

# Prevalence of High HDL-cholesterol and Its Associated Factors Among Childbearing Age Tunisian Women: a Cross-sectional Study

**Fatma Ben Cherifa**

National Institute of Nutrition and Food Technology

**Jalila El Ati**

National Institute of Food Science and Technology

**Radhouene Doggui**

National Institute of Food Science and Technology

**Myriam El Ati-Hellal** (✉ [mfh22002@yahoo.fr](mailto:mfh22002@yahoo.fr))

Preparatory Institute of scientific and technical study <https://orcid.org/0000-0002-3895-9714>

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## Research

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# Abstract

**Background:** The protective role of high HDL-C against cardiovascular risk has been questioned recently. Due to the increasing trend of CVD in Tunisia, this study aimed to determine the prevalence of high HDL-C and its associated factors in childbearing age Tunisian women.

**Methods:** A cross-sectional survey was conducted among a subsample of 1689 women, aged 20 to 49 y in the Great Tunis region. Data on socio-demographic and lifestyle factors were collected by a questionnaire. Overall adiposity was assessed by BMI. All biological variables were assayed in blood samples coated with EDTA by enzymatic methods. Stata software (2015) was used for data management and statistical analysis.

**Results:** High HDL-C values were recorded in 26.6% of selected women. After adjustment for all socio-demographic and lifestyle factors, age, hypertension and smoking were negatively associated with high HDL-C levels while family history of cancer was positively associated with high HDL-C in women.

**Conclusions:** Additional investigation on the relationship between high HDL-C and cancer risk should be performed due to controversial results.

## Background

Cardiovascular diseases (CVD) are the leading cause of deaths worldwide (1). In Tunisia, a Middle East and North African (MENA) country with eleven million inhabitants, CVD are responsible of 23.9 % and 28.7 % of deaths for men and women, respectively (2). Several epidemiological studies have shown an inverse and independent association between high density lipoprotein cholesterol (HDL-C) and CVD (3, 4). The protective effect of HDL-C is mainly due to its transport of excess cholesterol from peripheral tissues to the liver. This pathway is called the reverse cholesterol transport system (RCT) (5–7). Additional protective properties of HDL-C include its antioxidant, anti-inflammatory, anti-infectious and anti-thrombotic potential (8–10). Recently, the prognostic importance of HDL-C as a specific risk factor for CVD has been questioned since many therapies attempting to increase HDL-C failed to improve clinical outcomes (10, 11). Moreover, other studies reported that extremely high levels of HDL-C are associated with high mortality risk (12–14).

Due to the increasing trend of CVD in Tunisia, this study aimed to estimate the prevalence of HDL-C and to investigate the associations between high HDL-C levels and socio-demographic, metabolic and lifestyle factors in childbearing age Tunisian women.

## Methods

### Sampling and study population

A cross-sectional survey was carried out between March 2009 and January 2010 in the Greater Tunis region, a mainly urban area around the capital city (2.5 million inhabitants of whom 92% live in urban areas and 8% in rural areas). Sampling was carried out by the National Institute of Statistics, according to a stratified random survey in two stages. Totally, 76 districts were selected first according to the governorate of residence, then according to the environment (urban and rural). From each district, 20 households were randomly selected and all persons aged 6 mo to 49 y were included. In the present study, a sub-sample of non-pregnant women aged 20 to 49 y old was used.

## **Socio-economic and demographic variables**

Data on the woman's age, marital status, parity, menopause, level of education, lifestyle (smoking, alcoholism and sport activity), occupation and household size were collected by a questionnaire. An economic level score for the household was calculated from six variables describing the dwelling and eleven variables coding household ownership of appliances. The total score obtained per household is coded in terciles corresponding to "low", "medium" and "high" economic level (15).

## **Anthropometric variables**

Measurements of height, weight and waist circumference were performed according to standardized procedures (16). Height was measured to the nearest 0.1 cm with a stadiometer. Body weight was measured to the nearest 0.1 kg. Waist circumference (WC) was measured to the nearest 0.1 cm using a metric fiberglass tape. Overall adiposity was assessed by BMI (weight (kg)/height<sup>2</sup> (m<sup>2</sup>)). BMI was categorized as underweight < 18.5 kg/m<sup>2</sup>, overweight ≥ 25 kg/m<sup>2</sup> and obese ≥ 30 kg/m<sup>2</sup>.

## **Biological variables**

### **Analysis**

5 ml blood samples were collected on tubes coated with the anticoagulant Ethylene Diamine Tetra-Acetic (EDTA). All samples were kept at 4–5°C and sent the same day to the Clinical Biology Laboratory of the National Institute of Nutrition and Food Technology then centrifuged at 4000g for 10 minutes and stored at -20°C until analysis. Blood pressure (BP) was measured at rest, twice and at a time interval of at least 15 minutes, using a BP monitor. Fasting blood glucose, total cholesterol (TC), triglyceridemia, high density lipoprotein cholesterolemia (HDL-C), low density lipoprotein cholesterolemia (LDL-C) and apolipoproteins A-I (ApoA-I) and B (ApoB), were assayed by enzymatic methods on Synchron analyzer and calibrator, using Beckman reagents. The accuracy was evaluated by quality control samples (BioRad).

### **Threshold values**

Hypertension was defined as having an average systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg or taking medication for high BP (17). Diabetes mellitus was defined as a fasting glucose level ≥ 126 mg/dL (7 mmol/L) and/or the use of antidiabetic treatment(18). A HDL-C level of < 50 mg/dL in women was considered as low, while a HDL-C level of ≥ 60 mg/dL was considered as high (19). Metabolic syndrome was present in the case of women central obesity (WC > 80

cm) and at least two of the following risk factors: SBP  $\geq$  130 mm Hg or DBP  $\geq$  85 mm Hg or antihypertensive treatment; glucose  $\geq$  1 g/L (5.6 mmol/dL) or diagnosis of type 2 diabetes mellitus; triglyceridemia  $\geq$  1,5 g/L (1.7 mmol/L) or treatment of high triglyceridemia (20). Other CVD risk factors were obtained with ratios of TC/ HDL-C and Apo-B/Apo-A1 higher than 4.5 and 1, respectively (21, 22).

## Data management and statistical analysis

Data entry including quality checks as well as validation by double entry was performed with EpiData Software version 3.1(23). Stata software (24) was used for data management and statistical analysis. Results are shown as mean  $\pm$  standard error. The association between categorical variables was evaluated by the test of chi-square. The association of high HDL-C with the different cofactors was assessed by calculating odds-ratio (OR), after the selection of an appropriate reference category. For tests and confidence intervals an alpha threshold of 5% was chosen.

## Results

### General characteristics of subjects

The survey was conducted among 1689 women, aged 20 to 49 y (average age  $36.1 \pm 0.3$  y), of which 67.7% were married and 32.2% were single, separated, divorced or widowed at the time of the survey. The majority of women (40.2%) were multiparous, with 3 or more children while 26.9% had between 1 and 2 children. Only 10.9% of women had never attended school, 53.2% had reached secondary or university level and 32.8% reported working outside.

### Characteristics of women according to HDL-C levels

The average HDL-C concentration in childbearing age Tunisian women was  $1.36 \pm 0.02$  mmol/L ( $52.6 \pm 0.8$  mg/dL). High HDL-C values were recorded in 26.6% of subjects, while 14.3% were with low HDL-C concentrations. Table 1 displays the characteristics of the selected participants according to HDL-C levels. Age as well as area of living, menopause, professional activity, smoking, drinking alcohol, sport activity, diabetes, metabolic syndrome, lipid-lowering treatment, family history of CVD, family history of hypertension, family history of diabetes, family history of obesity, fasting blood glucose and LDL-C had no effects on HDL-C concentrations. However, marital status, parity, economic level, overweight, obesity, abdominal obesity, hypertension, family history of cancer, TC, triglyceridemia, TC/HDL-C ratio, ApoA-I, ApoB, ApoA-I/ApoB ratio, SBP and DBP were significantly associated with HDL-C values. Results of multivariate regression analysis (Fig. 1) revealed that age (30–39 y) (OR = 0.49 [0.32–0.73]), age (40–49y) (OR = 0.7 [0.49–1.00]), hypertension (OR = 0.56 [0.38–0.83]), smoking (OR = 0.56 [0.32–0.98]) and family history of cancer (OR = 1.53 [1.11–2.11]) were the only factors correlated with HDL-C levels in childbearing age Tunisian women.

Table 1  
 Characteristics of Tunisian women according to HDL-C levels

Variable	High HDL-C ≥ 60 mg/dL	Normal and low HDL-C < 60 mg/dL	<i>P</i> <sup>1</sup> value
Age (%)			
<i>20–29 y</i>	32.0	28.1	0.35
<i>30–39 y</i>	28.2	31.3	
<i>40–49 y</i>	39.8	40.6	
Area of living (%)			
<i>Rural</i>	6,8	7,5	0.68
<i>Urbain</i>	93,2	92,5	
Marital status (%)			
<i>Other<sup>b</sup></i>	61,4	69,2	0.005
<i>Married</i>	38,6	30,8	
Parity (%)			
<i>3 and more children</i>	34,8	42,2	0,029
<i>1 or 2 children</i>	26,6	26,9	
<i>0 children</i>	38,5	30,9	
Menopause (%)			
No	90.5	92.9	0.081
Yes	9.5	7.1	
Level of education (%)			
<i>No schooling</i>	7,7	12,0	< 10 <sup>-4</sup>
<i>Primary and secondary school</i>	28,3	38,8	
<i>Secondary complete and graduate</i>	64,0	49,2	
Professional activity (%)			
<i>No</i>	33,9	32,4	0,67
<i>Yes</i>	66,1	67,6	
Economic level (%)			
<i>Low</i>	42,5	35,1	0,007

Variable	High HDL-C ≥ 60 mg/dL	Normal and low HDL-C < 60 mg/dL	<i>P</i> <sup>1</sup> value
<i>Medium</i>	31,3	34,9	
<i>High</i>	26,2	30,0	
Smoking (%)			
No	94,8	93,6	0.21
Yes	5,2	6,4	
Drinking alcohol (%)			
No	100	99,4	0.24
Yes	0	0,6	
Sport activity (%)			
No	93,2	93,8	0.70
Yes	6.8	6.2	
Hypertension (%)	4,0	6,4	0,074
Diabetes Mellitus (%)	13,1	24,4	< 10 <sup>-4</sup>
Metabolic syndrome (%)	28,3	33,2	0,059
Family history of Cancer (%)	61,2	71,8	0,002
Family history of CVD (%)	61,9	66,1	0,17
Family history of Hypertension (%)	62,1	64,4	0,59
Family history of Diabetes (%)	60,0	57,7	0,48
Family history of Obesity (%)	55,2	54,6	0,86
Lipid lowering treatment (%)	1,3	1,3	0,97
Fasting blood glucose (mmol/L) <sup>2</sup>	4,93 ± 0,08	5,07 ± 0,06	0,102
TC (mmol/L)	5,17 ± 0,06	4,62 ± 0,05	< 10 <sup>-4</sup>
Triglyceridemia (mmol/L)	0,89 ± 0,03	1,12 ± 0,03	< 10 <sup>-4</sup>
LDL-C (mmol/L)	2,98 ± 0,06	2,91 ± 0,04	0,27

Table 1  
(continued)

<b>TC/HDL-C</b>	<b>2,92 ± 0,04</b>	<b>3,91 ± 0,04</b>	<b>&lt; 10<sup>-4</sup></b>
ApoA-I (mmol/L)	1,58 ± 0,03	1,31 ± 0,02	< 10 <sup>-4</sup>
ApoB (mmol/L)	0,79 ± 0,02	0,86 ± 0,02	0,003
ApoB/Apo AI	0,50 ± 0,03	0,66 ± 0,02	< 10 <sup>-4</sup>
SBP	119,5 ± 0,9	122,8 ± 0,8	0,001
DBP	74,5 ± 0,5	76,85 ± 0,51	10 <sup>-4</sup>
<sup>1</sup> : P value for logistic regression models accounting for survey design among categories of variable.			
<sup>2</sup> : Values are mean ± standard deviation.			

## Discussion

The mean HDL-C level found in this study ( $52.6 \pm 0.8$  mg/dL) is in the normal range (between 50 and 60 mg/dL) (19) and similar to that reported in a previous Tunisian research on dyslipidemia, conducted among 1484 women aged 35–70 y old, in the same sampling area (25). Compared to data registered elsewhere, the mean HDL-C value in childbearing age Tunisian women is higher than that recorded in Japanese (26), Korean (27), Hispanic and African American women (28) and lower than that reported in Canadian (29), Danish (14) and US women (30). The differences in HDL-C levels between various races and ethnic groups may in part be due to genetic factors but the role of behavioral, environmental and anthropometric covariates seems to be important too (31, 32).

Age appears to be an independent negative risk factor that can affect HDL-C levels in Tunisian women. This is consistent with previous studies reporting a decrease of HDL-C with age in women (27, 33). Many factors could explain this phenomenon such as the frequency of insulin resistance and impaired lipolysis at advanced age that could affect the RCT. Inflammatory processes in aged people as well as hormonal changes are other possible causes of decline in HDL-C with age (34).

Parity and marital status influenced negatively the HDL-C concentration in Tunisian women. After pregnancy, the level of cholesterol bound to HDL particles tends to decrease, which explains the tendency of multiparous women to have lower circulating HDL-C levels than women who have never given birth. These changes in circulating cholesterol levels are likely due to changes in estrogen levels which vary throughout a woman's genital life (35, 36).

Menopause didn't affect circulating HDL-C levels. This result is in contradiction with those of several authors showing that a worse lipid profile is observed in postmenopausal women in comparison to premenopausal ones due to hormonal changes involving the decrease in estrogen level and increase in

luteinizing hormone and follicle stimulating hormone levels (33, 37). In our study, the majority of women (92.3%) are premenopausal, which could explain the absence of relationship between menopause and lipid profile.

In this study, women with high HDL-C levels are more educated and have a lower socioeconomic status than those with mean or low levels of HDL-C. Agongo et al. (2018) (38) found a positive significant association between formal education and socioeconomic status with HDL-C levels in women from rural northern Ghana, while no significant association was found between HDL-C and socioeconomic status of Korean women (27). The mechanisms of association between HDL-C and socioeconomic status are complex due to the influence of lifestyle factors and dietary habits as well as stress variations by social class (39).

Results on the associations between HDL-C levels and lifestyle factors (physical activity, alcohol consumption and smoking) showed that smoking was the only negative risk factor of HDL-C in Tunisian women. Research has shown that physical activity and moderate alcohol consumption are positively correlated with HDL-C contrarily to smoking. According to King et al. (1995), a regular physical activity increases the HDL-C level by 3 to 9 percent in healthy sedentary persons (40). This increase depends on exercise frequency and intensity and is attributed to the stimulation of the production of pre- $\beta$  HDL-C and RCT (41). The effects of smoking on HDL-C are dose dependent and reversed upon smoking cessation. Nakamura et al. (2020), found that in both men and women, current smokers had significantly ( $p < 0.001$ ) lower HDL-C than non-smokers (-7.3%, -4.3%) (42). Likewise, Jain and Ducatman (2018) reported lower HDL-C in smokers than in non-smokers (48.8 vs 51.4 mg/dL,  $p < 0.01$ ) (43). Alcohol consumption in moderation raises the concentration of HDL-C, possibly by increasing cellular cholesterol efflux and plasma cholesterol esterification (44). Brien et al. (2011) reported an increase of HDL-C by 0.1 mmol/L with a quantity of alcohol of about 30 g/day (45). However, the cardioprotective effect of raised HDL-C by alcohol consumption is largely unknown.

While the univariate analysis showed a higher prevalence of chronic diseases in women with normal or low HDL-C levels (overweight, obesity, abdominal obesity and hypertension) than the counterpart group, the multivariate regression analysis revealed that hypertension was the only negative risk factor of HDL-C in Tunisian women. Due to epidemiological and nutritional transition, the prevalence of overall obesity and abdominal obesity in Tunisian women has increased drastically during the last decades (46). In this study, the overall obesity affected the third of Tunisian women and the abdominal obesity concerned almost the half, with a decreasing trend with HDL-C levels. The negative associations between obesity and HDL-C have long been reported and were attributed to the potential role of HDL-C or ApoA-I on adipose tissue content regulation (47, 48). Hypertension is a well-established risk factor for CVD and is strongly associated with dyslipidemia, a group of metabolic derangements including low HDL-C levels. This association occurs at the vascular endothelial level leading to an increase of oxidative stress and endothelial dysfunction (49). The inverse association between HDL-C and hypertension was reported elsewhere (50). Halperin et al. (2006) found that men in the highest quintile of HDL-C had a 32% decreased risk of developing hypertension compared with those in the lowest quintile (51). Likewise,

Tohidi et al. (2012) found that women with HDL-C level between 1.0 and 1.5 mmol L<sup>-1</sup> had 33% lower risk of hypertension compared with those having HDL-C levels < 1 mmol L<sup>-1</sup> (52).

Family history of chronic diseases (CVD, hypertension, diabetes, obesity) was not correlated with HDL-C levels in this study, except the family history of cancer. In addition, the intake of lipid-lowering drugs is evenly divided between participants. According to Steyn et al. (1989), women with high levels of HDL-C were less likely to have a history of hypertension or diabetes (53) than those with low HDL-C concentrations. Opoku et al. (2019) reported negative significant associations of the history of coronary heart disease and the history of stroke with HDL-C in Chinese women (50). In the Bogalusa Heart Study, children with fathers' history of myocardial infarction had low ApoA-I levels and a high ApoB/ApoA-I ratio, whereas their HDL-C levels were not outside normal limits (54). In this study, family history of cancer revealed an inverse association with HDL-C levels between the univariate and the multivariate analysis. After adjustment for all sociodemographic, metabolic and lifestyle factors, the family history of cancer was a strong positive predictor of HDL-C in Tunisian women. Similar findings were observed in a cohort study on US veterans, which reported a slight increase in cancer mortality among participants with high HDL-C levels (> 50 mg/dL). However, other epidemiological studies reported that a low HDL-C level may be a risk of cancer deaths or a prognostic factor of many types of cancer in obese subjects (29). These controversial results need further investigations on the relationship between HDL-C and cancer disease.

Significant differences were noticed between biological characteristics in women with high HDL-C levels and the counterpart group. Triglyceridemia, ApoB, TC/HDL-C and ApoB/ApoA-I ratios, SBP and DBP were lower in women with high HDL-C concentrations contrary to TC and ApoA-I levels. Increased plasma triglyceride levels have been associated with an increased risk of CVD even when HDL-C levels were adjusted for (55). ApoA-I is the major structural and functional HDL protein which accounts for approximately 70% of total HDL protein and is significantly associated with HDL particles (56). However, more than 90% of all ApoB in blood is found in LDL (57). Clinical studies have reported that elevated ApoB levels, an increased apoB/apoA-I ratio and low levels of apoA-I were better predictors of cardiovascular events than LDL-C, TC and triglyceride levels even in patients receiving statins (57). SBP and DBP were lower in women with high HDL-C levels. This result confirms the protective role of HDL-C against risk factors of CVD such as raised blood pressure or hypertension. Despite the significant differences in biological characteristics between women with high HDL-C and those with normal or low HDL-C, all mean concentrations were within the normal range for both groups in our study.

## Strengths And Limitations

This study has several strengths in terms of sample size and the evaluation of a large set of covariates as potential risk factors for high HDL-C levels in Tunisian women. The limitations concern the lack of dietary information that could affect HDL-C levels, especially fat intake, and the cross-sectional study which prevents from establishing causal relationships.

## Conclusions

The prevalence of high HDL-C and its associated physical, sociodemographic, biological and lifestyle factors were assessed in a cross-sectional study conducted among childbearing age Tunisian women. Almost the quarter of studied women were with high HDL-C levels. They were younger, more educated and had a lower socioeconomic status than those with mean or low levels of HDL-C. Age, hypertension and smoking were independent negative risk factors of high HDL-C in women while family history of cancer was positively associated with high HDL-C levels. Due to controversial findings on the association between high HDL-C and cancer disease, further investigations should be performed in this domain.

## Declarations

### *Ethics approval and consent to participate*

During this study, all applicable institutional and governmental regulations concerning the ethical use of human volunteers were respected. The project and the survey protocol were reviewed and approved by the Ethical Committee of the National Institute of Nutrition and Food Technology (decision on February 7<sup>th</sup> 2009) and the Tunisian National Council of Statistics, which assigned the identifier number 02/2009. After being thoroughly informed on the purpose, requirements, and procedures of the survey, all women gave their ethical approval and consent. All data were handled anonymously during analysis. This study is registered in the ClinicalTrials.gov registry. The Identifier number is NCT01844349.

### *Consent for publication*

Not applicable

### *Availability of data and materials*

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

### *Competing interests*

The authors declare that they have no competing interests

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### *Authors' contributions*

All authors conceived and designed the experiments. Data collection and analysis was performed by RD, FH and FBC. JEA and MEAH supervised the field survey, the collection and acquisition of data. FBC and

MEAH wrote the article. All authors read and approved the final manuscript.

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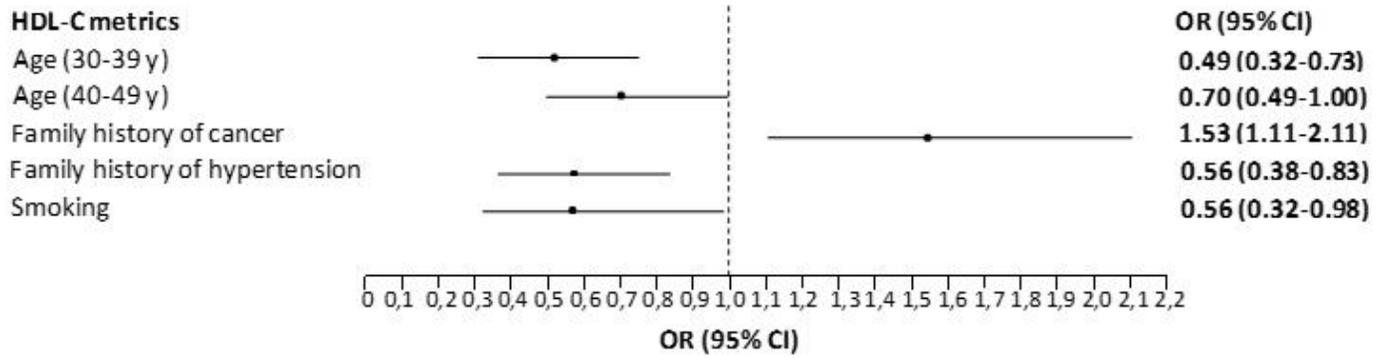
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# Figures



**Figure 1**

Adjusted odds ratio (OR; 95 % CI) of HDL-C for age and all socio-demographic, lifestyle and biological factors.