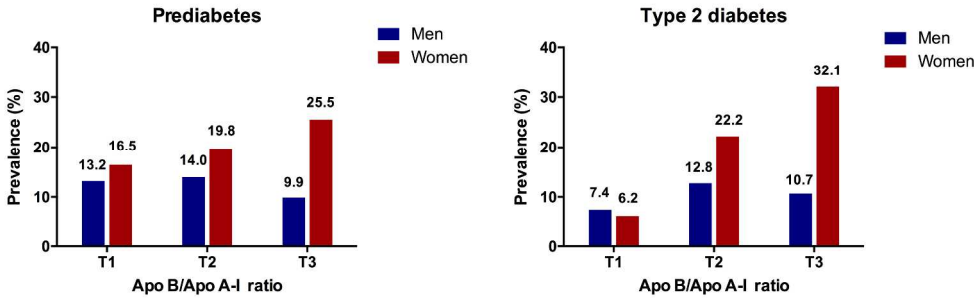
1 Data are relative ratios (RR), 95% confidential intervals (CI).

2 Model 1: unadjusted

3 Model 2: adjusted for age, SBP, DBP, BMI

4 Model 3: adjusted for Model 2+TC, TG, HDL-C, LDL-C

5 $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			7
Key results	18	Summarise key results with reference to study objectives	7-8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Associations of Apolipoprotein B to A-I ratio with pre-diabetes and diabetes risks: a cross-sectional study in Chinese adults

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Diagnostics, Evidence based practice, Public health
Keywords:	apolipoprotein B, apolipoprotein A-I, type 2 diabetes, prediabetes, dyslipidemia

Title Page

Associations of Apolipoprotein B to A-I ratio with pre-diabetes and diabetes risks: a cross-sectional study in Chinese adults

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Abstract

Objectives Apolipoprotein (Apo)B/ApoA-I ratio is a useful predictor of cardiovascular risk. However, the association between the ApoB/ApoA-I ratio and the risk of type 2 diabetes mellitus (T2DM) is still obscure. The aims of the study were to investigate the associations between the ApoB/ApoA-I ratio and the risk of T2DM and pre-diabetes in a Chinese population and also assess the role of gender in these associations.

Participants and Methods A stratified random sampling design was used in this cross-sectional study which included 264 men and 465 women with normal glucose tolerance (NGT), pre-diabetes or T2DM. Serum Apo B, Apo A-I and other lipid and glycaemic traits were measured. Pearson's partial correlation and multivariable logistic analysis were used to evaluate the associations between ApoB/ApoA-I ratio and the risk of T2DM and pre-diabetes.

Results The ApoB/ApoA-I ratios were significantly increased across the spectrum of NGT, pre-diabetes and T2DM. Women showed higher levels of ApoB/ApoA-I ratio and ApoB than men in pre-diabetic and T2DM groups, but not in NGT group. ApoB/ApoA-I ratio was closely related with TG, TC, HDL-C, LDL-C and other glycemic traits. Moreover, in women, the risk of diabetes and pre-diabetes in the top and middle tertiles of ApoB/ApoA-I ratio were 3.65- (95%CIs: 1.69-6.10) and 2.19-fold (95%CIs: 1.38-2.84) higher than in the bottom tertile respectively, after adjusting for potential confounding factors. However, the associations disappeared in men after adjusting for other factors.

Conclusions The ApoB/ApoA-I ratio showed positive associations with the risk of diabetes and pre-diabetes in Chinese women.

Strengths and limitations of this study

- This is an in-depth investigation of the associations between ApoB/ApoA-I ratio and diabetes or pre-diabetes in Chinese population.
- Stratified random sampling ensured equal chance for participant enrolment and the validity of results.
- Data collection and analysis were supported by trained survey team, which included researchers with differing areas of expertise and backgrounds.
- The cross-sectional design does not confirm the causality between ApoB/ApoA-I ratio and diabetes risk.
- Potential bias might exist in a single-centre design.

Keywords: apolipoprotein B; apolipoprotein A-I; type 2 diabetes; pre-diabetes; dyslipidemia

Introduction

Atherogenic dyslipidemia is a characteristic lipoprotein abnormality that includes high levels of triglyceride (TG)-rich lipoproteins (mainly very low-density lipoprotein [VLDL]), low levels of high-density lipoproteins (HDL) and an elevated proportion of small dense low-density lipoprotein (sd-LDL) particles [1]. To date, evaluation of the clinical relevance of atherogenic dyslipidemia has focused on its role as an effective predictor of cardiovascular disease (CVD) compared to other lipid parameters. Apolipoproteins are important structural and functional proteins in lipoprotein particles. Given that circulating levels of apolipoproteins indicate the number of lipoprotein particles, the level of Apo-B reflects the total number of potentially atherogenic particles, including VLDL, intermediate density lipoproteins, large buoyant LDL, and sd-LDL, and the level of ApoA-I represents the number of HDL particles [2]. Thus, the ratio of apolipoproteins B to A-I (ApoB/ApoA-I) would theoretically be an ideal indicator of atherogenic lipid disturbances and cardiovascular risk [3 4].

It is well established that atherogenic dyslipidemia is associated with T2DM and high risk of CVD in T2DM patients [5 6]. Moreover, the mortality rate of CVD in diabetic patients varies with gender [7]. Previous studies have demonstrated that ApoB/ApoA-I ratio may be a strong marker of metabolic syndrome and insulin resistance in certain population [8-10], but the associations of it with T2DM and pre-diabetes as well as its gender effects in Chinese population are still poorly clarified. Additionally, the correlations between ApoB/ApoA-I ratio and other lipid or glycaemic

traits, such as TG, TC, glucose, insulin sensitivity and secretion, need further investigation.

Therefore, in this observational study, we aimed to evaluate the associations between the level of ApoB/ApoA-I ratio and the risk of T2DM, pre-diabetes in both Chinese men and women and also investigate the correlations between the ratio and other lipid and glycaemic traits.

Subjects and Methods

Subjects

Stratified random sampling was performed to select participants from the database of Renji Hospital from January 2010 to December 2014. A total of 1538 subjects aged 18 to 80 years were included. All of them had visited the Department of Endocrinology, Renji Hospital, School of Medicine, Shanghai Jiaotong University for a health check-up.

The exclusion criteria were regular diabetic and/or lipid-lowing medication use, a history of cardiovascular disease, cerebrovascular disease, chronic renal or hepatic failure, cancer, pregnant, hyperthyroidism and hypothyroidism. Subjects with incomplete data were also excluded.

Finally, 729 subjects (264 men and 465 women) were involved in this study. The study was carried out in accordance with the declaration of Helsinki and the study protocol was approved by the Ethical Committee of Renji Hospital, School of Medicine, Shanghai Jiaotong University. Written informed consents were obtained from all

subjects included in the study.

Anthropometry measurements

Height, body weight, waist circumference (WC), hip circumference and blood pressure (BP) were measured by trained survey personnel. Height was measured once with a portable height scale to the nearest 0.1 cm. Weight was measured using a platform digital scale to the nearest 0.1kg. Both height and weight measurements were taken in light clothing without shoes. Waist circumference was recorded as the circumference midpoint between the iliac crest and the lowest rib. Hip circumference was recorded as the largest gluteal circumference. Circumference measurements were taken twice by a single observer and the mean value was reported. Blood pressure was measured twice in each subject on the right arm after a five-minute rest in a sitting position, and the mean of two measurements was used.

Laboratory analysis

All subjects underwent the standard 75g glucose oral glucose tolerance test (OGTT) after an 8-hour overnight fast. Serum ApoB (predominantly ApoB-100) and ApoA-I concentrations were determined by immunoturbidimetric methods using automatic immunoassay analyzer (Roche E-170, Roche, Basel, Switzerland). Glucose and other lipid levels were measured using fully automatic biochemistry analyzer (Hitachi 7600–110 and Hitachi 7020, respectively, Hitachi Co. Tokyo, Japan); Insulin concentration was determined by immunoradiometric assay kit (Dainabot, Tokyo, Japan);

Hemoglobin A1c (HbA1c) level was measured by high-performance liquid chromatography.

Definition of T2DM and pre-diabetes

According to the 2006 World Health Organization criteria [11], diabetes was defined as fasting plasma glucose (FPG) ≥7.0 mmol/L and/or 2-h post-load plasma glucose (2hPG) ≥11.1 mmol/L; pre-diabetes was defined as FPG between 6.1mmol/L and 7.0mmol/L and/or 2hPG between 7.8mmol/L and 11.1mmol/L. For diabetes, the diagnosis was predominately based on the results of the 75g OGTT. In addition, the level of HbA1c>6.5% was also considered as a supplementary criterion. If a subject met both criteria, then the diagnosis of diabetes was certain. However, if a subject met the criteria of OGTT but the level of HbA1c was <6.5%, then the OGTT would be repeated within one month. Two abnormal measurements of OGTT confirmed the diagnosis of diabetes. If a subject didn't meet the criteria of OGTT at the first time, then he or she would be excluded. For pre-diabetes, the diagnosis would be ensured with repeated OGTT in one month. Anyone who didn't meet the criteria of OGTT at the second time would be excluded. Besides, subjects who declined to take the second examination were also excluded.

Calculation

Body mass index (BMI) was defined as the body weight (kg) divided by the square

of body height (m^2). Waist to hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm). Indices of insulin resistance and insulin secretion were calculated from the OGTT data: homeostasis model assessment for insulin resistance (HOMA-IR) = fasting insulin (μU/ml) × fasting glucose (mmol/L) /22.5; homeostasis model assessment for β cell function index (HOMA-β) = 20×fasting insulin in μU/ml / (fasting glucose in mmol/L -3.5).

Statistical analysis

All statistical analyses were performed using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). The available-case analysis (pairwise deletion) was applied to handle missing data. Continuous data were expressed as median (Interquartile range 25-75%) due to the skewed distribution and compared by Kruskal-Wallis H test or Mann–Whitney U test. Adjusted means were calculated and compared with general linear models. Categorical variables were shown as percentages and compared with Chi-square test. A Pearson's partial correlation analysis was carried out to identify the correlativity between ApoB/ApoA-I ratio and other variables after adjusting for several covariates. Data with skewed distribution were log-transformed before analysis. A multivariable logistic regression model was conducted to test the associations between ApoB/ApoA-I ratio and the risk of pre-diabetes and diabetes after controlling for potential confounding factors. The relative ratios (RR) and 95% confidence intervals (CIs) of tertiles 2 to 3 were calculated and compared by using tertile 1 as reference. RR was calculated based on the formula: RR=OR/(1-P0+P0*OR), where OR was odds

ratio and P0 was the disease incidence in non-exposed group. Statistical significance was considered at $p<0.05$.

Results

Clinical and laboratory characteristics

After excluding ineligible subjects on the basis of exclusion criteria and those unable to finish the study, 729 subjects were finally included in this study. Among these eligible participants, 36.2% were men and 63.8% were women, with a mean age of 51.2 years. 30.5% of subjects (28.4% men and 31.6% women) were diagnosed as T2DM, 32.9% (34.1% men and 32.3% women) as pre-diabetes, and 36.6% (37.5% men and 36.1%women) as having normal glucose tolerance (NGT).

The anthropometric and metabolic characteristics of the participants are presented in Table 1. Subjects with T2DM had much higher ApoB/ApoA-I ratios than those with pre-diabetes and NGT, accompanied by worse glucose and lipid profiles. Moreover, T2DM subjects showed higher levels of BP, BMI and WHR. Subjects with pre-diabetes had higher ApoB/ApoA-I ratios than those with NGT. The levels of BP, BMI and WHR in the pre-diabetic group were also higher than those with NGT.

When men and women were analysed separately, the ApoB/ApoA-I ratio in women was higher than in men both in T2DM and pre-diabetic groups. However, the gender difference in NGT group was not significant. Additionally, the levels of ApoB in women were also higher than in men in both T2DM and pre-diabetic groups. But other lipid indices including TG, TC and LDL-C showed little difference between men and

women.

Correlations between ApoB/ApoA-I ratio and other variables

After adjusting for age, systolic and diastolic BP, Pearson's partial correlation analysis showed that ApoB/ApoA-I ratio was positively correlated with TG, TC, LDL-C and negatively correlated with HDL-C, in all 3 groups (Table 2). Gender difference was insignificant. In addition, ApoB/ApoA-I ratio was strongly associated with FPG, HbA1C and HOMA-IR both in men and women. However, the correlations between ApoB/ApoA-I ratio and HOMA-β, insulin levels were not significant.

Risk of pre-diabetes and diabetes according to ApoB/ApoA-I ratio

The ApoB/ApoA-I ratios were further divided into tertiles and the first tertile was regarded as the reference group. In men, the risk of pre-diabetes in tertile 2 was 1.60-fold higher than in the first tertile (RR=1.602, 95%CIs:1.080-2.122 $p<0.05$). However, this association disappeared after adjusting for age, SBP, DBP and TC. In parallel with pre-diabetes, the association of ApoB/ApoA-I ratio with diabetes also disappeared after adjusting for the aforementioned confounding factors in men (Table 3).

Nevertheless, the associations between ApoB/ApoA-I ratio and pre-diabetes or diabetes risk in women were more obvious than in men (Table 4). In women, the risk of pre-diabetes was increased across the tertile of ApoB/ApoA-I ratio (T2: RR=1.568, 95%CIs: 1.119-2.044, $p<0.01$; T3: RR=2.221, 95%CIs: 1.728-2.647, $p<0.001$). After

adjusting for age, SBP, DBP, BMI and other lipid levels, the association between ApoB/ApoA-I ratio and pre-diabetes was attenuated but still significant in T3 group (RR=2.186, 95%CIs: 1.376-2.842, p<0.01). Moreover, the crude RRs and 95%CIs of diabetes in tertile 2 to 3 were 3.943 (95%CIs: 2.540-5.500, p<0.001) and 5.940 (95%CIs: 4.353-7.272, p<0.001), respectively. After further adjusting for confounding factors, the risk of diabetes in the top tertile of ApoB/ApoA-I ratio was still 3.65-fold higher than in the bottom tertile (RR=3.651, 95%CIs: 1.685-6.099, p<0.01).

Prevalence of pre-diabetes and diabetes according to tertile of ApoB/ApoA-I ratio

As shown in **Fig 1**, the prevalence of pre-diabetes and T2DM in women were increased in sequence from the bottom to the top tertiles of ApoB/ApoA-I ratio (for pre-diabetes: T1:16.5%, T2:19.8%, T3:25.5%, p=0.014; for diabetes, T1:6.2%, T2:22.2%, T3:32.1%, p<0.001). However, the prevalence of pre-diabetes and diabetes in men were higher in T2 than in T1 and T3 (for pre-diabetes: T1:13.2%, T2:14.0%, T3:9.9%, p>0.05; for diabetes, T1:7.4%, T2:12.8%, T3:10.7%, p>0.05).

Discussion

In the current cross-sectional study, we observed strong positive associations between the ApoB/ApoA-I ratio and the risk of pre-diabetes and diabetes in women, independent of traditional metabolic risk factors. However, the associations in men were insignificant after adjusting for potential comfounding factors. ApoB/ApoA-I ratio was closely correlated with other lipid parameters and insulin resistance both in

men and women.

It is well known that ApoB/ApoA-I ratio is a better predictor of cardiovascular risk than other conventional lipid indices [12]. However, only a few studies have shown the associations between apolipoprotein levels and the risk of diabetes. Hwang et al. [13] indicated that ApoB/ApoA-I ratio is an effective predictor of T2DM in the Korean population. The ApoB/LDL-C ratio has been associated with T2DM in a population-based study of Turkish adults [14] and ApoB in the Aboriginal Canadian population [15]. Our results consistently suggested that ApoB/ApoA-I ratio was associated with diabetes and pre-diabetes in Chinese women. Furthermore, ApoB/ApoA-I ratio was closely correlated with TG, TC, HDL-C, LDL-C, FPG, HbA1C and HOMA-IR, which is in accordance with previous studies [10 16].

Apolipoproteins regulate the synthesis and metabolism of lipoprotein particles and stabilize their structures. Hence, it is not unexpected that ApoB/ApoA-I ratio was closely related with TG, TC, HDL-C and LDL-C. Apolipoprotein B and A-I are the major protein moieties of LDL and HDL, respectively. The level of ApoB reflects the number of potentially atherogenic particles [17]. Meanwhile, ApoA-I plays an important role in removing excess cholesterol from tissues and incorporating it into HDL for reverse transport to the liver, forming the basis for atheroprotective events [18 19]. Thus, ApoB/ApoA-I ratio reflects the balance of atherogenic and atheroprotective particles, so the higher the level, the higher the tendency of cholesterol deposition, and consequently the higher the risk of CVD [20].

Development of hyperglycemia is closely associated with lipid disturbances [21 22]. In diabetic dyslipidemia, ApoB-containing lipoprotein particles undergo compositional changes, including the increased formation of sd-LDL and large VLDL (VLDL-1) particles [23-25]. These features were present in up to 50% of T2DM patients [26 27] and even in pre-diabetic patients with insulin resistance but normal glucose tolerance [28]. This relationship has been demonstrated by several prospective studies, which indicated that increased levels of TG, sd-LDL, VLDL-1 and small HDL particles are closely associated with incident diabetes, whereas elevated levels of large HDL particles and Apo A-I are negatively associated with diabetes [29-31]. In our study, we found the levels of ApoB were significantly increased in subjects with diabetes and pre-diabetes while the levels of ApoA-I showed the opposite trend across the spectrum of NGT, pre-diabetes and diabetes. As a consequence, the ratio of ApoB/ApoA-I was positively associated with pre-diabetes and diabetes. Moreover, this ratio was significantly correlated with insulin resistance. Previous studies have demonstrated that the ApoB/ApoA-I ratio is an independent predictor of insulin resistance in US non-diabetic subjects [32] and Chinese obesity subjects [33]. A possible explanation for the positive association between the ApoB/ApoA-I ratio and insulin resistance could be that both ApoB and insulin resistance are linked to an inflammatory state [34]. However, detailed mechanisms interpreting this association need further exploration.

The mechanisms leading to the accumulation of triglyceride-rich lipoproteins (TRLs) in patients with T2DM have not been fully elucidated. Hogue et al. [35] demonstrated that the elevated apoB48-containing TRLs of intestinal origin and apoB100-containing TRLs of hepatic origin in diabetic subjects are due to the increased production rates and decreased catabolism of these particles. Furthermore, Duez et al. [36] showed that intestinal secretion of apoB48-containing TRLs is increased in insulin-resistant subjects with hyperinsulinemia.

The effects of gender on lipid and apolipoprotein metabolism have been reported in several studies. Anahnostis et al. [37] conducted a cross-sectional study in premenopausal and postmenopausal Caucasian women, and men and they showed that ApoB concentrations were higher in men than in women. In women, the levels rose with age. Apo A-I concentrations are highest in postmenopausal women and lowest in men. Li et al. [38] observed that postmenopausal status resulted in higher levels of all ApoB-containing lipoproteins. Hence, the risk of CVD was increased in women after menopause. The mechanisms of the gender effects on lipoprotein and apolipoprotein metabolism are not clear, but may be related to sex hormone changes. Some authors have reported that serum estrone or estradiol levels are positively correlated with HDL-C and TG and inversely associated with TC and LDL-C [39 40]. Androgen excess in premenopausal women, as is the case of polycystic ovary syndrome (PCOS), has been associated with increased TG and sd-LDL particles, as well as reduced HDL-C [41]. In addition, hyperandrogenemic women demonstrate increased insulin

resistance and incidence of CVD [42]. However, some other studies have reported conflicting results about the effects of estrone and androgen [43 44].

In our study, it is noticeable that the gender difference was not significant in NGT groups. In pre-diabetic and diabetic groups, the levels of ApoB were increased in women, as were the ApoB/ApoA-I ratios. The results might be interpreted to indicate that age, gender, hormone levels, glucose and lipid levels exist in a complicated relative network and the corroborative effects of hormone and glucose status may accentuate the gender difference. We found the association between ApoB/ApoA-I ratio and the risk of diabetes was still significant in women after adjusting for conventional factors. Unfortunately, women were not further divided into premenopausal and postmenopausal groups due to the lack of information on menopausal status. However, from the median age of women in pre-diabetic and diabetic groups (56.0 years old), we may make an inference that a great number of these women were in the postmenopausal status, which may, to some extent, explain the higher levels of ApoB in women groups and also the higher risk of pre-diabetes and diabetes in women. In men, hormonal changes in andropause are not as recognizable as in female menopause [45 46] but they could also have an influence on our data. The risk of diabetes in men could also be derived from various factors, such as work stress, smoking and drinking and the lack of physical exercise. The number of male participants included in this study was relatively small. These factors may be responsible for the lack of significant association between ApoB/ApoA-I ratio and diabetes risk in men.

There were some limitations in our study. First, it was performed using a cross-sectional design and did not control for potential biases from diet, physical activity, smoking and drinking history. Second, women were not further divided according to menopausal status. Therefore, a prospective and well-controlled study would be needed to elucidate the associations of apoB/ApoA-I ratio with diabetes and pre-diabetes risk.

In conclusion, our findings indicate positive associations between ApoB/ApoA-I ratio and the risk of pre-diabetes and diabetes in Chinese women, independent of traditional metabolic risk factors. However, the associations in men were insignificant after adjusting for potential comfounding factors. Collectively, the results of this study provide valuable evidence for a better understanding of ApoB/ApoA-I ratio in detecting pre-diabetes and diabetes risk in Chinese population, especially in women. Therefore, we propose the possibility of applying this ratio for risk assessment in Chinese women in epidemiologic investigation or routine clinical practice.

Competing interests

We declare that we have no conflict of interest.

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Author contributions

SZ, TH and HX attended the statistical analysis, data interpretation, manuscript writing and revision. HZ, XR, PW, YZ and LW contributed to data interpretation. ME, YJ, YC and HQ contributed to data collection. WL contributed to data collection and revision of the paper. YH contributed to acquisition of funding, study design, and revision of the paper. All authors revised and approved the final manuscript.

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Data sharing statement Additional research data will be made available to the scientific community with as few restrictions as possible.

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Figure legend

Fig 1 Prevalence of pre-diabetes and diabetes according to tertiles of ApoB/ApoA-I ratio

The numbers above the bars mean the prevalence of each outcome, respectively.

T1: tertile 1; T2: tertile 2; T3: tertile.

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Table 1 Characteristics of participants according to glucose status and gender

	NGT			Pre-diabetes			Diabetes					
	Total	Men	Women	Total	Men	Women	Total	Men	Women	*P*1	*P*2	*P*3
Number	267	99	168	240	90	150	222	75	147	NS	NS	NS
Age (years)	51.0 (41.0,57.0)	51.0 (41.5,57.5)	51.0 (40.0,57.0)	56.0 (45.0.61.0)	56.0 (44.0,59.0)	56.0 (47.0,62.0)	56.0 (46.0,60.0)	58.0 (46.0, 61.5)	56.0 (46.0,59.5)	<0.001	<0.001	NS
SBP (mmHg)	114.0 (113.0,116.0)	114.0 (102.0,127.0)	110.0 (102.0,120.5)	121.0 (119.0,123.0)	116.0 (110.0,131.0)	121.0* (114.0,132.0)	121.0 (119.0,123.0)	119.0 (113.0,129.5)	120.0 (110.0,130.5)	<0.001	<0.001	NS
DBP (mmHg)	74.0 (73.0,75.0)	72.0 (68.0,79.0)	74.0 (69.0,80.0)	77.0 (76.0,78.0)	78.0 (72.0,83.0)	78.0 (74.0,82.0)	80.0 (78.0,81.0)	79.0 (73.5,82.0)	79.0 (75.5,85.5)	<0.001	<0.001	0.005
BMI	23.03	23.11	23.06	23.92	24.12	23.64	25.09	27.67	23.37**	0.005	<0.001	<0.001

	(22.60,23.46)	(21.32,25.15)	(19.78,24.92)	(23.47,24.37)	(21.21,27.46)	(21.79,26.33)	(24.61,25.55)	(24.23,29.45)	(21.94,26.38)			
WHR	0.86 (0.85,0.87)	0.88 (0.82,0.91)	0.85* (0.81,0.90)	0.89 (0.88,0.89)	0.89 (0.84.0.93)	0.89 (0.86,0.92)	0.90 (0.90,0.91)	0.91 (0.89,0.94)	0.90* (0.87,0.93)	<0.001	<0.001	0.001
FPG (mmol/L)	4.98 (4.87,5.09)	4.98 (4.65,5.25)	5.01 (4.75,5.35)	5.57 (5.46,5.69)	5.44 (4.92,5.97)	5.60 (5.04,6.11)	7.31 (7.19,7.43)	7.33 (7.16,8.06)	7.15** (5.73,7.87)	<0.001	<0.001	<0.001
2hPG (mmol/L)	6.01 (5.77,6.26)	5.88 (5.30,6.55)	6.05 (5.19,6.83)	9.29 (9.03,9.54)	9.19 (8.51,9.85)	9.36 (8.58,10.19)	13.95 (13.68,14.21)	12.99 (12.23,14.76)	13.07 (11.92,14.73)	<0.001	<0.001	<0.001
FINS (μIU/L)	13.73 (12.85,14.61)	12.27 (9.51,16.90)	11.98 (8.76,20.11)	14.70 (13.78,15.61)	11.75 (10.59,17.71)	12.06 (10.74,18.71)	15.38 (14.42,16.33)	14.77 (10.80,20.03)	14.19 (9.82,18.29)	NS	0.014	NS
2hINS (μIU/L)	64.18 (57.49,70.87)	42.98 (24.02,87.40)	55.13 (35.57,71.38)	80.05 (73.08,87.02)	75.27 (41.60,119.56)	71.97 (48.35,103.81)	71.23 (63.97,78.49)	65.53 (24.57,90.22)	63.75* (34.21,110.37)	0.001	NS	NS
HbA1c （%）	5.5 (5.4,5.6)	5.5 (5.2,5.7)	5.6 (5.3,5.8)	5.8 (5.7,5.9)	5.8 (5.5,6.0)	5.9* (5.6,6.1)	6.9 (6.8,7.0)	6.9 (6.6,7.3)	6.7 (6.0,7.4)	<0.001	<0.001	<0.001

HOMA-IR	3.07 (2.81,3.33)	2.63 (2.01,3.86)	2.67 (1.95,4.60)	3.72 (3.46,3.99)	2.93 (2.27,4.18)	3.28 (2.58,4.58)	5.04 (4.76,5.32)	4.82 (3.46,7.29)	4.18 (3.15,5.85)	0.001	<0.001	<0.001
HOMA-β	218.63 (203.73,233.53)	185.08 (136.51,246.24)	161.87 (124.18,257.26)	154.67 (139.14,170.19)	123.17 (94.47,185.50)	122.29 (87.07,186.75)	93.41 (77.24,109.58)	77.45 (58.17,88.08)	74.54 (55.07,112.40)	<0.001	<0.001	<0.001
TG (mmol/L)	1.50 (1.36,1.65)	1.23 (0.77,1.70)	1.15 (0.77,1.77)	1.77 (1.62,1.92)	1.50 (1.06,1.99)	1.68 (1.09,2.24)	2.72 (2.56,2.88)	2.55 (1.73,4.14)	2.44 (1.69,3.50)	0.012	<0.001	<0.001
TC (mmol/L)	5.02 (4.92,5.12)	4.94 (4.67,5.20)	5.02* (4.67,5.40)	5.13 (5.03,5.23)	5.15 (4.31,5.78)	5.27 (4.66,5.55)	5.64 (5.53,5.75)	5.47 (5.13,6.18)	5.90 (4.93,6.29)	NS	<0.001	<0.001
HDL-C (mmol/L)	1.48 (1.44,1.51)	1.43 (1.19,1.69)	1.45 (1.24,1.68)	1.34 (1.31,1.38)	1.30 (1.14,1.48)	1.29 (1.15,1.46)	1.23 (1.19,1.27)	1.12 (1.09,1.28)	1.28* (1.07,1.38)	<0.001	<0.001	<0.001
LDL-C (mmol/L)	3.03 (2.95,3.12)	2.84 (2.58,3.29)	3.12 (2.58,3.45)	3.05 (2.96,3.14)	2.83 (2.60,3.78)	3.08 (2.76,3.54)	3.37 (3.28,3.47)	3.50 (2.88,3.69)	3.36 (3.02,4.18)	NS	<0.001	<0.001
ApoA-I	1.48	1.43	1.45	1.39	1.40	1.34	1.33	1.36	1.31	<0.001	<0.001	0.005

(g/L)	(1.45,1.51)	(1.31,1.68)	(1.28,1.63)	(1.36,1.43)	(1.26,1.56)	(1.25,1.52)	(1.29,1.36)	(1.22,1.38)	(1.17,1.42)			
ApoB	0.84	0.80	0.84	0.91	0.90	0.97**	0.97	0.97	1.05**	<0.001	<0.001	0.001
(g/L)	(0.81,0.86)	(0.68,0.97)	(0.68,0.97)	(0.88,0.93)	(0.70,0.98)	(0.84,1.03)	(0.94,1.00)	(0.80,1.03)	(0.87,1.17)			
ApoB/Apo	0.60	0.55	0.56	0.67	0.66	0.74**	0.76	0.71	0.78**	<0.001	<0.001	<0.001
A-I ratio	(0.57,0.62)	(0.42,0.72)	(0.44,0.72)	(0.64,0.70)	(0.48,0.77)	(0.56,0.81)	(0.73,0.78)	(0.60,0.82)	(0.68,0.94)			

1 Data were expresses as medians (interquartile ranges 25-75%).

2 SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; WHR: waist to hip ratio; FPG: fasting plasma glucose; 2hPG:

3 2 hour postload plasma glucose; FINS: fasting serum insulin; 2hINS:2 hour postload serum insulin; HbA1c: glycated hemoglobin A1c; HOMA-IR:

4 homeostatic model assessment of insulin resistance; HOMA-β: homeostatic model assessment of β-cell function; TG: triglyceride; TC: total

5 cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA-I: apolipoprotein A-I; ApoB:

6 apolipoprotein B.

7 *P*1: NGT versus pre-diabetic group, *P*2: NGT versus diabetic group, *P*3: pre-diabetic versus diabetic group

8 *P<0.05, **P<0.01 means the gender difference in each group

1 Comparisons among NGT, pre-diabetic and diabetic groups were performed after adjusting for age

Table 2 Partial correlation coefficients of ApoB/ApoA-I ratio with lipid profiles and glycometabolism-related traits

	NGT		Pre-diabetes		Diabetes	
	Men	Women	Men	Women	Men	Women
TG (mmol/L)	0.500***	0.474***	0.560***	0.570***	0.503***	0.654***
TC (mmol/L)	0.410***	0.350***	0.331**	0.271**	0.292*	0.648***
HDL (mmol/L)	-0.835***	-0.727***	-0.614***	-0.563***	-0.337**	-0.721***
LDL (mmol/L)	0.652***	0.597***	0.433***	0.228**	0.427***	0.767***
FPG (mmol/L)	0.340**	0.261**	0.432***	0.296***	0.675***	0.471***
2hPG (mmol/L)	0.550***	0.277***	0.198	0.287***	0.300*	0.162
FINS (μIU/mL)	0.281**	0.195*	0.370***	0.122	0.581***	0.463***
2hINS (μIU/mL)	0.279**	0.286***	0.696***	0.182*	0.109	0.172*
HbA1C (%)	0.253*	0.254**	0.274*	0.213*	0.265*	0.278**
HOMA-IR	0.326**	0.225**	0.427***	0.175*	0.677***	0.584***
HOMA-β	-0.007	-0.016	0.014	-0.084	0.208	-0.007

Data were analyzed after adjusting for age, SBP and DBP. Variables with skewed distributions were log-transformed before statistical analysis.

*P<0.05, **P<0.01, ***P<0.001

Table 3. The risk of pre-diabetes and Type 2 diabetes according to tertiles of ApoB/ApoA-I ratio in men

		T1 (0-0.5703)	T2 (0.5704-0.7723)	T3 (≥0.7724)
Pre-diabetes	n, cases/participants	32/102	34/90	24/72
	Model 1	1	1.602 (1.080, 2.122)*	1.427 (0.897, 1.997)
	Model 2	1	1.381 (0.868, 1.943)	1.160 (0.670, 1.758)
	Model 3	1	1.327 (0.813, 1.905)	1.113 (0.599, 1.769)
Type 2 Diabetes	n, cases/participants	18/102	31/90	26/72
	Model 1	1	2.461 (1.506, 3.510)**	2.394 (1.422, 3.485)**
	Model 2	1	2.035 (1.152, 3.126)*	1.901 (1.034, 3.022)*
	Model 3	1	1.643 (0.865, 2.723)	1.074 (0.481, 2.100)

1 Data are relative ratios (RR), 95% confidential intervals (CI).

2 Model 1: unadjusted

3 Model 2: adjusted for age, SBP, DBP

4 Model 3: adjusted for Model 2+ TC

5 $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$

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Table 4. The risk of pre-diabetes and Type 2 diabetes according to tertiles of ApoB/ApoA-I ratio in women

		T1 (0-0.5703)	T2 (0.5704-0.7723)	T3 (≥0.7724)
Pre-diabetes	n, cases/participants	40/141	48/153	62/171
	Model 1	1	1.568 (1.119, 2.044)**	2.221 (1.728, 2.647)***
	Model 2	1	1.317 (0.876, 1.826)	2.009 (1.472, 2.503)***
	Model 3	1	1.478 (0.898, 2.131)	2.186 (1.376, 2.842)**
Type 2 Diabetes	n, cases/participants	15/141	54/153	78/171
	Model 1	1	3.943 (2.540, 5.500)***	5.940 (4.353, 7.272)***
	Model 2	1	3.405 (2.078, 5.001)***	5.439 (3.767, 6.939)***
	Model 3	1	3.115 (1.598, 5.126)**	3.651 (1.685, 6.099)**

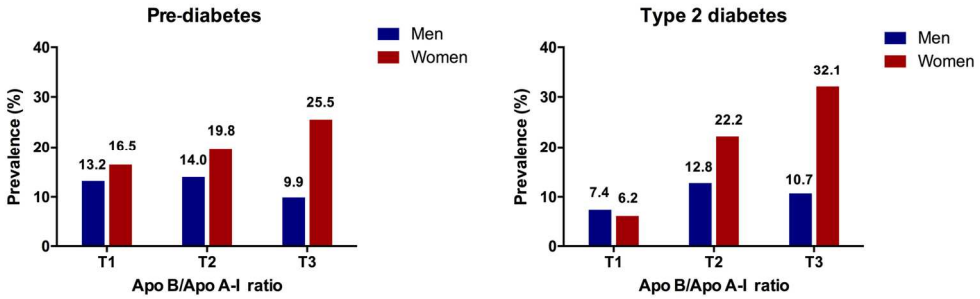
1 Data are relative ratios (RR), 95% confidential intervals (CI).

2 Model 1: unadjusted

3 Model 2: adjusted for age, SBP, DBP, BMI

4 Model 3: adjusted for Model 2+TC, TG, HDL-C, LDL-C

5 $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.