Lipids in Health and Disease

RESEARCH

Open Access

The U -shape relationship between free fatty acid level and adverse outcomes in coronary artery disease patients with hypertension: evidence from a large prospective cohort study

Ting-Ting Wu[1,2,3†], Ying Pan[1,2,3†], Ying-Ying Zheng[1,2,3], Zhi-Long Wang[1,2,3], Chang-Jiang Deng[1,2,3], Shun Wang[1,2,3] and Xiang Xie[1,2,3*]

Abstract

Background Evidence is scarce on the effect of free fatty acid (FFA) level in the prognosis of coronary artery disease (CAD) patients with hypertension. This study.

Methods A large prospective cohort study with a follow-up period of average 2 years was conducted at Xinjiang Medical University Affiliated First Hospital from December 2016 to October 2021. A total of 10,395 CAD participants were divided into groups based on FFA concentration and hypertension status, and then primary outcome mortality and secondary endpoint ischemic events were assessed in the different groups.

Results A total of 222 all-cause mortality (ACMs), 164 cardiac mortality (CMs), 718 major adverse cardiovascular events (MACEs) and 803 major adverse cardiovascular and cerebrovascular events (MACCEs) were recorded during follow-up period. A nonlinear relationship between FFA and adverse outcomes was observed only in CAD patients with hypertension. Namely, a "U -shape" relationship between FFA levels and long-term outcomes was found in CAD patients with hypertension. Lower FFA level (< 310 μmol/L), or higher FFA level (≥ 580 μmol/L) at baseline is independent risk factors for adverse outcomes. After adjustment for confounders, excess FFA increases mortality (ACM, HR = 1.957, 95%CI(1.240–3.087), $P = 0.004$; CM, HR = 2.704, 95%CI(1.495–4.890, $P = 0.001$) and MACE (HR = 1.411, 95%CI(1.077–1.848), $P = 0.012$), MACCE (HR = 1.299, 95%CI (1.013–1.666), $P = 0.040$) prevalence. Low levels of FFA at baseline can also increase the incidence of MACE (HR = 1.567,95%CI (1.187–2.069), $P = 0.002$) and MACCE (HR = 1.387, 95%CI (1.070–1.798), $P = 0.013$).

Conclusions Baseline FFA concentrations significantly associated with long-term mortality and ischemic events could be a better and novel risk biomarker for prognosis prediction in CAD patients with hypertension.

†Ting-Ting Wu and Ying Pan contributed equally to this work.

*Correspondence:
Xiang Xie
xiangxie999@sina.com

Full list of author information is available at the end of the article

Trial registration The details of the design were registered on https://www.chictr.org.cn/ (Identifier NCT05174143).

Key messages

What is known on this topic?

• Free fatty acid (FFA) plays an essential role in hepatic triglyceride synthesis . Several studies have shown that plasma FFA concentration is a modifiable risk factor for metabolic disease. However, no evidence is currently available regarding the link between FFA and prognosis in CAD patients with hypertension.

What does this paper add?

• We observed a "U -shape" relationship between FFA and adverse outcomes in CAD patients with hypertension, which address a novel knowledge gap in the risk classification of CAD patients with hypertension.

Keywords Free fatty acid, Adverse outcomes, Hypertension, Coronary artery disease

Introduction

As a major public health concern, hypertension is a leading cause of disability and mortality all over the world and imposes a heavy burden on health-care costs [1, 2]. However, the level of awareness, treatment and control of hypertension worldwide is overwhelmingly low [3]. Patients with coronary heart disease often suffer from high blood pressure. Evidence suggests that controlling blood pressure can help improve the prognosis of coronary artery disease (CAD) patients with hypertensive patients [4, 5]. Therefore, it is paramount to identify the risk factors to develop effective strategies to prevent or delay poor prognosis in CAD patients with hypertension.

Free fatty acid (FFA), also known as non-esterified fatty acid (NEFA), plays an essential role in hepatic triglyceride synthesis [6]. Several studies have shown that plasma FFA concentration is a modifiable risk factor for metabolic disease [7]. Its elevation has been observed in type 2 diabetes mellitus (T2DM), obesity, non-alcoholic fatty liver disease (NAFLD), poor myocardial function and related comorbidities [8–10]. Some researchers emphasize that elevated FFA is associated with the occurrence, development and poor prognosis of CAD [11, 12]. Evidence from the Paris prospective study proposes that FFA concentration could predict cancer mortality [13]. Pilz's work on FFA indicates that higher FFA is independently associated with the elevated risk for all-cause mortality (ACM) and cardiac death [14, 15]. Noteworthy, our previous study identified that both low and elevated FFA levels were related with the adverse outcomes in CAD patients with T2DM [16]. However, no evidence is currently available regarding the link between FFA and prognosis in CAD patients with hypertension. With this background and our large cohort data, this study was designed to investigate the impact of FFA concentration on adverse outcomes in CAD patients with hypertension.

Methods

Study design

The design of the PRACTICE study has been reported previously [16]. Briefly, this analysis was performed within the PRACTICE study, which is a population-based, prospective cohort. At baseline, 15,250 CAD patients were recruited between 2016 and 2021 and have continued to be followed up. The study protocol was approved by the ethics committee of Xinjiang Medical University First Affiliated Hospital. Informed consent was provided by all participants. Individuals were included in this study if they had at least one significant coronary artery stenosis of ≥70% lumen diameter or a≥50% stenosis of the left main, as shown by coronary angiography. Exclusion criteria were unavailable FFA data, severe infections, cancer, malignant liver, gallbladder and kidney disease, and blood disorders. The other exclusion criteria was described previously [16]. Finally, data from 10,395 CAD patients were analyzed. In this study, we divided all participants into four groups according to the quartiles of FFA concentration: quartile I (<310 μmol/L), quartile II (310–420 μmol/L), quartile III (420–580 μmol/L), and quartile IV (≥580 μmol/L). Then we analyzed data of individuals with different blood pressure (BP) conditions to examine the influence of FFA in the adverse clinical outcomes of CAD patients with hypertension. Figure 1 shows a flowchart of the study.

We also obtained demographic characteristics at admission, including age, sex, smoking status, alcohol use, and diabetes history. Hypertension was identified as systolic blood pressure (SBP)≥140 mmHg and/or diastolic blood pressure (DBP)≥90 mmHg at three times on different days or taking antihypertensive drugs [17]. Diabetes mellitus was diagnosed if patients with fasting blood glucose (FBG)≥7.1 mmol/L, or 2 h post-load glucose≥11.1 mmol/L, having a clear history of diabetes or using hypoglycaemic agents [18]. The medication was obtained from medication records. Haematological and biochemical data were tested using chemical analysis equipment (Dimension AR/AVL Clinical Chemistry System, Newark, NJ, USA) after patients fasted for at least 12 h in the Clinical Laboratory Department of the First Affiliated Hospital of Xinjiang Medical University.

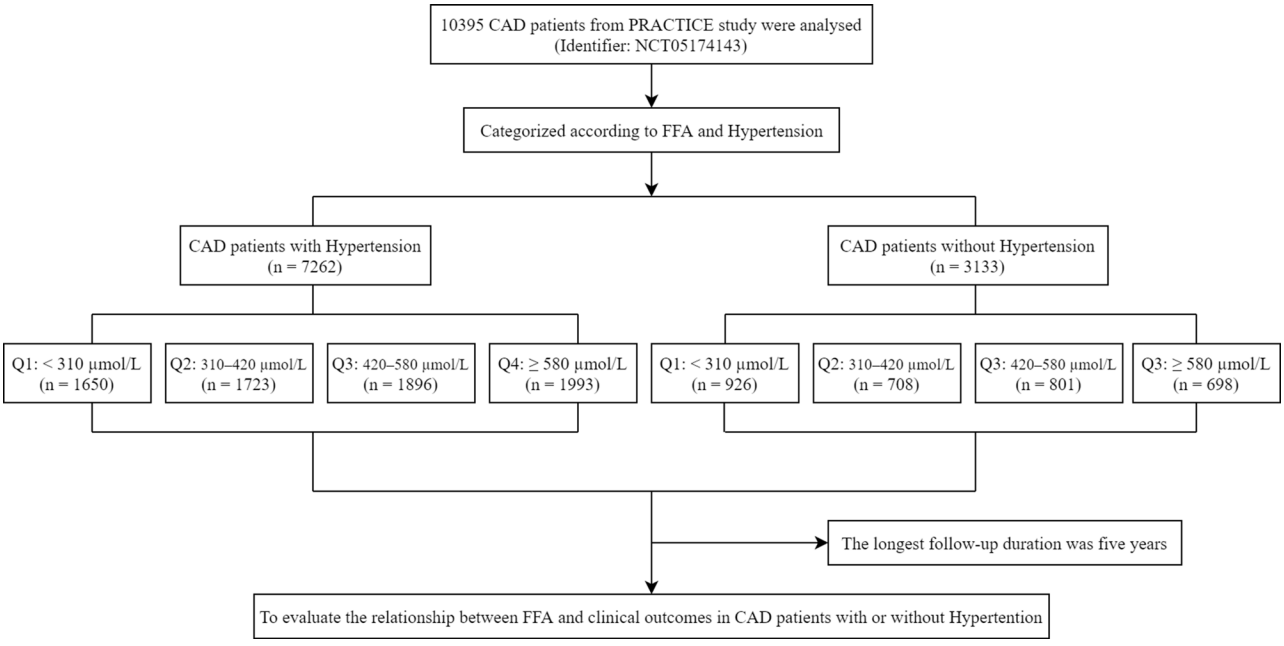

Fig. 1 Flowchart of the PRACTICE study. CAD, Coronary artery disease; FFA, Free Fatty Acids

The measurement of FFA

Serum samples were collected, separated and stored at −80 °C after patients fasted for at least 12 h. Samples were incubated for 15 min at room temperature and then the concentration of FFA was measured using enzymatic colorimetry assay in the Clinical Laboratory Department of the First Affiliated Hospital of Xinjiang Medical University. The reference range of FFA concentration is 100–900 μmol/L, as described by the manufacturer.

Endpoints

The primary endpoints were all-cause mortality (ACM) and cardiac mortality (CM). The secondary endpoints were ischemic events including major adverse cardiovascular and cerebrovascular events (MACCE) and major adverse cardiovascular events (MACE). MACE consists of cardiac death, nonfatal heart attack, and revascularization. MACCE incorporates MACE plus stroke.

Follow-up

Patients were followed up after discharge at the end of 1 month, 3 months, 6 months, 1 year, 3 years and 5 years. At each visit, structured interviews were conducted to obtain self-reported information on clinical outcomes through clinical visits, telephone calls and questionnaires. An independent endpoint adjudication committee evaluated all events.

Statistical analyses

All statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA) and R (version 4.0.3). We used proportions for qualitative data and means (SD) or median (IQR) for quantitative data to describe the baseline characteristics of the study cohort. We performed a χ^2 test to compare categorical variables. The unpaired t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. We analyze all time-to-event distributions. The Kaplan-Meier's method (K-M) was used to analyse all time-to-event distributions, and the log-rank test was used to evaluate differences. We calculated hazard ratios (HRs) and 95% CIs for adverse outcomes by Cox proportional-hazards regression models adjusting for history of smoking, alcohol use, hypertension, diabetes, sex, age, heart rate, UA, Cr, TGs, TC, HDL-C, LDL-C, EF and medication use. We also plotted restricted cubic spline (RCS) to further evaluate the non-linear association, using log [FFA (umol/L)]. For all analyses, a *P* value of <0.05 based 2-sided test is considered statistically significant.

Results

The 10,395 CAD participants were divided into 4 groups based on the quartile of FFA concentration. There were 7262 individuals with hypertension (Q1: $n=1650$, Q2: $n=1723$, Q3: $n=1896$, Q4: $n=1993$) and 3133 without hypertension (Q1: $n=926$, Q2: $n=708$, Q3: $n=801$, Q4: $n=698$). As shown in Table 1, some baseline characteristics vary significantly among different FFA groups in individuals with hypertension.The participants in Q4 quartile tend to be with a higher prevalence of TC, HDL-C, LDL-C, TB (total bilirubin) and TP (total protein) and a lower level of EF. The baseline characteristics for all patients and individuals without hypertension are shown

Table 1 Basic characteristics of participants with hypertension ($n=7262$)

Variables	Q1 (<310 μmol/L)	Q2 (310–420 μmol/L)	Q3 (420–580 μmol/L)	Q4 (≥580 μmol/L)
Female, *n* (%)	479(29.0)	479(27.8)	537(28.3)	596(29.9)
Smoking, *n* (%)	609(36.9)	633(36.7)	719(37.9)	701(35.2)
Alcohol use, *n* (%)	375(22.7)	426(24.7)	463(24.4)	476(23.9)
Diabetes, *n* (%)	654(39.6)	719(41.7)	853(45.0)	1084(54.4)
Age, years	60.7 ± 10.6	60.8 ± 10.8	61.0 ± 11.1	61.0 ± 11.6
SBP, mmHg	134.0 ± 18.8	133.9 ± 18.8	134.3 ± 19.1	134.6 ± 18.8
DBP, mmHg	78.8 ± 13.1	78.7 ± 13.3	79.9 ± 13.3	80.4 ± 13.5
HR, beats/min	76.2 ± 11.1	76.9 ± 11.9	77.1 ± 11.9	78.4 ± 12.1
Cr, μmol/L	69.0[59.0-80.7]	70.0[60.0–82.0]	59.2[71.0–83.0]	75.0[63.0–89.0]
UA, mmol/L	330.0[272.8–393.0]	339.5[286.0-416.0]	341.0[283.8–411.0]	350.0[292.8-432.4]
TG, mmol/L	1.3[1.0-1.8]	1.5[1.1-2.0]	1.5[1.1–2.1]	1.6[1.2–2.4]
TC, mmol/L	3.7 ± 1.0	3.8 ± 1.0	3.9 ± 1.1	4.1 ± 1.2
HDL-C, mmol/L	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3
LDL-C, mmol/L	2.3 ± 0.9	2.4 ± 0.8	2.5 ± 0.9	2.6 ± 0.9
TB, μmol/L	66.7[63.3–70.6]	67.1[64.0-71.1]	67.6[64.2–71.3]	68.4[64.8–72.6]
TP, g/L	67.1 ± 5.4	67.7 ± 5.5	67.9 ± 5.5	68.7 ± 5.8
EF, %	61.1 ± 6.9	61.5 ± 6.8	61.2 ± 7.2	60.3 ± 8.1
FBG, mmol/L	6.2 ± 2.2	6.3 ± 2.4	6.5 ± 2.5	7.1 ± 3.0
GSP, mmol/L	2.2 ± 0.5	2.3 ± 0.4	2.3 ± 0.5	2.4 ± 0.5
HbA1c, mmol/L	6.6 ± 1.5	6.5 ± 1.3	6.6 ± 1.4	6.9 ± 1.6
ARB or ACEI, *n* (%)	830(50.3)	819(47.5)	969(51.1)	1029(51.6)
β-Blockers, *n* (%)	941(59.6)	981(59.5)	1092(59.5)	1150(60.1)
CCB, *n* (%)	465(29.5)	511(31.0)	573(31.2)	605(31.6)
Aspirin, *n* (%)	1599(96.9)	1686(97.9)	1847(97.4)	1919(96.3)
Statins, *n* (%)	1568(95.0)	1623(94.2)	1775(93.6)	1833(92.0)
clopidogrel, n (%)	854(51.8)	879(51.0)	971(51.2)	1000(50.2)

Note: To describe the baseline characteristics of the study cohort, proportions was used for qualitative data and means (SD) or median (IQR) was used for quantitative data. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; Cr, creatinine; UA, uric acid; TG, total triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein-C; LDL-C, low-density lipoprotein-C; TB, total bilirubin; TP, total protein; EF, ejection fraction; FBG, Fasting blood glucose; GSP, Glycosylated serum protein; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blockers

in supplementary material (See supplementary material Table S1 and S2). Table 2 describes the clinical outcomes of individuals with or without hypertension. Over a median follow-up of 24 months, a total of 168 ACMs, 121 cm, 536 MACEs, and 603 MACCEs were recorded in individuals with hypertension during the follow-up period. The incidence of ACMs, CMs, MACEs and MACCEs was significantly different among four groups in individuals with hypertension [ACMs ($P<0.001$), CMs ($P<0.001$), MACEs ($P=0.001$), and MACCEs ($P=0.008$)]. In individuals without hypertension, only the incidence of ACMs and CMs was significantly different among four groups [ACMs ($P<0.006$) and CMs ($P<0.033$)]. Additionally, the incidence of MACEs and MACCEs in individuals with hypertension was significantly higher than those without hypertension, non significant in ACMs nor in CMs (Fig. 2). Kaplan–Meier survival analysis suggested that patients with high FFA or low FFA exhibited increased accumulated risk of poor outcomes (Fig. 3).

Then, we calculated HRs and 95% CIs for adverse outcomes by Cox proportional-hazards regression models adjusting for history of smoking, alcohol use, hypertension, diabetes, sex, age, heart rate, UA, Cr, TGs, TC, HDL-C, LDL-C, EF and medication use. Among individuals with hypertension, both Q4 group and Q1 group had a higher incidence of ACM, CM, MACE and MACCE, compared with Q3 group (Ps<0.05, Fig. 4). As shown in Table 3, compared with Q3, the incidence of ACM (adjusted HR=1.957(1.240–3.087), $P=0.004$) and CM (adjusted HR=2.704(1.495–4.890), $P=0.001$) in Q4 group was increased 0.957 times and 1.704 times, respectively. Moreover, using Q3 as reference, individuals in Q1 and Q4 both had higher risk of MACE (Q1: adjusted HR=1.567(1.187–2.069), $P=0.002$; Q4: adjusted HR=1.411(1.077–1.848), $P=0.012$) and MACCE (Q1: adjusted HR=1.387(1.070–1.798), $P=0.013$; Q4: adjusted HR=1.299 (1.013–1.666), $P=0.040$).

As Fig. 5 shown, RCS was plotted to present the nonlinear U-shaped relationship between FFA concentrations and mortality (ACM and CM) or ischemic events (MACE and MACCE).

Discussion

The present analysis, from a well-designed prospective cohort of a large sample population, reports the nonlinear relationship between FFA concentration and the prognosis of CAD patients with hypertension. That is to say, when subjects with lower (<310 μmol/L), or higher FFA level (≥580 μmol/L) at baseline were more easy to suffer from adverse outcomes. This "U-shape" relationship between FFA and poor prognosis in CAD patients with hypertension addresses a novel knowledge gap in risk classification.

Consistenting with previous conclusions [13–15], we found that hypertensive patients with high levels of FFA on admission are more likely to experience ischemic events among CAD group. Given that hypertension and certain lipid components have detrimental effects on clinical outcomes in cardiovascular disease patients [19–21], effectively managing relevant risk factors can improve the prognosis of CAD. As an important component of blood lipids, it is essential to further understand the role of FFA in CAD patients with hypertension. Previous studies have

Table 2 Clinical outcomes of participants

Variables	Q1	Q2	Q3	Q4	x2	*P* value
	(< 310 μmol/L)	(310–420 μmol/L)	(420–580 μmol/L)	(≥ 580 μmol/L)		
CAD patients with hypertension (n = 7262)						
ACM, *n (%)*	31(1.9)	29(1.7)	32(1.7)	76(3.8)	27.533	**< 0.001**
CM, *n (%)*	24(1.5)	21(1.2)	17(0.9)	59(3.0)	29.782	**< 0.001**
MACE, *n (%)*	142(8.6)	114(6.6)	109(5.7)	171(8.6)	16.675	**0.001**
MACCE, *n (%)*	151(9.2)	129(7.5)	132(7.0)	191(9.6)	11.837	**0.008**
CAD patients without hypertension (n = 3133)						
ACM, n (%)	12(1.3)	6(0.8)	14(1.7)	22(3.2)	12.617	**0.006**
CM, n (%)	10(1.1)	5(0.7)	11(1.4)	17(2.4)	8.734	**0.033**
MACE, n (%)	63(6.8)	35(4.9)	47(5.9)	37(5.3)	2.977	0.395
MACCE, *n (%)*	66(7.1)	41(5.8)	50(6.2)	43(6.2)	1.358	0.715

Note: A χ^2 test was performed to compare categorical variables. A P value of < 0.05 based 2-sided test is considered statistically significant. ACM, all-cause mortality; CM, cardiac mortality; MACE, major adverse cardiovascular events; MACCE, major adverse cardiovascular and cerebrovascular events

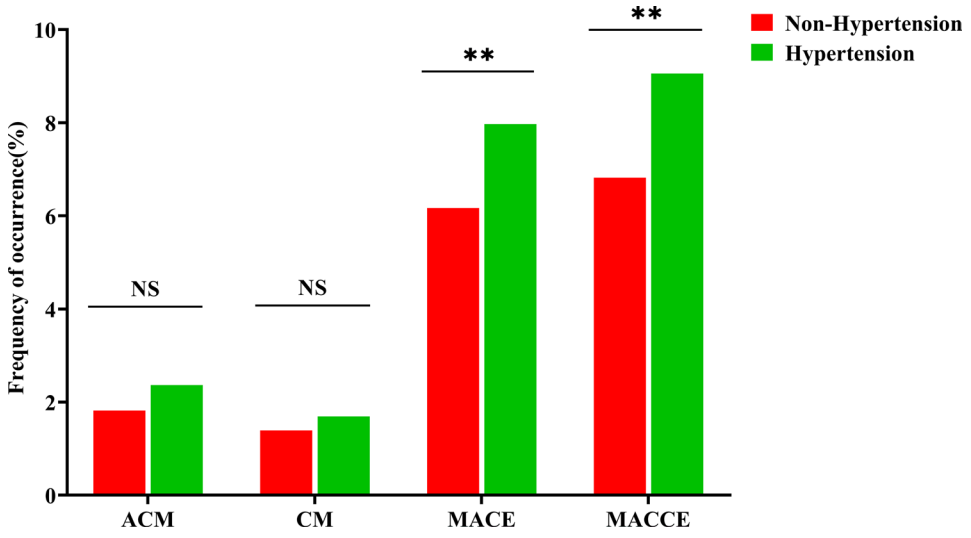

Fig. 2 The comparison of clinical outcomes between hypertensive and non-hypertensive patients. ACM, all-cause mortality; CM, cardiac mortality; MACE, major adverse cardiovascular events; MACCE, major adverse cardiac and cerebrovascular events

indicated that increased FFA concentration is associated with hypertension [22–24]. Magda M.I et al. conducted a study among white participants and found that baseline FFA was significantly higher in abdominally obese hypertensive subjects than in lean non-hypertensive individuals [22]. Similar results were reported by Bm E et al., who observed higher FFA concentration and turnover in obese hypertensive individuals compared to lean or obese normotensive individuals. They suggested that increased FFA plays an important role in elevating blood pressure [23].In the Paris Prospective Study included 2968 Caucasian men, baseline FFA was identified as a risk factor for hypertension (hazard rate ratio [RR] = 1.58, 95% confidence interval [CI] : 1.30–1.91] over 3 years of follow-up after controlling for possible confounding factors [24]. It may call for clinicians to pay more attention to FFA during lipid-lowering therapy in CAD patients with hypertension. Furthermore, we have innovatively discovered a "U-shaped" relationship between FFA and adverse outcomes in CAD patients with hypertension. This means that lower levels of FFA are also associated with poor prognosis in CAD patients with hypertension. It is worth exploring the intrinsic relationship and pathogenic mechanisms between low FFA levels and poor outcomes in CAD patients with hypertension. The study conducted by Tabara Y et al. demonstrated an inverse association between the augmentation index (AIx), a marker of central blood pressure, and quartiles of free fatty acids (FFA), namely with higher AIx observed in lower FFA quartiles [25]. Previous reports have indicated that elevated AIx is a risk factor for hypertension and cardiovascular disease [26, 27]. Therefore, it is plausible to suggest that low levels of FFA may exert reverse-regulatory effects on blood pressure through the elevation of AIx, potentially contributing to an unfavorable prognosis in hypertensive patients with coronary artery disease (CAD).

Given the intricate nature of biological systems, it is likely that additional mechanisms are at play. Studies

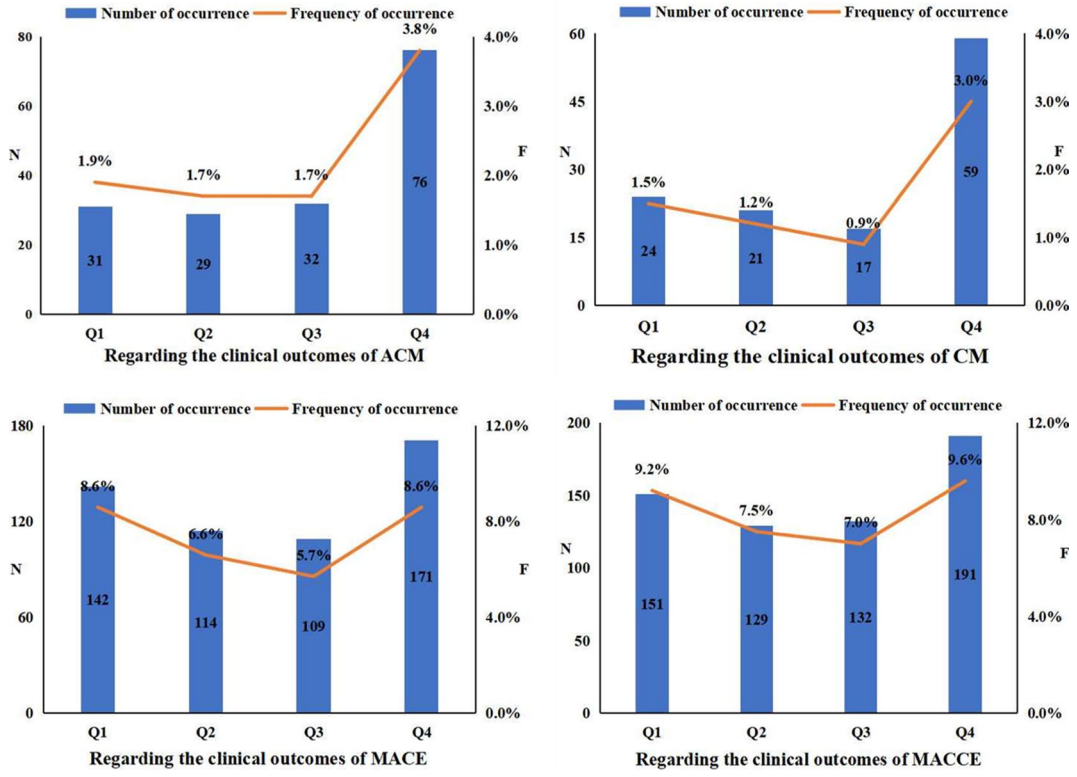

Fig. 3 Cumulative Kaplan-Meier estimates of the time to the occurrence of clinical outcomes in patients according to four FFA categories under different hypertension status. ACM, all-cause mortality; CM, cardiac mortality; MACE, major adverse cardiovascular events; MACCE, major adverse cardiac and cerebrovascular events

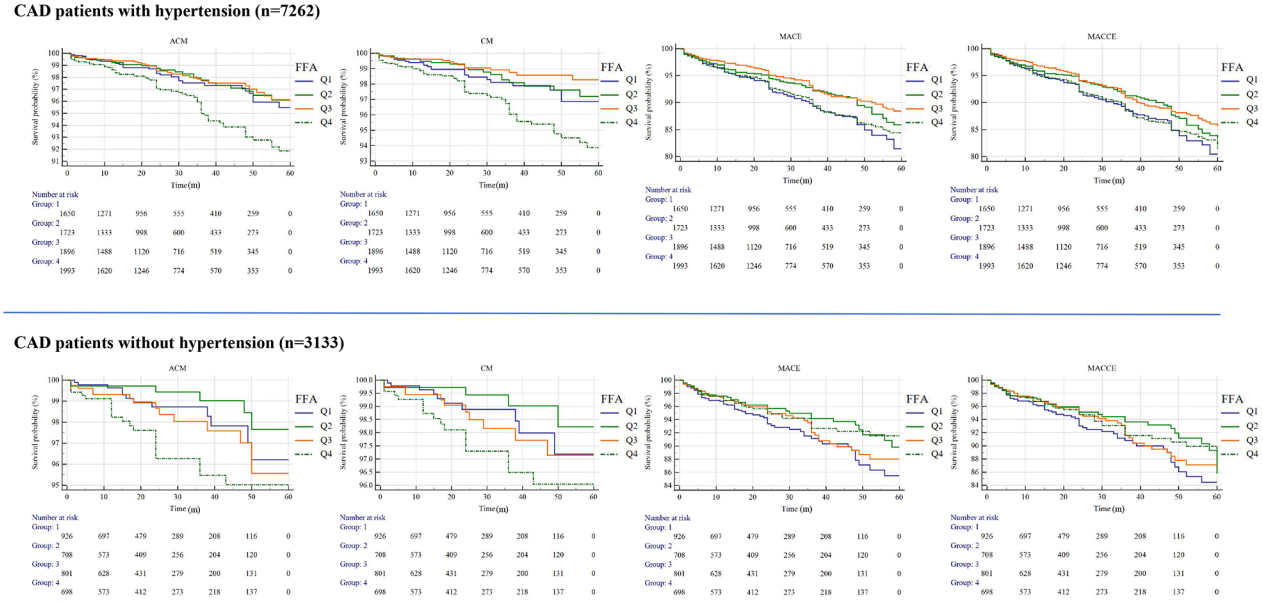

Fig. 4 The clinical outcome of CAD patients with hypertension. ACM, all-cause mortality; CM, cardiac mortality; MACE, major adverse cardiovascular events; MACCE, major adverse cardiac and cerebrovascular events

Table 3 Association between FFA levels and adverse outcomes

Variables	Q1		Q2		Q3		Q4	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
CAD patients with hypertension (n = 7262)								
ACM	1.138(0.667–1.944)	0.635	1.074(0.626–1.842)	0.795	Ref	/	1.957(1.240–3.087)	**0.004**
CM	1.686(0.867–3.279)	0.124	1.468(0.741–2.907)	0.271	Ref	/	2.704(1.495–4.890)	**0.001**
MACE	1.567(1.187–2.069)	**0.002**	1.293(0.970–1.724)	0.079	Ref	/	1.411(1.077–1.848)	**0.012**
MACCE	1.387(1.070–1.798)	**0.013**	1.163(0.890–1.520)	0.270	Ref	/	1.299(1.013–1.666)	**0.040**
CAD patients without hypertension (n = 3133)								
ACM	1.338(0.535–3.344)	0.534	0.363(0.096–1.372)	0.135	Ref	/	1.802(0.800-4.059)	0.155
CM	1.327(0.471–3.740)	0.593	0.348(0.072–1.679)	0.189	Ref	/	1.734(0.692–4.344)	0.240
MACE	1.258(0.820–1.931)	0.293	0.804(0.493–1.310)	0.380	Ref	/	0.851(0.528–1.373)	0.508
MACCE	1.217(0.805–1.841)	0.352	0.857(0.540–1.362)	0.515	Ref	/	0.926(0.590–1.455)	0.740

Note: a. Adjusting for history of smoking, alcohol use, hypertension, diabetes, sex, age, heart rate, UA, Cr, TGs, TC, HDL-C, LDL-C, EF and medication use; b, Using Q3 as reference. C, A *P* value of < 0.05 based 2-sided test is considered statistically significant. ACM, all-cause mortality; CM, cardiac mortality; MACE, major adverse cardiovascular events; MACCE, major adverse cardiovascular and cerebrovascular events

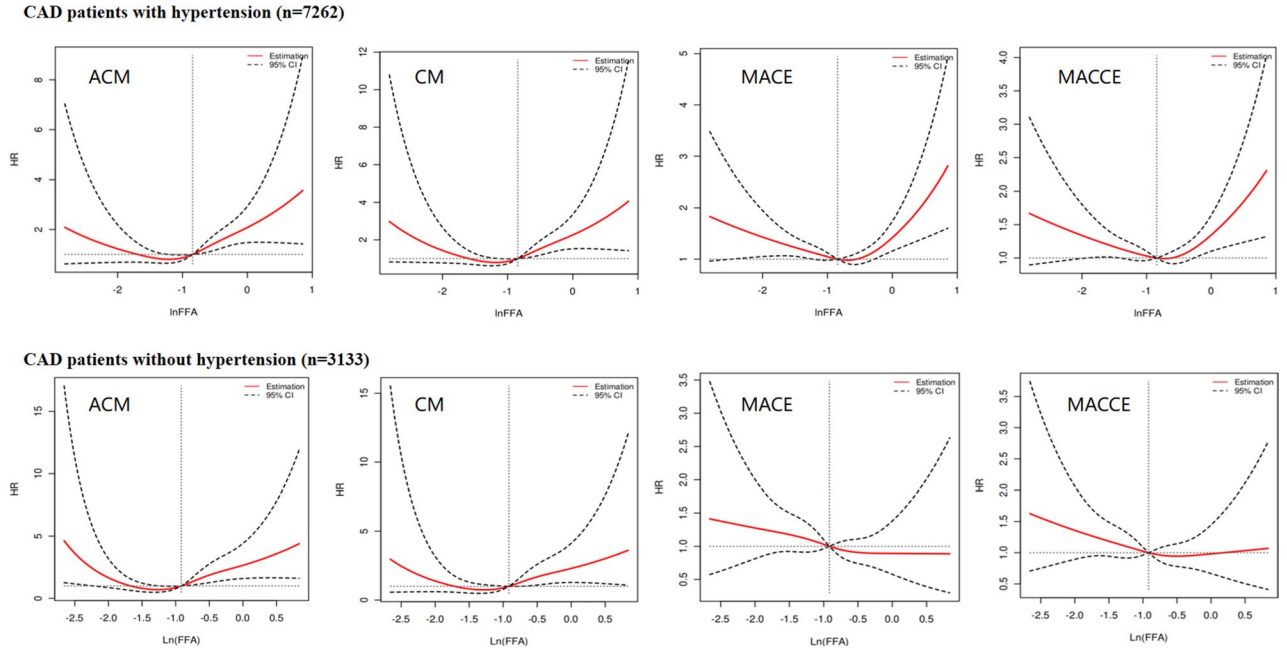

Fig. 5 Restricted cubic spline plots for mortality and ischemic events according to FFA on a continuous scale. ACM, all-cause mortality; CM, cardiac mortality; MACE, major adverse cardiovascular events; MACCE, major adverse cardiac and cerebrovascular events

have shown that the concentration of FFA in the blood increases when body is in a pathological state of T2DM or glycogen accumulation disease [28]. In this study, we similarly find an increase in FFA levels accompanied by a mild increase in FBG and HbA1c. The elevation of blood glucose and FFA can jointly lead to a large amount of reactive oxygen species (ROS) generation and oxidative stress, and at the same time cause a cascade of activation of multiple serine kinases, which in turn aggravates insulin resistance [29–31]. When insulin resistance increases, compensatory insulin secretion decreases, or both, the progression of diabetes is accelerated [32, 33]. This is consistent with our findings that the prevalence of diabetes in the high FFA group was observed to be higher, compared to that in the low group. Additionally, previous studies have shown that insulin resistance is associated with the pathogenesis of hypertension [34]. Therefore, it is reasonable to assume that the cross-linking of insulin resistance and FFA plays an important propulsive role in the development of malignant cardiovascular events. Furthermore, FFA actively promotes insulin resistance through macrophage activation and subsequent release of related cytokines, ultimately leading to endothelial dysfunction and vascular stiffness [35–38]. Considering arterial stiffness' independent status as a risk factor for adverse cardiovascular events and the bidirectional causality between blood pressure and arterial stiffness, there may be synergy leading to an accelerated occurrence of

adverse events [39, 40]. Additionally, FFA can impact established blood pressure regulatory systems such as the renin-angiotensin-aldosterone axis and the volume-vasopressin loop [7, 41]. FFA also has the potential to activate a1-adrenergic receptors, leading to heightened heart rate and blood vessel constriction, ultimately raising blood pressure [42]. Furthermore, elevated FFA levels in hepatocytes can result in increased production of ROS and endoplasmic reticulum (ER) stress [42, 43]. Potentially disrupting cellular metabolism due to excessive accumulation of FFA in the myocardium, leading to cellular dysfunction and death [44]. In summary, inappropriate FFA levels may exacerbate hypertension-related impairment, potentially contributing to a higher incidence of major adverse cardiovascular events (MACEs) and major adverse cardiac and cerebrovascular events (MACCEs) in individuals with hypertension compared to those without. Further research is necessary to confirm the significant role of FFA and hypertension in driving worse outcomes through these pathogenic pathways.

Limitations and strengths

This study should be interpreted with several limitations. First, we performed the analysis based on the baseline total FFA data without evaluating the FFA subclasses and their dynamic variants. Second, several metabolic factors and parameters, including insulin, diet, inflammation, oxygenated derivatives of FFA, and neural system activity, were not assessed in our analysis. Third, the participants in this analysis are all from a single cohort, and the exact cutoff used to define the FFA is likely to vary across cohorts. The strengths of this study include its large sample size, prospective study design, and longest follow-up duration.

Conclusions

We found a non-linear association between FFA concentration and hypertension in CAD patients, with an increased risk of poor long-term outcomes at reduced or increased FFA concentration, which should be further assessed.

Abbreviations

FFA	Free Fatty Acids
CAD	Coronary artery disease
ACM	All-cause mortality
CM	Cardiac mortality
MACCE	Major adverse cardiac and cerebrovascular events
MACE	Major adverse cardiovascular events
PRACTICE	Personalized Antiplatelet Therapy According to CYP2C19 Genotype in Coronary Artery Disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02273-z.

Supplementary Material 1

Acknowledgements

The authors acknowledged all nurses and doctors in the Heart Centre of Xinjiang Medical University Affiliated First Hospital. In addition, we acknowledged all patients of blood samples.

Author contributions

TTW and YP drafted the manuscript. YYZ and ZLW performed the statistical analysis. CJD and SW interpreted the data and prepared Figs. 1, 2, 3, 4 and 5. XX made substantial contributions to the critical revision, study conception and design. All authors reviewed and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (grant No. 82360097), Tianshan Talent, Xinjiang Science and Technology Project (2022TSYCLJ0029) and Key research and development projects of Xinjiang Province, China (2022B03022-5).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The ethics committee of Xinjiang Medical University Affiliated First Hospital approved this research. All patients provided written informed consent to participate.

Consent for publication

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. All authors agree to the publication of this work.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Cardiology, Xinjiang Medical University Affiliated First Hospital, No. 137, Liyushan Road, Urumqi 830054, China
[2]Key Laboratory of High Incidence Disease Research in Xingjiang, (Xinjiang Medical University, Ministry of Education), Urumqi, China
[3]Key Laboratory of Hypertension Research of Xinjiang Medical University, No. 137, Liyushan Road, Urumqi 830054, China

Received: 18 May 2024 / Accepted: 27 August 2024
Published online: 10 September 2024

References

1. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension[J]. Nat Rev Nephrol. 2020;16(4):223–37.
2. Murray CJL, Aravkin AY, Zheng P, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of Disease Study 2019[J]. Lancet. 2020;396(10258):1223–49.
3. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries[J]. Circulation. 2016;134(6):441–50.
4. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis[J]. Lancet. 2016;387(10022):957–67.
5. Vongpatanasin W. Management of hypertension in patients with coronary artery disease[J]. Curr Hypertens Rep. 2008;10(5):349–54.
6. Frayn KN, Coppack SW. Insulin resistance, adipose tissue and coronary heart disease[J]. Clin Sci. 1992;82(1):1–8.
7. Henderson GC. Plasma free fatty acid concentration as a modifiable risk factor for metabolic disease[J]. Nutrients. 2021;13(8):2590.

8. Kumar V, Xin X, Ma J, et al. Therapeutic targets, novel drugs, and delivery systems for diabetes associated NAFLD and liver fibrosis[J]. Adv Drug Deliv Rev. 2021;176:113888.
9. Hierons SJ, Marsh JS, Wu D, et al. The interplay between non-esterified fatty acids and plasma zinc and its influence on thrombotic risk in obesity and type 2 diabetes[J]. Int J Mol Sci. 2021;22(18):10140.
10. Martchenko A, Brubaker PL. Effects of obesogenic feeding and free fatty acids on circadian secretion of metabolic hormones: implications for the development of type 2 diabetes[J]. Cells. 2021;10(9):2297.
11. Yuan D, Xu N, Song Y et al. Association between free fatty acids and cardiometabolic risk in coronary artery disease: results from the PROMISE Study[J]. J Clin Endocrinol Metabolism, 2023: dgad416.
12. Jin JL, Cao YX, Liu HH, et al. Impact of free fatty acids on prognosis in coronary artery disease patients under different glucose metabolism status[J]. Cardiovasc Diabetol. 2019;18:1–9.
13. Aline Charles M, Fontbonne A, Thibult N, et al. High plasma nonesterified fatty acids are predictive of cancer mortality but not of coronary heart disease mortality: results from the Paris prospective Study[J]. Am J Epidemiol. 2001;153(3):292–8.
14. Pilz S, Scharnagl H, Tiran B, et al. Free fatty acids are independently associated with all-cause and cardiovascular mortality in subjects with coronary artery disease[J]. J Clin Endocrinol Metabolism. 2006;91(7):2542–7.
15. Pilz S, Scharnagl H, Tiran B, et al. Elevated plasma free fatty acids predict sudden cardiac death: a 6.85-year follow-up of 3315 patients after coronary angiography[J]. Eur Heart J. 2007;28(22):2763–9.
16. Pan Y, Wu TT, Mao XF, et al. Decreased free fatty acid levels associated with adverse clinical outcomes in coronary artery disease patients with type 2 diabetes: findings from the PRACTICE study[J]. Eur J Prev Cardiol. 2023;30(8):730–9.
17. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)[J]. Eur Heart J. 2018;39(33):3021–104.
18. Nathan DM. Diabetes: advances in diagnosis and treatment[J]. JAMA. 2015;314(10):1052–62.
19. Bartolomaeus H, Balogh A, Yakoub M, et al. Short-chain fatty acid propionate protects from hypertensive cardiovascular damage[J]. Circulation. 2019;139(11):1407–21.
20. Liu HH, Cao YX, Jin JL, et al. Lipoprotein (a), hypertension, and cardiovascular outcomes: a prospective study of patients with stable coronary artery disease[J]. Hypertens Res. 2021;44(9):1158–67.
21. Shieh SM, Shen M, Fuh MMT, et al. Plasma lipid and lipoprotein concentrations in Chinese males with coronary artery disease, with and without hypertension[J]. Atherosclerosis. 1987;67(1):49–55.
22. Hennes MM, I, O'Shaughnessy IM, Kelly TM, et al. Insulin-resistant lipolysis in abdominally obese hypertensive individuals: role of the renin-angiotensin system[J]. Hypertension. 1996;28(1):120–6.
23. Bm E. Obesity hypertension is relate more to insulin's fatty acid than glucose action[J]. Hypertension. 1996;27:723–8.
24. Fagot-Campagna A, Balkau B, Simon D, et al. High free fatty acid concentration: an independent risk factor for hypertension in the Paris prospective Study[J]. Int J Epidemiol. 1998;27(5):808–13.
25. Tabara Y, Takahashi Y, Kawaguchi T, et al. Association of serum–free fatty acid level with reduced reflection pressure wave magnitude and central blood pressure: the Nagahama study[J]. Hypertension. 2014;64(6):1212–8.
26. Weber T, Auer J, O'Rourke MF, et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease[J]. Circulation. 2004;109(2):184–9.
27. Nürnberger J, Keflioglu-Scheiber A, Saez AMO, et al. Augmentation index is associated with cardiovascular risk[J]. J Hypertens. 2002;20(12):2407–14.
28. Spiller S, Blüher M, Hoffmann R. Plasma levels of free fatty acids correlate with type 2 diabetes mellitus[J]. Diabetes Obes Metabolism. 2018;20(11):2661–9.
29. Ragheb R, Shanab GML, Medhat AM, et al. Free fatty acid-induced muscle insulin resistance and glucose uptake dysfunction: evidence for PKC activation and oxidative stress-activated signaling pathways[J]. Biochem Biophys Res Commun. 2009;389(2):211–6.
30. Pereira S, Park E, Mori Y, et al. FFA-induced hepatic insulin resistance in vivo is mediated by PKCδ, NADPH oxidase, and oxidative stress[J]. Am J Physiology-Endocrinology Metabolism. 2014;307(1):E34–46.
31. Stefanovski D, Punjabi NM, Boston RC, et al. Insulin action, glucose homeostasis and free fatty acid metabolism: insights from a novel model[J]. Front Endocrinol. 2021;12:625701.
32. Gerich JE. Contributions of insulin-resistance and insulin-secretory defects to the pathogenesis of type 2 diabetes mellitus[C]//Mayo Clinic Proceedings. Elsevier, 2003, 78(4): 447–456.
33. Porte D Jr. Clinical importance of insulin secretion and its interaction with insulin resistance in the treatment of type 2 diabetes mellitus and its complications[J]. Diab/Metab Res Rev. 2001;17(3):181–8.
34. da Silva AA, do Carmo JM, Li X, et al. Role of hyperinsulinemia and insulin resistance in hypertension: metabolic syndrome revisited[J]. Can J Cardiol. 2020;36(5):671–82.
35. Azekoshi Y, Yasu T, Watanabe S, et al. Free fatty acid causes leukocyte activation and resultant endothelial dysfunction through enhanced angiotensin II production in mononuclear and polymorphonuclear cells[J]. Hypertension. 2010;56(1):136–42.
36. Myers MA, McPhail LC, Snyderman R. Redistribution of protein kinase C activity in human monocytes: correlation with activation of the respiratory burst[J]. Journal of immunology (Baltimore, Md.: 1950), 1985, 135(5): 3411–3416.
37. Doctrow SR, Folkman J. Protein kinase C activators suppress stimulation of capillary endothelial cell growth by angiogenic endothelial mitogens[J]. J Cell Biol. 1987;104(3):679–87.
38. Osol G, Laher I, Cipolla M. Protein kinase C modulates basal myogenic tone in resistance arteries from the cerebral circulation[J]. Circulation research, Cecelja M, Keehn L, Ye L et al. Genetic aetiology of blood pressure relates to aortic stiffness with bi-directional causality: evidence from heritability, blood pressure polymorphisms, and Mendelian randomization[J]. European Heart Journal, 2020, 41(35): 3314-3322z.
39. Xuereb RA, Magri CJ, Xuereb RG. Arterial stiffness and its impact on cardiovascular health[J]. Curr Cardiol Rep. 2023;25(10):1337–49.
40. Watanabe S, Tagawa T, Yamakawa K et al. Inhibition of the renin-angiotensin system prevents free fatty acid–induced acute endothelial dysfunction in humans[J]. Arteriosclerosis, thrombosis, and vascular biology, 2005, 25(11): 2376–80.
41. Maison P, Byrne CD, Hales CN, et al. Hypertension and its treatment influence changes in fasting nonesterified fatty acid concentrations: a link between the sympathetic nervous system and the metabolic syndrome?[J]. Metabolism. 2000;49(1):81–7.
42. Brenner C, Galluzzi L, Kepp O, et al. Decoding cell death signals in liver inflammation[J]. J Hepatol. 2013;59(3):583–94.
43. Ramadori P, Kroy D, Streetz KL. Immunoregulation by lipids during the development of non-alcoholic steatohepatitis[J]. Hepatobiliary Surg Nutr. 2015;4(1):11.
44. Lipke K, Kubis-Kubiak A, Piwowar A. Molecular mechanism of lipotoxicity as an interesting aspect in the development of pathological states—current view of knowledge[J]. Cells. 2022;11(5):844.

Publisher's note