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Systematic Review/Meta-analysis

Estimating the Prevalence of Familial Hypercholesterolemia in Acute Coronary Syndrome: A Systematic Review and Meta-analysis

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See editorial by Gupta, pages 1270–1271 of this issue.

ABSTRACT

Background: Heterozygous familial hypercholesterolemia (FH) is one of the most common monogenic conditions but remains substantially underdiagnosed. One method for increasing the diagnosis is via opportunistic screening of individuals presenting with acute coronary syndrome (ACS). The prevalence of FH in the ACS population has been assessed in numerous studies using various diagnostic criteria, resulting in wide variability of prevalence estimates. The purpose of this study was to perform a systematic review and meta-analysis to provide a more robust estimate.

Methods: We searched MEDLINE, EMBASE, Pubmed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews to identify peer-reviewed articles reporting the prevalence of FH in ACS. We calculated pooled prevalence using a random-effects model. When multiple diagnostic criteria were used in a single study, we gave priority to DNA-based criteria, followed by Dutch Lipid Clinic

RÉSUMÉ

Contexte : L'hypercholestérolémie familiale hétérozygote est l'une des affections monogéniques les plus fréquentes, mais elle demeure nettement sous-diagnostiquée. L'une des méthodes permettant de favoriser son diagnostic est le dépistage opportuniste des personnes consultant pour un syndrome coronarien aigu (SCA). La prévalence de l'hypercholestérolémie familiale hétérozygote chez la population présentant un SCA a été évaluée dans de nombreuses études à l'aide de divers critères diagnostiques, donnant lieu à une importante variabilité de la prévalence estimée. L'objectif de cette étude était de réaliser un examen systématique et une méta-analyse afin d'obtenir une estimation plus solide.

Méthodologie : Nous avons mené des recherches dans les bases de données MEDLINE, EMBASE, Pubmed, Cochrane Central Register of Controlled Trials et Cochrane Database of Systematic Reviews afin d'y trouver des articles révisés par des pairs indiquant la prévalence de l'hypercholestérolémie familiale hétérozygote en présence d'un SCA. À l'aide

Heterozygous familial hypercholesterolemia (FH) is among the most common monogenic disorders in humans and causes elevated low-density lipoprotein cholesterol (LDL-C) and accelerated atherosclerosis, but FH is significantly underdiagnosed worldwide. FH is caused most commonly by pathogenic variants in the *LDLR*, *APOB*, *PCSK9*, and *LDLRAP1* genes.[1] A recent meta-analysis estimated the population prevalence of FH to be 1 in 250 people.[2] In most countries, fewer than 1% of persons with FH have been diagnosed and therefore may not be receiving appropriate treatment.[3] Patients with untreated FH have an approximately 20-fold increased risk of premature coronary artery disease (CAD) compared with the non-FH population.[4]

One method to improve the identification of patients with FH is via opportunistic screening of patients presenting with acute coronary syndrome (ACS). A number of studies have investigated the prevalence of FH in ACS. However, estimates of the prevalence of FH in ACS vary greatly among studies, and no meta-analyses have been conducted.[5] Therefore, the purpose of this study was to estimate the prevalence of FH in ACS based on the totality of available data by conducting a systematic review of the literature. Furthermore, we assessed the variance of the prevalence with patient age, diagnostic method used in the study, and patient sex.

Methods

Search strategy

We conducted a systematic review of the literature relating to the prevalence of FH in ACS. Databases searched included

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Network (DLCN) criteria. We also investigated the prevalence in sub-analyses according to age and diagnostic criteria.

Results: The overall pooled prevalence of FH in ACS, derived from 22 studies, was 4.7% (95% confidence interval [CI], 3.0-7.3). DNA-based criteria and DLCN criteria provided similar estimates of 5.0% (95% CI, 2.6-9.3) and 5.5% (95% CI, 3.0-10.0), respectively. The prevalence was 7.3% (95% CI, 5.3-10.0) for patients aged ≤ 60 years and increased to 13.7% (95% CI, 8.2-22.1) for those aged ≤45 years.

Conclusions: Approximately 1 in 21 patients with ACS has FH, and this increases to 1 in 7 among those ≤45 years. These results reinforce the importance of screening for FH in the ACS population.

d'un modèle à effets aléatoires, nous avons calculé la prévalence à partir des données groupées. Lorsque plusieurs critères diagnostiques étaient utilisés dans la même étude, nous avons privilégié les critères fondés sur l'ADN, puis les critères du Dutch Lipid Clinic Network (DLCN). Nous avons aussi évalué la prévalence dans des sous-analyses effectuées en fonction de l'âge et des critères diagnostiques.

Résultats : La prévalence globale de l'hypercholestérolémie familiale hétérozygote en présence d'un SCA selon les données groupées de 22 études a été de 4,7 % (intervalle de confiance [IC] à 95 % : de 3,0 à 7,3). Les critères fondés sur l'ADN et les critères du DLCN ont donné des estimations similaires, soit 5,0 % (IC à 95 % : de 2,6 à 9,3) et 5,5 % (IC à 95 % : de 3,0 à 10,0), respectivement. La prévalence était de 7,3 % (IC à 95 % : de 5,3 à 10,0) chez les patients âgés de ≤ 60 ans et passait à 13,7 % (IC à 95 % : de 8,2 à 22,1) chez les patients âgés de ≤ 45 ans.

Conclusion : Environ 1 patient sur 21 présentant un SCA était atteint d'hypercholestérolémie familiale hétérozygote, cette prévalence passait à 1 sur 7 chez les patients de ≤ 45 ans. Ces résultats soulignent l'importance du dépistage de l'hypercholestérolémie familiale hétérozygote chez la population présentant un SCA.

MEDLINE, EMBASE, Pubmed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. Searches were performed from date of inception to December 4, 2018, using a combination of MeSH terms and key words pertinent to the research question. Detailed information regarding the search strategy is provided in Supplemental Table S1. Publications in peer-reviewed journals from all date ranges were included in the search results. Reference lists for all articles included in the meta-analysis were also manually assessed. One additional eligible study was identified during the review process for this manuscript and was subsequently incorporated into our analysis.[6]

The titles and abstracts of all articles identified in the search were screened for inclusion and exclusion criteria by a single reviewer (A.I.K.). Ambiguous studies were reviewed by a second reviewer (L.R.B.). Studies proceeded to full text review if their design enabled the calculation of prevalence.

Eligibility, study selection, and diagnostic criteria for FH

To be eligible, we considered observational studies that were published in peer-reviewed journals, have full texts available in English, and provide the prevalence of heterozygous FH in humans with an ACS, defined as myocardial infarction (MI), including ST-elevation MI (STEMI) or non-ST elevation MI (NSTEMI), or unstable angina. Meta-analyses were considered eligible, although none were identified. Furthermore, we required that studies provide clear diagnostic criteria for FH and used a definition that does not rely on the patient's and/or relatives' cholesterol levels as the sole criterion for diagnosis. Acceptable criteria included but were not limited to Dutch Lipid Clinic Network (DLCN), Simon Broome Register (SB), Make Early Diagnosis—Prevent Early Death (MED-PED), American Heart Association (AHA), Canadian Simplified Definition, and Japanese Atherosclerotic Society (JAS) criteria.[7-12] Studies using DLCN criteria were eligible if they included patients with "probable" (DLCN score 6 to 8) or "definite" (score > 8) FH. For studies using the Simon Broome Criteria, a diagnosis of "definite" or "possible" FH was considered to be eligible.

If multiple studies were published using the same or overlapping cohorts or data sources, only the study with the largest sample size of patients with ACS or the study limited to patients with ACS was used, regardless of other differences in methodology. Studies for which the population included both ACS and patients with stable coronary artery disease (CAD)—and in which data for these groups were not presented separately—were considered eligible if at least 50% of the study population had ACS. In instances for which the proportion was not stated, we attempted to contact the study authors for clarification; studies were excluded if the proportions could not be confirmed. We excluded studies in which the study population was required to have a positive family history of CAD.

Data extraction

Data regarding country of enrollment, enrollment periods, type of coronary disease, eligible age range, FH diagnostic criteria, number of FH cases, and sample size were extracted from all articles selected for inclusion. Details regarding each included study are shown in Table 1. When a study reported the prevalence of ACS stratified by age groups, these were recorded separately and assessed in their corresponding age-based sub-analyses. Table 2 provides prevalence data from studies of persons aged 60 years and younger.

In the event multiple definitions of FH were used in a single study, we prioritized the use of a DNA-based diagnosis. When multiple clinical diagnostic methods were used, we prioritized DLCN criteria. If a study noted the FH diagnosis was "indeterminate" for some patients because of missing information but were still included in the study, these patients were assumed to have negative FH diagnoses.

Data analysis

Analyses were performed using the *meta* package for R (v3.5.2 for Windows).[13,14] Confidence intervals (CIs) for individual studies were calculated using the Clopper-Pearson method. Data were analysed using a DerSimonian-Laird estimator in a random-effects model, owing to the expected

Table 1. Studies included in the meta-analysis

Study	Country	Enrollment period	Population	Diagnostic criteria	Age (years)	Sample size	FH cases, N	Prevalence estimate (95% CI)	Female patients, N (%)
Al-Rasadi et al.[20] (2018)	Bahrain, Kuwait, Oman, United Arab Emirates	2012−2013	ACS	DLCN	≥ 18	3224	119	3.69% (3.07- 4.40)	1049 (32.5%)
Amor-Salamanca et al.[21] (2017)	Spain	2012−2016	ACS	DNA, DLCN, SB	≤ 65	103	9	8.74% (4.07-15.94)	13 (12.6%)
Auckle et al.[22] (2017)	China	2013−2015	STEMI	DLCN	< 55 male patients; < 60 female patients	498	19	3.82% (2.31-5.89)	135 (27.1%)
Benedek et al.[23] (2018)	Sweden	2009−2015	ACS	DNA, DLCN	NS	116	8	6.90% (3.02-13.14)	43 (37.1%)
Faggiano et al.[24] (2018)	Italy	2015	ACS	DLCN	NS	755	34	4.50% (3.14-6.24)	NS
Harada-Shiba et al.[25] (2018)	Japan	2015−2016	ACS	JAS	≥ 20	1944	52	2.67% (2.00-3.49)	383 (19.7%)
Hassan et al.[26] (2018)	Israel	2000−2017	ACS, Stable CAD (17%)	DLCN	≤ 35	71	18	25.35% (15.77-37.08)	NS
Koivisto et al.[27] (1993)	Finland	1987−1991	ACS	DNA	≤ 45	55	4	7.27% (2.02-17.59)	2 (3.6%)
Li et al.[28] (2016)	China	2011−2016	ACS	DLCN	NS	1843	72	3.91% (3.07-4.89)	274 (14.9%)
Mortensen et al.[29] (2016)	Denmark	2010−2012	ACS	DLCN, SB	NS	1381	28	2.03% (1.35-2.92)	474 (34.3%)
Nanchen et al.[30] (2015)	Switzer-land	2009−2014	ACS	DLCN, SB	> 18	4778	78	1.63% (1.29-2.03)	1008 (21.1%)
Ohmura et al.[31] (2017)	Japan	2012−2013	ACS	JAS	NS	296	17	5.74% (3.38-9.04)	61 (20.6%)
Pang et al.[32] (2015)	Australia	2011, 2013	ACS, Stable CAD (26%)	DLCN	< 60	175	25	14.29% (9.46-20.36)	33 (18.9%)
Pay et al.[33] (1997)	Turkey	NS	ACS	LDL-C > 90th percentile in proband and first-degree relative ± xanthomas	< 55	46	2	4.35% (0.5314.84)	8 (17.4%)
Rallidis et al.[34] (2016)	Greece	1996−2014	STEMI	DLCN	≤ 35	320	65	20.31% (16.04-25.14)	41 (12.81%)
Rerup et al.[35] (2016)	Denmark	1998−2012	ACS	DLCN	NS	13,174	55	0.42% (0.31-0.54)	3,922 (29.8%)
Singh et al.[6] (2019)	United States	2000−2016	ACS	DLCN	≤ 50	1996	180	9.02% (7.80-10.36)	382 (19.1%)
Vuorio et al.[36] (1999)	Finland	1989−1992	ACS	DNA	< 50	67	2	2.99% (0.36-10.37)	0 (0.0%)
Wald et al.[37] (2015)	United Kingdom	2011−2013	ACS	DNA	≤ 50	231	3	1.30% (0.27-3.75)	32 (13.9%)
Wiesbauer et al.[39] (2009)	Austria	2004−2008	ACS	SB	≤ 40	102	8	7.84% (3.45-14.87)	13 (12.8%)
Wyndham et al.[39] (1987)	South Africa	1980-1982	ACS	Cholesterol in proband and tendon xanthomas or cholesterol in first-degree relative	≤ 55	51	5	9.80% (3.26-21.41)	12 (23.5%)
Yudi et al.[40] (2012)	Australia	NS	ACS, Stable CAD (20%)	DLCN, SB, MEDPED	≤ 55 male patients; ≤ 60 female patients	210	3	1.43% (0.30-4.12)	84 (40.0%)

ACS, acute coronary syndrome (includes studies limited to myocardial infarction only and studies limited to both myocardial infarction and unstable angina); CAD, coronary artery disease (percentage of population with stable disease is indicated, if applicable); CI, confidence interval; DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolemia; JAS, Japan Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; MEDPED, Make Early Diagnosis to Prevent Early Deaths; SB, Simon-Broome; STEMI, ST-elevation myocardial infarction.

Table 2. Studies included in age-stratified subanalyses

Study	Population	Age (years)	Sample size	FH cases, N	Prevalence estimate (95% CI)
Auckle et al.[22] (2017)	STEMI	< 55 male patients; < 60 female patients	498	19	3.82% (2.31-5.89)
Harada-Shiba et al.[25] (2018)	ACS	< 40	36	3	8.33% (1.75-22.47)
Hassan et al.[26] (2018)	ACS, Stable CAD	≤ 35	71	18	25.35% (15.77-37.08)
Koivisto et al.[27] (1993)	ACS	≤ 45	55	4	7.27% (2.02-17.59)
Li et al.[28] (2016)	ACS	≤ 55 male patients; ≤ 60 female patients	889	63	7.09% (5.49-8.98)
Mortensen et al.[29] (2016)	ACS	< 55 male patients; < 60 female patients	291	20	6.87% (4.25-10.42)
Nanchen et al.[30] (2015)	ACS	< 55 male patients; < 60 female patients	1451	70	4.8% (3.78-6.06)
Ohmura et al.[31] (2017)	ACS	< 60	102	8	7.84% (3.45-14.87)
Pang et al.[32] (2015)	ACS, stable CAD	< 60	175	25	14.29% (9.46-20.36)
Pay et al.[33] (1997)	ACS	< 55	46	2	4.35% (0.53-14.84)
Rallidis et al.[34] (2016)	STEMI	≤ 35	320	65	20.31% (16.04-25.14)
Singh et al.[6] (2019)	ACS	≤ 50	1996	180	9.02% (7.80-10.36)
Vuorio et al.[36] (1999)	ACS	< 50	67	2	2.99% (0.36-10.37)
Wald et al.[37] (2015)	ACS	≤ 50	231	3	1.30% (0.27-3.75)
Wiesbauer et al.[38] (2009)	ACS	≤ 40	102	8	7.84% (3.45-14.87)
Wyndham et al.[39] (1987)	ACS	≤ 55	51	5	9.80% (3.26-21.41)
Yudi et al.[40] (2012)	ACS, stable CAD	≤ 55 male patients; ≤ 60 female patients	210	3	1.43% (0.30-4.12)

ACS, acute coronary syndrome (includes studies limited to myocardial infarction only and studies limited to both myocardial infarction and unstable angina); CAD, coronary artery disease; CI, confidence interval; FH, familial hypercholesterolemia; STEMI, ST-elevation myocardial infarction.

high heterogeneity.[15] Logit transformation was applied to the proportions. Studies were weighted according to the inverse-variance method. Subgroup analysis by sex was also performed with a random-effects model.

To assess for potential sources of heterogeneity in our overall pooled prevalence, we performed five meta-regression analyses with the predictors or independent variables as follows: mean age of study population, proportion of total sample that is female, diagnostic criteria, total sample size, and risk of bias. Categorical variables (diagnostic criteria and risk of bias) were dummy coded to enable analysis. Meta-regressions were performed on logit-transformed proportions using a mixed-effects model with DerSimonian-Laird estimator for τ^2.[15,16] Confidence intervals and R^2 statistic were adjusted using the Hartung-Knapp modification.[17]

Publication bias was assessed by inspection for asymmetry of a funnel plot of logit transformed prevalence against standard error (Supplemental Fig. S1). This was further evaluated by Egger's linear regression test, with $P < 0.10$ considered to be significant.[18] Egger's test suggested that asymmetry was not present (bias estimate $= 0.36 \pm 2.49$; $P = 0.89$). Given the high between-study heterogeneity ($I^2 = 97\%$, $P < 0.01$), funnel plot asymmetry may be due to variability in study design.

Risk of bias assessment

We assessed risk of bias using the tool developed by Hoy et al. for studies of disease prevalence.[19] Factors that were considered to increase risk in individual categories included single-site or limited geographical region, stringent age restrictions, LDL-C or triglyceride level use in eligibility criteria, extent of additional exclusion criteria, incomplete reporting of proportion of patients eligible or proportion that refused consent, low consent rate, incomplete application of validated FH diagnostic criteria or use of unvalidated criteria, inconsistent modes of data collection, sample selection that was nonrandom or selected, or sampling that included patients without ACS (ie, stable CAD). The risk of bias was not used to assign weighting to studies as part of the meta-analysis.

Results

Search results and study characteristics

Our search strategy (Fig. 1) identified a total of 1365 unique records. Of these records, 22 studies met our inclusion/exclusion criteria and were included in the final meta-analysis.[6,20-40] Five studies used DNA-based criteria to diagnose FH,[21,23,27,36,37] 12 included DLCN criteria as their primary method of diagnosis,[6,20,22,24,26,28-30,32,34,35,40] 2 studies were based on JAS criteria,[25,31] 1 study used SB criteria as its sole method,[38] and 2 studies used other diagnostic criteria.[33,39] Four studies used SB criteria in addition to DLCN and/or DNA-based criteria.[21,29,30,40] Two studies using DNA-based criteria also provided data based on DLCN criteria.[21,23] The details of the 22 studies included in our meta-analysis are shown in Table 1. The most common reason for exclusion of a study following full-text review was FH diagnosis based only on consideration of LDL-C or FH diagnostic criteria not provided (Fig. 1).

Prevalence of FH in the total ACS population and stratification by diagnostic criteria

We used a random-effects weighting methodology to estimate prevalence of FH from the included studies. Using this method, the pooled prevalence of FH in the ACS population was 4.7% (95% CI, 3.0-7.3; range 0.4% to 25.4%), with significant between-study heterogeneity ($I^2 = 97\%$, $P < 0.01$) (Fig. 2).

When limiting the analysis to studies using DNA-based diagnostic criteria for FH,[21,23,27,36,37] the pooled prevalence was 5.0% (95% CI, 2.6-9.3; range 1.3% to 8.7%) (Fig. 3). In comparison, the pooled prevalence based on DLCN criteria for probable or definite FH was 5.5% (95% CI, 3.0-10.0; range 0.4% to 27.2%) (Supplemental Fig. S2),[6,20-24,26,28-30,32,34,35,40] and the pooled value when using SB criteria for possible FH was 7.4% (95% CI, 4.1-13.1; range 3.3% to 27.2%) (Supplemental Fig. S3).[21,29,30,38,40] We did not estimate prevalence

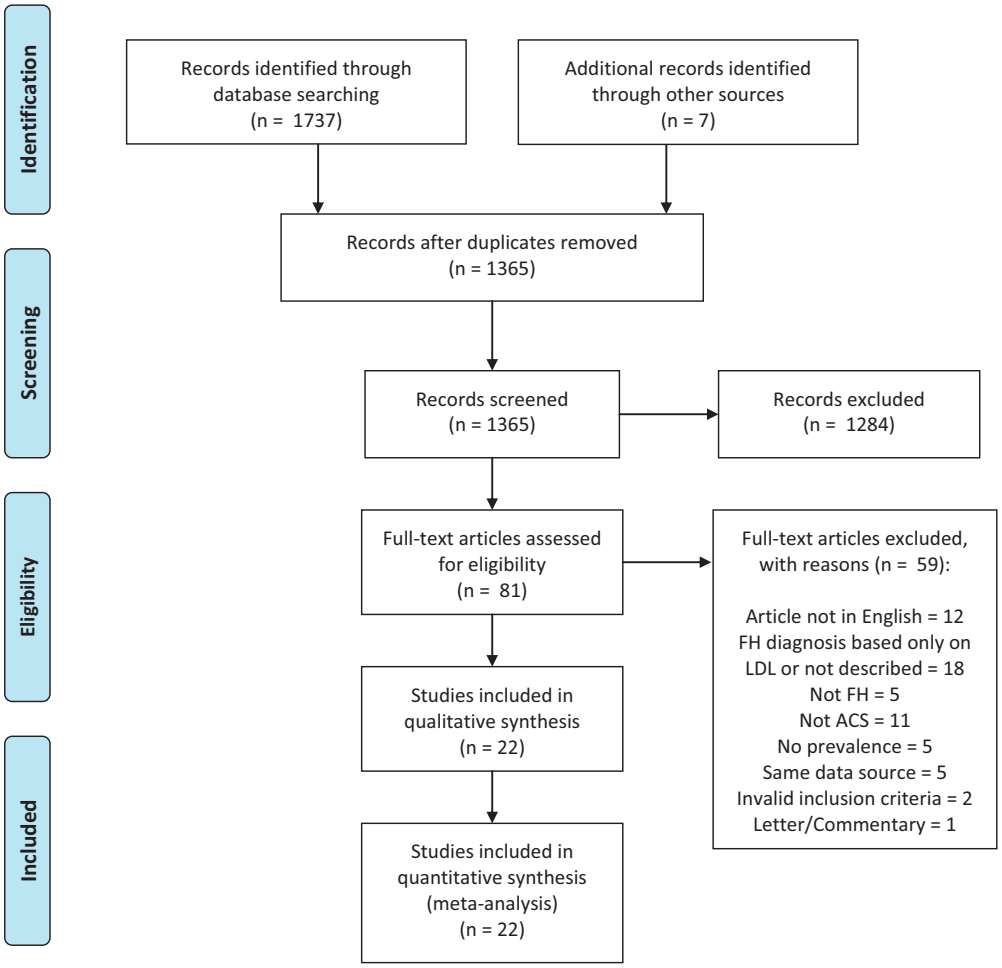

Figure 1. PRISMA flow diagram outlining the number of records (n) reviewed as part of the database searches, abstract screening, and full-text article review. The total number of articles included in the final meta-analysis and reasons for excluding the remaining full-text articles are indicated. ACS, acute coronary syndrome; FH, familial hypercholesterolemia; LDL, low-density lipoprotein.

separately for JAS criteria or other diagnostic methods, as they were used in fewer than 3 studies each.

Prevalence of FH in age-stratified cohorts

The excess cardiovascular risk conferred by FH is thought to be related primarily to premature cardiovascular events.[4] Accordingly, we next conducted subanalyses based on the patient ages represented in the individual studies. Seventeen studies were conducted using a population that was either entirely premature ACS (age $\leq$ 60 years) or contained separate FH prevalence data for this population.[6,22,25-34,36-40] We further evaluated a subset of 5 studies that examined patients age $\leq$ 45 years.[25-27,34,38] A summary of the studies included in the age-stratified sub-analyses is provided in Table 2.

The pooled prevalence of FH based on 17 cohorts of patients $\leq$ 60 years of age was 7.3% (95% CI, 5.3-10.0; range 1.3% to 25.4%) (Fig. 4). When restricted to cohorts of $\leq$ 45 years of age, the prevalence of FH increased to 13.7% (95% CI, 8.2-22.1; range 7.3% to 25.4%) (Fig. 5).

Notably, the cohorts with the 2 highest reported prevalence values out of the 17 studies were those in which the eligibility criteria included patients $\leq$ 35 years.[26,34] For comparison, we assessed the pooled prevalence of all studies for which no upper age limit was specified in the eligibility criteria.[20,23-25,28-31,35] Based on these 9 studies, the pooled prevalence in the absence of an upper age restriction was 2.7% (95% CI, 1.6-4.6; range 0.4% to 6.9%) (Supplemental Fig. S4), significantly lower than the value for cohorts that were limited to patients aged $\leq$ 45 years.

Prevalence of FH by sex

To assess for variation in FH prevalence according to sex, we used subgroup analysis to evaluate the 12 studies for which data for male and female patients were reported.[6,20,21,23,25,28-32,34,39] The total sample size for male patients was approximately 3-fold greater compared with female patients. Overall, the pooled prevalence of FH in ACS was 5.7% (95% CI, 3.5-9.0; range 1.8% to 21.2%) for female patients, similar to the prevalence of 5.5% (95% CI, 3.3-8.9; range 1.6% to 21.2%) for male patients ($Q = 0.01$, $P = 0.93$) (Supplemental Fig. S5). The combined prevalence from these female and male data was 5.6% (95% CI, 4.0-7.8).

Risk of study bias

A risk of bias assessment was conducted on all studies to evaluate the risk specifically in the context of determining the

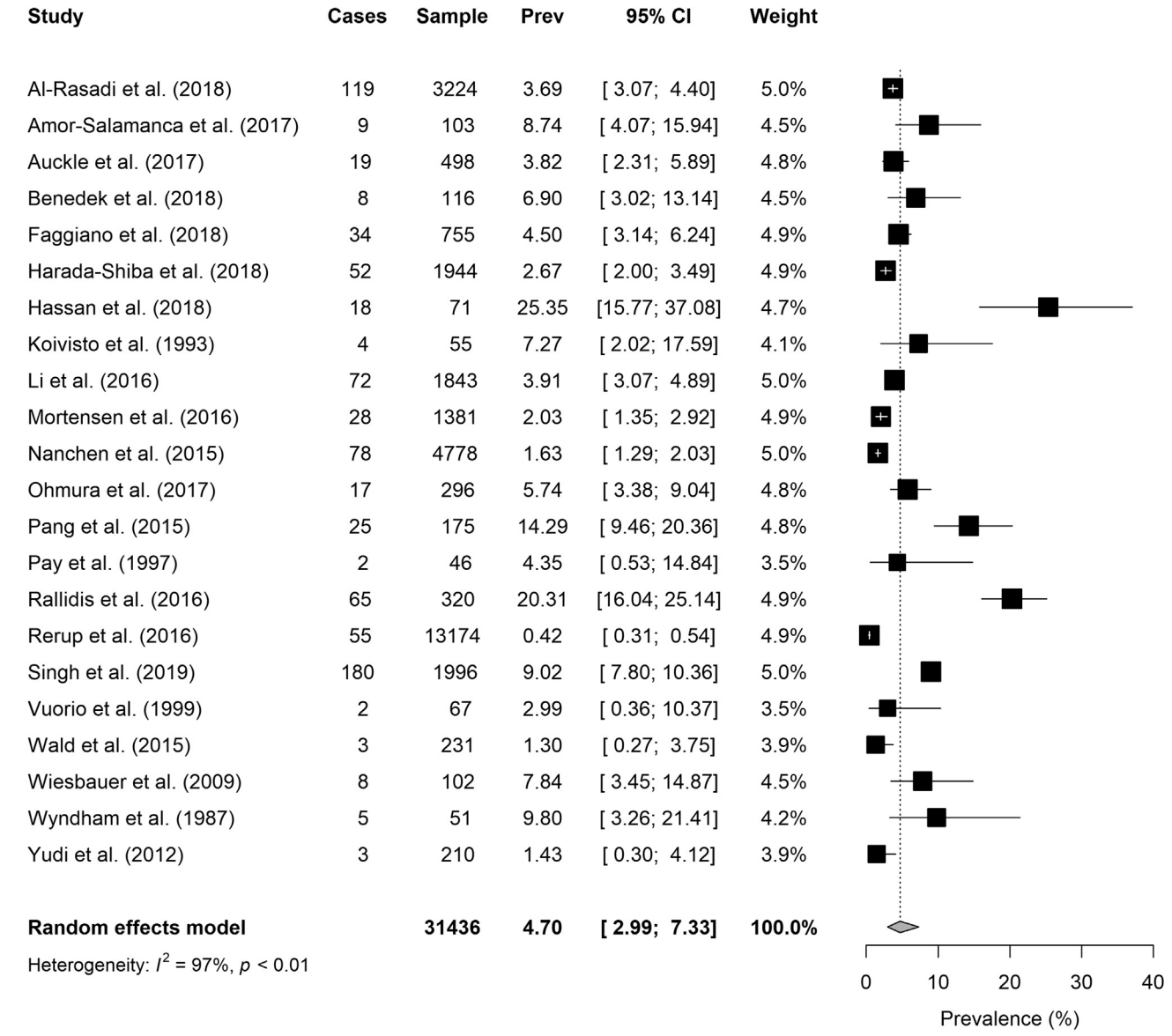

Figure 2. Overall pooled prevalence of familial hypercholesterolemia in acute coronary syndrome. All studies were incorporated regardless of patient age or familial hypercholesterolemia diagnostic criteria. When multiple diagnostic criteria were applied in a given study, DNA-based analysis was used (if applicable), and values determined by Dutch Lipid Clinic Network criteria were selected when multiple clinical diagnostic methods were used in the absence of DNA-based analysis. Prevalence was calculated using a random-effects model. The number of cases of familial hypercholesterolemia, total sample size, prevalence, and weighting of the study are indicated. A forest plot of the data is shown on the right. CI, confidence interval; I^2, between-study heterogeneity; Prev, prevalence.

prevalence of FH in the ACS population across all ages. Most studies were considered moderate or high risk (Supplemental Table S2).

Meta-regression and prevalence of FH

We conducted linear regression analyses to determine whether age, sex, diagnostic criteria, sample size, or risk of study bias may have influenced the overall pooled prevalence of FH in ACS. Accordingly, mean age-of-study population ($P = 0.007$) and total sample size ($P < 0.001$) were identified as significant sources of between-study heterogeneity (Table 3). Patient sex ($P = 0.11$), diagnostic criteria ($P = 0.97$), and risk of bias ($P = 0.41$) were not determined to have a significant effect on the overall pooled prevalence.

Discussion

Numerous studies have investigated FH in the context of ACS, with substantial variation in the reported prevalence of FH in ACS populations.[4,41] To obtain a more robust estimate of this prevalence, we systematically reviewed the literature and performed a meta-analysis of 22 studies, which involved a total of 31,436 patients, and found the pooled prevalence of FH in ACS to be 4.7% (95% CI, 3.0-7.3). This equates to 1 in 21 people presenting with ACS and is approximately

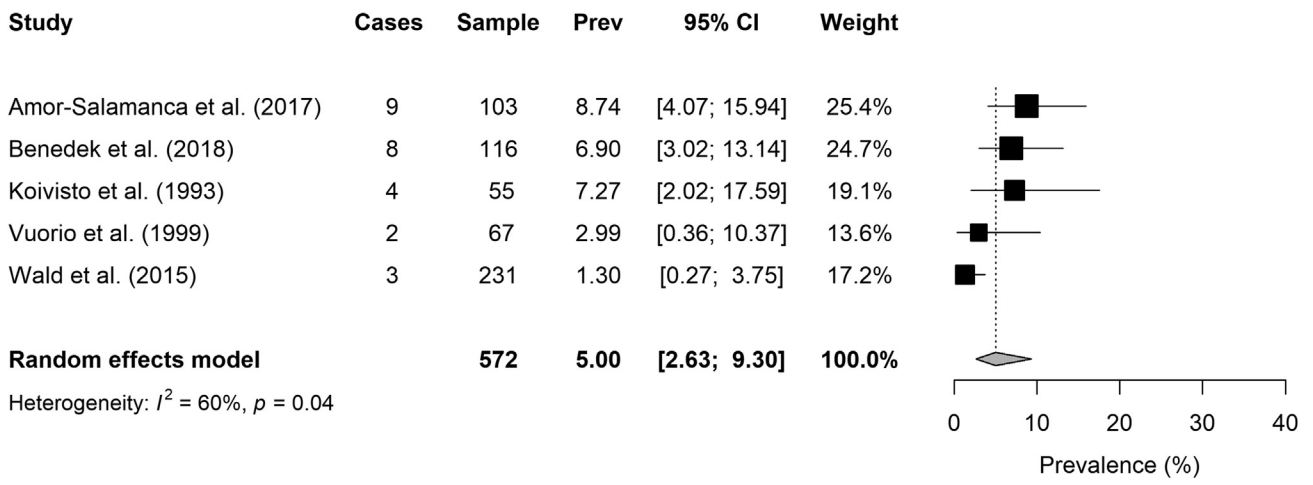

Figure 3. Pooled prevalence of familial hypercholesterolemia in acute coronary syndrome based on studies using DNA-based diagnosis. A random-effects model was used to determine the pooled prevalence. Familial hypercholesterolemia cases, sample size, prevalence, and weighting of each study are provided, and a forest plot is shown. CI, confidence interval; I^2, between-study heterogeneity; Prev, prevalence.

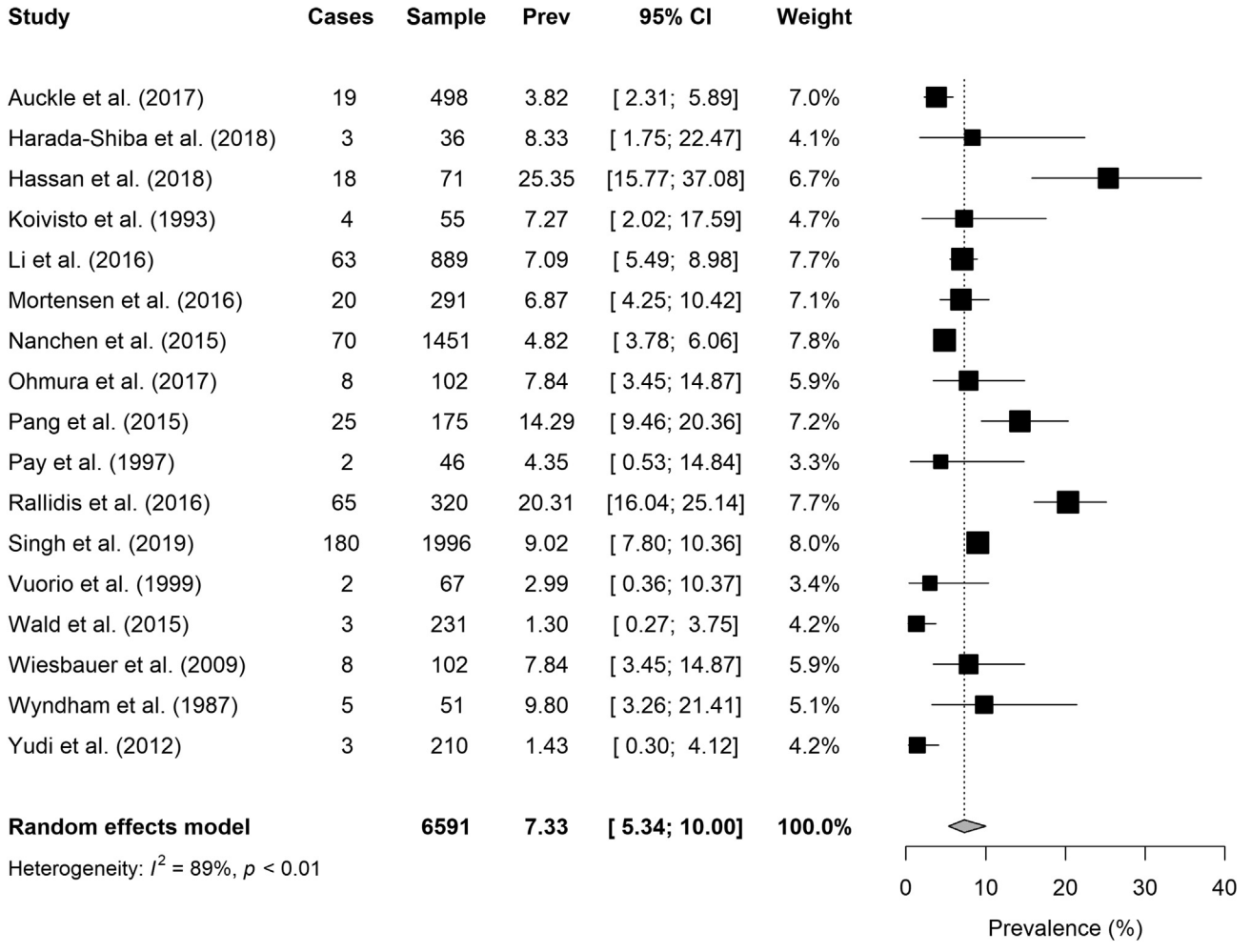

Figure 4. Pooled prevalence of familial hypercholesterolemia in acute coronary syndrome in individuals aged 60 years and under. A random-effects model was used. For each study, the number of familial hypercholesterolemia diagnoses, total sample size, and weighting are provided along with a forest plot. CI, confidence interval; I^2, between-study heterogeneity; Prev, prevalence.

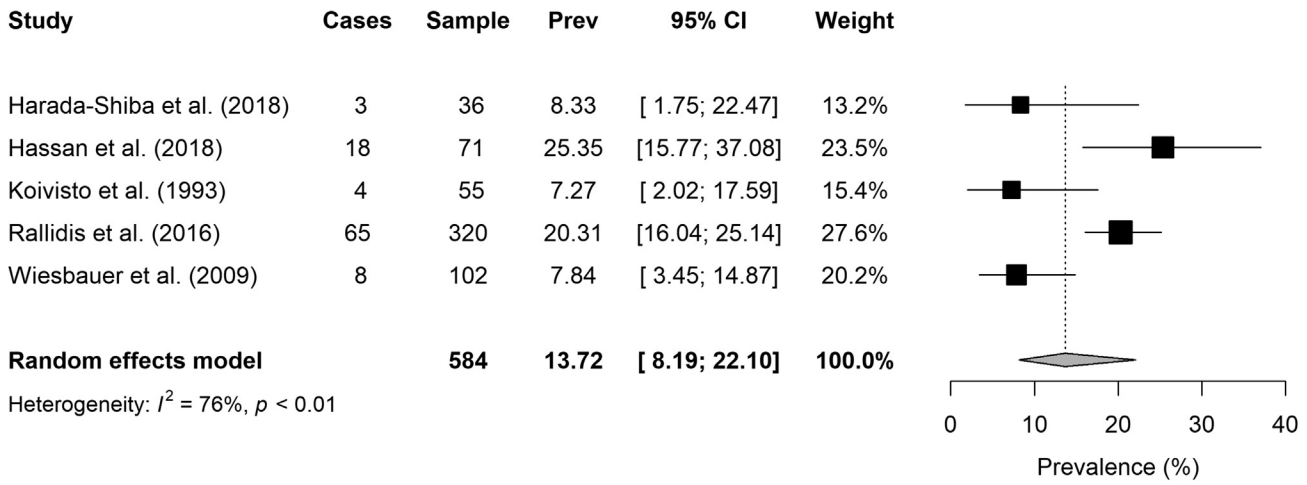

Figure 5. Pooled prevalence of familial hypercholesterolemia in acute coronary syndrome in individuals aged 45 years and under. Estimates were calculated using a random-effects model to determine study weighting. Weighting, sample size, and number of cases of familial hypercholesterolemia are provided, and a forest plot is shown. CI, confidence interval; I^2, between-study heterogeneity; Prev, prevalence.

12-fold higher than the general population prevalence of FH of 0.40%.[2] Consequently, patients with FH are disproportionately over-represented in the ACS population. The 12-fold greater prevalence of FH in the ACS population compared with the general population corresponds very closely with the estimated 8- to 11-fold increased risk for developing CAD in individuals with FH.[42]

Although there was some variation based on the FH diagnostic method used, we found similar pooled prevalence values with DNA-based criteria and DLCN criteria (5.0% vs 5.5%, respectively), indicating that these results are robust to the method used to identify FH. The estimate using SB criteria was slightly higher at 7.4%, although this value falls within the 95% CI for both DNA-based and DLCN-pooled estimates.

The studies included in our meta-analysis reported a wide range of prevalence values, from 0.4% to 25.4%.[26,35] This range likely reflects differences in study design, such as age restrictions in inclusion criteria, differences in FH diagnostic criteria, as well as ethnic and geographic variability in FH prevalence. We used a random-effects model to mitigate the influence of varied study design and the expected high heterogeneity among studies. The lowest stated prevalence among studies in our meta-analysis was determined to be 0.4% by the data reported in Rerup et al. based on the "probable" or "definite" DLCN definitions applied to a large patient sample who underwent coronary angiography because of NSTEMI or STEMI.[35] However, the diagnosis of FH in that study was based on only 2 aspects of the DLCN criteria; LDL-C level and personal history of premature CAD, cerebrovascular disease, or peripheral vascular disease. The use of only these 2 items of the complete DLCN criteria likely resulted in an underestimate of the true prevalence of FH. In contrast, the 5 studies reporting the highest prevalence values were all restricted to premature ACS.[6,26,32,34,39] In fact, our findings demonstrate a trend of increasing enrichment of FH among younger patients with ACS, especially aged $\leq$ 45 years.

A notable finding of our study is the very high prevalence of FH in young persons with ACS, with 1 in 14 patients with ACS $\leq$ 60 years and 1 in 7 patients with ACS $\leq$ 45 years having FH. This suggests that programs to systematically screen young patients with ACS for FH would be expected to have high yield. Making the diagnosis of FH in individuals with ACS is important, as these patients are likely to derive the greatest benefit from intensive lipid-lowering therapy.[43]

Establishing the diagnosis of FH also enables cascade screening of family members, which can identify additional affected people and facilitate the introduction of lipid-lowering therapy before the onset of clinical atherosclerotic cardiovascular disease.[44] On the basis of the findings of this study, we suggest that clinicians should maintain a high degree of suspicion for FH in young patients with an ACS, and we suggest that patients with an ACS be screened for FH using either a validated set of clinical criteria, such as the DLCN criteria or the Canadian Definition of FH, or by DNA testing, if available.[45]

Limitations

Our study has several limitations that warrant discussion. As indicated by our risk of bias assessment, most studies were

Table 3. Meta-regression analyses

Independent variable	No. of studies	β coefficient (95% CI)	*P* value	R^2 (%)
Age	20	-5.40×10^{-2} (-9.15×10^{-2} to -1.64×10^{-2})	0.007	63.49
Sex	20	−3.69 (−8.23 to 0.86)	0.11	18.04
Diagnostic criteria	22	NA	0.97	0.00
Sample size	22	-2.33×10^{-4} (-3.49×10^{-4} to -1.16×10^{-4})	< 0.001	62.59
Risk of bias	22	NA	0.41	0.00

95% CI, 95% confidence interval; NA, not applicable; No. of Studies, number of studies with observations for the indicated variable; R^2, between-study heterogeneity accounted for by the indicated variable and adjusted with the Hartung-Knapp modification.

considered moderate or high risk of bias for determining the prevalence of FH in the overall population with ACS; however, our regression analyses suggest that risk of bias was not a significant source of heterogeneity in the meta-analysis. There are a variety of diagnostic criteria that can be used to diagnose FH, as well as variability in the application of these criteria by different studies. It is noteworthy that the degree to which studies implemented the DLCN criteria varied greatly. In particular, few studies included physical examination features (ie, corneal arcus and tendon xanthomas) as a consideration when diagnosing FH, despite the fact that these characteristics can contribute heavily to a DLCN score. For a given study, this would tend toward an underestimation of the prevalence of FH according to the DLCN criteria. In an effort to distinguish between FH and "severe hypercholesterolemia" (LDL-C >5 mmol/L), we excluded studies that used only an LDL-C cutpoint as their definition of FH. In addition, in some studies, patients were deemed “indeterminate” for FH diagnosis because of missing information. We considered this equivalent to incomplete implementation of diagnostic criteria and therefore included these patients in the total sample by assuming their diagnoses to be negative for FH; this methodology similarly tends toward underestimating FH prevalence.

Other limitations include the inconsistent definition of ACS used among studies. To be more inclusive, we accepted any definition of ACS. Owing to limited availability of required data, we were unable to compare the prevalence of FH among patients with STEMI, NSTEMI, and unstable angina. Geographic and ethnic variability are also potential confounders when considering the prevalence of FH as a genetic condition; notably, our data lack representation from Canada, Central America, and South America, as no studies conducted on these populations met the inclusion criteria for the meta-analysis. Finally, some studies incorporated minimum LDL-C or total cholesterol levels as part of their eligibility criteria, which may bias toward the enrichment of patients with FH in their samples.

Conclusions

In summary, we find that the prevalence of FH is 4.7% among patients with ACS. This prevalence increases with younger age. To our knowledge, this represents the most robust estimate to date of the true prevalence of FH in ACS. These results point toward the important opportunity to establish systematic screening programs for FH in patients with ACS.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.06.017.