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Worldwide Prevalence of Familial Hypercholesterolemia

Meta-Analyses of 11 Million Subjects

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ABSTRACT

BACKGROUND Despite the greater prevalence of familial hypercholesterolemia (FH) in subjects with ischemic heart disease (IHD), premature IHD, and severe hypercholesterolemia (low-density lipoprotein ≥190 mg/dl), overall prevalence estimates are not available.

OBJECTIVES The aim of this study was to provide worldwide estimates of FH prevalence in subjects with IHD, premature IHD, and severe hypercholesterolemia compared with those in the general population.

METHODS In this systematic review and meta-analyses, Embase, PubMed, and the Web of Science were searched until June 3, 2019, for peer-reviewed papers and conference abstracts reporting heterozygous FH prevalence in nonfounder populations, revealing 104 studies eligible for inclusion.

RESULTS Estimates of FH prevalence were pooled using random-effects meta-analyses and were 0.32% (95% confidence interval [CI]: 0.26% to 0.39% [corresponding to 1:313]) among 10,921,310 unique subjects in the general population (33,036 patients with FH) on the basis of 44 studies, 3.2% (95% CI: 2.2% to 4.3% [1:31]) among 84,479 unique subjects with IHD (2,103 patients with FH) on the basis of 28 studies, 6.7% (95% CI: 4.9% to 8.7% [1:15]) among 31,316 unique subjects with premature IHD (1,471 patients with FH) on the basis of 32 studies, and 7.2% (95% CI: 4.6% to 10.8% [1:14]) among 17,728 unique subjects with severe hypercholesterolemia (920 patients with FH) on the basis of 7 studies. FH prevalence in the general population was similar using genetic versus clinical diagnoses. Seventeen of 195 countries (9%) in the world have reported FH prevalence for the general population, leaving 178 (91%) countries in the world with unknown prevalence.

CONCLUSIONS Compared with 1:313 among subjects in the general population, FH prevalence is 10-fold higher among those with IHD, 20-fold higher among those with premature IHD, and 23-fold higher among those with severe hypercholesterolemia. The prevalence of FH is unknown in 90% of countries in the world.

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Familial hypercholesterolemia (FH) is the most common autosomal-dominant genetic disorder, affecting about 30 million subjects worldwide, and is characterized by lifelong highly elevated low-density lipoprotein (LDL) cholesterol levels and thus an increased risk for ischemic heart disease (IHD) (1). FH is caused by mutations in *LDLR*, *APOB*, and *PCSK9* genes, encoding the LDL receptor, its ligand apolipoprotein B, and proprotein convertase subtilisin/kexin type 9, which marks the LDL receptor for degradation, respectively. In addition, elevated lipoprotein(a) may explain 25% of clinical FH

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

FH = familial hypercholesterolemia

IHD = ischemic heart disease

LDL = low-density lipoprotein

diagnoses (2). Subjects with FH are identified using various diagnostic criteria in either primary care by a positive family history of premature IHD and personal hypercholesterolemia or in hospital settings among patients with premature IHD. European and U.S. guidelines recommend identifying subjects with FH in order to start LDL cholesterol-lowering therapy early in life to prevent IHD and early death (3–5).

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More than 45 years ago, Goldstein et al. (6) presented a rough estimate of FH prevalence in the general population of 1:500 on the basis of 176 survivors of myocardial infarction. This was long considered the prevalence of FH in the general population. However, recent renewed interest in FH has led to numerous new studies estimating FH prevalence, with many of these reporting estimates of 1:200 to 1:250 in the general population (7–12). Also, many studies have reported FH prevalence in various IHD and hyperlipidemia cohorts. FH is more common in these subpopulations, but overall prevalence estimates are not available in these groups. Establishing a thorough overall estimate of FH prevalence among subjects with IHD, premature IHD, and severe hypercholesterolemia (LDL ≥190 mg/dl), respectively, and comparing this with the prevalence in the general population would shed additional light on the worldwide underdiagnosis of FH and possibly aid future efforts aimed at identifying subjects with FH.

We therefore conducted systematic reviews and meta-analyses of the prevalence of FH in: 1) the general population; 2) subjects with IHD; 3) subjects with premature IHD; and 4) subjects with severe hypercholesterolemia. Analyses comprised a total of 104 publications (>11 million subjects and >37,000 patients with FH), including 44 studies in the general population, 28 studies in subjects with IHD, 32 studies in subjects with premature IHD, and 7 studies in subjects with severe hypercholesterolemia.

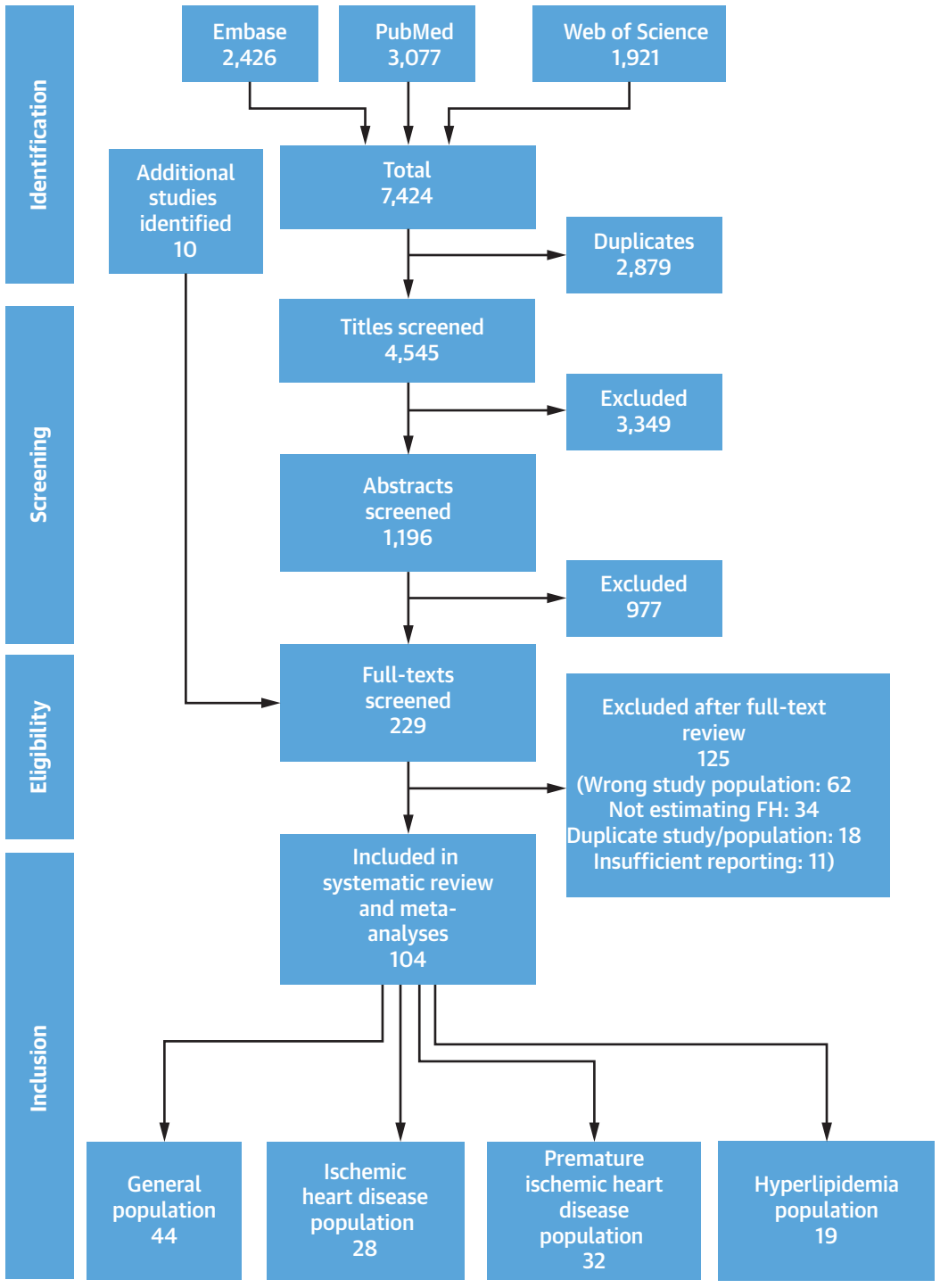
METHODS

Systematic reviews and meta-analyses were conducted, according to the Meta-Analysis of Observational Studies in Epidemiology consensus guidelines (13), on FH prevalence in 4 different populations: 1) the general population; 2) subjects with IHD; 3) subjects with premature IHD; and 4) subjects with severe hypercholesterolemia. Studies were grouped under "general population" if their investigators stated that subjects represented the population at large, rather than specific subgroups. IHD was a composite of fatal and nonfatal myocardial infarction, angina pectoris, and coronary revascularization.

SEARCH STRATEGY. PubMed (MEDLINE), Embase, and the Web of Science were searched until June 3, 2019. Reference lists of all included studies and relevant reviews were searched to identify peer-reviewed studies and conference abstracts reporting FH prevalence or providing data to calculate FH prevalence in the 4 study populations. Conference abstracts were included for completeness; however, in sensitivity analyses they were excluded. Premature IHD was distinguished from IHD if a defined age cutoff (explored in sensitivity analyses) for included subjects was present or if the investigators stated that IHD was premature. Studies with subjects with hyperlipidemia were any that reported FH prevalence in subjects with either severe hypercholesterolemia with LDL cholesterol ≥190 mg/dl (4.9 mmol/l) or other cutoffs defined by the investigators (Supplemental Table 1).

Combinations of following terms were used as keywords and/or Medical Subject Heading terms for the search: "familial hypercholesterol(a)emia," "prevalence," "frequency," and "screening." Only studies in English were included, and no attempts were made to contact investigators of studies with missing data. First, titles were screened and irrelevant publications excluded (**Figure 1**). Then, abstracts and full texts were reviewed. Fourteen studies were excluded because full-text versions could not be obtained and abstracts provided insufficient information. Studies reporting FH prevalence in founder populations or a mix of the 4 populations without the possibility of distinguishing among subpopulations were excluded. Founder populations with amplification of certain genetic variants as a result of random genetic drift developed because of inbreeding in population isolates and may bias general population prevalence toward higher values. Also, if 2 publications used the same population source, only the study with the largest number of subjects was included. Last, if studies were found not to estimate FH prevalence or provided insufficient information on which FH criteria were used or on the number of subjects or patients with FH (and no means to calculate this), they were excluded. No further exclusion criteria were applied, as Meta-Analysis of Observational Studies in Epidemiology guidelines recommend broad inclusion criteria and subsequent analyses relating design features to outcome (13). In 18 publications, FH prevalence was reported for more than 1 of the 4 populations, making the sum of the

FIGURE 1 Flowchart of the Inclusion of Studies for Meta-Analyses



Additional studies were identified through the reference lists of all included studies as well as relevant reviews. The sum of the populations exceeds 104, as 18 studies are included in multiple populations. FH = familial hypercholesterolemia.

4 populations higher than the number of publications included in the systematic review and meta-analyses.

DATA EXTRACTION AND SYNTHESIS. Data on investigators, publication year, journal, study design, study purpose, population type, age, sex, ethnicity, geographic region, FH criteria used, total number of subjects, number of patients with FH, and number of new papers identified from reference lists were extracted by one author (S.O.B.) according to an a priori form for each included study. One author (C.M.M.) independently extracted data on investigators, year of publication, FH criteria used, total number of subjects, and number of patients with FH and subsequently confirmed the full data extraction by S.O.B. Controversies were resolved through consensus among S.O.B., C.M.M., and B.G.N.

If studies reported prevalence on the basis of multiple FH diagnostic criteria, the criteria chosen for the main analysis were in the following order: 1) genetic; 2) Dutch Lipid Clinic Network criteria; 3) Simon Broome criteria; 4) MEDPED (Make Early Diagnosis to Prevent Early Death) criteria; and 5) other criteria, including LDL cholesterol cutpoint and family studies, usually when high cholesterol was documented vertically in at least 2 kindred. This was to provide the best possible criteria for FH diagnosis. Subsequently, all criteria were analyzed in subgroup analyses. For the Dutch Lipid Clinic Network criteria, probable and definite FH were pooled, as were possible and definite FH for the Simon Broome criteria.

When homozygous FH prevalence was reported (3 studies in the general population from the Netherlands, Spain, and Italy), heterozygous prevalence was calculated using the Hardy-Weinberg principle (Supplemental Methods), and the number of heterozygous subjects with FH in the cohort was found by multiplying the number of subjects in the study by the calculated prevalence. Whenever the response or reexamination rate was <100% for the stated sample size, this size was adjusted to reflect the actual number of subjects examined on the basis of response or examination rate.

QUALITY ASSESSMENT. Study quality was assessed independently by two authors (S.O.B. and C.M.M.) using a tool developed by Loney et al. (14) for critical appraisal of the prevalence of health problems. This scoring system consists of 8 items assessing: 1) validity of study methods; 2) interpretation; and 3) applicability of results. Each item, if fulfilled, generates 1 point, making 0 the minimum and 8 the maximum score possible. If there was a >2-point difference between S.O.B.'s and C.M.M.'s scoring, this was resolved through consensus among S.O.B., C.M.M., and B.G.N. Subsequently, the mean of S.O.B.'s and C.M.M.'s scorings was used to generate 3 quality categories for subgroup analyses: low quality if 0 to 3 points, moderate if 4 or 5 points, and high if 6 to 8 points. The required sample size to fulfill item 3 of the scoring system was calculated according to Naing et al. (15).

STATISTICAL ANALYSES. Data were analyzed using MetaXL version 5.3 (EpiGear International), an add-in for meta-analysis in Microsoft Excel (Microsoft, Redmond, Washington), and subgroup forest plots were displayed using the metan add-on for Stata/SE version 13.1 (StataCorp, College Station, Texas). Heterogeneity was assessed using the I^2 statistic, describing the percentage of total variation across studies due to heterogeneity rather than sample variation only. An I^2 value >75% indicates high heterogeneity and warrants the use of a random-effects model (16). Random-effects summary prevalence was estimated using the method of DerSimonian and Laird (17), and for comparison, fixed-effects prevalence was estimated using the inverse variance method (18).

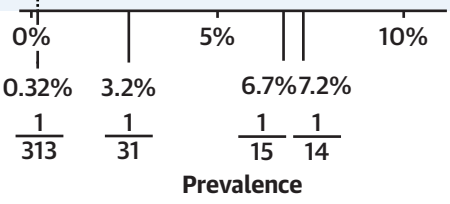
Using the inverse variance method in meta-analysis, the variance becomes very small when the prevalence tends toward 0% or 100% in a study, resulting in such studies' receiving larger weights. The double arcsine transformation in the Excel add-in was used to avoid disproportionate large weights for studies with small prevalence (19). Final summary prevalence and 95% confidence interval (CI) were transformed back for ease of interpretation.

Causes of heterogeneity were investigated using subgroup analyses. Subgroups were divided into categories according to study size, publication year, geography, ethnicity, age of subjects, FH criteria used, and quality score. Only if >90% of subjects in a study shared ethnicity were they categorized as such, or if no data were present and it was likely that sparse migration had taken place in that country (the United Arab Emirates, Bosnia and Herzegovina, China, Japan, South Korea, Latvia, Malaysia, and Romania). Additionally, for subjects with hyperlipidemia, studies reporting FH prevalence among participants with LDL ≥190 mg/dl (4.9 mmol/l) were also analyzed separately. Publication bias was assessed graphically using funnel plots, and on this basis, cutpoints for large versus small studies were chosen for stratified analysis to exclude smaller studies that sometimes are prone to publication bias (20).

A world map with color indicators of FH prevalence in the general population in different countries was

FIGURE 2 FH Prevalence in the General Population Compared With Subjects With IHD, Those With Premature IHD, and Those With Severe Hypercholesterolemia

Population	Number of Studies	N	FH Cases	Prevalence (%)	95 % LCI (%)	95 % HCI (%)
General	44	10,921,310	33,036	0.32	0.26	0.39
Ischemic heart disease	28	84,479	2,103	3.16	2.18	4.30
Premature ischemic heart disease	32	31,316	1,471	6.65	4.87	8.68
Severe hypercholesterolemia	7	17,728	920	7.22	4.56	10.8



Severe hypercholesterolemia is defined as low-density lipoprotein cholesterol ≥190 mg/dl. FH = familial hypercholesterolemia; HCI = higher confidence interval; IHD = ischemic heart disease; LCI = lower confidence interval.

made in Microsoft Excel. If more than 1 publication reported FH prevalence for a given country, a random-effects pooled prevalence estimate for the given country was displayed. Prevalence in founder populations in 4 countries was also depicted.

To depict how perceived prevalence of FH in the general population has changed over time from the Goldstein et al. (6) estimate of 1:500, cumulative FH prevalence over time was estimated. Overall prevalence estimates and 95% CIs were calculated by simply summing the number of subjects investigated, and patients with FH found, respectively, in all studies published up until and including the year. To illustrate the impact of the Benn et al. (7) publication on FH prevalence from 2012, it was included in these estimates except the estimate by year 2018, for which the Benn et al. (10) publication from 2016 using the same population source but with a greater number of subjects included, as in all main analyses.

RESULTS

A total of 104 publications including more than 11 million subjects covering FH prevalence in the general population (44 studies), subjects with IHD (28 studies), subjects with premature IHD (32 studies), and subjects with severe hypercholesterolemia (7 studies) were included in meta-analyses (**Figure 1**, Supplemental Tables 1 to 3). Eighteen publications reported FH prevalence for more than 1 population and were thus included in multiple subpopulations.

FH PREVALENCE: SUBJECTS WITH IHD AND THOSE WITH SEVERE HYPERCHOLESTEROLEMIA COMPARED WITH THE GENERAL POPULATION. The pooled FH prevalence from 44 studies with 10,921,310 subjects (33,036 patients with FH) in the general population was 0.32% (95% CI: 0.26% to 0.39% [corresponding to 1:313]) using a random-effects model because heterogeneity was present (I^2 = 100%, p < 0.001) (**Figure 2**, Supplemental Figure 1). In comparison, FH prevalence was 3.2% (95% CI: 2.2% to 4.3% [1:31]) for 84,479 subjects with IHD (2,103 patients with FH) in 28 studies, 6.7% (95% CI: 4.9% to 8.7% [1:15]) for 31,316 subjects with premature IHD (1,471 patients with FH) in 32 studies, and 7.2% (95% CI: 4.6% to 10.8% [1:14]) for 17,728 subjects with severe hypercholesterolemia (920 patients with FH) in 7 studies (**Figure 2**, Supplemental Figures 2 to 5). Results were similar when we excluded 3 studies from the Netherlands, Spain, and Italy, where heterozygous FH prevalence was estimated from homozygous FH prevalence (compare Supplemental Figure 6 with **Figure 2**) and when we excluded 17 studies from conference abstracts (compare Supplemental Figure 7 with **Figure 2**).

Corresponding estimates using fixed-effects models were 0.28% (95% CI: 0.28% to 0.28% [1:357]), 2.0% (95% CI: 1.9% to 2.1% [1:50]), 3.9% (95% CI: 3.6% to 4.1% [1:26]), and 4.9% (95% CI: 4.5%

to 5.2% [1:21]) in the general population, subjects with IHD, those with premature IHD, and those with severe hypercholesterolemia, respectively (Supplemental Figures 8 to 11).

Funnel plots for the 4 populations were asymmetrical, which may indicate publication bias or be due to "small-study effects," that is, the tendency for smaller studies to show a larger estimate (Supplemental Figure 12).

FH PREVALENCE: STRATIFIED ANALYSES. Stratified analysis of study characteristics in the general population revealed a tendency for the FH prevalence estimate to decrease with increasing study size (0.28% and 0.51% in studies with ≥5,000 and <5,000 subjects, respectively) and to increase with later publication years (0.20% in studies published from 2001 to 2010 vs. 0.34% in those published from 2016 to 2018) (**Figure 3**). Also, a lower prevalence (0.19%; 95% CI: 0.10% to 0.29%) in 4 studies from Asia and a higher prevalence in 3 studies using the Simon Broome criteria (0.91%; 95% CI: 0.00% to 4.52%) were found compared with overall prevalence. There was concordance in prevalence between clinical and genetic criteria for FH in the general population (0.32% vs. 0.34%).

FH prevalence in subjects with IHD in strata of study size and publication year showed similar results as in the general population (**Figure 4**). Higher estimates were found in 1 study from the Pacific region (11.5%; 95% CI: 8.1% to 15.2%) and in 1 study from South America (18.1%; 95% CI: 14.2% to 22.2%). Interestingly, FH prevalence in Asia was comparable with overall FH prevalence in subjects with IHD (3.6% vs. 3.2%), which is in contrast to the lower FH prevalence estimate among Asians in the general population. Genetic FH criteria showed lower prevalence compared with both clinical criteria and overall prevalence (0.7% vs. 3.6% vs. 3.2%, respectively).

In subjects with premature IHD, FH prevalence was lower in 1 study using subjects from multiple geographic locations (1.9%; 95% CI: 1.6% to 2.3%) (**Figure 5**). However, that study used genetic FH criteria, which in general reported a lower estimate compared with overall prevalence (2.1% vs. 6.7%). FH prevalence increased with decreasing age, as subjects ≤35 years of age had a prevalence of 16.2% compared with 4.4% among those ≤55 years of age for men and ≤60 years of age for women.

FH PREVALENCE: WORLDWIDE. Seventeen of 195 countries (9%) in the world have reported FH prevalence for the general population, with an additional 4 countries reporting FH prevalence only in founder populations (**Figure 6**). This leaves 178 of countries in the world (91%) with unknown FH prevalence. Studies reporting FH prevalence were primarily from Europe, North America, East Asia, and Australia, leaving out large parts of Africa, South America, and Asia.

FH PREVALENCE: ESTIMATES OVER TIME. By 2012, a total of 14 studies with 417,972 subjects and 723 patients with FH had established an overall FH prevalence of 0.17% (1:588) in the general population (**Figure 7**). This estimate increased as more studies emerged and was 0.21% (1:476) by 2015, 0.22% (1:456) by 2016, 0.31% (1:323) by 2017, and finally 0.30% (1:333) by 2018, with a total of 44 studies, 10,921,310 subjects, and 33,036 FH cases. This estimate is close to the estimate from the meta-analysis (0.30% vs. 0.32%).

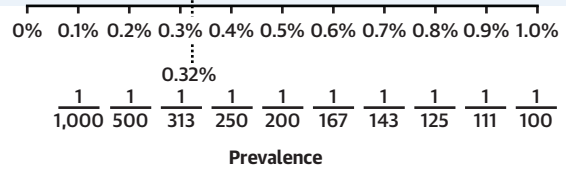
DISCUSSION

Compared with 1:313 among subjects in the general population, FH prevalence is 10-fold higher among subjects with IHD, 20-fold higher among those with premature IHD, and 23-fold higher among those with severe hypercholesterolemia (**Central Illustration**). The prevalence of FH in the general population is unknown in 90% of countries in the world. Novel aspects of the present study include: 1) a meta-analysis of >11 million subjects, compared with up to 2.5 million subjects in a previous meta-analysis; 2) a comparison of FH prevalence between healthy and diseased subjects; 3) documentation of the lack of FH prevalence information in most countries; and 4) an attempt to understand important sources of heterogeneity of the results, including genetic versus clinical diagnosis. Because of large heterogeneity among studies, the overall FH prevalence estimates should be interpreted cautiously.

Never has LDL cholesterol lowering in subjects with FH been as effective as today, with statins being the first breakthrough, in 1987 (21), and now with the possibility of added lowering by ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors (22). To mitigate the detrimental cumulative effect of lifelong highly elevated LDL cholesterol on risk for IHD, early identification and treatment is of paramount importance (1). Nevertheless, FH is underdiagnosed (<1% in most countries) and undertreated (1). In our study, we demonstrate that worldwide knowledge of FH prevalence in the general population is limited to 1 in 10 countries. Determining this prevalence in different population settings is the crucial starting point for clinical practice, as it reflects the burden of FH in these populations and can help decision makers direct health care investments (23).

FIGURE 3 FH Prevalence in the General Population in Different Strata

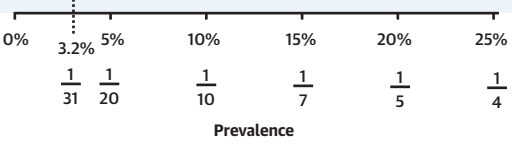
Subgroup	Number of Studies	N	FH Cases	Prevalence (%)	95% LCI (%)	95% HCI (%)	I^2 (%)	p Value*
Pooled prevalence	44	10,921,310	33,036	0.32	0.26	0.39	100	0.00
Study size								
≥5,000 subjects	30	10,902,146	32,947	0.28	0.22	0.35	100	0.00
<5,000 subjects	14	19,163	88	0.51	0.37	0.67	46	0.03
Publication year								
Before 2001	7	7,598	41	0.59	0.32	0.89	54	0.04
2001-2010	4	80,171	153	0.20	0.14	0.27	62	0.05
2011-2015	10	4,719,112	9,847	0.25	0.18	0.32	99	0.00
2016-2018	23	6,114,428	22,995	0.34	0.25	0.44	100	0.00
Geography								
Europe	19	7,161,101	23,366	0.32	0.22	0.44	100	0.00
Pacific region	6	107,404	275	0.39	0.23	0.56	86	0.00
North America	9	2,326,989	6,578	0.32	0.21	0.44	99	0.00
South America	3	53,568	106	0.33	0.07	0.65	95	0.00
Asia	4	561,359	659	0.19	0.10	0.29	92	0.00
Middle-East	1	685,314	1,932	0.28	0.27	0.29		
Multiple	2	25,575	120	0.47	0.39	0.56	0	0.89
Ethnicity								
White	6	545,446	1,488	0.32	0.19	0.46	97	0.00
East Asian	4	561,359	659	0.19	0.10	0.29	92	0.00
Age (years)								
Infant (0-1)	6	5,513	29	0.61	0.26	1.00	61	0.03
Child (2-18)	8	157,413	457	0.35	0.20	0.52	95	0.00
Adult (>18)	31	10,812,120	32,799	0.30	0.24	0.37	100	0.00
FH Criteria								
Clinical	34	10,583,944	31,811	0.32	0.25	0.39	100	0.00
DLCN	14	2,049,755	4,600	0.31	0.21	0.43	99	0.00
Simon Broome	3	108,926	3,915	0.91	0.00	4.52	100	0.00
MEDPED	7	1,555,071	3,652	0.26	0.13	0.41	100	0.00
Family study	8	56,476	132	0.51	0.24	0.81	81	0.00
Other	9	7,364,831	24,939	0.31	0.18	0.46	100	0.00
Genetic	10	337,366	1,225	0.34	0.27	0.42	91	0.00
Quality score								
High	18	996,554	2,304	0.32	0.23	0.43	98	0.00
Moderate	18	8,260,554	26,679	0.35	0.25	0.46	100	0.00
Low	8	1,664,201	4,052	0.29	0.11	0.50	99	0.00



*p value is for I^2. DLCN = Dutch Lipid Clinic Network; MEDPED = Make Early Diagnosis to Prevent Early Death; other abbreviations as in Figure 2.

FIGURE 4 FH Prevalence in Subjects With Ischemic Heart Disease in Different Strata

Subgroup	Number of Studies	N	FH Cases	Prevalence (%)	95% LCI (%)	95% HCI (%)	I^2 (%)	p Value*
Pooled prevalence	28	84,479	2,103	3.16	2.18	4.30	99	0.00
Study size								
≥900 subjects	16	80,253	1,899	2.20	1.21	3.41	99	0.00
<900 subjects	12	4,226	204	4.99	2.38	8.07	94	0.00
Publication year								
Before 2001	3	500	28	5.60	1.73	10.34	5	0.31
2001-2011	1	948	8	0.80	0.31	1.47		
2012-2016	10	65,612	1,422	1.94	0.74	3.46	99	0.00
2017-2019	14	17,419	645	4.01	2.44	5.83	97	0.00
Geography								
Europe	17	53,762	1,448	2.26	1.15	3.61	99	0.00
Pacific region	1	316	36	11.48	8.11	15.15		
North America	3	7,054	80	4.38	0.00	11.94	95	0.00
South America	1	357	64	18.06	14.18	22.17		
Asia	4	9,047	302	3.57	2.85	4.41	52	0.10
Middle-East	2	13,943	173	1.69	0.00	5.59	99	0.00
Ethnicity								
White	1	42	2	5.75	0.09	13.8		
Black	1	150	7	4.95	1.78	8.72		
East Asian	4	9,407	302	3.60	2.85	4.41	52	0.10
Arab	1	3,224	119	3.70	3.07	4.37		
FH Criteria								
Clinical	24	74,907	2,029	3.56	2.41	4.90	99	0.00
DLCN	16	61,074	1,827	3.12	1.83	4.63	99	0.00
Simon Broome	3	9,473	434	4.43	3.07	5.97	91	0.00
MEDPED	1	150	7	4.92	1.78	8.72		
Family study	2	350	21	5.99	0.00	14.66	89	0.00
Other	5	13,333	174	4.23	0.93	8.41	98	0.00
Genetic	4	9,572	75	0.73	0.41	1.17	60	0.06
Quality score								
High	12	47,781	1,287	2.73	1.30	4.47	99	0.00
Moderate	11	34,081	794	4.29	2.44	6.45	99	0.00
Low	5	2,617	23	1.80	0.31	3.79	84	0.00

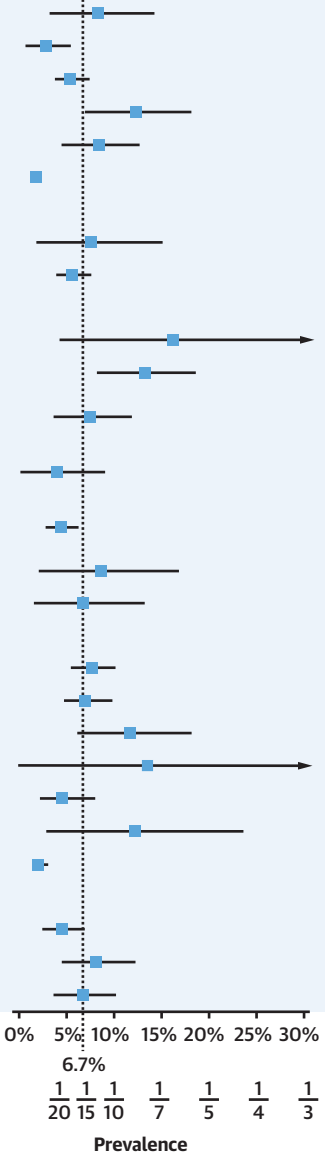


*p value is for I^2. Abbreviations as in Figures 2 and 3.

Given the high prevalence as well as underdiagnosis in subjects with (premature) IHD, this setting may be feasible to launch national screening programs to identify index cases and subsequently initiate cascade screening (24,25). To obtain this, it is important to increase FH awareness, particularly among cardiologists. A survey conducted among a panel of 300 to 500 American College of Cardiology CardioSurve members (>10 years' experience in cardiovascular practice) in 2011 revealed that about 80% were unaware of FH prevalence (defined as 1:300 to 1:500), 60% did not know that one-half of all

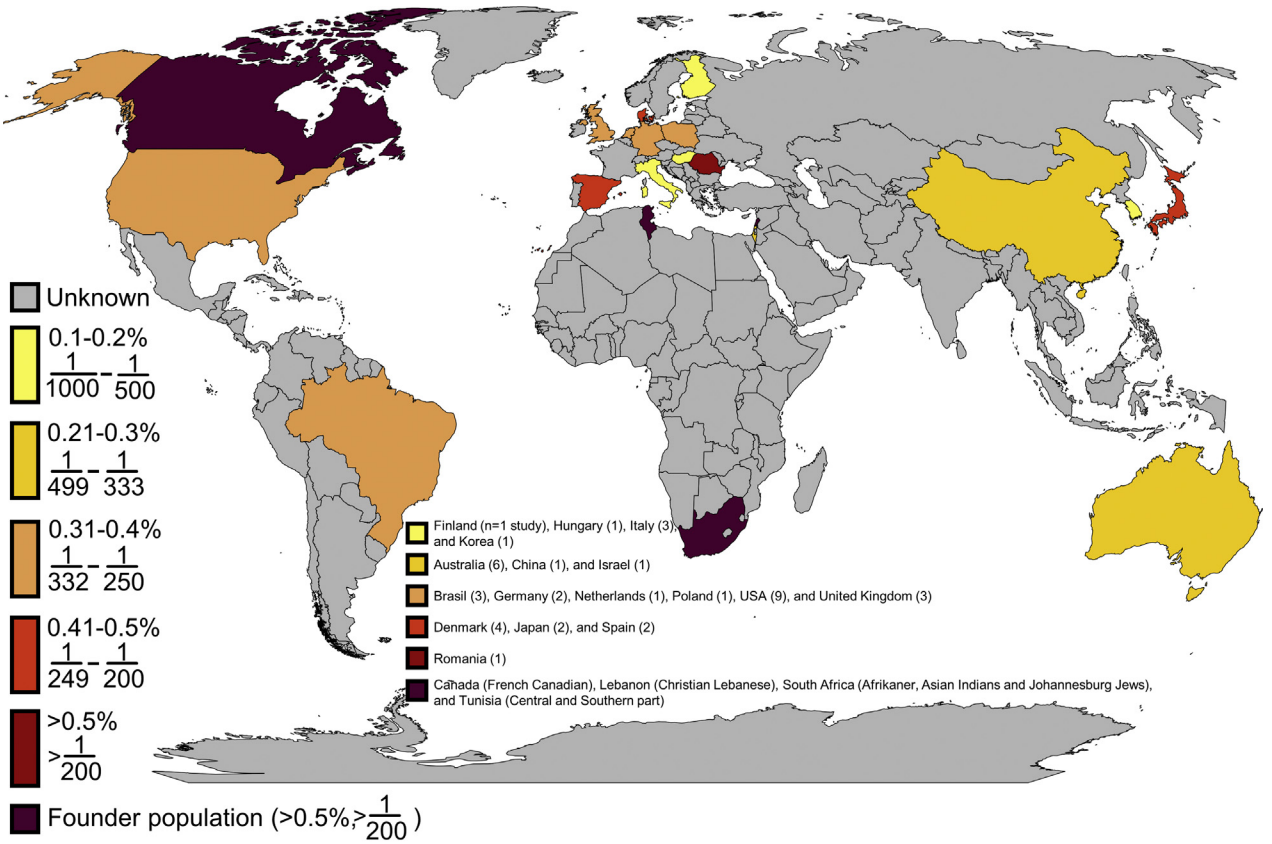
FIGURE 5 FH Prevalence in Subjects With Premature Ischemic Heart Disease in Different Strata

Subgroup	Number of Studies	N	FH Cases	Prevalence (%)	95% LCI (%)	95% HCI (%)	I^2 (%)	p Value*
Pooled prevalence	32	31,316	1,471	6.65	4.87	8.68	98	0.00
Study size								
≥400 subjects	12	27,727	1,091	3.66	1.84	5.87	99	0.00
<400 subjects	20	3,589	380	9.17	6.42	12.24	89	0.00
Publication year								
Before 2001	3	293	17	5.98	2.89	9.64	35	0.22
2001-2011	3	335	20	8.50	0.51	19.33	88	0.00
2012-2016	12	18,239	872	5.69	2.91	8.97	99	0.00
2017-2019	14	12,449	562	7.41	4.48	10.75	98	0.00
Geography								
Europe	14	8,042	691	8.04	4.19	12.48	98	0.00
Pacific region	5	860	79	8.23	3.24	14.16	88	0.00
North America	5	13,173	346	2.83	0.78	5.50	98	0.00
Asia	5	4,232	235	5.43	3.73	7.40	71	0.01
Middle-East	1	134	16	12.16	6.94	18.03		
Russia	1	172	14	8.32	4.46	12.75		
Multiple	1	4,703	90	1.85	1.54	2.33		
Ethnicity								
White	3	378	34	7.56	1.65	15.02	83	0.00
East Asian	5	4,232	235	5.41	3.73	7.40	71	0.01
Age (years)								
≤35	3	1,484	154	16.16	4.22	30.41	97	0.00
≤40	4	25,714	1,392	13.07	8.17	18.48	53	0.10
≤45 or ≤45 M, ≤50 W	2	155	11	7.44	3.62	11.90	0	0.33
≤50 or ≤50 M, ≤60 W	4	25,714	1,392	4.08	0.37	9.13	98	0.00
≤55 or ≤55 M, ≤60 W or ≤65 W	12	12,880	453	4.42	2.85	6.26	94	0.00
≤65	6	3,606	418	9.07	2.14	17.65	98	0.00
No Data	4	6,802	171	6.71	1.60	13.11	98	0.00
FH Criteria								
Clinical	27	22,077	1,335	7.68	5.51	10.11	97	0.00
DLCN	20	20,764	1,197	7.06	4.73	9.78	98	0.00
Full DLCN	2	2,378	238	11.71	6.05	18.22	92	0.00
Simon Broome	5	3,464	795	13.41	0.00	37.25	91	0.00
Family study	2	203	9	4.65	2.04	7.89	0	0.32
Other	3	626	52	12.08	2.86	23.44	91	0.00
Genetic FH	7	10,285	176	2.10	1.38	3.12	79	0.00
Quality score								
High	8	16,720	1,008	4.43	2.37	6.91	79	0.00
Moderate	13	9,072	332	8.08	4.50	12.19	97	0.00
Low	11	5,524	131	6.72	3.62	10.31	99	0.00



*p value is for I^2. Abbreviations as in Figures 2 and 3.

FIGURE 6 Worldwide FH Prevalence in the General Population



If more than 1 study from a country reported a familial hypercholesterolemia (FH) prevalence, a pooled prevalence estimate using a random-effects model was calculated. Founder populations are depicted to highlight the entire body of knowledge of worldwide FH prevalence.

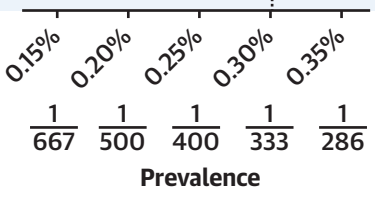
first-degree relatives of index patients with FH also have the disease, and none knew that patients with FH are 20-fold more likely to develop premature IHD compared with those in the general population (26).

For years, heterozygous FH prevalence in the general population was believed to be 1:500, on the basis of the study by Goldstein et al. (6), which by the Hardy-Weinberg principle resulted in an estimated homozygous FH prevalence of 1:1,000,000. In recent years there has been a dramatic increase in the interest of FH concurrent with the development of proprotein convertase subtilisin/kexin type 9 inhibitors, and the number of studies examining FH prevalence has increased, with newer and larger studies finding higher prevalence rates of FH. On the basis of our pooled heterozygous FH prevalence estimate (1:313), homozygous FH prevalence is about 1:400,000. In the Netherlands, Sjouke et al. (27) found a similar estimate on the basis of identifying 41 subjects with homozygous FH nationwide among 16,722,387 inhabitants (homozygous FH prevalence = 41/16,722,387 = 1:407,863). From this, estimated prevalence of heterozygous FH is 1:319 on the basis of the Hardy-Weinberg principle.

In a meta-analysis in 2017, Akioyamen et al. (28) estimated a general population FH prevalence of 0.40% on the basis of 2,458,456 subjects (28), corresponding to our estimate of 0.32%. They included 19 studies, whereas we included 43 studies; because of our exclusion criteria, 5 studies included by those investigators, of which 3 presented very high FH prevalence, were excluded from our analysis, offering a possible explanation for the lower prevalence detected in our study. Also, their search was limited to studies published after January 1990 and did not include studies assessing heterozygous FH prevalence on the basis of homozygous FH prevalence using the Hardy-Weinberg principle. A recent

FIGURE 7 FH Prevalence: Estimates Over Time in the General Population

By year	Number of Studies	N	FH Cases	Prevalence (%)	95 % LCI (%)	95 % HCI (%)
2012	14	417,972	723	0.17	0.16	0.19
2015	22	4,875,898	10,350	0.21	0.21	0.22
2016	35	6,885,876	15,243	0.22	0.22	0.22
2017	41	10,294,262	32,056	0.31	0.31	0.31
2018	44	10,921,310	33,036	0.30	0.30	0.31



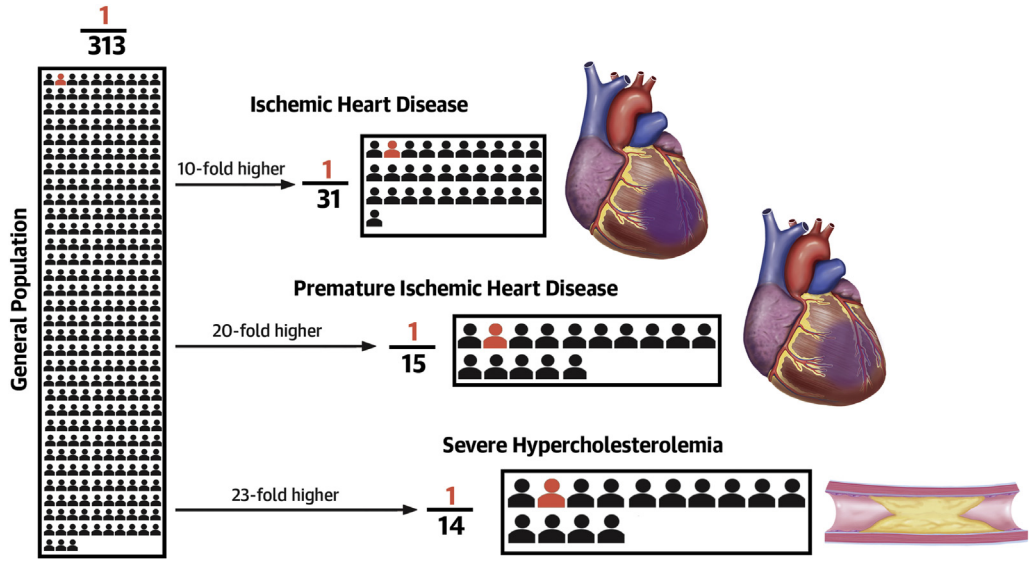
Overall prevalence estimates were calculated using the total number of subjects investigated and patients with FH found in all studies published up until and including that year. To illustrate the impact of the Benn et al. (7) publication from 2012, it was included instead of the publication from 2016 (10) in all analyses, except for the estimate by year 2018. Abbreviations as in Figure 2.

meta-analysis from 2019 revealed an FH prevalence of 4.7% among 31,436 patients with acute coronary syndrome (29), comparable with our estimate of 3.2% on the basis of 84,479 subjects with IHD. Their estimate was a composite of premature and nonpremature cases, driving the estimate up, whereas we report FH prevalence among subjects with premature IHD separately. Also, there were other methodological differences, such as the inclusion of fewer subjects in their sample size but the same number of cases when including the same studies, which also resulted in higher prevalence. Furthermore, we investigated additional sources of heterogeneity, including study size, publication year, geography, ethnicity, and quality score. In a previous systematic review, the investigators stated that FH prevalence estimates in Latin America are unavailable because of small sample sizes (30). Also, nonsystematic reviews estimated general population FH prevalence (31-34). A narrative review from 2004 reports FH prevalence among subjects with IHD between 3% and 5% on the basis of studies from the 1970s (35), and a review from 2016 states FH prevalence to be 10-fold higher among patients with IHD compared with those in the general population (36).

The exact FH prevalence of a population is dependent on several factors, such as the FH criteria used, ethnicity, age of the population, and others. In this study, we found FH prevalence in the general population in Asia to be 0.19%, compared with prevalence in Europe and North America of 0.32%. This lower prevalence may be due to genetic differences among ethnicities. Although some Japanese studies use FH diagnostic criteria developed by the Japan Atherosclerosis Society in 2012 (37), many FH diagnostic criteria used in Asia were developed in Western populations, and even though they are often modified, applying these criteria in Asia may not be appropriate, as these populations traditionally have lower cholesterol levels (33). If FH indeed is less frequent in Asia, one would expect the prevalence among subjects with IHD to be equally lower. However, FH prevalence among subjects with IHD in Asia was similar to estimates from Europe and North America. Also, when looking at subgroup analyses, there was good consistency between estimates based on clinical FH criteria and those based on genetic criteria in the general population, but the prevalence was generally lower for the genetic criteria for all subpopulations. In addition, the Simon Broome criteria demonstrate higher FH prevalence, as the inclusion criteria are broader (38).

Strengths of our study are the large number of publications included, with the earliest from 1971 and the latest from 2019, including conference abstracts, totaling 11 million subjects. Also, we investigated

CENTRAL ILLUSTRATION **Prevalence of Familial Hypercholesterolemia**



Beheshti, S.O. et al. J Am Coll Cardiol. 2020;75(20):2553–66.

Severe hypercholesterolemia is defined as low-density lipoprotein cholesterol ≥190 mg/dl.

causes of heterogeneity by dividing studies into strata according to study characteristics.

STUDY LIMITATIONS. Limitations include heterogeneity in the populations studied, making it more difficult to interpret on the pooled estimates; however, we attempted to account for this using a random-effects model, and this challenge elucidates the need for an international homogenous framework to align FH prevalence reporting. Funnel plots for all 4 populations were asymmetrical, which may indicate publication bias or be due to small-study effects, that is, the tendency for smaller studies to show larger estimate effects; and as prevalence is confined to positive values, a low prevalence might introduce asymmetry to the funnel plot without this necessarily being caused by publication bias. That said, when focusing only on studies in the general population with ≥5,000 subjects, the prevalence was lower.

It is uncertain if the same underlying prevalence exists in different parts of the world and among different ethnicities, with the subgroup analysis showing lower FH prevalence in the general population in Asia. However, this was not supported by the similar FH prevalence among subjects with IHD when comparing Asia with Western countries, and looking at the world map, even within Asia, there seems to be no trend toward lower FH prevalence, as Japan and China report prevalence estimates in similar size order compared with Western countries. Furthermore, studies reporting on subjects in the general population may have some geographic biases, especially in large countries.

Another limitation is that the approach to infer heterozygous FH prevalence on the basis of reported homozygous FH prevalence may be questionable, although it intuitively makes sense. This method may not be useful for countries with substantial consanguinity or small countries with limited migration, or if homozygotes die undiagnosed. However, when we excluded the 3 studies from the Netherlands, Spain, and Italy using this approach, results were similar.

Finally, most clinical FH criteria were modified, as not all information were available, probably leading to an underestimation of FH prevalence.

CONCLUSIONS

Compared with 1:313 among subjects in the general population, FH prevalence is 10-fold higher among

subjects with IHD, 20-fold higher among subjects with premature IHD, and 23-fold higher among subjects with severe hypercholesterolemia. Because of large heterogeneity among studies, the overall FH prevalence estimates should be interpreted cautiously. The prevalence of FH in the general population is unknown in 90% of countries in the world.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: The prevalence of FH is 1:313 in the general population and up to 23-fold greater in high-risk groups, but the prevalence in the general population is unknown in 90% of countries.

TRANSLATIONAL OUTLOOK: Given the greater prevalence of FH in patients with IHD, particularly premature IHD, and in populations with severe hypercholesterolemia, future studies should investigate the cost-effectiveness of implementing screening strategies in these populations.

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KEY WORDS epidemiology, frequency, myocardial infarction, premature, severe hypercholesterolemia, systematic review

APPENDIX For a supplemental Methods section, tables, figures, and references, please see the online version of this paper.