


Non-high-density lipoprotein cholesterol is more informative than traditional cholesterol indices in predicting diabetes risk for women with normal glucose tolerance

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ABSTRACT

Aims/Introduction: Limited data are available regarding the performance of non-high-density lipoprotein cholesterol (non-HDL) in predicting incident diabetes. We aimed to analyze the association between non-HDL and development of diabetes, and to estimate the cut-off point of non-HDL for discriminating incident diabetes in people with normal glucose tolerance.

Materials and Methods: Of 3,653 middle-aged and elderly Chinese with normal glucose tolerance at enrollment, 1,025 men and 1,805 women returned to the 3-year follow up and were involved in the final analysis. Logistic regression analysis was used to test the association between cholesterol indices and incident diabetes, and receiver operating characteristic analyses were used to identify the optimal cut-off of each cholesterol variable for incident diabetes.

Results: Non-HDL was an independent risk factor for diabetes for women, but not for men. In women, a 1-standard deviation increment in non-HDL was associated with a 1.43-fold higher risk of diabetes (95% confidence interval 1.14–1.79; $P = 0.002$), whereas odds ratios for total cholesterol and low-density lipoprotein cholesterol were 1.33 (95% confidence interval 1.06–1.67; $P = 0.015$) and 1.30 (95% confidence interval 1.04–1.64; $P = 0.024$), respectively. The discriminatory power and the optimal cut-off value of non-HDL for incident diabetes increased across body mass index categories. For women with obesity, the threshold of non-HDL for screening of diabetes was estimated as 3.51 mmol/L.

Conclusions: Non-HDL had better performance than traditional cholesterol indices in predicting diabetes in women, but not in men. A body mass index-specific threshold value for a non-HDL-controlling target is required in the prevention of type 2 diabetes.

INTRODUCTION

In face of the unprecedented growth in the number of people with diabetes worldwide,^{1,2} preventing the onset of diabetes is indispensable in reducing the burden of diabetes.³ It is well

established that traditional cholesterol indices, including higher low-density lipoprotein cholesterol (LDL)⁴ and lower high-density lipoprotein cholesterol (HDL),^{5,6} are important risk factors for diabetes. In recent years, non-high-density lipoprotein cholesterol (non-HDL) has proved to be a more potent predictor of cardiovascular disease incidence than LDL,^{7,8} and is

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recommended as the secondary monitoring target in the management of atherosclerotic cardiovascular disease risk.^{9,10}

However, the performance of non-HDL in predicting incident diabetes, especially in comparison with routine cholesterol panels, has not been well documented. A prospective study carried out with 540 diabetes-free participants reported that non-HDL was a superior independent risk factor for type 2 diabetes than LDL or HDL in Aboriginal Canadians.¹¹ Subsequently, a retrospective study further validated the superior role of non-HDL in predicting diabetes in people with normal glucose tolerance (NGT).¹² On the contrary, there is also a study that observed no solid association between non-HDL and the development of diabetes.¹³ Therefore, a well-designed prospective study with a larger sample size is still imperative to elucidate the role of non-HDL in predicting incident diabetes for people with NGT.

In contrast, for clinical practice and health promotion strategies, an accurate estimate of the cut-off of non-HDL to discriminate incident diabetes is necessary. Furthermore, to direct precise preventive strategies, it is important to develop cut-offs according to the identification of similar risk levels across the population.¹⁴ To the best of our knowledge, there is no longitudinal study available that has estimated the threshold of non-HDL in predicting diabetes.

The objective of the present prospective study was to analyze the association between non-HDL and the development of diabetes in comparison with traditional cholesterol indices, and to estimate the cut-offs of cholesterol parameters for discriminating incident diabetes in people with NGT.

METHODS

Study population

The present article reports on the data from the Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal (REACTION) Study, which was a prospective observational cohort study and enrolled 259,657 Chinese adults (aged ≥ 40 years) from 25 communities in mainland China between 2011 and 2012, with follow-up measurements planned 3, 5 and 10 years later.¹⁵ In the present study, baseline data were obtained from 7,068 residents of Ningyang County, Shandong Province, one of the 25 communities. After excluding the individuals with disturbance in glucose metabolism (diabetes or pre-diabetes, $n = 3,415$), or who had missing important information (such as age, sex or medical history, $n = 82$), or had severe diseases (including malignant tumors or serious liver or renal dysfunction, $n = 44$), or receiving medications in the 3 months before the baseline survey that affect lipid metabolism (including statins, fibrates, estrogens, androgens, glucocorticoids, anti-epileptic drugs, furosemide, heparin, and β -adrenoceptor blockers, $n = 211$), 3,653 individuals with NGT, as detected by the standardized oral glucose tolerance test carried out at baseline survey, were eligible for this study. At the 3-year follow-up evaluation carried out in 2014–2015, 43 participants died and 443 were lost to the follow up, representing

1,025 men and 1,805 women remained in the present analysis (Figure S1).

The protocol of the present study conformed to the 1975 Declaration of Helsinki. The Committee on Human Research at Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine approved this study, and all participants provided written informed consent.

Study measurements

The baseline and 3-year follow-up examination included measurements of anthropometry, plasma glucose and serum lipids, and a face-to-face interview regarding sociodemographic characteristics, medical history and family history. Information about age, sex, education level, lifestyle, smoking and alcohol use was collected by trained interviewers according to a standardized questionnaire. Physical activity was estimated by the Global Physical Activity Questionnaire and was measured by the metabolic equivalent.¹⁶ Measurements of anthropometry, including weight, standing height and waist circumference, were carried out by trained nurses according to a standard protocol.¹⁷ An electronic sphygmomanometer (OMRON Model HEM-725FUZZY; Omron Company, Dalian, China) was used to measure blood pressure three times consecutively on the non-dominant arm with a 3-min interval after a 5-min rest. The average of the three readings was used for analysis.

Blood samples were drawn after an overnight fast of at least 10 h. Fasting total cholesterol (TC), LDL, HDL and triglyceride were measured using an auto-analyzer (ARCHITECT c16000 System; Abbott Laboratories, Abbott Park, IL, USA). Non-HDL was calculated by subtracting HDL from TC.¹⁸ High-performance liquid chromatography (VARIANT™ II and D-10™ Systems; Bio-Rad Laboratories, Hercules, CA, USA) was used to quantify capillary hemoglobin A_{1c}, with capillary blood samples collected by the Hemoglobin Capillary Collection System (Bio-Rad Laboratories).¹⁹ Participants without a known history of diabetes underwent the oral glucose tolerance test, and plasma glucose was measured at 0 h (FPG) and 2 h (2hPG) by the glucose oxidase method.

Definition of glycemic status

Glycemic status was evaluated by a standardized oral glucose tolerance test and was defined based on the World Health Organization 1999 criteria²⁰: NGT, FPG < 6.1 mmol/L and 2hPG < 7.8 mmol/L; diabetes, FPG ≥ 7.0 mmol/L and/or 2hPG ≥ 11.1 mmol/L; pre-diabetes was defined as meeting either of the following two criteria: (i) 6.1 mmol/L \leq FPG < 7.0 mmol/L and 2hPG < 11.1 mmol/L; and (ii) FPG < 7.0 mmol/L and 7.8 mmol/L \leq 2hPG < 11.1 mmol/L.

Statistical analysis

Continuous characteristics of the participants are presented as mean \pm standard deviation (SD) or median (interquartile range) based on their distributions, which were determined by a histogram. Categorical data are expressed as number

Table 1 | Baseline characteristics of the participants

Variables	Women			Men		
	Incident DM <i>n</i> = 97	No incident DM <i>n</i> = 1,708	<i>P</i> -value	Incident DM <i>n</i> = 91	No incident DM <i>n</i> = 934	<i>P</i> -value
Age (years)	55.04 ± 7.85	52.85 ± 8.07	0.553	54.65 ± 8.78	55.26 ± 8.52	0.692
BMI (kg/m ²)	25.87 ± 3.59	24.93 ± 3.57	0.951	24.75 ± 3.46	24.74 ± 3.29	0.243
Waist (cm)	87.78 ± 13.67	85.36 ± 10.24	0.062	89.52 ± 10.69	88.29 ± 9.34	0.076
TC (mmol/L)	5.32 ± 1.15	4.97 ± 1.10	0.681	4.99 ± 1.18	4.95 ± 1.09	0.127
TG (mmol/L)	1.16 (1.17)	1.03 (0.67)	0.025	1.28 (0.93)	1.11 (0.79)	0.100
HDL (mmol/L)	1.45 ± 0.33	1.48 ± 0.35	0.525	1.43 ± 0.42	1.39 ± 0.34	0.027
LDL (mmol/L)	3.15 ± 0.89	2.89 ± 0.86	0.906	2.90 ± 1.01	2.95 ± 0.87	0.022
Non-HDL (mmol/L)	3.87 ± 1.04	3.49 ± 0.95	0.221	3.57 ± 1.05	3.56 ± 0.98	0.180
SBP (mmHg)	138.84 ± 20.79	133.01 ± 20.39	0.879	143.77 ± 21.29	138.19 ± 19.37	0.600
DBP (mmHg)	80.45 ± 11.99	78.05 ± 11.27	0.454	84.48 ± 13.35	82.51 ± 10.79	0.002
FPG (mmol/L)	5.49 ± 0.45	5.40 ± 0.39	0.007	5.54 ± 0.40	5.48 ± 0.35	0.126
2hPG (mmol/L)	6.30 ± 0.94	6.20 ± 1.01	0.431	6.18 ± 1.16	5.98 ± 1.20	0.978
HbA _{1c} (%)	5.9 ± 0.54	5.7 ± 0.34	0.001	5.8 ± 0.41	5.6 ± 0.35	0.066
Positive FHD, <i>n</i> (%)	1 (1.0)	27 (1.6)	1.000	1 (1.1)	13 (1.4)	1.000
Education, <i>n</i> (%)			0.206			0.719
Primary	46 (47.4)	921 (53.9)		30 (33.0)	286 (30.6)	
Junior high school	26 (26.8)	468 (27.4)		27 (29.7)	258 (27.6)	
Senior high school	25 (25.8)	319 (18.7)		34 (37.4)	390 (41.8)	
†Current smoker, <i>n</i> (%)	6 (6.2)	58 (3.4)	0.152	32 (35.2)	325 (34.8)	0.938
Cigarette-years	104 ± 58	82 ± 69	0.448	650 ± 394	639 ± 421	0.812
‡Current drinker, <i>n</i> (%)	10 (10.3)	205 (12.0)	0.617	44 (48.4)	441 (47.2)	0.829
§Physical inactive, <i>n</i> (%)	52 (54.2)	756 (44.8)	0.073	31 (34.1)	383 (41.6)	0.162

2hPG, 2-h plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FHD, family history of diabetes; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; non-HDL, non-high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride. Values for quantitative data are presented as mean ± standard deviation, or median (interquartile range); values for categorical variables are presented as number (percentage). †Current smoker was defined as currently smoking cigarettes at the time of the survey and having smoked >100 cigarettes in their lifetime. ‡Current drinker was defined as alcohol intake more than once per month during the past 12 months. §Physical inactive was defined as the total metabolic equivalent did not reach the World Health Organization recommendation (600 min/week).

(percentage). Independent Student's *t*-test, the Mann–Whitney *U*-test or χ^2 -test were used to test differences in baseline characteristics between patients with or without new-onset diabetes in men or women, respectively.

The participants were divided into quartiles according to their baseline value for each cholesterol parameter (TC, LDL, HDL or non-HDL) to compare the incidence of diabetes. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using the multivariate logistic regression analysis adjusted by age, family history of diabetes, education level, smoking, lifetime number of cigarette-years (estimated as the product of the average number of cigarettes per day and number of years smoked), drinking, physical inactive, body mass index (BMI), systolic blood pressure and FPG, using the first quartile of each variable as the reference group. To compare the effect size of each cholesterol index on the development of diabetes, ORs per 1-SD increase in the cholesterol variables were calculated using univariate and multivariate logistic regression analysis, respectively. Receiver operating characteristic analysis was used to

compare the ability of each cholesterol index in discriminating incident diabetes. The area under curve was used to identify the specificity and sensitivity of cholesterol variable possible cut-off points for predicting incident diabetes. The optimal cut-off values were identified as the point at which the value of “sensitivity + specificity-1” (Youden index) was maximum.

SPSS version 22.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analyses, and a two-tailed *P*-value of <0.05 was regarded as significant.

RESULTS

At the 3-year follow up, 188 new-onset type 2 diabetes cases were identified, representing a total incidence rate of 6.6%. Baseline characteristics of the participants and a comparison of individuals who developed type 2 diabetes vs individuals who did not develop diabetes are shown in Table 1. In both women and men, participants who progressed from NGT to diabetes were more obese, more likely to have higher blood pressure and more likely to be current smokers compared with those

Table 2 | Incidence and odds ratios of diabetes according to different levels of cholesterol indices

	Female					Male				
	Cholesterol range	n	DM, n (%)	OR (95% CI) [†]	P	Cholesterol range	n	DM, n (%)	OR (95% CI) [†]	P
TC (mmol/L)					0.176					0.750
Quartile 1	<4.26	451	16 (3.5)	1		<4.22	256	25 (9.8)	1	
Quartile 2	4.26–4.94	443	19 (4.3)	1.21 (0.60–2.45)	0.593	4.22–4.95	252	21 (8.3)	0.86 (0.46–1.62)	0.650
Quartile 3	4.94–5.67	457	27 (5.9)	1.52 (0.79–2.94)	0.215	4.95–5.65	260	20 (7.7)	0.78 (0.41–1.50)	0.460
Quartile 4	≥5.67	454	35 (7.7)	1.97 (1.04–3.76)	0.039	≥5.65	257	25 (9.7)	1.10 (0.59–2.06)	0.770
LDL (mmol/L)					0.047					0.222
Quartile 1	<2.30	448	11 (2.5)	1		<2.37	255	29 (11.4)	1	
Quartile 2	2.30–2.85	450	24 (5.3)	1.73 (0.84–3.61)	0.118	2.37–2.89	253	16 (6.3)	0.52 (0.27–1.01)	0.053
Quartile 3	2.85–3.44	454	29 (6.4)	2.10 (1.04–4.20)	0.036	2.89–3.53	256	21 (8.2)	0.70 (0.37–1.32)	0.273
Quartile 4	≥ 3.44	453	33 (7.3)	2.32 (1.12–4.72)	0.012	≥3.53	261	25 (9.6)	0.91 (0.49–1.68)	0.752
HDL (mmol/L)					0.967					0.774
Quartile 1	<1.24	439	25 (5.7)	1		<1.16	250	22 (8.8)	1	
Quartile 2	1.24–1.45	457	27 (5.9)	0.95 (0.52–1.71)	0.855	1.16–1.36	252	26 (10.3)	1.20 (0.64–2.26)	0.566
Quartile 3	1.45–1.69	466	23 (4.9)	0.89 (0.49–1.64)	0.713	1.36–1.60	259	18 (6.9)	0.85 (0.43–1.69)	0.647
Quartile 4	≥1.69	443	22 (5.0)	0.86 (0.46–1.64)	0.713	≥1.60	264	25 (9.5)	0.97 (0.51–1.87)	0.972
non-HDL (mmol/L)					0.034					0.451
Quartile 1	<2.83	439	14 (3.2)	1		<2.91	255	27 (10.6)	1	
Quartile 2	2.83–3.43	460	19 (4.1)	1.18 (0.57–2.44)	0.660	2.91–3.49	256	19 (7.4)	0.62 (0.33–1.17)	0.142
Quartile 3	3.43–4.11	454	26 (5.7)	1.64 (0.82–3.28)	0.163	3.49–4.12	256	20 (7.8)	0.75 (0.39–1.45)	0.397
Quartile 4	≥4.11	452	38 (8.4)	2.39 (1.22–4.68)	0.011	≥4.12	258	25 (9.7)	0.94 (0.50–1.77)	0.844

CI, confidence interval; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; non-HDL, non-high-density lipoprotein cholesterol; TC, total cholesterol. †Adjusted for age, family history of diabetes, education, smoking status (ever and never), cigarette-years, drinking, physical inactive, body mass index, systolic blood pressure and fasting plasma glucose.

who did not develop diabetes. Levels of serum TC, non-HDL, triglyceride, FPG, 2hPG and hemoglobin A_{1c} also tended to be higher in individuals who developed diabetes in both women and men.

Table 2 shows the incidence rate and OR for the development of diabetes according to different levels of cholesterol indices stratified by sex. In men, none of these four cholesterol indices had a significant linear relationship with the development of diabetes. In women, the incidence rate of diabetes increased significantly as the TC, LDL and non-HDL increased from the first to the fourth quartile. In the multivariable-adjusted model, compared with the lowest quartile, ORs of future diabetes for the higher quartiles were higher with a trend of the dose–response relationship for serum TC, LDL and non-HDL. The multivariable-adjusted ORs of incident diabetes in the highest quartile non-HDL were 2.39 (95% CI 1.22–4.68; *P* = 0.011), higher than that of either TC (OR 1.97, 95% CI 1.04–3.76; *P* = 0.039) or LDL (OR 2.32, 95% CI 1.12–4.72; *P* = 0.012). The incidence rate of diabetes in higher HDL quartiles tended to be lower than that in the lower quartiles, but after adjustment for traditional confounders, there was no significant association between serum HDL and diabetes in women.

Table 3 shows the ORs of incident diabetes per 1-SD increment for the four cholesterol variables by sex. In accordance with the analysis of diabetes risk across the quartiles of

cholesterol parameters (Table 2), in men, there was no statistical significant relationship between the four indices and incident diabetes in neither univariate nor multivariate models. In women, except for HDL, the other three cholesterol indices were significantly associated with the risk of diabetes in the univariate model. In age- and family history of diabetes-adjusted analysis (model 2), associations between TC, LDL or non-HDL and diabetes were attenuated, but were still significant. Further adjustment for education, smoking status (ever and never), cigarette-years, drinking and physical inactivity (model 3) did not materially affect these associations. In the fully adjusted models (model 4), TC, LDL and non-HDL remained independently associated with the risk of incident diabetes, with non-HDL having the strongest effect size: a 1-SD increment in serum non-HDL was associated with a 1.43-fold higher risk of diabetes (95% CI 1.14–1.79; *P* = 0.002), whereas ORs for TC and LDL were 1.33 (95% CI 1.06–1.67; *P* = 0.015) and 1.30 (95% CI 1.04–1.64; *P* = 0.024), respectively.

As TC, LDL and non-HDL were identified as independent risk factors for the development of diabetes in women, we further estimated the discriminatory power and the optimal cut-off values of TC, LDL and non-HDL for incident diabetes in women (Table 4). For an overview of all of the cholesterol indices, non-HDL had the largest area under the curve for new-onset diabetes. In the general population, the cut-off for non-HDL with better properties for screening of incident

Table 3 | Comparison of the effect size of different cholesterol indices on development of diabetes

	TC		LDL		Non-HDL	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Female						
Model 1	1.51 (1.22–1.87)	0.000	1.51 (1.22–1.87)	0.000	1.63 (1.33–2.00)	0.000
Model 2	1.43 (1.15–1.78)	0.001	1.44 (1.15–1.79)	0.001	1.56 (1.26–1.92)	0.000
Model 3	1.43 (1.14–1.78)	0.002	1.43 (1.14–1.79)	0.002	1.57 (1.26–1.94)	0.000
Model 4	1.33 (1.06–1.67)	0.015	1.30 (1.04–1.64)	0.024	1.43 (1.14–1.79)	0.002
Male						
Model 1	1.13 (0.91–1.41)	0.258	1.01 (0.81–1.26)	0.952	1.11 (0.89–1.37)	0.356
Model 2	1.14 (0.92–1.43)	0.234	1.02 (0.81–1.26)	0.940	1.10 (0.89–1.37)	0.364
Model 3	1.14 (0.92–1.43)	0.234	1.02 (0.81–1.28)	0.873	1.12 (0.90–1.39)	0.320
Model 4	1.05 (0.84–1.33)	0.657	0.96 (0.76–1.21)	0.708	1.04 (0.83–1.31)	0.735

Model 1: unadjusted; model 2: adjusted for age and family history of diabetes; model 3: adjusted for model 2 plus education, smoking status (ever and never), cigarette-years, drinking and physical inactivity; model 4: adjusted for model 3 plus body mass index, systolic blood pressure and fasting plasma glucose. CI, confidence interval; LDL, low-density lipoprotein cholesterol; non-HDL, non-high-density lipoprotein cholesterol; TC, total cholesterol.

Table 4 | Receiver operator curve characteristics for cholesterol in predicting diabetes and cut-off points for women with normal glucose tolerance

	ROC		Cut-off (mmol/L)	Sensitivity	Specificity	Youden index
	AUC (95% CI)	<i>P</i>				
TC						
Overall	0.62 (0.56–0.67)	0.000	5.25	0.53	0.66	0.19
BMI <24	0.56 (0.45–0.67)	0.313	–	–	–	–
24 ≤ BMI < 28	0.60 (0.52–0.69)	0.024	5.30	0.53	0.65	0.19
BMI ≥28	0.66 (0.54–0.79)	0.011	5.90	0.48	0.82	0.29
LDL						
Overall	0.61 (0.56–0.67)	0.000	2.95	0.62	0.59	0.21
BMI <24	0.58 (0.48–0.68)	0.159	–	–	–	–
24 ≤ BMI < 28	0.60 (0.52–0.68)	0.021	2.81	0.73	0.50	0.24
BMI ≥28	0.61 (0.48–0.74)	0.095	–	–	–	–
Non-HDL						
Overall	0.63 (0.58–0.69)	0.000	3.48	0.65	0.58	0.22
BMI <24	0.58 (0.47–0.68)	0.186	–	–	–	–
24 ≤ BMI < 28	0.62 (0.54–0.71)	0.006	3.39	0.73	0.51	0.24
BMI ≥28	0.67 (0.54–0.80)	0.007	3.51	0.83	0.50	0.32

AUC, area under receiver operating characteristic curve; LDL, low-density lipoprotein cholesterol; non-HDL, non-high-density lipoprotein cholesterol; ROC, receiver operating characteristic; TC, total cholesterol.

diabetes was identified as 3.48 mmol/L. Then, the detailed performance of these cholesterol indices in predicting diabetes was investigated in each obese category, respectively. It was observed that none of these cholesterol indices was a good discriminator of incident diabetes in women with a BMI <24 kg/m². The discriminatory power and the optimal cut-off values of TC and non-HDL for incident diabetes increased across BMI categories. For women with obesity (BMI ≥28 kg/m²),²¹ the cut-offs of TC and non-HDL for screening of diabetes were estimated to be 5.90 mmol/L and 3.51 mmol/L, respectively. The sensitivity and specificity of the cut-off of TC was 48% and 82%,

respectively, whereas that for non-HDL was 83% and 50%, respectively.

DISCUSSION

In the present prospective study, the performance of non-HDL in predicting incident diabetes for people with NGT was investigated. We found that non-HDL was associated with the development of diabetes independent of age, BMI, blood pressure, FPG, family history of diabetes and lifestyle in women, but not in men. Furthermore, compared with traditional cholesterol parameters, non-HDL highlighted a higher risk for new-onset

diabetes. In this population, the cut-off for non-HDL for screening of incident diabetes in women with NGT was identified as 3.48 mmol/L. Remarkably, the discriminatory power and the optimal cut-off values of non-HDL in predicting diabetes increased across BMI categories.

Being a surrogate marker that reflects the total number of atherogenic lipoprotein particles, non-HDL is computed simply as total cholesterol minus HDL without additional costs.²² In recent decades, non-HDL has been highlighted as an important secondary therapeutic goal in the management of dyslipidemia.^{9,10} In contrast with the well acknowledged potent role of non-HDL in predicting cardiovascular diseases,^{7,23} previous studies that focused on the association between non-HDL and development of diabetes arrived at contrary conclusions.^{11,13} Furthermore, there is only one study that investigated the utility of non-HDL in assessing incident type 2 diabetes risk in people who are relatively insulin-sensitive and at low risk for diabetes.¹² In the present study, participants with NGT were prospectively followed up for 3.3 years. We observed that non-HDL was superior to traditional cholesterol parameters in predicting incident diabetes in women, but not in men. In addition, previous studies have observed that there was a significantly positive correlation between non-HDL and insulin resistance.²⁴ Given its predictive accuracy and ease of measurement, we therefore propose that non-HDL level should be monitored for developing diabetes in women with NGT.

It has been established that disturbance in serum cholesterol profiles was a significant risk factor for type 2 diabetes.^{4,6} Interestingly, we observed that there was a sex difference in the association between cholesterol levels and the incidence of diabetes. When divided by sex, TC, LDL and non-HDL were significant risk factors for incident diabetes independent of other confounders in women with NGT, but not in men. Previous cross-sectional studies have reported that there was a greater degree of lipoprotein abnormality above control in women with diabetes than in men.^{25,26} In light of a recent report,²⁷ evidence showed that there was an independent association between diabetes and LDL size and pattern in women, but not in men. These results combined show that cholesterol levels might be a sex-specific risk factor for diabetes. Further studies are required to validate this finding in other populations, and to expound the potential mechanism underlying this sex difference.

In the present analysis, we used receiver operating characteristic analysis to evaluate the ability of different cholesterol indices in discriminating between participants with and without incident type 2 diabetes. Although non-HDL showed stronger performance for diabetes prediction than TC and LDL in women, there was no significant difference in discriminatory power. We further assessed appropriate cut-off values of each cholesterol measure for predicting diabetes in women with NGT. Although the specificity and sensitivity for the cut-offs calculated in the present were not so high, they had clinical value in recognizing people at diabetes risk. Another remarkable finding is that the discriminatory power and the optimal cut-off values of TC and non-HDL in

predicting diabetes increased across BMI categories. Given that obesity is regarded as the primary risk factor for diabetes,²⁸ this result is reasonable, and might indicate that for women with obesity, controlling bodyweight should be superior to controlling elevated serum lipid levels.

We acknowledge certain limitations to the present analysis. First of all, although there was no significant difference with respect to the baseline characteristics, including demographic, anthropometric or biochemical parameters between the 2,830 responders and the 486 (43 dead and 443 lost) non-responders (data shown in Table S1), the missing rate of the present study was still relatively high, which could not be ignored. Second, as the participants were not re-tested periodically during the 3-year follow up, we could not combine the time when the participants developed diabetes and event outcome together by means of Cox proportional hazards. Also, because the cohort was followed up for a median of 3.3 years, the generalization of results to the long-term effects of non-HDL on the development of diabetes was limited. Third, data from statin trials showed that statin therapy might increase the risk of new-onset diabetes.²⁹ Although we excluded individuals who used statins at enrollment, we could not account for the use of statins during follow up because of the lack of interim data. Furthermore, we did not evaluate the composition and size of lipoprotein particles, which has been proved to have more a significant association with diabetes.³⁰

In conclusion, in the present prospective cohort study, we first reported that non-HDL had better performance than traditional cholesterol indices in predicting diabetes in women, but not in men. However, the discriminatory power of non-HDL and other cholesterol parameters was similar. In addition, the cut-off values of TC and non-HDL in predicting diabetes increased as BMI elevated, indicating a BMI-specific threshold value for the lipid-controlling target in the prevention of type 2 diabetes. Studies with a longer follow-up period in other populations are required to validate these findings and make the findings more suitable for generalization to all populations.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Participant selection and follow-up flow diagram.

Table S1 | Baseline characteristics of individuals with and without follow up