



Is lower low-density lipoprotein cholesterol associated with lower androgen and erectile dysfunction in men?

C. Chen ^{a,1}, H. Zhai ^{a,1}, G. Huang ^{b,1}, J. Cheng ^a, F. Xia ^a, L. Zhao ^a, Y. Chen ^a, Y. Chen ^a, B. Han ^a, Q. Li ^a, B. Jiang ^a, N. Wang ^{a,*,2}, Y. Lu ^{a,*,2}

^a Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China

^b Institute and Department of Endocrinology and Metabolism, Fengcheng Hospital, Shanghai, China

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Abstract *Background and aims:* Therapeutic possibilities now exist to lower low-density lipoprotein cholesterol (LDL-C) to very low levels. However, substantial controversy remains in clinical practice with regard to its safety, and the question of whether low LDL-C levels *per se* may provoke adverse effects in humans arises. We aimed to explore the association of LDL-C with androgen and erectile dysfunction (ED) in a general population of men.

Methods and results: A total of 4203 men without hormone replacement therapy were enrolled from 22 sites in East China. Total testosterone (T) and Free T were assessed. Free androgen index (FAI) was calculated. The IIEF-5 questionnaire was used to assess ED. We found that free T and FAI gradually and markedly increased with increasing LDL-C levels. Using linear regression, after adjusting for age, educational level, economic status, smoking status, drinking status, BMI, diabetes, and use of lipid-lowering medication, LDL-C was positively associated with free T ($B = 0.175$, 95% CI: 0.084, 0.266) and FAI ($B = 0.064$, 95% CI: 0.016, 0.112). Meanwhile, there was a U-shaped curvilinear relationship between LDL-C and prevalence of ED. In the logistic regression analysis, compared to those with LDL-C among the 10th–90th percentile, the ORs of ED in men in the lowest and highest deciles were 1.938 (95% CI: 1.121, 3.349) and 1.804 (95% CI: 1.117, 2.916), respectively.

Conclusion: Lower LDL-C levels were significantly associated with lower free T and lower FAI in a general population of men. Moreover, both low and high levels of LDL-C might be risk factors for ED.

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Introduction

Recent evidence has established that low-density lipoprotein cholesterol (LDL-C) is not only a biomarker of increased risk, but also a causal factor in the pathophysiology of atherosclerotic cardiovascular disease (ASCVD) [1].

Following the growing evidence suggesting that reducing LDL-C levels do have a beneficial role in the prevention and treatment of ASCVD, therapeutic

* Corresponding author. Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, 200011 China.

** Corresponding author. Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, 200011 China.

E-mail addresses: wnj486@126.com (N. Wang), luyingli2008@126.com (Y. Lu).

¹ These authors contributed equally to this work.

² Fax: +86 21 63136856.

possibilities now exist to lower LDL-C to very low levels [2,3]. Some scholars now even argue that the lower the LDL-C level attained, the greater the clinical benefit accrued [4]. However, substantial controversy remains in regard to its safety in clinical practice, and the question of whether low LDL-C levels *per se* may provoke adverse effects in humans arises [5].

Cholesterol is an important regulator of cell membrane fluidity and is a precursor of steroid hormones. Currently available lipid-lowering agents, particularly the emergence of proprotein convertase subtilisin kexin type 9 (PCSK9) monoclonal antibodies, can induce considerable reductions in LDL-C levels [3]. However, LDL particles serve as an important delivery vehicle for transporting cholesterol to steroidogenic tissues. There are lingering concerns that LDL-C lowering may adversely impact the capacity of steroidogenic glands to produce sex steroids, such as testosterone (T), and cause erectile dysfunction (ED).

Studies exploring the association of LDL-C with sex steroids and ED are limited and inconclusive. Although some observational studies suggested that low serum T levels were associated with high LDL-C levels [6,7], a recent Mendelian randomization analysis raised the possibility that higher T levels may be associated with higher LDL-C levels [8]. Baspinar et al. [9] also reported reducing LDL-C with a statin was significantly associated with decreased total T and free T levels and decreased ED prevalence in male hypercholesterolemic patients. However, two other studies have suggested that capacities of steroid sex production were preserved at low LDL-C levels [10,11].

Considering the conflicting results of previous studies and the lack of data on the association between LDL-C and ED in large epidemiological settings, we conducted an investigation called the Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China) in 2014–2015. We aimed to explore the association of LDL-C with sex steroids and ED in a general population of men.

Methods

Study population

SPECT-China is a cross-sectional survey on the prevalence of metabolic diseases and risk factors in East China (ChiCTR-ECS-14005052, www.chictr.org.cn). The recruitment and enrollment protocols followed in this study were previously described in detail [12–14]. Briefly, we used a stratified and cluster sampling method. The first level of sampling was stratified by urban and rural areas, and the second level was stratified by economic development area. Chinese citizens ≥ 18 years old who had lived in their current area for at least 6 months were selected. The overall response rate was 90.8%. From January 2014 to December 2015, 10,441 subjects who were 18–93 years old were recruited for the SPECT-China study from 22 sites in Shanghai, Zhejiang, Jiangxi, Jiangsu and Anhui Province, among whom 4307 men were not taking hormone replacement therapy. We further excluded participants with missing values of LDL-C ($n = 4$) or reproductive hormones

($n = 100$). Finally, a total of 4203 male subjects were enrolled in the study. The subjects were classified into 3 categories based on LDL-C level: <10 th percentile [LDL-C < 2.18 mmol/L (84 mg/dL)], 10th–90th percentile [LDL-C, 2.18–4.05 mmol/L (84–156 mg/dL)], and >90 th percentile [LDL-C > 4.05 mmol/L (156 mg/dL)].

We also categorized our subjects into four categories based on the treatment goals of LDL-C with different ASCVD risks [15]: <1.81 mmol/L (70 mg/dL), 1.81–2.58 mmol/L (70–100 mg/dL), 2.59–3.35 mmol/L (100–130 mg/dL), >3.35 mmol/L (130 mg/dL).

Ethics approval was obtained from the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. All procedures were performed in accordance with the ethical standards of the responsible committees for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Each participant gave written informed consent before data collection.

Measurements

A standard questionnaire, which was completed by the same trained investigators, was used to collect data about sociodemographic characteristics, medical history and lifestyle-related risk factors at all of the survey sites. Body height and weight were measured with the participants wearing light clothing and no shoes. BMI was calculated as weight, in kilograms, divided by height, in square meters (kg/m^2).

Venous blood samples were drawn from the participants after an overnight fast of 8 h or longer. Blood samples were stored at -20°C after being collected and shipped in dry ice by air to a central laboratory, which was certified by the College of American Pathologists, within 2–4 h of collection. Total T, estradiol (E2), luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were measured using chemiluminescence assays (SIEMENS Immulite 2000, Germany). Free T was detected using enzyme-linked immunosorbent assay (Bio-Tek ELx808, USA). Sex hormone binding globulin (SHBG) levels were detected using Cobas e601 electrochemiluminescence immunoassays (Roche, Switzerland). The minimum detection limit for each hormone was as follows: 0.7 nmol/L (total T), 73.4 pmol/L (E2), 0.1 IU/L (LH and FSH), and 0.35 nmol/L (SHBG). The intra-assay and inter-assay coefficients of variation for each hormone were as follows: total T, 5.74% and 6.59%; LH, 4.9% and 6%; FSH, 3.82% and 4.48%; E2, 6.24% and 7.52%, respectively; free T, 15% for both; and SHBG, 7% for both. Samples with values below the minimal detectable limit were given a value midway between zero and the minimal detectable limit for the analyses (0.35 nmol/L for TT, and 36.7 pmol/L for E2). Glycated hemoglobin (HbA1c) was assessed via HPLC (MQ-2000PT, Medconn, Shanghai, China). Fasting plasma glucose (FPG), low-density lipoprotein (LDL), triglycerides (TG) and total cholesterol (TC) were tested by BECKMAN COULTER AU 680 (Germany). Free androgen index (FAI) was calculated as total T (nmol/L) \times 100/SHBG (nmol/L).

Based on the American Diabetes Association 2014 criteria, diabetes was defined as a previous diagnosis by a health-care professional, fasting plasma glucose (FPG) level ≥ 7.0 mmol/L, or glycated hemoglobin (HbA1c) level $\geq 6.5\%$. The current economic status of each site was assessed by the gross domestic product per capita in 2013. Each of the 22 sites was allocated to high or low economic status in comparison with the GDP per capita of the whole nation (6807 US dollars from World Bank) in 2013.

Analysis of erectile dysfunction

In the study sites of Jiangsu and Anhui provinces, we also used the International Index of Erectile Dysfunction-5 (IIEF-5) questionnaire to assess ED. The IIEF-5 questionnaire consists of 5 questions with responses scored from 0 to 5 points, and it has been shown to be a good diagnostic tool for ED [16]. Men with scores ≤ 21 are considered to have ED.

In total, 1356 men from the Jiangsu and Anhui provinces took part in our survey. Those who refused to complete the IIEF-5 questionnaire ($n = 142$) or had no sex life within the last six months ($n = 186$) were excluded. Finally, a total of 1028 men were enrolled in the subgroup analysis. Because only 11 of the participants were in the LDL-C < 1.81 mmol/L (70 mg/dL) group, we decided to categorize subjects into deciles according to LDL-C distribution, with the 10th–90th percentile [LDL-C, 2.50–4.32 mmol/L (97–167 mg/dL)] as the reference group.

Statistical analysis

We performed the analyses using IBM SPSS version 24 statistical software (IBM Corporation, Armonk, NY, USA). Sociodemographic and laboratory characteristics were presented as the median with interquartile range for continuous variables and as the number with the proportion for categorical variables. To test for variable differences between different groups, the Kruskal–Wallis test was used for continuous variables with non-normal distributions, and the Pearson chi-square test was used for categorical variables.

The associations of LDL-C (independent variable) with total T, Free T, FAI, SHBG, E2, FSH and LH (dependent variables) were assessed using linear regression. Model 1 was unadjusted. Model 2 was adjusted for age, educational level and economic status. Model 3 was further adjusted for smoking status, drinking status, BMI, diabetes, and use of lipid-lowering medication. Total T, Free T, FAI, SHBG, E2, FSH, LH and LDL-C were log-transformed because they had non-normal distributions. The results were expressed as the unstandardized coefficient (B) and 95% confidence interval (CI).

We used binary logistic regression to determine the association between LDL-C and ED, with those in the 10th–90th percentile of LDL-C as the reference group. Odds ratios (OR) with 95% CIs were calculated. Model 1 was unadjusted. Model 2 was adjusted for age, educational level and economic status. Model 3 was further adjusted

for smoking status, drinking status, BMI, diabetes and use of lipid-lowering medication. Model 4 was additionally adjusted for FAI.

Results

General characteristics of the study participants according to the LDL-C categories

The socio-demographic and biochemical characteristics of the study population categorized by LDL-C are summarized in Table 1. With increasing LDL-C levels, men had significantly higher FT, FAI and BMI, and significantly lower SHBG and E2 (P for trend < 0.05). Meanwhile, those in the highest LDL-C decile also had a significantly higher prevalence of diabetes. The same trend was also observed when LDL-C was classified into four categories (P for trend < 0.05) (Supplementary Table 1).

Association of LDL-C with reproductive hormones

Table 2 summarizes the results of the linear regression models exploring the association of LDL-C with total T, free T, FAI, E2, SHBG, LH and FSH. In the unadjusted models, higher levels of LDL-C were associated with higher free T ($B = 0.200$), higher FAI ($B = 0.091$), lower SHBG ($B = -0.106$) and lower E2 ($B = -0.247$) (all $P < 0.01$). After adjusting for age, educational level, economic status, smoking status, drinking status, BMI, diabetes, and use of lipid-lowering medication, the association between LDL-C and SHBG was further attenuated to the extent that it was no longer significant. However, free T ($B = 0.175$), FAI ($B = 0.064$) and E2 ($B = -0.288$) were still associated with LDL-C (all $P < 0.05$).

The prevalence of erectile dysfunction according to the LDL-C categories

Compared to the men with LDL-C among the 10th–90th percentile, the men in the lowest decile and highest decile of LDL-C had a significantly higher prevalence of ED (72.6% and 74.0% vs. 61.5%, respectively, both $P < 0.05$). Interestingly, the results showed a U-shaped curvilinear relationship between the LDL-C level and the prevalence of ED (Fig. 1).

Notably, among the 11 men in the LDL-C < 1.81 mmol/L (70 mg/dL) group, 9 had ED.

Association of LDL-C with erectile dysfunction

Table 3 shows the results of the binary logistic regression analysis measuring the association of LDL-C with ED. In the unadjusted model, compared to those with LDL-C among the 10th–90th percentile, the ORs of ED in men in the lowest and highest deciles were 1.800 (95% CI: 1.108, 2.923) and 1.727 (95% CI: 1.104, 2.701), respectively (Table 3, model 1). Further adjusting for age, educational level, economic status, smoking status, drinking status, BMI, diabetes, use of

Table 1 General characteristics of the study participants by LDL-C categories.

	LDL-C categories			P for trend
	<10th percentile	10th–90th percentile	>90th percentile	
N	412	3370	421	
Use of lipid-lowering medication, N	9	35	1	
LDL-C, mmol/L	<2.18	2.18–4.05	>4.05	
Age, yrs	56 (43–66)	55 (45–65)	56 (47–65)	0.656
Body mass index, kg/m ²	23.2 (20.9–25.4)	24.8 (22.6–27.0)	25.9 (23.8–28.4)	<0.001
Total cholesterol, mmol/L	3.79 (3.45–4.14)	5.05 (4.58–5.56)	6.52 (6.19–7.11)	<0.001
Triglyceride, mmol/L	1.02 (0.76–1.54)	1.40 (1.02–2.13)	1.85 (1.31–2.51)	0.008
Total testosterone, nmol/L	16.0 (13.0–20.8)	15.7 (12.6–19.8)	15.8 (12.5–20.0)	0.456
Free testosterone, pmol/L	12.60 (7.97–17.20)	12.90 (9.10–17.50)	13.20 (9.78–18.53)	0.04
SHBG, nmol/L	44.05 (29.63–67.00)	41.10 (28.70–58.53)	40.50 (29.40–57.20)	0.001
Free androgen index, %	36.70 (27.30–49.08)	38.06 (29.77–48.74)	39.23 (31.10–48.58)	<0.001
Estradiol, pmol/L	111.00 (83.70–147.30)	103.00 (70.83–140.00)	97.80 (58.00–126.75)	<0.001
Follicle stimulating hormone, IU/l	7.20 (4.80–11.20)	7.00 (4.80–10.60)	7.80 (5.30–11.13)	0.961
Luteinizing hormone, IU/l	5.00 (3.50–7.21)	4.88 (3.50–7.00)	5.60 (3.90–7.56)	0.425
Educational level, %				0.077
< High school	60.8	56.1	60.7	
>High school	39.2	43.9	39.3	
Economic status (low/high, %)	27.2/72.8	39.3/60.7	59.4/40.6	<0.001
Diabetes, %	15.3	14.1	22.8	0.002
Current smoker, %	46.4	47.8	52.1	0.106
Current drinker, %	44.6	43.9	41.0	0.307

Data are summarized as the median (interquartile range) for continuous variables and as the number and proportion for categorical variables. LDL-C, low-density lipoprotein cholesterol; SHBG, sex hormone binding globulin.

Table 2 Association between LDL-C and sex steroids.

Dependent variables	LDL-C		
	Model 1	Model 2	Model 3
Total T	–0.015 (–0.063, 0.033)	–0.023 (–0.070, 0.025)	0.020 (–0.027, 0.067)
Free T	0.200 (0.111, 0.290)***	0.196 (0.110, 0.281)***	0.175 (0.084, 0.266)***
FAI	0.091 (0.037, 0.144)**	0.112 (0.064, 0.159)***	0.064 (0.016, 0.112)*
SHBG	–0.106 (–0.169, –0.042)**	–0.167 (–0.222, –0.112)***	–0.044 (–0.098, 0.012)
E2	–0.247 (–0.320, –0.174)***	–0.278 (–0.350, –0.205)***	–0.288 (–0.366, –0.210)***
FSH	0.023 (–0.053, 0.099)	–0.033 (–0.096, 0.031)	–0.009 (–0.075, 0.059)
LH	0.052 (–0.014, 0.118)	–0.057 (–0.115, 0.002)	–0.017 (–0.078, 0.045)

T, testosterone; FAI, free androgen index; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin; LDL-C, low-density lipoprotein cholesterol.

Since total T, free T, FAI, SHBG, E2, FSH, LH and LDL-C were non-normally distributed, they were log-transformed.

Data are expressed as the B coefficient (95% confidence interval). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Model 1 was unadjusted.

Model 2 was adjusted for age, educational level and economic status.

Model 3 was additionally adjusted for smoking status, drinking status, BMI, diabetes and use of lipid-lowering medication.

lipid-lowering medication, and FAI did not weaken this association (OR: 1.938, 95% CI 1.121, 3.349 and OR: 1.804, 95% CI 1.117, 2.916, respectively) (Table 3, model 4).

Discussion

In this population-based study, we found that lower LDL-C levels were significantly associated with lower free T levels and lower FAI after adjusting for age, educational level, economic status, smoking status, drinking status, BMI, diabetes and use of lipid-lowering medication in a general population of men. In addition, to the best of our knowledge, this study is the first to detect a U-shaped curvilinear relationship between LDL-C and the prevalence of ED in an epidemiological setting.

Although some observational studies suggested an inverse association between LDL-C and androgen [6,7], a recent Mendelian randomization analysis raised the possibility that higher T levels may be associated with higher LDL-C levels [8], which concurred with our study results. In addition, although still open to debate [11,17,18], a meta-analysis of placebo-controlled randomized trials showed that statins lowered the testosterone level by -0.44 nmol/L [19]. The controversy in the results of previous clinical trials may lie in the pharmacokinetics of the lipid-lowering agents used, variable LDL-C values of the participants recruited and different methods adopted for T detection [17,19].

We found that naturally lowering LDL-C levels was associated with lower free T and FAI. The mechanism

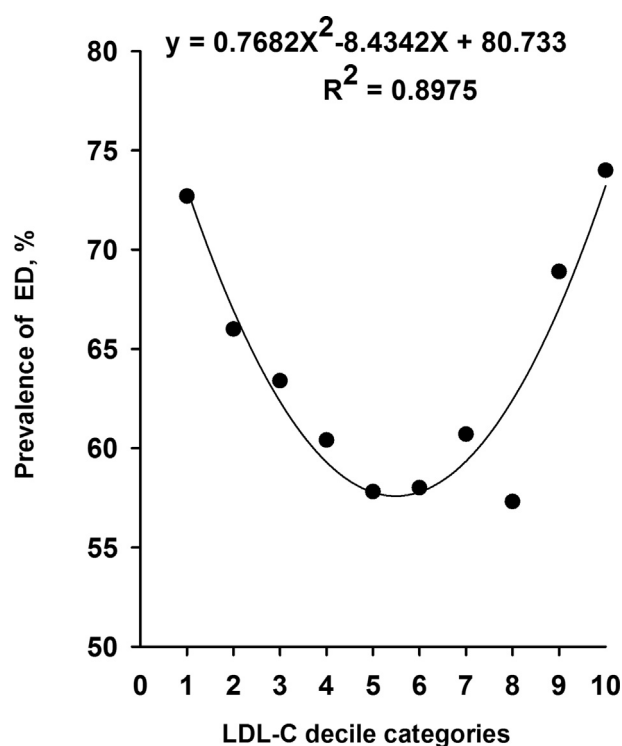


Figure 1 The relationship between LDL-C and the prevalence of erectile dysfunction.

underlying the association of LDL-C *per se* with free T and FAI is not yet fully understood. LDL particles are believed to be an important source of cholesterol for testicular steroid synthesis [20]. Hence, in states of low LDL-C levels, the continuous supply of cholesterol to the testis may be impaired, causing a subsequent reduction in the conversion of cholesterol to steroid hormones. This is in accordance with what is expected, and it strengthens our finding.

ED is a worldwide problem that adversely influences quality of life in over 150 million men >40 years old and is projected to influence 300 million men by the year 2025 [21]. The prevalence of ED was 63.7% among our participants with a mean age of 56 years. Such a high prevalence of ED was found to be associated with both the lowest decile and the highest decile of LDL-C. Prior studies investigating ED caused by low LDL-C levels due to statin therapy have reported discordant results.

Solomon and colleagues [22] treated 93 male patients with high cardiovascular risk factors with a statin for 6 months and observed that their mean IIEF-5 scores decreased from 21 at baseline to 6.5 after statin treatment. Recently, another study also reported that IIEF-5 scores decreased significantly from 24.1 at baseline to 16.1 and 9.7 in patients treated to LDL-C levels of 100–130 mg/dL and <100 mg/dL, respectively [9]. However, Chou et al. [23] reported that statin use was associated with a reduced risk for incident ED in middle-aged Taiwanese men.

We found that low LDL-C levels were associated with an increased prevalence of ED, which is consistent with the observed associations of LDL-C with free T and FAI. Androgens are well-known to be indispensable in maintaining the erectile response. As shown in the Testosterone Trials, free T was independently and positively associated with sexual desire, erectile function and sexual activity in American men [24]. Notably, the association between LDL-C and ED in our population was independent of the FAI (Table 3, model 4). At present, little is known about this field, so further investigation is warranted.

Interestingly, although higher LDL-C levels were associated with higher androgen levels, they were still associated with an increased prevalence of ED. First, it is possible that hyperlipidemia may impair erectile function by directly damaging the normal structure of the penis and by causing corpora cavernosum fibrosis [25]. In addition, as a vascular event, penile erection requires an intact endothelium, and endothelial dysfunction is a manifestation of ED [26]. Circulating LDL particles could penetrate the endothelium and become oxidized, promote inflammation, and cause injury to the overlying endothelium and surrounding smooth muscle cells, all of which contribute to the pathogenesis of ED [27,28]. However, the direct role of androgen replacement therapy specifically on erectile function remains unknown. Previous researches did not find a consistently beneficial role of T therapy in hypogonadal men with ED, and as a result, in 2014, the FDA requested that any misleading advertising to that effect be stopped [29]. In the present analysis, there was no association between FAI and ED (OR: 0.993, 95% CI: 0.982, 1.005, $P = 0.235$). Accordingly, it is reasonable to deduce that LDL-C might play a more crucial role than androgen in the pathogenesis of ED, which requires further investigation.

Table 3 Association between LDL-C and erectile dysfunction.

LDL-C	Model 1	Model 2	Model 3	Model 4
10th–90th percentile	Ref.	Ref.	Ref.	Ref.
<10th percentile	1.800 (1.108–2.923)*	1.796 (1.059, 3.046)*	1.949 (1.127, 3.370)*	1.938 (1.121, 3.349)*
>90th percentile	1.727 (1.104, 2.701)*	1.834 (1.151, 2.924)*	1.810 (1.121, 2.923)*	1.804 (1.117, 2.916)*

LDL-C, low-density lipoprotein cholesterol.

Data are expressed as the odds ratio (95% confidence interval). * $P < 0.05$.

Model 1 was unadjusted.

Model 2 was adjusted for age, educational level and economic status.

Model 3 was additionally adjusted for current smoker, current drinker, BMI, diabetes and use of lipid-lowering medication.

Model 4 was further adjusted for free androgen index.

Of note, although a higher prevalence of diabetes was shown for the highest LDL-C decile (Table 1), the lowest LDL-C category showed the highest prevalence of diabetes (Supplementary Table 1). Considering the fact that there were only 105 men in the LDL-C < 1.81 mmol/L category, we speculate the results shown in Supplementary Table 1 were obtained just by chance. In the present study, those with diabetes did have significantly greater LDL-C levels than the non-diabetic subjects [3.15 (2.65–3.73) mmol/L vs. 3.01 (2.54–3.51) mmol/L, $P < 0.001$].

Our study may have important clinical implications. With the advent of powerful LDL-lowering drugs, especially PCSK9 monoclonal antibodies, it is now possible to reduce LDL-C to levels seen in newborn infants. In addition to the need to document possible side effects, such as myalgia and the onset of diabetes from the agents used in intensive LDL-C lowering therapy [30], it has become important and urgent to consider adverse effects of low LDL-C levels in their own right [5]. A modest decrease of T in a population level might hide a substantial decrease in a handful of individuals, and in those who already have low testosterone, it might be clinically meaningful. Of note, in the IMPROVE-IT study, though lowering LDL-C to levels below previous targets improved cardiovascular outcomes, 42% of the participants prematurely discontinued the medication for any reason, with a rate of approximately 7% per year [2]. Considering that lipid lowering is presumably a lifelong goal, this diminishment in long-term medication use is of great practical clinical concern, and our study suggests that lower androgen and ED might be important reasons for this discontinuation. More importantly, based on the guidelines of the American Heart Association, even in high-risk patients, secondary prevention should focus on not only LDL-C management but also comprehensive management of lifestyle modification, weight management, aspirin use and blood pressure control [31].

Our study has some limitations. First, the cross-sectional nature of the study limits the ability for the results to be generalized, and causation cannot be assumed. Second, the number of current users of lipid-lowering drugs in our study was too low (1%) to perform a subgroup analysis of users vs. nonusers. However, this may be a novel area of our study since we are the first to detect associations of LDL-C with sex steroids and ED in a general population. The direct effect of statins and other lipid-lowering therapy on androgen and erectile dysfunction warrants further investigation in well-designed randomized control trials with a larger number of participants and longer duration of follow-up.

In conclusion, lower LDL-C levels *per se* were significantly associated with lower free T and FAI after multi-variable adjustment in a general population of men. Moreover, both low and high levels of LDL-C might be risk factors for ED.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.numecd.2018.08.006>.

References

- [1] Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;38:2459–72.
- [2] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387–97.
- [3] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713–22.
- [4] Jarcho JA, Keaney Jr JF. Proof that lower is better—LDL cholesterol and IMPROVE-IT. *N Engl J Med* 2015;372:2448–50.
- [5] Olsson AG, Angelin B, Assmann G, Binder CJ, Björkhem I, Cedazo-Minguez A, et al. Can LDL cholesterol be too low? Possible risks of extremely low levels. *J Intern Med* 2017;281:534–53.
- [6] Simon D, Charles MA, Nahoul K, Orssaud G, Kremski J, Hully V, et al. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: the telecom study. *J Clin Endocrinol Metab* 1997;82:682–5.
- [7] Zhang N, Zhang H, Zhang X, Zhang B, Wang F, Wang C, et al. The relationship between endogenous testosterone and lipid profile in middle-aged and elderly Chinese men. *Eur J Endocrinol* 2014;170:487–94.
- [8] Zhao J, Jiang C, Lam TH, Liu B, Cheng KK, Xu L, et al. Genetically predicted testosterone and cardiovascular risk factors in men: a Mendelian randomization analysis in the Guangzhou Biobank cohort study. *Int J Epidemiol* 2014;43:140–8.
- [9] Baspınar O, Bayram F, Korkmaz S, Aksu M, Kocer D, Dizdar OS, et al. The effects of statin treatment on adrenal and sexual function and nitric oxide levels in hypercholesterolemic male patients treated with a statin. *J Clin Lipidol* 2016;10:1452–61.
- [10] Blom DJ, Djedjos CS, Monsalvo ML, Bridges I, Wasserman SM, Scott R, et al. Effects of evolocumab on vitamin E and steroid hormone levels: results from the 52-week, phase 3, double-blind, randomized, placebo-controlled DESCARTES study. *Circ Res* 2015;117:731–41.
- [11] Santini SA, Carrozza C, Lulli P, Zuppi C, CarloTonolo G, Musumeci S. Atorvastatin treatment does not affect gonadal and adrenal hormones in type 2 diabetes patients with mild to moderate hypercholesterolemia. *J Atherosclerosis Thromb* 2003;10:160–4.
- [12] Wang N, Wang X, Han B, Li Q, Chen Y, Zhu C, et al. Is exposure to famine in childhood and economic development in adulthood associated with diabetes? *J Clin Endocrinol Metab* 2015;100:4514–23.
- [13] Chen Y, Chen Y, Xia F, Wang N, Chen C, Nie X, et al. A higher ratio of estradiol to testosterone is associated with autoimmune thyroid disease in males. *Thyroid: Off J Am Thyroid Assoc* 2017;27:960–6.
- [14] Wang N, Shao H, Chen Y, Xia F, Chi C, Li Q, et al. Follicle-stimulating hormone, its association with cardiometabolic risk factors, and 10-year risk of cardiovascular disease in postmenopausal women. *J Am Heart Assoc* 2017;6.
- [15] Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical

- Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract: Off J Am Coll Endocrinol Am Assoc Clin Endocrinol* 2017;23:1–87.
- [16] Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49:822–30.
- [17] Kanat M, Serin E, Tunckale A, Yildiz O, Sahin S, Bolayirli M, et al. A multi-center, open label, crossover designed prospective study evaluating the effects of lipid lowering treatment on steroid synthesis in patients with type 2 diabetes (MODEST Study). *J Endocrinol Invest* 2009;32:852–6.
- [18] Dobs AS, Schrott H, Davidson MH, Bays H, Stein EA, Kush D, et al. Effects of high-dose simvastatin on adrenal and gonadal steroidogenesis in men with hypercholesterolemia. *Metab Clin Exp* 2000;49:1234–8.
- [19] Schooling CM, Au Yeung SL, Freeman G, Cowling BJ. The effect of statins on testosterone in men and women, a systematic review and meta-analysis of randomized controlled trials. *BMC Med* 2013;11:57.
- [20] Carr BR, Parker Jr CR, Ohashi M, MacDonald PC, Simpson ER. Regulation of human fetal testicular secretion of testosterone: low-density lipoprotein-cholesterol and cholesterol synthesized de novo as steroid precursor. *Am J Obstet Gynecol* 1983;146:241–7.
- [21] Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int* 1999;84:50–6.
- [22] Solomon H, Samarasinghe YP, Feher MD, Man J, Rivas-Toro H, Lumb PJ, et al. Erectile dysfunction and statin treatment in high cardiovascular risk patients. *Int J Clin Pract* 2006;60:141–5.
- [23] Chou CY, Yang YF, Chou YJ, Hu HY, Huang N. Statin use and incident erectile dysfunction – a nationwide propensity-matched cohort study in Taiwan. *Int J Cardiol* 2016;202:883–8.
- [24] Cunningham GR, Stephens-Shields AJ, Rosen RC, Wang C, Ellenberg SS, Matsumoto AM, et al. Association of sex hormones with sexual function, vitality, and physical function of symptomatic older men with low testosterone levels at baseline in the testosterone trials. *J Clin Endocrinol Metab* 2015;100:1146–55.
- [25] Li R, Cui K, Wang T, Wang S, Li X, Qiu J, et al. Hyperlipidemia impairs erectile function in rats by causing cavernosal fibrosis. *Andrologia* 2017;49.
- [26] Aversa A, Bruzziches R, Francomano D, Natali M, Gareri P, Spera G. Endothelial dysfunction and erectile dysfunction in the aging man. *Int J Urol: Off J Jpn Urolog Assoc* 2010;17:38–47.
- [27] Wadhera RK, Steen DL, Khan I, Giugliano RP, Foody JM. A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality. *J Clin Lipidol* 2016;10:472.
- [28] Shafik NM, Baalash A, Ebeid AM. Synergistic cardioprotective effects of combined chromium picolinate and atorvastatin treatment in Triton X-100-induced hyperlipidemia in rats: impact on some biochemical markers. *Biol Trace Elem Res* 2017;180:255–64.
- [29] Nangia AK. Testosterone replacement should be given to men with erectile dysfunction: con. *J Urol* 2017;197:285–6.
- [30] Leibowitz M, Karpati T, Cohen-Stavi CJ, Feldman BS, Hoshen M, Bitterman H, et al. Association between achieved low-density lipoprotein levels and major adverse cardiac events in patients with stable ischemic heart disease taking statin treatment. *JAMA Int Med* 2016;176:1105–13.
- [31] Smith Jr SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol* 2011;58:2432–46.