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Prevalence and Treatment of familial hypercholesterolemia in France

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ABSTRACT

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

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 three 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 35–74 years (50% were men). The prevalence of definite or probable FH was 0.85% [95% CI: 0.63–1.06]. Among subjects with definite or probable FH, 12% had a history of premature cardiovascular disease (versus less than 1% among subjects without FH; $P < .0001$), 70% were treated (13% with high-intensity, 83% with moderate-intensity and 4% 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 LDL-C target (<2.5 or <1.8 mmol/L for subjects in primary prevention versus 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 35–74 years, the prevalence of FH was close to 1/120 and the subjects with FH were undertreated.

BRIEF SUMMARY

Familial hypercholesterolemia (FH) is known to be underdiagnosed and undertreated. The prevalence of FH is unknown in France. The prevalence of FH was close to 1/120. More than 1/4 of subjects with FH were not treated.

KEYWORDS

Familial hypercholesterolemia; Prevalence; General population; France; Dutch Lipid Clinic Network diagnostic criteria

INTRODUCTION

Familial hypercholesterolemia (FH) is known to be underdiagnosed and undertreated whereas patients with FH are at very high cardiovascular risk [1]. The prevalence of heterozygous FH is estimated at 1/500. 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 1/250 and that it varies by geographical location with a lower prevalence in the European subgroup [2]. Moreover, two later European studies, not included in the meta-analysis, estimated prevalence at 1/278 in the German population [3] and at 1/192 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 35–74, living in northern (Lille area), north-eastern (Strasbourg area) or south-western France (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 center, town size (rural versus urban), age and sex, in order to obtain 200 subjects in each sex and center 10-year age group (35–44, 45–54, 55–64 years for the MONICA and MONALISA studies; 65–74 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 the participant. Information on exposures was collected. Data concerning socio-economic 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 a drug prescribed by a physician 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 via 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 drop-out. Smoking was categorized as current, former and never smoking. Consumption of cigarettes, cigars, cigarillos and pipe tobacco were 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 (1-2 drinks/day(d) (10-20 grams/d) for men and 1 drink/d for women) and high current consumption (≥ 3 drinks/d for men and ≥ 2 drinks/d 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 (i.e. causing shortness of breath or sweating, during at least 20 minutes, once or twice a week)

and high physical activity (i.e. causing shortness of breath or sweating, during at least 20 minutes, three times a week or more). Height, weight and arterial blood pressure (mean of two 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/m²).

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 dehydrogenase." 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) ≥ 8.5 mmol/L (8 points), 6.5–8.4 mmol/L (5 points), 5.0–6.4 mmol/L (3 points) or

4.0–4.9 mmol/L (1 point). 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 6–8, 3–5 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, USA).

We first described the main characteristics of the participants according to definite, probable, possible or unlikely FH (Table S1 in Supplementary Materials). The prevalence of FH was presented as a percentage together with the 95% confidence interval [95% CI]. The prevalence of FH was weighted according to the age and sex distribution of the 35–74 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 between groups using the χ^2 -test (or Fisher's exact test when necessary). Student's t-test was 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). Lastly, 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 $<.20$. A backward analysis was then applied until only variables significantly and independently associated with premature cardiovascular disease (P -value $<.05$) 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 were significant. All reported P -values were two-sided and the significance threshold was $<.05$.

Results

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

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 (versus less than 1% among subjects without FH; odds ratio (OR) = 17.6 [8.1–38.5]; $P <.001$). 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]; $P <.001$) (Table 3). This was also true according

to age with adjusted OR = 18.8 [1.5–240.1] ($P = .024$), 15.2 [5.2–45.1] ($P < .001$) and 19.7 [4.0–97.5] ($P < .001$) for subjects aged 35–44, 45–54 and 55–74 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 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 ± 1.3) versus 6.2 mmol/L (± 1.7) in 1995; $P = .0144$). 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 (Figure 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 versus 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 subjects with definite or probable FH with and without treatment, respectively ($P < .0001$), and the mean distance to target was 3.0 mmol/L (± 1.5).

Discussion

Prevalence of FH

In the French general population aged 35–74 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 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 x 1.43) and the prevalence was very close to the result of Akioyamen et al. (0.41% [95% CI: 0.27–0.56] versus 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 60–69 years and a decline thereafter. Moreover, we found that the prevalence of FH tended to be higher in men similarly 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 which 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 of 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 French-Canadian population, FH seems to be more prevalent because

of genetic founder effect with a prevalence reaching 1/81 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 a family history of premature cardiovascular disease or high cholesterol or tendon xanthomas, or when LDL-C >5 mmol/L) in order to identify FH as soon as possible and initiate adequate therapy [28]. The treatment strategy recommended by French experts is based on high-intensity statin in combination with ezetimibe and bile acid sequestrant in order to obtain $\geq 50\%$ 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 versus 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 FH patients 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]; $P < .001$). 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 FH patients have also a lower coronary artery disease risk

than other FH patients in other parts in the World. Currently, three care pathways, involving general practitioners, cardiologists, endocrinologists, pharmacists and medical laboratories were launched in 2018 in three French regions (Nantes, Toulouse and Marseille Regions) in order to improve the knowledge, the diagnostic and the management of FH [37]. Results will be available in the next 3 years and should improve the screening and the 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 which 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 two 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 two 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 FH [4,25].

Conclusions

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

Figure legend:

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), 6.5–8.4 mmol/L (5 points), 5.0–6.4 mmol/L (3 points), 4.0–4.9 mmol/L (1 point). LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors [\[14\]](#)) for subjects under statins or ezetimibe. Familial hypercholesterolemia (FH) was considered as definite, probable, possible or unlikely for a total >8, equal to 6–8, 3–5 or <3 points, respectively. The intensity of statin therapy (high, moderate and low) was assessed using the 2013 ACC/AHA blood cholesterol guideline [\[11\]](#).

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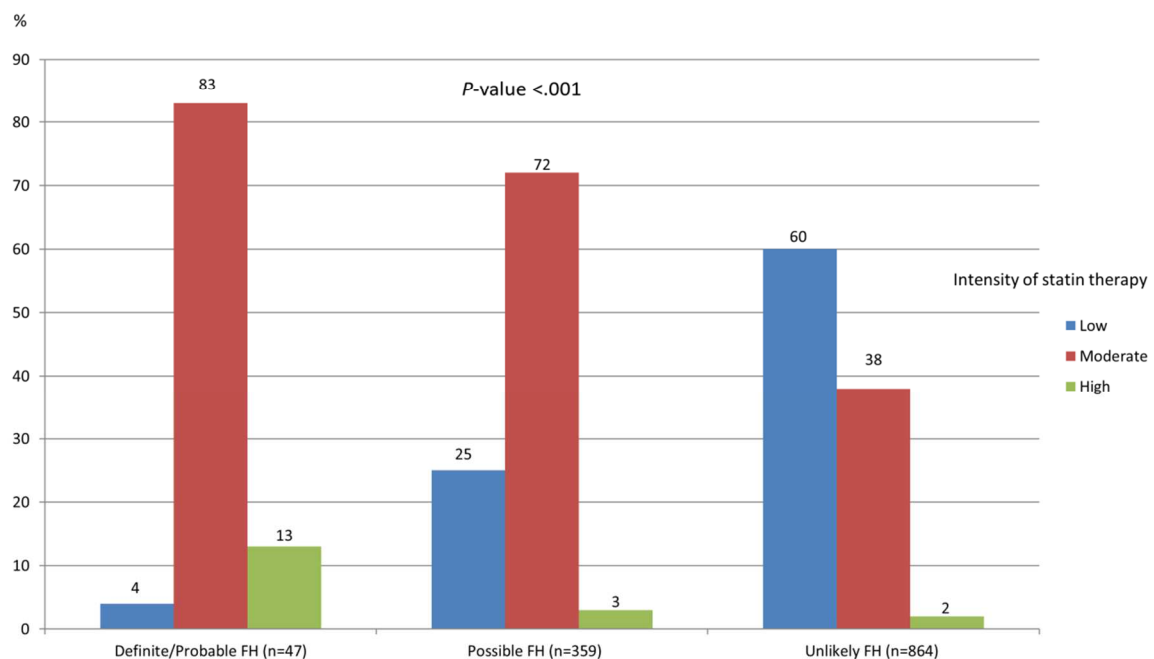
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Figure 1 Frequency of low, moderate and high-intensity statin therapy in treated subjects with definite/probable, possible or unlikely familial hypercholesterolemia (FH) according to the Dutch Lipid Clinic Network criteria (DLCN)



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), 6.5–8.4 mmol/L (5 points), 5.0–6.4 mmol/L (3 points), 4.0–4.9 mmol/L (1 point). LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors [14]) for subjects under statins or ezetimibe. Familial hypercholesterolemia (FH) was considered as definite, probable, possible or unlikely for a total >8, equal to 6–8, 3–5 or <3 points, respectively. The intensity of statin therapy (high, moderate and low) was assessed using the 2013 ACC/AHA blood cholesterol guideline [11].

Table 1 Prevalence* of familial hypercholesterolemia according to age and sex

	FH (DLCN), % [95% CI]					
	Possible FH			Probable or Definite FH		
Age, y	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 \geq 8.5 mmol/L (8 points), 6.5–8.4 mmol/L (5 points), 5.0–6.4 mmol/L (3 points), 4.0–4.9 mmol/L (1 point). LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors [14]) for subjects under statins or ezetimibe. Familial hypercholesterolemia (FH) was considered as definite, probable or possible for a total >8, equal to 6–8 or 3–5 points, respectively.

95% CI, 95% confidence interval.

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

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

Definite or probable familial hypercholesterolemia			
	No n = 7861	Yes n = 67	P-value
Age, y, n(%)			.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(%)			.7299
Male	3940 (50.1)	35 (52.2)	
Female	3921 (49.9)	32 (47.8)	
Educational level, n(%)			.2195
< High school completion	4820 (61.3)	46 (68.7)	
≥ High school completion	3040 (38.7)	21 (31.3)	
Physical activity*, n(%)			.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(%)			<.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(%)			<.0001
No	7227 (91.9)	50 (74.6)	
Yes	634 (8.1)	17 (25.4)	
Smoking, n(%)			.1790
Never	3653 (46.5)	27 (40.3)	
Former	2484 (31.6)	19 (28.4)	
Current	1724 (21.9)	21 (31.3)	
Drinking, n (%)			.0522
Men, 1 to 2 drinks/d OR			
Women, 1 drink/d	3909 (49.8)	28 (41.8)	
Non-drinkers	2124 (27.0)	15 (22.4)	
Men, ≥3 drinks/d OR			
Women, ≥2 drinks/d	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]	.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]	.0272
Diabetes***, n(%)			.6249
No	7347 (93.5)	62 (92.5)	
Yes	514 (6.5)	5 (7.5)	
Systolic blood pressure (mmHg)			
n	7844	67	
Mean (SD)	133.4 (20.0)	134.8 (18.2)	.5873
Median	131.0	132.0	
IQR	[119.5-145.0]	[121.0-141.5]	
Diastolic blood pressure (mmHg)			
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]	.9027
Blood pressure, n(%)			.4985
<140 and 90 mmHg	4834 (61.6)	44 (65.7)	
≥140 or 90 mmHg	3009 (38.4)	23 (34.3)	
Antihypertensive drug treatment, n(%)			.0751
No	6315 (80.3)	48 (71.6)	
Yes	1546 (19.7)	19 (28.4)	
Lipid-lowering drug treatment, n(%)			<.0001
No	6638 (84.4)	20 (29.9)	
Yes	1223 (15.6)	47 (70.1)	
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]	<.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]	<.0001
HDL-cholesterol (mmol/L)			
n	7861	67	
Mean (SD)	1.5 (0.4)	1.5 (0.4)	.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]	<.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]	<.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]	<.0001
<p>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 \geq8.5 mmol/L (8 points), 6.5–8.4 mmol/L (5 points), 5.0–6.4 mmol/L (3 points) or 4.0–4.9 mmol/L (1 point). LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors [14]) for subjects under statins or ezetimibe. Familial hypercholesterolemia (FH) was considered as definite or probable for a total >8 or equal to 6–8 points, respectively.</p> <p>n, number; SD, standard deviation; IQR, inter-quartile range; d, day.</p> <p>* No regular physical activity versus low physical activity (such as walking or bicycling, without causing shortness of breath or sweating, almost every week) versus moderate physical activity (i.e. causing shortness of breath or sweating, during at least 20 minutes, once or twice a week) versus high physical activity (i.e. causing shortness of breath or sweating, during at least 20 minutes, three times a week or more)</p> <p>** <55 years in men; <60 years in women</p> <p>*** Diabetes was assessed for subjects with fasting blood glucose \geq7 mmol/L (126 mg/dL) or under hypoglycemic drug treatment</p> <p>**** LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors [14]) for subjects under statins or ezetimibe.</p>			

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**				
No	1.00	<.001	1.00	<.001
Yes	17.6 [8.1–38.5]		14.1 [6.3–31.7]	
Sex				
Female	1.00	.152		
Male	1.4 [0.9–2.3]			
Educational level				
≥ High school completion	1.00	.023	1.00	.037
< High school completion	1.9 [1.1–3.3]		1.8 [1.0–3.1]	
Physical activity***				
No	1.00	.116		
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				
No	1.00	.002	1.00	.018
Yes	2.7 [1.5–4.9]		2.1 [1.1–4.0]	
Smoking				
Never	1.00	.080		
Former	1.5 [0.9–2.7]			
Current	1.9 [1.1–3.5]			
Drinking				
Men, 1 to 2 drinks/d OR Women, 1 drink/d	1.00	.119		
Non-drinkers	1.4 [0.8–2.5]			
Men, ≥3 drinks/d OR Women, ≥2 drinks/d	1.8 [1.0–3.2]			
Body mass index				
<30 kg/m ²	1.00	.099		
≥30 kg/m ²	1.6 [0.9–2.7]			
Diabetes****				
No	1.00	.787		
Yes	1.1 [0.5–2.8]			

High blood pressure				
<140 and 90 mmHg and without antihypertensive drug treatment	1.00	.128		
≥140 or 90 mmHg or under drug treatment	1.4 [0.9–2.3]			
Triglycerides				
<1.14 mmol/L (100 mg/dL)	1.00	.018		
≥1.14 mmol/L	1.8 [1.1–2.9]			
HDL-cholesterol (mmol/L)				
≤1.0 mmol/L (40 mg/dL)	1.00	.001	1.00	.003
>1.0 mmol/L	0.4 [0.2–0.7]		0.4 [0.2–0.7]	
Corrected LDL-cholesterol*****		<.001		
<5.0 mmol/L (190 mg/dL)	1.00			
≥5.0 mmol/L	2.6 [1.6–4.4]			

OR, odds ratio; 95% CI, 95% confidence interval; d, day.

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

** Familial hypercholesterolemia (FH) was considered as definite or probable for a total >8 or equal to 6–8 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), 6.5–8.4 mmol/L (5 points), 5.0–6.4 mmol/L (3 points) or 4.0–4.9 mmol/L (1 point). LDL-C was corrected (using dose- and statin- or ezetimibe-specific correction factors [14]) for subjects under statins or ezetimibe.

*** No regular physical activity versus low physical activity (such as walking or bicycling, without causing shortness of breath or sweating, almost every week) versus moderate physical activity (i.e. causing shortness of breath or sweating, during at least 20 minutes, once or twice a week) versus high physical activity (i.e. causing shortness of breath or sweating, during at least 20 minutes, three 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 subjects under statins or ezetimibe.