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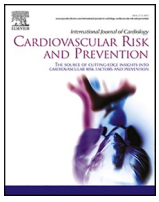

Case detection of familial hypercholesterolemia using various criteria during an annual health examination in the workplace

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ABSTRACT

Background: Early diagnosis and appropriate treatment of subjects with familial hypercholesterolemia (FH) could prevent cardiovascular disease (CAD).
Objective: We aimed to identify potential cases of FH during a workplace screening and to explore their clinical data.
Method: Personnel who attended an annual health examination were invited to answer a questionnaire and to provide consent to review their laboratory results. FH was clinically diagnosed using any one of the three standard criteria: Dutch Lipid Clinic Network (DLCN), Simon Broome (SB), and Make Early Diagnosis to Prevent Early Deaths (MEDPED). Clinical characteristics were compared between FH and unlikely FH subjects.
Results: Among 6607 participants, potential cases of FH were identified in 2.5 % by DLCN, 4.0 % by SB, and 0.8 % by MEDPED alone. Premature CAD, hypertension, and current smoking were significantly more common in potential FH subjects than in unlikely FH subjects. Potential FH subjects also had significantly higher body mass index, waist circumference, blood pressure, fasting plasma glucose and triglyceride levels than unlikely FH subjects. Among potential FH subjects, lipid-lowering medication was used in 28.4 %. The achievement of the LDL-C goal (<100 mg/dL) in potential FH subjects was significantly lower than that in unlikely FH subjects (15 % vs. 28 %, respectively, P = 0.005) despite a higher rate of high-intensity statin use (25 % vs. 10 %, respectively, P = 0.002).
Conclusion: The workplace screening of FH detected a significant number of potential FH subjects with higher cardiovascular risk. This strategy identified individuals for whom intensification of both lifestyle modifications and pharmacological treatment should be a priority.

1. Introduction

Familial hypercholesterolemia (FH) is a genetic disease causing abnormally high levels of low-density lipoprotein (LDL)-cholesterol (LDL-C). Before the statin era, FH patients were found to have a 20-fold increase in the risk of coronary artery disease (CAD) [1,2], resulting from long-standing increases in circulating LDL-C levels. Unfortunately, FH is underdiagnosed and is rarely detected in routine clinical practice [3]. Even in those with established FH diagnosis, most have not been adequately treated [4]. Although FH can be diagnosed phenotypically or genetically, several underlying reasons for underdiagnosis and undertreatment have been proposed. First, FH is usually recognized as a rare disease, which is true only for homozygous FH. Heterozygous FH is, however, known to be one of the most common heritable cardiovascular diseases [5,6]. Second, the criteria used for diagnosis are not universally agreed upon and vary among different ethnicities. Third, the high cost and dedicated expertise required in genetic testing are limiting factors to get a definite FH diagnosis. Fourth, the misconception about the risks

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and benefits of cholesterol-lowering medications leads to reluctance to start treatment and early discontinuation after prescription.

Recent meta-analyses and systematic reviews have reported the prevalence of heterozygous FH in the general population at around 1:300 [7,8]. Currently, three diagnostic criteria widely accepted for the clinical diagnosis of FH are the Dutch Lipid Clinic Network (DLCN) [9], the Simon Broome (SB) [10], and the Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria [11]. In Asia, Japan [12], China [13,14], and Korea [15] developed their FH diagnostic criteria for their populations. These Asian criteria generally use lower LDL-C cut-point values for diagnosis since the mean LDL-C levels in their countries are lower than those in the Western populations.

Several strategies have been employed to identify FH individuals since early diagnosis is the critical first step in the care of FH subjects. These strategies include universal screening in children and adolescents, opportunistic screening based on lipid levels, clinical history, and family history, systematic identification from the electronic medical records using a predictive algorithm and machine learning, and cascade screening of family members of the index cases [16]. Once FH is detected, early initiation of high-intensity statin to achieve LDL-C goals and comprehensive management of cardiovascular risk factors is necessary to prevent premature CAD in these FH subjects.

In Thailand, the result of the Thai FH registry has recently shown that FH is diagnosed rather late, and several FH subjects have been diagnosed after the onset of premature CAD [17]. Early detection of asymptomatic FH cases is a crucial first step. In this study, we report the result of the case detection of potential FH during an annual health examination in the workplace using the three standard criteria (the DLCN, SB, and MEDPED criteria). We also examined clinical predictors associated with premature CAD, lipid-lowering medication (LLM) use, and achievement of LDL-C goals in this workplace cohort.

2. Methods

The retrospective cohort study was conducted at Chulalongkorn University and the Thai Red Cross Society in Bangkok, Thailand, with the approval of the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University. The criteria used for the detection of potential FH cases in this study were DLCN (probable or definite with a score $\geq$6), SB (possible or definite), and MEDPED. In addition, the Japanese and the Chinese criteria for FH diagnosis were also explored [12–14]. All the diagnostic criteria used in this study are shown in Supplementary Tables S1–S5. The study was started during an annual health examination in the fiscal year 2018, organized from October 2018 to March 2019. All personnel were invited to participate and to answer a self-administered questionnaire. The questionnaire consisted of non-medical term questions according to the DLCN and the SB clinical diagnostic criteria, which included a personal history and family history of elevated total cholesterol $\geq$290 mg/dL or LDL-C $\geq$190 mg/dL and a history of premature cardiovascular diseases (CAD, ischemic cerebrovascular disease (CBVD) and peripheral artery disease) before 55 years in men and before 60 years in women. Written consent was obtained to review their fasting laboratory results from the annual health examinations from 2009 to 2018. Personnel with a history of LDL-C levels of 190 mg/dL or more during 2009–2017 were further invited to receive an additional physical examination specifically for cutaneous/tendon xanthoma and corneal arcus by a single physician during the health examination period. The physician who performed the physical examination was blinded to the invited personnel's personal history, family history, and potential FH diagnosis.

Data from the questionnaires were reviewed together with the laboratory results obtained from the hospital database. The highest total cholesterol (TC) and LDL-C levels from 2009 to 2018 were used for FH diagnosis. The LDL-C values were calculated using the Friedewald formula. In personnel with plasma triglyceride results exceeding 400 mg/dL, the calculated LDL-C value was unavailable, and only the TC level was used to determine FH diagnosis. Total cholesterol and LDL-C burden values were calculated by multiplying the plasma TC or LDL-C level (mg/dL) in the year 2009 by the age at the year 2009 and adding the values of TC or LDL-C in the following years yearly until 2018 [18]. The statin intensity was according to the classification by the American College of Cardiology/American Heart Association [19]. Clinical data collected from the questionnaire, the physical examination, and laboratory data from the hospital database were used to diagnose FH by the DLCN, the SB, and the MEDPED criteria. Participants who met any of the above criteria were defined as having potential FH. The unlikely FH group included the other participants who did not meet the above criteria. Genetic data on the potential FH subjects are not available.

Descriptive results were reported as counts, percentages, means, and standard deviations. Differences in the clinical characteristics between the potential FH and the unlikely FH groups were tested using unpaired Student's t-test and χ^2 or Fisher's exact test. Clinical parameters associated with premature CAD and ischemic CBVD were analyzed with multiple logistic regression analysis by a stepwise method, performed by removing potential explanatory variables with $P < 0.15$ and adding possible variables with $P < 0.10$ to estimate odds ratio and 95 % confidence interval (CI). Clinical factors associated with LLM use and achievement of LDL-C goal were also analyzed by a stepwise logistic regression method. A two-tailed test with a P-value <0.05 was defined as statistical significance. All analyses were performed using Stata Statistical Software (Release 16.1).

3. Results

3.1. Study population

The total number of personnel from both institutions in 2018 was 15,059 and 11,284 (74.9 %) attended the annual health examination (Fig. 1). Among those who attended the health examination, 9013 (79.9 %) participated in the study by answering a self-administered questionnaire. One thousand nine hundred ninety-three participants were excluded because they did not consent to have their laboratory results reviewed. Among the remaining 7020 subjects, 413 were excluded since they did not have lipid laboratory results. The final number of participants included in the analysis was 6607.

3.2. Detection of potential cases of FH and the clinical characteristics

Among 6607 subjects, 1232 did not have LDL-C results. Therefore, potential cases of FH using the DLCN criterion were evaluated in 5375

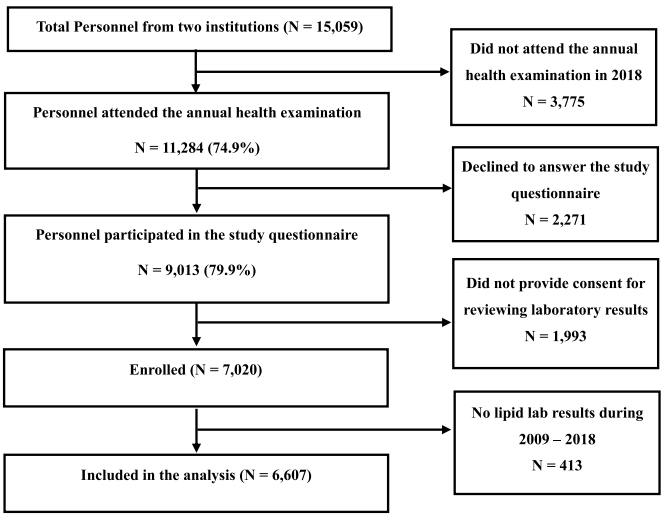


Fig. 1. Flow diagram of study enrolment.

subjects. Possible FH (DLCN score 3–5), probable FH (DLCN score 6–8), and definite FH (DLCN score >8) were found in 747 (13.9 %), 51 (0.9 %), and 86 (1.6 %), respectively as shown in Table 1. Possible FH and definite FH by the SB criterion were found in 206 (3.1 %) and 62 (0.9 %), respectively. The number of subjects met the MEDPED criterion was 50 (0.8 %). Overall, 338 subjects from 6607 personnel fulfilled any of the three criteria, giving the detection rate of potential FH of 5.1 %, with a 95 % CI of 4.5 %–5.6 %. One hundred sixty-nine subjects fulfilled only the SB criterion alone, whereas 51 and 18 subjects fulfilled only the DLCN and MEDPED criteria alone. Seventeen subjects fulfilled all three diagnostic criteria (Fig. 2). In addition, the detection rate using the diagnostic criteria of the Japan Atherosclerosis Society [10] was 5.2 % (280/5375) with a 95 % CI of 4.6–5.8. Using the modified DLCN criterion (score ≥6) proposed for the Chinese population [13], the corresponding detection rate of potential FH was 5.8 % (314/5375) with a 95 % CI of 5.2–6.5.

Clinical characteristics of potential FH subjects according to each diagnostic category were then compared (Table 1). The mean age of FH subjects by the DLCN and the SB criteria was comparable, whereas those with the MEDPED criterion were younger. The mean highest TC and LDL-C levels were lowest in possible FH by SB but highest in definite FH by MEDPED.

3.3. Clinical characteristics of potential FH and unlikely FH

Three hundred and thirty-eight subjects with potential FH were compared with 6269 subjects with unlikely FH (Table 2). Most (76.9 %) of the enrolled personnel were women since female nurses were the predominant personnel in one institution. The mean age of potential FH subjects was significantly higher than that of unlikely FH subjects. Hypertension, premature CAD, premature ischemic CBVD and current smoking were significantly more common in potential FH subjects than in unlikely FH subjects. Among potential FH subjects, LLM use was found in 28.4 %, and only 25.3 % were on statin.

During the annual health examination in 2018, body mass index (BMI), waist circumference, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were significantly higher in potential FH subjects than in unlikely FH subjects (Table 2).

Among 839 subjects with a history of LDL-C levels of at least 190 mg/dL, 271 subjects (137 in the potential FH group and 134 in the unlikely FH group) voluntarily agreed to be specifically examined for physical signs of xanthoma and corneal arcus. Tendon xanthoma was found in 81 subjects, who were all in the potential FH group. None in the unlikely FH group had tendon xanthoma. Corneal arcus was found in 68 subjects, 66 of whom were in the potential FH group and only two were in the unlikely FH group.

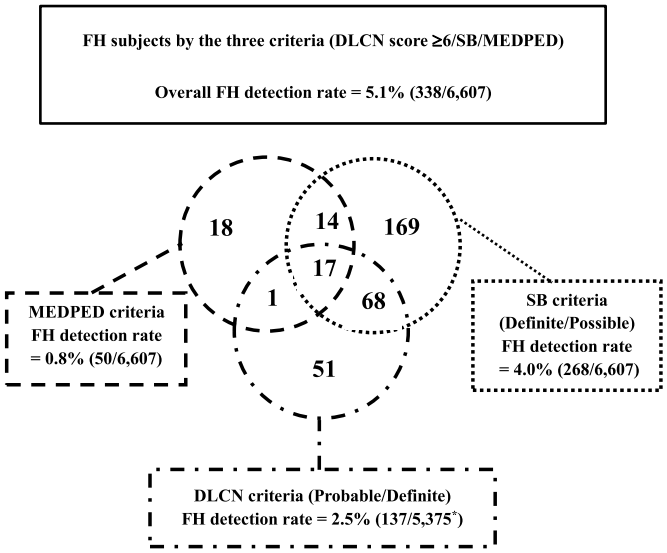


Fig. 2. The detection rates of FH subjects by the three criteria(DLCN score ≥ 6, SB, and MEDPED).

Fasting plasma glucose (FPG), total cholesterol, triglyceride, and LDL-C levels were also significantly higher in FH subjects. From 2009 to 2018, the highest total cholesterol levels, the highest LDL-C levels, total cholesterol burden, and LDL-C burden were significantly higher in potential FH subjects than in unlikely FH subjects. Clinical characteristics in male and female subjects with potential FH are shown in Supplementary Table S6. There were no significant differences in BMI, highest total cholesterol levels, highest LDL-C levels, total cholesterol burden,

Table 1
Detection rates and clinical characteristics of potential FH subjects by each category of the Dutch Lipid Clinic Network, the Simon Broome and the MEDPED criteria (N = 6607).

Clinical characteristics	Dutch Lipid Clinic Network		Simon Broome		MEDPED
	Probable (score 6–8)	Definite (score >8)	Possible	Definite	
No. of potential FH/No. of included personnel	51/5375	86/5375	206/6607	62/6607	50/6607
Detection rate, % (95 % CI)	0.9 (0.7–1.2)	1.6 (1.3–2.0)	3.1 (2.7–3.6)	0.9 (0.7–1.2)	0.8 (0.6–1.0)
Age (y)	51 ± 8.1	49 ± 7.8	47 ± 9.1	49 ± 8.1	39 ± 11.3
Female, n (%)	34 (66.7)	52 (60.5)	146 (70.9)	43 (69.4)	30 (60)
Family history, n/n. total (%)	14/51 (27.5)	14/86 (16.3)	59/205 (28.8)	9/62 (14.5)	9/50 (18.0)
- Premature CAD in the 1st-degree relative	16/51 (31.4)	14/86 (16.3)	71/205 (34.6)	9/62(14.5)	10/50 (20.0)
- Premature CAD in the 1st or 2nd-degree relative					
- Premature ischemic CBVD in the 1st-degree relative	6/25(24.0)	3/18 (16.7)	19/183 (10.4)	2/12 (16.7)	3/38 (7.9)
- Premature ischemic CBVD in the 1st or 2nd-degree relative	8/25 (32.0)	3/18 (16.7)	27/183 (14.8)	2/12 (16.7)	4/38 (10.5)
-Total cholesterol ≥290 mg/dL or LDL-C ≥190 mg/dL in the 1st-degree relative,	15/50 (30.0)	4/85 (4.7)	109/205 (53.2)	4/62 (6.5)	13/42 (31.0)
- Total cholesterol ≥290 mg/dL or LDL-C ≥190 mg/dL in the 1st or 2nd-degree relative	15/50 (30.0)	4/85 (4.7)	180/205 (87.8)	4/62 (6.5)	22/42 (52.4)
Personal history, n/n. total (%)	6/51 (11.8)	1/86 (1.2)	3/205 (1.5)	1/62 (1.6)	3/50 (6.0)
- Premature CAD	1/51 (2.0)	3/86 (3.5)	3/205 (1.5)	2/62 (3.2)	1/48 (2.1)
- Premature ischemic stroke					
- Tendon xanthoma, any site	1/34 (2.9)	80/85 (94.1)	0/24 (0)	62/62 (100)	11/15 (73.3)
- Corneal arcus	32/34 (94.1)	34/85 (40)	8/24 (33.3)	23/62 (37.1)	4/15 (26.7)
- Highest total cholesterol (mg/dL)	317 ± 39[a]	318 ± 39[a]	315 ± 27[b]	328 ± 35[b]	371 ± 43[c]
- Highest LDL-C (mg/dL)	234 ± 36[a]	236 ± 39[a]	223 ± 24[b]	243 ± 39[b]	259 ± 66[c]

Table 2
Clinical characteristics of all subjects, potential FH subjects (diagnosed by any of the three criteria [DLCN score ≥6, possible and definite SB, and MEDPED]), and unlikely FH subjects.

Clinical Characteristics	All (N = 6607)	Potential FH (N = 338)	Unlikely FH (N = 6269)	P-value
Female, n (%)	5087 (76.9)	228 (67.5)	4859 (77.5)	<0.001
Age (y), mean ± SD	41.6 ± 10.6	47.4 ± 9.0	41.3 ± 10.6	<0.001
Hypertension, n (%)	724 (12.6)	60 (18.7)	664 (12.2)	0.001
Diabetes, n (%)	180 (3.1)	13 (4.0)	167 (3.1)	0.337
Premature coronary artery disease, n (%)	63 (0.9)	10 (2.9)	53 (0.9)	<0.001
Premature ischemic cerebrovascular disease, n (%)	57 (0.8)	7 (2.0)	50 (0.8)	0.014
Current smoker, n (%)	162 (2.7)	18 (5.5)	144 (2.6)	0.005
Current alcohol drinker, n (%)	2303 (39.4)	94 (28.5)	2209 (40.0)	<0.001
Lipid-lowering medication use, n (%)	690 (10.5)	97 (28.4)	593 (9.6)	<0.001
Current use of statin, n (%)	635 (9.8)	83 (25.3)	552 (8.9)	<0.001
BMI (kg/m^2)	24.6 ± 4.6	25.7 ± 4.6	24.5 ± 4.6	<0.001
Waist circumference (cm)	82.4 ± 11.5	85.3 ± 10.4	82.2 ± 11.6	<0.001
SBP (mmHg)	116 ± 14	122 ± 16	116 ± 14	<0.001
DBP (mmHg)	74 ± 9	77 ± 10	74 ± 9	<0.001
Tendon xanthoma, any site, n (%)	81/271 (29.8)	81/137 (59.1)	0/134 (0.0)	<0.001
Corneal arcus, n (%)	68/271 (25.0)	66/137 (48.2)	2/134 (1.4)	<0.001
FPG (mg/dL)	91 ± 20	99 ± 32	91 ± 19	<0.001
Triglyceride (mg/dL)	104 ± 68	155 ± 116	101 ± 63	<0.001
HDL-C (mg/dL)	57 ± 13	58 ± 13	57 ± 13	0.422
Highest total cholesterol (mg/dL)	228 ± 42	317 ± 34	223 ± 37	<0.001
Total cholesterol burden (mg-y/dL)				
- All (N = 6557)	8164 ± 2860	12,245 ± 2966	7942 ± 2682	<0.001
- Age 20–34 (N = 1889)	5395 ± 1253	8936 ± 1709	5330 ± 1146	<0.001
- Age 35–49 (N = 2997)	8101 ± 1792	10,719 ± 1974	7971 ± 1679	<0.001
- Age 50–64 (N = 1671)	11,409 ± 2314	14,277 ± 2424	11,101 ± 2079	<0.001
LDL-C burden (mg-y/dL)				
- All (N = 5327)	5894 ± 2036	9017 ± 2223	5694 ± 1853	<0.001
- Age 20–34 (N = 675)	3782 ± 1218	7051 ± 2087	3687 ± 1042	<0.001
- Age 35–49 (N = 2986)	5493 ± 1500	7995 ± 1594	5370 ± 1383	<0.001
- Age 50–64 (N = 1666)	7468 ± 7371	10,138 ± 2125	7182 ± 1780	<0.001

Results are presented as mean ± SD or n (%), N for BMI = 6545 (potential FH = 329 and unlikely FH = 6216), N for waist circumference = 6524 (potential FH = 324 and unlikely FH = 6200), N for SBP/DBP = 6539 (potential FH = 329 and unlikely FH = 6210), N for FPG = 6476 (potential FH = 333 and unlikely FH = 6143), N for total cholesterol = 6539 (potential FH = 337 and unlikely FH = 6202), N for triglyceride = 6534 (potential FH = 337 and unlikely FH = 6197), N for HDL-C = 5269 (potential FH = 321 and unlikely FH = 4948), N for LDL-C = 5225 (potential FH = 311 and unlikely FH = 4914).

and LDL-C burden between men and women.

3.4. Clinical parameters associated with premature CAD and ischemic CBVD

Since the number of potential FH subjects with premature CAD and premature ischemic CVBD was small, we examined clinical parameters associated with premature CAD and premature ischemic CBVD in the total cohort using univariate and multivariate logistic regression analyses. For premature CAD, age ≥50 y, gender, diabetes, hypertension, clinical diagnosis of probable/definite FH (by DLCN) and FH (by MEDPED), LDL-C burden levels of 75th percentile and over and premature CAD in the 1st-degree relative were significant parameters from the univariate analysis (Table 3). In multivariate analysis, women were less likely to have premature CAD than men (adjusted OR 0.39, 95 % CI:0.21–0.73, P = 0.003), whereas subjects with probable/definite FH by DLCN criteria were highly associated with premature CAD (adjusted OR 39.12, 95 % CI: 17.04–89.83, P < 0.001).

For premature ischemic CVBD, age ≥50 y, diabetes, hypertension, clinical diagnosis of probable/definite FH (by DLCN) and premature ischemic CBVD in the 1st-degree relative demonstrated a significant association from the univariate analysis. In the multivariate analysis, only hypertension, clinical diagnosis of probable/definite FH (by DLCN) and premature ischemic CBVD in the 1st-degree relative remained significant.

3.5. Clinical characteristics associated with LLM use

The number of subjects on LLM in the total cohort was 690 (Table 2), and the statin use was documented in 635 participants (83 in the potential FH group and 552 in the unlikely FH group). Among those with statin use, data on statin type and dose were available in 53 in the potential FH group and 316 in the unlikely FH group. A significantly higher percentage of potential FH subjects received high-intensity statin than unlikely FH subjects, whereas unlikely FH subjects were significantly more likely to receive low-intensity statin (Fig. 3A). A multivariate analysis of subjects with potential FH showed that women, diabetes, hypertension, premature CAD, and higher total cholesterol burden levels were significant predictors of LLM use (Supplementary Table S7).

3.6. Clinical characteristics associated with achievement of LDL-C goals

Among those on LLM, the percentage of subjects who achieved LDL-C goal <100 mg/dL was significantly higher in the unlikely FH group than in the potential FH group (29 % vs. 15 %, P = 0.005, as shown in Fig. 3B). For LDL-C goal <70 mg/dL, the achievement rate was only 5 % and 1 % in the unlikely FH and the potential FH groups, respectively, with no statistically significant difference between the two groups. Clinical predictors of achievement of LDL-C goals in potential FH subjects were not further explored due to a low number of subjects.

4. Discussion

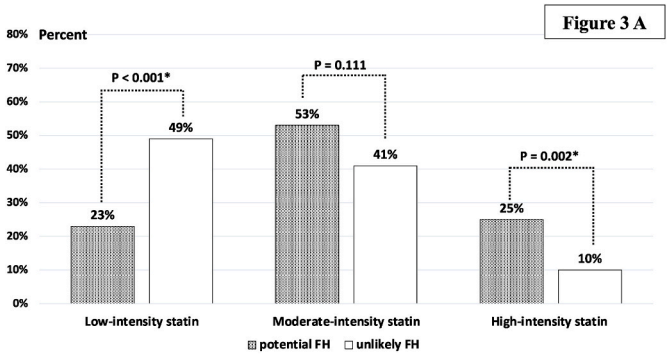
In this study, we reported the detection of potential FH cases during an annual health examination in the workplace using three commonly used diagnostic criteria for FH: DLCN (probable/definite with score ≥6), SB (possible/definite), and MEDPED. The detection rate of potential FH by each criterion showed that SB resulted in the highest rate of 4.0 %, followed by DLCN of 2.5 % and MEDPED of 0.7 %. Premature CAD, hypertension, and current smoking were significantly more common in potential FH subjects than in unlikely FH subjects. Besides higher LDL-C levels, potential FH subjects had significantly higher BMI, waist circumference, blood pressure, fasting plasma glucose and triglyceride levels, reflecting higher cardiovascular risk than unlikely FH subjects. Of all 338 potential FH subjects by any of the three criteria, only 97 (28 %) received LLM. The rate of achievement of LDL-C goal (LDL-C <100 mg/dL) in potential FH subjects was significantly lower than that in unlikely FH subjects despite a higher rate of high-intensity statin use.

There are several strategies for detecting FH individuals, such as a universal screening in children or adolescents, an opportunistic screening based on plasma lipid levels, systematic detection using a computerized predictive algorithm or machine learning, a targeted screening in high-risk patients with premature CAD, and a cascade screening of family members of the index cases [16]. Therefore, the

Table 3
Univariate and multivariate logistic regression analyses of clinical characteristics associated with premature CAD and premature ischemic CBVD in the total cohort (N = 6607).

Clinical characteristics	Premature CAD				Premature ischemic CVBD			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Odds ratio (95 % CI)	P-value	Adjusted odds ratio (95 % CI)	P-value	Odds ratio (95 % CI)	P-value	Adjusted odds ratio (95 % CI)	P-value
Age	Reference	0.271	–	0.008	Reference	0.220	–	
- 20–34 y	1.55 (0.71–3.37)	<0.001	–		1.62 (0.75–3.51)	0.004	–	
- 35–50 y	3.98 (1.90–8.37)		2.57 (1.28–5.17)		3.11 (1.45–6.67)		–	
- ≥50 y								
Women	0.45 (0.27–0.75)	0.002	0.39 (0.21–0.73)	0.003	0.60 (0.34–1.04)	0.067	–	
Diabetes	4.22 (1.78–10.03)	0.001	2.39 (0.90–6.33)	0.079	3.47 (1.36–8.86)	0.009	2.48 (0.93–6.64)	0.071
Hypertension	3.74 (2.10–6.65)	<0.001	2.11 (1.08–4.11)	0.028	3.22 (1.77–5.85)	<0.001	2.38 (1.23–4.60)	0.010
Probable/Definite FH by DLCN (DLCN score ≥6)	22.78 (11.77–41.11)	<0.001	39.12 (17.04–89.83)	<0.001	4.42 (2.55–7.67)	<0.001	4.25 (2.29–7.89)	<0.001
Possible/Definite FH by SB	1.60 (0.58–4.44)	0.365	–		2.28 (0.90–5.76)	0.081	–	
FH by MEDPED	6.84 (2.07–22.59)	0.002	–		2.44 (0.33–18.03)	0.381	–	
LDL-C burden[a]	Reference	0.011	Reference	<0.001	Reference	0.968	–	–
- < 7099 (75thP)	2.13 (1.19–3.81)	0.001	0.24 (0.11–0.53)	0.002	1.01 (0.50–2.05)	0.138		
- 7099–9606 (75th-95th P)	3.82 (1.74–8.37)		0.21 (0.08–0.57)		2.04 (0.79–5.23)			
- ≥ 9607 (≥95th P)								
Premature CAD in the 1st -degree relative	2.97 (1.71–5.17)	<0.001	2.31 (1.15–4.63)	0.018	–	–	–	–
Premature ischemic CBVD in the 1st -degree relative	–	–	–		3.07 (1.57–6.01)	0.001	2.20 (1.00–4.83)	0.049

[a] LDL-C burden level in mg-y/dL are categorized into <75th percentile, 75th – 95th percentile, and >95th percentile.



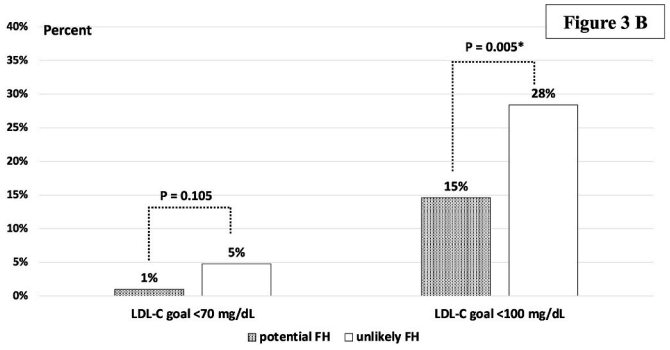


Fig. 3. A. The rate of statin use according to statin intensity in the potential FH (N = 53) and the unlikely FH groups (N = 316), Fig. 3B. Achievement of LDL-C goals in the potential FH (N = 82) and the unlikely FH groups (N = 545), *significant P-value.

detection rate of FH varies among different studies depending on the study populations. A recent meta-analysis reported the prevalence of FH as 0.32 % in the general population, 3.16 % in patients with ischemic heart disease, 6.65 % in patients with premature ischemic heart disease, and 7.22 % in patients with severe hypercholesterolemia [8]. Interestingly, a similar prevalence of FH in the general population was found using either the genetic or clinical criteria [8]. Universal screening of FH is the least cost-effective method of identifying FH cases [20]. Although cascade screening has been shown to be the most cost-effective screening method of FH, it is limited by the identification of new index cases. The laboratory-based opportunistic screening for FH has been proposed as a practical and convenient method to identify new cases, especially in low-resource settings [21], as it provides a higher diagnostic yield at a lower cost than population-based screening. Our screening for potential FH in the workplace combined a questionnaire, a review of laboratory results of lipid levels and a physical examination to verify the clinical diagnosis of FH. This strategy allowed us to identify new cases of potential FH in whom intensive treatment should be focused and cascade screening in the family members should be further considered. It should be noted that our detection rate of potential FH cases should not be compared with the prevalence of FH in the general population due to differences in the study populations.

It is well known that different diagnostic criteria exhibit varied sensitivity, specificity, and correlation with mutation detection rates. A study in 855 FH cases in Australia reported sensitivity of 94.0 %, 91.8 %, and 56.8 %, and specificity of 33.2 %, 43.5 %, and 88.9 % for SB (possible/definite FH), DLCN (probable/definite FH), and MEDPED criteria, respectively [22]. Another study in 408 FH subjects in Danish showed a mutation detection rate of 38.5 %, 48.1 %, and 51.6 % using SB (possible/definite FH), DLCN (probable/definite FH), and MEDPED criteria, respectively [23]. A similar result was also found in 97 FH subjects in Korea [24]. Collectively, these data showed that the SB criterion had higher sensitivity than the other two criteria, whereas the MEDPED criterion had the highest specificity and mutation detection rate. The DLCN had relatively high sensitivity, moderate specificity and an acceptable mutation detection rate. Based on these data, the DLCN would be a diagnostic criterion of choice and is also feasible as shown in our large working population.

A predictive value of each clinical diagnostic criterion for identifying FH patients compared to genetic diagnosis have been reported. A study in a lipid clinic in a hospital setting included FH cases by definition of DLCN score at least 3 (possible/probable/definite FH) and reported 31.2 % (267/855) of pathogenic FH-causing mutation [22]. From the FH

cases included, the positive predictive value (PPV) and negative predictive value (NPV) of various criteria were analyzed. The results of PPV and NPV were 37.8 % and 92.8 % by SB (possible/definite), 41.2 % and 92.4 % by DLCN (probable/definite), 78.7 % and 74.1 % by MEDPED, and 37.7 % and 88.5 % by American Heart Association (AHA) criteria, respectively. A study in patients with acute coronary syndrome with aged ≤65 years and LDL-C ≥160 mg/dL reported 8.7 % (9/103) of positive pathogenic FH variants [25]. The PPV and NPV of SB criteria were 21.4 % and 96.0 %. The PPV and NPV of the DLCN (probable/definite) were 17.9 % and 94.7 %, respectively. Thus, the relatively low PPV rates of all clinical criteria except for the MEDPED criteria demonstrated rather high false positive rates of these clinical FH diagnostic criteria compared to genetic diagnosis. However, high NPV rates were observed in all criteria, especially in SB and DLCN, demonstrating the low false negative rate using these FH clinical diagnosis criteria.

Our study also assessed potential FH cases by using Asian-derived diagnostic criteria. We detected 5.2 % and 5.8 % of FH cases using the Japanese and the Chinese FH diagnostic criteria, respectively. These detection rates are higher than the three standard criteria due to the lower LDL-C cut-off levels. The ethnic-specific LDL-C cut-off levels were ≥180 and ≥ 135 mg/dL in the Japanese and the Chinese criteria, respectively [12–14]. The LDL-C cut-off levels for the Thai population have not been reported and should be further explored to derive the specific diagnostic criteria for FH in Thailand.

FH subjects are at greater risk for premature CVD than the general population due to a lifelong elevation of LDL-C levels. Our study also found that a history of hypertension and current smoking were significantly more common in potential FH subjects than unlikely FH subjects. In addition, potential FH subjects had significantly higher BMI, waist circumference, blood pressure and levels of fasting plasma glucose and triglyceride than unlikely FH subjects. These data indicated that potential FH subjects in our current study had higher cardiovascular risk than unlikely FH subjects, above and beyond elevated LDL-C levels. A recent meta-analysis has shown that hypertension, smoking, and BMI are independent risk factors for CVD in heterozygous FH [26]. The presence of abdominal obesity and metabolic syndrome also enhanced the risk of CVD in FH subjects [27–29]. Therefore, these modifiable risk factors, in addition to elevated LDL-C levels, should be specifically targeted to further reduce cardiovascular risk. Importantly, maintaining healthy lifestyles is associated with reduced cardiovascular risk among FH subjects [30]. Smoking cessation, for example, is associated with a decline in cardiovascular risk in FH [31].

Among 338 potential cases of FH in the current study, only 22.8 % received LLM. Among those on LLM, the percentage of potential FH subjects who achieved LDL-C goal <100 mg/dL was only 29 %. These findings may not be surprising since almost all of these cases have not been diagnosed with FH prior to our study. Even among known cases of FH in Thailand, the rate of LLM use in the Thai FH registry was only 64.2 %, and among those on LLM, the LDL-C goal <100 mg/dL was achieved in only 25.2 % [32]. From the global FH registry data of 42,167 cases collected by the European Atherosclerosis Society – Familial Hypercholesterolaemia Studies Collaboration (EAS-FHSC) [33], the rate of LLM use was reported in 59.5 %, and the rates of LDL-C goal attainment <100 mg/dL and <70 mg/dL were only 13.6 % and 2.7 %, respectively. These data demonstrated that almost half of the subjects with FH worldwide were not treated. Of those treated patients, only a very few achieved the LDL-C goal <70 mg/dL. This pattern of undertreatment represents significant therapeutic inertia in the care of FH subjects worldwide that should be actively focused upon [34–36].

Our study is the first to systematically investigate the detection rate of potential FH using various criteria in a large cohort of working personnel in Thailand. However, several limitations merit further consideration. First, most personnel in both institutions are working-age women, so our data may not reflect what happens in the general population. Second, we cannot exclude selection bias in our study since we have no clinical data on the personnel who did not attend the annual health examination or those who declined to participate. The prevalence of premature CAD among potential FH subjects in this study at 2.9 % was much lower than that previously reported in the Thai FH registry data at 11.9 % [32]. It is likely that some of the personnel who already had been diagnosed with FH, CAD or cerebrovascular disease might not attend the annual health examination since they already had regular follow-ups with their physicians for their medical conditions. Although a high number of personnel who attended the health examination participated in answering the questionnaire (79.9 %), a significant number of those who answered the questionnaire did not consent to review their laboratory results (22.1 %). Whether and how much our results are affected by these unknown data is not clear. Third, we used only the clinical criteria of FH, and we selected only those with high LDL-C levels for examination for xanthoma and corneal arcus. The genetic data are not yet available in our current study. It is known that clinical diagnostic criteria have high false positive rates, and a number of probable or even definite cases of FH by DLCN or SB will turn out to be mutation negative. Our ongoing genetic analysis may give us important insights into the mutation detection rate among various diagnostic criteria in our population in the near future.

In conclusion, the workplace screening in this study identified a significant number of potential FH subjects with multiple cardiovascular risk factors. Moreover, the LLM use and achievement of LDL-C among FH subjects were suboptimal. This screening strategy allowed us to identify personnel in whom lifestyle modifications should be intensified, pharmacological treatment should be optimized, and cascade screening should be considered.

CRediT authorship contribution statement

Poranee Ganokroj: Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Suwanna Muanpetch:** Validation, Resources, Investigation, Data curation. **Nitt Hanprathet:** Writing – review & editing, Validation, Resources, Investigation, Data curation. **Wiroj Jiamjarasrangsi:** Writing – review & editing, Validation, Supervision, Resources, Methodology. **Weerapan Khovidhunkit:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Funding acquisition, Conceptualization.

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Appendix A. Supplementary data

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