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Nonlinear Association Between Estimated Glucose Disposal Rate and Incident Type 2 Diabetes: Mediation Role of Lipid Profiles

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Abstract

Objectives

Estimated glucose disposition rate (eGDR) is a feasible alternative for evaluating insulin resistance (IR). The relationship and the intermediate mechanism between eGDR and type 2 diabetes mellitus (T2DM) still needs to be elucidated.

Methods

15464 individuals from the NAGALA cohort were Included in the study, who was categorized into five groups by the eGDR. A Cox proportional hazard regression model was used to assess the association of eGDR with the incidents of T2DM. The Cox proportional hazards models incorporating threshold-saturation effects and restricted cubic splines were used in evaluating potential nonlinear associations. And mediation analysis is used to estimate the mediating mechanism of blood lipids in it.

Results

Over a median follow-up period of 1967.00 days, 373 (2.41%) participants devel oped T2DM. After adjusting for correction models, eGDR showed a negative correlation with T2DM, and there showed a non-linear relationship between eGDR and T2DM. The inflection point of eGDR was detected to be 9.82 mg/kg/min. When eGDR <9.82 mg/kg/min, higher eGDR levels were associated with increased risk for T2DM (HR: 1.16, 95%CI: 1.02 to 1.32, P = 0.0192). In the mediation analyses, eGDR has a substantial direct impact on the risk of T2DM, and the indirect effects mediated by HCL-C, TC and TG account for 28%, 7.7% and 18.7% of the total effects respectively.

Conclusion

Lipid profiles mediated in the nonlinear association between eGDR and incident type 2 diabetes.

1 Introduction

Diabetes is a major global health problem. There are 589 million adults suffering from diabetes in 2024 and the number will reach 853 million by 2050[1].Type 2 diabetes mellitus (T2DM) accounts for between 90% and 95% of all diabetes cases, and around half of T2DM remain undiagnosed[2]. Early detection, management, and prevention are important for the early control, prevention, or delay of complications of T2DM.

Insulin resistance (IR) is an important pathophysiological feature of T2DM, which precedes the clinical manifestations and diagnosis of T2DM[3][4]. While multiple indicators exist for assessing insulin

resistance (IR)—including the hyperinsulinemic-euglycemic (HIEG) clamp, the triglyceride glucose index (TyG), and the homeostasis model assessment for insulin resistance (HOMA-IR)—the estimated glucose disposal rate (eGDR) emerges as a particularly viable alternative[5][6][7][8]. Its calculation, derived from routinely available clinical measures, offers a favorable balance between practical accessibility and a level of accuracy that approaches that of the reference HIEG clamp technique[7][9][10][11][12].

There are few studies on the correlation between eGDR and the risk of type 2 diabetes, and the intermediate mechanism needs to be clarified. Evaluating the correlation and intermediate mechanism between eGDR and T2DM can help verify the predictability of eGDR, further clarify the relationship between IR and T2DM, and provide key evidence for the necessity of IR intervention in T2DM. Based on the above reasons, we proformed the following historical cohort research.

2 Research design and methods

2.1 Data Source and Participants

This secondary analysis utilized data from the NAGALA cohort, a longitudinal study of NAfld in Gifu, Japan[13]. The study population comprised 15464 individuals who underwent regular physical examinations at the Medical Health Checkup Center of Murakami Memorial Hospital (Gifu, Japan) from 2004 to 2015. We excluded participants with alcoholic fatty liver disease, viral hepatitis (defined by measurements of hepatitis B antigen and hepatitis C antibody), any medication usage at baseline, and diabetes at the baseline examination. In addition, we also excluded the participants with missing data of covariates. The schematic diagram of patient inclusion process is shown in Fig. 1.

2.2 Data collection

The raw data obtained from the Dryad database comprised information on incident T2DM, follow-up duration, and a comprehensive set of baseline variables. From the baseline data, we extracted the estimated glucose disposal rate (eGDR), along with the following covariates: demographic characteristics (age, sex), anthropometric measures (body mass index [BMI], waist circumference [WC]), lifestyle factors (ethanol intake [alcohol consumption], exercise habit, smoking status), clinical parameters (systolic and diastolic blood pressure[SBP and DBP], fatty liver status), biochemical indices (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [γ-GGT], high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], triglycerides [TG], fasting plasma glucose [FPG], and haemoglobin A1c [HbA1c]), and conditions such as hypertention (HTN), incident of diabetes.

2.3 Definitions

The calculation formula for the research variable eGDR is 21.158 − (0.09 x WC) − (3.407 x HTN) − (0.551 x HbA1c)[7][15], and then eGDR was categorized into five groups: Q1(< 11.02), Q2(11.02–11.61), Q3(11.61–12.09), Q4(12.09–12.60), Q5(12.60-15.17).

Alcohol consumption was evaluated by the type and amount of alcohol consumed per week in the previous month. Smoking status was categorized as never, past, or current. Exercise habit was defined as engaging in any physical activity at least weekly. Fatty liver diagnosis was ascertained by abdominal ultrasonography, with images independently reviewed by experienced gastroenterologists who were blinded to participant identity. Diagnosis was based on standard sonographic criteria including hepatorenal echo contrast, hepatic parenchymal brightness, deep attenuation, and vascular blurring. T2DM was defined according to established criteria: HbA1c ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), or self-reported diabetes during follow-up[13][14].

2.4 Statistical Analyses

All statistical analysis is based on EmpowerStats(https://www.empowerstats.net/cn/) and R software calculations, with significance set at P-values < 0.05. Study participants were classifed into five groups according to quintile of the eGDR (< 11.02, 11.02–11.61, 11.61–12.09, 12.09–12.60, 12.60-15.17). The difference across the five eGDR quintile groups was assessed using the Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables. Categorical variables were presented as proportions and continuous variables were presented as mean value±standard deviation (M ± SD). Kaplan-Meier survival analysis was performed to estimate cumulative incidence and generate survival curves stratified by eGDR levels during follow-up.

A Cox proportional hazard regression model was used to assess the association of eGDR with the incidents of T2DM. Candidate covariates were chosen on the basis of prior clinical knowledge and published literature. Three nested models were examined: Model 1 was unadjusted; Model 2 was adjusted for age, sex, and BMI; and Model 3 was further adjusted for lifestyle and metabolic covariates, including smoking status, alcohol consumption, exercise habits, fatty liver, ALT, AST, γ-GGT, HDL-C, TC, TG, and FPG. Collinearity among covariates was assessed using variance inflation factors (VIF), and variables with a VIF > 5 were excluded from the multivariate models. Results are reported as hazard ratios (HR) with corresponding 95% confidence intervals (CI).

To evaluate potential nonlinear associations between eGDR and incident T2DM, we fit Cox proportional hazards models incorporating threshold-saturation effects and restricted cubic splines. When evidence of nonlinearity was present, we identified the inflection point via a recursive algorithm and subsequently two-piecewise Cox proportional hazards regression model on each side of this threshold. Model comparisons were conducted using likelihood ratio tests, contrasting a standard linear Cox model against the two-piecewise Cox model to determine the optimal functional form for the eGDR-T2DM association.

To assess the robustness of findings across population subgroups, we conducted stratified analyses based on six characteristics: sex, BMI, fatty liver status, excessive waist circumference, exercise habits, and smoking status. Associations were estimated within each stratum, and interaction terms were tested to evaluate effect heterogeneity. Furthermore, we performed formal causal mediation analyses to

estimate the proportion of the total association between eGDR and T2DM risk that was independently mediated by HDL-C, TC, and TG levels.

3 Results

3.1 Study Participants and Baseline Characteristics

After a specific inclusion process (as shown in Figure 1 of the data source and participants), the baseline data of 15464 patients are lists in the supplementary table 1, which provides a comparison of the baseline clinical characteristics among five groups of eGDR. Among five subgroups according to eGDR (<11.02, 11.02-11.61, 11.61-12.09, 12.09-12.60, 12.60-15.17), we can see that participants with higher eGDR commonly had higher HDL and proportion of never-smoking and had lower age, BMI, WC, SBP, DBP, FPG, HbA1c, TG, total cholesterol, ALT, AST, GGT, ethanol consumption, proportion of men, fatty liver, past and current smokers. Besides, hypertension only found in group Q1 and there was no obvious relevance about exercise among theses groups. Over a median follow-up period of 1967.00 days, 373(2.41%) participants devel oped T2DM, and the higher incident T2DM is with lower eGDR. ROC analysis was performed on eGDR (Figure 2), and the area under the curve was 0.773. The cumulative incident T2DM according to the baseline eGDR for participants was presented in Figure 3. As we can see, with the increase of follow-up time, the incidence rate of T2DM gradually increases and the incidence rate of T2DM increases with the decrease of eGDR.

Table 1 Baseline characteristics of the study participants according to the eGDR quintile

Variables	Q1 (N=3087)	Q2 (N=3098)	Q3 (N=3084)	Q4 (N=3120)	Q5 (N=3093)	*p* value
Age, yrs, M±SD	46.39 ± 8.93	45.25 ± 8.95	43.50 ± 8.43	42.62 ± 8.60	40.79 ± 8.47	<0.001
BMI, kg/m^2, M±SD	25.85 ± 3.07	23.51 ± 1.72	21.84 ± 1.62	20.44 ± 1.58	18.95 ± 1.62	<0.001
Alcohol consumption, g/week, M±SD	67.19 ± 97.52	59.20 ± 91.45	52.06 ± 84.58	37.34 ± 69.94	23.08 ± 52.47	<0.001
ALT, IU/L, M±SD	28.82 ± 18.89	22.18 ± 11.77	18.50 ± 9.14	16.06 ± 16.75	14.40 ± 6.12	<0.001
AST, IU/L, M±SD	21.66 ± 9.87	18.88 ± 6.54	17.95 ± 6.86	17.24 ± 11.86	16.29 ± 5.37	<0.001
GGT, IU/L, M±SD	29.37 ± 23.48	23.56 ± 20.15	19.84 ± 17.12	15.71 ± 11.66	13.09 ± 9.65	<0.001
HDL-C, mmol/L, M±SD	48.14 ± 12.65	50.97 ± 13.38	56.57 ± 14.76	61.29 ± 15.08	65.72 ± 14.82	<0.001
TC, mmol/L, M±SD	209.41 ± 33.65	203.20 ± 32.60	197.70 ± 32.85	192.32 ± 31.97	188.41 ± 31.71	<0.001
TG, mmol/L, M±SD	117.80 ± 72.04	98.38 ± 65.55	76.71 ± 48.55	60.91 ± 36.56	50.24 ± 25.61	<0.001
FPG, mmol/L, M±SD	97.36 ± 6.52	95.27 ± 6.68	93.04 ± 6.83	90.97 ± 6.85	88.21 ± 6.68	<0.001
eGDR, mg/kg/min, M±SD	9.70 ± 1.43	11.34 ± 0.17	11.85 ± 0.14	12.34 ± 0.15	12.99 ± 0.30	<0.001
WC, cm, M±SD	88.19 ± 7.33	81.75 ± 2.57	76.51 ± 2.29	71.30 ± 2.36	64.64 ± 3.41	<0.001
SBP, mmHg, M±SD	128.72 ± 16.36	116.64 ± 11.09	113.16 ± 11.20	109.38 ± 11.81	104.61 ± 11.55	<0.001
DBP, mmHg, M±SD	81.46 ± 11.08	73.12 ± 8.14	70.52 ± 8.27	67.85 ± 8.48	64.98 ± 8.02	<0.001
HBA1C, %, M±SD	5.32 ± 0.34	5.23 ± 0.31	5.16 ± 0.30	5.12 ± 0.29	5.02 ± 0.29	<0.001
Sex, n(%)						<0.001
Female	640 (20.73%)	776 (25.05%)	1212 (39.30%)	1799 (57.99%)	2607 (84.29%)	

Table 1 Baseline characteristics of the study participants according to the eGDR quintile

Variables	Q1 (N=3087)	Q2 (N=3098)	Q3 (N=3084)	Q4 (N=3120)	Q5 (N=3093)	*p* value
Male	2447 (79.27%)	2322 (74.95%)	1872 (60.70%)	1303 (42.01%)	486 (15.71%)	
Fatty liver, n(%)						<0.001
No	1542 (49.95%)	2282 (73.66%)	2795 (90.63%)	3023 (97.45%)	3081 (99.61%)	
Yes	1545 (50.05%)	816 (26.34%)	289 (9.37%)	79 (2.55%)	12 (0.39%)	
Exercise habit, n(%)						<0.001
No	2630 (85.20%)	2547 (82.21%)	2479 (80.38%)	2509 (80.88%)	2590 (83.74%)	
Yes	457 (14.80%)	551 (17.79%)	605 (19.62%)	593 (19.12%)	503 (16.26%)	
Smoking status, n(%)						<0.001
Never	1345 (43.57%)	1417 (45.74%)	1734 (56.23%)	2071 (66.76%)	2464 (79.66%)	
Former	851 (27.57%)	779 (25.15%)	617 (20.01%)	464 (14.96%)	241 (7.79%)	
Current	891 (28.86%)	902 (29.12%)	733 (23.77%)	567 (18.28%)	388 (12.54%)	
HTN, n(%)						<0.001
No	2170 (70.29%)	3098 (100.00%)	3084 (100.00%)	3102 (100.00%)	3093 (100.00%)	
Yes	917 (29.71%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Incident T2DM, n(%)						<0.001
No	2858 (92.58%)	3029 (97.77%)	3041 (98.61%)	3079 (99.26%)	3084 (99.71%)	
Yes	229 (7.42%)	69 (2.23%)	43 (1.39%)	23 (0.74%)	9 (0.29%)	

3.2 The association between eGDR and incident T2DM

The univariate analysis between various related parameters and incident T2DM was showed in table 2, which demonstrated that men, age, BMI, fatty liver, ALT, AST, GGT, TG, TC, past and current smokers, FPG, SBP, DBP, WC, HbA1c, and obesity were positively related to the incident T2DM. Besides eGDR and HDL-C levels were negtively related to the incident T2DM. Then we further explored the relationship between eGDR and incident T2DM through multiple factor analysis and the results showed in table 3. In order to fully demonstrate the relationship, eGDR is presented in three different forms: continuous variables, binary grouping based on ROC analysis's optimal cut-off point 11.12, and quintuple grouping. After two correction models, eGDR still showed a negative correlation with incident T2DM.

Table 2 The univariate analysis between various related parameters and incident T2DM

Variables	Statistics	HR (95% CI) *p* value
Sex, n(%)		
Female	7034 (45.49%)	1
Male	8430 (54.51%)	2.52 (1.98, 3.21) <0.0001
Age, yrs, M±SD	43.71 ± 8.90	1.06 (1.04, 1.07) <0.0001
BMI, kg/m^2, M±SD	22.12 ± 3.13	1.24 (1.22, 1.27) <0.0001
Alcohol consumption, g/week, M±SD	47.76 ± 82.34	1.00 (1.00, 1.00) 0.0012
Fatty liver, n(%)		
No	12723 (82.27%)	1
Yes	2741 (17.73%)	7.02 (5.70, 8.63) <0.0001
ALT, IU/L, M±SD	19.99 ± 14.34	1.01 (1.01, 1.01) <0.0001
AST, IU/L, M±SD	18.40 ± 8.64	1.01 (1.01, 1.01) <0.0001
Exercise habit, n(%)		
No	12755 (82.48%)	1
Yes	2709 (17.52%)	0.76 (0.56, 1.02) 0.0641
GGT, IU/L, M±SD	20.31 ± 18.14	1.01 (1.01, 1.01) <0.0001
HDL-C, mmol/L, M±SD	56.54 ± 15.57	0.95 (0.94, 0.96) <0.0001
TC, mmol/L, M±SD	198.20 ± 33.41	1.01 (1.01, 1.01) <0.0001
TG, mmol/L, M±SD	80.79 ± 58.05	1.01 (1.01, 1.01) <0.0001
Smoking status, n(%)		
Never	9031 (58.40%)	1
Former	2952 (19.09%)	1.65 (1.26, 2.18) 0.0004
Current	3481 (22.51%)	2.58 (2.06, 3.24) <0.0001
FGP, mmol/L, M±SD	92.97 ± 7.44	1.20 (1.18, 1.22) <0.0001
eGDR, mg/kg/min, M±SD	11.65 ± 1.30	0.64 (0.61, 0.67) <0.0001
WC, cm, M±SD	76.47 ± 9.11	1.09 (1.08, 1.10) <0.0001
SBP, mmHg, M±SD	114.50 ± 14.97	1.03 (1.03, 1.04) <0.0001
DBP, mmHg, M±SD	71.58 ± 10.50	1.05 (1.04, 1.06) <0.0001

HTN, n(%)		
No	14547 (94.07%)	1
Yes	917 (5.93%)	2.65 (1.97, 3.55) <0.0001
HBA1C, %, M±SD	5.17 ± 0.32	54.27 (39.49, 74.59) <0.0001

Table 3 Association Between eGDR and Incident T2DM in Different Models

Variable	Unadjusted	Model I	Model II
eGDR	0.64 (0.61, 0.67) <0.0001	0.84 (0.78, 0.91) <0.0001	0.93 (0.86, 1.01) 0.0728
eGDR categorical			
11.12	1	1	1
≥11.12	0.15 (0.12, 0.18) <0.0001	0.35 (0.26, 0.46) <0.0001	0.56 (0.42, 0.74) <0.0001
eGDR 5 quantiles			
Q1	1	1	1
Q2	0.30 (0.23, 0.39) <0.0001	0.41 (0.31, 0.55) <0.0001	0.53 (0.39, 0.71) <0.0001
Q3	0.18 (0.13, 0.25) <0.0001	0.33 (0.23, 0.48) <0.0001	0.59 (0.40, 0.87) 0.0079
Q4	0.10 (0.06, 0.15) <0.0001	0.21 (0.13, 0.35) <0.0001	0.50 (0.30, 0.85) 0.0106
Q5	0.03 (0.02, 0.06) <0.0001	0.09 (0.04, 0.20) <0.0001	0.26 (0.12, 0.56) 0.0006
p for trend	<0.0001	<0.0001	<0.0001

Model I: adjust for sex, age and BMI.

Model II: adjust for sex, age, BMI, alcohol consumption, fatty liver, ALT, AST, exercise habit, GGT, HDL-C, TC, TG, smoking status and FPG.

Further more, threshold analysis was applied to assess whether there was a non-linear relationship between eGDR and incident T2DM in Table 4, after adjusting for sex, age, BMI, ethanol consumption, fatting liver, ALT, AST, exercise, GGT, HDL, TC, TG, smoking status,FPG. The inflection point of eGDR was detected to be 9.82 mg/kg/min. When eGDR 9.82 mg/kg/min, we observed that higher eGDR levels were associated with increased risk for T2DM (HR: 1.16, 95%CI: 1.02 to 1.32, P=0.0192). While when

eGDR > 9.82 mg/kg/min, the result showed that elevated eGDR levels might be associated with an decrease risk of T2DM. The fitting curve made from the above results is shown in Figure 4.

Table 4 Threshold saturation effect between eGDR and incident T2DM

Outcome:	Incident T2DM
Model I Linear effect	0.93 (0.86, 1.01) 0.0728
Model II	
turning point (K)	9.82
< K effect 1	1.16 (1.02, 1.32) 0.0192
> K effect 2	0.59 (0.49, 0.72) <0.0001
difference between 1 and 2	0.51 (0.39, 0.67) <0.0001
Log Likelihood Ratio Tests	<0.001
95% confidence interval for turning points (K)	9.34, 10.39

Adjust for: sex, age, BMI, alcohol consumption, fatty liver, ALT, AST, excercise habit, GGT, HDL-C, TC, TG, smoking status, FPG.

3.3 Stratified analysis

To evaluate the potential modifying effects of key covariates, we conducted stratified analyses for the association between eGDR and T2DM incidence. As shown in Table 5, the population was stratified by age, fatty liver, high WC (baseline WC≥90 cm for men, ≥80 cm for women), BMI, smoking status and regular exercise habit. And we calculated stratum-specific hazard ratios to assess trends in effect sizes across these subgroups.. Because six subgroups were tested, we applied Bonferroni correction and set the threshold for statistical significance at $P < 0.0083$ ($0.05 \div 6$). After correction, the HR difference by sex remained the largest, although this exploratory finding requires independent validation.

Table 5 The result of stratified analysis

Variable	N	HR (95% CI) *p* value	*p* for interaction
Sex			0.0065
No	7034	0.09 (0.06, 0.14) <0.0001	
Yes	8430	0.19 (0.15, 0.25) <0.0001	
Fatty liver			0.487
No	12723	0.25 (0.18, 0.35) <0.0001	
Yes	2741	0.30 (0.21, 0.42) <0.0001	
High WC (Baseline WC≥90cm for men, ≥80cm for women)			0.7183
No	13450	0.18 (0.14, 0.23) <0.0001	
Yes	2014	0.15 (0.07, 0.35) <0.0001	
BMI			0.0482
≤25	12940	0.17 (0.13, 0.22) <0.0001	
>25	2524	0.32 (0.19, 0.54) <0.0001	
Exercise habit			0.6902
No	12755	0.14 (0.11, 0.18) <0.0001	
Yes	2709	0.16 (0.09, 0.29) <0.0001	
Smoking status			0.1206
Never	9031	0.13 (0.09, 0.18) <0.0001	
Past	2952	0.24 (0.15, 0.38) <0.0001	
Current	3481	0.16 (0.11, 0.22) <0.0001	

Table 5 The result of stratified analysis

Variable	N	HR (95% CI) *p* value	*p* for interaction

Note: eGDR is a binary form based on ROC analysis of the optimal cut-off point.

3.4 The results of mediating effect test

Mediating analysis examines the extent to which HDL-C, TG, and TC mediate the relationship between eGDR and the onset of T2DM. After adjusting for multiple confounding variables, we observed significant direct and indirect effects in all study populations. As shown in Figure 5, in the three mediation analyses, we can see that eGDR has a substantial direct impact on the risk of diabetes, and the indirect effects mediated by HCL-C, TC and TG are also significant, and they account for 28%, 7.7% and 18.7% of the total effects respectively.

4 Discussion

Traditional IR assessments such as HOMA-IR are complex, lengthy, and limited in scope. eGDR is now considered a simple and effective alternative biomarker for IR in T1DM patients[15]. Compared with other indicators for evaluating IR, eGDR is more strongly correlated with easily obtainable clinical parameters such as hypertension, WC, and HbA1c, and has higher accuracy and clinical application value[15][16][17][18][19]. Now the research on the application scope of eGDR has been expanded to include non diabetes patients[20], type 2 diabetes patients[17][21] and acute ischemic stroke patients[17][22]. These studies mainly reveal that there is a significant correlation between eGDR and a series of results, such as diabetes complications, cardiovascular disease (CVD) and all-cause mortality[23][24][25][26]. eGDR has been identified as an independent predictor of coronary artery disease[27], depression[28], all-cause mortality[29]and peripheral vascular disease[30] in T1DM patients.

Alexander Zabala et al. also mentioned in their stuy in 2021[31] that the mean age, the proportion of men, diabetes duration, HbA1c levels, blood pressure, physical inactivity, proportion of individuals with cardiovascular disease, nephropathy may decrease with the increase of eGDR. Also people with lower eGDR were more likely to receive antihypertensive treatments, lipid-lowering drugs, oral glucose-lowering agents and insulin therapy. And the research results of Yang Geng et al.[32] demonstrate that eGDR plays a significant mediating role between the weight-adjusted waist index (WWI) and T2DM mortality risk.

However, the above studies are about the correlation between eGDR and type 2 diabetes related complications, and it is hard to find researches on the correlation between eGDR and type 2 diabetes, which still needs to be explored. Our results directly show that there is a negative correlation between eGDR and the incidence rate of T2DM, and the incidence of T2DM increases significantly with the decrease of eGDR. The above conclusion is basically consistent with previous studies.

Diabetes patients generally have dyslipidemia and extensive research has shown that lipid metabolism disorders lead to insulin resistance[33][34]. So we included blood lipids in the mediation analysis of eGDR and T2DM, and the results showed that blood lipids are a key mediating factor. According to the proportion of intermediary influence, HCL-C, TG, and TC account for 28%, 18.8%, and 7.7% of the total influence, respectively.

The relationship between TC and T2DM is clear, that is the higher the total cholesterol level in the blood, the greater the risk of developing type 2 diabetes in the future[35][36]. The relationship between the following blood lipids and T2DM is more interesting.

Some studies showed, TG plays a critical role in the pathogenesis of type 2 diabetes. Obesity and hypertriglyceridemia lead to insulin resistance and enhanced hyperinsulinemia by causing ectopic fat deposition in non fat tissues such as the liver, pancreas, and skeletal muscle[37], meanwhile elevated insulin levels promote the absorption of fatty acids and exacerbate ectopic triglyceride deposition[38], forming a self reinforcing cycle. This study confirms that TG may play a certain role in the pathogenesis of T2DM.

LDL seems to reduce insulin secretion and beta cell proliferation, and LDL receptors play a central role in mediating the adverse effects of LDL on insulin secretion[39]. Some studies have shown that ceramide is a lipid metabolite primarily associated with LDL, and its binding to LDL has been shown to be associated with increased insulin resistance in skeletal muscle cells[40][41]. However, under the above research background, there are some controversial research results in the follow-up, that is, anti-LDL statins have the risk of diabetes[42]. In view of the above controversies, LDL is temporarily not included in the mediation analysis.

HDL, known as "good cholesterol," has multiple protective functions, including enhancing insulin sensitivity[43][44][45]. Researches show that higher HDL-C is strongly related to a lower risk of T2DM in the future[46][47] and directly influences glucose metabolism[48]. It could be seen that HDL has the highest proportion of influencing factors in promoting T2DM in our study. However, it is worth noting that the use of drugs to increase HDL-C levels in large-scale clinical trials did not reduce cardiovascular events[49]. Perhaps the increased amount of HDL did not have corresponding functions, which suggests that the mechanism and relationship between HDL-C quantity and its function in cardiovascular disease and T2DM deserve further researches.

This study has the following significant advantages. First, previous studies have mostly focused on the correlation between eGDR and complications or death outcomes of type 2 diabetes. This study is the first to study the risk correlation between eGDR and type 2 diabetes. Moreover, our study sample size is large and we have found a non-linear relationship between eGDR and the incidence of type 2 diabetes through threshold effect analysis and fitting curves. Finally, we clarified the mediating effect of blood lipids between eGDR and incident T2DM in our study. Of course, our research also has certain limitations: firstly, this article is a secondary study, and its fundamental limitation depends entirely on the

original research data it includes - only publicly available data selected by the original researchers can be used, which may lead to information loss or bias; Secondly, the accuracy of some data may be limited, such as the ultrasound diagnosis of fatty liver not being as accurate as liver biopsy preparation, and the diagnosis of T2DM not being rigorously validated by OralGlucoseToleranceTest (OGTT). Thirdly, there are limitations in the study population. This study is only applicable to Japanese adults, as research has shown significant differences in insulin sensitivity among populations with different genetic backgrounds. Therefore, the results of this study cannot be universally applicable to other ethnic groups; Fourthly, although eGDR has been proven to be a reliable indicator for assessing insulin sensitivity, future research using the gold standard high insulin level isoglycemic clamp technique to measure insulin sensitivity is still necessary to further validate current research results.

In conclusion, we identified a nonlinear association between eGDR and incident type 2 diabetes: risk rose sharply below a critical threshold and plateaued thereafter. Lipid profiles mediated a substantial share of this relationship.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CVD	Cardiovascular disease
CIs	Confidence intervals
DBP	Diastolic blood pressure
eGDR	Estimated glucose disposition rate
FPG	Fasting plasma glucose
γ-GGT	Gamma-glutamyl transferase
HbA1c	Haemoglobin A1c
HIEG	Hyperinsulinemic-euglycemic
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment for insulin resistance
HRs	Hazard ratios
HTN	Hypertention
IR	Insulin resistance
M±SD	mean value±Standard deviation
OGTT	OralGlucoseToleranceTest
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
TyG	Triglyceride-glucose index
VIF	Variance inflation factors
WC	Waist circumference
WWI	the weight-adjusted waist index

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data used to support the findings of this study are openly available in Dryad (http://www.datadryad.org/).

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Study conception and design, acquisition and analysis of data, writing—review and editing, communication and interpretation, Xiaohua Wang and Beitao Gong;

Investigation, writing—original draft preparation, writing—review and editing, communication and interpretation, Di Kang and Mengfen Zhao;

Investigation, writing—original draft preparation, Jiacheng Cao, Min Wei, Yanbo Wang, Jingyan Chen, Huibin Wu.

All authors read and approved the final manuscript.

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Figures

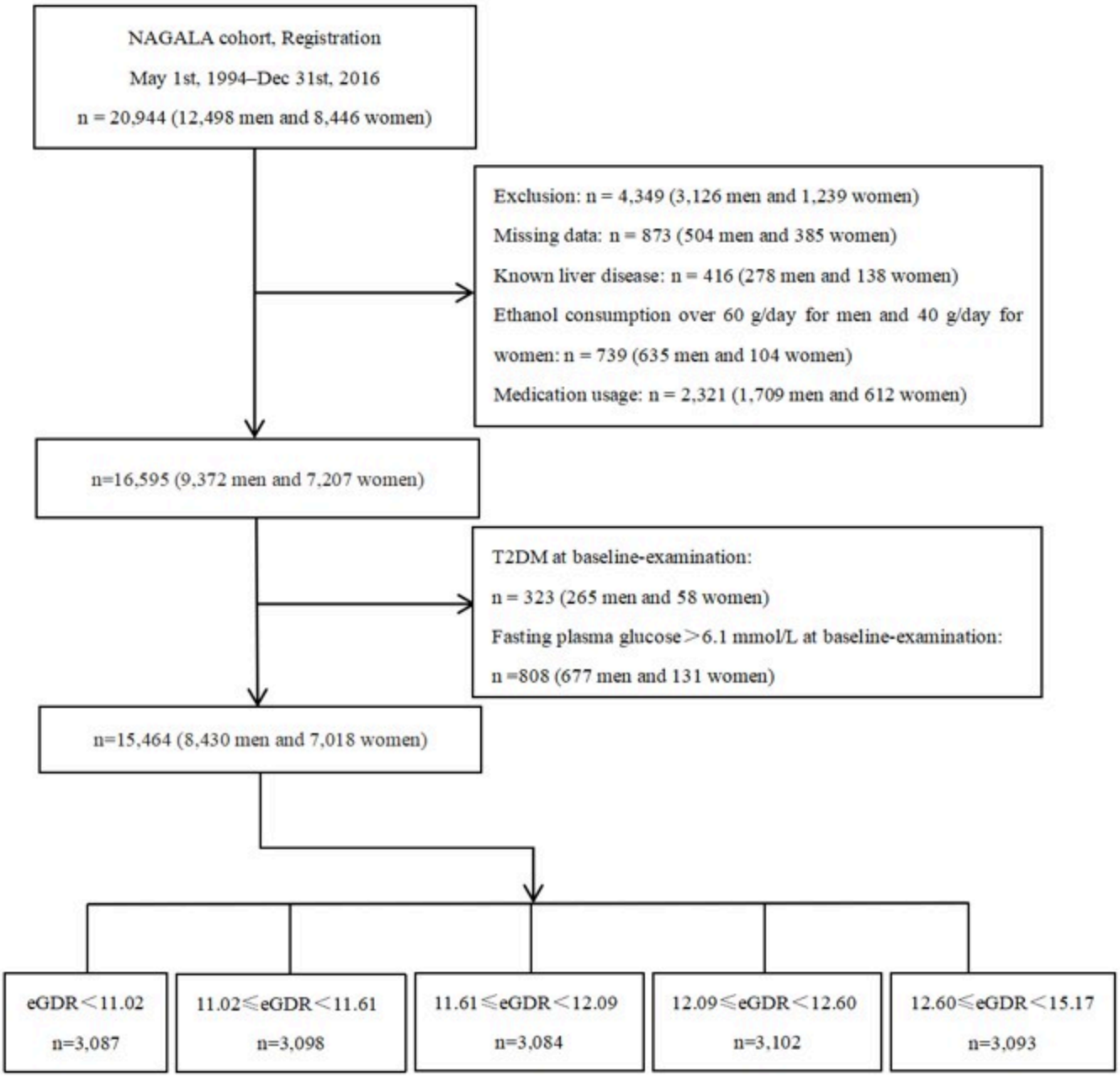


Figure 1

Flowchart of study participant selection.

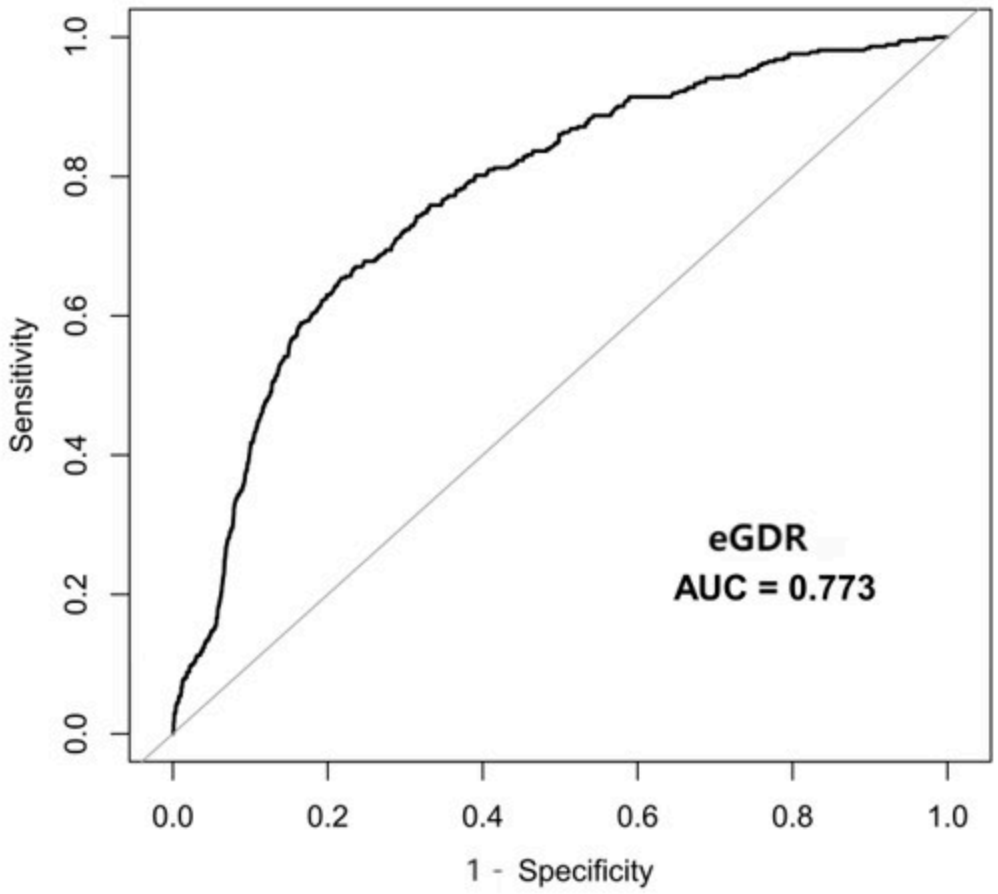


Figure 2

The ROC analysis.

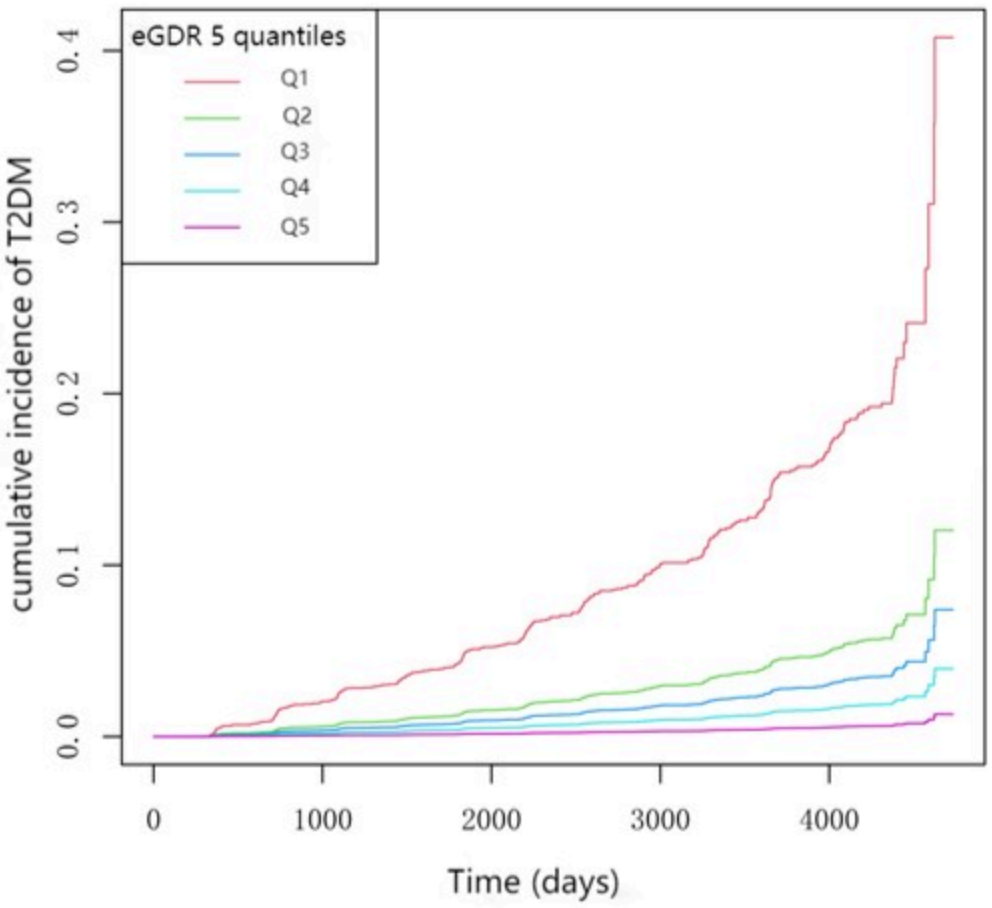


Figure 3

The cumulative incidence T2DM of eGDR 5 quantiles groups. All variables exhibit a monotonic increase over the observation period. Group Q1 show the steepest growth, while the rest groups increase more gradually.

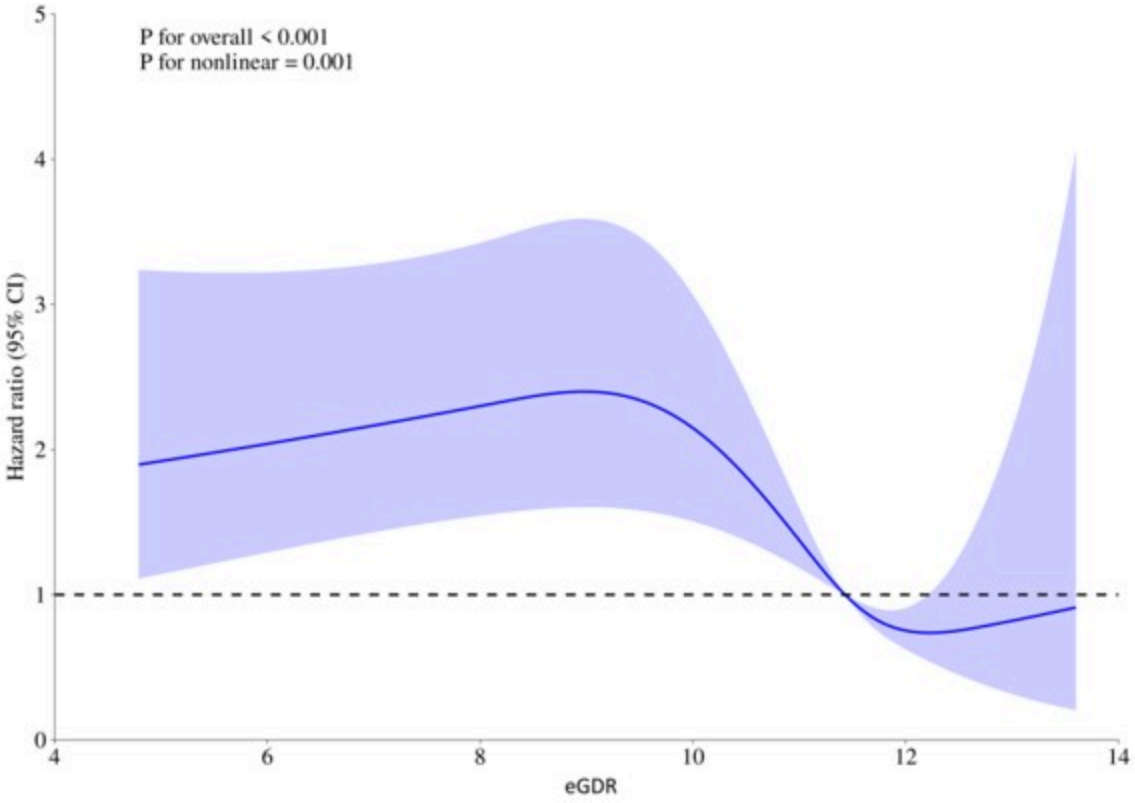


Figure 4

The fitting curve of association between eGDR and the incident T2DM.

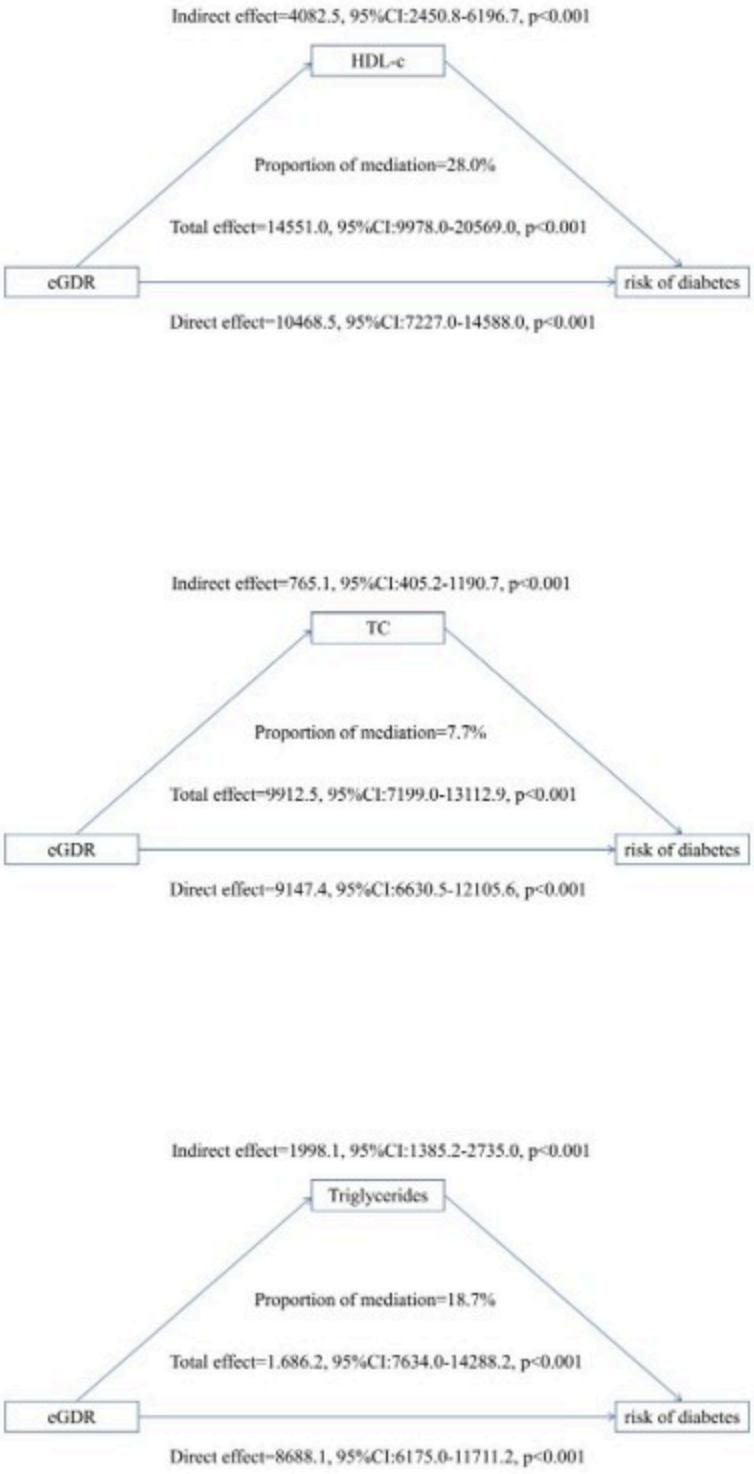


Figure 5

The mediating effect between eGDR and risk of T2DM.

Supplementary Files

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- Supplementarytable.docx