Non-HDL cholesterol and long-term follow-up outcomes in patients with metabolic syndrome

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Abstract

Background Non-high-density lipoprotein-cholesterol (non-HDL-C) has been identified as a potential biomarker for metabolic syndrome (MetS). However, its predictive capability for MetS varies among different ethnic groups, necessitating further investigation. This study aimed to assess the role of non-HDL-C in the early diagnosis of MetS in the Iranian population through a longitudinal study with a 10-year follow-up period.

Methods Our study enrolled 4684 individuals from the MASHAD (Mashhad Stroke and Heart Atherosclerotic Disorder) cohort who were followed for 10 years to examine the association between non-HDL-C and the incidence of MetS. Additionally, the contribution of individual MetS components to the overall burden was evaluated.

Results A total of 1599 subjects developed MetS, while 3085 did not. Non-HDL-C levels ≥ 130 were associated with a 42% higher risk of developing MetS (relative risk (RR), 1.42; 95% confidence interval (CI), 1.25–1.62). Regarding MetS components, elevated waist circumference (WC) showed the strongest association with MetS incidence (RR, 2.32; 95% CI, 1.45–2.9), whereas triglyceride (TG) levels ≥ 150 mg/dL demonstrated the weakest association (RR, 1.23; 95% CI, 1.04–1.46). Additionally, higher HDL-C levels were reported to be 20% protective against the risk of MetS (RR, 0.8; 95% CI, 0.73–0.86). Moreover, fasting blood glucose (FBG) levels ≥ 100 mg/dL were not significantly linked to MetS burden, while systolic blood pressure (BP) levels ≥ 130 mmHg or diastolic BP levels ≥ 85 mmHg increased the risk of MetS incidence (RR, 1.25; 95% CI: 1.11–1.41).

Conclusions Elevated non-HDL-C and increased WC serve as significant predictors of MetS in Iranians. Strategies targeting non-HDL-C levels and weight loss should be emphasized to mitigate the risk of MetS development.

Keywords non-HDL-C, Metabolic syndrome, Cohort study, Waist circumference, Triglyceride, Blood pressure, HDL

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Background

Metabolic syndrome (MetS) is defined as a group of cardiovascular risk factors, including glucose disorders accompanied by dyslipidemia, which significantly increase the risk of cardiovascular disease (CVD) events and the prevalence of type 2 diabetes mellitus [1–3]. Given the rising global prevalence of MetS, epidemiological studies are required to investigate its prevalence and associated risk factors across diverse groups of people [4]. In recent studies, two definitions of MetS have been utilized and compared [5]. The modified National Cholesterol Education Program Adult Treatment Panel III (ATP III) characterizes MetS in meeting at least three of five criteria, which include blood pressure≥130/85 mmHg, waist circumference (WC) over 102 cm (men) or 88 cm (women), fasting triglyceride (TG) level≥150 mg/dL, fasting high-density lipoprotein-cholesterol (HDL-C)<40 mg/dL (men) or 50 mg/dL (women), and fasting blood glucose (FBG)≥100 mg/dL [6]. On the other hand, the International Diabetes Foundation (IDF) criteria for defining MetS involve the presence of obesity based on specific cutoff points for each ethnicity, in addition to meeting at least two of the ATP III criteria [4]. That is, IDF characterizes MetS more specifically, while ATP III diagnoses MetS with higher sensitivity [1]. Emerging evidence indicates that individuals with MetS are at 50–60% higher risk of cardiovascular events; therefore, early diagnosis of MetS can potentially decrease the rate of mortality and morbidity [7].

Multiple studies have highlighted the potential role of atherogenic dyslipidemia in the development of MetS, and non-high-density lipoprotein cholesterol (non-HDL-C) has been proposed as an appropriate marker for identifying MetS prevalence, as it reflects all atherogenic particles [8–11]. Unlike LDL-C, non-HDL-C refers to the cholesterol content found in all the lipoproteins that contribute to atherosclerosis. Therefore, subtracting HDL cholesterol from the total cholesterol yields the non-HDL cholesterol value, which represents the cholesterol carried by all the lipoproteins except HDL. Regarding the linkage between MetS and non-HDL-C, previous evidence demonstrated that individuals with MetS had higher levels of non-HDL-C [12]. Non-HDL-C offers the advantage of not being affected by the prandial situation and is easily applicable in clinical practice [13]. In addition, the predictive ability of non-HDL-C may vary in different ethnicities, emphasizing the need to validate the association between MetS and non-HDL-C among diverse populations [14]. We aimed to investigate the explicit and long-term contribution of non-HDL-C to the incidence of MetS among an Iranian population, utilizing recent data and a 10-year follow-up period.

Methods

Study design

The Mashhad stroke and heart atherosclerotic disorder (MASHAD) study commenced in 2010 and is scheduled to extend until 2020 [15]. The population size of Mashhad, obtained from the national Iranian census conducted in 2006, was used to estimate the total population. Participants for the study were selected from three specific regions in Mashhad, situated in the northeastern part of Iran, employing a stratified cluster random sampling method. The MASHAD cohort study recruited subjects aged 35–65 years who had no previous history of coronary artery disease (CAD), stroke, or peripheral arterial disease [15]. Additionally, subjects were not taking any medications for hypertension, diabetes, or abnormal lipid levels. Individuals who completed follow-up were evaluated based on a cardiovascular disease questionnaire and electrocardiography. The eligibility of the individuals was determined through physical examination and medical interviews conducted by cardiologists. The medical examinations were performed by two interventional cardiologists and one electrophysiologist using data obtained from computerized tomography (CT) angiography, angiography, stress echocardiography, and exercise tolerance testing. Prior to participation, all the study participants provided informed written consent. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences.

Follow-up

Over the 10-year follow-up period, individuals were examined for MetS burden. The incidence of MetS was considered our primary end point and was adjudicated by two independent cardiologists who were blinded to all the participants` results. The diagnosis of MetS in the present study was based on the criteria set by IDF with specific cutoff points for the Middle East population [16]. The criteria for defining abdominal obesity using WC vary across different ethnic groups and global regions. Although IDF provides specific cutoff points for Europeans (94 cm in men and 80 cm in women), there is a lack of updated data on the normal range of WC in Middle Eastern regions. Consequently, the IDF recommends using the European cutoff points as a reference to define the normal range of WC in these regions [17, 18]. According to these criteria, subjects with central obesity based on WC≥94 cm in males and ≥80 cm in females plus having at least two of the following factors were considered positive for MetS: (1): systolic blood pressure (SBP)≥130 mmHg or diastolic blood pressure (DBP)≥85 mmHg, or currently taking hypertension medication; (2) HDL<40 mg/dL in males and <50 mg/dL in females, or currently taking medication; (3) TG≥150 mg/dL, or currently taking medication for higher TG levels; and (4)

FBG≥100 mg/dL, or previously diagnosed with type 2 diabetes. Based on these criteria, a total of 1599 subjects were diagnosed with MetS (Fig. 1).

Demographic, anthropometric, and biochemical data

The data on demographic and anthropometric variables, including age, sex, weight, BMI, WC, hip circumference (HC), waist hip ratio (WHR), SBP, and DBP, were gathered. The levels of blood glucose, cholesterol, TG, HDL-C, low-density lipoprotein-cholesterol (LDL-C), non-HDL-C, high-sensitivity C-reactive protein (hsCRP), and uric acid were measured [19]. To measure total cholesterol, LDL-C, TG, and HDL-C, enzyme-linked assays on a multiple sample analyzer (Parsazmun, Karaj, Iran) were used [19]. To calculate the non–HDL-C level, the HDL concentration was subtracted from the total cholesterol level. The standard suggested cutoff point for non-HDL-C (130 mg/dL) was applied in our study.

Statistical analyses

All statistical analyses were performed using SPSS software, version 22. Mean±SD, median and interquartile range were reported for normally and nonnormally distributed parameters. Baseline characteristics of participants were compared by Student's t test for normally distributed data and χ2 for categorical data. To analyze parameters with a skewed distribution, the Mann–Whitney test was used. Demographic and biochemical variables were compared between the two groups of participants. The association between non-HDL-C and MetS and its components was evaluated using Cox regression model analysis after adjustment for age, sex, marriage status, job status and education level. Finally, *P* values less than 0.05 were considered significant.
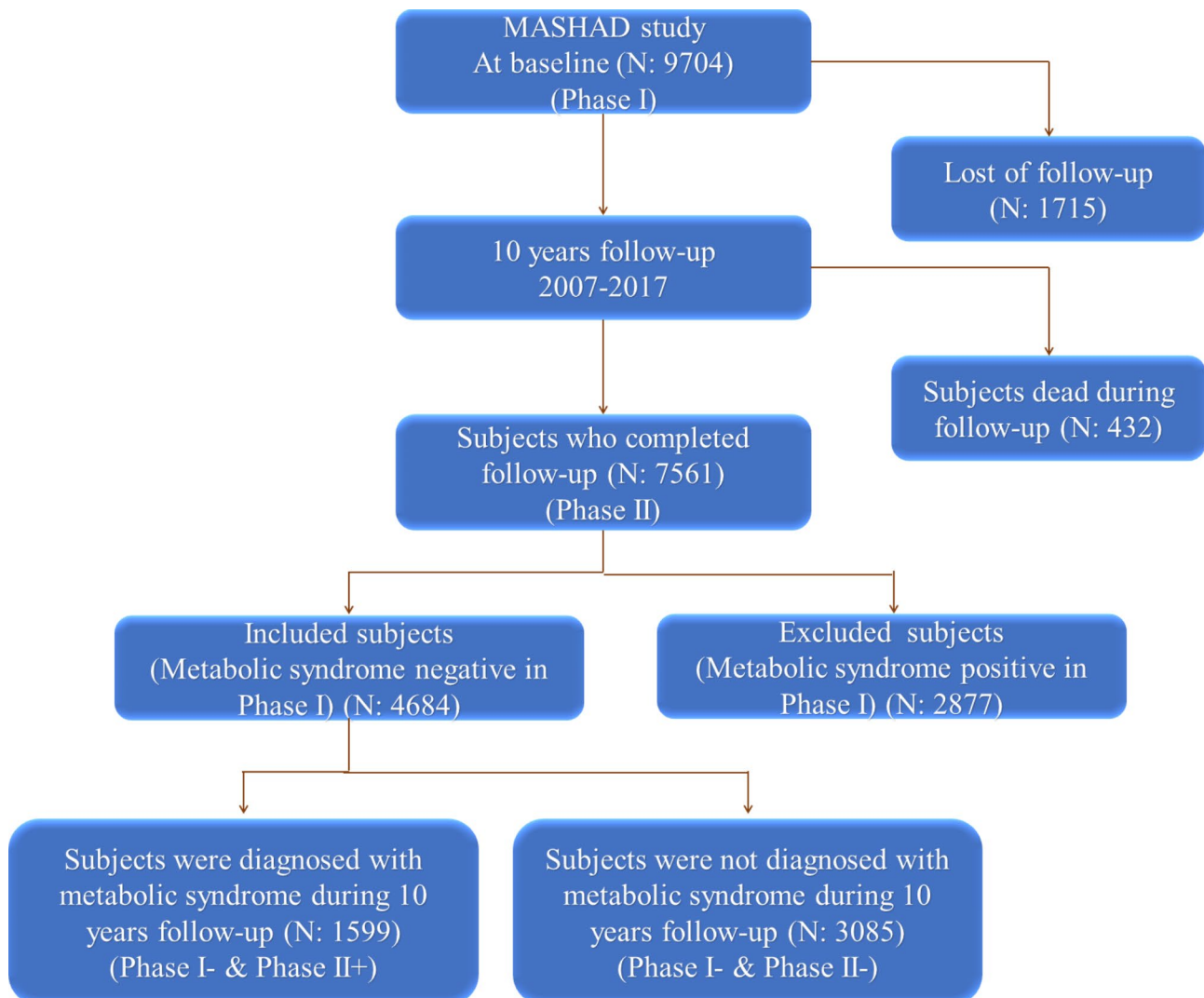

Fig. 1 Flowchart of the study

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Results

Baseline characteristics of participants

A total of 4684 participants were investigated and were divided into two groups: healthy individuals and MetS patients. Accordingly, 1599 individuals (31% men) with a mean age of 47.03 years old were evaluated in the MetS group, while the healthy controls comprised 3085 subjects (52.6% men) with an average age of 46.15 years old. All anthropometric and biochemical values differed significantly between the two groups except for HDL-C level and smoking (Table 1).

The prevalence of the components of MetS among the subjects

As illustrated in Fig. 2, the prevalence of each criterion for MetS was compared in the two groups of healthy individuals and MetS patients. All the criteria differed significantly between the two groups except for FBG≥100 mg/dL.

In comparison to the control group, a total of 66.1% of individuals who were diagnosed with MetS after follow-up had non-HDL-C≥130 mg/dL (*P*<0.001). Furthermore, approximately 79.6% of subjects in the MetS group comprised men with WC≥94 cm and women who had WC≥80 cm compared to the control group (p<0.001). The results showed that 49.9% of the group with MetS and 44.3% of the subjects in the healthy group had SBP≥130 mmHg or DBP≥85 mmHg (p<0.001). A total of 58.5% of individuals with MetS included men with HDL<40 mg/dL and women with HDL<50 mg/dL in comparison to the control group (p<0.001). There was no significant difference regarding FBG among the two groups of participants (p=0.53).

Association of non-HDL-C and five components of MetS with the occurrence of MetS after a 10-year follow-up

As shown in Table 2, non-HDL-C was stratified by levels, and non-HDL-C<130 mg/dL was considered as a reference in our analysis. The relative risk (RR) for elevated non-HDL-C was estimated as 1.42 (95% confidence interval (CI), 1.25–1.62) for the occurrence of MetS after 10 years. Regarding the five components of MetS, elevated WC had the highest contribution to the incidence of MetS among patients (RR, 2.32; 95% CI, 1.45–2.9), and TG levels≥150 mg/dL indicated the lowest association with the occurrence of MetS (RR, 1.23; 95% CI, 1.04–1.46). Our analysis demonstrated that the association between MetS incidence and FBG≥100 mg/dL was not statistically significant after a 10-year follow-up (RR, 1.08; 95% CI, 0.84–1.37). Moreover, there was a significant contribution of higher HDL-C levels to the occurrence of MetS (RR, 0.8; 95% CI, 0.73–0.86). We also found that BP≥130 mmHg or DBP≥85 mmHg could increase the risk of MetS (RR, 1.25; 95% CI, 1.11–1.41).

Discussion

The key finding of the present study is that elevated non-HDL-C levels are significantly associated with MetS burden. Individuals with increased non-HDL-C levels are at approximately 42% greater risk of clustering metabolic abnormalities, which can further promote the likelihood of CVD development in their lifetime.

Table 1 Baseline characteristics of patients according to have MetS after 10-year follow-up in MASHAD cohort study

Variables		Healthy	MetS	P value
N (4684)		3085	1599	
Anthropometrics				
Age (year)		46.15 ± 8.01	47.03 ± 7.81	< 0.001
Sex (n%)	Male (n%)	1622 (52.6%)	496 (31%)	< 0.001
	Female (n%)	1463 (47.4%)	1103 (69%)	
Smoking	No	1170 (73.2%)	2137 (69.3%)	0.061
	Ex smoker	130 (8.1%)	285 (9.2%)	
	Current	299 (18.7%)	663 (21.5%)	
Marriage	Single	13 (0.8%)	17 (0.6%)	< 0.001
	Married	1482 (92.7%)	2967 (96.2%)	
	Divorced	28 (1.8%)	31 (1%)	
	Widow	76 (4.8%)	70 (2.3%)	
Job	Employee	539 (33.7%)	1511 (49%)	< 0.001
	Unemployed	933 (58.3%)	1277 (41.4%)	
	Retired	127 (7.9%)	295 (9.6%)	
Education level	Low	902 (56.4%)	1384 (44.9%)	< 0.001
	Moderate	550 (34.4%)	1223 (39.7%)	
	High	147 (9.2%)	475 (15.4%)	
Weight (kg)		66.67 ± 11.36	73.03 ± 11.73	< 0.001
BMI (kg/m^2)		25.45 ± 4.17	28.7 ± 4.06	< 0.001
WC (cm)		88.84 ± 10.78	96.21 ± 11.46	< 0.001
HC (cm)		99.8 ± 8.39	105.08 ± 8.52	< 0.001
WHR (cm)		0.55 ± 0.07	0.6 ± 0.07	< 0.001
Blood glucose				
Glucose (mg/dL)		82.38 ± 25.6	85.81 ± 27.79	< 0.001
Lipid profile				
Cholesterol (mg/dL)		183.98 ± 36.02	190.87 ± 37.59	< 0.001
TG (mg/dL)		92(69–124)	111(86–137)	< 0.001
HDL-C (mg/dL)		45.09 ± 10.39	44.57 ± 10.02	0.1
LDL-C (mg/dL)		117.65 ± 33.95	146.29 ± 34.65	0.003
Non-HDL-C (mg/dL)		114.57 ± 32.7	138.88 ± 34.14	< 0.001
Blood pressure				
SBP (mmHg)		114.71 ± 14.95	117.46 ± 14.32	< 0.001
DBP (mmHg)		75.48 ± 10.72	76.67 ± 9.51	< 0.001
Inflammation				
HsCRP (mg/dL)		1.3(0.82–2.4)	1.69(1.02–3.47)	< 0.001
Uric acid (mg/dL)		4.44 ± 1.24	4.58 ± 1.57	0.001

Data are reported as mean±SD except for TG and hsCRP, that were reported as median (interquartile range).

Abbreviations: N, number; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; non-HDL-C, non-high-density lipoprotein-cholesterol; HsCRP, high-sensitivity C-reactive protein.
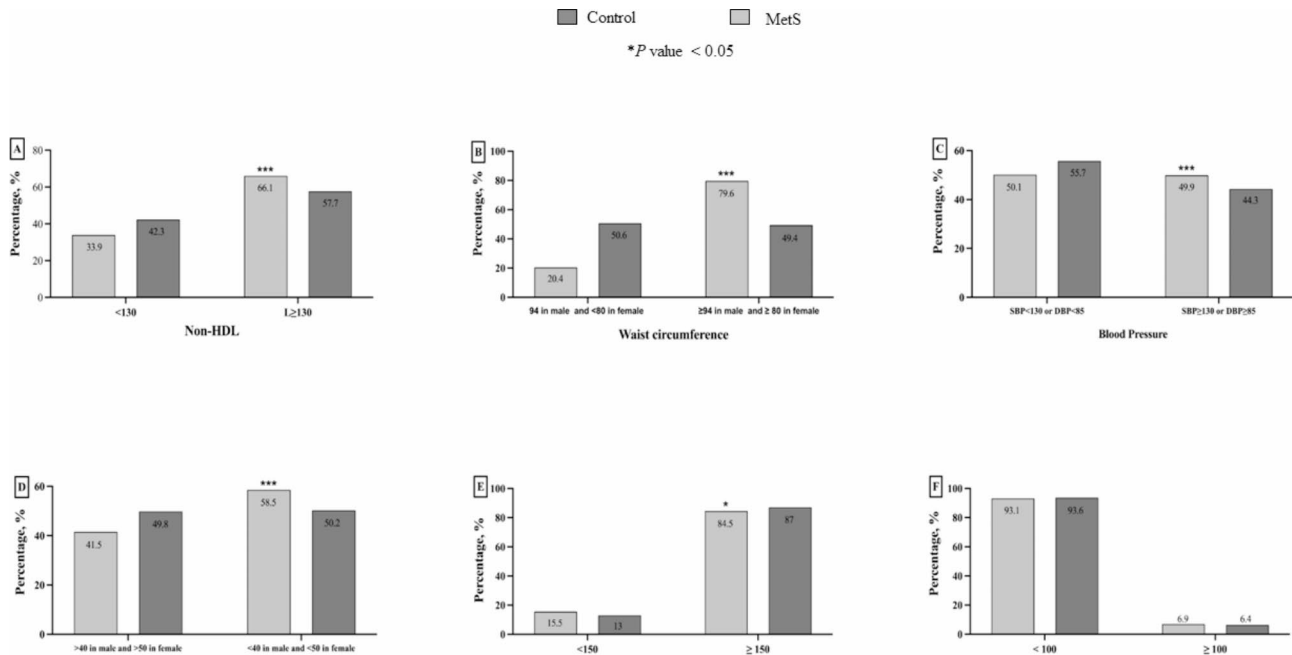
Fig. 2 The prevalence of MetS criteria among the two groups of controls and subjects with MetS. The prevalence of MetS is plotted against (A) non-HDL-C (B) waist circumference (C) blood pressure (D) HDL-C (E) triglyceride, and (F) fasting blood sugar. *P value < 0.05. Abbreviations: non-HDL-C, non-high-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose

Table 2 Risk of metabolic syndrome after 10 years follow-up according to MetS components

	P value	RR	95% CI for Exp(B)	
			Lower	Upper
Non-HDL-C ≥130 (< 130, ref)	0.000	1.428	1.259	1.62
WC ≥ 94 in male and ≥ 80 in female	0.000	2.32	1.459	2.9
BP SBP ≥ 130 or DBP ≥ 85	0.003	1.255	1.112	1.416
HDL-C < 40 in male and < 50 in female	0.039	0.801	0.738	0.869
TG ≥150	0.000	1.236	1.041	1.468
FBG ≥100	0.11	1.08	0.848	1.375

Abbreviations: MetS, metabolic syndrome; RR, risk ratio; CI, confidence interval; non-HDL-C, non-high-density lipoprotein-cholesterol; WC, waist circumference; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; TG, triglyceride; FBG, fasting blood glucose.

Note. The risk ratio was adjusted for age, sex, marriage status, job status and education level.

A series of metabolic disorders, including elevated TG, blood sugar, obesity, and hypertension, are essential for MetS development. These characteristics of MetS contribute to multiple pathogenic mechanisms, such as inflammation, oxidative stress, and endothelial dysfunction, which in turn promote atherosclerosis [20, 21]. Non-HDL-C reflects all the atherogenic lipid fractions and is an associated factor for atherosclerosis. Given the common cross-linking pathophysiology pathways shared with MetS and plaque formation, an increased level of non-HDL-C is expected to have a predictive ability in determining individuals susceptible to MetS burden [22].

Consistent with our results, a study conducted in 2022 and 60,799 individuals reported that both non-HDL-C levels higher than 247 mg/dL and 118–247 mg/dL were significantly associated with an increased risk of MetS (odds ratio (OR),17.18; 95% CI, 14.29–20.65 and OR, 3.08; 95% CI, 2.77–3.42, respectively) [23]. In addition, in a recent meta-analysis investigating studies from 2000 to 2021 among 17,860 subjects, a significant linkage between non-HDL-C and MetS was reported. The analysis demonstrated that non-HDL-C was a robust predictor of MetS in adults (OR, 3.53; 95% CI, 2.29–4.78; n, 8,549) and in children (OR, 2.27; 95% CI, 1.65–2.90; n, 9,311). Moreover, when considering the two different definitions for MetS, non-HDL-C still showed a significant contribution to the development of MetS based on ATP III (OR, 3.77; 95% CI, 2.14–5.39; n, 12,490) and IDF (OR, 2.71; 95% CI, 1.98–3.44; n, 5,370). Since non-HDL-C was associated with the risk of MetS utilizing both MetS definitions, measurement of non-HDL-C could predict the subjects at elevated risk of MetS regardless of MetS criteria. This meta-analysis also reported that non-HDL-C had a notable linkage with MetS-associated factors, including hypertriglyceridemia, obesity, diabetes, and hypertension [24].

In contrast, Lee kh. et al. investigated 511 women to find the relationship between non-HDL-C and MetS

using ATP III and IDF criteria. As demonstrated by this study, by comparing non-HDL-C>151 mg/dL to non-HDL-C<122 mg/dL, non-HDL-C was a predictive marker for MetS according to the ATP III definition (OR, 4.005; 95% CI, 1.151–13.939), but the association between non-HDL-C and MetS using IDF criteria was not statistically significant (OR, 1.77; 95% CI, 0.51–6.16) [25]. Looking at the inconsistent findings between the study by Lee kh. et al., and the present study, cross-sectional studies cannot provide causality and long-term effects of non-HDL-C with respect to MetS incidence. In addition, focusing only on the female population may not provide a comprehensive representation of the total society. Further investigations in large population studies involving both male and female participants are required to better understand the association between non-HDL-C and the development of MetS.

Our findings indicated that among the five MetS components, WC had the highest contribution to the MetS burden after a 10-year follow-up. As indicated by our results, elevated WC was responsible for an approximately 2.3-fold higher risk of metabolic disorders after adjustment for age, sex, marriage status, job status and education level. In agreement with our findings, a recent study conducted on 5,026 individuals showed higher WC as a significant marker in determining subjects having greater odds of MetS incidence in both men and women (men: OR, 6.38; 95% CI, 5.07–8.02 and women: OR, 3.98; 95% CI, 3.39–4.69) [26]. The observed increase in both non-HDL-C and WC among the participants may be influenced by dietary intake and behavioral lifestyle, which have a role in abnormal metabolic status and further contribute to a higher risk of MetS burden. A sedentary lifestyle and lack of physical activity, consuming a high-calorie diet and unhealthy fat and sugars lead to both lipid abnormalities and weight gain that can further increase the likelihood of having elevated WC and non-HDL-C levels [27, 28]. Moreover, some other reasons can contribute to higher WC and non-HDL-C, such as hormonal imbalance, including thyroid dysfunction and insulin resistance, which highlight the importance of educating subjects about regular monitoring and health check-ups [29, 30]. Reductions in non-HDL-C and WC will subsequently reduce the risk of MetS-associated risk factors and MetS burden through different pathways, including reducing atherogenic lipid factors, modulating inflammatory and oxidative stress pathways, and enhancing endothelial function [31, 32].

The present study demonstrated that individuals with elevated BP and TG are exposed to an increased risk of having abnormal metabolic disorders in long-term follow-up. Consistent with our evidence, a recent cohort study recruiting 2,935 middle-aged Chinese individuals with a 3-year follow-up showed a higher risk of MetS

incidence in participants with higher BP than in the normotensive group (hazard ratio (HR), 1.823; 95% CI, 1.538–2.162) [33]. With respect to the significant association between TGs and metabolic disorders in our study, investigating the population in southern Iran demonstrated a notable linkage between high TGs and MetS burden [34].

Evidence obtained from our study demonstrated a long-term association of HDL with abnormal metabolic disorders. We found a statistically significant association between reduced HDL-C levels and the risk of MetS among the Iranian population by considering HDL<40 mg/dL in men and HDL<50 mg/dL in women as reference levels (RR, 0.8; 95% CI, 0.73–0.86). Our finding was consistent with previous evidence that displayed a reverse relationship between HDL-C concentration and MetS [3]. In contrast, this association was found to be insignificant by some prospective investigations that compared two groups of healthy individuals and cardiovascular events [35, 36]. Furthermore, multiple studies have demonstrated various antiatherogenic properties of HDL including antioxidant effects, HDL lipid peroxidation, and cholesterol efflux in patients with metabolic disorders [37–39].

With respect to the association between FBG and MetS incidence, our results demonstrated no linkage between FBG and metabolic disorders after a 10-year follow-up. FBG≥100 mg/dL was not significantly associated with the risk of MetS (RR, 1.08; 95% CI, 0.85–1.38). Consistent with our finding, the same insignificant contribution of FBG to MetS development was found in a study recruiting the Iranian participants [40].

The present study recruited a large population and evaluated the association of non-HDL-C and other MetS components with the risk of metabolic abnormalities over a 10-year follow-up. Our results identified non-HDL-C, an easily applicable clinical measurement, as a robust marker for the prediction of MetS among the Iranian population.

Based on the definition criteria by IDF, the national prevalence of MetS is approximately 43.5% (42.7–44.4) in the Iranian population [41]. Several previous studies showed the predictive value of non-HDL-C and diet in the likelihood of MetS prevalence among the Iranian population [22, 42, 43].

Study strengths and limitations

The current study is among the first to explore the association between non-HDL-C and specific MetS components, focusing on a large Iranian population and demonstrating the linkage of those components with MetS prevalence in a longitudinal design. Our study addressed the research gap regarding the association of non-HDL-C with the incidence of MetS and its

components over a long follow-up period. Our findings have clinical implications and provide information for health care settings involved in MetS management and prevention by indicating the predictive value of each MetS component and the long-term impact of higher non-HDL-C levels on the development of MetS. Some limitations in our study should be addressed. As we focused on a specific population (Iranian subjects), the generalizability of our findings is limited. Different races may have variations in genetic background, lifestyle, and health care factors, which may influence the risk and prevalence of MetS. Moreover, although we studied the long-term effects of non-HDL-C and different MetS components on the prevalence of MetS over a 10-year follow-up, further clinical trials and prospective cohorts could establish causality for the associations. Furthermore, we adopted the IDF criteria for MetS diagnosis in the present study, which may limit the comparability of our findings to other studies using different criteria for MetS definition. Finally, no measurement of apolipoprotein-B (APO-B) concentration was provided in the present study, which may provide additional insights into the linkage between MetS incidence and lipid profile. Future research can further expand upon our findings and consider the external validity of our results through inclusion of different ethnicities, implementation of interventional studies, and measurement of additional biomarkers such as APO-B to enhance the accuracy of prediction in MetS burden.

Conclusion

An explicit association of non-HDL-C with abnormal metabolic disorders was found in our study in which individuals with elevated non-HDL-C were exposed to an approximately 42% increased risk of MetS in their lifetime. The present study suggested that in terms of establishing a platform for the prevention of MetS prevalence, clinicians should consider non-HDL-C lowering therapy among subjects with high non-HDL-C concentrations. Furthermore, among the various components of MetS, WC was found to have the highest contribution to metabolic disorders, as higher WC was associated with a 2.3 times greater risk of MetS incidence after a 10-year follow-up, demonstrating that weight loss strategies, specifically abdominal fat management, can benefit subjects susceptible to MetS development.

List of abbreviations

MetS	Metabolic syndrome
CVD	Cardiovascular disease
ATP III	Adult Treatment Panel III
WC	Waist circumference
TG	Triglyceride
HDL	High-density lipoprotein cholesterol
FBG	Fasting blood glucose
IDF	International Diabetes Foundation
Non-HDL-C	Non-high-density lipoprotein cholesterol
MASHAD	Mashhad stroke and heart atherosclerotic disorder
CAD	Coronary artery disease
CT	Computerized tomography
HTN	Hypertension
BMI	Body mass index
HC	Hip circumference
WHR	Waist hip ratio
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
LDL	Low-density lipoprotein cholesterol
HsCRP	High-sensitivity C-reactive protein
RR	Relative risk
CI	Confidence interval
OR	Odds ratio
HR	Hazard ratio
APO-B	Apolipoprotein B

Authors' contributions
All authors contributed to the study's conception and design. Sara Samadi, Mohsen Mouhebati, and Majid Ghayour Mobarhan provided the conception and design of research. Fatemeh Vazirian, Susan Darroudi, Hamid Reza Rahimi, and Mohamad Reza Latifi performed experiments, analyzed data, and interpreted the results of experiments. Behrouz Shakeri and Amir Hooshang Mohammadpour prepared figures and tables. Fatemeh Vazirian, Samaneh Abolbashari, and Habibollah Esmaily wrote the manuscript. All authors read and approved the final manuscript.

Data availability
Datasets analyzed during the study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Informed written consent was provided by all study participants. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Nilsson PM, et al. The metabolic syndrome and incidence of cardiovascular disease in non-diabetic subjects—a population-based study comparing three different definitions. Diabet Med. 2007;24:464–72.
2. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the american Diabetes Association and the European Association for the study of diabetes. Diabetes Care. 2005;28:2289–304.
3. Kharazmi-Khorassani S, Kharazmi-Khorassani J, Rastegar-Moghadam A, Samadi S, Ghazizadeh H, Tayefi M, Ferns GA, Ghayour-Mobarhan M, Avan A, Esmaily H. Association of a genetic variant in the angiopoietin-like protein 4 gene with metabolic syndrome. BMC Med Genet. 2019;20:1–6.
4. Zhu L, Spence C, Yang JW, Ma GX. The IDF definition is better suited for screening metabolic syndrome and estimating risks of diabetes in asian american adults: evidence from NHANES 2011–2016. J Clin Med 2020, 9.
5. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech. 2009;2:231–7.
6. Saif-Ali R, Kamaruddin NA, Al-Habori M, Al-Dubai SA, Ngah WZW. Relationship of metabolic syndrome defined by IDF or revised NCEP ATP III with glycemic control among Malaysians with type 2 diabetes. Diabetol Metab Syndr. 2020;12:67.
7. Qiao Q, Gao W, Zhang L, Nyamdorj R, Tuomilehto J. Metabolic syndrome and cardiovascular disease. Ann Clin Biochem. 2007;44:232–63.
8. Ruotolo G, et al. Dyslipidemia of the metabolic syndrome. Curr Cardiol Rep. 2002;4:494–500.
9. Nie G, Hou S, Zhang M, Peng W. High TG/HDL ratio suggests a higher risk of metabolic syndrome among an elderly chinese population: a cross-sectional study. BMJ Open. 2021;11:e041519.
10. Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, Bush TL. Non–high-density lipoprotein cholesterol level as a predictor of Cardiovascular Disease Mortality. Arch Intern Med. 2001;161:1413–9.
11. Tsai S-S, Lin Y-S, Chen S-T, Chu P-H. Metabolic syndrome positively correlates with the risks of atherosclerosis and diabetes in a chinese population. Eur J Intern Med. 2018;54:40–5.
12. Khan SH, Asif N, Ijaz A, Manzoor SM, Niazi NK, Fazal N. Status of non-HDL-cholesterol and LDL-cholesterol among subjects with and without metabolic syndrome. J Pak Med Assoc. 2018;68:554–8.
13. Desmeules S, Arcand-Bossé JF, Bergeron J, Douville P, Agharazii M. Nonfasting non-high-density lipoprotein cholesterol is adequate for lipid management in hemodialysis patients. Am J Kidney Dis. 2005;45:1067–72.
14. Angoorani P, Khademian M, Ejtahed H-S, Heshmat R, Motlagh ME, Vafaeenia M, Shafiee G, Mahdivi-Gorabi A, Qorbani M, Kelishadi R. Are non-high–density lipoprotein fractions associated with pediatric metabolic syndrome? The CASPIAN-V study. Lipids Health Dis. 2018;17:257.
15. Ghayour-Mobarhan M, Moohebati M, Esmaily H, Ebrahimi M, Parizadeh SM, Heidari-Bakavoli AR, Safarian M, Mokhber N, Nematy M, Saber H, et al. Mashhad stroke and heart atherosclerotic disorder (MASHAD) study: design, baseline characteristics and 10-year cardiovascular risk estimation. Int J Public Health. 2015;60:561–72.
16. Xi B, Zong X, Kelishadi R, Litwin M, Hong YM, Poh BK, Steffen LM, Galcheva SV, Herter-Aeberli I, Nawarycz T, et al. International Waist circumference percentile cutoffs for central obesity in children and adolescents aged 6 to 18 years. J Clin Endocrinol Metab. 2020;105:e1569–1583.
17. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006;23:469–80.
18. Ahranjani Sh A, Kashani H, Forouzanfar M, Meybodi HA, Larijani B, Aalaa M, Mohajeri-Tehrani M. Waist circumference, weight, and body Mass Index of Iranians based on National Non-Communicable Disease Risk factors Surveillance. Iran J Public Health. 2012;41:35–45.
19. Sadabadi F, Moohebati M, Heidari-Bakavoli A, Darroudi S, Nazarpour S, Khorrami Mohebbseraj MS, Asadi Z, Esmaeily H, Ghazizadeh H, Barati E. Factors Associated with the incidence of Coronary Heart Disease in the Mashad: a Cohort Study. J Biostatistics Epidemiol 2022, 8.
20. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735–52.
21. Xu J, Kitada M, Ogura Y, Koya D. Relationship between Autophagy and metabolic syndrome characteristics in the pathogenesis of atherosclerosis. Front Cell Dev Biol. 2021;9:641852.
22. Ghodsi S, Meysamie A, Abbasi M, Ghalehtaki R, Esteghamati A, Malekzadeh MM, Asgari F, Gouya MM. Non-high-density lipoprotein fractions are strongly associated with the presence of metabolic syndrome independent of obesity and diabetes: a population-based study among iranian adults. J Diabetes Metab Disord. 2017;16:25.
23. Wang S, et al. Threshold Effects in the relationship between serum non-high-density lipoprotein cholesterol and metabolic syndrome. Diabetes Metab Syndr Obes. 2019;12:2501–6.
24. Mardi P, Abdi F, Ehsani A, Seif E, Djalalinia S, Heshmati J, Shahrestanaki E, Gorabi AM, Qorbani M. Is non-high-density lipoprotein associated with metabolic syndrome? A systematic review and meta-analysis. Front Endocrinol (Lausanne). 2022;13:957136.
25. Ki-ho L, Jung-cheon S, Bum-taek K, Byum-Hee C, Jung Sun H, Choong Keun C, Joon-young C, Young-jin L, Youhern A. Non-HDL cholesterol as a risk factor of metabolic syndrome in Korean Women. J Obes Metabolic Syndrome. 2007;16:102–10.
26. Lopez-Lopez JP, Cohen DD, Ney-Salazar D, Martinez D, Otero J, Gomez-Arbelaez D, Camacho PA, Sanchez-Vallejo G, Arcos E, Narvaez C, et al. The prediction of metabolic syndrome alterations is improved by combining waist circumference and handgrip strength measurements compared to either alone. Cardiovasc Diabetol. 2021;20:68.
27. Alexander L, Christensen SM, Richardson L, Ingersoll AB, Burridge K, Golden A, Karjoo S, Cortez D, Shelver M, Bays HE. Nutrition and physical activity: an obesity Medicine Association (OMA) Clinical Practice Statement 2022. Obes Pillars. 2022;1:100005.
28. Castro-Barquero S, Ruiz-León AM, Sierra-Pérez M, Estruch R, Casas R. Dietary strategies for metabolic syndrome: a Comprehensive Review. Nutrients 2020, 12.
29. Mahdavi M, Amouzegar A, Mehran L, Madreseh E, Tohidi M, Azizi F. Investigating the prevalence of primary thyroid dysfunction in obese and overweight individuals: Tehran thyroid study. BMC Endocr Disorders. 2021;21:89.
30. Ramírez-Manent JI, Jover AM, Martinez CS, Tomás-Gil P, Martí-Lliteras P, López-González. Á A: Waist circumference is an essential factor in Predicting insulin resistance and early detection of metabolic syndrome in adults. Nutrients 2023, 15.
31. Khan AA, Mundra PA, Straznicky NE, Nestel PJ, Wong G, Tan R, Huynh K, Ng TW, Mellett NA, Weir JM, et al. Weight loss and Exercise alter the high-density lipoprotein lipidome and improve high-density lipoprotein functionality in metabolic syndrome. Arterioscler Thromb Vasc Biol. 2018;38:438–47.
32. Wang J, Miao R, Chen Z, Wang J, Yuan H, Li J, Huang Z. Age-specific association between non-HDL-C and arterial stiffness in the chinese population. Front Cardiovasc Med. 2022;9:981028.
33. Ma L, Li H, Zhuang H, Zhang Q, Peng N, Hu Y, Han N, Yang Y, Shi L. The incidence of metabolic syndrome and the valid blood pressure Cutoff Value for Predicting Metabolic Syndrome within the normal blood pressure range in the Population over 40 Years Old in Guiyang, China. Diabetes Metab Syndr Obes. 2021;14:2973–83.
34. Farmanfarma K, Ansari-Moghaddam A, Kaykhaei M, Mohammadi M, Adineh H, Aliabd H. Incidence of and factors associated with metabolic syndrome, south-east Islamic Republic of Iran. East Mediterr Health J. 2021;27:1084–91.
35. Sadabadi F, Gholoobi A, Heidari-Bakavol A, Mouhebati M, Javandoost A, Asadi Z, Saberi-Karimian M, Darroudi S, Mohebbseraj MSK, Rahmani F. Decreased threshold of fasting serum glucose for cardiovascular events: MASHAD cohort study. Rep Biochem Mol Biology. 2020;9:64.
36. Aghasizadeh M, Samadi S, Sahebkar A, Miri-Moghaddam E, Esmaily H, Souktanloo M, Avan A, Mansoori A, Ferns GA, Kazemi T. Serum HDL cholesterol uptake capacity in subjects from the MASHAD cohort study: its value in determining the risk of cardiovascular endpoints. J Clin Lab Anal. 2021;35:e23770.

37.   Annema W, Dikkers A, de Boer JF, van Greevenbroek MMJ, van der Kallen CJH, Schalkwijk CG, Stehouwer CDA, Dullaart RPF, Tietge UJF. Impaired HDL cholesterol efflux in metabolic syndrome is unrelated to glucose tolerance status: the CODAM study. Sci Rep. 2016;6:27367.

38.   Hansel B, Giral P, Nobecourt E, Chantepie S, Bruckert E, Chapman MJ, Kontush A. Metabolic syndrome is Associated with elevated oxidative stress and dysfunctional dense high-density lipoprotein particles displaying impaired antioxidative activity. J Clin Endocrinol Metabolism. 2004;89:4963–71.

39.   Samadi S, Mehramiz M, Kelesidis T, Mobarhan MG, Sahebkar AH, Esmaily H, Moohebati M, Farjami Z, Ferns GA, Mohammadpour Ah, Avan A. High-density lipoprotein lipid peroxidation as a molecular signature of the risk for developing cardiovascular disease: results from MASHAD cohort. J Cell Physiol. 2019;234:16168–77.

40.   Hadaegh F, Zabetian A, Harati H, Azizi F. Metabolic syndrome in normal-weight iranian adults. Ann Saudi Med. 2007;27:18–24.

41.   Tabatabaei-Malazy O, Saeedi Moghaddam S, Rezaei N, Sheidaei A, Hajipour MJ, Mahmoudi N, Mahmoudi Z, Dilmaghani-Marand A, Rezaee K, Sabooni M, et al. A nationwide study of metabolic syndrome prevalence in Iran; a comparative analysis of six definitions. PLoS ONE. 2021;16:e0241926.

42.   Amini MR, Shahinfar H, Djafari F, Sheikhhossein F, Naghshi S, Djafarian K, Clark CC, Shab-Bidar S. The association between plant-based diet indices and metabolic syndrome in iranian older adults. Nutr Health. 2021;27:435–44.

43.   Shahavandi M, Amini MR, Shahinfar H, Shab-Bidar S. Major dietary patterns and predicted cardiovascular disease risk in an iranian adult population. Nutr Health. 2021;27:27–37.

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