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Prevalence and Treatment of Familial Hypercholesterolemia in France

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See editorial by Francis and Brunham, pages 699–700 of this issue.

ABSTRACT

Background: Familial hypercholesterolemia (FH) is known to be underdiagnosed and undertreated. The prevalence of heterozygous FH is estimated to be 1 in 500. Nevertheless, a recent meta-analysis of screening in the general population seems to show that the prevalence of FH is more likely to be 1 in 250.

Methods: Analysis was based on the third French MONICA and MONALISA population surveys. Participants were randomly recruited in 1995 and 2005 from the general population of 3 regions of France. FH was diagnosed using a modified version of the Dutch Lipid Clinic Network (DLCN) without genetic testing.

Results: The DLCN score was assessed in 7928 participants aged 35 to 74 years; 50% were men. The prevalence of definite or probable FH was 0.85% (95% CI, 0.63-1.06). Among patients with definite or probable FH, 12% had histories of premature cardiovascular disease (vs less than 1% among subjects without FH; $P < 0.0001$), 70% were treated (13% with high-intensity, 83% with moderate-intensity, and 4%

RÉSUMÉ

Contexte : L'hypercholestérolémie familiale (HF) est connue pour être sous-diagnostiquée et sous-traitée. La prévalence de la HF hétérozygote est estimée à 1 sur 500. Néanmoins, une méta-analyse récente sur le dépistage dans la population générale semble montrer qu'elle serait plutôt de 1 sur 250.

Méthodologie : L'analyse s'est fondée sur les résultats de la troisième enquête de population française MONICA et de l'enquête MONA LISA. Les participants ont été recrutés de façon aléatoire en 1995 et en 2005 dans la population générale de trois régions de France. Le diagnostic de HF a été posé à l'aide d'une version modifiée du score du Dutch Lipid Clinic Network (DLCN) sans effectuer de tests génétiques.

Résultats : Le score DLCN a été évalué chez 7928 participants âgés de 35 à 74 ans, dont 50 % d'hommes. La prévalence de la HF confirmée ou probable était de 0,85 % (intervalle de confiance [IC] à 95 %, de 0,63 à 1,06). Parmi les individus présentant une HF confirmée ou probable, 12 % avaient des antécédents de maladie cardiovasculaire

Familial hypercholesterolemia (FH) is known to be underdiagnosed and undertreated, although patients with FH are at very high cardiovascular risk.[1] The prevalence of heterozygous FH is estimated at 1 in 500. Nevertheless, screening in the general population, recently reported in a meta-analysis, seems to show that the prevalence of FH is more likely to be 1 in 250 and that it varies by geographical location, with a lower prevalence in the European subgroup.[2] Moreover, 2 later European studies, not included in the meta-analysis, estimated prevalence at 1 in 278 in the German population[3] and at 1 in 192 in the Spanish population.[4] The prevalence of FH in the French general population has never been studied. We assessed, for the first time, the prevalence and treatment of FH in a sample recruited from the French general population.

Methods

Study population and design

A sample of 8171 subjects was randomly recruited from the general population to participate in the third French MONICA[5-8] and MONALISA[9,10] cross-sectional surveys on the prevalence of cardiovascular risk factors in 1995 and 2005. Men and women, aged 35 to 74, living in northern (Lille area), northeastern (Strasbourg area), or southwestern France

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with low-intensity statin therapy), 90% had cholesterol screening within the past 12 months, and 97% were aware of their hypercholesterolemia. None reached the recommended low-density lipoprotein cholesterol (LDL-C) target (< 2.5 or < 1.8 mmol/L for subjects in primary prevention vs in secondary prevention or with diabetes, respectively), with a mean distance to target of 3.0 mmol/L.

Conclusions: In a sample from the French general population aged 35 to 74 years, the prevalence of FH was close to 1 in 120, and the patients with FH were undertreated.

précoce (vs moins de 1 % chez ceux sans HF; $p < 0{,}0001$), 70 % étaient traités par une statine (13 % à haute intensité, 83 % à intensité modérée et 4 % à faible intensité), 90 % avaient bénéficié d'une évaluation du taux de cholestérol au cours des 12 derniers mois et 97 % étaient informés de leur hypercholestérolémie. Aucun des répondants n'a atteint la cible recommandée pour le cholestérol-LDL (< 2,5 ou < 1,8 mmol/l pour les patients en prévention primaire vs en prévention secondaire ou atteints de diabète, respectivement), avec un écart moyen par rapport à l'objectif de 3,0 mmol/l.

Conclusions : Dans un échantillon de la population générale française où les répondants étaient âgés de 35 à 74 ans, la prévalence de la HF était proche de 1 sur 120, et les personnes atteintes de cette affection étaient sous-traitées.

(Toulouse area) were recruited between December 1994, and July 1997, for the MONICA study and between October 2005, and January 2008, for the MONALISA study. Polling lists available in each town hall of the survey areas were used to obtain the stratified random sample. Stratification was applied according to centre, town size (rural vs urban), age, and sex to obtain 200 subjects in each sex and centre 10-year age group (35 to 44, 45 to 54, 55 to 64 years for the MONICA and MONALISA studies; 65 to 74 years for the MONALISA study). No incentive to participate (in particular, no financial incentive) was offered. Written informed consent to participate in the study was obtained from each subject after full explanation of the nature of the research. The study protocol was approved by an institutional ethics committee in accordance with French law on human biomedical research and the Declaration of Helsinki.

Questionnaires, measurements of clinical parameters, and laboratory methods

Extensive questionnaires were filled in by specifically trained medical staff during a face-to-face interview with participants. Information on exposures was collected. Data concerning socioeconomic level, previous personal and family medical history, cardiovascular risk factors, lifestyle habits, and drug intake were recorded. Lipid-lowering, antihypertensive, and hypoglycemic drug use was defined as the current consumption of drugs prescribed by physicians for treating cholesterol, blood pressure, or glucose disturbances. The intensity of statin therapy (high-, moderate-, and low-intensity statin therapy) was assessed using the 2013 ACC/AHA blood cholesterol guideline.[11] Cholesterol screening within the past 12 months was determined by self-report, together with awareness of hypercholesterolemia, using the following question: "Have you ever been told by a doctor or other health professional that your blood cholesterol level was high?" Educational level was assessed by a report of graduation or level of school dropout. Smoking was categorized as "current," "former," and "never." Consumption of cigarettes, cigars, cigarillos, and pipe tobacco was taken into account. Alcohol consumption was quantified in grams of alcohol per day with a 7-day recall method of a typical week and was categorized into no current consumption, moderate current consumption (1 to 2 drinks per day,10 to 20 grams per day) for men and 1 drink per day for women) and high current consumption ($\geq$ 3 drinks per day for men and $\geq$ 2 drinks per day for women). Four levels of leisure-time physical activity were defined: no regular physical activity, low physical activity (such as walking or bicycling—without causing shortness of breath or sweating—almost every week), moderate physical activity (ie, causing shortness of breath or sweating, during at least 20 minutes, once or twice a week) and high physical activity (ie, causing shortness of breath or sweating, during at least 20 minutes, 3 times a week or more). Height, weight, and arterial blood pressure (mean of 2 measurements performed with a standard sphygmomanometer in a sitting position after at least a 5-minute rest) were measured according to standardized protocols by the medical staff. Body mass index (BMI) was calculated as weight divided by the square of height in meters (kg/m^2).

Laboratory methods

Blood samples were taken after at least 10 hours of overnight fasting. Serum total cholesterol and triglycerides were measured by enzymatic assays (Boehringer, Mannheim, Germany). High-density lipoprotein cholesterol (HDL-cholesterol) measurement was performed after sodium phosphotungstate-magnesium chloride precipitation of apo B-containing lipoproteins. Low-density lipoprotein cholesterol (LDL-cholesterol) was determined by the Friedewald formula when triglycerides were below 4.6 mmol/L (400 mg/dL).[12] Fasting blood glucose (FBG) levels were measured using a conventional enzymatic method based on hexokinase-glucose-6-phosphate deshydrogenase. All blood samples were analyzed in a core laboratory (Toulouse University Hospital for the MONICA study and the Pasteur Institute of Lille for the MONALISA study).

Definition of FH

FH was diagnosed using the following modified version of the Dutch Lipid Clinic Network (DLCN) diagnostic criteria[13]: first-degree relative (parents) with known premature (< 55 years in men; < 60 years in women) coronary or vascular (cerebral or peripheral) disease or hypercholesterolemia (1 point); subject with premature coronary artery disease (2 points); subject with premature cerebral or peripheral vascular disease (1 point); LDL-C (LDL-cholesterol) $\geq$ 8.5 mmol/L (8 points), 6.5 to 8.4 mmol/L (5 points), 5.0 to 6.4 mmol/L (3 points) or 4.0 to 4.9 mmol/L (1 point).

Table 1. Prevalence* of FH according to age and sex

	FH (DLCN), % [95% CI]					
	Possible FH			Probable or definite FH		
Age, years	Men	Women	Total	Men	Women	Total
35−44	12.6 [10.6-14.5]	3.97 [2.83-5.11]	8.37 [7.22-9.51]	0.69 [0.21-1.18]	0.18 [0.00-0.44]	0.44 [0.17-0.72]
45−54	15.6 [13.4-17.7]	8.14 [6.51-9.76]	11.9 [10.6-13.3]	0.94 [0.38-1.51]	0.91 [0.34-1.49]	0.93 [0.53-1.33]
55−64	14.4 [12.3-16.5]	15.0 [12.9-17.2]	14.7 [13.2-16.2]	0.98 [0.39-1.56]	1.02 [0.41-1.63]	1.00 [0.58-1.42]
65−74	13.7 [10.9-16.6]	17.9 [14.6-21.1]	15.9 [13.8-18.1]	0.82 [0.10-1.53]	1.57 [0.54-2.59]	1.22 [0.58-1.87]
Total	13.6 [12.5-14.7]	9.00 [8.13-9.87]	11.3 [10.6-12.0]	0.89 [0.58-1.19]	0.80 [0.51-1.10]	0.85 [0.63-1.06]

DLCN (modified version of the Dutch Lipid Clinic Network criteria): first degree relative (parents) with known premature (< 55 years in men; < 60 years in women) coronary or vascular (cerebral or peripheral) disease or hyperlipidemia (1 point); subject with premature coronary artery disease (2 points); subject with premature cerebral or peripheral vascular disease (1 point); LDL-C ≥ 8.5 mmol/L (8 points), 6.5 to 8.4 mmol/L (5 points), 5.0−6.4 mmol/L (3 points), 4.0 to 4.9 mmol/L (1 point). LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors[14]) for subjects taking statins or ezetimibe. FH was considered as definite, probable, or possible for a total > 8 equal to 6 to 8 or 3 to 5 points, respectively.

CI, confidence interval; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

*Weighted according to the age and sex distribution of the population aged 35 to 74 years in the French 1995 and 2005 censuses.

Baseline LDL-C was imputed for subjects under statin or ezetimibe treatment using dose- and statin- or ezetimibe-specific correction factors that have been previously validated.[14] FH was considered as definite, probable, possible, or unlikely for a total >8, equal to 6 to 8, 3 to 5, or <3 points, respectively. Subjects with potential secondary hypercholesterolemia (hypothyroidism, chronic renal failure, chronic liver disease, or cirrhosis without fatty liver) or mixed dyslipidemia (triglycerides > 3.4 mmol/L) were not considered to have FH. Among the 8171 participants, 243 (3%) had missing data for the DLCN score (LDL-C), thus leading to a sample of 7928 subjects analyzed.

Statistical analysis

Statistical analysis was performed on STATA statistical software, release 14.2 (STATA Corporation, College Station, TX). We first described the main characteristics of the participants according to definite, probable, possible, or unlikely FH (Supplemental Table S1). The prevalence of FH was presented as a percentage together with the 95% confidence interval (CI). The prevalence of FH was weighted according to the age and sex distribution of the 35- to 74-year-old populations in the French 1995 and 2005 censuses (in Lille, Strasbourg, and Toulouse areas) using Taylor linearization[15,16] (Table 1). We then compared the main characteristics of the participants with and without definite or probable FH (Table 2). Categorical variables were compared among groups using the χ^2-test (or Fisher's exact test when necessary). Students' *t*-tests were used to compare the distribution of continuous data (Mann-Whitney's test was used when the distribution departed significantly from normality or when homoscedasticity was rejected). Finally, we assessed whether FH was independently associated with premature cardiovascular disease using logistic regression (Table 3). Variables initially introduced into the multivariate analyses were standard cardiovascular risk factors associated with premature cardiovascular disease in univariate analyses with a *P* value < 0.20. A backward analysis was then applied until only variables significantly and independently associated with premature cardiovascular disease (*P* value < 0.05) remained. When the linearity hypothesis was not respected, continuous variables were transformed into ordered data. Interactions between independent covariates were tested in the final models. None was significant. All reported *P* values were 2-sided, and the significance threshold was <0.05.

Results

The DLCN score was assessed in 7928 participants (n = 3260 for the MONICA study and 4668 for the MONALISA study) aged 35 to 74 years, of whom 50% were men. The main characteristics of the participants according to DLCN diagnostic criteria for FH are detailed in Supplemental Table S1.

The prevalence of definite or probable FH was 0.85% (95% CI, 0.63-1.06) (Table 1). This prevalence tended to be higher for men and increased according to age, without reaching the significant threshold.

As expected, the frequency of DLCN criteria (such as a personal or family history of premature coronary artery disease, cerebral, or peripheral vascular disease) and LDL-C levels were significantly higher in subjects with definite or probable FH. On the other hand, levels of standard cardiovascular risk factors not included in the DLCN score did not significantly differ between subjects with and without definite or probable FH (Table 2).

Among subjects with definite or probable FH (n = 67), 12% had premature coronary artery disease, cerebral, or peripheral vascular disease (vs less than 1% among subjects without FH; odds ratio [OR] = 17.6 [95% CI: 8.1-38.5]; $P < 0.001$). After adjustment for standard cardiovascular risk factors, FH was still significantly and independently associated with premature cardiovascular disease (OR = 14.1 [6.3-31.7]; $P < 0.001$) (Table 3). This was also true according to age with adjusted OR = 18.8 [1.5−240.1] ($P = 0.024$), 15.2 [5.2-45.1] ($P < 0.001$) and 19.7 [4.0-97.5] ($P < 0.001$) for subjects aged 35 to 44, 45 to 54, and 55 to 74 years, respectively.

On the other hand, 70% (n = 47) of the subjects with definite or probable FH were treated, 13% (n = 6) with high-intensity statin therapy (n = 3 with atorvastatin 40 mg, n = 3 with rosuvastatin 20 mg), 83% (n = 39) with moderate-intensity statin therapy (n = 11 with pravastatin 40 mg, n = 8 with simvastatin 20 mg, n = 1 with simvastatin 40 mg, n = 4 with atorvastatin 10 mg, n = 7 with atorvastatin 20 mg, n = 1 with rosuvastatin 5 mg, n = 5 with rosuvastatin

Table 2. Comparison of the main characteristics of the participants with and without definite or probable FH (defined by the Dutch Lipid Clinic Network criteria)

	Definite or probable FH		
	No (n = 7861)	Yes (n = 67)	*P* value
Age, years, n (%)			0.0627
35-44	2272 (28.9)	10 (14.9)	
45-54	2277 (29.0)	21 (31.3)	
55-64	2197 (27.9)	22 (32.8)	
65-74	1115 (14.2)	14 (20.9)	
Sex, n (%)			0.7299
Male	3940 (50.1)	35 (52.2)	
Female	3921 (49.9)	32 (47.8)	
Educational level, n (%)			0.2195
< High school completion	4820 (61.3)	46 (68.7)	
≥ High school completion	3040 (38.7)	21 (31.3)	
Physical activity*, n (%)			0.7133
No	1676 (21.4)	11 (16.4)	
Low	3751 (47.9)	35 (52.2)	
Moderate	1579 (20.2)	15 (22.4)	
High	830 (10.6)	6 (9.0)	
Subjects with premature† coronary or cerebral/peripheral vascular disease, n (%)			< 0.0001
No	7801 (99.2)	59 (88.1)	
Yes	60 (0.8)	8 (11.9)	
First-degree relative (parents) with premature† coronary or cerebral/peripheral vascular disease, n (%)			< 0.0001
No	7227 (91.9)	50 (74.6)	
Yes	634 (8.1)	17 (25.4)	
Smoking, n (%)			0.1790
Never	3653 (46.5)	27 (40.3)	
Former	2484 (31.6)	19 (28.4)	
Current	1724 (21.9)	21 (31.3)	
Drinking, n (%)			0.0522
Men, 1 to 2 drinks/day OR			
Women, 1 drink/day	3909 (49.8)	28 (41.8)	
Non-drinkers	2124 (27.0)	15 (22.4)	
Men, ≥ 3 drinks/day OR			
Women, ≥ 2 drinks/day	1824 (23.2)	24 (35.8)	
Body mass index (kg/m^2)			
n	7804	67	
Mean (SD)	26.5 (4.8)	27.5 (5.7)	
Median	25.7	25.5	
IQR	[23.1-28.9]	[24.0-29.4]	0.2941
Fasting blood glucose (mmol/L)			
n	7832	66	
Mean (SD)	5.4 (1.2)	5.7 (1.6)	
Median	5.2	5.4	
IQR	[4.9-5.7]	[5.1-5.8]	0.0272
Diabetes‡, n (%)			0.6249
No	7347 (93.5)	62 (92.5)	
Yes	514 (6.5)	5 (7.5)	
Systolic blood pressure (mm Hg)			
n	7844	67	
Mean (SD)	133.4 (20.0)	134.8 (18.2)	0.5873
Median	131.0	132.0	
IQR	[119.5-145.0]	[121.0-141.5]	
Diastolic blood pressure (mm Hg)			
n	7842	67	
Mean (SD)	81.7 (11.2)	81.6(8.4)	
Median	81.0	81.5	
IQR	[74.0-88.5]	[76.5-85.5]	0.9027
Blood pressure, n (%)			0.4985
< 140 and 90 mm Hg	4834 (61.6)	44 (65.7)	
≥ 140 or 90 mm Hg	3009 (38.4)	23 (34.3)	
Antihypertensive drug treatment, n (%)			0.0751
No	6315 (80.3)	48 (71.6)	
Yes	1546 (19.7)	19 (28.4)	
Lipid-lowering drug treatment, n (%)			< 0.0001
No	6638 (84.4)	20 (29.9)	
Yes	1223 (15.6)	47 (70.1)	

Continued

Table 2. Continued.

	Definite or probable FH		
	No (n = 7861)	Yes (n = 67)	*P* value
Total cholesterol (mmol/L)			
n	7861	67	
Mean (SD)	5.8 (1.0)	7.6 (1.5)	
Median	5.7	7.4	
IQR	[5.1- 6.4]	[6.3-8.7]	< 0.0001
Triglycerides (mmol/L)			
n	7861	67	
Mean (SD)	1.3 (0.7)	1.7 (0.7)	
Median	1.1	1.5	
IQR	[0.8- 1.5]	[1.2-2.0]	< 0.0001
HDL-cholesterol (mmol/L)			
n	7861	67	
Mean (SD)	1.5 (0.4)	1.5 (0.4)	0.6059
Median	1.4	1.4	
IQR	[1.2- 1.7]	[1.1-1.7]	
LDL-cholesterol (mmol/L)			
n	7861	67	
Mean (SD)	3.7 (0.9)	5.4 (1.5)	
Median	3.6	5.1	
IQR	[3.1- 4.3]	[4.2-6.4]	< 0.0001
Corrected LDL-cholesterol (mmol/L)[§]			
n	7861	67	
Mean (SD)	3.9 (1.0)	8.1 (1.6)	
Median	3.8	8.0	
IQR	[3.2-4.5]	[6.9-8.7]	< 0.0001
DLCN			
n	7861	67	
Mean (SD)	0.9 (1.2)	7.0 (1.2)	
Median	1.0	6.0	
IQR	[0.0-1.0]	[6.0-8.0]	< 0.0001

DLCN (modified version of the Dutch Lipid Clinic Network criteria): first-degree relative (parents) with known premature (< 55 years in men; < 60 years in women) coronary or vascular (cerebral or peripheral) disease or hyperlipidemia (1 point); subject with premature coronary artery disease (2 points); subject with premature cerebral or peripheral vascular disease (1 point); LDL-C ≥ 8.5 mmol/L (8 points), 6.5 to 8.4 mmol/L (5 points), 5.0 to 6.4 mmol/L (3 points), or 4.0 to 4.9 mmol/L (1 point). LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors[14]) for patients taking statins or ezetimibe. FH was considered as definite or probable for a total > 8 or equal to 6 to 8 points, respectively.

FH, familial hypercholesterolemia; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SD, standard deviation.

*No regular physical activity vs low physical activity (such as walking or bicycling, without causing shortness of breath or sweating, almost every week) vs moderate physical activity (ie, causing shortness of breath or sweating, during at least 20 minutes, once or twice a week) vs high physical activity (ie, causing shortness of breath or sweating, during at least 20 minutes, 3 times a week or more).

†< 55 years in men; < 60 years in women.

‡Diabetes was assessed for subjects with fasting blood glucose ≥ 7 mmol/L (126 mg/dL) or under hypoglycemic drug treatment.

§LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors[14]) for patients taking statins or ezetimibe.

10 mg, n = 1 with fluvastatin 40 mg, n = 1 with simvastatin 20 mg and ezetimibe 10 mg), and 4% (n = 2) with low-intensity statin therapy (n = 1 with pravastatin 10 mg and n = 1 with pravastatin 20 mg). These frequencies of treatment were the same in 1995 and 2005, whereas mean LDL-C was significantly lower in 2005 (5.1 mmol/L (standard deviation [SD] ± 1.3) vs 6.2 mmol/L (± 1.7) in 1995; $P = 0.0144$). The frequency of high- or moderate-intensity statin therapy was significantly higher for treated subjects with definite or probable FH than for treated subjects with possible or unlikely FH (Fig. 1).

None of the subjects with definite or probable FH reached the recommended target[1] (LDL-C < 2.5 mmol/L or < 1.8 mmol/L for subjects in primary prevention vs in secondary prevention or with diabetes, respectively), whereas 90% (n = 60) had cholesterol testing within the past 12 months, and 97% (n = 65) were aware of their hypercholesterolemia. Mean measured LDL-C was 4.9 mmol/L (± 1.0) and 6.6 mmol/L (± 1.7) in patients with definite or probable FH with and without treatment, respectively ($P < 0.0001$), and the mean distance to target was 3.0 mmol/L (± 1.5).

Discussion

Prevalence of FH

In the French general population aged 35 to 74 years, we described, for the first time—in nearly 8000 participants—a prevalence of definite or probable FH of 0.85% (95% CI, 0.63-1.06). This is significantly higher than the pooled prevalence of FH estimated in the recent meta-analysis of Akioyamen et al. (0.40% [95% CI, 0.29-0.54]; n = 19 studies; n = 2,458,456 subjects[2]). This difference is explained by the method of correction of the LDL-C. We corrected LDL-C for subjects under statins or ezetimibe using dose- and statin- or ezetimibe-specific correction factors recently validated,[14] whereas all the studies included in the meta-analysis of Akioyamen et al., which corrected LDL-C, had

Table 3. Independent association of definite or probable familial hypercholesterolemia (defined by the Dutch Lipid Clinic Network criteria) with premature* coronary or cerebral/peripheral vascular disease (n = 68 events in the entire study population of 7928 participants)

	Univariate analysis		Multivariate analysis	
	OR [95% CI]	*P* value	OR [95% CI]	*P* value
FH[†]		< 0.001		< 0.001
No	1.00		1.00	
Yes	17.6 [8.1-38.5]		14.1 [6.3-31.7]	
Sex		0.152		
Female	1.00			
Male	1.4 [0.9-2.3]			
Educational level		0.023		0.037
≥ High school completion	1.00		1.00	
< High school completion	1.9 [1.1-3.3]		1.8 [1.0-3.1]	
Physical activity[‡]		0.116		
No	1.00			
Low	0.9 [0.5-1.6]			
Moderate	0.8 [0.4-1.7]			
High	0.2 [0.1-1.0]			
First-degree relative (parents) with premature* coronary or cerebral/peripheral vascular disease		0.002		0.018
No	1.00		1.00	
Yes	2.7 [1.5-4.9]		2.1 [1.1-4.0]	
Smoking		0.080		
Never	1.00			
Former	1.5 [0.9-2.7]			
Current	1.9 [1.1-3.5]			
Drinking		0.119		
Men, 1 to 2 drinks/day OR Women, 1 drink/day	1.00			
Nondrinkers	1.4 [0.8-2.5]			
Men, ≥ 3 drinks/day OR Women, ≥ 2 drinks/day	1.8 [1.0-3.2]			
Body mass index		0.099		
< 30 kg/m^2	1.00			
≥ 30 kg/m^2	1.6 [0.9-2.7]			
Diabetes[§]		0.787		
No	1.00			
Yes	1.1 [0.5-2.8]			
High blood pressure		0.128		
< 140 and 90 mm Hg and without antihypertensive drug treatment	1.00			
≥ 140 or 90 mm Hg or under drug treatment	1.4 [0.9-2.3]			
Triglycerides		0.018		
< 1.14 mmol/L (100 mg/dL)	1.00			
≥ 1.14 mmol/L	1.8 [1.1-2.9]			
HDL-C (mmol/L)		0.001		0.003
≤ 1.0 mmol/L (40 mg/dL)	1.00		1.00	
> 1.0 mmol/L	0.4 [0.2-0.7]		0.4 [0.2-0.7]	
Corrected LDL-C[¶]		<0.001		
< 5.0 mmol/L (190 mg/dL)	1.00			
≥ 5.0 mmol/L	2.6 [1.6-4.4]			

CI, confidence interval; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

* < 55 years in men; < 60 years in women.

† FH was considered as definite or probable for a total > 8 or equal to 6 to 8 points, respectively, according to a modified version of the Dutch Lipid Clinic Network criteria: first-degree relative (parents) with known premature (< 55 years in men; < 60 years in women) coronary or vascular (cerebral or peripheral) disease or hyperlipidemia (1 point); subject with premature coronary artery disease (2 points); subject with premature cerebral or peripheral vascular disease (1 point); LDL-C ≥ 8.5 mmol/L (8 points), 6.5 to 8.4 mmol/L (5 points), 5.0 to 6.4 mmol/L (3 points) or 4.0 to 4.9 mmol/L (1 point). LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors[14]) for patients taking statins or ezetimibe.

‡ No regular physical activity vs low physical activity (such as walking or bicycling, without causing shortness of breath or sweating, almost every week) vs moderate physical activity (ie, causing shortness of breath or sweating, during at least 20 minutes, once or twice a week) vs high physical activity (ie, causing shortness of breath or sweating, during at least 20 minutes, 3 times a week or more).

§ Diabetes was assessed for subjects with fasting blood glucose ≥ 7 mmol/L (126 mg/dL) or under hypoglycemic drug treatment.

¶ LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors[14]) for patients taking statins or ezetimibe.

multiplied by 1.43 (corresponding to an estimated 30% reduction).[17-23] In a sensitivity analysis, we assessed the prevalence of FH using this method of correction (LDL-C × 1.43), and the prevalence was very close to the result of Akioyamen et al. (0.41% [95% CI, 0.27-0.56] vs 0.40% [95% CI, 0.29-0.54]). Moreover, whereas the prevalence of FH is expected to decrease with age (considering that FH is a genetic disease with a very high risk of premature cardiovascular death), we found that it tended to increase with age. Akioyamen et al. showed, similarly, that the pooled prevalence of FH increased according to age with a peak between 60 to 69 years and a decline thereafter. Moreover, we found that the

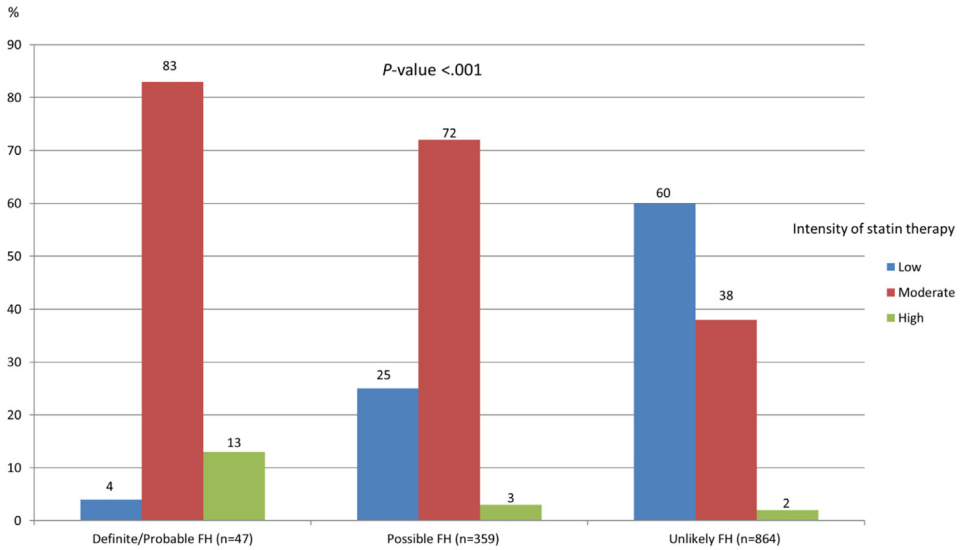

Figure 1. Frequency of low, moderate and high-intensity statin therapy in treated subjects with definite/probable, possible or unlikely familial hypercholesterolemia (FH) according to the Dutch Lipid Clinic Network criteria (DLCN). DLCN (modified version of the Dutch Lipid Clinic Network criteria): first-degree relative (parents) with known premature (< 55 years in men; < 60 years in women) coronary or vascular (cerebral or peripheral) disease or hyperlipidemia (1 point); subject with premature coronary artery disease (2 points); subject with premature cerebral or peripheral vascular disease (1 point); LDL-C ≥ 8.5 mmol/L (8 points), 6.5 to 8.4 mmol/L (5 points), 5.0 to 6.4 mmol/L (3 points), and 4.0 to 4.9 mmol/L (1 point). LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors[14]) for subjects taking statins or ezetimibe. Familial hypercholesterolemia was considered as definite, probable, possible, or unlikely for a total > 8, equal to 6 to 8, 3 to 5, or < 3 points, respectively. The intensity of statin therapy (high, moderate, and low) was assessed using the 2013 ACC/AHA blood cholesterol guideline.[11]

prevalence of FH tended to be higher in men, similar to the results of Zamora et al.[4] These unexpected higher prevalences may be due to the use of FH diagnostic criteria based on LDL-C, which is known to increase with age and that is lower in premenopausal women.[23,24] Finally, in the meta-analysis of Akioyamen et al., the prevalence of FH was significantly lower in the European subgroup (0.21% [95% CI, 0.14-0.28]). This lower prevalence seems to be linked to the diagnostic method used. Half the studies included in the European meta-analysis subgroup used DNA-based evidence of mutations, which is known to be associated with lower prevalence of FH.[19,21,25] Accordingly, Séguro et al. showed that an FH mutation was identified in only 57% of patients with clinical FH.[26] In the French-Canadian population, FH seems to be more prevalent because of genetic founder effect with a prevalence reaching 1 in 81 in one region of the Province of Quebec.[27]

Management of FH

Screening of FH is recommended by French experts for high-risk patients (patients with premature cardiovascular disease or with family histories of premature cardiovascular disease, high cholesterol, or tendon xanthomas, or LDL-C > 5 mmol/L) to identify FH as soon as possible and initiate adequate therapy.[28] The treatment strategy recommended by French experts is based on high-intensity statins in combination with ezetimibe and bile acid sequestrant to obtain ≥ 50% reduction in LDL-C.[28] For severe FH, if the reduction of LDL-C failed to obtain the target, the addition of a PCSK9 inhibitor should be considered.[28] This French treatment strategy is very closed to the guidelines of Canadian experts.[29,30] In our population-based survey, only 70% of subjects with definite or probable FH were treated, and none reached the recommended LDL-C target[1] (LDL-C < 2.5 mmol/L or < 1.8 mmol/L for subjects in primary prevention vs in secondary prevention or with diabetes, respectively) with a mean distance to target of 3.0 mmol/L. These results were concordant with the contemporary trend in the management of FH in Canada, although, in the Canadian study, the average distance to target in patients with FH was 1.7 mmol/L.[31] Moreover, in our population-based survey, FH is independently associated with premature cardiovascular disease (adjusted OR = 14.1 [6.3-31.7]; $P < 0.001$). Our findings confirmed that, despite the very high associated cardiovascular risk,[21,32] FH is undertreated.[1,4,33,34] This may be explained by the fact that French physicians involved in the management of the disease seems to have a lack of knowledge of FH and its associated cardiovascular risk.[35] Perhaps, in the context of the "French Paradox" (low incidence of coronary artery disease in Southern Europe),[36] French physicians think that patients with FH also have a lower risk of coronary artery disease than other patients with FH in other parts of the world. At present, 3 care pathways—involving general practitioners, cardiologists, endocrinologists, pharmacists, and medical laboratories—were launched in 2018, in 3 French regions (Nantes, Toulouse, and Marseille) to improve the knowledge, the diagnosis, and the management of FH.[37] Results will be available in the next 3 years and should improve the screening and treatment of FH in France.

Strengths and limitations of the study

The main limitation of our study is the use of a modified version of the DLCN criteria without genetic testing and with the possibility of overestimation of the prevalence of FH.

Nevertheless, modified DLCN criteria without genetic testing are those most frequently used in studies assessing FH in population surveys.[2] Moreover, the use of clinical criteria without genetic testing has demonstrated good diagnostic[38] and predictive[39] performance, leading Canadian researchers to publish a novel simplified definition that takes DNA-negative patients into consideration.[29,40,41] The strength of our study is that it is the first to be conducted in a representative sample of the French general population,[7] with nearly 8000 participants (and with LDL-C levels analyzed in core laboratories). Only 2 studies have assessed the prevalence of FH in France, but the first was conducted in statin-treated patients,[42] and the second used a large database of patients of a French university hospital.[43] These studies were not representative of the French general population. Moreover, we can consider that our study was the first to be conducted in the general population in southern Europe. The other 2 studies conducted in southern Europe (in Spain[4] and in Italy[44]) used primary-care patients, and the SAFEHEART Spanish registry includes only FH with genetic diagnosis,[45] underestimating the number of patients with FH.[4,25]

Conclusions

In the French general population aged 35 to 74 years, the prevalence of FH was close to 1 in 120, and subjects with FH were undertreated.

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References

1. Nordestgaard BG, Chapman MJ, Humphries SE, et al. European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34. 3478-90a.

2. Akioyamen LE, Genest J, Shan SD, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open 2017;7:e016461.

3. Schmidt N, Schmidt B, Dressel A, et al. Familial hypercholesterolemia in primary care in Germany. Diabetes and cardiovascular risk evaluation: Targets and Essential Data for Commitment of Treatment (DETECT) study. Atherosclerosis 2017;266:24-30.

4. Zamora A, Masana L, Comas-Cufí M, et al. XULA and ISV-Girona groups. Familial hypercholesterolemia in a European Mediterranean population: prevalence and clinical data from 2.5 million primary care patients. J Clin Lipidol 2017;11:1013-22.

5. Bérard E, Bongard V, Dallongeville J, et al. Impact of cardiovascular risk factor control on long-term cardiovascular and all-cause mortality in the general population. Ann Med 2016;48:559-67.

6. Bérard E, Bongard V, Haas B, et al. Score of adherence to 2016 European cardiovascular prevention guidelines predicts cardiovascular and all-cause mortality in the general population. Can J Cardiol 2017;33:1298-304.

7. Bérard E, Séguro F, Bongard V, et al. Predictive accuracy of the European Society of Cardiology SCORE among French people. J Cardiopulm Rehabil Prev 2016;36:38-48.

8. Marques-Vidal P, Ruidavets JB, Amouyel P, et al. Change in cardiovascular risk factors in France, 1985-1997. Eur J Epidemiol 2004;19:25-32.

9. Bongard V, Dallongeville J, Arveiler D, et al. Attainment of low-density lipoprotein cholesterol target in the French general population according to levels of cardiovascular risk: Insights from the MONA LISA study. Arch Cardiovasc Dis 2013;106:93-102.

10. Bongard V, Arveiler D, Dallongeville J, et al. Food groups associated with a reduced risk of 15-year all-cause death. Eur J Clin Nutr 2016;70:715-22.

11. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S1-45. Erratum in: Circulation 2015;132:e396. Circulation 2014;129:S46-8.

12. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1978;18:499-502.

13. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Curr Opin Lipidol 2012;23:282-9.

14. Ruel I, Aljenedil S, Sadri I, et al. Imputation of baseline LDL cholesterol concentration in patients with familial fypercholesterolemia on statins or ezetimibe. Clin Chem 2018;64:355-62.

15. Shah BV. Linearization methods of variance estimation. In: Armitage P, Colton T, eds. Encyclopedia of Biostatistics. 2nd ed. Chichester, UK: John Wiley and Sons Ltd, 1998:2276-9.

16. Wolter KM. Introduction to Variance Estimation. 2nd ed. New York: Springer, 2007.

17. Shi Z, Yuan B, Zhao D, Taylor AW, Lin J, Watts GF. Familial hypercholesterolemia in China: prevalence and evidence of underdetection and undertreatment in a community population. Int J Cardiol 2014;174:834-6.

18. Watts GF, Shaw JE, Pang J, Magliano DJ, Jennings GL, Carrington MJ. Prevalence and treatment of familial hypercholesterolaemia in Australian communities. Int J Cardiol 2015;185:69-71.

19. Benn M, Watts GF, Tybjærg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. Eur Heart J 2016;37:1384-94.

20. Catapano AL, Lautsch D, Tokgözoglu L, et al. Prevalence of potential familial hypercholesteremia (FH) in 54,811 statin-treated patients in clinical practice. Atherosclerosis 2016;252:1-8.

21. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol 2016;67:2578-89.

22. Pang J, Martin AC, Mori TA, Beilin LJ, Watts GF. Prevalence of familial hypercholesterolemia in adolescents: potential value of universal screening? J Pediatr 2016;170:315-6.

23. De Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). Circulation 2016;133:1067-72.

24. Wang X, Magkos F, Mittendorfer B. Sex differences in lipid and lipoprotein metabolism: it's not just about sex hormones. J Clin Endocrinol Metab 2011;96:885-93.

25. Catapano AL, Graham I, De Backer G, et al; ESC Scientific Document Group. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2016;37:2999-3058.

26. Séguro F, Rabès JP, Taraszkiewicz D, Ruidavets JB, Bongard V, Ferrières J. Genetic diagnosis of familial hypercholesterolemia is associated with a premature and high coronary heart disease risk. Clin Cardiol 2018;41:385-91.

27. Paquette M, Genest J, Baass A. Familial hypercholesterolemia: experience from the French-Canadian population. Curr Opin Lipidol 2018;29:59-64.

28. Farnier M, Civeira F, Descamps O; FH expert working group. How to implement clinical guidelines to optimise familial hypercholesterolaemia diagnosis and treatment. Atheroscler Suppl 2017;26:25-35.

29. Brunham LR, Ruel I, Aljenedil S, et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia: update 2018. Can J Cardiol 2018;34:1553-63.

30. Baass A, Hegele RA. Getting real with PCSK9 inhibitors in familial hypercholesterolemia. Can J Cardiol 2018;34:959-61.

31. Brunham LR, Cermakova L, Lee T, et al. Contemporary Trends in the Management and Outcomes of Patients With Familial Hypercholesterolemia in Canada: A Prospective Observational Study. Can J Cardiol 2017;33:385-92.

32. Abul-Husn NS, Manickam K, Jones LK, et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. Science 2016;354.

33. Bucholz EM, Rodday AM, Kolor K, Khoury MJ, de Ferranti SD. Prevalence and predictors of cholesterol screening, awareness, and statin treatment among US adults with familial hypercholesterolemia or other forms of severe dyslipidemia (1999-2014). Circulation 2018;137:2218-30.

34. Rodriguez F, Knowles JW, Maron DJ, Virani SS, Heidenreich PA. Frequency of statin use in patients with low-density lipoprotein cholesterol ≥190 mg/dl from the Veterans Affairs Health System. Am J Cardiol 2018;122:756-61.

35. Ferrières J, Bruckert É, Béliard S, et al. Familial hypercholesterolemia: a largely underestimated cardiovascular risk. Ann Cardiol Angeiol 2018;67:1-8.

36. Ferrières J. The French paradox: lessons for other countries. Heart 2004;90:107-11.

37. Rabès JP, Béliard S, Carrié A. Familial hypercholesterolemia: experience from France. Curr Opin Lipidol 2018;29:65-71.

38. Civeira F, Ros E, Jarauta E, et al. Comparison of genetic versus clinical diagnosis in familial hypercholesterolemia. Am J Cardiol 2008;102:1187-93.

39. Séguro F, Bongard V, Bérard E, Taraszkiewicz D, Ruidavets JB, Ferrières J. Dutch Lipid Clinic Network low-density lipoprotein cholesterol criteria are associated with long-term mortality in the general population. Arch Cardiovasc Dis 2015;108:511-8.

40. Ruel I, Brisson D, Aljenedil S, et al. Simplified Canadian definition for familial hypercholesterolemia. Can J Cardiol 2018;34:1210-4.

41. McPherson R. The cardiovascular burden of undiagnosed familial hypercholesterolemia: need to modify guidelines to encourage earlier diagnosis and therapy. Can J Cardiol 2018;34:1112-3.

42. Catapano AL, Lautsch D, Tokgözoglu L, et al. Prevalence of potential familial hypercholesteremia (FH) in 54,811 statin-treated patients in clinical practice. Atherosclerosis 2016;252:1-8.

43. Ferrières J, Combis MS, Verdier C, et al. Big data and lipoproteins: prevalence of dyslipidemias in 100 762 individuals. Eur Heart J 2016;37(abstr suppl):11.

44. Guglielmi V, Bellia A, Pecchioli S, et al. What is the actual epidemiology of familial hypercholesterolemia in Italy? Evidence from a national primary care database. Int J Cardiol 2016;223:701-5.

45. Mata N, Alonso R, Badimón L, et al. Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). Lipids Health Dis 2011;10:94.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.02.013.