The Connection Between Triglycerides and Ectopic Fat Obesity: An Inverted U-Shaped Curve

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Abstract

Background: Ectopic fat obesity and Triglycerides are risk factors for diabetes and multiple cardiovascular diseases, but the data on the relationship between Triglycerides and the risk of ectopic fat obesity are limited. The purpose of this study is to explore the connection between Triglycerides and ectopic fat obesity.

Methods: This is a cross-sectional study, we retrospectively analyzed 15464 adult participants recruited by Murakami Memorial Hospital from 2004-2015 (8430 men and 7034 women, average age 43.71±8.9), to performed the relationship between Triglycerides and ectopic fat obesity, we divided all patients into 4 groups according to the quartile of Triglycerides. Logistic regression model was used to analyze the relationship between Triglycerides and the risk of ectopic fat obesity, and the generalized additive model was used to identify the nonlinear relationship.

Results: In the study population, the prevalence of ectopic fat obesity was 17.73%, and gradually increased in the quartile of Triglycerides (2.86, 7.89, 18.25 and 41.22% respectively, P < 0.001). After adjusting other covariables, Triglycerides was positively correlated with the risk of ectopic fat obesity (OR:1.55, 95%CI:1.41-1.69, p<0.00001). Then we carried out smooth curve fitting and found that there was an inverted U-shaped curve relationship between Triglycerides and ectopic fat obesity, even if those adjusted covariables were removed from the model, the result remained unchanged, and the inflection point of the curve was 3.98. On the left side of the inflection point, Triglycerides was positively correlated with the risk of ectopic fat obesity (OR:1.784, 95%CI:1.611-1.975, p<0.0001), while on the right side of the inflection point, there was a negative correlation (OR:0.519, 95%CI:0.333-0.810, p=0.0039).

Conclusions: Our research shows that there is a significant correlation between Triglycerides and ectopic fat obesity, this relation is not a simple linear relationship, but it was an inverted U-shaped curve relationship.

Background

Obesity is often regarded as a collection of oversized and overweight physical features in our daily life. The World Health Organization defines obesity as abnormal or excessive fat accumulation, which
may damage health[1]. Abnormal metabolism of blood lipids is particularly important in obesity. As we know, adipose tissue is a very active metabolic organ, and they participate in physiological activities among various systems, however, excessive fat accumulation will adversely affect almost all physiological functions of the human body, it directly or indirectly increases the risk of hypertension, chronic kidney disease, type 2 diabetes, obstructive sleep apnea and a variety of cardiovascular and cerebrovascular diseases, and even plays an important role in the pathogenesis of cancer[2-8]. Obesity is gradually bringing an extremely serious economic and disease burden to the world[2,8]. Since the 1980s, the global prevalence of overweight and obesity has doubled in more than 70 countries, and nearly 1/3 of the world's population is now classified as overweight or obese[2]. Obesity was regarded as a body surface characteristic in the past, now it is regarded as a complex disease with multiple causes, which has been paid more and more attention by more and more people[9]. In the past, obesity was mainly assessed on the basis of body mass index (BMI), however, some studies clearly point out that the sensitivity of BMI is low, and there is a great difference in the ratio of owning fat among individuals, relying solely on BMI to evaluate obesity may hinder future interventions[2]. Recently, a series of studies based on obesity phenotype have become potential hotspots, namely “visceral fat obesity” and “ectopic fat obesity”[2,10-12]. Ectopic fat is defined as extra adipose tissue that appears in locations unrelated to the initial storage of adipose tissue, such as fat storage in the liver and muscle, pericardial fat, perivascular fat and perirenal fat, and the liver fat is considered to be the representative of ectopic fat accumulation[13][14]. Previous studies have reported that there is a close relationship between ectopic fat obesity and dyslipidemia, diabetes and cardiovascular disease[7,15-17]. Søndergaard E et al have pointed out that the storage of Triglycerides (TG) in different tissues may lead to ectopic fat accumulation and contribute to the progression of type 2 diabetes[18], in the cardiovascular field, the relationship between TG and a variety of cardiovascular diseases has a similar positive correlation[19-21]. At present, there is little research data on the relationship between TG and the risk of ectopic fat obesity, in the guidelines, there are no clear instructions of the treatment of ectopic fat obesity for the management of blood
lipids. Ectopic fat obesity is still a healthy problem that has not been widely pay attention to, in the society. Therefore, it is very important to explore and intervene the risk factors of ectopic fat obesity. The purpose of this study is to test the hypothesis that there is a correlation between TG and ectopic fat obesity.

In this study, we conducted a secondary data analysis based on previously published data. In this paper, author Okamura T et al investigated the correlation between ectopic fat obesity and the risk of diabetes[16]. In the secondary analysis, we take TG as the independent variable, and ectopic fat obesity as the result variable, and other covariables are consistent with the covariates in the original analysis, in order to explore the relationship between Triglycerides and the risk of ectopic fat obesity.

Methods

Research population and design

This is a cross-sectional study that designed to evaluate the relationship between TG and ectopic fat obesity. The clinical data of our study population are from a public database (https://datadryad.org), which provided by Okamura T et al [16]. According to the Dryad terms of Service, we referenced Dryad packets in this study. (Okamura, Takuro et al. (2019), Data from: Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study, Dryad, Dataset, https://doi.org/10.5061/dryad.8q0p192). In the study all participants were at least 18 years old, and clinical data were extracted from individual cases who took participated in the physical examination program at Murakami Memorial Hospital from 2004 to 2015, who were recruited to participate in the human dock physical examination program, which was originally designed to detect chronic diseases and their risk factors in order to promote public health, we performed an investigation of the effect of TG on the risk of ectopic fat obesity. Research ethical approval and participants' informed consent were obtained in previous studies, so this study no longer requires research ethical approval.

Data collection

In order to obtain the baseline data of all populations We used a standardized self-administered questionnaire to obtain the medical history and lifestyle factors, including smoking habits, drinking
habits and physical activities. In this observational study, cases with the following characteristics were excluded: 1. Alcoholic fatty liver disease[22]. 2. Viral hepatitis (defined by measuring hepatitis B antigen and hepatitis C antibodies). 3. Participants who took any drug at baseline and who had diabetes at the time of baseline examination. 4. Participants with missing covariable data. 5. Participants with fasting blood glucose $\geq 6.1$ mmol/L.

**Definition**

Alcohol consumption: alcohol consumption was assessed by asking participants about the type and amount of alcohol consumed per week in the previous month, and then estimating the average weekly alcohol intake. Participants were divided into the following four groups: no or a small amount of alcohol, $< 40$ g/week; light drinking, 40-140 g/week; moderate, 140-280 g/week; or heavy drinking, $> 280$ g/week.

Smoking status: participants were divided into three groups according to their smoking status: never smokers, past smokers or current smokers. Non-smokers were defined as participants who never smoked, past smokers were defined as participants who used to smoke but quit before the baseline visit, and current smokers were defined as participants who smoked during the baseline visit.

Habit of exercise: Defined as a participant who regularly participates in any type of exercise more than once a week.

Ectopic fat obesity: In this research, ectopic fat obesity is defined as fatty liver confirmed by abdominal ultrasound, and the diagnosis of fatty liver is made by trained technicians and gastroenterologists by examining the results of abdominal ultrasonography, based on the scores of the following four ultrasound examinations (hepatorenal echo contrast, liver brightness, deep attenuation and vascular blurring)[23].

**Statistical analysis**

First of all, we will stratify the study population according to the quartile of TG, expressed by Q1-Q4, Kolmogorov-Smirnov test is used to test the normal distribution of continuous variables, continuous variables are expressed by mean±standard, classified variables are described by n or %. The analysis process of whether there is significant difference between the groups is as follows: one-way analysis
of variance is performed for continuous variables that meet the normal distribution, and the continuous variables for the skewed distribution are processed using the Kruskal-Wallis H test, the classified variables are analyzed by chi-square test or Fisher exact probability method. Then univariate analysis was performed on all variables to initially assess the risk of ectopic fat obesity, and multiple linear regression was used to test the collinearity between variables. According to the variance inflation factor (VIF)[24], the variables with VIF > 5 were excluded from the regression equation, and the multivariate logical regression model was used to calculate the correlation between TG and ectopic fat obesity and evaluate its risk degree. The adjusted odds ratios (OR) of 95% confidence interval (CI) estimation is used to evaluate the risk of TG. Based on the STROBE statement, we show both the results of the unadjusted analysis, the fine-tuning adjustment analysis and the full adjustment analysis, and whether the adjustment of the covariance follows the following principle: when we add this model, the matching odds ratios is changed by at least 10%[25]. In order to further verify the robustness of the result analysis of TG as a continuous variable, we continue the sensitivity analysis, we treat the TG as a classified variable and calculate the p for trend. As a result of TG is a continuous variable, we use the generalized additive model (GAM) to identify whether there is a nonlinear relationship between TG and ectopic fat obesity, if the result is nonlinear correlation, the inflection point of the curve is identified by the Engauge Digitizer software, and the two-stage linear regression model is used to calculate the threshold effect of TG on the occurrence of ectopic fat obesity according to the smoothing curve. In addition, the hierarchical logistic regression models was used to analyze the results of each subgroup(Sex, Age, Habit of exercise, Smoking status, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, AST: aspartate amino transferase, HbA1c: hemoglobin A1c, HDL cholesterol: HDL: high-density lipoprotein cholesterol, Total cholesterol, SBP: systolic blood pressure, Fasting plasma glucose and BMI). For continuous variables, we converted them into classified variables according to the clinical entry point, and each stratification was adjusted on the basis of all factors, except the stratification factor itself. Likelihood ratio was used to test the modification and interaction of subgroups, bilateral tail p < 0.05 is the significant standard. All of the Statistical analyses were performed using with the software package
Results

Study population baseline characteristics

In this study, a total of 20944 participants were recruited, including 12498 men and 8446 women, 5480 participants were excluded who did not meet the inclusion criteria, of whom including 863 people without covariant data, 416 patients with hepatitis B or C virus, 739 people with heavy drinking habits, 2321 people who took drugs at baseline, 323 patients with diabetes, 808 people with baseline fasting blood glucose exceeding 6.1mmol/L, and 10 other patients who did not participate in the study for unknown reasons. Finally, we evaluated 15464 people who met the inclusion and exclusion criteria (8430 men and 7034 women, with an average age of 43.71±8.9), including 2741 patients with ectopic fat obesity, we divided them into quartiles according to the quartile of TG(≤0.497, 0.497 to ≤0.734, 0.734 to ≤1.118, ≥1.118). Table 1 summarizes the clinical baseline characteristics of the study population. We found that in the TG group, male participants and people diagnosed with fatty liver accounted for a higher proportion of the higher TG group, and generally had higher Age, BMI, Body weight, Waist circumference, ALT, AST, GGT, Total cholesterol, HbA1c. Fasting plasma glucose and blood pressure in the group with higher TG level. On the contrary Habit of exercise and HDL cholesterol had more exercise times and HDL cholesterol levels in the groups with lower TG values, and there were statistical differences in all independent variables among different TG groups, p<0.05.

Univariate analysis

The results of univariate analysis are shown in Table 2. Univariate analysis showed that heavy drinking, smoking, ALT, AST, Total cholesterol, GGT, Triglycerides, HbA1c, Fasting plasma glucose, SBP, DBP: Diastolic blood pressure, Sex, Age, BMI and Waist circumference were positively correlated with the risk of ectopic fat obesity. Nevertheless, HDL cholesterol, Habit of exercise, and Light drinking were negatively correlated with the incidence of ectopic fat obesity. We also found that women had a lower risk of ectopic fat obesity than men.
The results of relationship between TG and incident of Ectopic fat obesity

Before establishing the Logistic regression model, we carried out multiple linear regression tests on all variables, and judged the collinearity between variables according to VIF. Finally, we eliminated three variables: body weight, SBP and Waist circumference. In this research, we used a Logistic regression model to evaluate the relationship between TG and ectopic fat obesity. The unadjusted and adjusted models are shown in Table 3. In the rough model, there was a positive correlation between TG and ectopic fat obesity (OR=4.14, 95%CI:3.85-4.44,p<0.00001), but there was no significant change in the fine-tuning model(Model I: adjust for: Sex, Age and BMI) (OR:2.09, 95%CI:1.94-2.26,p<0.00001). After adjusting the whole model(Model II: adjust for: Sex, Age, ALT, AST, Habit of exercise, GGT, HDL cholesterol, Total cholesterol, HbA1c. Smoking status, Fasting plasma glucose. SBP and BMI), we can still see that there is a positive correlation between them(OR: 1.55, 95%CI:1.41-1.69, p<0.00001). Moreover, we conducted a sensitivity analysis, and we treated TG as a classification variable, and we found that after adjusting the model, the risk of ectopic fat obesity in the group with higher TG(≥1.118) was 3.16 times higher than that in the group with lower TG(≤0.497). In addition, from the change of the effect value (1, 1.41, 2.16, 3.16), it can be seen that the risk of ectopic fat obesity increases gradually with the increase of TG content(P for trend<0.00001), indicating that this trend is significant.

The analyses of non-linear relationship

In this study, due to TG is a continuous variable, we use the GAM to identify the nonlinear relationship between TG and ectopic fat obesity, after adjusting Sex, Age, ALT, AST, Habit of exercise, GGT, HDL cholesterol, Total cholesterol, HbA1c. Smoking status, Fasting plasma glucose. SBP and BMI. we find that there is an inverted U-shaped curve relationship between TG and ectopic fat obesity and there is a curve inflection point in TG within the range of 3.5-4mmol/l, as shown in figure 1. In addition, according to gender as a stratification factor, we fitted the relationship between TG and ectopic fat obesity in different genders. In figure 2, we can observe that there is a similar inverted U-shaped curve relationship between men and women, and after multivariable adjustment, the inverted U-shaped curve relationship still exists. Through Engauge Digitizer software, we identified the inflection
point of the curve of the relationship between TG and ectopic fat obesity in the study population was
3.98, while the inflection point was 3.93 in men and 5.18 in women, we used a two-stage linear
regression model, calculated the threshold effect of TG on the incidence of ectopic fat obesity
according to the smoothing curve and its inflection point, and found that there was a positive
correlation between TG and ectopic fat obesity on the left side of the inflection point
(OR:1.784,95%CI:1.611-1.975,p<0.0001), and on the right side of the inflection point, there is a
negative correlation between them(OR:0.519,95%CI:0.333-0.810,p=0.0039)(Table4).

**Subgroup analyses**

Through the subgroup, we can further explore other risks in the association between TG and ectopic
fat obesity. We transformed variables with p-values <0.05 in univariate analysis (exclude collinearity
variable) into categorical variables for hierarchical analysis based on clinical entry points(Sex, Age,
ALT, AST, Habit of exercise, GGT, HDL cholesterol, Total cholesterol, HbA1c, Smoking status, Fasting
plasma glucose. SBP and BMI), and observed whether the stratified variables interaction with TG,
showing on the table 5, we observed significant interactions between TG and gender, HDL, BMI,
smoking status, and fasting blood glucose (P for interaction <0.05), while the interaction tests were
not statistically significant in Age, Habit of exercise, Total cholesterol, HbA1c, SBP, ALT, AST and GGT.
Among other risks associated with ectopic fat obesity and TG, We can see that the correlation
between TG and men is higher than that of women, the correlation between TG and TG is higher in
people with higher HDL cholesterol (>1.04mmol/l) than in those with lower HDL cholesterol
(≤1.04mmol/l), and the correlation between lower fasting blood glucose (≤4.5mmol/l) and TG is
higher than that of higher fasting blood glucose (>4.5mmol/l). In people with higher BMI (>28kg/m2),
there is a significantly higher risk of ectopic obesity after the increase of TG values. In addition, we
also found an interesting phenomenon that the correlation with TG among non-smokers was slightly
higher than that among smokers.

**Discussion**

Our results show that after adjusting for other covariates, there is a positive correlation between TG
and the incidence of ectopic fat obesity (OR:1.55,95%CI:1.41-1.69, p<0.00001), which is consistent
with previous findings[26-28], however, previous studies have not determined the nonlinear relationship, they just evaluate the linear relationship, while in the current study, based on a larger data sample to match the smooth curve fitting, we found that there is an inverted U-shaped curve relationship between TG and ectopic fat obesity, even if the adjusted covariates are removed from the model or dealing with gender as a stratification factor, the results are consistent. We use Engauge Digitizer software to confirm the inflection point of the curve is 3.98, by use a two-stage linear regression model to calculate the threshold effect of TG on the risk of ectopic fat obesity according to the inflection point. It's obvious effect on the left and right side of the inflection point is the opposite. There is a positive correlation between TG and ectopic fat obesity on the left side of the inflection point (OR:1.784,95%CI:1.611-1.975,p<0.0001), but on the right side of the inflection point, There is a negative correlation between TG and ectopic fat (OR:0.519,95%CI:0.333-0.810,p=0.0039), previous studies have not identified the existence of nonlinear relationship and inflection points [26-28]. The inverted U-shaped curve relationship between TG and ectopic fat obesity and the mechanism behind the inflection point are not clear, on account of the relationship between ectopic fat and metabolic dysfunction, this problem has important physiological and clinical significance. In a recent study, Bril F and his colleagues reported the link between intrahepatic triglyceride (IHTG) and ectopic liver fat. They pointed out that when the accumulation of IHTG reached about 6% ±2%, the serum TG would not continue to increase[29]. We speculate that the accumulation of IHTG may be related to the inflection point of the inverted U curve we have studied at present. When the accumulation of IHTG reaches the threshold, there is saturation effect, which further leads to the saturation effect of TG accumulation, that is, the inflection point of TG in the curve.

For the past few years, the research on ectopic fat obesity has gradually increased, it has been found that ectopic fat obesity is an important risk factor for a variety of cardiovascular diseases and type 2 diabetes[7,15-17], while the status of TG has been gradually improved in the cardiovascular and endocrine fields[11,19-21], but there is no clear standard for the evaluation of ectopic fat obesity at present. In this study, after adjusting covariates, it is confirmed that TG is related to ectopic fat obesity (OR:1.55,95%CI:1.41-1.69,p<0.00001), and the risk of ectopic fat obesity in the higher TG
group (≥1.118 mmol/l) was 3.16 times higher (OR:3.16, 95% CI:2.45-4.07, p<0.00001, P for trend<0.00001) than that in the lower TG group (≤0.497 mmol/l). Furthermore, subgroup analysis helped us to better understand the changing trend of TG and the incidence of ectopic fat obesity in different populations. The results showed that gender, HDL, BMI, smoking status and fasting blood glucose were strongly correlated with the incidence of ectopic fat obesity (P for interaction<0.05). In terms of our long-term clinical practice and literature study, we suggest that the lipid management requirements of ectopic fat obesity should be improved and more attention should be paid to the influence of TG.

As far as we know, this is the first study to evaluate the non-linear relationship between TG and ectopic fat obesity. In this study, we proved that TG can be highly positively correlated with the incidence of ectopic fat obesity, and the relationship between the two is a rare inverted U-shaped curve. the results of this study are helpful for clinicians to evaluate the ability of patients to benefit from the current management of blood lipids.

There are still some limitations in this observational study, and the interpretation of the results should be cautious. First of all, the design of the study is cross-sectional, he cannot explain the causal link between TG and ectopic fat obesity, and our case comes from a single medical center, which will limit the universal applicability of the sample, however, because this study has a large enough clinical sample size. The conclusion of the study can be considered to be relatively objective. Second, because of our limited detection ability for the diagnosis of ectopic fat, fatty liver is used to replace ectopic fat in the study, but in fact, fatty liver can’t be completely equated with ectopic fat, because ectopic fat accumulates in the liver, skeletal muscle, pancreas, heart and many internal organs. Third, owing to the lack of low density lipoprotein and other apolipoproteins in the study data, we have evaluated only a few common lipoproteins, and there may be some data collection bias from uncollected lipoprotein data, but we have made strict statistical adjustments to minimize residual confounding factors. Fourth, because the previous study design excluded patients with diabetes and impaired fasting blood glucose and patients with more missing data, given the prevalence of obesity, people with ectopic fat obesity may be underestimated and need to be explained more carefully.
Fifth, although we have adjusted a wide range of confounding factors, there are still some non-measurable factors that cannot be ruled out, such as dietary factors and psycho-emotional factors, because the assessment of confounding factors has residual confounding caused by measurement errors.

**Conclusion**

All in all, our research shows that there is a significant correlation between TG and ectopic fat obesity, and there is an inverted U-shaped curve relationship between them. At present, ectopic fat obesity is still a health problem that has not aroused widespread social attention, there is no unified standard for the treatment of regulating blood lipids. Therefore, it is of great significance to find a relatively simple, stable, cheap and convenient index to evaluate the risk of ectopic fat obesity and guide its treatment.

**Abbreviations**

TG: Triglycerides; BMI: body mass index; VIF: variance inflation factor; CI: confidence interval; OR: odds ratios; GAM: generalized additive model; HbA1c: hemoglobin A1c, ALT: alanine aminotransferase, AST: aspartate amino transferase, GGT: gamma glutamyl transferase, HDL: high-density lipoprotein, SBP: systolic blood pressure. DBP: Diastolic blood pressure; IHTG: intrahepatic triglyceride.

**Declarations**

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**Authors’ contributions**
Conceptualization, Methodology: Guobo Xie, Guotai Sheng and Yang Zou; Project administration: Guobo Xie; Software: Yang Zou; Visualization: Yang Zou; Supervision: Guotai Sheng, Guobo Xie and Meng Yu; Writing-Original draft preparation: Yang Zou and Meng Yu; Writing- Reviewing and Editing: Yang Zou, Guotai Sheng, Guobo Xie and Meng Yu.

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**Ethics approval and consent to participate**
Research ethics approval and informed consent from participants were obtained in previous studies, so research ethics approval is no longer required for this study.

**Competing interests:**
The authors declare that they have no competing interests.

**Availability of data and materials:**
Data can be downloaded from ‘DA TADRY AD’ database (www.Datadryad.org).

**Consent for publication:**
Not applicable.

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### Table 1. Baseline Characteristics of participants (N=15464)

| Variables                              | Q1 (≤0.497) | Q2 (0.497 to≤0.734) | Q3 (0.734 to≤1.118) | Q4 (≥1.118) | P-value |
|----------------------------------------|-------------|---------------------|---------------------|-------------|---------|
| No. of participants                    | 3812        | 3826                | 3901                | 3925        |         |
| Sex, (men)                             | 1057 (27.73%) | 1798 (46.99%)      | 2405 (61.65%)       | 3170 (80.76%) | <0.001  |
| Age, (years)                           | 40.66±8.26  | 43.46 ± 8.93        | 44.98 ± 8.88        | 45.64±8.8   | <0.001  |
| BMI (kg/m²)                            | 20.46 ± 2.41| 21.41 ± 2.71        | 22.45 ± 2.98        | 24.08 ± 3.13| <0.001  |
| Body weight (kg)                       | 54.20 ± 8.92| 58.11 ± 10.14       | 61.81 ± 10.89       | 68.20±11.47 | <0.001  |
| Waist circumference (cm)               | 71.15 ± 7.18| 74.23 ± 8.10        | 77.61 ± 8.47        | 82.69 ± 8.32| <0.001  |
| Ectopic fat obesity                    | 109 (2.86%)  | 302 (7.89%)         | 712 (18.25%)        | 1618 (41.22%)| <0.001  |
| Habit of exercise                      | 686 (18.00%) | 729 (19.05%)        | 669 (17.15%)        | 625 (15.92%) | 0.003   |
| Drinking status                        |             |                     |                     |             | <0.001  |
| Never                                  | 3274 (85.89%)| 2978 (77.84%)       | 2887 (74.01%)       | 2666 (67.92%)|         |
| Light                                  | 295 (7.74%)  | 458 (11.97%)        | 486 (12.46%)        | 519 (13.22%) |         |
| Moderate                               | 201 (5.27%)  | 284 (7.42%)         | 376 (9.64%)         | 499 (12.71%) |         |
| Heavy                                  | 42 (1.10%)   | 106 (2.77%)         | 152 (3.90%)         | 241 (6.14%)  |         |
| Never                                  | 2908 (76.29%)| 2425 (63.38%)       | 2093 (53.65%)       | 1605 (40.89%)| <0.001  |
| Past                                   | 480 (12.59%) | 696 (18.19%)        | 813 (20.84%)        | 963 (24.54%) |         |
| Current                                | 424 (11.12%) | 705 (18.43%)        | 995 (25.51%)        | 1357 (34.57%)|         |
| ALT (IU/L)                             | 15.30 ± 8.05| 17.26 ± 9.14        | 20.33 ± 17.67       | 26.86 ± 16.73| <0.001  |
| AST, (IU/L)                            | 17.05 ± 6.66| 17.39 ± 6.12        | 18.29 ± 11.40       | 20.80 ± 8.78 | <0.001  |
| GGT (IU/L)                             | 14.03 ± 9.30| 16.91 ± 12.48       | 20.58 ± 16.52       | 29.45 ± 25.61| <0.001  |
| HDL cholesterol (mmol/L)               | 1.70 ± 0.39  | 1.57 ± 0.38         | 1.41 ± 0.35         | 1.18 ± 0.30  | <0.001  |
| Total cholesterol (mmol/L)             | 4.69 ± 0.76  | 5.01 ± 0.79         | 5.22 ± 0.80         | 5.56 ± 0.86  | <0.001  |
| Triglycerides (mmol/L)                 | 0.36 ± 0.09  | 0.61 ± 0.07         | 0.90 ± 0.11         | 1.76 ± 0.75  | <0.001  |
| HbA1c (%)                              | 5.13 ± 0.30  | 5.15 ± 0.32         | 5.18 ± 0.32         | 5.22 ± 0.34  | <0.001  |
| Fasting plasma glucose (mmol/L)        | 4.97 ± 0.39  | 5.11 ± 0.40         | 5.21 ± 0.39         | 5.34 ± 0.38  | <0.001  |
| SBP (mmHg)                             | 108.38 ± 13.03| 112.25 ± 13.99      | 115.87 ± 14.79      | 121.27 ± 14.88| <0.001  |
| DBP (mmHg)                             | 67.00 ± 9.21 | 69.97 ± 9.81        | 72.60 ± 10.18       | 76.58 ± 10.32| <0.001  |

Values are n(%) or mean±SD. Abbreviations: BMI: body mass index, ALT: alanine aminotransferase, AST: aspartate amino transferase, GGT: gamma glutamyl transferase, HDL: high-density lipoprotein, HbA1c: hemoglobin A1c, SBP: systolic blood pressure. DBP: Diastolic blood pressure.
Table 2 The results of univariate analysis

| Variables       | OR(95%CI)     | P-value |
|-----------------|---------------|---------|
| Sex(men)        | 4.920 (4.434, 5.459) | <0.00001 |
| Age             | 1.017 (1.012, 1.021)  | <0.00001 |
| BMI             | 1.638 (1.607, 1.670)  | <0.00001 |
| Body weight     | 1.128 (1.123, 1.134)  | <0.00001 |
| Waist circumference | 1.200 (1.192, 1.209)  | <0.00001 |
| Habit of exercise | 0.773 (0.689, 0.868) | 0.00001 |
| OR(95%CI)       | P-value       |
| Non             | Ref           |         |
| Light           | 0.904 (0.790, 1.035)  | 0.14425  |
| Moderate        | 1.048 (0.907, 1.212)  | 0.52546  |
| Heavy           | 1.284 (1.041, 1.584)  | 0.01962  |
| Smoking status  |               |         |
| Never           | Ref           |         |
| Past            | 2.076 (1.873, 2.302)  | <0.00001 |
| Current         | 1.866 (1.689, 2.061)  | <0.00001 |
| ALT             | 1.102 (1.097, 1.107)  | <0.00001 |
| AST             | 1.088 (1.081, 1.095)  | <0.00001 |
| GGT             | 1.032 (1.030, 1.035)  | <0.00001 |
| Total cholesterol | 1.560 (1.533, 1.588)  | <0.00001 |
| Triglycerides   | 4.135 (3.850, 4.440)  | <0.00001 |
| HbA1c           | 4.211 (3.686, 4.809)  | <0.00001 |
| Fasting plasma glucose | 6.591 (5.882, 7.385)  | <0.00001 |
| SBP             | 1.051 (1.048, 1.054)  | <0.00001 |
| DBP             | 1.076 (1.071, 1.080)  | <0.00001 |

Abbreviations: CI: confidence; OR: odds ratios; Ref: reference; other abbreviations as in Table 1.

Table 3 Relationship between TG and Ectopic fat obesity in different models

| Variable          | Crude Model | Model I | Model II |
|-------------------|-------------|---------|----------|
|                  | OR(95%CI)   | P       | OR(95%CI) | P       | OR(95%CI) | P       |
| TG                | 4.144 (3.85, 4.44) | <0.0000 | 2.091 (1.94, 2.26) | <0.0000 | 1.551 (1.41, 1.69) | <0.0000 |
| TG quartile       |             |         |          |         |          |         |
| Q1                | 2.91 (2.33, 3.64) | <0.0000 | 1.71 (1.34, 2.17) | 0.00001 | 1.41 (1.09, 1.81) | <0.0005 |
| Q2                | 7.59 (6.17, 9.33) | <0.0000 | 3.1 (2.48, 3.88) | <0.0000 | 2.16 (1.69, 2.75) | <0.0001 |
| Q3                | 23.83 (19.49, 29.13) | <0.0000 | 6.03 (4.84, 7.51) | <0.0000 | 3.16 (2.45, 4.07) | <0.0001 |
| P for trend       | <0.0000     |         | <0.0000   |         | <0.0000   |         |

Crude model: we did not adjust other Variables; Model I adjust for: Sex, Age and BMI; Model II adjust for: Sex, Age, ALT, AST, Habit of exercise, GGT, HDL cholesterol, Total cholesterol, HbA1c. Smoking status, Fasting plasma glucose, SBP and BMI; Abbreviations: CI: confidence; OR: odds ratios; PP-value; Ref: reference.

Table 4 The result of two-stage linear regression model

| Ectopic fat obesity (OR,95%CI) | P-value |
|---------------------------------|---------|
| Model I                         |         |
| Fitting model by standard linear regression | 1.545 (1.413, 1.688) | <0.0001 |
| Model II                        |         |
| Fitting model by two-stage linear regression |         |
| Inflection point of CAR ≤3.98 | 3.98 1.784 (1.611, 1.975) | <0.0001 |
| >3.98 | 0.519 (0.333, 0.810) | 0.0039 |

Model II adjusted Sex, Age, ALT, AST, Habit of exercise, GGT, HDL cholesterol, Total cholesterol, HbA1c. Smoking status, Fasting plasma glucose, SBP and BMI; Abbreviations: CI: confidence; OR: odds ratios;

Table 5 Effect size of TG on Ectopic fat obesity in prespecified and exploratory subgroups

| Characteristic | No. of participants | OR (95%CI) | P-value | P for interaction |
|----------------|---------------------|------------|---------|------------------|
| Age (year)     |                     |            |         |                  |
| 18-29          | 416                 | 2.308 (0.846, 6.298) | 0.1025 | 0.1035 |

Abbreviations: OR: odds ratios; CI: confidence; P-value; P for interaction.
| Age Group | Women | ALT (IU/L) | Sex | Men | AST (IU/L) | Smoking Status | BMI (kg/m²) | HDL cholesterol (mmol/l) | Total cholesterol (mmol/l) | HbA1c | SBP (mmHg) | Fasting plasma glucose (mmol/l) |
|-----------|-------|------------|-----|-----|------------|---------------|------------|------------------------|------------------------|-------|----------|---------------------------|
| 30-39     | 5175  | 1.845 (1.566, 2.175) | 5786 | 1.521 (1.344, 1.722) | 3375 | 1.409 (1.210, 1.641) | 656 | 1.269 (0.965, 1.669) | 56 | 1.712 (0.231, 12.715) | 0.907 (0.435, 1.889) | 0.3068 |
| 40-49     | 7034  | 1.472 (1.343, 1.613) | 5786 | 1.521 (1.344, 1.722) | 850  | 1.367 (1.077, 1.736) | 211 | 1.664 (1.153, 2.400) | 15253 | 1.500 (1.371, 1.642) | 1.552 (1.411, 1.707) | 0.5170 |
| 50-59     | 3375  | 1.409 (1.210, 1.641) | 5786 | 1.521 (1.344, 1.722) | 850  | 1.367 (1.077, 1.736) | 211 | 1.664 (1.153, 2.400) | 15253 | 1.500 (1.371, 1.642) | 1.552 (1.411, 1.707) | 0.5170 |
| 60-69     | 656   | 1.269 (0.965, 1.669) | 5175 | 1.845 (1.566, 2.175) | 850  | 1.367 (1.077, 1.736) | 211 | 1.664 (1.153, 2.400) | 15253 | 1.500 (1.371, 1.642) | 1.552 (1.411, 1.707) | 0.5170 |
| ≥70       | 56    | 1.712 (0.231, 12.715) | 0.8039 | 1.339 (1.188, 1.510) | 0.0071 |

| Age Group | Women | ALT (IU/L) | Sex | Men | AST (IU/L) | Smoking Status | BMI (kg/m²) | HDL cholesterol (mmol/l) | Total cholesterol (mmol/l) | HbA1c | SBP (mmHg) | Fasting plasma glucose (mmol/l) |
|-----------|-------|------------|-----|-----|------------|---------------|------------|------------------------|------------------------|-------|----------|---------------------------|
| 30-39     | 5175  | 1.845 (1.566, 2.175) | 5786 | 1.521 (1.344, 1.722) | 3375 | 1.409 (1.210, 1.641) | 656 | 1.269 (0.965, 1.669) | 56 | 1.712 (0.231, 12.715) | 0.907 (0.435, 1.889) | 0.3068 |
| 40-49     | 7034  | 1.472 (1.343, 1.613) | 5786 | 1.521 (1.344, 1.722) | 850  | 1.367 (1.077, 1.736) | 211 | 1.664 (1.153, 2.400) | 15253 | 1.500 (1.371, 1.642) | 1.552 (1.411, 1.707) | 0.5170 |
| 50-59     | 3375  | 1.409 (1.210, 1.641) | 5786 | 1.521 (1.344, 1.722) | 850  | 1.367 (1.077, 1.736) | 211 | 1.664 (1.153, 2.400) | 15253 | 1.500 (1.371, 1.642) | 1.552 (1.411, 1.707) | 0.5170 |
| 60-69     | 656   | 1.269 (0.965, 1.669) | 5175 | 1.845 (1.566, 2.175) | 850  | 1.367 (1.077, 1.736) | 211 | 1.664 (1.153, 2.400) | 15253 | 1.500 (1.371, 1.642) | 1.552 (1.411, 1.707) | 0.5170 |
| ≥70       | 56    | 1.712 (0.231, 12.715) | 0.8039 | 1.339 (1.188, 1.510) | 0.0071 |

| Age Group | Women | ALT (IU/L) | Sex | Men | AST (IU/L) | Smoking Status | BMI (kg/m²) | HDL cholesterol (mmol/l) | Total cholesterol (mmol/l) | HbA1c | SBP (mmHg) | Fasting plasma glucose (mmol/l) |
|-----------|-------|------------|-----|-----|------------|---------------|------------|------------------------|------------------------|-------|----------|---------------------------|
| 30-39     | 5175  | 1.845 (1.566, 2.175) | 5786 | 1.521 (1.344, 1.722) | 3375 | 1.409 (1.210, 1.641) | 656 | 1.269 (0.965, 1.669) | 56 | 1.712 (0.231, 12.715) | 0.907 (0.435, 1.889) | 0.3068 |
| 40-49     | 7034  | 1.472 (1.343, 1.613) | 5786 | 1.521 (1.344, 1.722) | 850  | 1.367 (1.077, 1.736) | 211 | 1.664 (1.153, 2.400) | 15253 | 1.500 (1.371, 1.642) | 1.552 (1.411, 1.707) | 0.5170 |
| 50-59     | 3375  | 1.409 (1.210, 1.641) | 5786 | 1.521 (1.344, 1.722) | 850  | 1.367 (1.077, 1.736) | 211 | 1.664 (1.153, 2.400) | 15253 | 1.500 (1.371, 1.642) | 1.552 (1.411, 1.707) | 0.5170 |
| 60-69     | 656   | 1.269 (0.965, 1.669) | 5175 | 1.845 (1.566, 2.175) | 850  | 1.367 (1.077, 1.736) | 211 | 1.664 (1.153, 2.400) | 15253 | 1.500 (1.371, 1.642) | 1.552 (1.411, 1.707) | 0.5170 |
| ≥70       | 56    | 1.712 (0.231, 12.715) | 0.8039 | 1.339 (1.188, 1.510) | 0.0071 |
Note 1: Above model adjusted for Sex, Age, ALT, AST, Habit of exercise, GGT, HDL cholesterol, Total cholesterol, HbA1c. Smoking status, Fasting plasma glucose. SBP and BMI.
Note 2: In each case, the model is not adjusted for the stratification variable.
Abbreviations: CI: confidence; OR: odds ratios;

Figures

Figure 1

Inverted U-shaped curve relationship between triglycerides of unadjusted (A) and adjusted (B) and ectopic fat obesity. adjusted Sex, Age, ALT, AST, Habit of exercise, GGT, HDL cholesterol, Total cholesterol, HbA1c, Smoking status, Fasting plasma glucose, SBP and BMI, and the dotted lines represented the 95% confidence.
Figure 2

Inverted U-shaped curve relationship between unadjusted (A) and adjusted (B) triglycerides and ectopic fat obesity in men and women. adjusted Sex, Age, ALT, AST, Habit of exercise, GGT, HDL cholesterol, Total cholesterol, HbA1c, Smoking status, Fasting plasma glucose, SBP and BMI.