

# BMJ Open Association between normal triglyceride and insulin resistance in US adults without other risk factors: a cross-sectional study from the US National Health and Nutrition Examination Survey, 2007–2014

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**To cite:** Bi C, Wang L, Sun C, *et al.* Association between normal triglyceride and insulin resistance in US adults without other risk factors: a cross-sectional study from the US National Health and Nutrition Examination Survey, 2007–2014. *BMJ Open* 2019;**9**:e028652. doi:10.1136/bmjopen-2018-028652

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-028652>).

Received 18 December 2018  
Revised 01 July 2019  
Accepted 11 July 2019



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## ABSTRACT

**Objective** Traditionally, the absence of insulin resistance risk factors (IRRFs) was considered a low risk for insulin resistance (IR). However, IR also existed in certain individuals without IRRFs; thus this study aims to explore predictors of IR targeted at the population without IRRFs.

**Design** Cross-sectional survey.

**Setting** National Health and Nutrition Examination Survey.

**Participants** Participants without regular IRRFs (IRRF-Free, n=2478) and a subgroup without optimal IRRFs (IRRF-Optimal, n=1414) were involved in this study.

**Primary and secondary outcome measure** IRRFs and the optimal cut-off value of triglyceride (TG) to predict IR.

**Results** Overall, the prevalence of IR was 6.9% and 5.7% in the IRRF-Free group and the IRRF-Optimal group, respectively. TG and waist circumference were independently associated with the prevalence of IR in both the groups (OR=1.010 to 10.20; p<0.05 for all), where TG was positively associated with IR. The area under the receiver operating characteristic curve of TG was 0.7016 (95% CI: 0.7013 to 0.7018) and 0.7219 (95% CI: 0.7215 to 0.7222), and the optimal cut-off value of TG to predict IR was 79.5 mg/dL and 81.5 mg/dL in the IRRF-Free group and the IRRF-Optimal group, respectively.

**Conclusion** There is an association between TG and IR even in the normal range of TG concentration. Therefore, normal TG could be used as an important indicator to predict the prevalence of IR in the absence of IRRFs.

## BACKGROUND

Insulin resistance (IR) is a metabolic status in which insulin-dependent tissues become insensitive to insulin while the body does not respond to the glucose load and results in metabolic imbalance of carbohydrate, lipid and protein.<sup>1–3</sup> It is indicated that systemic toxicity, such as endothelial dysfunction, increase in inflammation stress, pro-thrombogenesis and pro-oxidation,<sup>4 5</sup> could be

## Strengths and limitations of this study

- Strengths of this study included the quality and scale of the National Health and Nutrition Examination Survey database and the rigour of its measures. Moreover, there has been scarce information in the articles exploring insulin resistance (IR) risk factors in relatively healthy individuals.
- Limitations of this study included that we can only determine the association between triglyceride and IR in cross-sectional studies, and not the causality.
- In this study, we used the homeostasis model assessment of IR as an alternative to diagnose IR, with some limitations related to its poor reproducibility and reliability.

caused by IR, which leads to the development of diabetes mellitus,<sup>6</sup> cardiovascular diseases<sup>7</sup> and cancer.<sup>8</sup>

A 3.2-year prospective study found out that the incidence of diabetes was much higher in aged people with IR (12.22%) than those without IR (3.6%).<sup>9</sup> Another 13-year follow-up study in patients with hypertension showed that the total number of cardiovascular diseases and events were significantly higher among patients with IR as compared with patients who are sensitive to insulin.<sup>10</sup> In addition, a 15-year cohort study demonstrated that the overall mortality of patients with cancer with IR is as much greater (14.3%) than in those without IR (8.7%).<sup>11</sup> Thus, IR is considered as a potent as well as strong predictor of diabetes, cardiovascular diseases and cancer.<sup>9 12 13</sup>

As the number of studies on IR is burgeoning, various IR risk factors (IRRFs),

such as smoking,<sup>14</sup> obesity,<sup>15</sup> dyslipidaemia and hypertension,<sup>16</sup> have been recognised and are generally agreed on as common IRRFs. A cohort survey on healthy children from eight European countries revealed that the incidence of IR was 10.9% within the follow-up 2 years,<sup>17</sup> which implied that people might still develop IR even in the absence of IRRFs. However, these individuals, who were without IRRFs, tend to be ignored and do not serve as a focus group for disease prevention.

The study of the effects of blood lipids on IR is more pronounced in studies on IRRFs<sup>18</sup> and has shown that IR is mostly associated with elevation of blood lipids, especially triglyceride (TG).<sup>19</sup> Typically, the incidence of IR will be of concern when the level of TG elevates abnormally. However, individuals will still develop IR in the normal range of blood lipids, which has not received sufficient attention. In this study, we explored potential predictors of IR in the population with the absence of IRRFs based on the data from the 2007–2014 National Health and Nutrition Examination Survey (NHANES). Our study showed that TG was a good predictor of IR even in the absence of IRRFs. The optimal cut-off value of TG to predict IR was 79.5 mg/dL and 81.5 mg/dL in the IRRF-Free group and the IRRF-Optimal group, which was lower than the normal value, respectively. It suggested that early TG monitoring has implications to prevent IR and to decrease the onset of IR related to chronic diseases.

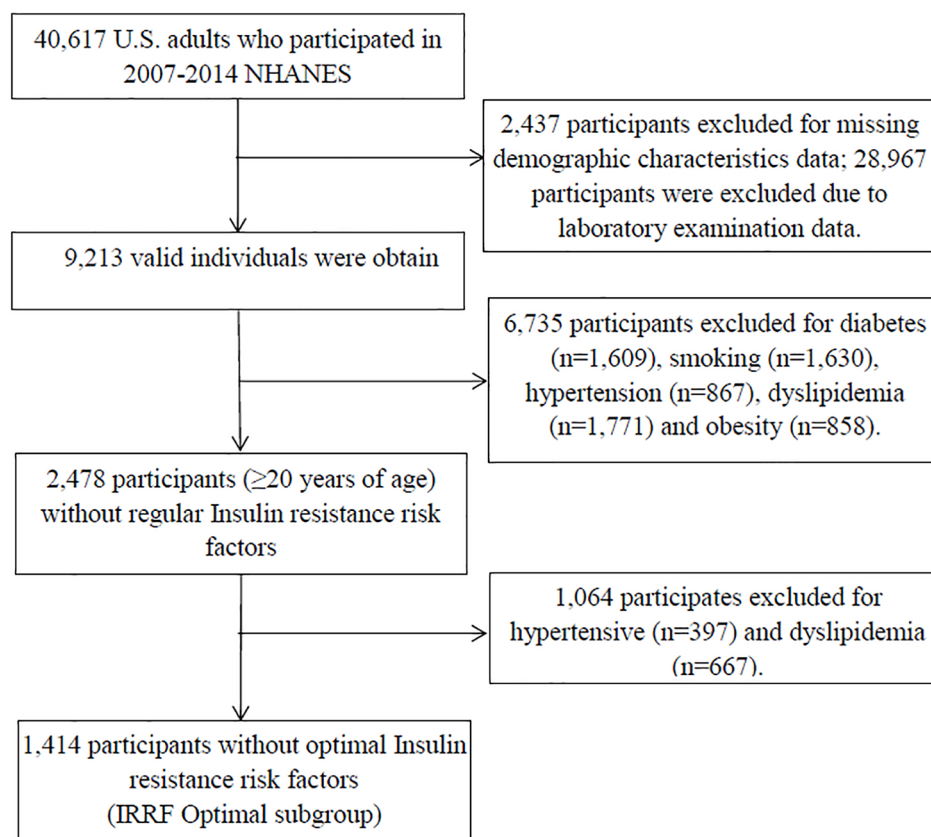
## METHODS

### Study design and study population

Data were derived from a cross-sectional study of the NHANES conducted by the National Centre for Health Statistics (NCHS) of the Centres for Disease Control and Prevention (<http://www.cdc.gov/nchs/nhanes/>). NHANES was based on a complex, layered, multistage probability design, which obtained the national representative sample of non-institutionalised residents in the USA.<sup>20</sup> In this study, a total of 40 617 subjects were enrolled in 2007–2014 NHANES. First, 31 404 subjects were excluded because they lacked demographic characteristics and laboratory examination information. Furthermore, 6 735 subjects were excluded due to diabetes (1 609 subjects), smoking (1 630 subjects), hypertension (867 subjects), dyslipidaemia (1 771 subjects) and obesity (858 subjects). Finally, 2 478 subjects ( $\geq 20$  years of age) were enrolled in the IRRF-Free group. Within the IRRF-Free group, we also defined a subgroup as without optimal IRRFs (IRRF-Optimal). In all, 1 064 subjects were excluded due to stricter blood pressure (BP;  $n=397$ ) and blood lipids ( $n=667$ ). Subsequently, 1 414 subjects were involved in the IRRF-Optimal group (figure 1).

### Data collection and measurement

All information was collected by investigators who had been uniformly trained. The data included demographics



**Figure 1** Study design and participant flow diagram for the present study. IRRF, insulin resistance risk factor; NHANES, National Health and Nutrition Examination Survey.

**Table 1** Baseline characteristics of IR and non-IR IRRF-Free versus IRRF-Optimal among US adult, 2007–2014\*

Variable	IRRF-Free		IRRF-Optimal			
	Total (N=2478)	IR (N=200)	Non-IR (N=2278)	Total (N=1414)		
<b>Baseline characteristics</b>						
Age †	43.7 (42.5–44.8)	47.0 (43.8–50.1)	43.5 (42.2–44.7)	39.8 (38.5–41.0)	43.1 (37.5–48.7)	39.6 (38.3–40.8)
<b>Gender ‡</b>						
Male	1143 (46.2)	115 (64.4)	1028 (44.8)	622 (43.7)	46 (63.2)	576 (42.5)
Female	1335 (53.8)	85 (35.6)	1250 (55.2)	792 (56.3)	43 (36.8)	749 (57.5)
<b>Race</b>						
Mexican American	357 (8.0)	36 (11.9)	321 (7.7)	205 (8.5)	19 (14.1)	186 (8.2)
Other Hispanics	264 (5.5)	29 (6.8)	235 (5.4)	140 (5.9)	8 (3.8)	132 (6.0)
Non-Hispanic whites	1129 (69.5)	74 (63.0)	1055 (70.0)	645 (68.3)	33 (64.5)	612 (68.5)
Non-Hispanic black	369 (8.5)	40 (12.6)	329 (8.2)	209 (8.5)	18 (12.8)	191 (8.2)
Non-Hispanics multiracial	359 (8.5)	21 (5.6)	338 (8.7)	215 (8.8)	11 (4.8)	204 (9.1)
<b>Marital status</b>						
Married	1347 (59.5)	110 (56.0)	1237 (69.8)	731 (56.9)	49 (52.7)	682 (57.2)
Widowed	115 (3.2)	11 (4.7)	104 (3.1)	52 (2.1)	3 (1.0)	49 (2.2)
Divorce	211 (7.3)	12 (6.7)	199 (7.3)	96 (5.4)	4 (2.9)	92 (5.5)
Separation	66 (1.5)	6 (1.6)	60 (1.5)	40 (1.7)	1 (0.5)	39 (1.8)
unmarried	556 (21.3)	48 (26.0)	508 (20.9)	387 (26.1)	27 (36.9)	360 (25.4)
Live with your partner	183 (7.2)	13 (5.0)	170 (7.3)	108 (7.8)	5 (6.1)	103 (7.9)
<b>Educational level</b>						
Less than grade 9 education	189 (3.8)	15 (3.4)	174 (3.8)	89 (3.4)	7 (2.3)	82 (3.5)
Grade 9–11 education	242 (6.7)	28 (12.5)	214 (6.3)	135 (6.4)	14 (15.9)	121 (5.8)
High school graduate/GED or equivalent	427 (16.4)	42 (23.5)	385 (15.9)	230 (15.8)	16 (21.3)	214 (15.5)
Some college students or joint AA degrees	697 (27.7)	67 (34.0)	630 (27.3)	416 (29.2)	32 (35.6)	384 (28.8)
Bachelor degree or above	923 (45.4)	48 (26.7)	875 (46.8)	544 (45.2)	20 (24.9)	524 (46.5)
Weight (kg)	71.0 (70.3–71.7)	79.9 (77.4–82.4)	70.3 (69.6–71.1)	69.4 (68.6–70.2)	78.5 (74.7–82.7)	68.8 (68.0–69.7)
Height (cm)	169.5 (168.9–170.1)	172.3 (170.4–174.2)	169.3 (168.7–169.9)	169.3 (168.6–170.7)	171.9 (169.1–174.7)	169.1 (168.4–169.9)
BMI (kg/m <sup>2</sup> )	24.6 (24.4–24.8)	26.8 (26.3–27.3)	24.4 (24.2–24.6)	24.1 (23.9–24.3)	26.4 (25.6–27.2)	23.9 (23.7–24.2)
WC (cm)	88.2 (87.6–88.8)	96.6 (95.0–98.1)	87.6 (86.9–88.3)	86.0 (85.4–86.7)	95.0 (92.3–97.8)	85.5 (84.7–86.2)
<b>Biomarkers</b>						
Total cholesterol (mg/dL)	183.9 (182.7–185.2)	186.3 (179.9–192.7)	183.8 (182.5–185.1)	168.9 (167.6–170.1)	169.6 (164.7–174.5)	168.8 (167.5–170.1)
Triglycerides (mg/dL)	84.1 (82.4–86.1)	107.1 (101.2–112.9)	82.4 (80.5–84.4)	73.5 (71.7–75.3)	95.0 (86.1–104.0)	72.2 (70.3–74.1)
LDL-C (mg/dL)	105.4 (104.3–106.6)	110.6 (104.7–116.5)	105.0 (104.0–106.1)	93.4 (92.2–94.6)	97.4 (92.2–102.7)	93.1 (91.8–94.5)

Continued

Table 1 Continued

Variable	IRRF-Free			IRRF-Optimal		
	Total (N=2478)	IR (N=200)	Non-IR (N=2278)	Total (N=1414)	IR (N=89)	Non-IR (N=1325)
HDL-C (mg/dL)	61.7 (60.9–62.5)	54.3 (51.8–56.8)	62.2 (61.4–63.1)	60.8 (59.9–61.7)	53.2 (49.6–56.9)	61.2 (60.3–62.2)
HbA1c (%)	5.3 (5.2–5.3)	5.5 (5.4–5.5)	5.3 (5.2–5.3)	5.2 (5.2–5.3)	5.4 (5.3–5.5)	5.2 (5.2–5.3)
Fasting glucose (mg/dL)	95.4 (94.9–95.9)	103.9 (101.6–106.2)	94.8 (94.3–95.2)	94.2 (93.6–94.7)	104.1 (101.3–106.9)	93.6 (93.0–94.1)
Insulin ( $\mu$ U/mL)	7.8 (7.5–8.1)	19.5 (18.1–20.9)	7.0 (6.8–7.1)	7.4 (7.1–7.8)	19.8 (17.1–22.5)	6.7 (6.4–7.0)
SBP (mm Hg)	113.2 (112.6–113.9)	117.3 (115.1–119.4)	112.9 (112.3–113.6)	110.1 (109.5–110.8)	113.0 (110.8–115.1)	110.0 (109.3–110.6)
DBP (mm Hg)	67.1 (66.5–67.7)	68.8 (66.3–71.3)	67.0 (66.3–67.6)	65.1 (64.5–65.7)	66.8 (64.3–69.3)	65.0 (64.3–65.6)

\*Data are from the National Health and Nutrition Examination Surveys. All data except for sample size are weighted according to the complex study design according to the directions of the National Centre for Health Statistics.

†Continuous variables (means and 95% CIs).

‡Categorical variables (counts and weighted percentages).

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated haemoglobin; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; WC, waist circumference.

(eg, sex, age, race/ethnicity, etc), health-related behaviour (eg, smoking), anthropometric measurements (eg, height, weight, etc) and biochemical tests (total cholesterol (TC), TG, etc). BP was measured using a mercury sphygmomanometer, and subjects were required to have rested for at least 5 min before testing their BP.<sup>21</sup> The average of three measurements, the average of two measurements and the unique reading of one value was used for the data analysis.<sup>22</sup> The participants' height, weight and waist circumference (WC) were measured according to standardised protocols and techniques.<sup>23</sup> Body mass index (BMI) was calculated using the following formula: BMI=weight (kg)/height (m<sup>2</sup>).<sup>24</sup> BMI cut-off points of categories were determined according to WHO criteria for underweight ( $\leq 18.5$  kg/m<sup>2</sup>), normal (18.5–24.9 kg/m<sup>2</sup>), overweight (25.0–29.9 kg/m<sup>2</sup>) and obese ( $\geq 30.0$  kg/m<sup>2</sup>).<sup>25</sup> Non-obese was defined as BMI  $< 30.0$  kg/m<sup>2</sup>.

### Assessment criteria

#### Smoking

Smoking status was categorised into current smoker (who had smoked at least one cigarette per day in the past 30 days), former smoker (who had smoked at least 100 cigarettes in one's lifetime but who at the time of the survey did not smoke at all), and never-smoker (who had never smoked cigarettes or had smoked less than 100 cigarettes in one's lifetime).<sup>26 27</sup> Former smokers and never-smokers were collectively defined as non-smokers since there were few never-smokers in this study.

#### Hypertension

Hypertension was defined as resting systolic BP (SBP) and/or diastolic BP (DBP)  $\geq 140/90$  mm Hg following the Seventh Report of Joint National Committee standard.<sup>28</sup> Another relatively strict criterion was based on the 2017 American College of Cardiology/American Heart Association Blood Pressure Guide.<sup>29</sup> It was recommended that BP  $< 130/80$  mm Hg was considered normal.

#### Dyslipidemia

In this study, dyslipidaemia was defined as follows: TC  $> 240$  mg/dL, TG  $> 200$  mg/dL, low-density lipoprotein cholesterol (LDL-C)  $> 160$  mg/dL or male high-density lipoprotein cholesterol (HDL-C)  $< 40$  mg/dL, female HDL-C  $< 50$  mg/dL.<sup>30</sup> A more stringent criterion was defined in the guidelines provided in the third report of the National Cholesterol Education Programme Adult Treatment Group III (NCEP ATP III)<sup>31</sup>: TC  $> 200$  mg/dL, TG  $> 150$  mg/dL, LDL-C  $> 130$  mg/L, male HDL-C  $< 40$  mg/dL, female HDL-C  $< 50$  mg/dL.

#### Diabetes mellitus

NHANES defined type 2 diabetes through questionnaires, fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA1c) levels.<sup>32</sup> Diabetes was diagnosed according to self-reported responses or currently using anti-diabetic drugs or insulin. Undiagnosed diabetes was defined according to the 2015 American Diabetes



**Table 2** Multivariate analysis for the prevalence of IR in IRRF-Free among US adult, 2007–2014\* N=2478

Variable	P	OR	95% CI	
			Lower	Upper
Intercept	<0.001	6.719E-6	1.369E-7	0.000
Race	0.041			
Mexican American	0.918	1.044	0.452	2.414
Other Hispanics	0.824	1.107	0.446	2.744
Non-Hispanic whites	0.410	0.699	0.295	1.656
Non-Hispanic black	0.270	1.689	0.657	4.390
Non-Hispanic multiracial	–	1.000	–	–
Educational level	0.038			
Less than grade 9 education	0.776	1.158	0.414	3.242
Grade 9–11 education	0.050	2.346	1.000	5.508
High school graduate/GED or equivalent	0.021	2.209	1.134	4.302
Some college students or joint AA degrees	0.024	2.149	1.108	4.168
Bachelor degree or above	–	1.000	–	–
WC (cm)	<0.001	1.092	1.044	1.142
TG (mg/dL)	<0.001	1.010	1.005	1.015

\*Data are from the National Health and Nutrition Examination Surveys. All data except for sample size are weighted accounting for the complex study design according to the directions of the National Centre for Health Statistics. IR, insulin resistance; IRRF, IR risk factor; TG, triglyceride; WC, waist circumference.

Association standard<sup>33</sup>: FPG $\geq$ 126 mg/dL or HbA1c $\geq$ 6.5% (48 mmol/mL). IR was indexed by the homeostasis model assessment (HOMA) formula: [fasting insulin ( $\mu$ U/mL) $\times$ fasting glucose (mmol/L)]/22.5.<sup>34</sup> IR was defined

by the values equal to or greater than the 75th percentile of the HOMA-IR.<sup>35</sup> In this study, the value was 3.7, which represented the diagnostic value of IR in the non-diabetic population rather than a general sample.

**Table 3** Multivariate analysis for the prevalence of IR in IRRF-Optimal among US adult, 2007–2014\* N=1414

Variable	P	OR	95% CI	
			Lower	Upper
Intercept	<0.001	3.792E-5	1.73E-7	0.0134
WC (cm)	<0.001	1.098	1.040	1.160
TG (mg/dL)	<0.001	1.020	1.008	1.031

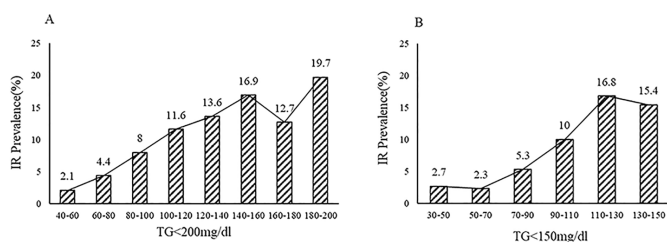
\*Data are from the National Health and Nutrition Examination Surveys. All data except for sample size are weighted accounting for the complex study design according to the directions of the National Centre for Health Statistics. IR, insulin resistance; IRRF, IR risk factor; TG, triglyceride; WC, waist circumference.

### Definition of IRRF-Free group and IRRF-Optimal group

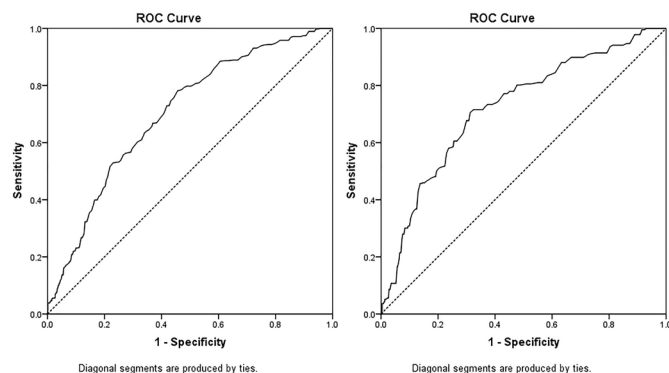
The IRRF-Free group included people who met the following conditions: (1) untreated SBP <140 mm Hg and/or DBP <90 mm Hg; (2) untreated FPG <126 mg/dL; (3) untreated TC  $\leq$ 240 mg/dL, TG  $\leq$ 200 mg/dL, LDL-C  $\leq$ 160 mg/dL and male HDL-C  $\geq$ 40 mg/dL, female HDL-C  $\geq$ 50 mg/dL; (4) BMI <30 kg/m<sup>2</sup>; (5) no smoking and (6) non-diabetics. Within the IRRF-Free group, we also defined a subgroup of individuals with Optimal IRRFs (IRRF-Optimal): (1) SBP <130 mm Hg and/or DBP <80 mm Hg, (2) TC  $\leq$ 200 mg/dL, TG  $\leq$ 150 mg/dL, LDL-C  $\leq$ 130 mg/dL.

### Statistical analysis

To generate nationally representative estimates, all analyses were accounted for the complex, stratified nature of NHANES to explain complex survey design, survey non-response and planned oversampling.<sup>36</sup> We used the SURVEY procedure including the morning fasting subsample 2-year weights (WTSF2YR), stratum (SDMVSTRA) and primary sampling unit (SDMVPSU) recommended by the National Institutes of Health (NCHS) for the NHANES analysis. The prevalence of IR was a weighted percentage of IR under complex sampling, which was equal to the number of IR divided by the total number of people. Complex sample package of IBM SPSS Statistics



**Figure 2** Relation between TG and IR in IRRF-Free and IRRF-Optimal groups. IR, insulin resistance; IRRF, IR risk factor; TG, triglyceride.



**Figure 3** Area under ROC curves of triglyceride to predict IR in IRRF-Free and IRRF-Optimal groups. IR, insulin resistance; IRRF, IR risk factor; ROC, receiver operating characteristic.

V.24.0 (IBM Corp, Armonk, NY, USA) was used to perform statistical analyses. Continuous variables were presented as means and 95% CIs using complex sample descriptions. Categorical variables were presented as counts and weighted percentages using complex sample frequencies. A complex sample univariate logistic regression analysis was used to assess differences in baseline characteristics between participants with and without IR. Univariate logistic regression analysis of statistically significant differences included in complex samples multivariate logistic regression analysis to analyse the association for multiple covariates with the presence of IR in the IRRF-Free group and the IRRF-Optimal group. To estimate optimal cut-off values, TG was used as the test variable, excluding other control variables, and IR was used as a state variable. The optimal cut-off value of TG to predict IR was determined by the highest score of the Jordan index of the receiver operating characteristic (ROC) curve. Statistical significance was set at a p value < 0.05.

### Consent to participate

All participants provided a written informed consent, and the study was approved by the NCHS Research Ethics Review Board (<https://www.cdc.gov/nchs/nhanes/default.aspx>).<sup>37</sup>

### Patient and public involvement

Patients and the general public were not involved in the development of the research question or outcome measure, study design or recruitment and conduct of

this study. There are no plans for the study results to be disseminated directly to participants.

## RESULTS

### Characterisation of the IRRF-Free and IRRF-Optimal study population

Table 1 shows the basic characteristics of the participants. Overall, data from 2478 subjects (1143 men and 1335 women) in the IRRF-Free group and 1441 subjects (622 men and 792 women) in the IRRF-Optimal groups were assessed. The prevalence of IR was 6.9% and 5.7% in both the groups, respectively. The anthropometric, clinical and biochemical characteristics of the participants are summarised in table 1. Patients with IR had higher levels of TG, TC, LDL-C, FPG and insulin than those without IR in the two groups.

### Predictors of IR presence

#### Univariate logistic regression analysis

Regarding the risk factors of IR, our outcomes, which were based on univariate logistic regression analysis, are presented in online supplementary table 1. In the IRRF-Free group, the result of univariate logistic regression demonstrated that age ( $p=0.038$ ; OR=1.013, 95% CI=1.001 to 1.025), male ( $p<0.001$ ; OR=2.229, 95% CI=1.376 to 3.612), non-Hispanic black ( $p=0.039$ ; OR=1.384, 95% CI=0.648 to 2.956), grade 9–11 education ( $p<0.001$ ; OR=3.465, 95% CI=1.655 to 7.212), BMI ( $p<0.001$ ; OR=1.344, 95% CI=1.244 to 1.452), WC ( $p<0.001$ ; OR=1.102, 95% CI=1.078 to 1.126), TG ( $p<0.001$ ; OR=1.017, 95% CI=1.013 to 1.021), HDL-C ( $p<0.001$ ; OR=0.946, 95% CI=0.923 to 0.969) and SBP ( $p<0.001$ ; OR=1.035, 95% CI=1.018 to 1.051) were associated with IR. In the IRRF-Optimal group, the result of univariate logistic regression demonstrated that male ( $p=0.004$ ; OR=2.322, 95% CI=1.202 to 4.485), non-Hispanic black ( $p=0.011$ ; OR=2.964, 95% CI=1.293 to 6.792), grade 9–11 education ( $p<0.001$ ; OR=5.134, 95% CI=1.971 to 13.369), BMI ( $p<0.001$ ; OR=1.322, 95% CI=1.174 to 1.487), WC ( $p<0.001$ ; OR=1.108, 95% CI=1.070 to 1.148), TG ( $p<0.001$ ; OR=1.027, 95% CI=1.015 to 1.040), HDL-C ( $p=0.002$ ; OR=0.933, 95% CI=0.892 to 0.976) and SBP ( $p=0.005$ ; OR=1.035, 95% CI=1.001 to 1.061) were associated with IR.

**Table 4** The optimal cut-off of triglyceride to predict insulin resistance among US adult 2007–2014\*

	TG (mg/dL)	Sensitivity (%)	Specificity (%)	Youden index	AUC	P	AUC (95% CI)	
							Lower	Upper
IRRF-Free	79.5	0.782	0.543	0.325	0.7016	<0.001	0.7013	0.7018
IRRF-Optimal	81.5	0.706	0.687	0.393	0.7219	<0.001	0.7215	0.7222

\*Data are from the National Health and Nutrition Examination Surveys. All data except for sample size are weighted accounting for the complex study design according to the directions of the National Centre for Health Statistics. AUC, area under curve; CI, confidence interval.

**Table 5** Prevalence of IR and AR% in IRRF-Free and IRRF-Optimal groups among US adult, 2007–2014\*

TG (mg/dL)	IRRF-Free (N=2478)			TG (mg/dL)	IRRF-Optimal (N=1414)		
	IR (n)	Prevalence of IR (%)	AR%		IR (n)	Prevalence of IR (%)	AR%
<79.5	55	2.9	–	<81.5	34	2.5	–
79.5–200	145	11.2	74	81.5–150	55	12	79
Total	200	6.9	–	Total	89	5.7	–

\*Data are from the National Health and Nutrition Examination Surveys. All data except for sample size are weighted accounting for the complex study design according to the directions of the National Centre for Health Statistics. AR%, attributable risk per cent; IR, insulin resistance; IRRF, insulin resistance risk factor; TG, triglyceride.

### Multivariate logistic regression analysis

The results of multivariate logistic regression analysis results are shown in [tables 2 and 3](#). In the IRRF-Free group, the results indicated that the significant predictors of IR developing were non-Hispanic black ( $p=0.041$ ; OR=1.689, 95% CI=0.657 to 4.390), Grade 9–11 education ( $p=0.038$ ; OR=2.436, 95% CI=1.000 to 5.508), WC ( $p<0.001$ ; OR=1.092, 95% CI=1.044 to 1.142) and TG ( $p<0.001$ ; OR=1.010, 95% CI=1.005 to 1.015). In the IRRF-Optimal group, WC ( $p<0.001$ ; OR=1.098, 95% CI=1.040 to 1.160) and TG ( $p<0.001$ ; OR=1.020, 95% CI=1.008 to 1.031) were associated with IR

### Normal TG was independently associated with IR

The relationship between TG and IR in the absence of dyslipidaemia, hypertension, diabetes and smoking is illustrated in [figure 2](#). As TG levels increased, there was an increase in the prevalence of IR. In the IRRF-Free group, the prevalence of IR increased from 2.1% in the 40–60 mg/dL category to 19.7% in the 180–200 mg/dL category. In the IRRF-Optimal group, IR prevalence increased from 2.7% in the 30–50 mg/dL category to 15.4% in the 130–150 mg/dL category.

### ROC curve of TG to predict IR

[Figure 3](#) shows the ROC curves of TG to predict IR in the IRRF-Free group and the IRRF-Optimal group. The area under the curve (AUC) of TG was 0.7016 (95% CI=0.7013 to 0.7018) and 0.7219 (95% CI=0.7215 to 0.7222), respectively. The optimal cut-off value of TG to predict IR was 79.5 mg/dL and 81.5 mg/dL, respectively ([table 4](#)). [Table 5](#) shows the prevalence of IR and attributable risk per cent (AR%). When TG ranged in 79.5–200 mg/dL, the prevalence of IR was 11.2% and, 75.0% of IR was attributed to this TG range in the IRRF-Free group. When TG ranged in 81.5–150 mg/dL, the prevalence of IR was 12.0% and, 79.0% of IR was attributed to this TG range in the IRRF-Optimal group.

## DISCUSSION

In this study, the prevalence of IR in the IRRF-Free group and the IRRF-Optimal group were 6.9% and 5.7%, respectively. Moreover, TG was independently associated with IR, the optimal cut-off value of TG to predict IR for the two groups were 79.5 mg/dL and 81.5 mg/dL, respectively. In

the IRRF-Free group, when TG ranged in 79.5–200 mg/dL, the prevalence of IR was 11.2% and the number of IR was accounted for 72.5% of the total number of IR, while 75.0% of IR was attributed to the TG level. In the IRRF-Optimal group, when TG ranged in 81.5–150 mg/dL, the prevalence of IR was 12.0% and the number of IR was accounted for 61.8% of the total number of IR, while 79.0% of IR was attributed to TG ranged in 81.5–150 mg/dL. Thus, TG was an effective marker for the prediction of IR for the population with absence of IRRFs.

The prevalence of IR was 47.0% in an NHANES study of the population with obesity deficiency,<sup>38</sup> which was far beyond our findings. This may be due to the restrictions of our study population as they were relatively strict. However, in our study, the prevalence of IR was at least 5.7% in the IRRF-Optimal population who are non-smokers, non-diabetic and non-obese with normal BP and lipids, which indicated that additional factors play a major role in affecting the early IR. In the present study, we found that TG was independently associated with IR despite the IRRF-Free group or the IRRF-Optimal group, which was consistent with the results of previous similar study.<sup>39</sup> The possible mechanism is that TG was hydrolysed into free fatty acid (FFA) by various lipases, and FFA disrupts the insulin signalling pathway through multi pathways.<sup>40</sup> For example, FFA could interrupt the expression of lipid regulation and lead to the accumulation of lipid, which will disrupt the insulin metabolism in liver and resulting in IR.<sup>41</sup> FFA can induce IR by activating oxidative stress<sup>42</sup> and activate the inflammation pathway to induce the functional disorder of insulin-secreting cells, resulting in IR.<sup>43</sup>

Interestingly, there was a significant association between TG and IR even when TG was in the normal range which was stated in the NCEP ATP III guideline, and 81.5 mg/dL can be acted as the cut-off value of TG to predict the prevalence of IR. Other studies have reported that 158 mg/dL and 132 mg/dL could be used as a cut-off value of TG for men and women to predict IR,<sup>44</sup> respectively, both were much higher than 81.5 mg/dL. In the IRRF-Free group and the IRRF-Optimal group, when TG ranged in 81.5–150 mg/dL, the prevalence of IR was at least 12.0% and the number of IR in this range accounted for more than half of the total number of IR. Despite the IRRF-Free group and the IRRF-Optimal group, 74.0% and 79.0% of



IR were attributed to TG ranged in 79.5–200 mg/dL and 81.5–150 mg/dL, respectively. The finding implied that at least 74.0% of IR would be prevented in the absence of IRRFs if the normal level of TG was adjusted from 150 to 81.5 mg/dL. It is also possible that the ideal TG level can be much lower than the recommended value in the guideline. We recommend that effective measures should be taken to prevent the prevalence of IR when TG reaches 81.5 mg/dL. In addition, in a meta-analysis, TG has been identified as an independent predictor of coronary heart disease (CHD) even after adjustment for other confounders,<sup>45</sup> and recent observational data suggest that TG levels exceeding 100 mg/dL predict future CHD events.<sup>46</sup> Therefore, it is possible that our findings may have implications to pave a new way to prevent the development of diabetes, cardiovascular diseases, cancers, etc.

In our study, WC was associated with IR, which consisted of previous studies.<sup>47</sup> However, previous studies have shown that the relationship between WC and IR was more significant only in the elderly; therefore, WC was not suitable to be used as a predictor of IR in the whole population.<sup>48</sup> Overall, TG is a common clinical parameter and will be an effective marker of IR to evaluate the health status of an individual, and it is of great significance for early intervention of IR and related diseases.

Some limitations should be noted in this study. First, the data were obtained from a cross-sectional survey; therefore, further studies are needed to explore the associations in a longitudinal setting. Second, HOMA-IR was used as an alternative to diagnose IR, with some limitations on its reproducibility and reliability. Finally, we did not evaluate the genetic contribution to disease development, which can be independent of IRRFs and could thus play an important role in our population.

In conclusion, the prevalence of IR was 6.9% and 5.7% in the IRRF-free group and the IRRF-optimal group, respectively. There is an association between TG and IR even in the normal range of TG concentration. Further studies are needed before any recommendation about lowering TG levels that are already in the normal range can be made. Thus, our findings are important for guiding the primary prevention and understanding of early IR.

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**Contributors** YY, CB, LJ and LW conceived the original idea for the study and designed the work. LJ and YY provided valuable insight regarding the methodological approach and organisation of the manuscript. CB, CS, MS, ZX and LJ carried out the statistical analyses and reviewed the consistency of data included in the paper. Chunli Bi drafted the manuscript. LS, PP, PZ, YL, JL, AZ, BL, XZ, and LJ revised the manuscript. All authors read and approved the final manuscript.

**Funding** This work was supported by the Natural Science Foundation of Science and Technology Department of Jilin Province, China [grant number:

20180101129JC]; the Outstanding Youth Foundation of Science and Technology Department of Jilin Province, China [grant number: 20170520049JH]; the National Natural Science Foundation of China [grant number: 11301213 and 11571068]; the National Key Research and Development Program of China [grant number: 2016YFC1303800].

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** NHANES obtained Ethics Committee/Institutional Review Board approval by NCHS Research Ethics Review Board under Continuation of Protocol #2005-06, Protocol #2011-17 and Continuation of Protocol #2011-17 for 2007–2008/2009–2010 cycles, 2011–2012 cycles and for 2013–2014 cycle, respectively.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available in a public, open access repository.

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