

TITLE PAGE

Title: Hypertriglyceridemic-waist is more predictive of abnormal liver and renal function in an Australian population than a Chinese population

Running Title: HTGW impact on liver and renal function

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ABSTRACT

Objective

We aimed to compare the association of hypertriglyceridemic-waist (HTGW), with glycaemia, liver and renal function between a Chinese and an Australian population using 3 HTGW definitions.

Methods

1,454 Australian and 5,824 Chinese adults, from randomly selected households provided clinical history, glucose, lipids, anthropometric, and blood pressure measurements. Liver and renal functions were assessed using Alanine Aminotransferase and estimated Glomerular Filtration Rate respectively. The impact of interaction between HTGW and glucose on the liver and renal functions were measured by General Linear Model. Logistic regression was used to estimate the association between this interaction and abnormal liver and renal function.

Results

HTGW was associated with abnormal liver and renal function in both Chinese and Australian populations using all 3 HTGW definitions. The highest sensitivity (93 (95% confidence interval: 87, 97) %) and specificity (81 (80, 84) %) were observed for abnormal renal function in the Australian population. The probability of having abnormal liver or renal function increased with glucose in the presence of HTGW phenotype only in the Australian population. Similar findings were revealed in people without type 2 diabetes.

Conclusions

In both Chinese and Australian populations, HTGW is associated with abnormal liver and renal function using any of the 3 definitions. HTGW is a potential tool to identify high-risk individuals with impaired renal function especially in the Australian population. HTGW interacted with the fasting glucose in its association with impaired liver and renal function only in the Australian population, suggesting different underlying interactions between environmental and genetic backgrounds.

Keywords: Hypertriglyceridemic waist; liver function; renal function;

INTRODUCTION

It has been estimated that 3.4 million deaths, 3.9% of years of life lost and 3.8% of disability-adjusted life-years were caused by overweight and obesity globally in 2010¹. In spite of the well-recognized increased morbidity and mortality associated with an elevated body weight, there is clear evidence that visceral adiposity conveys the highest risk of metabolic complications, especially type 2 diabetes. Visceral adiposity accumulation (visceral obesity) rather than subcutaneous (non-visceral) obesity is associated with increased risk of chronic kidney disease^{2, 3} and metabolic liver disease⁴.

Although BMI is easy to calculate, it is a poor estimate of fat mass and its distribution, as muscular individuals or those with more subcutaneous fat may have a BMI as high as individuals with larger visceral adiposity. From a risk standpoint, there is now evidence that the simultaneous presence of an elevated waist circumference and fasting triglyceride (known as the hypertriglyceridemic waist, HTGW) may represent a phenotype for visceral obesity. So far, there are three definitions developed in diverse populations and utilised to identify individuals at higher risk of metabolic disorders^{5, 6, 7}. Although the concept of the HTGW was proposed in 2000⁸, its association with other features of visceral obesity including abnormal liver and renal function, and the extent of any interaction with fasting hyperglycaemia remain undefined. Moreover, since different definitions of HTGW were derived from different ethnic groups, it is unclear whether these different definitions were due to the study specific analyses or genuine ethnic variations. Our study now aims to address these uncertainties by comparing the relationships between HTGW phenotypes and abnormal liver and renal function, and any associated interactions with fasting glucose between two populations: one Chinese and one predominantly Australian of European descent.

MATERIALS AND METHODS

Data setting

The Australian population data were derived from the Crossroads study (>98% European descent)⁹ carried out between June 2001 and March 2003 among residents of the seven main towns in the Goulburn Valley, Victoria, Australia (populations 2094–35,828), as previously described^{8,9,10}. A two-step approach was used: interviews were conducted with all residents in randomly selected households (a ‘census’) and then invitations were given for all usual residents (resident in the area for at least 6 months) aged ≥ 25 years to attend for a ‘clinic’. An initial census of 2376 randomly selected households (half in the regional centre, a twelfth in each of the six smaller towns) was undertaken (response rate 70%). Houses were revisited until a response was received.

The Chinese population data were derived from the Nanjing Community Cardiovascular Risk Survey, using random cluster sampling¹¹, between July 2011 and April 2013 among the residents of 6 communities in Nanjing, Jiangsu Province, China (population 0.7 million-1.3 million). In each community, one street district or township was randomly selected. All households (n=6,445) in the selected street or town were included with only one participant aged ≥ 20 years selected from each household, without replacement. Overall, 5,824 residents completed the survey and examination (response rate of 90%).

In both studies, questionnaires were completed, wherever possible, through face-to-face interviews by trained research staff. Questions included age, sex, ethnicity, education, and known diabetes.

In both studies, blood pressure and body measurements including height, weight, and waist circumference were taken three times using a standardized methodology on the same day in the local clinical center and the mean of the two closest recordings was used.

Height, weight, and waist circumference were measured by use of a metric scale and a vertical weight scale. Weight was measured in light indoor clothing without shoes to the nearest 10th of a kilogram. Height was measured without shoes to the nearest 10th of a centimetre. Waist circumference was measured at 1 cm above the navel at minimal respiration. In both studies all observers participated in a training session on the use of a standardized protocol for anthropometric measurement techniques.

Fasting blood specimens were collected using a vacuum tube containing sodium fluoride. The fasting time was verified prior to collecting the blood specimen. Participants who had not fasted for at least 10 h did not have their blood drawn and processed at the examination center (Nanjing) or a centralized Laboratory (Crossroads), where the specimens were stored at -70°C until laboratory assays could be carried out. Plasma glucose, alanine aminotransferase (ALT), creatinine, and lipid levels were measured by automated analyser (Australian: Hitachi 917R autoanalyser (Hitachi, Tokyo, Japan); Nanjing: Olympus AU600 autoanalyser (Olympus Optical, Tokyo, Japan)). Type 2 diabetes was defined using WHO criteria ¹⁰ or by self-report if previously diagnosed (confirmed by doctor prescription (Nanjing) or medical records (Crossroads)), and metabolic syndrome (MS) using International Diabetes Federation (IDF) criteria ¹¹. Hypertension was considered present if reported as having previously been diagnosed by a doctor or nurse ¹². The estimated Glomerular Filtration Rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation ¹³. Due to non-standardised creatinine measurement, (Isotope Dilution Mass Spectrometry (IDMS) standardized creatinine assay) adjusted creatinine was applied in the eGFR estimation in the Crossroads study ¹⁴. Abnormal liver function was defined as ALT $\geq 40\text{U/L}$ ¹⁵ and abnormal renal function was defined as eGFR $< 60\text{ ml/min/1.73m}^2$ ¹⁶.

The exposure 'HTGW' were defined in three ways: ("Definition-1") both men and women: WC \geq 85 cm and triglyceride (TG) \geq 1.5 mmol/L (133 mg/dl) ⁵; ("Definition-2") for men, WC \geq 90 cm and TG \geq 2.0 mmol/L (177mg/dl) ; for women, WC \geq 85 cm and TG \geq 1.5 mmol/L (133 mg/dl) ⁶; ("Definition-3") for men: WC \geq 90cm and TG \geq 2.0 mmol/L (177mg/dl); for women, WC \geq 85cm and TG \geq 2.0 mmol/L (177mg/dl) ⁷.

Statistical analysis

Continuous variables were characterized by their mean and standard deviation, and differences across groups were tested using Student's t test. Binary factors were characterized by percentages, and difference across groups were tested using Fisher's exact test.

Associations between the three HTGW definitions and abnormal liver and renal function were assessed by logistic regression after adjusting for age, gender and BMI. Since the number of HTGW cases and normal samples were severely unbalanced in most cases, weighted logistic regression was performed with higher weight on samples from the smaller group to achieve similar prediction rates in both the case and normal groups. Odds ratio (OR), as the measurement between exposures (HTGW and glucose) and outcomes (abnormal liver and renal function), and the confidence interval, were calculated from the regression coefficient for HTGW and its standard deviation. Predictions from the regression model were compared with the observed values to obtain the prediction sensitivities and specificities. The estimated sensitivity/specificity and their confidence intervals were calculated. The sensitivity is defined as the proportion of patients with abnormal liver and renal function having the HTGW phenotype. The specificity is defined as the proportion of patients without abnormal liver and renal function who did not have the HTGW phenotype.

The relationships between fasting glucose and the outcomes (continuous outcomes: ALT and eGFR; binary outcomes: abnormal liver function and abnormal renal function) were modelled for the dose-response effect using fractional polynomials. Sensitivity analyses were performed to refit the models within the data rich range (5th percentile to 95th percentile). In another sensitivity analysis, all analyses were performed among participants without diabetes. We have a 95% chance of detecting 10% increased risk of abnormal renal/liver function in HTGW subjects at an alpha level of 0.05. All analyses were conducted using R, CRAN version 3.2.2 with $P < 0.05$ considered statistically significant.

The Goulburn Valley Health Ethics Committee approved the Crossroads study (approval number GVH – 3/99). The Institutional Review Board of Jiangsu Province Hospital on Integration of Chinese and Western Medicine approved the Nanjing study (approval number 11-006). Signed, informed consent was obtained from all participants.

RESULTS

The characteristics of the study participants by the three HTGW phenotype definitions in both the Chinese and Australian populations are presented in **Table-1**. Irrespective of definitions of HTGW phenotypes, participants with HTGW were more likely to have higher age, WC, body mass index, fasting glucose, triglycerides, and low-density lipoprotein, and lower levels of high-density lipoprotein both in the Chinese and Australian populations. The prevalence of metabolic disorders (metabolic syndrome or type 2 diabetes) was higher among participants with the HTGW phenotype both in the Chinese and Australian populations. Chinese participants with HTGW defined by Definition-1, and Australian participants with HTGW defined by Definition-1 and Definition-3, respectively were more likely to be men.

213

214 Higher concentrations of ALT and a reduced eGFR were more common among
215 participants with HTGW phenotypes irrespective of definitions of HTGW in both Chinese
216 and Australian populations (**Figure S1**).

217

218 The associations between presence of HTGW phenotypes and abnormal liver and renal
219 function are presented in Table-2. Having HTGW phenotype was significantly associated
220 with a higher odds ratio of abnormal liver function by each definition of HTGW in the
221 Chinese population, and by Definition-1 and Definition-3 in the Australian population.
222 Having HTGW phenotype was only significantly associated with a higher odds ratio of
223 abnormal renal function by Definition-2 and only in the Chinese population (**Table-2**). In
224 the stratified analysis, having HTGW phenotype was more likely to be significantly
225 associated with a higher odds ratio of abnormal renal function and liver function among
226 those with high fasting plasma glucose ($FPG \geq 5.6$ mmol/L) (**Figure-1**).

227

228 Utilization of the HTGW phenotype to screen for abnormal liver function was tested by
229 the three definitions. The highest sensitivity was found using Definition-2 both in Chinese
230 and Australian populations, and the highest specificity using Definition-1 in the Chinese
231 population and using Definition-3 in the Australian population. Screening for abnormal
232 renal function using HTGW phenotypes was also tested using the three definitions, with
233 similar sensitivity and specificity in both the Chinese and Australian populations (**Table-2**).

234

235 The dose-response relationships between ALT and fasting glucose were observed among
236 participants with and without the HTGW phenotype by the three definitions both in the
237 Chinese and Australian populations (**Figure-S2**). Among Australian participants with the
238 HTGW phenotype, ALT tended to be stable using the fasting glucose with glucose

concentrations below 5.5 mmol/L, and increased with glucose concentrations above 5.5 mmol/L. Among Australian participants without phenotype, ALT increased with the glucose at glucose concentrations below 5.5 mmol/L and tended to be stable with glucose concentrations above 5.5 mmol/L. Among Chinese participants with or without HTGW phenotype, ALT tended to be stable at glucose concentrations below 6.0 mmol/L and increased as glucose increased at concentrations above 6.0 mmol/L (**Figure S3**).

The dose-response relationships between eGFR and glucose were observed among participants with and without HTGW phenotype using the three definitions in both the Chinese and Australian populations (**Figure-S4**). Among Australian participants with the HTGW phenotype, eGFR decreased as glucose increased at glucose concentrations below 6.7 mmol/L and tended to be stable at glucose concentrations above 6.7 mmol/L. Among Australian participants without the HTGW phenotype, eGFR decreased as glucose increased below 5.5 mmol/L and then tended to be stable at glucose concentrations above 5.5 mmol/L. Among Chinese participants with or without HTGW phenotype, the eGFR decreased as glucose increased below 5.5 mmol/L and tended to be stable at glucose concentrations above 5.5 mmol/L.

The dose-response relationship between the glucose level and log odds ratio of having abnormal liver function is presented in **Figure-2**. Among Australian participants with the HTGW phenotype, the log odds ratio of having abnormal liver function decreased as glucose increased up to 5.5 mmol/L and then increased as glucose increased. Among Australian participants without the HTGW phenotype, the log odds ratio of having abnormal liver function decreased as glucose increased up to 5.5 mmol/L and then tended to be stable. Among Chinese participants with or without the HTGW phenotype, the log odds ratio decreased as the glucose increased up to 5.5 mmol/L and then increased

The dose-response relationships between the log odds ratio of abnormal renal function and fasting glucose were observed among participants with and without the HTGW phenotype by the three definitions in both the Chinese and Australian populations (**Figure-3**). Among Australian participants with the HTGW phenotype, the log odds ratio of abnormal renal function decreased with increasing fasting glucose up to 6.0 mmol/L and increased thereafter. Among Australian participants without the HTGW phenotype, the log odds ratio of abnormal renal function increased as the fasting glucose increased up to 5.0 mmol/L and then tended to be stable. Among Chinese participants with and without the HTGW phenotype, the log odds ratio of abnormal renal function decreased as the fasting glucose increased up to 5.0 mmol/L and then increased.

All dose-response relationships were analysed in the data rich range with similar findings as shown as **Figures S5-S7**.

All dose-response relationships were analysed among participants without diabetes, and the same shapes of dose-response curves and thresholds were identified **Figure S8-S11**.

DISCUSSION

Using two independent populations, we found that the HTGW phenotype, defined by each of three definitions, was associated with abnormal liver and renal function in both the Chinese and the Australian populations. However, the patterns of these relationships differed. Among the Australians, but not the Chinese, the HTGW phenotype could be used to screen for abnormal renal function with high sensitivity and specificity. Among Australians, the ALT

increased and eGFR decreased (ie the probability of having abnormal liver or renal function increased) with increasing fasting glucose, especially in the presence of the HTGW defined by each definition. No such relationships were found in the Chinese cohort with or without HTGW and using any HTGW definition.

Visceral obesity is thought to play a key role in the pathway to developing metabolic disorders (metabolic syndrome or type 2 diabetes)¹⁷. The HTGW concept was developed as a proxy for visceral obesity, and has previously been shown to be associated with hypertension, metabolic syndrome, type 2 diabetes, atherosclerosis and several other disorders¹⁸. In an Iranian cross-sectional study, the HTGW, defined by Definition-3, was found to be associated with chronic kidney disease¹⁹. In the Insulin Resistance Atherosclerosis Study, the HTGW was associated with an elevated ALT²⁰. However, it has been unclear whether these associations were independent of fasting glycaemia, another correlate of abnormal liver and renal function. In our study, the HTGW phenotype was associated with abnormal liver and renal function both in the Chinese and Australian populations. We have now shown heterogeneity in the interaction between the HTGW phenotype and the fasting glucose, as it was only present in the Australian, not the Chinese population. This suggests that HTGW and fasting glucose have independent impacts on the development of abnormal liver and renal function.

Definition-2 (for men, WC ≥ 90 cm and TG ≥ 2.0 mmol/L(177mg/dl) ; for women, WC ≥ 85 cm and TG ≥ 1.5 mmol/L(133 mg/dl)) appeared to be the optimal definition and

therefore could be an effective screening tool to identify individuals who are potentially at high risk of developing abnormal liver and/or renal function. Definition 2 had both high sensitivity and specificity, particularly for abnormal renal function, in the Australian population. The relatively low sensitivity and specificity of HTGW in the Chinese population might be due to the relatively low waist circumference and triglyceride concentrations, which also hints at the potential for future exploration for appropriate definitions of HTGW in Chinese population ²¹.

Several mechanisms may contribute to the findings of this study. Impaired liver and renal function might result from an altered systemic balance between inflammatory factors and adipokines, as both the acute-phase inflammatory reactant, C-reaction protein, and the proinflammatory cytokines, such as TNF- α and IL-6 were previously found to be associated with HTGW phenotype ²². On the other hand, a decreased adiponectin level was found to be associated with HTGW phenotype ²². Adiponectin, the only adipokine inversely associated with metabolic disorders including insulin resistance, is a signalling protein that is predominantly synthesized and secreted by adipose tissue and is one of the most abundant plasma proteins in humans ²³.

The principal limitation of the present study is the use of cross-sectional data in both China and Australia, whereby HTGW phenotypes and abnormal liver and renal function were assessed at the same time. It is difficult to make causal inference between HTGW and impaired liver and renal function. The role of

339 HTGW in screening for abnormalities were emphasized in the current analysis
340 particularly among Australians. Analysis of longitudinal data would be the next
341 step in examining these relationships further. Another limitation of this joint study
342 is that the data were not collected within the same survey, although the data do
343 appear to be comparable. Although the clinical measurements were managed
344 using a standard approach in both China and Australia, the two research teams
345 worked independently, processing the measurements and blood samples using
346 different equipment including automated analysers. The laboratories were both
347 involved in their respective national laboratory quality assurance programmes and
348 would have therefore had external quality controls on the precision and accuracy
349 of their analyses. The temporal difference in data collection from the two
350 countries might also have some impact on the research population.

351 Finally, the conventional methods (stratification analyses and multivariable
352 modelling strategy) to adjust more confounders were restricted by the current
353 sample size (especially low outcome counts per variable). Therefore, the
354 adjustment of more covariables or potential confounders in the current models
355 was not optional and future external validation studies with further adjustment of
356 more confounders, alongside a meta-analysis are needed to better determine
357 whether HTGW does have the potential to be used as a simple screening tool in
358 clinical practice.

359
360 In conclusion, both in the Chinese and Australian population, HTGW was found to
361 be associated with abnormal liver and renal functions using three previously
362 developed definitions. HTGW has the potential as a screening tool to identify

individuals at high risk of impaired renal function particularly in the Australian population. Only in the Australian population, did the HTGW interact with fasting glucose in its associations with impaired liver and renal function.

Conflicts of interest

None.

Acknowledgement

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FIGURE LEGENDS

Figure-1. Adjusted associations between hyperglyceridaemic waist phenotype definitions and abnormal liver and renal function by fasting plasma glucose level

Age and body mass index were adjusted. Point estimation (95% confidence interval) was presented for each measurement.

HTGW definition 1: both men and women: WC ≥ 85 cm & a triglyceride (TG) ≥ 1.5 mmol/L (133 mg/dl); HTGW definition 2: for men, WC ≥ 90 cm and TG ≥ 2.0 mmol/L (177mg/dl) ; for women, WC ≥ 85 cm and TG ≥ 1.5 mmol/L (133 mg/dl); and HTGW definition 3: for men: WC ≥ 90 cm and TG ≥ 2.0 mmol/L (177mg/dl); for women, WC ≥ 85 cm and TG ≥ 2.0 mmol/L (177mg/dl).

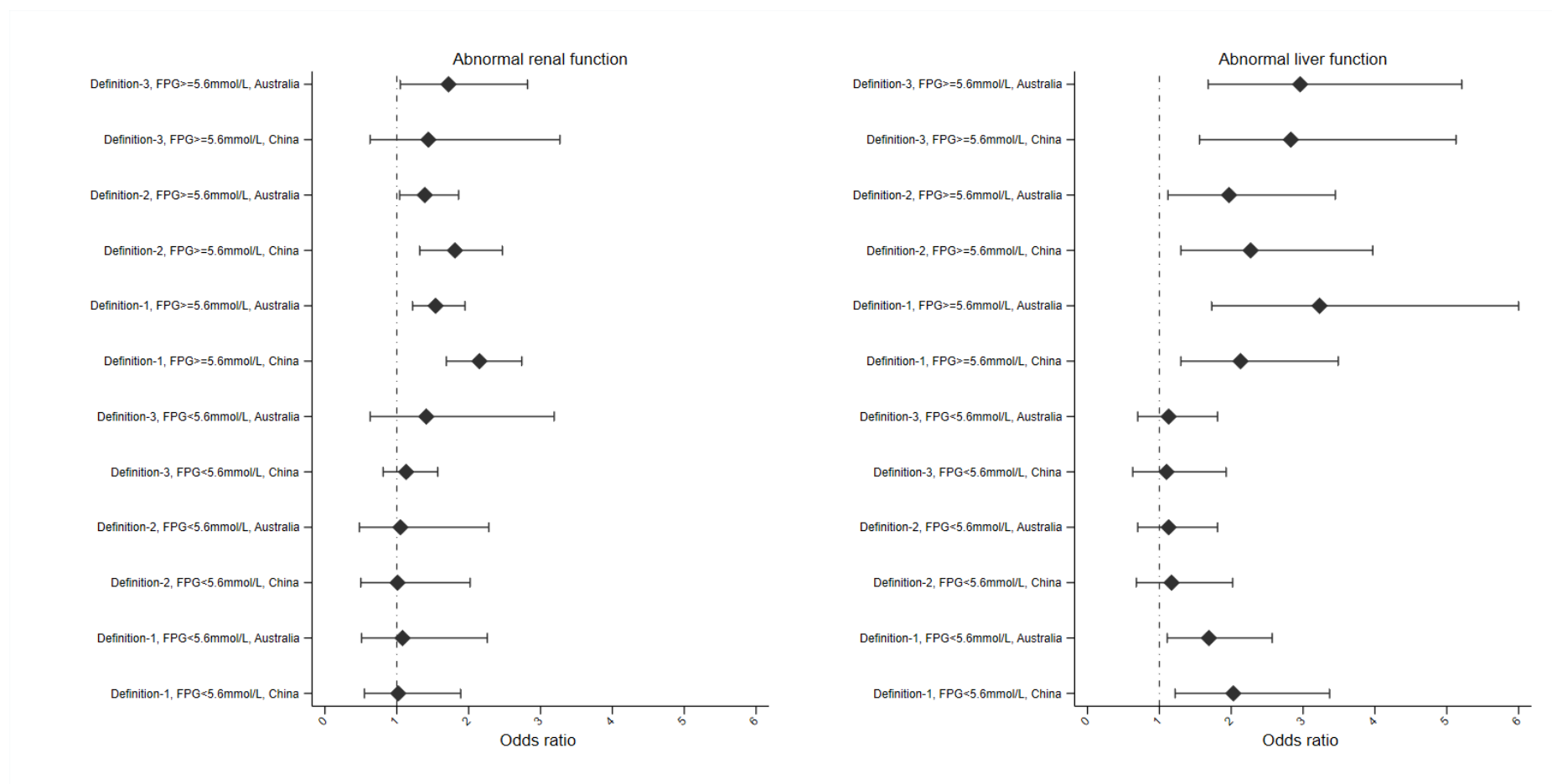


Figure-2. Dose-response curves between abnormal liver function and glucose by hypertriglyceridaemic waist phenotype definitions

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted log odds ratio of having abnormal liver function (solid line) and the 95% confidence interval (dot line) from Logistic Regression Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population). The upper panel indicates association between glucose and abnormal liver function among those with HTGW phenotypes; the below panel indicates association between glucose and abnormal liver function among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: WC \geq 85 cm & a triglyceride (TG) \geq 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, WC \geq 90 cm and TG \geq 2.0 mmol/L (177mg/dl) ; for women, WC \geq 85 cm and TG \geq 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: WC \geq 90cm and TG \geq 2.0 mmol/L (177mg/dl); for women, WC \geq 85cm and TG \geq 2.0 mmol/L (177mg/dl)).

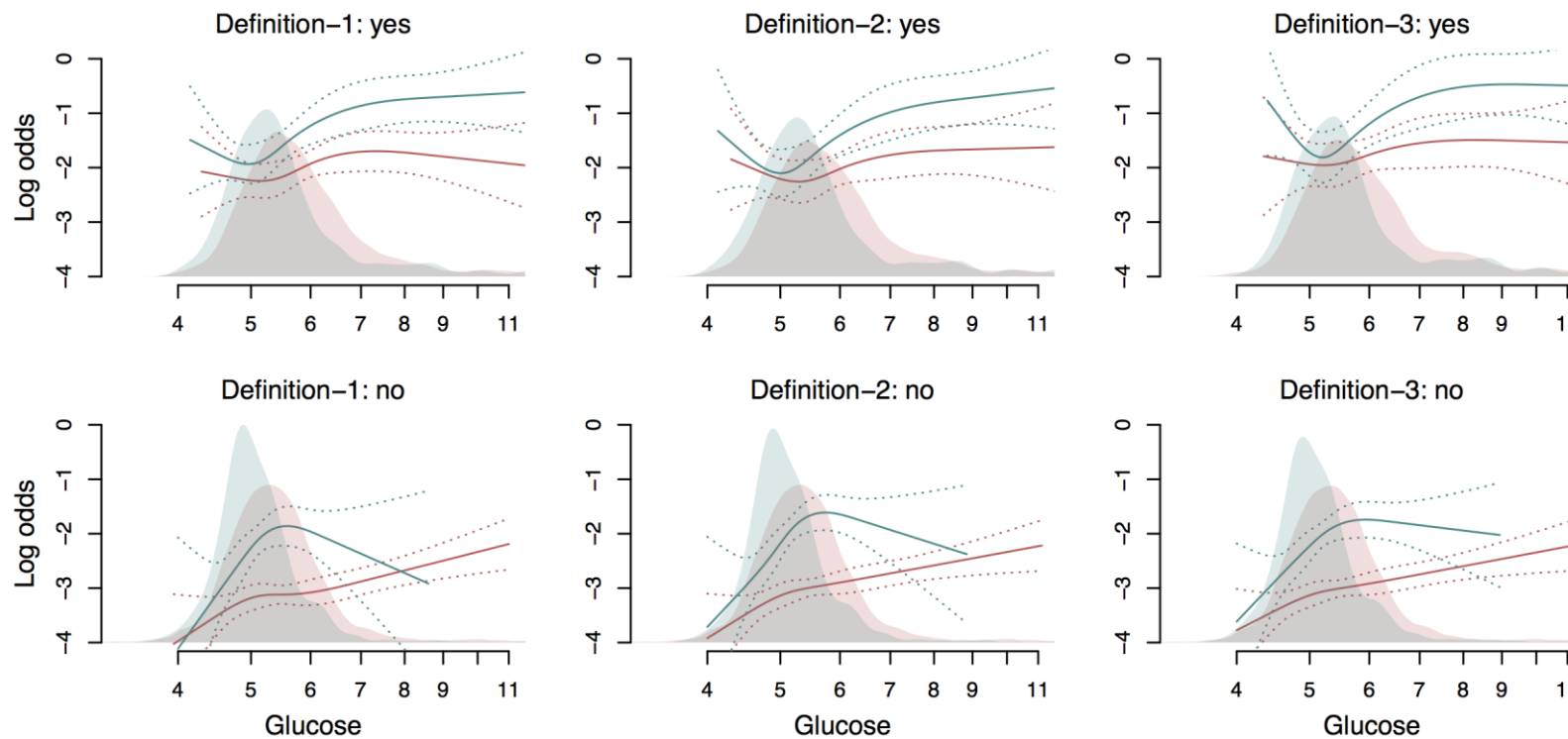
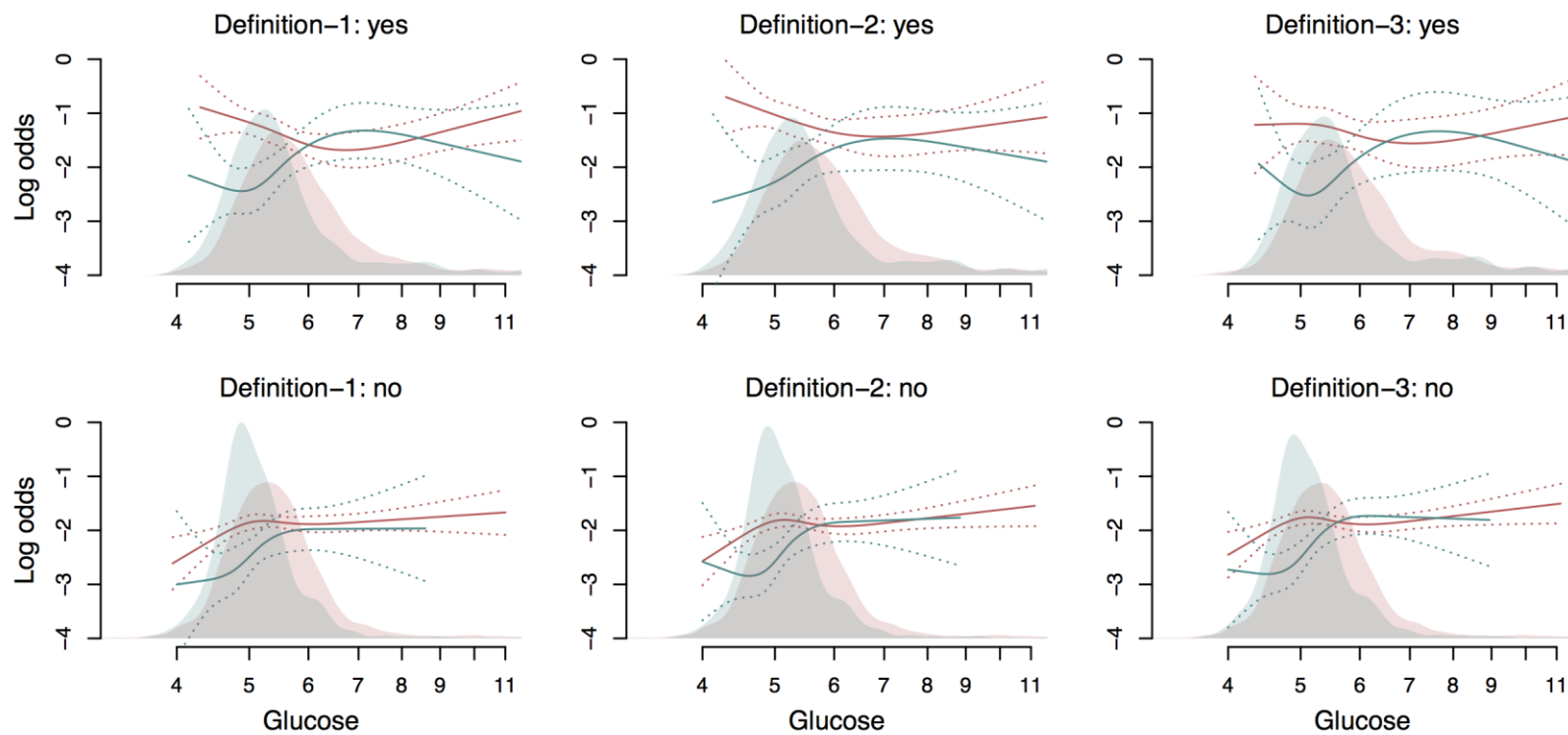


Figure-3. Dose-response curves between abnormal renal function and glucose by hypertriglyceridaemic waist phenotype definitions

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted log odds ratio of having abnormal renal function (solid line) and the 95% confidence interval (dot line) from Logistic Regression Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population). The upper panel indicates association between glucose and abnormal renal function among those with HTGW phenotypes; the below panel indicates association between glucose and abnormal renal function among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: WC ≥ 85 cm & a triglyceride (TG) ≥ 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, WC ≥ 90 cm and TG ≥ 2.0 mmol/L (177mg/dl) ; for women, WC ≥ 85 cm and TG ≥ 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: WC ≥ 90 cm and TG ≥ 2.0 mmol/L (177mg/dl); for women, WC ≥ 85 cm and TG ≥ 2.0 mmol/L (177mg/dl)).



TABLES

Table-1. Characteristics of study participants by hyperglyceridaemic waist phenotype definitions

Country	Characteristics*	Definition-1			Definition-2			Definition-3		
		No	Yes	P-values	No	Yes	P-values	No	Yes	P-values
	N	4773	983	---	5074	682	---	5267	489	---
China	Gender, Female %	2759 (57.8)	481 (48.9)	<0.001	2760 (54.4)	481 (70.5)	P<0.001	2955 (56.1)	288 (58.9)	0.230
	Age, years	51.37(9.89)	53.71(9.55)	<0.001	51.47(9.92)	54.02(9.22)	P<0.001	51.6(9.91)	53.61(9.25)	<0.001
	Waist circumference, cm	78.25(8.59)	91.95(5.91)	<0.001	78.97(8.89)	92.65(6.14)	P<0.001	79.44(9.17)	92.96(5.55)	<0.001
	Body mass index, kgm ²	23.3(3.83)	27.37(3.37)	<0.001	23.47(3.83)	27.88(3.57)	P<0.001	23.63(3.88)	27.92(3.79)	<0.001
	Fasting Glucose, mmol/L	5.53(1.26)	6.04(1.68)	<0.001	5.55(1.29)	6.08(1.67)	P<0.001	5.56(1.29)	6.21(1.81)	<0.001
	Systolic blood pressure, mmHg	129.04(20.24)	139.47(20.75)	<0.001	129.53(20.31)	140.39(21.08)	P<0.001	129.89(20.47)	140.81(20.57)	<0.001
	Diastolic blood pressure, mmHg	80.36(11.36)	87.34(11.99)	<0.001	80.71(11.46)	87.82(12.07)	P<0.001	80.88(11.52)	88.75(11.92)	<0.001
	Total cholesterol, mmol/L	4.38(0.84)	4.84(0.98)	<0.001	4.4(0.84)	4.9(1.01)	<0.001	4.41(0.85)	4.94(1.05)	<0.001
	High density lipoprotein, mmol/L	1.33(0.31)	1.23(0.3)	<0.001	1.33(0.31)	1.22(0.3)	<0.001	1.32(0.31)	1.19(0.3)	<0.001
	Low density lipoprotein, mmol/L	2.46(0.68)	2.35(0.85)	<0.001	2.45(0.69)	2.33(0.85)	<0.001	2.46(0.7)	2.18(0.86)	<0.001
	Triglyceride, mmol/L	1.25(1.04)	2.82(1.77)	<0.001	1.32(1.11)	2.99(1.85)	<0.001	1.33(1.09)	3.5(1.96)	<0.001
	Metabolic disorders, n (%)	1136 (23.8)	675 (68.7)	<0.001	1223 (24.1)	590 (86.5)	<0.001	1401 (26.6)	413 (84.5)	<0.001
	Abnormal liver function, n (%)	200 (4.2)	115 (11.7)	<0.001	235 (4.6)	80 (11.7)	<0.001	244 (4.6)	71 (14.5)	<0.001
	Abnormal renal function, n (%)	619 (13.0)	201 (20.4)	<0.001	662 (13.0)	158 (23.2)	<0.001	717 (13.6)	103 (21.1)	<0.001
Australia	N	902	552	---	1021	433	---	1158	296	---
	Gender, female%	550 (61.0)	269 (48.7)	<0.001	550 (53.9)	629 (62.1)	0.0038	687 (59.3)	132 (44.6)	<0.001
	Age, years	51.49(16.22)	55.21(14.38)	<0.001	51.9(16.13)	55.27(14.18)	<0.001	52.6(16.08)	54.1(13.78)	0.110
	Waist circumference, cm	89.93(16.19)	100.86(13.08)	<0.001	91.58(16.24)	99.98(13.68)	<0.001	91.73(15.94)	103.27(12.48)	<0.001
	Body mass index, kgm ²	26.75(5.06)	29.74(5)	<0.001	27.01(4.97)	29.96(5.28)	<0.001	27.23(5.09)	30.45(5.04)	<0.001
	Fasting Glucose, mmol/L	5.16(0.91)	5.72(1.61)	<0.001	5.18(0.91)	5.82(1.75)	<0.001	5.2(0.93)	6.03(1.94)	<0.001

Systolic blood pressure, mmHg	128.69(21.8)	136.8(22.6)	<0.001	129.84(21.78)	136.32(23.36)	<0.001	130.42(22.18)	137.03(22.75)	<0.001
Diastolic blood pressure, mmHg	70.75(9.74)	74.53(10.35)	<0.001	71.38(9.87)	74.08(10.51)	<0.001	71.34(9.91)	75.47(10.35)	<0.001
Total cholesterol, mmol/L	5.08(0.89)	5.63(1.08)	<0.001	5.11(0.91)	5.71(1.1)	<0.001	5.17(0.93)	5.76(1.16)	<0.001
High density lipoprotein, mmol/L	1.54(0.38)	1.25(0.3)	<0.001	1.5(0.38)	1.26(0.32)	<0.001	1.5(0.37)	1.16(0.27)	<0.001
Low density lipoprotein, mmol/L	3.1(0.79)	3.35(0.95)	<0.001	3.13(0.8)	3.35(0.97)	<0.001	3.16(0.82)	3.34(1.01)	0.0069
Triglyceride, mmol/L	0.96(0.29)	2.35(1.34)	<0.001	1.04(0.36)	2.53(1.46)	<0.001	1.11(0.39)	2.95(1.61)	<0.001
Metabolic disorders, n (%)	171 (19.0)	393 (71.2)	<0.001	234 (22.9)	330 (76.2)	<0.001	309 (26.7)	255 (86.1)	<0.001
Abnormal liver function, n (%)	80 (8.9)	100 (18.1)	<0.001	107 (10.5)	73 (16.9)	<0.001	116 (10.0)	64 (21.6)	<0.001
Abnormal renal function, n (%)	74 (8.2)	65 (11.8)	<0.001	87 (8.5)	52 (12.0)	<0.001	106 (9.2)	33 (11.1)	<0.001

* Continuous variables were presented as means (standard deviation). Categorical variables were presented as percentage. Metabolic disorder indicates metabolic syndrome or type 2 diabetes.

Table-2. Adjusted associations between hyperglyceridaemic waist phenotype definitions and abnormal liver and renal function
Age and body mass index were adjusted. Point estimation (95% confidence interval) was presented for each measurement.

			Definition-1	Definition-2	Definition-3
Abnormal liver function	China	Odds ratio	2.07 (1.34 to 3.21)	1.72 (1.05 to 2.82)	2.24 (1.30 to 3.86)
		Sensitivity	0.57 (0.52 to 0.63)	0.58 (0.52 to 0.63)	0.56 (0.51 to 0.62)
		1 - specificity	0.28 (0.27 to 0.30)	0.32 (0.31 to 0.33)	0.30 (0.28 to 0.31)
	Australia	Odds ratio	2.00 (1.24 to 3.23)	1.51 (0.92 to 2.47)	2.09 (1.22 to 3.59)
		Sensitivity	0.59 (0.52 to 0.67)	0.63 (0.56 to 0.70)	0.62 (0.54 to 0.69)
		1 - specificity	0.35 (0.32 to 0.37)	0.34 (0.32 to 0.37)	0.32 (0.30 to 0.35)
Abnormal Renal function	China	Odds ratio	1.20 (0.86 to 1.66)	1.46 (1.01 to 2.09)	1.23 (0.81 to 1.87)
		Sensitivity	0.73 (0.70 to 0.764)	0.74 (0.71 to 0.77)	0.74 (0.71 to 0.77)
		1 - specificity	0.32 (0.31 to 0.33)	0.31 (0.30 to 0.33)	0.32 (0.31 to 0.33)
	Australia	Odds ratio	1.41 (0.64 to 3.1)	1.60 (0.71 to 3.64)	1.60 (0.61 to 4.18)
		Sensitivity	0.92 (0.86 to 0.96)	0.93 (0.87 to 0.97)	0.93 (0.87 to 0.97)
		1 - specificity	0.18 (0.16 to 0.20)	0.18 (0.16 to 0.20)	0.18 (0.16 to 0.20)

Online Supplemental:

Figure S1. Distribution of Alanine transaminase liver and estimated glomerular filtration rate by hypertriglyceridaemic waist phenotype definitions

The upper panel indicates association between glucose and alanine aminotransferase among those with HTGW phenotypes; the below panel indicates association between glucose and alanine aminotransferase among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: $WC \geq 85$ cm & a triglyceride (TG) ≥ 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, $WC \geq 90$ cm and TG ≥ 2.0 mmol/L (177mg/dl) ; for women, $WC \geq 85$ cm and TG ≥ 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: $WC \geq 90$ cm and TG ≥ 2.0 mmol/L (177mg/dl); for women, $WC \geq 85$ cm and TG ≥ 2.0 mmol/L (177mg/dl)).

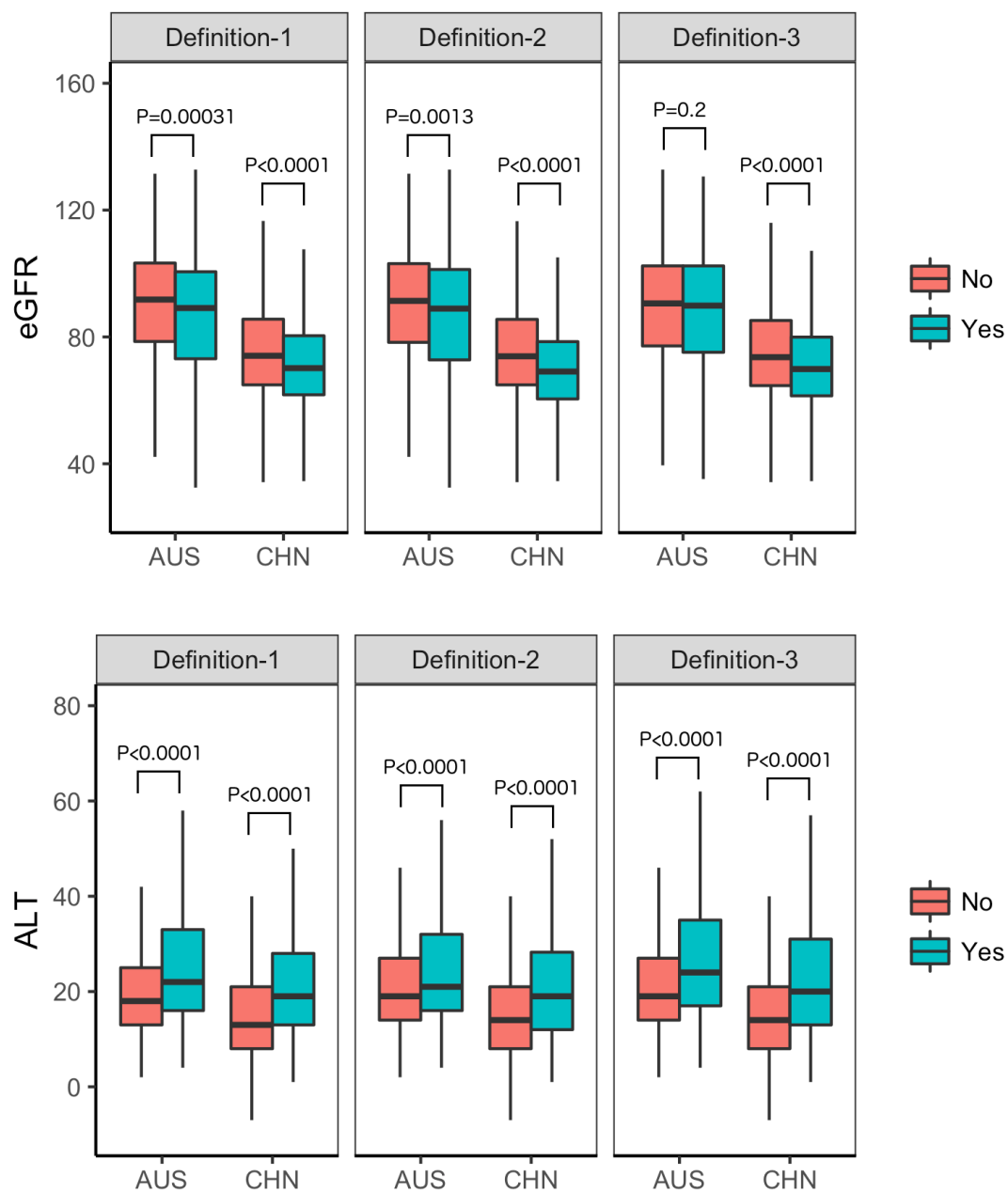


Figure-S2. Dose-response curves between alanine aminotransferase and glucose by hypertriglyceridaemic waist phenotype definitions

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted ALT (solid line) and the 95% confidence interval (dot line) from Generalised Linear Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population).

The upper panel indicates association between glucose and alanine aminotransferase among those with HTGW phenotypes; the below panel indicates association between glucose and alanine aminotransferase among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: WC \geq 85 cm & a triglyceride (TG) \geq 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, WC \geq 90 cm and TG \geq 2.0 mmol/L (177mg/dl) ; for women, WC \geq 85 cm and TG \geq 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: WC \geq 90cm and TG \geq 2.0 mmol/L (177mg/dl); for women, WC \geq 85cm and TG \geq 2.0 mmol/L (177mg/dl)).

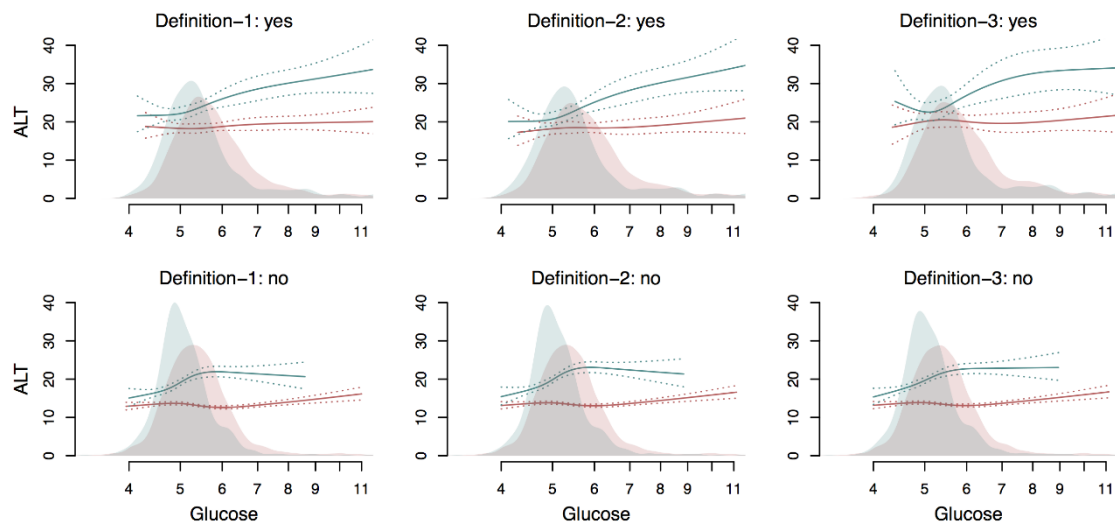


Figure S3. Dose-response curves between alanine aminotransferase and glucose by hypertriglyceridaemic waist phenotype definitions, 90% sample

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted ALT (solid line) and the 95% confidence interval (dot line) from Generalised Linear Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population).

The upper panel indicates association between glucose and alanine aminotransferase among those with HTGW phenotypes; the below panel indicates association between glucose and alanine aminotransferase among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: $WC \geq 85$ cm & a triglyceride (TG) ≥ 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, $WC \geq 90$ cm and TG ≥ 2.0 mmol/L (177mg/dl) ; for women, $WC \geq 85$ cm and TG ≥ 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: $WC \geq 90$ cm and TG ≥ 2.0 mmol/L (177mg/dl); for women, $WC \geq 85$ cm and TG ≥ 2.0 mmol/L (177mg/dl)).

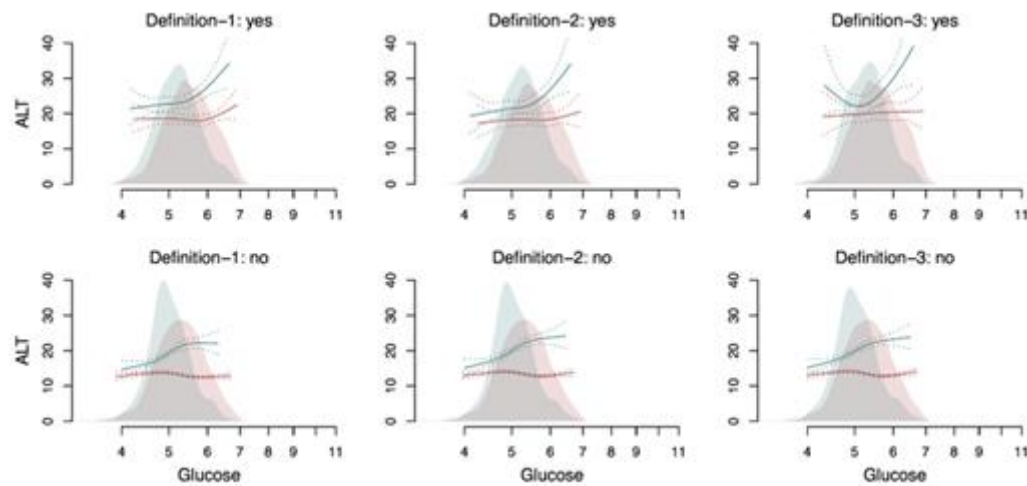


Figure-S4. Dose-response curves between estimated glomerular filtration rate and glucose by hypertriglyceridaemic waist phenotype definitions

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted eGFR (solid line) and the 95% confidence interval (dot line) from Generalised Linear Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population). The upper panel indicates association between glucose and glomerular filtration among those with HTGW phenotypes; the below panel indicates association between glucose and glomerular filtration among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: WC \geq 85 cm & a triglyceride (TG) \geq 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, WC \geq 90 cm and TG \geq 2.0 mmol/L (177mg/dl) ; for women, WC \geq 85 cm and TG \geq 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: WC \geq 90cm and TG \geq 2.0 mmol/L (177mg/dl); for women, WC \geq 85cm and TG \geq 2.0 mmol/L (177mg/dl)).

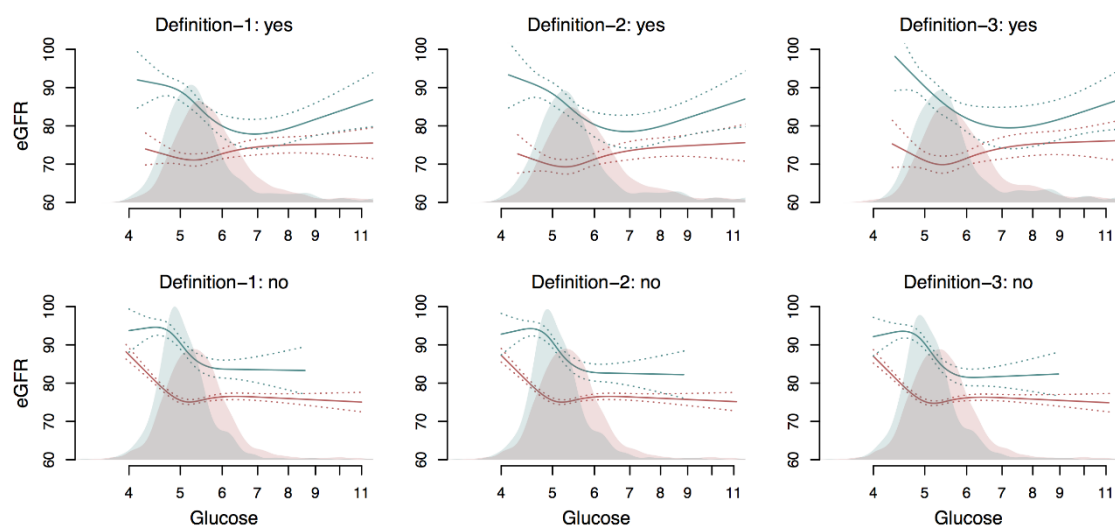


Figure S5. Dose-response curves between estimated glomerular filtration rate and glucose by hyperglyceridaemic waist phenotype definitions, 90% sample

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted estimated glomerular filtration rate (solid line) and the 95% confidence interval (dot line) from Generalised Linear Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population). The upper panel indicates association between glucose and glomerular filtration among those with HTGW phenotypes; the below panel indicates association between glucose and glomerular filtration among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: WC \geq 85 cm & a triglyceride (TG) \geq 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, WC \geq 90 cm and TG \geq 2.0 mmol/L (177mg/dl) ; for women, WC \geq 85 cm and TG \geq 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: WC \geq 90cm and TG \geq 2.0 mmol/L (177mg/dl); for women, WC \geq 85cm and TG \geq 2.0 mmol/L (177mg/dl)).

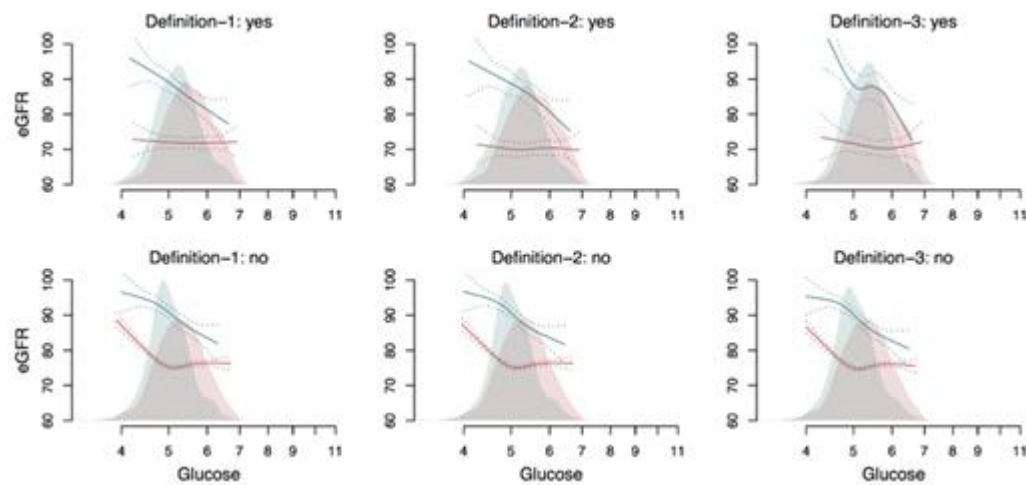


Figure S6. Dose-response curves between abnormal liver function and glucose by hyperglyceridaemic waist phenotype definitions, 90% sample

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted log odds ratio of having abnormal liver function (solid line) and the 95% confidence interval (dot line) from Logistic Regression Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population). The upper panel indicates association between glucose and abnormal liver function among those with HTGW phenotypes; the below panel indicates association between glucose and abnormal liver function among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: $WC \geq 85$ cm & a triglyceride (TG) ≥ 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, $WC \geq 90$ cm and TG ≥ 2.0 mmol/L (177mg/dl) ; for women, $WC \geq 85$ cm and TG ≥ 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: $WC \geq 90$ cm and TG ≥ 2.0 mmol/L (177mg/dl); for women, $WC \geq 85$ cm and TG ≥ 2.0 mmol/L (177mg/dl)).

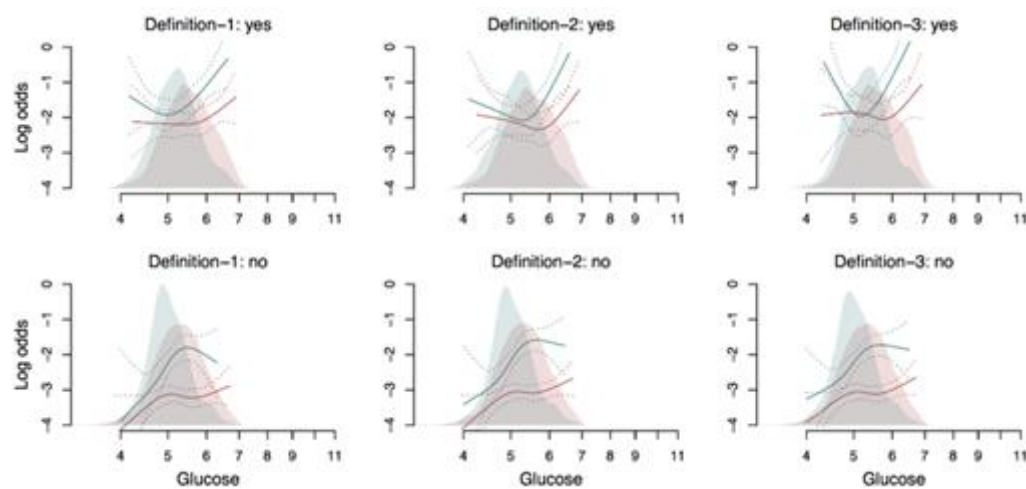


Figure S7. Dose-response curves between abnormal renal function and glucose by hyperglyceridaemic waist phenotype definitions, 90% sample

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted log odds ratio of having abnormal renal function (solid line) and the 95% confidence interval (dot line) from Logistic Regression Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population). The upper panel indicates association between glucose and abnormal renal function among those with HTGW phenotypes; the below panel indicates association between glucose and abnormal renal function among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: $WC \geq 85$ cm & a triglyceride (TG) ≥ 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, $WC \geq 90$ cm and $TG \geq 2.0$ mmol/L (177mg/dl) ; for women, $WC \geq 85$ cm and $TG \geq 1.5$ mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: $WC \geq 90$ cm and $TG \geq 2.0$ mmol/L (177mg/dl); for women, $WC \geq 85$ cm and $TG \geq 2.0$ mmol/L (177mg/dl)).

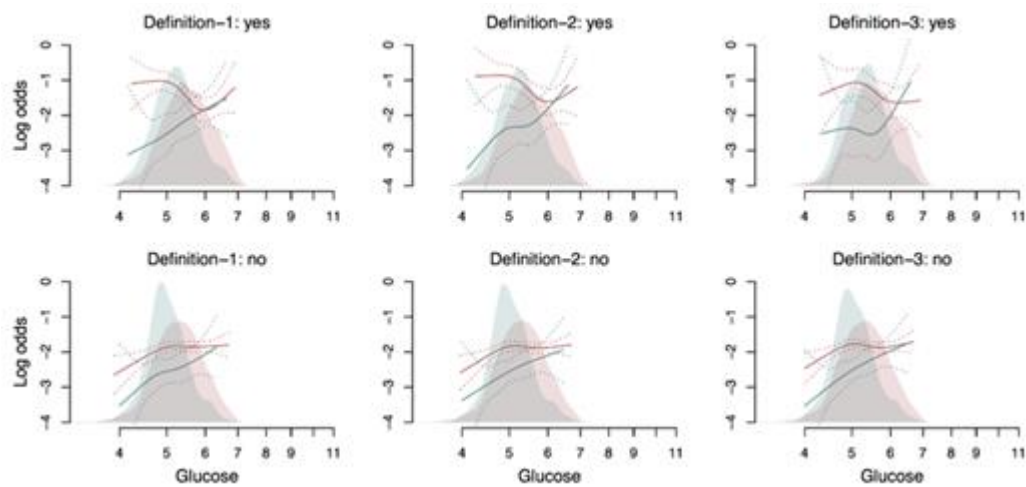


Figure S8. Dose-response curves between alanine aminotransferase and glucose by hypertriglyceridaemic waist phenotype definitions among participants without diabetes

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted estimated alanine aminotransferase (solid line) and the 95% confidence interval (dot line) from Generalised Linear Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population). The upper panel indicates association between glucose and alanine aminotransferase among those with HTGW phenotypes; the below panel indicates association between glucose and alanine aminotransferase among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: WC ≥ 85 cm & a triglyceride (TG) ≥ 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, WC ≥ 90 cm and TG ≥ 2.0 mmol/L (177mg/dl) ; for women, WC ≥ 85 cm and TG ≥ 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: WC ≥ 90 cm and TG ≥ 2.0 mmol/L (177mg/dl); for women, WC ≥ 85 cm and TG ≥ 2.0 mmol/L (177mg/dl)).

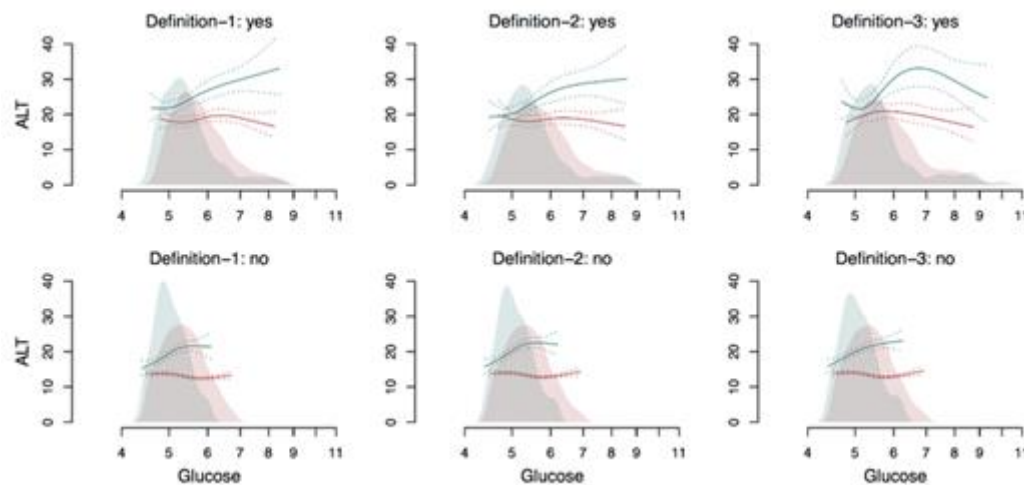


Figure S9. Dose-response curves between estimated glomerular filtration rate and glucose by hypertriglyceridaemic waist phenotype definitions among participants without diabetes

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted estimated glomerular filtration (solid line) and the 95% confidence interval (dot line) from Generalised Linear Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population). The upper panel indicates association between glucose and glomerular filtration among those with HTGW phenotypes; the below panel indicates association between glucose and glomerular filtration among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: WC ≥ 85 cm & a triglyceride (TG) ≥ 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, WC ≥ 90 cm and TG ≥ 2.0 mmol/L (177mg/dl) ; for women, WC ≥ 85 cm and TG ≥ 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: WC ≥ 90 cm and TG ≥ 2.0 mmol/L (177mg/dl); for women, WC ≥ 85 cm and TG ≥ 2.0 mmol/L (177mg/dl)).

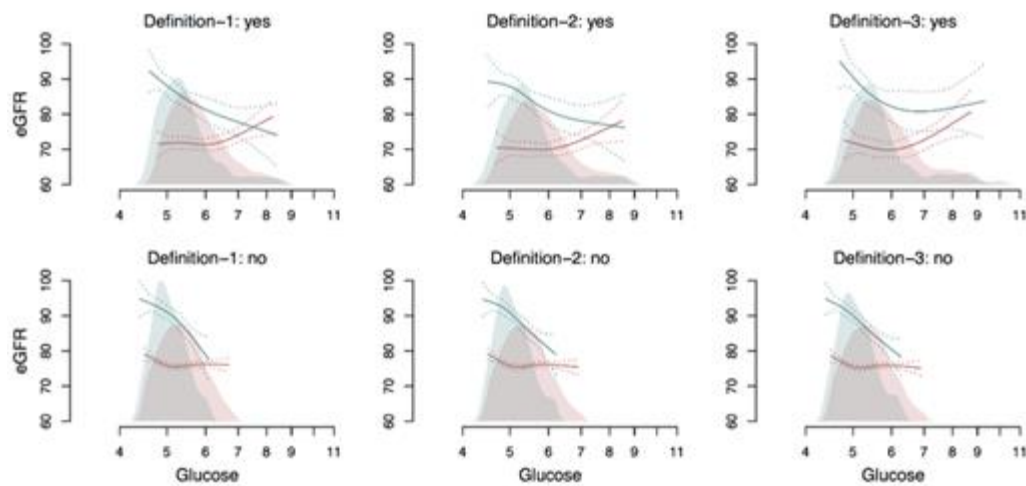


Figure S10. Dose-response curves between abnormal liver function and glucose by hypertriglyceridaemic waist phenotype definitions among participants without diabetes

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted log odds ratio of having abnormal liver function (solid line) and the 95% confidence interval (dot line) from Logistic Regression Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population). The upper panel indicates association between glucose and abnormal liver function among those with HTGW phenotypes; the below panel indicates association between glucose and abnormal liver function among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: WC \geq 85 cm & a triglyceride (TG) \geq 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, WC \geq 90 cm and TG \geq 2.0 mmol/L (177mg/dl) ; for women, WC \geq 85 cm and TG \geq 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: WC \geq 90cm and TG \geq 2.0 mmol/L (177mg/dl); for women, WC \geq 85cm and TG \geq 2.0 mmol/L (177mg/dl)).

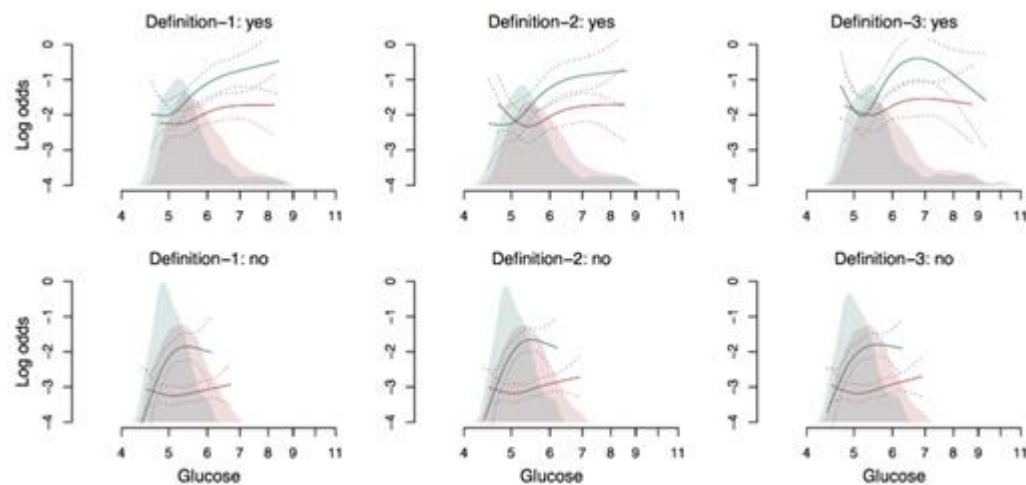


Figure S11. Dose-response curves between abnormal renal function and glucose by hypertriglyceridaemic waist phenotype definitions among participants without diabetes

The area indicates the distribution of fasting glucose (cyan area for Australian population; red area for Chinese population). The adjusted log odds ratio of having abnormal renal function (solid line) and the 95% confidence interval (dot line) from Logistic Regression Model with adjustment of age and body mass index (cyan line for Australian population and red line for Chinese population). The upper panel indicates association between glucose and abnormal renal function among those with HTGW phenotypes; the below panel indicates association between glucose and abnormal renal function among those without HTGW phenotypes. The three columns represent three definitions: left column indicates the HTGW definition 1 (both men and women: WC \geq 85 cm & a triglyceride (TG) \geq 1.5 mmol/L (133 mg/dl)); middle column indicates the HTGW definition 2 (for men, WC \geq 90 cm and TG \geq 2.0 mmol/L (177mg/dl) ; for women, WC \geq 85 cm and TG \geq 1.5 mmol/L (133 mg/dl)); and the right column indicates the HTGW definition 3 (for men: WC \geq 90cm and TG \geq 2.0 mmol/L (177mg/dl); for women, WC \geq 85cm and TG \geq 2.0 mmol/L (177mg/dl)).

