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RESEARCH ARTICLE

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Lipid profile and non-alcoholic fatty liver disease detected by ultrasonography: is systemic inflammation a necessary mediator?

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ABSTRACT

Aims: To examine the relationship between lipid profile and non-alcoholic fatty liver (NAFL), compare the predictive strengths of different lipid indicators to NAFL, and explore the possible mechanisms.

Methods: Male workers from a baseline survey of a cohort of workers in southern China were included. Basic information was collected through face-to-face interviews. Plasma concentrations of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were determined using a blood biochemical analyzer. Liver sonography was used to identify NAFL cases. Regression models were used to calculate ORs, and examine the association between C-reactive protein (CRP) levels and lipid profiles. Restricted cubic spline regression with four knots was used to examine the dose-response relationship, and mediation analysis was employed to examine the mediation effect.

Results: h Among the 4016 male workers, 829 (20.64%) were diagnosed with NAFL. Compared with normal lipid profile, individuals with abnormal lipid profile had higher prevalence of NAFL (OR=2.27, 95%CI: 1.85-2.79 for TG; OR=1.45, 95%CI: 1.03-2.04 for TC; OR=1.56, 95%CI: 1.21-2.02 for HDL; OR=1.65, 95%CI: 1.25-2.18 for LDL; OR=2.28, 95%CI: 1.87-2.77 for dyslipidaemia) after adjusting for potential confounders. Dose-response relationships were observed among TG, HDL, and NAFL. In addition, no significant mediation effect of C-reactive protein (CRP) was found in the association between lipid profiles and NAFL.

Conclusions: Abnormal TG, TC, HDL, and LDL levels were all positively associated with NAFL, while CRP has no mediating effect, and TG tended to be a better predictor of NAFL.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of diseases, including simple non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), and cirrhosis. NAFLD has become the leading cause of chronic liver disease globally [1,2], and is a global health problem because of its ability to cause liver related complications such as cirrhosis and hepatocellular carcinoma [3].

Studies showed that an unhealthy lifestyle, particularly high-fat diet was associated with an increased risk of hyperlipidaemia [4,5] and NAFL [6], while the latter is recognized as the most common type of chronic liver disease linked to the development of cirrhosis of the liver and premature death [7–9]. Targeted policy on the primary prevention of NAFLD may be informed by seeking a better understanding of the association between the highly prevalent abnormal lipid profile and the risk of NAFL, as well as the possible mechanisms. Previous animal and human epidemiological studies have suggested that hypertriglyceridemia is an important risk factor for NAFLD [10,11]. Plasma levels of total cholesterol (TC)

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were also found to be positively correlated with NAFLD risk among adults [12], whilst only non-HDL-cholesterol was identified as an important risk factor for NAFLD in adolescents [13]. Although the biological mechanism is still elusive, the "two-hits hypothesis" is considered as the main pathogenetic process of NAFL [14] involving hepatocellular inflammation induced by the toxic effects of the excessive lipids in the liver, while the intrahepatic accumulation of lipids itself further aggravates the burden of the liver and causes fibrosis of the liver [15]. However, epidemiological studies on the association between lipid profile and NAFL have been limited, as most of the previous studies only focused on a single lipid index, and few studies depicted a whole picture of the impacts of different lipid indexes on the risks of NAFL.

Recent studies showed chronic systemic inflammation is a key hallmark of metabolic dysfunction-associated fatty liver disease [16,17], and C-reactive protein (CRP), an important index of chronic systemic inflammation, has been linked to NAFLD in the recent studies [18–20], but whether CRP also mediates the association between dyslipidemia and NAFL is not known. Therefore, we conducted this study to examine the associations of NAFL with lipid profiles, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), and to evaluate which lipid index is the best for predicting the risk of NAFL, as well as to explore possible mechanisms.

Methods

Study design and population

The detailed study design has been described previously [21]. Briefly, the prospective cohort study was initiated from May 2013 to October 2015, with the original purpose of investigating the health impact of shift work. All the participants were recruited from five enterprises in South China, which are machinery and semiconductor manufacturers, printing house, electric power and petroleum industries. Abdominal ultrasounds were performed by two experienced sonographers using B-ultrasound machine model (WED-9618C) produced by Shenzhen Zhongke New Materials Technology Co., Ltd, and images were captured in a standard fashion with the subject in the supine position and with his right arm raised above his head. Blood draw and US examination were conducted on the same morning. After excluding data with missing lipid profiles and abdominal ultrasound findings, 4047 individuals remained. Furthermore, we excluded 31 female workers due to uneven gender distribution in these enterprises; thus, a total of 4016 male workers were included in the present study. Among 4016 individuals, 1673 were tested for plasma CRP levels. (Supplementary Figure 1).

Information on each participant's sociodemographic (age, gender, education, marital status, height, weight, waist circumference), lifestyle (smoking, physical activity, alcohol drinking), and shift work were collected using a standardized questionnaire. Alcohol drinking was defined as drinking at least once per week for more than half a year. Physical exercise was defined as performing physical exercise >3 times/week for at least 20 min per session. Smoking (including current and ever smoking) was defined if individuals who had ever smoked at least one cigarette per day for more than half a year. The health examinations were performed by certified physicians and nurses. Body mass index (BMI) was calculated as the body weight (kg) divided by the square of height (kg/m^2). In the present study, we used the ultrasonography (US) for diagnosis of NAFLD, which is a safe, non-invasive and cost-effective imaging method to assess patients with suspected NAFLD for diagnosis [22,23] and a large systematic review with meta-analysis showed that ultrasonography allows for reliable and accurate detection of moderate-severe fatty liver, compared to histology, and considering its low cost, safety, and accessibility, ultrasound is likely the imaging technique of choice for screening for fatty liver in population settings [24]. Ultrasonographic diagnosis of NAFL was defined as the presence of a diffuse increase in fine echoes in the liver parenchyma compared with those in the kidney or spleen parenchyma [25].

The present study adheres to the Declaration of Helsinki, and informed consent for participation in the study has been written and obtained.

Biochemical measurements

Fasting blood samples were drawn in tubes, separated into serum and plasma, and stored at −80 °C until analysis. The plasma concentrations of fasting plasma glucose (FPG), TC, TG, HDL-C, and LDL-C were determined in a clinical laboratory using a blood biochemical analyzer. Abnormal blood lipids on specific blood lipid were defined according to the following standards: TC ≥ 6.2 mmol/L, TG ≥ 1.69 mmol/L, HDL < 1.03 mmol/L, LDL > 3.3 mmol/L, and dyslipidaemia was considered if any of the defined lipid index was abnormal. Abnormal blood glucose was considered when the glucose ≥ 6.1 mmol/L. Plasma CRP concentrations were measured using a commercially available

Table 1. Baseline characteristics of male workers in the present study.

	All (4016)	Non- NAFL (3187, 79.36%)	NAFL (829, 20.64%)	*P*
Age (year)	32.08 ± 8.155	31.22 ± 7.831	35.39 ± 8.524	<0.0001
20 ~ 40	3229 (80.40)	2664 (83.59)	565 (68.15)	
> =40	787 (19.60)	523 (16.41)	264 (31.85)	
BMI (kg/m^2)	23.84 ± 2.886	23.08 ± 2.471	26.77 ± 2.471	<0.0001
<18.5	54 (1.34)	54 (1.69)	0 (0.00)	
18.5 ~ 24	2100 (52.29)	2001 (62.79)	99 (11.94)	
> =24	1862 (46.36)	1132 (35.52)	730 (88.06)	
Education				0.058
High school and below	266 (6.62)	199 (6.24)	67 (8.08)	
College and above	3750 (93.38)	2988 (93.76)	762 (91.92)	
***Marital status**				<0.0001
Single	1508 (37.55)	1338 (41.98)	170 (20.51)	
Married	2508 (62.45)	1849 (58.02)	659 979.49)	
Drinking				<0.0001
No	3170 (78.93)	2557 (80.23)	613 (73.94)	
Yes	846 (21.07)	630 (19.77)	216 (26.06)	
Exercise				0.001
No	1162 (28.93)	885 (27.77)	277 (33.41)	
Yes	2854 (71.07)	2302 (72.23)	552 (66.59)	
Shift work				0.360
No	2860 (71.22)	2259 (70.88)	601 (72.50)	
Yes	1156 (28.78)	928 (29.12)	228 (27.50)	
Smoking				<0.0001
No	2952 (73.51)	2390 (74.99)	562 (67.79)	
Yes	1064 (26.49)	797 (25.01)	267 (32.21)	
Waist (cm)	84.33 ± 8.256	82.28 ± 7.199	92.23 ± 7.234	<0.0001
<90	2957 (73.63)	2667 (83.68)	290 (34.98)	
> =90	1059 (26.37)	520 (16.32)	539 (65.02)	
Glucose (mmol/L)	5.07 ± 0.603	5.01 ± 0.537	5.29 ± 0.767	<0.0001
Normal	3893 (96.94)	3128 (98.15)	765 (92.28)	
Abnormal	123 (3.06)	59 (1.85)	64 (7.72)	
TG (mmol/L)	1.03 (0.71-1.55)	0.94 (0.64-1.38)	1.60 (1.12-2.42)	<0.0001
TC (mmol/L)	4.67 (4.12-5.30)	4.59 (4.05-5.18)	5.02 (4.43-5.68)	<0.0001
HDL (mmol/L)	1.32 (1.16-1.50)	1.34 (1.18-1.53)	1.22 (1.06-1.39)	<0.0001
LDL (mmol/L)	2.42 (2.02-2.89)	2.36 (1.98-2.80)	2.66 (2.24-3.12)	<0.0001

NAFL, non-alcoholic fatty liver; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index.
*Single included unmarried, divorced, and widowed individuals.

enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA). All tests were performed in duplicate according to the manufacturer's instructions.

Statistical analyses

Sociodemographic and socioeconomic characteristics of the participants are reported as mean (standard deviation [SD]) for continuous variables and as number (percentages) for categorical variables. Differences in these characteristics between subjects with and without NAFL were tested separately using the independent t-test and χ^2 test. Multivariable unconditional logistic regression was used to calculate the odds ratio (OR) of NAFL in relation to lipid profile (TC, TG, HDL-C, and LDL-C) after adjusting for variables (age, marital status, education, smoking status, alcohol consumption, leisure time exercise, BMI, waist circumference, shift work, and glucose level). Stratified analyses were performed according to adjusted variables. Logistic regression was used to estimate the association between CRP levels and NAFL. Generalized linear regression was used to examine the association between CRP levels and lipid profiles. Restricted cubic spline regression with four knots (5th, 35th, 65th, and 95th) was used to examine the dose-response relationship between the lipid profile and NAFL, with the minimum value of the lipid profile as the reference. R package 'Mediation' (V.4.4.5) was used to analyze the mediation effect of CRP in the relationship between lipid profile and NAFL. A receiver operating characteristic (ROC) curve was further explored to obtain the best lipid predictor for NAFL using the Z-test. All statistical analyses were carried out using SAS (version 9.4; SAS Institute, Inc., Cary, North Carolina, USA) or R software version 4.0.5 (R Core Team 2020). Statistical significance in this study was determined at a two-sided $p < 0.05$.

Results

Characteristics of the study participants

Among the 4016 male workers, 829 (20.64%) were diagnosed with NAFL. As shown in Table 1, the mean

age was 32.08 (SD: 8.155). The mean values of TG, TC, HDL, and LDL were 1.29 ± 0.937 mmol/L, 4.74 ± 0.929 mmol/L, 1.34 ± 0.284 mmol/L and 2.48 ± 0.652 mmol/L, respectively. There were significant differences in age, BMI, marital status, drinking, exercise, smoking, waist circumference, glucose, TG, TC, HDL, and LDL levels between subjects with non-NAFL and NAFL (all $p < 0.05$), while no significant difference was observed for education and shift work ($p = 0.558$ and 0.360, respectively).

Table 2. Associations between lipid profile and NAFL.

Abnormal lipids	Unadjusted	*Adjusted
TG	4.68 (3.96–5.54)	2.27 (1.85–2.79)
TC	2.31 (1.76–3.03)	1.45 (1.03–2.04)
HDL	2.49 (2.03–3.06)	1.56 (1.21–2.02)
LDL	2.15 (1.72–2.68)	1.65 (1.25–2.18)
Dyslipidemia	4.20 (3.58–4.93)	2.28 (1.87–2.77)

NAFL, non-alcoholic fatty liver; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*Adjusted for age (continuous), marital status (single, married), education (high school and below, college and above), drinking (yes or no), exercise (yes or no), smoking (yes or no), shift work (yes or no), waist circumference (continuous), body mass index (continuous), and glucose (continuous).

Associations of lipid profile and NAFL

Associations between lipid profile and NAFL are shown in Table 2. Compared with normal lipid profile, individuals with abnormal lipid profile had higher prevalence of NAFL (OR = 2.27, 95%CI: 1.85-2.79 for TG; OR = 1.45, 95%CI: 1.03-2.04 for TC; OR = 1.56, 95%CI: 1.21-2.02 for HDL; OR = 1.65, 95%CI: 1.25-2.18 for LDL; OR = 2.28, 95%CI: 1.87-2.77 for dyslipidaemia) after adjusting for potential confounders. Dose-response relationships with NAFL were observed for TG and HDL levels (Figure 1). Stratified analyses of the lipid profile and NAFL are shown in Table 3. Abnormal TG was associated with NAFL in all groups except for those with abnormal glucose levels, and dyslipidemia was associated with NAFL in all groups except for those with low education levels.

Mediation analyses

Supplementary Table 1 shows the associations of lipid profile and CRP, with a significant relationship between TC, LDL and CRP (ß = 0.70, 95% CI: 0.13-1.28 for TC; ß = 1.28, 95% CI: 0.67-1.88 for LDL), after adjusting for

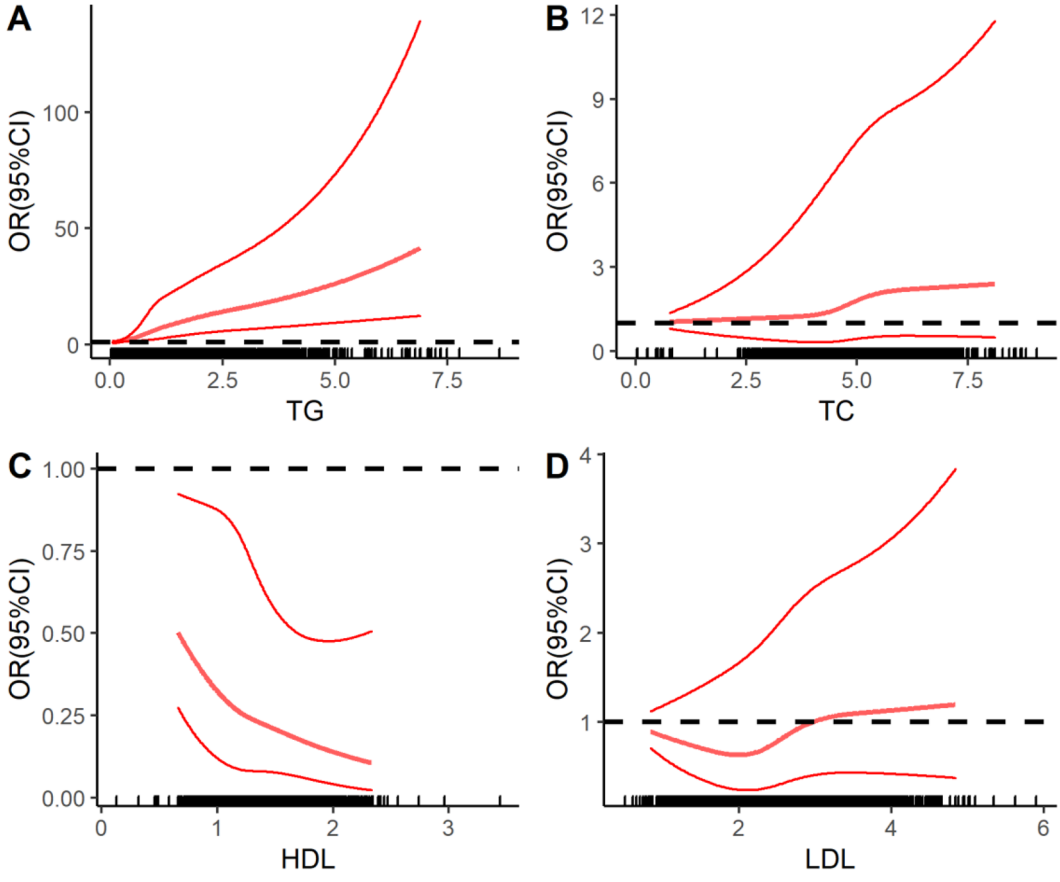

Figure 1. The dose-response relationship between lipid profile and NAFL, and (A) for TG, (B) for TC, (C) for HDL, (D) for LDL. Adjusted for age (continuous), marital status (single, married), education (high school and below, college and above), drinking (yes, no), exercise (yes, no), smoking (yes, no), shift work (yes, no), waist (continuous), body mass index (continuous), glucose (continuous).

Table 3. Stratified analyses on lipid profile and NAFL.

	TG	TC	HDL	LDL	Dyslipidemia
Age					
20 ~ 40	2.69 (2.10–3.43)	1.54 (0.99–2.40)	1.89 (1.39–2.57)	1.66 (1.16–2.37)	2.54 (2.02–3.21)
≥40	1.54 (1.06–2.25)	1.41 (0.83–2.39)	1.03 (0.64–1.66)	1.56 (0.99–2.45)	1.81 (1.25–2.61)
BMI					
<18.5	–	–	–	–	–
18.5 ~ 24	2.88 (1.79–4.63)	0.72 (0.27–1.91)	1.60 (0.79–3.25)	1.77 (0.96–3.27)	2.55 (1.65–3.94)
≥24	2.25 (1.81–2.81)	1.68 (1.16–2.42)	1.69 (1.29–2.21)	1.77 (1.30–2.39)	2.38 (1.92–2.94)
Education					
High school and below	2.19 (1.10–4.37)	0.55 (0.18–1.74)	0.85 (0.38–1.89)	0.82 (0.33–1.99)	1.84 (0.90–3.74)
College and above	2.27 (1.83–2.81)	1.57 (1.10–2.25)	1.68 (1.28–2.21)	1.77 (1.32–2.37)	2.30 (1.88–2.82)
Marital status					
Single	2.96 (1.90–4.62)	0.97 (0.37–2.54)	1.68 (0.99–2.86)	2.16 (1.16–4.00)	2.70 (1.79–4.06)
Married	2.11 (1.67–2.66)	1.54 (1.07–2.23)	1.51 (1.13–2.04)	1.53 (1.12–2.09)	2.16 (1.73–2.69)
Drinking					
No	2.25 (1.77–2.85)	1.46 (0.98–2.19)	1.62 (1.21–2.15)	1.90 (1.38–2.62)	2.24 (1.78–2.80)
Yes	2.24 (1.48–3.38)	1.39 (0.73–2.64)	1.28 (0.71–2.32)	1.00 (0.56–1.79)	2.31 (1.55–3.44)
Exercise					
No	2.29 (1.58–3.30)	2.09 (1.14–3.82)	1.44 (0.90–2.31)	1.79 (1.09–2.95)	2.27 (1.58–3.25)
Yes	2.24 (1.74–2.87)	1.22 (0.80–1.86)	1.60 (1.18–2.18)	1.59 (1.13–2.23)	2.26 (1.78–2.85)
Shift work					
No	2.20 (1.73–2.80)	1.42 (0.95–2.11)	1.56 (1.15–2.12)	1.36 (0.98–1.89)	2.22 (1.77–2.79)
Yes	2.43 (1.63–3.63)	1.58 (0.81–3.08)	1.65 (1.00–2.72)	2.75 (1.60–4.72)	2.45 (1.68–3.57)
Smoking					
No	2.16 (1.68–2.79)	1.40 (0.91–2.16)	1.47 (1.07–2.02)	1.68 (1.18–2.38)	2.16 (1.71–2.73)
Yes	2.54 (1.78–3.64)	1.57 (0.90–2.73)	1.72 (1.11–2.68)	1.59 (1.01–2.52)	2.63 (1.83–3.77)
Waist					
<90	2.48 (1.85–3.32)	1.27 (0.77–2.08)	1.40 (0.97–2.02)	1.47 (1.00–2.15)	2.24 (1.70–2.94)
≥90	2.09 (1.58–2.78)	1.75 (1.08–2.83)	1.62 (1.13–2.33)	1.77 (1.18–2.67)	2.27 (1.72–2.99)
Glucose					
Normal	2.31 (1.87–2.85)	1.38 (0.97–1.97)	1.57 (1.21–2.04)	1.74 (1.30–2.31)	2.30 (1.88–2.81)
Abnormal	2.48 (0.98–6.28)	2.89 (0.74–11.36)	1.59 (0.42–6.01)	0.84 (0.25–2.81)	2.72 (1.03–7.18)

NAFL, non-alcoholic fatty liver; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index.
Adjusted for age (continuous), marital status (single, married), education (high school and below, college and above), drinking (yes or no), exercise (yes or no), smoking (yes or no), shift work (yes or no), waist circumference (continuous), body mass index (continuous), and glucose (continuous).

Table 4. Mediation analysis of CRP in the link between lipid profile and NAFL.

	Total effect	Direct effect	Indirect effect	Proportion mediated	*P*
TG	0.18 (0.14-0.21)	0.17 (0.14-0.21)	0.0005 (-0.001 ~ 0.000)	0.19%	0.68
TC	0.06 (-0.004 ~ 0.11)	0.05 (-0.006 ~ 0.11)	0.003 (-0.0003 ~ 0.01)	2.90%	0.28
HDL	0.06 (-0.05 ~ 0.16)	0.06 (-0.05 ~ 0.16)	0.003 (-0.0006 ~ 0.01)	3.40%	0.44
LDL	0.0004 (-0.005 ~ 0.06)	−0.0002 (-0.005 ~ 0.05)	0.0006 (<0.0001-001)	3.48%	0.92
Dyslipidemia	0.11 (0.07-0.15)	0.11 (0.07-0.15)	0.001 (-0.0006 ~ 0.000)	0.80%	0.24

CRP, C-reactive protein; NAFL, non-alcoholic fatty liver; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Adjusted for age (continuous), marital status (single, married), education (high school and below, college and above), drinking (yes or no), exercise (yes or no), smoking (yes or no), shift work (yes or no), waist circumference (continuous), body mass index (continuous), and glucose (continuous).

Table 5. The areas under the ROC curve for different lipid index to predict the risk of NAFL in male workers.

Lipid profile	AUC	95% CI	Youden index	Cut-off	Sensitivity	Specificity
TG	0.754	0.736–0.771	0.378	1.12	0.753	0.625
TC	0.635	0.614–0.656	0.207	4.80	0.605	0.601
HDL	0.639	0.618–0.660	0.140	4.44	0.345	0.795
LDL	0.623	0.602–0.645	0.192	2.54	0.574	0.618

NAFL, non-alcoholic fatty liver disease; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

potential confounders. An increased OR (OR = 1.04, 95% CI: 1.00-1.09) was found between CRP and NAFL (Supplementary Table 2). However, no significant mediation effect of CRP was found on the association between an abnormal lipid profile and NAFL (all $p > 0.05$) (Table 4).

ROC analyses

The AUCs of specific lipid indices including TG, TC, HDL and LDL in predicting NAFL were significantly greater than 0.5, and among them, TG (0.754, 95%CI: 0.736-0.771) had a significantly higher AUC and Youden index (with 1.12 cut-off) than other indices (Table 5 and Supplementary Figure 2).

Discussions

Approximately 1 in 3 people in the US had NAFLD [26], and in Asian populations such as Japan, Korea, and China, the prevalence of NAFLD is approximately 25%–45% [27] and it continues to increase as a result of the westernization of dietary habits, decreased

physical activity, and increased obesity [28,29]. In the present study, 20.64% of male workers were diagnosed with NAFL, which was lower than the prevalence of 24.81% in males from a meta-analysis of 48 studies in mainland China [30]. The lower prevalence of NAFL in our study subjects may be related to their younger age (80.40% aged 20–40 years) and relatively healthier behaviors (such as less drinking, less smoking, and more exercise) [31,32], while using US for diagnosis of fatty liver may be also the possible reasons for low prevalence of NAFLD as US may miss patients with early fatty liver. Besides, our study showed the lipid levels of TG, TC and LDL were lower than US male in 2018, however the lipid concentration of HDL was higher than US male [33].

We found that an abnormal lipid profile was linked to the increased prevalence of NAFL, despite the study being conducted among people with a relatively healthier lifestyle. NAFLD is a clinicopathological condition characterized by significant lipid deposition. High consumption of fat has been associated with an increased risk of dyslipidaemia [34], causing accumulation of lipids in the liver, which in turn increases the amount of free fatty acids (FFAs), free cholesterol (FC), and other dangerous lipid metabolites, and triggers toxic effects in the liver, consequently resulting in NAFL and the development of NAFLD [35]. The hepatic accumulation of TG in lipid droplets was revealed to be a prerequisite for the development of NAFLD [36], which may provide an explanation for our study in which TG was associated with NAFL in a dose-response manner, and abnormal TG was significantly and stably associated with NAFL, and the results were in line with those of previous studies [37]. Furthermore, we also found that TG is a more suitable index to predict the risk of NAFL based on ROC curves; however, this is a less studied area that deserves further research to seek supportive evidence from cohort studies.

The underlying mechanism linking abnormal lipids with NAFL may involve insulin resistance, which makes adipose tissue resistant to the antilipolytic effect of insulin, leading to TG breakdown and the final formation of free fatty acids and glycerol [38], which are taken up by the liver, as is the case with the accumulation of TG in the liver [39]. Moreover, higher insulin levels modulate hepatic lipid metabolism by increasing TG synthesis, which promotes steatosis, lipotoxicity, and progressive liver injury [40]. At present, multifactorial pathogenesis has been postulated; however, the pathogenesis of NAFLD is still not completely understood.

Using ultrasonography to diagnose NAFLD requires expertise and specific instrumentation [41] that is generally not available in the general clinic; thus, specific risk factors based on biochemical examination would contribute to the estimation of the impact of fat accumulation on NAFL. Both previous mechanistic studies and our study indicated that the measures of lipid profiles in blood plasma could serve as surrogates, to some extent, for the fatty level in the liver, which serves as a suitable index for monitoring liver health. It has been known that inflammatory cytokines and adipose tissue cytokines have been considered to be significant factors contributing to the development and progression of NAFLD [42]. For instance, C-reactive protein (CRP), interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and intercellular adhesion molecule-1 (ICAM-1) were reported to be positively associated with higher risks of NAFLD [43,44]. Consistent with a previous study [42] in which CRP was found to be significantly associated with non-alcoholic steatohepatitis and hepatic fibrosis, our study also indicated that CRP was significantly associated with NAFL; however, our study did not find a mediating effect of CRP on the association between lipid profile and NAFL, which needs to be examined in future studies. In addition, the role of above-mentioned inflammatory cytokines and adipose tissue cytokines in the association between lipid profile and non-alcoholic fatty liver disease are also need to be assessed in the future.

Several studies have shown that obesity is the most important risk factor for simple steatosis [45]. In our study, a significantly increased OR of NAFL was demonstrated among subjects with higher BMI and waist circumference. One possible reason may be that obesity is also a key risk factor for dyslipidemia, and the joint effect of obesity and abnormal blood lipid levels could increase the risk of NAFL [46]. A previous study showed that hypertriglyceridemic waist circumference had the highest risk of NAFLD [11], which also supported our results. Higher risks of NAFL with abnormal lipid indexes were observed in shift workers, which provided further evidence of the harmful effect of shift work on NAFLD [47]. These findings suggest that shift workers should pay more attention to their blood lipid indices to mitigate the disease burden related to abnormal lipid profiles. In addition, our results showed that an abnormal lipid profile was linked with the prevalence of NAFL in the normal glucose group but not in the abnormal glucose group, although a higher OR was observed in the abnormal glucose group (not significant); however, the possibility could not be ruled out due to the relatively small sample size. Considering that NAFLD and type 2 diabetes are common medical conditions that regularly co-exist in the real world and may act synergistically to drive adverse outcomes [48], blood glucose should also be emphasized when considering blood lipid profiles.

The findings of this study highlight the importance of lipid biomarkers for the noninvasive diagnosis of NAFL, and TG may be a more suitable lipid index to predict the prevalence of NAFL. These findings may have important public health implications for the early diagnosis and intervention of NAFL. In addition, our study suggested that CRP was not the main mechanism in the pathway of blood lipids and the risk of NAFL, although CRP was associated with both blood lipids and the prevalence of NAFL. However, some limitations of this study should be acknowledged. The observational cross-sectional design based on the cohort's baseline survey limits inferences about temporality and causality. Moreover, in the present study, we could not distinguish simple steatosis from non-alcoholic steatohepatitis owing to data limitations. Besides, depending on ultrasound in diagnosis of fatty liver may miss a significant proportion of early stages of fatty infiltration, male workers only were included in the present study, and lack of any information of participants medications including anti hyperlipidemic drugs may also decrease the prevalence of NAFLD. Further comprehensive analyses with more detailed information should be conducted in the future.

Conclusions

Our study demonstrates that abnormal blood lipid levels are positively associated with NAFL, and TG tends to be a better predictor of NAFL. Abnormal lipids are more likely to exert a direct effect on NAFL rather than through the mediation effect of CRP. More human epidemiology and animal studies should be conducted to examine our findings and explore the related biological mechanisms.

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Patient consent

Obtained.

Authors' contributions

WZL wrote the manuscript and performed the statistical analysis. WZL and LAT conceived and designed the study and interpreted the data. ZML, WTF, and HYH conducted the survey and collected data. FW and MPK critically revised the manuscript and approved its final version. LAT is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. All authors agree to be accountable for all aspects of the work and the final approval of the version to be published.

Ethics approval

The protocol was approved by the Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee (CREC Ref No: CRE-2013.107).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Availability of data and material

Data could be available on reasonable request by contacting the author at shelly@cuhk.edu.hk.

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