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Original Article

Low-density lipoprotein cholesterol and metabolic syndrome in an Iranian high-risk population

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ABSTRACT

Aim: Currently, one study support the hypothesis that low-density lipoprotein cholesterol (LDLC) is associated with metabolic syndrome (MetS) independent of pre-existing components of MetS. In this study we further evaluated the ability of the LDLC to predict prevalence and incidence of MetS in an Iranian high-risk population.

Materials and methods: We analyzed baseline ($n = 3396$) and 7-year follow-up data ($n = 865$) in first-degree relatives (FDR) of consecutive patients with type 2 diabetes 30–70 years old. We used logistic regression to estimate the odds ratio (OR) for prevalent MetS, and Cox proportional hazard models to estimate hazard ratio (HR) for incident MetS across quartiles of LDLC and plotted a receiver operating characteristic (ROC) curve to assess discrimination.

Results: The highest quartile of LDLC compared with the lowest quartile was associated with MetS in both the prevalent (OR 1.39, 95% CI 1.13, 1.70) and incident in unadjusted models (HR 1.24, 95% CI 1.03, 1.49). Adjusted for age, gender and pre-existing components of MetS attenuated association for both prevalent (OR 1.15, 95% CI 0.83, 1.59) and incident MetS (HR 1.13, 95% CI 0.93, 1.38). The area under the ROC was 52.8% (95% CI 50.7, 55.0) for prevalent and 51.8% (95% CI 47.2, 56.3) for incident MetS.

Conclusion: The results of this study highlight that LDLC level is not a robust predictor of MetS, independent of age, gender or the pre-existing components of MetS, in high-risk individuals in Iran.

1. Introduction

Metabolic syndrome (MetS), a cluster of metabolic and cardiovascular risk factors including obesity, dyslipidemia, hypertension, and insulin resistance leads to increased risk of cardiovascular diseases and type 2 diabetes [1]. It is estimated that around a quarter of the world's adult population have MetS [2,3] and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome [4]. People with MetS have a fivefold greater risk of developing type 2 diabetes [5]. Thus, having MetS means having a significantly reduced quality and quantity of life. The cause of the syndrome remains obscure but the pathophysiology seems to be largely attributable to insulin resistance, excessive flux of fatty acids, endothelial dysfunction, and a chronic proinflammatory state [1]. There is no specific treatment for MetS. Therapeutics includes lifestyle changes and pharmaceutical agents, but prevention would be preferred.

High low-density lipoprotein cholesterol (LDLC) is an established risk factor for cardiovascular disease [6] but is not included in the components of MetS, although both conditions are associated with adiposity [7].

Although there are not many supporting evidences for the association between LDLC and risk of MetS [8,9], the role of LDLC as a risk factor for MetS remains unsettled: one study reported no association [9], while a recent study performed in Japan revealed that LDLC was associated with MetS [8] and postulates that the relationship between LDLC and MetS could be attributable to

Abbreviations: BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; CI, confidence interval; FPG, fasting plasma glucose; FDR, first-degree relatives; HbA1c, glycosylated hemoglobin; HDLC, high density lipoprotein cholesterol; HC, hip circumference; HR, hazard ratio; IDPS, Isfahan Diabetes Prevention Study; LDLC, low-density lipoprotein cholesterol; MetS, metabolic syndrome; OR, odds ratio; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic curve; SD, standard deviation; WC, aist circumference; WHR, waist–hip ratio.

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endothelial dysfunction and vascular inflammation, independent of adiposity or the pre-existing components of MetS. However, while Oda [8] referred to LDLC as a predictor of MetS, it is likely that genetic factors also influence LDLC and MetS. LDLC and MetS components such as adiposity are determined by genetic and early environmental influences. The first-degree relatives (FDR) of patients with type 2 diabetes which have a genetic basis are at high risk of MetS and might be more appropriate for testing this hypothesis.

In order to fill some of these gaps, the objective of this cross-sectional and longitudinal study, therefore, was to evaluate the ability of the LDLC to predict the prevalence and incidence of MetS in an Iranian high-risk population. We hypothesized that LDLC is not associated with the incidence and prevalence of MetS.

2. Subjects and methods

2.1. Data collection

This study was conducted within the framework of the Isfahan Diabetes Prevention Study (IDPS), an ongoing cohort in central Iran to assess the various potential risk factors for diabetes in subjects with family history of type 2 diabetes (one of the main risk factors for diabetes). The recruitment methods and examination procedures of the IDPS have been described before [10]. Our study sample at baseline comprised 3396 (889 men and 2507 women) first-degree relatives (FDR) of consecutive patients with type 2 diabetes. All patients were attendees at clinics at Isfahan Endocrine and Metabolism Research Center, which is affiliated to Isfahan University of Medical Sciences, Iran. The study was conducted between the years 2003 and 2005. All participants were from Isfahan city and adjoining areas. They completed laboratory tests including a standard 75 g 2-h oral glucose tolerance test (OGTT), a questionnaire on their health status and on various potential risk factors for diabetes. Participants received follow-up tests according to Standard of Medical Care in Diabetes [11] to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed diabetes. Accordingly, if OGTT was normal at baseline, repeat testing was carried out at least at 3-year intervals. Otherwise, repeat testing was usually carried out annually. Tenets of the current version of the Declaration of Helsinki were followed, institutional ethical committee approval was granted, and an informed consent form was signed by each participant.

2.2. Follow-up and ascertainment of MetS

Cases of MetS were identified according to the joint interim statement criteria released in 2009 [12]. It was considered present when at least three of the following characteristics were observed: central obesity, defined using ethnic-specific cut points of waist (waist circumference $\geq$ 89 cm in men and $\geq$91 cm in women [13]); triglycerides $\geq$150 mg/dl; HDL $<$ 40 mg/dl in men and $<$50 mg/dl in women; blood pressure (BP) $\geq$ 130/85 mmHg or on antihypertensive medication, or raised plasma glucose, defined as fasting plasma glucose (FPG) $\geq$ 100 mg/dl.

Participants with type 2 diabetes mellitus were excluded in longitudinal study because there is controversy whether the diagnosis of MetS convey additional meaning in individuals with type 2 diabetes who should already be aggressively treated due to high cardiovascular risk. Other than these, individuals who already had MetS, or subjects with history of taking antidiabetic, or lipid-lowering agents were also excluded for longitudinal study. Among 3396 persons who participated at baseline, 1472 subjects were excluded because of diagnosis of type 1 and type 2 diabetes or MetS or with history of taking antidiabetic or lipid-lowering agents at baseline and 1059 have no follow-up, leaving 865 participants with a mean age 42.0 (6.4) (range 30–70) years for the longitudinal analysis, all of whom had at least one subsequent review during a mean (standard deviation [SD]) follow-up period of 7.0 (1.6) (range 2–9) years. Attendees at the follow-up visit did not differ significantly from non-attendees regarding most baseline characteristics: height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR) and levels of HbA1c, LDLC, triglyceride, systolic and diastolic blood pressure (BP) and obesity. However, non-attendees had slightly lower fasting plasma glucose (FPG) (98.8 mg/dl versus 105.4 mg/dl, $P < 0.001$), plasma glucose (PG) at 30 min (145.8 mg/dl versus 152.5 mg/dl, $P < 0.001$), 60 min (151.1 mg/dl versus 161.3 mg/dl, $P < 0.001$), and 120 min (120.8 mg/dl versus 132.2 mg/dl, $P < 0.001$) and cholesterol (196.4 mg/dl versus 200.1 mg/dl, $P < 0.01$), high-density lipoprotein cholesterol (HDLC) (45.0 mg/dl versus 46.2 mg/dl, $P < 0.01$) and were slightly older (43.6 year versus 43.1 year, $P < 0.05$).

2.3. Procedures

Information on age, gender, body size, HbA1c, cholesterol, LDLC, HDLC, triglycerides and BP, family and personal medical history was collected at baseline and through follow-ups. The same methodology was used for baseline and follow-up studies. The participants included siblings and children of patients with type 2 diabetes. Participants reported to clinics in the morning after an overnight fast. They were asked to abstain from vigorous exercise in the evening, and in the morning of their visit. Smokers were encouraged to abstain from smoking in the morning of the investigations. First, on arrival at the clinic, the information provided by the participants in the questionnaire on family history was verified. Then, with the subjects in light clothing and without shoes, height, weight, WC and HC were measured using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height, WC, and HC were measured to the nearest 0.5 cm with a measuring tape. The waist was measured midway between the lower rib margin and the iliac-crest at the end of gentle expiration in the standing position. Hip circumference was measured over the greater trochanters directly over the underwear. The body mass index (BMI) was calculated as the weight in kg divided by square of the height in meters. Resting BP was measured after the participants had been seated for 10 min with a mercury sphygmomanometer and appropriately sized cuffs, using standard techniques. FPG was measured with the glucose oxidase method. Participants with FPG $\geq$ 200 mg/dl or pharmacological treatment were considered as persons with diabetes. If FPG was $\geq$126 mg/dl and $<$200 mg/dl, a second FPG was measured on another day. If the second FPG was also $\geq$126 mg/dl, participants were considered as persons with diabetes. Those with FPG $<$ 126 mg/dl underwent a standard OGTT (75 g glucose 2-h) at baseline and the follow-up visits. Venous blood was sampled 0, 30, 60, and 120 min after oral glucose administration. Plasma samples were centrifuged and analyzed the same day. Impaired glucose tolerance (IGT) was defined as FPG $<$ 126 mg/dl, but the 2hPG concentration $\geq$ 140 and $<$200 mg/dl. If the FPG was in the range of 100–126 mg/dl and the 2hPG was $<$140 mg/dl, it was considered as impaired fasting glucose (IFG); whereas, if the FPG was below 100 mg/dl and the 2hPG $<$ 140 mg/dl, it was considered a sign of normal glucose tolerance [14].

Glycosylated hemoglobin (HbA1c) (measured by ion-exchange chromatography), total cholesterol, triglycerides, HDLC, LDLC were recorded. The LDLC levels were calculated with the Friedewald Equation [15] provided total triglycerides did not exceed 400 mg/dl. All blood sampling procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using enzyme-linked method.

To convert triglycerides to millimoles per liter, multiply by 0.0113; HDLC, LDLC, and total cholesterol to millimoles per liter, multiply by 0.0259; and glucose to millimoles per liter, multiply by 0.0555.

2.4. Determination of MetS incidence

Incidence was expressed as the number of cases of MetS per 100 person-years of follow-up beginning on the date of completion of the baseline examination in 2003–2005 and continuing until the occurrence of MetS, the date of the last completed follow-up, death, or end of follow-up on September 31, 2011, whichever came first.

2.5. Analysis

Statistical methods included the Student's *t*-test, the chi squared test, binary logistic regression and Cox proportional hazards models. The prevalence and incidence of MetS and its components was calculated according to the quartile of LDLC level and compared the risk of developing MetS in each quartile with the lowest category of risk (reference group). Univariate and multivariate binary logistic regression equations and Cox's proportional hazards models were fitted to identify predictors of prevalent and new-onset MetS using the SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA). Diastolic BP was not included in multivariate analysis to avoid co-linearity between systolic and diastolic BP. The ability of LDLC and each component of MetS to predict incidence and prevalence MetS were examined with receiver operating characteristic (ROC) curves and their respective areas under the curve, in which sensitivity was plotted as a function of 1-specificity. The area under the ROC curve is a global summary statistic of the discriminative value of a model, describing the probability that the LDLC is higher in an individual developing than in an individual not developing MetS. Areas under the ROC curves were compared by the algorithm developed by DeLong et al. [16]. All tests for statistical significance were two-tailed, and all were done assuming a type I error probability of <0.05.

3. Results

Baseline characteristics of the 2067 (60.9%) participants without and 1329 (39.1%) with MetS are shown in Table 1. As expected, those who had MetS were older and had higher mean weight, BMI, WC, HC, WHR, FPG, and PG at 30, 60 and 120 min, higher HbA1c, triglyceride, cholesterol, LDLC, systolic and diastolic BP and lower HDLC at baseline and a higher proportion of overweight, abdominal obesity, high BP, high fasting glucose, low HDLC, IFG and IGT. The mean (SD) age was 44.7 (6.6) years for those with and 42.6 (6.7) years for those without MetS. The mean (SD) LDLC was 123.0 (34.3) for those with and 119.0 (33.4) for those without MetS.

The baseline characteristics of the study participants by LDLC quartile in cross-sectional and longitudinal study are shown in Table 2. In comparisons of variables at baseline in cross-sectional study, all variables except triglyceride were more likely to increase and height and low HDLC was more likely to decrease across all four subject groups. In longitudinal study, age, WC, BMI, FPG, PG at 60 min, cholesterol and LDLC were also more likely to increase across all four subject groups.

Table 1
Means (SD) and proportions of selected baseline characteristics in 1329 first-degree relatives of patients with and 2067 without metabolic syndrome at baseline.

Variables	MetS Mean (SD)	No Mets Mean (SD)	Difference (95% CI)
Age (years)	44.7 (6.6)	42.6 (6.7)	2.1 (1.7, 2.6)*
Height (cm)	161.1 (8.9)	158.7 (7.8)	2.4 (1.9, 3.0)*
Weight (kg)	79.7 (11.9)	70.2 (11.1)	9.5 (8.8, 10.3)*
Body mass index (kg/m^2)	30.8 (4.4)	27.9 (3.9)	2.9 (2.6, 3.2)*
Waist circumference (cm)	95.2 (8.6)	85.6 (8.6)	9.6 (9.0, 10.2)*
Waist-to-hip ratio	0.86 (0.07)	0.81 (0.06)	0.05 (0.04, 0.06)*
Hip circumferences (cm)	110.4 (9.4)	105.7 (8.2)	4.7 (4.1, 5.3)*
Systolic BP (mmHg)	123.7 (17.4)	110.3 (14.1)	13.4 (12.3, 14.5)*
Diastolic BP (mmHg)	80.8 (12.1)	71.5 (10.8)	9.3 (8.5, 10.1)*
Baseline fasting glucose (mg/dl)	110.1 (35.5)	95.1 (20.5)	15.0 (13.1, 16.9)*
Plasma glucose 30 min (mg/dl)	163.1 (47.5)	140.7 (37.5)	22.4 (19.4, 25.4)*
Plasma glucose 60 min (mg/dl)	178.9 (62.6)	142.5 (47.9)	36.4 (32.5, 40.2)*
Plasma glucose 120 min (mg/dl)	140.9 (63.6)	117.9 (43.3)	23.0 (19.3, 26.7)*
HbA1c (%)	5.4 (1.2)	5.1 (0.9)	0.3 (0.29, 0.44)*
Triglyceride (mg/dl)	219.3 (120.8)	132.8 (71.8)	86.5 (79.9, 93.2)*
Cholesterol (mg/dl)	205.2 (40.3)	193.9 (38.9)	11.3 (8.6, 14.1)*
HDL cholesterol (mg/dl)	40.7 (9.8)	49.0 (12.1)	−8.3 (-9.1, −7.5)*
LDL cholesterol (mg/dl)	123.0 (34.3)	119.0 (33.4)	4.0 (1.6, 6.4)**
	No. (%)	**No. (%)**	
Men	477 (35.9)	412 (19.9)	16.0 (12.9, 19.1)*
Overweight (BMI ≥ 25)	1237 (93.4)	1589 (78.2)	15.2 (13.0, 17.5)*
Normal glucose tolerance	399 (30.0)	1340 (65.7)	−35.6 (−38.8, −32.4)*
Impaired fasting glucose	367 (27.6)	250 (12.2)	15.4 (12.6, 18.2)*
Impaired glucose tolerance	340 (25.6)	365 (17.9)	7.7 (4.8, 10.6)*
Abdominal obesity	1012 (77.4)	488 (24.6)	52.8 (49.8, 55.7)*
High blood pressure	705 (54.4)	249 (12.7)	41.7 (38.6, 44.8)*
High fasting glucose	841 (63.4)	475 (23.3)	40.1 (36.9, 43.3)*
High triglycerides	1023 (77.7)	471 (24.1)	53.6 (50.7, 56.5)*
Low HDL cholesterol	1049 (81.0)	939 (49.0)	32.0 (28.9, 35.1)*

Differences in the mean or percentage values of variables between metabolic syndrome and no metabolic syndrome.
CI = confidence interval.
* $P < 0.001$.
** $P < 0.01$.
CI = confidence interval.

Table 2
Mean (SD) and proportion characteristics of first-degree relatives of patients with type 2 diabetes by low-density lipoprotein cholesterol (LDLC) quartile in cross-sectional and longitudinal study, The Isfahan Diabetes Prevention Study.

Characteristic	Total	Quartiles of LDLC at cross-sectional study			
		1st (≤98.6)	2nd (98.7–118.8)	3rd (118.9–140.8)	4th (>140.8)
Participants no. (%)	3098 (100)	782 (25.2)	771 (24.9)	776 (25.0)	769 (24.8)
Age (years)	43.3 (6.5)	42.0 (6.6)	42.8 (6.2)	43.6 (6.4)†	44.9 (6.5)†‡*
Height (cm)	159.6 (8.4)	160.9 (8.5)	159.4 (8.0)†	159.3 (8.4)†	158.9 (8.5)†‡*
Weight (kg)	73.9 (12.3)	74.2 (13.0)	72.7 (12.2)	73.8 (12.2)	74.7 (11.8)‡***
Waist circumference (cm)	89.3 (9.8)	88.3 (10.3)	88.5 (9.8)	89.5 (9.6)	90.9 (9.4)†‡*
Hip circumference (cm)	107.6 (9.0)	107.3 (9.3)	107.0 (8.7)	107.6 (8.9)	108.6 (9.0)†‡**
Waist-to-hip ratio	0.83 (0.07)	0.82 (0.08)	0.83 (0.07)	0.83 (0.07)	0.84 (0.07)†‡**
Body mass index (kg/m^2)	29.0 (4.3)	28.7 (4.6)	28.6 (4.3)	29.1 (4.2)	29.6 (4.2)†‡*
FPS (mg/dl)	100.5 (26.8)	96.8 (20.7)	99.5 (24.9)	101.2 (26.5)†	104.7 (33.0)†‡*
PG 30 min (mg/dl)	148.6 (41.4)	143.6 (38.1)	144.6 (37.4)	151.1 (43.4)†‡	155.3(45.2)†‡*
PG 60 min (mg/dl)	155.9 (55.9)	148.6 (53.1)	150.3 (50.8)	159.0 (59.3)†‡	166.0 (58.4)†‡*
PG 120 min (mg/dl)	126.4 (51.9)	121.2 (45.6)	123.5 (48.3)	127.7 (54.5)	133.5 (57.6)†‡*
HbA1c (%)	5.2 (1.0)	5.1 (0.9)	5.2 (1.0)	5.2 (1.0)	5.3 (1.1)†*
Cholesterol (mg/dl)	197.4 (38.6)	156.9 (22.2)	183.9 (16.7)†	205.5 (15.9)†‡	243.9 (29.8)†‡*
LDLC (mg/dl)	120.6 (33.8)	80.4 (15.7)	108.9 (5.8)†	129.7 (6.4)†‡	164.0 (23.1)†‡*
HDLC (mg/dl)	45.8 (11.7)	44.5 (12.9)	45.0 (10.9)	45.8 (10.9)	48.0 (11.6)†‡*
Triglyceride (mg/dl)	155.1 (71.9)	160.1 (86.3)	150.2 (70.7)	150.5 (65.2)	159.4 (62.3)**
Systolic BP (mm Hg)	115.4 (16.7)	113.4 (15.9)	113.9 (16.5)	115.7 (15.9)	118.5 (17.9)†‡*
Diastolic BP (mm Hg)	75.0 (12.2)	73.6 (12.4)	74.6 (12.4)	75.1 (11.9)	76.7 (12.0)†‡*
MetS, no. (%)	1214 (39.2)	287 (36.7)	286 (37.1)	298 (38.4)†	343 (44.6)†‡**
Abdominal obesity, no. (%)	1350 (44.9)	318 (41.9)	301 (40.5)	343 (45.5)	388 (51.9)*
High BP, no. (%)	858 (28.7)	182 (24.3)	182 (24.7)	227 (30.1)	267 (35.8)*
High fasting glucose, no. (%)	1194 (38.6)	253 (32.4)	274 (35.5)	317 (40.9)	350 (45.5)*
High triglycerides, no. (%)	1355 (43.7)	350 (44.8)	315 (40.9)	326 (42.0)	364 (47.3)***
Low HDL, no. (%)	1904 (61.5)	513 (65.7)	489 (63.4)	484 (62.4)	418 (54.4)*
		Quartiles of LDLC at longitudinal study			
		1st (≤96.0)	2nd (96.1–113.8)	3rd (113.9–135.5)	4th (>135.5)
Number (%)	865 (100)	218 (25.2)	216 (25.0)	215 (24.9)	216 (25.0)
Age (years)	41.9 (6.2)	40.1 (5.2)	41.3 (6.1)	42.1 (6.2)	44.2 (6.5)†‡*
Height (cm)	158.5 (7.7)	159.7 (7.6)	158.8 (7.4)	157.7 (7.9)	157.7 (7.6)***
Weight (kg)	69.7 (10.3)	69.7 (10.7)	69.5 (10.8)	68.9 (9.6)	70.8 (10.1)
Waist circumference (cm)	85.2 (8.1)	84.1 (8.3)	85.2 (8.9)	85.0 (7.4)	86.6 (7.5)†***
Hip circumference (cm)	105.8 (7.8)	105.4 (7.9)	105.7 (8.0)	105.7 (7.9)	106.6 (7.5)
Waist-to-hip ratio	0.81 (0.06)	0.80 (0.06)	0.81 (0.06)	0.81 (0.06)	0.81 (0.06)
Body mass index (kg/m^2)	27.8 (3.7)	27.4 (3.7)	27.6 (3.9)	27.8 (3.7)	28.5 (3.4)†***
FPS (mg/dl)	92.6 (11.2)	90.5 (11.6)	92.4 (11.0)	93.1 (11.1)	94.4 (10.9)†**
PG 30 min (mg/dl)	139.9 (30.5)	137.1 (29.9)	137.1 (29.4)	141.6 (31.6)	143.9 (30.6)
PG 60 min (mg/dl)	142.0 (41.5)	139.1 (40.6)	137.6 (38.7)	141.0 (41.6)	150.4 (44.1)†‡**
PG 120 min (mg/dl)	117.2 (31.8)	117.1 (31.8)	113.7 (30.0)	117.0 (32.8)	121.1 (32.4)
HbA1c (%)	5.0 (0.7)	4.9 (0.8)	5.0 (0.8)	5.0 (0.8)	5.0 (0.6)
Cholesterol (mg/dl)	190.5 (38.0)	152.1 (24.6)	175.5 (14.1)†	198.5 (14.2)†‡	236.1 (30.2)†‡*
LDLC (mg/dl)	116.5 (33.9)	76.7 (17.3)	105.0 (5.2)†	125.2 (6.2)†‡	159.4 (24.0)†‡*
HDLC (mg/dl)	48.0 (11.7)	47.6 (13.3)	46.6 (10.4)	48.4 (10.1)	49.3 (12.5)
Triglyceride (mg/dl)	130.0 (57.4)	139.0 (73.7)	119.3 (53.2)†	124.7 (47.0)	136.9(49.7)‡*
Systolic BP (mm Hg)	109.7 (13.3)	108.9 (14.5)	109.0 (11.6)	109.3 (12.3)	111.3 (14.6)
Diastolic BP (mm Hg)	71.1 (10.4)	69.7 (9.9)	71.1 (11.1)	71.5 (9.7)	72.1 (10.7)
MetS, no. (%)	228 (26.4)	57 (26.1)	54 (25.0)	52 (24.2)	65 (30.1)
Abdominal obesity, no. (%)	187 (22.2)	42 (20.3)	44 (20.9)	46 (21.8)	55 (25.6)
High BP, no. (%)	84 (10.1)	19 (9.3)	21 (10.1)	16 (7.7)	28 (13.1)
High fasting glucose, no. (%)	196 (22.7)	39 (17.9)	41 (19.0)	56 (26.0)	60 (27.8)***
High triglycerides, no. (%)	205 (23.7)	63 (28.9)	36 (16.7)	46 (21.4)	60 (27.8)**
Low HDL, no. (%)	456 (52.8)	116 (53.5)	124 (57.4)	112 (52.1)	104 (48.1)

Data are expressed as mean (SD) or number (%).
Difference in the mean value of variables compared to the †1st quartile and ‡2nd quartile.
* $P < 0.001$.
** $P < 0.01$.
*** $P < 0.05$ comparison across all four groups.

3.1. Prevalence

Of the 3396 FDR of people with type 2 diabetes (889 men and 2507 women), 1329 had MetS (477 men and 852 women). Overall prevalence of MetS was 39.1% (95% CI: 37.5, 40.8). Prevalence of MetS was higher in men (53.7%; 95% CI: 50.4, 56.9) than women (34.0%; 95% CI: 32.1, 35.8) (Table 2). As expected, in both gender there was a statistically increasing prevalence of MetS with increasing age.

The prevalence of MetS was 44.6% (95% CI 41.1, 48.1) for participants in the highest quartile of LDLC, and 36.7% (95% CI 33.3, 40.1) for the lowest quartile. The prevalence of MetS slightly increased with increasing quartiles of LDLC. Compared with participants in the lowest quartile, the prevalence of MetS was 39% higher in those in the highest quartile at baseline (odds ratio (OR) 1.39; 95% CI: 1.13, 1.70) but not higher in those in the 3rd quartile (OR 1.08; 95% CI: 0.88, 1.32) or the 2nd quartile (OR 1.02; 95% CI: 0.83, 1.25) in unadjusted models. Controlling for age,

gender, triglycerides, HDLC, WC, and BP did not appreciably alter the OR compared to the unadjusted model. Further adjustment for FPG attenuated association for highest quartile of MetS (OR 1.15; 95% CI: 0.83, 1.59). There was no association after adjustment for FPG (Table 3).

3.2. Incidence

During 6003 (1080 men and 4923 women) person-years of follow-up, 228 (26.4%) (54 men and 174 women) incident cases of MetS occurred. The overall incidence of subsequent MetS was 3.8 (95% CI: 3.3, 4.3) per 100 person-years. Incidence rates were lower in women (3.5, 95% CI: 3.0, 4.1 per 100 person-years) than men (5.0, 95% CI: 3.8, 6.5) but the difference was not statistically significant.

The incidence of MetS was 4.5 per 100 person-years (95% CI 3.5, 5.7) for participants in the highest quartile of LDLC, and 3.6 per 100 person-years (95% CI 2.4, 4.6) for the lowest quartile. Compared with participants in the lowest quartile, the risk of MetS was 24% higher in those in the highest quartile at baseline (hazard ratio (HR) 1.24; 95% CI: 1.03, 1.49) and 21% higher in those in the 3rd quartile (HR 1.21; 95% CI: 1.003, 1.46) but not higher in the 2nd quartile (HR 1.12; 95% CI: 0.93, 1.35) in unadjusted models. Controlling for gender, triglycerides, WC, HDLC did not appreciably alter the HR compared to the unadjusted model. Further controlling for age and FPG attenuated association for highest quartile of MetS (OR 1.13; 95% CI: 0.93, 1.38). There was no association after adjustment for age (Table 3).

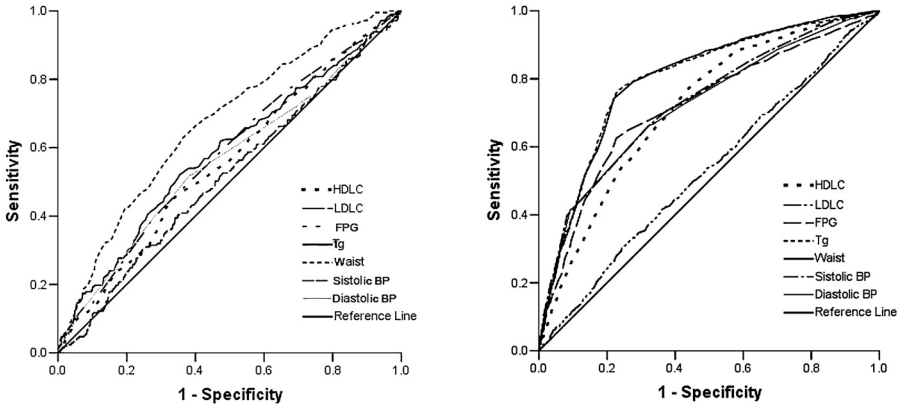
The ROC curves for the prevalence and incidence of MetS for LDLC and each component of MetS are shown in Fig. 1. In cross-sectional study, the areas under the ROC curves from the largest to the least area were 0.798 (95% CI: 0.781, 0.814) for WC, 0.797 (95% CI: 0.780, 0.814) for triglycerides, 0.729 (95% CI: 0.710, 0.748) for systolic, 0.721 (95% CI: 0.702, 0.740) for diastolic BP, and 0.717 (95% CI: 0.698, 0.737) for FPG, 0.713 (95% CI: 0.695, 0.731) for HDLC, and 0.528 (0.507, 0.550) for LDLC. All parameters were significant predictors of MetS ($P < 0.001$). LDLC had area smaller than that of other components of MetS ($P < 0.001$).

Similarly in longitudinal study, the areas under the ROC curves from the largest to the least area were also WC, triglycerides, systolic and diastolic BP, FPG, HDLC and LDLC. All parameters, except LDLC, were significant predictors for future risk of MetS ($P < 0.001$). LDLC had area smaller than that of other components of MetS ($P < 0.001$).

Table 3
Prevalence proportions and odds ratio (OR)[a] and incidence rates and hazard ratios (HR)[b] of metabolic syndrome by low-density lipoprotein cholesterol (LDLC) quartile in cross-sectional and longitudinal study, The Isfahan Diabetes Prevention Study.

	Quartiles of LDLC at cross-sectional study			
	1st (≤98.6)	2nd (98.7–118.8)	3rd (118.9–140.8)	4th (>140.8)
Number of cases (%)	287 (23.6)	286 (23.6)	298 (24.5)	343 (28.3)
Prevalence (%) (95% CI)	36.7 (33.3, 40.1)	37.1 (33.7, 40.5)	38.4 (35.0, 41.8)	44.6 (41.1, 48.1)
Odds ratio (95% CI)				
Unadjusted	1.00	1.02 (0.83, 1.25)	1.08 (0.88, 1.32)	1.39 (1.13, 1.70)**
Gender adjusted	1.00	1.04 (0.84, 1.28)	1.10 (0.89, 1.35)	1.45 (1.18, 1.78)*
Age and gender adjusted	1.00	0.99 (0.80, 1.22)	1.00 (0.81, 1.23)	1.24 (1.001, 1.53)***
Age, gender and triglyceride adjusted	1.00	1.19 (0.94, 1.53)	1.23 (0.97, 1.57)	1.37 (1.08, 1.75)**
Age, gender, triglyceride and HDLC adjusted	1.00	1.24 (0.97, 1.62)	1.36 (1.05, 1.76)***	1.80 (1.39, 2.32)*
Age, gender, triglyceride, HDLC and WC adjusted	1.00	1.29 (0.96, 1.74)	1.24 (0.93, 1.66)	1.56 (1.16, 2.09)**
Age, gender, triglyceride, HDLC, WC and systolic BP adjusted	1.00	1.35 (0.99, 1.84)	1.21 (0.89, 1.66)	1.37 (1.00, 1.87)***
Age, gender, and MetS components adjusted	1.00	1.22 (0.88, 1.71)	1.06 (0.76, 1.46)	1.15 (0.83, 1.59)
	Quartiles of LDLC at longitudinal study			
	1st (≤96.0)	2nd (96.1–113.8)	3rd (113.9–135.5)	4th (>135.5)
Number of cases (%)	218 (25.2)	216 (25.0)	215 (24.9)	216 (25.0)
Person year	1589	1519	1463	1440
Incidence/100 person-year (95% CI)	3.6 (2.4, 4.6)	3.6 (2.7, 4.6)	3.6 (2.7, 4.6)	4.5 (3.5, 5.7)
Hazard ratio (95% CI)				
Unadjusted	1.00	1.12 (0.93, 1.35)	1.21 (1.003, 1.46)***	1.24 (1.03, 1.49)***
Gender adjusted	1.00	1.12 (0.93, 1.35)	1.21 (1.002, 1.46)***	1.24 (1.03, 1.50)***
Age and gender adjusted	1.00	1.10 (0.91, 1.33)	1.18 (0.98, 1.43)	1.18 (.97, 1.43)
Gender and triglycerides adjusted	1.00	1.13 (0.94, 1.37)	1.22 (1.01, 1.48)***	1.24 (1.03, 1.50)***
Gender, triglyceride and WC adjusted	1.00	1.13 (0.93, 1.37)	1.24 (1.02, 1.50)***	1.22 (1.01, 1.48)***
Gender, triglyceride, HDLC and WC adjusted	1.00	1.15 (0.95, 1.40)	1.23 (1.01, 1.49)***	1.23 (1.01, 1.49)***
Gender, triglyceride, HDLC, WC and BP adjusted	1.00	1.13 (0.93, 1.38)	1.22 (1.00, 1.48)***	1.20 (0.99, 1.46)
Gender, triglyceride, HDLC, WC, systolic BP and FPG adjusted	1.00	1.11 (0.91, 1.35)	1.19 (0.98, 1.45)	1.17 (0.97, 1.43)
Age, gender and MetS components adjusted	1.00	1.09 (0.89, 1.33)	1.17 (0.95, 1.42)	1.13 (0.93, 1.38)

CI = confidence interval.
[a] Odds ratio (with 95% CI) calculated by binary logistic regression.
[b] Hazard ratio (with 95% CI) calculated by Cox proportional hazards models.
* $P < 0.001$.
** $P < 0.01$.
*** $P < 0.05$.



Area under the curve (95% CI)

	Longitudinal study (A)	Cross-sectional study (B)
LDL cholesterol	0.518 (0.472, 0.563)	0.528 (0.507, 0.550)
Waist circumference	0.669 (0.628, 0.710)	0.798 (0.781, 0.814)
Triglyceride	0.584 (0.538, 0.629)	0.797 (0.780, 0.814)
Systolic blood pressure	0.579 (0.534, 0.623)	0.729 (0.710, 0.748)
Diastolic blood pressure	0.563 (0.516, 0.609)	0.721 (0.702, 0.740)
Fasting plasma glucose	0.548 (0.502, 0.594)	0.717 (0.698, 0.737)
HDL	0.556 (0.513, 0.599)	0.713 (0.695, 0.731)

Fig. 1. Receiver operating characteristic (ROC) curves for low-density lipoprotein cholesterol (LDLC), triglyceride (Tg), waist circumference (WC), high-density lipoprotein cholesterol (HDLC), fasting plasma glucose (FPG), systolic and diastolic blood pressure (BP) to predict metabolic syndrome in first-degree relatives of patients with type 2 diabetes in longitudinal (A) and cross-sectional (B) study. The estimates of the area under the ROC curves and their 95% confidence intervals are shown.

4. Discussion

Current study showed that the LDLC level was not able to predict MetS independent of age or the pre-existing components of MetS, in a cohort of high-risk individuals in Iran, with an area under the ROC of 53% in prevalent and 52% in incident study. Our data are in agreement with the previous observation that LDLC is not associated with MetS [9,17]. Holvoet et al. [9] reported that LDLC was not associated with incidence MetS or with any of its components in the fully adjusted model containing oxidized LDLC. In the Insulin Resistance Atherosclerosis Study, Williams et al. [17] compared the association between the level of apolipoprotein B (apoB), which reflects the number of small dense LDLC particle in plasma, and LDLC and CVD risk factors and reported that individuals with an elevated apoB level with a normal LDLC level have higher associated CVD risks than those with an elevated LDLC level with normal apoB level. After adjusting for the LDLC level, the correlation between the apoB level and CVD risk remained significant, whereas several correlations with the LDLC became significant in the direction of lower risk after adjustment for the apoB level. In contrast, recently, Oda in a Japanese Health Screening Population found that the LDLC level is a predictor of MetS, independent of BMI or the pre-existing five components of MetS [8]. Our findings do not confirm this association in this population of FDR of people with type 2 diabetes. We found LDLC was associated with MetS in unadjusted model and no association when adjusted for age and FPG. When we controlled for age and FPG, the association of LDLC quartiles and MetS attenuated but not reached the level of statistical significant. The difference in results between the present study and the study by Oda could be partially attributed to the differences in the ethnicity, higher obesity, triglycerides, insulin resistance, younger participants and the higher length of the follow-up period and lower HDLC in our study.

Our study has several strengths and limitations. The strengths include use of a sample consisting of both men and women, performance of standard OGTT, and information on potential determinants of MetS. Selection and information bias were unlikely because of the prospective design. At follow-up, non-attendees in the entire population did not differ from attendees according to major risk factors for progression to MetS, although a difference too small to explain the high progression rate to MetS in our study was seen in the mean levels of lipid profiles and PG. Our database is one of the few that followed FDR of patients with type 2 diabetes, thereby enabling us to simultaneously control the genetic factors that may predict MetS. Our study was limited to a cohort of individuals who are at increased risk of developing type 2 diabetes and MetS, because they had a FDR with the patients with type 2 diabetes, thus, the selection bias may lead to an underestimation of associations.

In term of our definition of incidence MetS, some selection bias may be present as participants who attend for screening may have been more likely to be tested and consequently diagnosed as having MetS. Thus, participants with MetS who had lower risk may have been missed through lack of testing. However, it is necessary to validate the association of LDLC and MetS in other populations

In conclusion, these data provides further evidence that LDLC level is not a robust predictor of MetS, independent of age, gender, FPG or the pre-existing components of MetS, in high-risk individuals in Iran.

Author's contributions

Janghorbani, M. conceived and designed the study, analyzed the data and wrote the manuscript, Amini, M. recruited samples and contributed to the discussion and revision of the manuscript and obtained funding for the IDPS.

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