





BMJ Open Association between adiponectin and newly diagnosed type 2 diabetes in population with the clustering of obesity, dyslipidaemia and hypertension: a cross-sectional study

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To cite: Hong X, Zhang X, You L, *et al.* Association between adiponectin and newly diagnosed type 2 diabetes in population with the clustering of obesity, dyslipidaemia and hypertension: a cross-sectional study. *BMJ Open* 2023;**13**:e060377. doi:10.1136/bmjopen-2021-060377

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-060377>).

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Received 21 December 2021

Accepted 05 February 2023



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ABSTRACT

Objectives Adiponectin is closely related to glucose metabolism and traditional diabetes risk factors (obesity, hypertension and dyslipidaemia). We aimed to explore the association between adiponectin levels and newly diagnosed type 2 diabetes mellitus (T2DM) and pre-diabetes in subgroups classified according to T2DM risk factors.

Setting Sun Yat-sen Memorial Hospital of Sun Yat-sen University.

Participants 3680 individuals (1753 men and 1927 women) aged 18–70 years from Guangzhou and Dongguan, China, were enrolled from December 2018 to October 2019.

Primary and secondary outcome measures T2DM was defined as fasting plasma glucose (FPG)≥7.0 mmol/L or HbA1c≥6.5%, and pre-diabetes was defined as 6.1 mmol/L≤FPG<7.0 mmol/L or 5.7≤HbA1c<6.5%.

Results With the increasing number of T2DM risk factors, the proportion of the population with high-quartile adiponectin levels gradually decreased ($p<0.001$). A low level of adiponectin was significantly associated with diabetes and pre-diabetes in a population with ≥1 T2DM risk factor, whereas its association was not consistently significant in the population with all three T2DM risk factors. For instance, participants were more likely to have diabetes or prediabetes with low levels of adiponectin when they had ≥ one T2DM risk factor (quartile 2 vs. 1: OR 0.71 [95%CI: 0.56–0.89]; $P=0.003$; quartile 3 vs. 1: OR 0.57 [95%CI: 0.44–0.72]; $P<0.001$; and quartile 4 vs. 1: OR 0.52 [95%CI: 0.40–0.67]; $P<0.001$).

Conclusion Adiponectin was negatively associated with diabetes and pre-diabetes in a population with few T2DM risk factors, while their relationship gradually attenuated with the accumulation of T2DM risk factors, especially in a population with coexisting diseases such as obesity, hypertension and dyslipidaemia.

INTRODUCTION

Type 2 diabetes mellitus (T2DM), characterised by impaired glucose metabolism and

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This cross-sectional analysis was performed in a large population.
- ⇒ This study investigated the relationship between adiponectin and type 2 diabetes in individuals with complex metabolic status.
- ⇒ Results should be interpreted cautiously due to the observational design.
- ⇒ The fact that oral glucose tolerance test was not used as the diabetes diagnostic criterion would reduce the observed prevalence of diabetes in our study population.
- ⇒ Further studies would be needed to verify these findings in populations with a different racial or ethnic background.

insulin resistance coupled with complex metabolic disorders and multiple complications, is an increasing global health problem.¹ According to the International Diabetes Federation Diabetes Atlas, the number of patients with diabetes worldwide is 463 million and is predicted to reach 700 million by 2045.² Considering the irreversibility and incurability of diabetes and its tremendous social and economic burden on health systems worldwide, the rational and preferred method of detecting new-onset diabetes is of great realistic significance.³

Adiponectin, an adipose tissue-derived insulin sensitiser, is a key component of the inter-relationship between adiposity and insulin resistance and is a major risk factor for type 2 diabetes.⁴ Lower adiponectin levels were observed a decade before T2DM was discovered.⁵ A meta-analysis of 15 prospective studies suggested that higher adiponectin levels were associated with a lower risk of diabetes across diverse populations, which is

consistent with a dose–response relationship.⁶ In addition, accumulating evidence has confirmed that low adiponectin levels are closely related to a high prevalence of abnormal glycolipid metabolism.⁷

Metabolic syndrome (MetS), a constellation of obesity, hyperglycaemia, dyslipidaemia and hypertension, precedes the occurrence of diabetes by almost 5 years and serves as a risk factor for the development of diabetes.^{8,9} Obesity, hypertension and dyslipidaemia, which are common diabetes risk factors, often occur concurrently in patients with diabetes.¹⁰ The severity of MetS is related to the risk of T2DM, and that additional risk will continue to grow with the increase in MetS severity score, which may help integrate the risk associated with the aggregation of individual components.^{11,12} Notably, adiponectin is closely related to glucose metabolism and traditional diabetes risk factors.^{8,13,14} The effect of adiponectin on glucose metabolism can be affected by metabolic biomarkers, including glycaemia, insulin sensitivity, plasma lipid levels and inflammatory markers.¹³ In addition, Kim *et al* suggested that the plasma adiponectin level is a possible biomarker for the development of adiposity-related hypertension, serving as a potential therapeutic target in blood pressure regulation.¹⁵ Since adiponectin serves as part of the common biological background of insulin resistance and inflammation in T2DM and its risk factors, their relationship should be more complicated.¹⁶ Obesity, hypertension and dyslipidaemia may influence this relationship. However, to our knowledge, the complex relationship between adiponectin and T2DM in a population with various clusters of obesity, dyslipidaemia and hypertension remains unknown.

Therefore, we conducted an epidemiological study in a community-based population in southern China. This study aimed to explore the association between adiponectin levels and newly diagnosed T2DM and pre-diabetes in subgroups stratified by T2DM risk factors.

MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted in China between December 2018 and October 2019. The enrolled study population in Guangzhou came from the Sun Yat-sen Memorial Hospital of Physical Examination Center. Meanwhile, the population recruited in Dongguan mainly came from communities (Dalingshan community, Zhangmu community, Daojiao community, Qiaotou community, Songshan Lake community, Qingxi community, Zhang'an community and Meinian Physical Examination Center). Because the study population were from physical examination centre and communities, they were not inpatients or from a particular department. First, clinicians verbally questioned the study population to determine whether they satisfied the inclusion criteria. The inclusion criteria were as follows: (1) those aged 18–70 years; (2) of Han ethnicity and (3) with permanent residency in one of the aforementioned regions for ≥ 3 years.

Then, subjects that met the inclusion criteria were asked to complete a questionnaire, and were subjected to physical examination, laboratory tests and serum adiponectin measurement. The questionnaire mainly includes birth date, gender, ethnicity, previous medical history, present medical history, drug use and dietary supplement use, and is filled in by trained staff. Subsequently, subjects meeting the following exclusion criteria were excluded: (1) pregnancy; (2) self-reported mental illness or severe physical diseases, such as hepatic cirrhosis, chronic renal failure or evident cardiac insufficiency; (3) self-reported infectious disease or malignant tumours; (4) self-reported hypertension, dyslipidaemia, cardiovascular disease or cerebrovascular disease; (5) other self-reported endocrine diseases or (6) long-term use of drugs, dietary supplements or functional food (≥ 3 times/week for more than 3 months). Therefore, the population in our study excluded those who were diagnosed with diabetes or were more likely to have diabetes, instead of a nationally representative sample of adults across China. During the recruitment phase, 3866 participants were recruited and completed the questionnaire, physical examination, laboratory test and serum adiponectin measurement. Next, 168 individuals were excluded since they had a history of diabetes or incomplete information on adiponectin and diagnostic indicators of diabetes (fasting plasma glucose (FPG) or glycosylated haemoglobin (HbA1c)). Finally, 3680 (99.78%) eligible participants, including 2449 normoglycaemic individuals, 1077 individuals with newly diagnosed pre-diabetes and 154 individuals with newly diagnosed T2DM, were enrolled in our final data analyses. The details are presented in a flow chart (figure 1).

Procedures

With the assistance of trained staff, the participants completed anthropometric measurements according to standard procedures. Body weight and height were measured while the participants wore light indoor clothing without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in metres squared (kg/m^2). While the patients were standing and breathing steadily, waist circumference (WC) was measured in a horizontal plane mid-way between the inferior margin of the ribs and the superior border of the iliac crest using a tape measure. Hip circumference (HC) was measured in a horizontal plane at the widest part of the subject's hips using a tape measure. Waist-to-hip ratio (WHR) was calculated as WC divided by HC. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice in the right arm using an electronic sphygmomanometer (OMRON, Omron Company, Japan) after each patient rested for more than 5 min. The mean of the two blood pressure readings was used for data analysis.

Venous blood samples were drawn from the study participants after they fasted overnight. FPG, glycated haemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C)

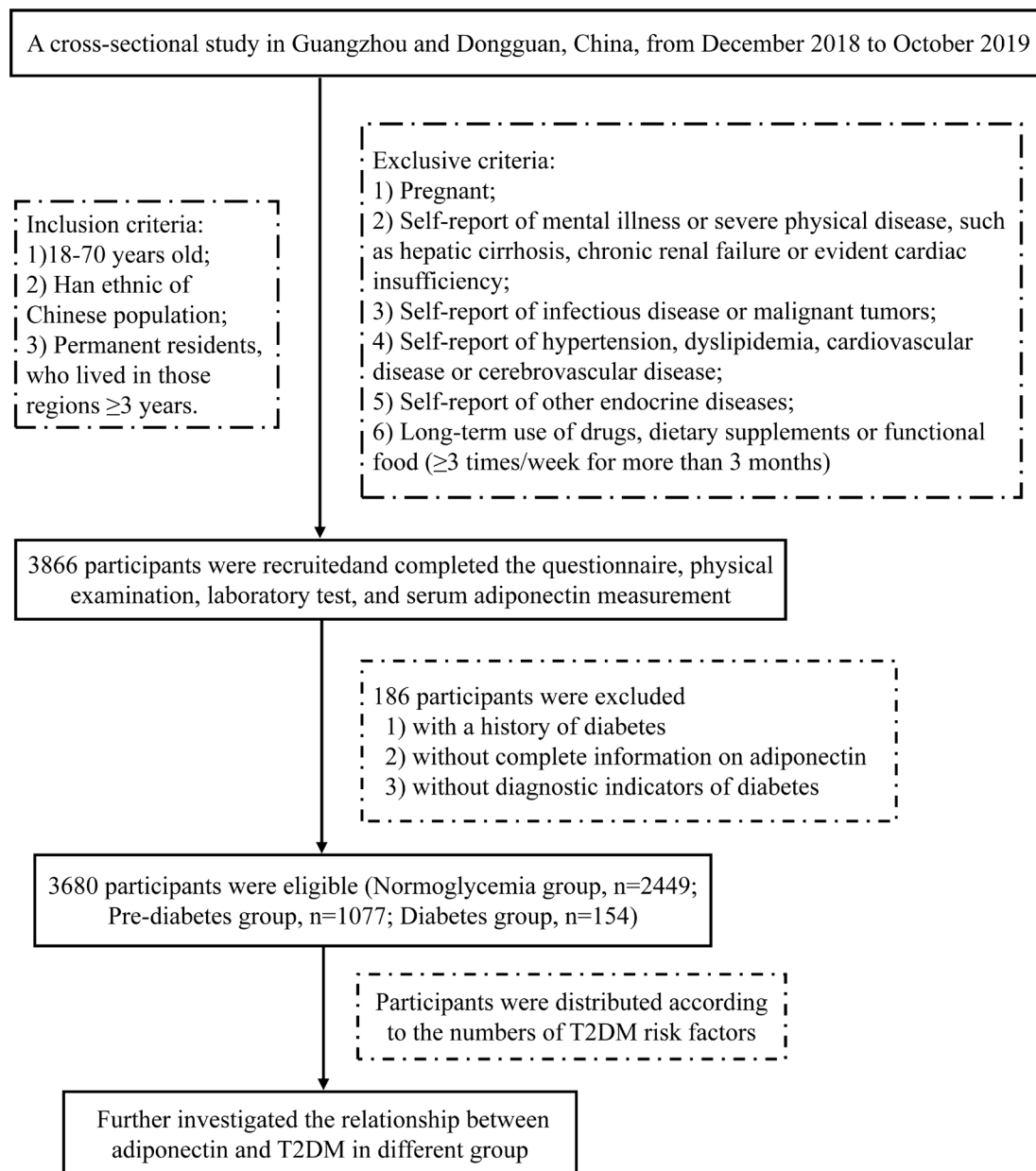


Figure 1 Flow chart of the study design. T2DM, type 2 diabetes mellitus.

and high-density lipoprotein cholesterol (HDL-C) levels were measured using an autoanalyser (Beckman CX-7 Biochemical Autoanalyzer, Brea, California, USA). Serum adiponectin concentrations were measured using a latex-enhanced turbidimetric immunoassay (Uniten Biotechnology, Guangdong, China; Catalogue No 20182400947) using a BS-600 automatic biochemical instrument (Mindray, China). According to the manufacturer's instructions, the range of laboratory measurements was 2.0–40.0 $\mu\text{g}/\text{mL}$, and the intra-assay and interassay coefficients of variation were $<10\%$ and 15% , respectively. The aforementioned tests were performed in the laboratory of the Endocrinology Department of Sun Yat-sen Memorial Hospital. The assay was calibrated and standardised according to the manufacturer's protocol.

Definitions

According to the American Diabetes Association 2020 criteria, individuals were diagnosed with T2DM if they had $\text{FPG} \geq 7.0 \text{ mmol}/\text{L}$ or $\text{HbA1c} \geq 6.5\%$ and diagnosed with pre-DM if $6.1 \text{ mmol}/\text{L} \leq \text{FPG} < 7.0 \text{ mmol}/\text{L}$ or $5.7 \leq \text{HbA1c} < 6.5\%$.¹⁰

There has been increasing evidence of a high prevalence of T2DM among Asian populations with a lower BMI and WC than in Caucasian populations.¹⁷ Combined with the criteria for obesity in Chinese adults,¹⁸ our study defined high BMI levels as $\text{BMI} \geq 24.0 \text{ kg}/\text{m}^2$, high WC levels as a $\text{WC} \geq 80 \text{ cm}$ for females or waistline $\geq 85 \text{ cm}$ for males, obesity as high BMI or WC levels and compound obesity as the combination of high BMI and WC levels.

According to the 'Guideline for Prevention and Treatment of Dyslipidemia in Chinese Adults',¹⁹ the diagnosis of dyslipidaemia was based on the presence of one or more of the following criteria: TC \geq 5.20 mmol/L, TG \geq 1.70 mmol/L, HDL-C $<$ 1.00 mmol/L and LDL-C \geq 3.4 mmol/L.

According to the 'Chinese guidelines for the management of hypertension',²⁰ hypertension was diagnosed as SBP \geq 140 mm Hg or DBP \geq 90 mm Hg.

The features of MetS include increased WC, blood pressure elevation, low HDL-C, high TG and hyperglycaemia, which also serve as risk factors for diabetes.²¹ In this study, we divided the patients into three subgroups, characterised by \geq 1, \geq 2 or \geq 3 diabetes risk factors. Meanwhile, a correlation between adiponectin levels and diabetes and/or pre-diabetes was observed in different subgroups.

Statistical analysis

The baseline characteristics of the study participants were expressed as the mean \pm SD for continuous variables with a normal distribution, and categorical variables were summarised as numbers and proportions. Owing to a skewed distribution, TGs and adiponectin were logarithmically transformed prior to analysis. Differences between groups were tested with one-way analyses of variance, and post hoc comparisons were performed using the Bonferroni correction. Comparisons between categorical variables were performed using the χ^2 test or Fisher's exact test. The distribution of population-clustered T2DM risk factors according to adiponectin quartiles was determined. Based on sociodemographic data and laboratory testing from this survey and previous studies, age, sex, obesity, hypertension and dyslipidaemia were further adjusted in the multiple logistic regression analyses. Multiple logistic regression analyses were used to calculate the incidence of T2DM and pre-diabetes in subgroups that were stratified by the number of clustered T2DM risk factors, including MetS components of obesity, hypertension and dyslipidaemia, and the results were expressed as ORs and 95% CIs after adjusting for sex and age. All of the statistical analyses were performed using the RStudio V.3.6.1. The statistical tests were two sided, and p values $<$ 0.05 were considered statistically significant.

Patient and public involvement

Patients and members of the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

This cross-sectional study enrolled 3680 individuals, including 154 individuals with newly diagnosed T2DM and 1077 individuals with newly diagnosed pre-diabetes; their characteristics are shown in [table 1](#). Compared with the population with normoglycaemia, those with pre-diabetes and diabetes were more likely to be female, older and had higher obesity indicators (BMI, WC, HC

and WHR), hypertension indicators (SBP and DBP) and dyslipidaemia indicators (TC, TG and LDL-C) ($p<$ 0.05). This indicated that the population with a worse glycaemic status tended to have poorer metabolic profiles. Our results also showed that participants with diabetes had significantly lower adiponectin levels than did those with pre-diabetes ($p<$ 0.05), and that there was a decreasing trend of adiponectin levels in populations with normoglycaemia (4.0 (2.9–5.5) mg/L), pre-diabetes (3.7 (2.7–5.3) mg/L) and diabetes (3.2 (2.1–4.7) mg/L). The characteristics of the participants according to adiponectin quartile are shown in [table 2](#). Those with higher plasma adiponectin levels were more likely to be male and older ($p<$ 0.001). Adiponectin quartiles were negatively associated with diabetes indicators (FPG and HbA1c), obesity indicators (BMI, WC, HC and WHR), hypertension indicators (SBP and DBP) and dyslipidaemia indicators (TG, LDL-C and HDL-C) ($p<$ 0.05).

We screened for three traditional diabetes risk factors: obesity (four types: high BMI and WC, obesity and compound obesity), hypertension and hyperlipidaemia. The prevalence rates of diabetes risk factors (including obesity, hypertension and hyperlipidaemia) in different distributions according to adiponectin quartiles are shown in [table 3](#). The prevalence of obesity was 78.71%, 63.71%, 50.68% and 38.05% ($p<$ 0.001); the prevalence of hypertension was 12.67%, 9.59%, 10.28% and 7.56% ($p<$ 0.05); and the prevalence of dyslipidaemia was 76.12%, 59.52%, 53.85% and 53.80% ($p<$ 0.001) in adiponectin quartiles 1–4, respectively. The results of the linear-by-linear association also showed that all diabetes risk factors were negatively correlated with adiponectin levels (p value for trend $<$ 0.001).

[Table 4](#) shows the distribution of the population with clustered T2DM risk factors according to adiponectin quartile. Among the population without T2DM risk factors, the proportion of high-quartile adiponectin was higher, and the exact percentages were as follows: quartile 1, 10.68%; quartile 2, 22.47%; quartile 3, 31.88%; and quartile 4, 34.97%. The opposite trend was observed in populations with two or three T2DM risk factors. Moreover, with the increasing number of T2DM risk factors, the proportion of the population with high-quartile adiponectin levels gradually decreased, and the difference was statistically significant ($p<$ 0.001).

Subsequently, the interactive effects of adiponectin and T2DM risk factors were determined ($p<$ 0.05). Thus, we further analysed the adjusted ORs for diabetes and pre-diabetes according to quartiles of adiponectin in individuals with various combinations of diabetes risk factors ([table 5](#)). We divided the patients into three subgroups, characterised by \geq 1, \geq 2 or \geq 3 diabetes risk factors. Meanwhile, a correlation between adiponectin levels and diabetes and/or pre-diabetes was observed in different subgroups. After adjusting for sex and age, negative associations between adiponectin and T2DM and/or pre-diabetes were consistently detected in populations with various diabetes risk factors. In the population with one

Table 1 Baseline characteristics of study population according to glucometabolic state

| Variables | Total population | Normoglycaemia | Pre-diabetes | Diabetes | P value |
|--------------------------|------------------|------------------|-------------------|--------------------|------------------|
| n (%) | 3680 (100.0) | 2449 (66.55) | 1077 (29.27) | 154 (4.18) | – |
| Male (%) | 1753 (47.77) | 1114 (45.54) | 561 (52.28) | 78 (51.66) | 0.001 |
| Age (years) | 45.42±13.80 | 42.09±13.18 | 51.92±12.69* | 53.03±11.80* | <0.001 |
| Height (cm) | 161.76±8.73 | 162.03±8.62 | 161.28±8.82 | 160.91±9.61 | 0.032 |
| Weight (kg) | 63.0±12.0 | 61.98±11.78 | 64.60±11.99* | 67.78±13.26*† | <0.001 |
| BMI (kg/m ²) | 23.98±3.57 | 23.51±3.46 | 24.74±3.52* | 26.08±4.02*† | <0.001 |
| WC (cm) | 82.09±10.31 | 80.21±10.22 | 85.40±9.31* | 88.56±9.97*† | <0.001 |
| HC (cm) | 94.82±7.22 | 94.06±7.24 | 96.11±6.87* | 97.60±7.43*† | <0.001 |
| WHR | 0.86±0.07 | 0.85±0.07 | 0.89±0.06* | 0.91±0.07*† | <0.001 |
| SBP (mm Hg) | 119.5±15.0 | 117.3±14.2 | 123.4±15.0* | 127.0±18.7*† | <0.001 |
| DBP (mm Hg) | 73.18±10.0 | 72.0±9.7 | 75.2±9.8* | 78.0±11.4*† | <0.001 |
| TC (mmol/L) | 5.13±1.06 | 5.01±1.01 | 5.36±1.08* | 5.60±1.13*† | <0.001 |
| TG (mmol/L) | 1.22 (0.84–1.83) | 1.10 (0.79–1.62) | 1.45 (1.02–2.10)* | 1.78 (1.22–2.78)*† | <0.001 |
| LDL-C (mmol/L) | 3.05±0.88 | 2.94±0.82 | 3.25±0.95* | 3.30±0.99* | <0.001 |
| HDL-C (mmol/L) | 1.48±0.54 | 1.48±0.51 | 1.49±0.59 | 1.44±0.64 | 0.585 |
| Adiponectin (mg/L) | 3.9 (2.8–5.4) | 4.0 (2.9–5.5) | 3.7 (2.7–5.3) | 3.2 (2.1–4.7)*† | <0.001 |

Data are expressed as mean±SD or medians (IQRs) for skewed variables or numbers (proportions) for categorical variables.

TG and adiponectin are skewed in distribution, log transformation before variance analysis and comparison in pairs.

P values were for the analysis of variance (ANOVA) or χ^2 analyses across the groups. Bold indicates statistical significance.

*P<0.001 compared with normoglycaemia population.

†P<0.05 compared with pre-diabetes.

BMI, body mass index; DBP, diastolic blood pressure; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WHR, waist-to-hip ratio.

or more risk factors, multiple logistic regression analyses showed that adiponectin levels in quartile 1 had a significant protective effect against the occurrence of glucose metabolism disorders compared with quartiles 2–4. With the increasing number of diabetes risk factors, only adiponectin quartiles 3 and 4 showed statistically significant differences compared with adiponectin quartile 1. Finally, compared with adiponectin quartile 1, only quartile 4 had a significant protective effect against the occurrence of glucose metabolism disorders in the subpopulation with all three traditional diabetes risk factors. For instance, participants were more likely to have diabetes or prediabetes with low levels of adiponectin when they had \geq one T2DM risk factor (quartile 2 vs. 1: OR 0.71 [95%CI: 0.56–0.89]; P=0.003; quartile 3 vs. 1: OR 0.57 [95%CI: 0.44–0.72]; P<0.001; and quartile 4 vs. 1: OR 0.52 [95%CI: 0.40–0.67]; P<0.001).

DISCUSSION

In this study, we found that adiponectin showed a decreasing trend in populations with normoglycaemia, pre-diabetes and diabetes, indicating that adiponectin may be involved in the progression from pre-diabetes to diabetes. Our study indicated that adiponectin was associated with abnormal glucose metabolism; however, this relationship might not be stable and could be affected

by various diabetes risk factors (obesity, hypertension and dyslipidaemia). When the number of diabetes risk factors was low, increased adiponectin levels were positively associated with abnormal glucose metabolism. However, with an increasing number of diabetes risk factors, the relationship between adiponectin levels and abnormal glucose metabolism gradually decreased. In the subpopulation with all three traditional diabetes risk factors, only the highest adiponectin quartile showed a significant positive association with glucose metabolism compared with quartile 1. Therefore, adiponectin may be used to evaluate glucose metabolism risk; however, it should be combined with obesity-related indicators, blood pressure and blood lipid levels in the application process.

T2DM is a global health problem, and its burden is expected to increase in the coming years. Therefore, it is important to investigate the risk factors for diabetes and identify suitable biomarkers for the prevention and control of diabetes. Pre-diabetes, typically defined as blood glucose concentrations higher than normal but lower than the threshold for diabetes, is a high-risk state for the development of diabetes.²² Notably, adiponectin, a newly established biomarker, enables a statistically significant improvement in the assessment of the risks of both diabetes and pre-diabetes beyond the use of traditional risk factors.⁶ In the Whitehall II study that explored the

Table 2 Clinical characteristics of participants according to quartiles of adiponectin

| Characteristics | Adiponectin | | | | χ^2 /F/Z | P value |
|--------------------------|-------------------|-------------------|-------------------|-------------------|---------------|------------------|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | | |
| n (%) | 941 (25.58) | 928 (25.22) | 917 (24.93) | 893 (24.28) | – | – |
| Distribution (mg/L) | 2.30 (1.90; 2.50) | 3.40 (3.10; 3.70) | 4.60 (4.30; 4.90) | 6.80 (6.00; 7.90) | – | – |
| Male (%) | 315 (33.51) | 449 (48.59) | 536 (58.58) | 617 (69.33) | 255.96 | <0.001 |
| Age (years) | 42.75±11.35 | 44.18±13.10 | 45.49±14.19 | 49.45±15.48 | 40.76 | <0.001 |
| Height (cm) | 164.54±8.29 | 162.63±8.62 | 160.86±8.75 | 158.86±8.21 | 74.83 | <0.001 |
| Weight (kg) | 69.96±12.10 | 64.58±10.45 | 60.67±11.11 | 56.44±9.86 | 252.6 | <0.001 |
| FPG (mmol/L) | 5.26±1.18 | 5.05±0.93 | 4.99±0.89 | 4.98±0.84 | 16.10 | <0.001 |
| HbA1c (%) | 5.55±0.76 | 5.40±0.61 | 5.38±0.56 | 5.40±0.66 | 13.01 | <0.001 |
| BMI (kg/m ²) | 25.75±3.40 | 24.37±3.11 | 23.38±3.46 | 22.35±3.40 | 170.9 | <0.001 |
| WC (cm) | 87.42±9.51 | 83.40±9.34 | 80.01±9.62 | 77.34±9.92 | 179.6 | <0.001 |
| HC (cm) | 97.72±6.87 | 95.85±6.31 | 93.66±7.19 | 91.93±7.13 | 116.3 | <0.001 |
| WHR | 0.89±0.06 | 0.87±0.07 | 0.85±0.07 | 0.84±0.07 | 98.91 | <0.001 |
| SBP (mm Hg) | 121.04±15.30 | 119.47±14.36 | 119.12±15.56 | 118.17±14.59 | 5.684 | 0.0007 |
| DBP (mm Hg) | 74.97±10.35 | 73.31±9.48 | 72.75±10.25 | 71.62±9.49 | 17.78 | <0.001 |
| TC (mmol/L) | 5.14±1.08 | 5.07±0.97 | 5.12±1.11 | 1.20±1.05 | 2.21 | 0.085 |
| TG (mmol/L) | 2.08±1.42 | 1.53±1.07 | 1.33±0.85 | 1.11±0.72 | 141.20 | <0.001 |
| LDL-C (mmol/L) | 3.13±0.88 | 3.03±0.82 | 3.03±0.90 | 3.00±0.91 | 3.889 | 0.009 |
| HDL-C (mmol/L) | 1.31±0.48 | 1.43±0.51 | 1.53±0.53 | 1.67±0.56 | 74.87 | <0.001 |

Data are expressed as mean±SD or medians (IQRs) for skewed variables or numbers (proportions) for categorical variables. P values were for the χ^2 or analysis of variance or Z test across the groups. Significant p-values ($p < 0.05$) were in bold.

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WHR, waist-to-hip ratio.

prediagnosis trajectories of adiponectin in individuals who developed T2DM, Tabák *et al* observed lower adiponectin levels more than a decade before the diagnosis of diabetes.⁵ Furthermore, in a meta-analysis of 13 prospective studies in diverse populations, higher adiponectin levels were consistently associated with a lower risk of T2DM, and the associations did not differ substantially by ethnicity, mean BMI, adiponectin measurement method, diagnostic criteria for diabetes, duration of follow-up or number of diabetes cases.⁶ However, the relative risks of T2DM vary from 0.11 (0.01–0.96) to 1.04 (0.69–1.56) in different study populations with high levels of adiponectin after adjusting for different metabolic markers, including BMI, hypertension and TG.⁶ Therefore, it is still difficult to exclude the possibility that other metabolic factors are responsible for such an association in epidemiological studies.

In addition to being closely related to the occurrence of abnormal glucose metabolism, accumulating evidence suggests that adiponectin is significantly inversely correlated with obesity, hypertension, dyslipidaemia and insulin resistance, which are well-known risk factors for diabetes.^{8 13 14} Extensive studies have shown that the plasma adiponectin level in overweight or obese populations is significantly decreased and negatively correlated

with BMI and WC.^{23 24} Adults with hypertension also have lower mean adiponectin levels than do normotensive adults, and there is an inverse monotonic relationship between adiponectin levels and a future risk of hypertension.¹⁵ In addition, adiponectin was found to be correlated with various parameters of lipoprotein metabolism and is especially associated with the metabolism of HDL-C and TG.^{25–27} Although data on adiponectin-specific interventions are currently lacking, several lifestyle and pharmacological interventions have been shown to increase adiponectin levels by reducing weight and improving blood pressure and lipid levels.^{28 29} Epidemiological studies also found that diabetes risk factors, such as obesity, hyperlipidaemia and hypertension, often coexist with T2DM and jointly cause complex metabolic disorders. MetS is a cluster of factors that include abdominal obesity, hyperglycaemia, dyslipidaemia and hypertension and also serves as a risk factor for the development of diabetes.³⁰ Additionally, adiponectin is inversely associated with incidental MetS and each individual trait, which is accompanied by a graded dose–response relationship.^{31–33} This is concordant with our finding that greater clusters of diabetes risk factors are associated with lower adiponectin levels.

Table 3 The prevalence rate of population with T2DM risk factor according to quartiles of adiponectin

| T2DM risk factor | Adiponectin | | | | χ^2 | P value | P value* |
|------------------|-------------|-------------|-------------|-------------|----------|------------------|------------------|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | | | |
| High BMI level | | | | | | | |
| No | 281 (30.25) | 434 (47.54) | 553 (61.10) | 655 (73.60) | 379.29 | <0.001 | <0.001 |
| Yes | 648 (69.75) | 479 (52.26) | 352 (38.90) | 235 (26.40) | | | |
| High WC level | | | | | | | |
| No | 277 (31.33) | 393 (45.07) | 513 (58.83) | 577 (67.80) | 266.31 | <0.001 | <0.001 |
| Yes | 607 (68.67) | 479 (54.93) | 359 (41.17) | 274 (32.20) | | | |
| Obesity | | | | | | | |
| No | 195 (21.29) | 327 (36.29) | 434 (49.32) | 534 (61.95) | 333.79 | <0.001 | <0.001 |
| Yes | 721 (78.71) | 574 (63.71) | 446 (50.68) | 328 (38.05) | | | |
| Compound obesity | | | | | | | |
| No | 363 (40.47) | 500 (56.56) | 632 (70.46) | 698 (79.41) | 326.59 | <0.001 | <0.001 |
| Yes | 534 (59.53) | 384 (43.44) | 265 (29.54) | 181 (20.59) | | | |
| Hypertension | | | | | | | |
| No | 793 (87.33) | 811 (90.41) | 803 (89.72) | 807 (92.44) | 13.123 | 0.004 | 0.001 |
| Yes | 115 (12.67) | 86 (9.59) | 92 (10.28) | 66 (7.56) | | | |
| Dyslipidaemia | | | | | | | |
| No | 219 (23.88) | 368 (40.48) | 414 (46.15) | 401 (46.20) | 127.09 | <0.001 | <0.001 |
| Yes | 698 (76.12) | 541 (59.52) | 483 (53.85) | 467 (53.80) | | | |

P values were for the χ^2 analyses across the groups. Significant p-values ($p < 0.05$) were in bold.

High BMI level was defined as $\text{BMI} \geq 24.0 \text{ kg/m}^2$.

High WC level was defined as a waistline $\geq 80 \text{ cm}$ for females or $\geq 85 \text{ cm}$ for males.

Obesity was defined as high BMI level or high WC level.

Compound obesity was defined as the combination of high BMI level and high WC level.

Hypertension was defined as $\text{SBP} \geq 140 \text{ mm Hg}$ or $\text{DBP} \geq 90 \text{ mm Hg}$.

Dyslipidaemia was defined as the presence of one or more of the following criteria: $\text{TC} \geq 5.20 \text{ mmol/L}$ or $\text{TG} \geq 1.70 \text{ mmol/L}$ or $\text{HDL-C} < 1.00 \text{ mmol/L}$ or $\text{LDL-C} \geq 3.4 \text{ mmol/L}$.

*Linear-by-linear association.

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference.

Adiponectin may be a critical link between obesity, hypertension, dyslipidaemia, insulin resistance and T2DM. The true extent of adiponectin as a causal intermediate versus concurrent pathological processes of complex metabolic status remains unknown. Therefore, it is necessary to consider the different metabolic states of the population when using adiponectin levels to assess the risk of diabetes. Although numerous cross-sectional and

prospective studies carried out in populations of various ethnicities, ages, sexes and physical status (such as obesity, dyslipidaemia, cardiac disease and nephropathy) have repeatedly demonstrated that lower adiponectin levels are consistently associated with a higher risk of T2DM,⁶ the complex role of clustered diabetes risk factors in the association between adiponectin and diabetes still needs to be elucidated.

Table 4 Distribution of population-clustered T2DM risk factors according to quartiles of adiponectin

| Groups according to T2DM risk factors | Adiponectin | | | | χ^2 | P value |
|---------------------------------------|-------------|-------------|-------------|-------------|----------|------------------|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | | |
| Number of risk factors, n (%) | | | | | | |
| 0 | 76 (10.68) | 160 (22.47) | 227 (31.88) | 249 (34.97) | 306.52 | <0.001 |
| 1 | 212 (18.14) | 313 (26.77) | 301 (25.75) | 343 (29.34) | | |
| 2 | 474 (36.90) | 322 (26.44) | 264 (21.22) | 194 (15.44) | | |
| 3 | 92 (40.18) | 61 (26.64) | 47 (20.52) | 29 (12.66) | | |

T2DM risk factors including obesity, hypertension and dyslipidaemia.

P values were for the χ^2 analyses across the groups. Significant p-values ($p < 0.05$) were in bold.

T2DM, type 2 diabetes mellitus.

Table 5 Adjusted ORs for diabetes and pre-diabetes by quartiles of adiponectin (compared with normoglycaemia population)

| T2DM risk factors (n) | Diabetes | | | Pre-diabetes | | | Pre-diabetes or diabetes | | | |
|-----------------------|------------|--------------|---------------------|--------------|--------------|---------------------|--------------------------|--------------|---------------------|--------|
| | n (%) | OR (95% CI)* | P value | n (%) | OR (95% CI)* | P value | n (%) | OR (95% CI)* | P value | |
| ≥1 | Quartile 1 | 60 (11.83) | 1.00 | 271 (37.74) | 1.00 | - | 331 (42.54) | 1.00 | - | |
| | Quartile 2 | 27 (5.86) | 0.38 (0.23 to 0.63) | <0.001 | 235 (35.13) | 0.79 (0.62 to 1.00) | 0.048 | 262 (37.64) | 0.71 (0.56 to 0.89) | 0.003 |
| | Quartile 3 | 24 (5.84) | 0.33 (0.19 to 0.55) | <0.001 | 201 (34.18) | 0.63 (0.49 to 0.81) | <0.001 | 225 (36.76) | 0.57 (0.44 to 0.72) | <0.001 |
| | Quartile 4 | 25 (6.94) | 0.30 (0.17 to 0.51) | <0.001 | 206 (38.08) | 0.58 (0.45 to 0.76) | <0.001 | 231 (40.81) | 0.52 (0.40 to 0.67) | <0.001 |
| ≥2 | Quartile 1 | 51 (14.45) | 1.00 | 213 (41.36) | 1.00 | - | 264 (46.64) | 1.00 | - | |
| | Quartile 2 | 21 (9.10) | 0.43 (0.24 to 0.76) | 0.005 | 152 (41.99) | 0.83 (0.62 to 1.11) | 0.208 | 173 (45.17) | 0.75 (0.57 to 0.99) | 0.043 |
| | Quartile 3 | 20 (10.70) | 0.46 (0.25 to 0.82) | 0.010 | 124 (42.61) | 0.72 (0.52 to 0.99) | 0.043 | 144 (46.30) | 0.67 (0.49 to 0.90) | 0.009 |
| | Quartile 4 | 14 (11.20) | 0.38 (0.18 to 0.75) | 0.007 | 98 (46.89) | 0.68 (0.46 to 0.98) | 0.040 | 112 (50.22) | 0.61 (0.43 to 0.87) | 0.007 |
| 3 | Quartile 1 | 11 (22.92) | 1.00 | 44 (54.32) | 1.00 | - | 55 (59.78) | 1.00 | - | |
| | Quartile 2 | 8 (23.53) | 0.57 (0.17 to 1.80) | 0.345 | 27 (50.94) | 0.63 (0.30 to 1.33) | 0.229 | 35 (57.38) | 0.64 (0.31 to 1.29) | 0.210 |
| | Quartile 3 | 4 (17.39) | 0.33 (0.07 to 1.30) | 0.131 | 24 (55.81) | 0.72 (0.32 to 1.61) | 0.424 | 28 (59.57) | 0.66 (0.30 to 1.44) | 0.297 |
| | Quartile 4 | 1 (5.88) | 0.08 (0.00 to 0.54) | 0.028 | 12 (42.86) | 0.33 (0.12 to 0.89) | 0.030 | 13 (44.83) | 0.29 (0.11 to 0.73) | 0.010 |

P values were for the χ^2 analyses across the groups. Significant p-values ($p < 0.05$) were in bold.

*Adjusted by sex and age.

T2DM, type 2 diabetes mellitus.

To calculate the prevalence of type 2 diabetes and/or pre-diabetes according to adiponectin level, previous multivariate regression analyses mainly adjusted following covariates: age, sex, obesity indicators, blood pressure, and dyslipidaemia indicators.⁶ In this study, we aimed to explore the association between adiponectin levels and newly diagnosed diabetes and/or pre-diabetes according to the accumulation of T2DM risk factors (obesity, hypertension and dyslipidaemia). We divided the patients into three subgroups, characterised by ≥ 1 , ≥ 2 or ≥ 3 diabetes risk factors (obesity, hypertension and dyslipidaemia) for this purpose. Therefore, covariate adjustments in the logistic regression analysis only included age and sex, instead of more confounding factors (such as obesity indicators, blood pressure and dyslipidaemia indicators). After analysing the relationship between adiponectin and the number of risk factors for diabetes, we further analysed whether the correlation between adiponectin and the risk of diabetes would be disturbed after gradually increasing the number of risk factors for diabetes. Intriguingly, our group found that adiponectin was only associated with glucose metabolism in a population with more than one diabetes risk factor, while the relationship gradually decreased with an increasing number of diabetes risk factors. If obesity, hypertension and dyslipidaemia coexist, the effect of adiponectin on dysglycaemia is significantly reduced. Thus, our study indicates that the relationship between adiponectin and diabetes in different metabolic states is complex and should be regarded by clinicians as a warning sign in clinical applications. When using adiponectin to construct a clinical prediction model for diabetes, it is necessary to comprehensively consider the complex metabolism of the individual. The results revealed that the risk assessment effect of adiponectin on T2DM is limited, especially in individuals with a complex metabolic status. Thus, we propose that adiponectin plays a distinctive role in assessing T2DM risk in subgroups with various diabetes risk factors (obesity, hypertension and dyslipidaemia). This interesting discovery is thought provoking.

Adiponectin modifies glucose homeostasis, favours adipose tissue expansion, inhibits renin-angiotensin system activation and exhibits both anti-inflammatory and antiatherogenic effects in the regulation of insulin sensitivity and glucose and lipid metabolism.³⁴ Therefore, serving as a common biological background for these factors, it is unsurprising that adiponectin may gradually play a smaller role in diabetes risk assessment in populations with obesity, hypertension and dyslipidaemia. There are several possible explanations for these results. On one hand, it is hypothesised that low levels of adiponectin are a combined reflection of T2DM and its risk factors, and T2DM or pre-DM has been latent or has appeared in the case of three diabetes risk factors. Another possibility is that the role of adiponectin in the risk assessment is limited. Adiponectin may be partly involved in the pathogenesis and process of diabetes, which is contributed to by diabetes risk factors. The occurrence of obesity,

hypertension and dyslipidaemia has weakened the role of adiponectin, making it lose its risk assessment capacity for diabetes. Whether or not the aggregation of other metabolic components will interfere with other metabolic diseases (such as obesity) and the risk assessment capacity of adiponectin is not known; this is also an interesting topic for future investigation. Notably, our study population excluded those who were diagnosed with hypertension and dyslipidaemia, which likely resulted in the fewest participants having all three traditional diabetes risk factors. The small number of subgroup samples led to insignificant differences. In general, our results suggest that adiponectin should be used cautiously to assess the risk of diabetes or pre-diabetes in individuals with metabolic disorders.

This study had some limitations. First, it is necessary to highlight that this study had a cross-sectional design, which only permits association, but not causality, to be established among different variables. Second, because this epidemiological study was performed in a community-based population in Guangzhou and Dongguan, China, our findings may not be generalisable to other populations. To some extent, the population in the present study was still a convenience sample, and selection bias was inevitable. Third, FPG and HbA1c were used for the diagnosis of diabetes in our study, and the fact that the oral glucose tolerance test was not used as a diagnostic criterion for diabetes reduced the observed prevalence of diabetes in our study population. However, FPG and HbA1c are commonly used as diagnostic criteria for diabetes in large-scale epidemiological investigations.^{35–37} Thus, it is suggested that our study still has favourable application prospects and provides the basis for follow-up scientific research. Last but not least, due to the exploratory nature of the study, the findings should be interpreted with caution. Nevertheless, to our knowledge, the present study is the first population-based study to explore the association between adiponectin and diabetes in different metabolic states, which may better guide clinicians in recognising and applying adiponectin.

CONCLUSIONS

In conclusion, adiponectin may be negatively associated with diabetes and pre-diabetes in populations with or without T2DM risk factors, while their relationship gradually attenuates with the accumulation of T2DM risk factors, especially in a population with coexisting diseases such as MetS. Our study indicated that the relationship between adiponectin and diabetes might be affected by various metabolic factors and should be considered by clinicians as a warning sign in clinical application. Clinicians should take a rational view of the predictive effects of adiponectin on dysglycaemia.

Acknowledgements We are indebted to the participants of the present study for their persistent outstanding support and to our colleagues for their valuable assistance.

Contributors KS is responsible for the overall content as guarantor. KS, CW, MR and YL conceived and designed the experiments. CW, XZ, HL, NM and JW acquired the clinical data. FL, XH, XZ and HL performed the experiments. XH, XZ and LY analysed the data. KS, XH and LY wrote the manuscript. All of the authors read and approved the final manuscript.

Funding This work was supported by grants from the following sources: (1) National Key Research and Development Project of China (2016YFC0901204); (2) National Science Foundation of China (81970696); (3) Natural Science Foundation of China (82000784); (4) Sun Yat-sen Clinical Research Cultivating Program (SYS-Q-201801); (5) Sun Yat-sen University Clinical Research 5010 Program (2018021); (6) Medical Science and Technology Research Fund Project of Guangdong Province (A2019391); (7) Science and Technology Planning Project of Guangdong Province, China (2014A020212069); (8) Natural Science Foundation of Guangdong Province, China (2022A1515012111) and (9) Guangzhou Basic Research Program (Basic and Applied Basic Research Project) (202102080101).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Institutional Review Board of Sun Yat-sen Memorial Hospital affiliated with Sun Yat-sen University (number: (2019) Ethical Approval Research No 38) and was in accordance with the principles of the Declaration of Helsinki II. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request. The work described was original research that has not been published previously, and not under consideration for publication elsewhere, in part or in whole. All authors believe that the manuscript represents valid work and have reviewed and approved the final version. Main document data and additional unpublished data from the study are available by sending email to skendo@163.com with proper purposes.

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