BMJ Open

Estimating the prevalence of heterozygous familial hypercholesterolemia: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016461
Article Type:	Research
Date Submitted by the Author:	16-Feb-2017
Complete List of Authors:	Akioyamen, Leo ; University of Toronto Faculty of Medicine Genest, Jacques; McGill University Faculty of Medicine, Canada Shan, Shubham; University of Toronto Faculty of Medicine Reel, Rachel; University of Toronto Faculty of Medicine Albaum, Jordan; University of Toronto Faculty of Medicine Chu, Anna; Institute for Clinical Evaluative Sciences Tu, Jack; The Institute for Clinical,
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Coronary heart disease < CARDIOLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY

TITLE: Estimating the prevalence of heterozygous familial hypercholesterolemia: a systematic review and meta-analysis

SHORT TITLE: Prevalence of heterozygous FH

Leo E Akioyamen[a,b] BScN, MD(c) (sele.akioyamen@mail.utoronto.ca)

Jacques Genest MD[c,d] (jacques.genest@mcgill.ca)

Shubham D Shan HBSc, MD(c)[a.b] (shubham.shan@mail.utoronto.ca)

Rachel L Reel HBSc[a] (rachel.reel@gmail.com)

Jordan M Albaum MSc, MD(c)[a] (jordan.albaum@mail.utoronto.ca)

Anna Chu MHSc[a,b] (anna.chu@ices.on.ca)

Jack V Tu MD, PhD[a,b,e] (tu@ices.on.ca)

a – Faculty of Medicine, University of Toronto, Toronto ON, M5S 1A8, Canada
b – Institute for Clinical Evaluative Sciences, Toronto ON, M4N 3M5, Canada
c – Faculty of Medicine, McGill University, Montreal QC, H3G 2M1, Canada
d – McGill University Health Centre, Royal Victoria Hospital, Montreal QC, H3A 1A1, Canada
e – Schulich Heart Centre, Sunnybrook Health Sciences Centre, Toronto ON, M4N 3M5, Canada

CORRESPONDING AUTHOR
Jack V. Tu MD, PhD
Institute for Clinical Evaluative Sciences
G106-2075 Bayview Avenue
Toronto, ON
M4N 3M5
tu@ices.on.ca

TABLES: 2
FIGURES: 6
WORD COUNT: 3572

SOURCES OF FUNDING
LA was supported by the Comprehensive Research Education for Medical Students Scholar Program at the University of Toronto. JG holds the McGill/Novartis Chair at McGill University. JT is funded by a Canada Research Chair in Health Services Research from the Canadian Institutes of Health Research (CIHR) and an Eaton Scholar Award from the Department of Medicine at the University of Toronto. This research is also funded by an Institute for Circulatory Health-Canadian Institutes of Health Research Chronic Diseases Team grant (no. TCA 118349) to the Cardiovascular Health in Ambulatory Care Research Team (http://www.canheart.ca); and the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ABSTRACT

Objectives

Heterozygous familial hypercholesterolemia (FH) confers a significant risk for premature cardiovascular disease CVD). However, the estimated prevalence of FH varies substantially amongst studies. To provide a summary estimate of FH prevalence in the general population and assess variations in frequency across different sociodemographic characteristics.

Setting, participants and outcome measures

We searched MEDLINE, EMBASE, Global Health, the Cochrane Library, and PubMed for peer-reviewed literature using validated strategies. Results were limited to studies published in English between January 1990 and January 2017. Studies were eligible if they determined FH prevalence using clinical criteria or DNA-based analyses. We determined a pooled point prevalence of FH in adults and children and assessed the variation of the pooled frequency by age, sex, geographical location, and study quality. Estimates were pooled using random-effects meta-analysis. Differences by study-level characteristics were investigated through subgroups and meta-regression analyses.

Results

The pooled prevalence of FH from sixteen studies including 2,431,053 unique individuals was 0.40% [95% CI: 0.29%, 0.54%] which corresponds to a frequency of 1 in 250 individuals in adults. FH prevalence was found to vary by age and geographical location but not by sex. In children, pooled analysis of four included studies resulted in a prevalence of 0.36% [95%: 0.29%, 0.45%].

Conclusions

Our systematic review suggests that FH is a common disorder, affecting 1 in 250 adults. These findings underscore the need for early detection and management to decrease CVD risk.

Keywords: familial hypercholesterolemia, prevalence, frequency, systematic review, meta-analysis

STRENGTHS & LIMITATIONS

- Use of an extensive search strategy and adherence to predetermined inclusion/exclusion criteria.
- Use of evidence-based inverse variance weighted random effects meta-analysis to quantify a robust estimate of the pooled frequency of heterozygous familial hypercholesterolemia in adults.
- Our study possesses a large sample-size (n = 2,431,053).
- We include only English-language peer-reviewed studies making it possible that some relevant articles were not included.
- Our analyses possessed considerable amount of quantifiable heterogeneity.

BACKGROUND

The frequency of heterozygous familial hypercholesterolemia (FH) was originally reported as 1 in 500 (0.2 percent) [1]. This estimate is based on work that determined the prevalence in homozygous individuals and used Hardy-Weinberg principles to calculate the frequency in heterozygotes [2]. Similar frequencies have been described in subsequent reports of population-based samples[3–7]. However, this estimate has recently been criticized for its imprecision[8]. Human behavior does not adhere to Hardy-Weinberg assumptions (e.g., random mating, no migration) and violations of these principles have been shown to significantly impact the results of gene-disease association studies[9]. Further, recent work indicates as many as 1 in 200 people may be affected by FH [10–12] and there is some data to suggest that regional variations in FH frequency exist [13–19].

The population prevalence of FH is difficult to determine for several reasons. Most countries lack national FH registers or large observational databases. Yet even when such databases exist, they often contain insufficient data on aspects of clinical histories essential for FH diagnosis. No uniform criteria for FH diagnosis exist and the three sets of criteria commonly used vary in the amount of emphasis placed on clinical characteristics in determining FH. Additionally, the ability to detect such findings may vary based on the clinical acumen and experiences of assessors[20]. Genetic diagnosis has the potential to mitigate confounding inherent in clinical diagnostic criteria. However, the feasibility and cost-effectiveness of genetic screening continues to be debated, [8,21–23] a high proportion of patients with clinical FH diagnoses may not be identified[24] and all of the genetic mutations that cause FH may not yet be known. Together, these factors suggest the potential for a different FH frequency than original estimates.

Ascertaining the prevalence of FH has important clinical and public health implications, especially in light of the availability of new but expensive treatments (e.g., proprotein convertase subtilisin/kexin type 9 [PCKS9] inhibitors) for this condition. FH is caused by defects in the low-density lipoprotein receptor (LDLR) pathway, resulting in elevated LDL-cholesterol (LDL-C) concentrations that are largely resistant to caloric restriction, weight loss, and physical exercise interventions in affected individuals[24]. FH also predicts a very high risk of cardiovascular disease even in the absence of other traditional risk factors as patients possess these LDL-C concentrations from

birth[25]. Early diagnosis and treatment of FH with lipid lowering therapy has proven to be both cost efficient and effective in mitigating cardiovascular morbidity and mortality risk[26,27]. Despite these benefits, numerous reports suggest that FH is currently underdiagnosed and undertreated in the general population[27]. Clinicians routinely consider estimates of disease prevalence, variations in different population groups (e.g., age, sex, ethnicity), and the presence of known risk factors in formulating differential diagnoses. These factors also form important considerations when evaluating national strategies for the optimal identification and treatment of individuals[28]. Thus, determining the prevalence of FH and its variation by sociodemographic factors provides an important first step in reducing disease burden.

While a number of narrative and systematic reviews have summarized studies of FH[8,13,29–33], there has been no attempt to consolidate these studies to derive a robust prevalence estimate or to assess variation according to sociodemographic factors. We therefore aimed to systematically review the existing literature presenting estimates of FH in the adult general population and explore variation in prevalence estimates by age, sex, geographical location and study quality.

METHODS

We carried out a systematic review and meta-analyses in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) consensus statement[34]. The protocol for this review was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42016042208).

Study Identification & Selection

This study was part of a series of systematic reviews with a standardized search strategy examining the disease burden posed by heterozygous familial hypercholesterolemia. We searched MEDLINE, EMBASE, PYSCInfo, Global Health, the Cochrane Library, and Pubmed (for publications ahead of print) for published, peer-reviewed literature using controlled vocabulary and keywords related to familial hypercholesterolemia and relevant epidemiological terms. Results were limited to human studies published in English between January 1 1990 and January 31 2017. We reviewed reference lists of all included articles and relevant literature reviews, systematic reviews and meta-

analyses for additional eligible studies. A detailed search strategy is included in the supplement to this manuscript (eTable 1).

Titles and abstracts and full-texts were evaluated in duplicate by independent reviewers (LEA, SDS) using standardized forms (eTable 2). Disagreements were resolved through discussion to consensus. For inclusion in the systematic review of prevalence, studies were required to include live human participants and to report on the prevalence of FH. Studies were included if they ascertained FH frequency using one of the following methods (eTables 3-5): (1) DNA-based evidence of LDLR, Apolipoprotein-B (Apo B), or PCSK9 mutations; (2) Dutch Lipid Clinic Network (DLCN) Criteria; (3) Simon Broome Registry (SBR) Criteria; (4) Making Early Diagnosis to Prevent Early Death (MEDPED) Criteria; or (5) total cholesterol levels or LDL-C levels[33]. We did not include articles reporting on the prevalence of or regional variations in specific LDLR, Apo B or PCSK9 mutations in study populations given their potential to underestimate FH frequencies.

Data Extraction

One reviewer (LEA) independently extracted data regarding study characteristics (e.g., design, population characteristics, diagnostic measures, prevalence estimates) from the full-text of included articles. Another reviewer (RLR) checked the extracted data and any detected discrepancies were resolved. We did not attempt to contact authors of studies with missing or incomplete data nor did we exclude any such studies from our synthesis.

Study Quality Assessment

Two reviewers (LEA, RLR) independently assessed the quality of eligible studies using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (http://www.ephpp.ca/tools.html) and resolved discrepancies through consensus. It has been shown to be acceptable for use in evaluating a variety of study designs including randomized controlled trials, before-and-after studies and case control studies (eTable 6). The tool assesses study quality across six domains: [1] selection bias; [2] study design; [3] confounding variables; [4] blinding protocols; [5] data collection methods; and [6] handling of withdrawals and dropouts. Each dimension is rated on a three-point scale - strong, moderate, and weak – and these ratings feed into a global rating of study

quality. Global study quality is considered to be strong if none of the quality domains is rated as weak, moderate if one domain is rated as weak, and weak if two or more domains are rated as weak.

Data Synthesis

Our primary analysis consisted of a pooled estimate of adult (age ≥ 20 years) prevalence across all studies using a random effects model[35,36]. We also calculated the pooled prevalence of FH in children (ages 0 – 19) under the random effects model. Where studies presented multiple diagnostic criteria, estimates derived from genetic testing were used in the analysis as this was thought to provide a more conservative estimate. Where studies derived estimates using DLCN criteria, we pooled reported cases of "definite" or "probable" FH to determine individual study estimates. Similarly, "definite" or "possible" FH diagnoses using Simon Broome criteria were pooled in the meta-analyses. Where multiple studies reported prevalence estimates from a single cohort, estimates were taken from the paper reporting the largest sample.

Potential influences on prevalence estimates were investigated using subgroup analyses and meta-regression. Where studies allowed, we descriptively compared prevalence estimates by age, sex, prevalence estimation method, study quality, and geographical location within studies. We then assessed the influence of these factors on variation in the estimated prevalence using meta-regression models.

Statistical analysis

We calculated pooled prevalence figures with 95% confidence intervals (CIs) using the DerSimonian & Laird random effects model[36]. Under the model, we. In meta-analyses of prevalence using inverse variance methods, when the frequency estimate of a single study approaches the limits of prevalence (i.e., 0% or 100% of the population), the variance for that study moves toward zero, leading to the resulting weight in the meta-analysis being overestimated [35]. To accommodate for this, we conducted the meta-analysis with prevalence estimates that had been transformed using the double arcsine method[35]. The final pooled result and 95% CIs were then back transformed and expressed as percentages for ease of interpretation. We assessed heterogeneity in our pooled analyses using the I^2 statistic as it is not sensitive to the scale of effect size or the total number of studies included in the meta-analysis[37]. Finally, publication bias was examined formally using Egger's weighted regression, with significance set at $P < 0.10$ [38]. Publication bias was also assessed visually using Begg's funnel plot

as well as a *Doi* plot [39]. Analyses were performed using the MetaXL add-in for Microsoft Excel (www.epigear.com).

Meta-regression was used to discern the influence of age, sex, prevalence estimation method, study quality, and geographical location on our pooled prevalence. We used Stata version 13.1 to perform the meta-regression analysis on the log scale of the back transformed effect size (i.e., prevalence), with each trial weighting equal to the that derived under the random effects model and between study variance estimated with the restricted maximum likelihood method. The pooled prevalence estimate was used as the dependent variable whereas, sample size, study quality scores, mean sample age and male:female ratio used as continuous predictive variables. Categorical covariates such as prevalence estimation method and geographical location were dummy-coded and examined through a joint test for all dummy-coded covariates.

RESULTS

Study Selection

Our search identified 4153 citations, of which 3574 were unique. After applying our inclusion and exclusion criteria 90 articles progressed to screening at the full-text level, of which 21 articles were included in this review. The flow of included studies is presented in Figure 1.

Characteristics of included studies

Twenty one studies estimating point prevalence of FH were included in this review (Table 1). The majority of these studies were European (n = 9), while others were conducted in North America (n = 4), Asia (n = 2), Australia (n = 3), and Africa (n = 1). Two of the studies pooled data from international cohorts[10,40]. Combined, they represented data from 28 countries across four continents. Studies representing multiple countries included data from coronary artery disease[10] and dyslipidemia cohorts[40]. FH is overexpressed among those with coronary heart disease as well as statin-treated individuals[24]. For these reasons, we elected against pulling country-specific data from these papers. Among all included studies, females comprised between 26.4% and 55.0% of the total sample.

Four studies diagnosed FH using DLCN criteria[40–43], three studies used genetic sequencing[44–46], three studies utilized LDL-C measurements[47–49], one study used SBR criteria[7] and one employed MEDPED criteria[6]. Another four included studies reported prevalence estimates using more than one method for comparison [10,11,50,51]. Prevalence estimates reported in individual studies ranged from 0.05% [95% CI: 0.05%, 0.06%] to 5.62% [95% CI: 5.44%, 5.79%]. When evaluated by the EPHPP tool, most studies were rated as being moderate (n = 7) or strong (n = 13) in quality. On EPHPP domains, studies were most likely to receive weak ratings due to a low likelihood of representing the general population, a failure to accounting for missing participant data or adjust for relevant confounders (eTable 7).

Meta-analysis

Adult prevalence

Sixteen prevalence estimates were included in the meta-analysis of adult prevalence, representing 2,431,053 unique individuals [6,7,10,40–46,51–55]. A further two studies reported data from cohorts represented by other studies within a shorter sampling frame, creating the potential for the overlap of cohorts [11,47]. These estimates were excluded to avoid overweighting a population. The overall random effects pooled prevalence of FH was 0.40% [95% CI: 0.29%, 0.54%](Figure 2). Pooled prevalence estimates were comparable between DLCN [0.46%; 95% CI: 0.25%, 0.70%], LDL-C [0.47%; 95% CI: 0.34, 0.62%], and DNA-based subgroups [0.42%; 95% CI: 0.25%, 0.63%] (eFigure 1). Of two studies exclusively using SBR[7] or MEDPED[6] criteria; both reported lower frequencies than our pooled prevalence estimate. When stratified by study quality ratings, studies rated strong had a slightly lower estimate of FH prevalence with greater precision [0.33%; 95% CI: 0.24%, 0.44%] than studies rated moderate in quality [0.88%; 95% CI: 0.31%, 1.56%] (eFigure 2).

Meta-regression analyses

Considerable heterogeneity existed between studies [I^2: 99.44%; 95% CI: 99.35%, 99.52%]. The results of six meta-regression analyses (Table 2) showed little evidence of an effect of age (p = 0.19), sex (p = 0.34) or sample size (p = 0.23) on our pooled prevalence estimate. However, the quality of our included studies *was* significantly related to the variance in our pooled estimate (p = 0.03). Joint meta-regression tests showed significant differences in

prevalence estimates among categories of studies when stratified by diagnostic criteria ($p < 0.001$) or geographical location ($p < 0.001$).

Major asymmetry was present in both Begg's funnel plot and the Doi plot (eFigure 3) and the results of Egger's test suggested that publication bias may have been present ($p = 0.03$)[56]. Using the "trim and fill" approach to try and account for unpublished results produced seven filled studies, all of which were indicative of a lower FH prevalence[57].

Variation in adult prevalence by age

Six studies[7,11,41,47,51,53] reported age-stratified data on the adult prevalence of FH, but only two of these presented data in forms amenable for pooled analysis (Figure 3) [7,51]. All studies showed variation in FH frequency with age, with an increase in prevalence that peaked between ages 60 and 69 and declined thereafter, a trend reflected in our pooled estimates.

Variation in adult prevalence by sex

Nine studies presented prevalence figures by sex, [7,10,40–42,44,45,50,51] most of which reported similar FH frequencies between men and women. Our pooled prevalence estimates (Figure 4) were comparable between males [0.42%; 95% CI: 0.18%, 0.75%] and females [0.45, 95% CI: 0.19%, 0.82%] [OR: 0.85; 95% CI: 0.0.69, 1.07].

Variation by in adult prevalence geographic location

When FH was analyzed by continent (eFigure 3), European and Asian studies tended to report lower prevalence estimates than our overall pooled prevalence estimate, while North American and Australasian studies reported estimates comparable to it. The one study from South Africa reported a greater pooled FH prevalence than our pooled estimate; as did studies of international cohorts.

Prevalence of FH in children

Combining four studies [41,48,49,58] which reported FH prevalence estimates in individuals aged under 19 (eTable 8), we calculated a pooled prevalence of 0.36% [95%: 0.28%, 0.45%], with little heterogeneity [I^2 = 13.32%].

DISCUSSION

Our meta-analysis of 16 cohort studies including 2,431,053 unique individuals found an FH prevalence of 0.40% in the adult population. This suggests that as many as 1 in 250 individuals may be affected by FH [95% CI: 1 in 345, 1 in 185], equating to nearly 30 million people worldwide[59]. This is a higher frequency than observed in prior reports and supports current thinking that FH is underdiagnosed, and thus likely undertreated in the general population [60]. Interestingly, we detected a slightly lower prevalence of FH in those aged 0-19 [1 in 278; 95% CI: 1 in 345, 1 in 222]. Further, FH prevalence tended to increase with age. This trend runs counterintuitively to expectations given the high risk of CVD-related mortality in FH. Our findings may be explained by insufficient dyslipidemia screening in children and adolescents[61–63]. Indeed, follow-up data from the Simon Broome FH registry, following more than 300,000 patients, found that only a quarter of affected patients received diagnoses by middle age, with the highest rates of under-diagnosis among children and adolescents[7]. However, LDL-C levels also rise with age, making it likely for older individuals to be diagnosed using established clinical criteria. It remains possible that the disparity in prevalence may be due to the inability of population-based studies to account for age-related increases in LDL-C and the reduced sensitivity this confers in detecting FH [64].

Our finding that FH affects males and females equally has important implications. Many cases of FH are diagnosed following the first cardiac event, which has a later onset for women relative to men[27]. This makes it possible that women with FH may go unrecognized for longer. Yet, more women may be expected to qualify for diagnosis using clinical characteristics at later ages, primarily due to the delayed onset of coronary artery disease. Whether delayed FH detection in women relative to men confers poorer clinical outcomes has yet to be formally explored in the literature. However, one of our included studies observed that after age 60, higher proportions of women met criteria for an FH diagnosis, suggesting that many men with FH had died at an earlier age[11]. Identifying sex-related differences in FH presentation may allow for the earlier FH diagnosis and represents an important clinical

priority. New diagnostic criteria developed through improved use of routinely collected health data may make this possible[65].

We found lower prevalence reports in Europe and Asia relative to regions elsewhere. Thus far, much of the regional variation in FH prevalence has been attributed to the presence of founder populations. Founder effects occur when subpopulations are formed by the immigration of "founder subjects", leading to a higher proportion of individuals who share a mutation in subsequent generations due to genetic drift[13]. Though influenced by a predominance of European studies, our review suggests the potential for variations in FH frequency between countries extending beyond founder effects. This is important given that for many of the world's countries, rates of FH still remain unknown. This includes North America, where studies from the USA comprise the evidence base for ascertaining study prevalence. Cardiovascular disease remains the leading cause of death worldwide [66] and, left untreated, nearly 85% of males and 50% of females with FH are expected to suffer coronary events prior to age 65[27]. Thus, greater efforts should be made to explore region-specific frequencies of FH prevalence and more accurately characterize disease burden. Accurate prevalence estimates, augmented by recent big data approaches and the introduction of *International Classification of Diseases, 10th Revision* codes for FH should facilitate increased awareness and improved management.

How FH should be identified remains an area of continued debate. A number of organizations have recommended universal lipid screening in childhood as a strategy to identify FH [67–69]. However, a recent report by the US Preventive Services Task Force concluded that there was "inadequate direct evidence on the benefit of screening for familial hypercholesterolemia" [70]. In addition, these programs come with the added risks of potential over-diagnosis, fiscal and non-fiscal health system burden, and adverse psychosocial impacts for children and families[71]. As an alternative, some European countries have developed genetic FH screening strategies. However, such programs are not currently universally accessible nor deemed to be cost-effective [8,21–23]. Yet, DNA-based identification may fail to capture individuals with undiscovered mutations or those with polygenic forms of FH that still demonstrate the clinical phenotype. Finally, the diagnostic accuracy of these programs has been challenged by

findings that up to 30% of estimated cases may not be identified in countries with some of the most robust screening programs, due lack of index cases to inform cascade screening [72]. In light of these limitations, the high degree of concordance between our pooled prevalence estimates derived through DLCN and DNA-based analyses are clinically important. Due to a simplified approach – facilitated by the use of readily observable clinic characteristics and biochemical parameters – DLCN criteria may facilitate the more ready identification of patients affected by FH in primary care. Though other clinical criteria may have comparable clinical utility, our study currently provides insufficient evidence in strong support of them. Regardless, improving the identification of FH and mitigating cardiovascular disease and mortality requires a multi-faceted approach involving clinical, biochemical and genetic parameters.

These findings provide new insights into FH prevalence. Yet, they should be interpreted in light of some important limitations. First, despite an extensive search strategy, our pooled prevalence estimate was derived from a modest number of studies. We included only peer-reviewed English language studies indexed in six online databases and it remains possible that other relevant studies went unpublished or were indexed in other languages, in print repositories or within the grey literature[73]. Second, we did not contact study authors for additional data or clarifications of their published studies. While this was counterbalanced in part by the use of a tool with high inter-rater agreement for quality assessment[74], agreement levels between reviewers and authors have yet to be explored with the EPHPP tool. Third, while diagnostic criteria employed, geographical location of our included studies was significantly associated with variance in FH prevalence, our meta-analysis possessed a considerable amount of between-study heterogeneity, the majority of which remains unexplained. This may be attributed to limited power in our meta-regression analyses due to small numbers of observations[37]. In which case, our subgroup analyses provide more credible insight into the sociodemographic variation of FH prevalence. It is important to note that the high degree of heterogeneity in our meta-analyses does not imply imprecision in our prevalence estimate [37]. Indeed, a key strength of our study is its sample size and the greater power and precision it conferred to our analyses. The heterogeneity between studies are thus more likely reflective of real differences

in study populations, designs, and outcome measurements [35]. This heterogeneity was anticipated and accommodated for through random effects meta-analysis.

CONCLUSIONS

Our systematic review found that FH currently affects 1 in 250 people in the adult population. While FH affects males and females equally, regional and age specific variations exist in FH frequency. With the range of treatment options available for this condition increased, particularly with the recent advent of PCKS9 inhibitors, greater efforts should be made to identify individuals who could stand to benefit from therapy.

ACKNOWLEDGEMENTS

The authors would like to thank staff at the Institute for Clinical Evaluative Sciences for logistical support of this systematic review.

AUTHOR CONTRIBUTIONS

LA – conceived and designed the study; conducted the study; provided methodological support; conducted the analyses; interpreted the results; wrote, read and edited the manuscript.

JG – interpreted the results; read and edited the manuscript.

SS – conducted the study; read and edited the manuscript.

RR – conducted the study; read and edited the manuscript.

JA – conducted the study; read and edited the manuscript.

AC – conceived and designed the study; provided methodological support; and read and edited the manuscript.

JT – conceived and designed this study; provided methodological support; interpreted the results; guided the analysis; and read and edited the manuscript.

COMPETING INTERESTS

The authors have no competing interests to declare.

DATA SHARING AGREEMENT

Additional data is presented in supplemental files.

REFERENCES

1 Goldstein JL, Schrott HG, Hazzard WR, *et al.* Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest* 1973;**52**:1544–68. doi:10.1172/JCI107332

2 Slack J. Inheritance of familial hypercholesterolemia. *Atheroscler Rev* 1979;**5**:35–66.

3 Heiberg A, Berg K are. The inheritance of hyperipoproteinaemia with xanthomatosis: A study of 132 kindreds. *Clin Genet* 1976;**9**:203–33.

4 Andersen GE, Lous P, Friis-Hansen B. SCREENING FOR HYPERLIPOPROTEINEMIA IN 10 000 DANISH NEWBORNS Follow-up Studies in 522 Children with Elevated Cord Serum VLDL-LDL-Cholesterol. *Acta Paediatr* 1979;**68**:541–5. doi:10.1111/j.1651-2227.1979.tb05052.x

5 Mabuchi H, Haba T, Ueda K, *et al.* Serum lipids and coronary heart disease in heterozygous familial hypercholesterolemia in the Hokuriku district of Japan. *Atherosclerosis* 1977;**28**:417–23. doi:10.1016/0021-9150(77)90068-5

6 Kalina Á, Császár A, Czeizel AE, *et al.* Frequency of the R3500Q mutation of the apolipoprotein B-100 gene in a sample screened clinically for familial hypercholesterolemia in Hungary. *Atherosclerosis* 2001;**154**:247–51. doi:10.1016/S0021-9150(00)00648-1

7 Neil HA, Hammond T, Huxley R, *et al.* Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. *BMJ* 2000;**321**:148.

8 Marks D, Wonderling D, Thorogood M, *et al.* Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. *BMJ* 2002;**324**:1303. doi:10.1136/bmj.324.7349.1303

9 Trikalinos TA, Salanti G, Khoury MJ, *et al.* Impact of Violations and Deviations in Hardy-Weinberg Equilibrium on Postulated Gene-Disease Associations. *Am J Epidemiol* 2006;**163**:300–9. doi:10.1093/aje/kwj046

10 Khera AV, Won H-H, Peloso GM, *et al.* Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. *J Am Coll Cardiol* 2016;**67**:2578–89. doi:10.1016/j.jacc.2016.03.520

11 Benn M, Watts GF, Tybjaerg-Hansen A, *et al.* Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease, and Cholesterol-Lowering Medication. *J Clin Endocrinol Metab* 2012;**97**:3956–64. doi:10.1210/jc.2012-1563

12 Goldberg AC, Gidding SS. Knowing the Prevalence of Familial Hypercholesterolemia Matters. *Circulation* 2016;**133**:1054–7.

13 Austin MA, Hutter CM, Zimmern RL, *et al.* Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am J Epidemiol* 2004;**160**:407–20. doi:10.1093/aje/kwh236

14 Patterson D, Slack J. Lipid abnormalities in male and female survivors of myocardial infarction and their first-degree relatives. *Lancet Lond Engl* 1972;**1**:393–9.

15 Moorjani S, Roy M, Gagne C, *et al.* Homozygous familial hypercholesterolemia among French Canadians in Québec province. *Arterioscler Thromb Vasc Biol* 1989;**9**:211–6.

16 Slimane MN, Pousse H, Maatoug F, *et al.* Phenotypic expression of familial hypercholesterolaemia in central and southern Tunisia. *Atherosclerosis* 1993;**104**:153–8.

17 Seftel HC, Baker SG, Sandler MP, *et al.* A host of hypercholesterolaemic homozygotes in South Africa. *Br Med J* 1980;**281**:633–6.

18 Seftel HC, Baker SG, Jenkins T, *et al.* Prevalence of familial hypercholesterolemia in Johannesburg Jews. *Am J Med Genet* 1989;**34**:545–7.

19 Rubinsztein DC, Van der Westhuyzen DR, Coetzee GA, *et al.* Monogenic primary hypercholesterolaemia in South Africa. *SOUTH Afr Med J-CAPE TOWN-Med Assoc SOUTH Afr* 1994;**84**:339–339.

20 Hegele RA. Improving the Monitoring and Care of Patients With Familial Hypercholesterolemia∗. *J Am Coll Cardiol* 2016;**67**:1286–8. doi:10.1016/j.jacc.2016.01.041

21 Oliva J, López-Bastida J, Moreno SG, *et al.* [Cost-effectiveness analysis of a genetic screening program in the close relatives of Spanish patients with familial hypercholesterolemia]. *Rev Esp Cardiol* 2009;**62**:57–65.

22 Wonderling D, Umans-Eckenhausen MAW, Marks D, *et al.* Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. *Semin Vasc Med* 2004;**4**:97–104. doi:10.1055/s-2004-822992

23 Chen CX, Hay JW. Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. *Int J Cardiol* 2015;**181**:417–24. doi:10.1016/j.ijcard.2014.12.070

24 Najam O, Ray KK. Familial Hypercholesterolemia: a Review of the Natural History, Diagnosis, and Management. *Cardiol Ther* 2015;**4**:25–38. doi:10.1007/s40119-015-0037-z

25 Sharifi M, Rakhit RD, Humphries SE, *et al.* Cardiovascular risk stratification in familial hypercholesterolaemia. *Heart* 2016;:heartjnl – 2015–308845. doi:10.1136/heartjnl-2015-308845

26 Versmissen J, Oosterveer DM, Yazdanpanah M, *et al.* Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008;**337**:a2423.

27 Civeira F, International Panel on Management of Familial Hypercholesterolemia. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2004;**173**:55–68. doi:10.1016/j.atherosclerosis.2003.11.010

28 Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. *Science* 1996;**274**:740–3.

29 Austin MA, Hutter CM, Zimmern RL, *et al.* Familial hypercholesterolemia and coronary heart disease: a HuGE association review. *Am J Epidemiol* 2004;**160**:421–9. doi:10.1093/aje/kwh237

30 Hutter CM, Austin MA, Humphries SE. Familial hypercholesterolemia, peripheral arterial disease, and stroke: a HuGE minireview. *Am J Epidemiol* 2004;**160**:430–5. doi:10.1093/aje/kwh238

31 Wong B, Kruse G, Kutikova L, *et al.* Cardiovascular Disease Risk Associated With Familial Hypercholesterolemia: A Systematic Review of the Literature. *Clin Ther* 2016;**38**:1696–709. doi:10.1016/j.clinthera.2016.05.006

32 Mundal L, Retterstl K. A systematic review of current studies in patients with familial hypercholesterolemia by use of national familial hypercholesterolemia registries: *Curr Opin Lipidol* 2016;**27**:388–97. doi:10.1097/MOL.0000000000000300

33 Henderson R, O'Kane M, McGilligan V, *et al.* The genetics and screening of familial hypercholesterolaemia. *J Biomed Sci* 2016;**23**. doi:10.1186/s12929-016-0256-1

34 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–12.

35 Barendregt JJ, Doi SA, Lee YY, *et al.* Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;**67**:974–8.

36 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88. doi:10.1016/0197-2456(86)90046-2

37 Borenstein M, Hedges LV, Higgins JPT, *et al.* Identifying and Quantifying Heterogeneity. In: *Introduction to Meta-Analysis*. John Wiley & Sons, Ltd 2009. 107–25.http://onlinelibrary.wiley.com/doi/10.1002/9780470743386.ch16/summary (accessed 7 Aug2016).

38 Egger M, Smith GD, Schneider M, *et al.* Bias in Meta-Analysis Detected by a Simple, Graphical Test. *ResearchGate* 1997;**315**:629–34.

39 Doi SAR, Williams GM, editors. *Methods of Clinical Epidemiology*. Berlin, Heidelberg: : Springer Berlin Heidelberg 2013. http://link.springer.com/10.1007/978-3-642-37131-8 (accessed 7 Aug2016).

40 Catapano AL, Lautsch D, Tokgözoglu L, *et al.* Prevalence of potential familial hypercholesteremia (FH) in 54,811 statin-treated patients in clinical practice. *Atherosclerosis* 2016;**252**:1–8. doi:10.1016/j.atherosclerosis.2016.07.007

41 De Ferranti SD, Rodday AM, Mendelson MM, *et al.* Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation* 2016;**133**:1067–72. doi:10.1161/CIRCULATIONAHA.115.018791

42 Pajak A, Szafraniec K, Polak M, *et al.* Prevalence of familial hypercholesterolemia: a meta-analysis of six large, observational, population-based studies in Poland. *Arch Med Sci AMS* 2016;**12**:687–96. doi:10.5114/aoms.2016.59700

43 Watts GF, Shaw JE, Pang J, *et al.* Prevalence and treatment of familial hypercholesterolaemia in Australian communities. *Int J Cardiol* 2015;**185**:69–71. doi:10.1016/j.ijcard.2015.03.027

44 Lahtinen AM, Havulinna AS, Jula A, *et al.* Prevalence and clinical correlates of familial hypercholesterolemia founder mutations in the general population. *Atherosclerosis* 2015;**238**:64–9. doi:10.1016/j.atherosclerosis.2014.11.015

45 Steyn K, Goldberg YP, Kotze MJ, *et al.* Estimation of the prevalence of familial hypercholesterolaemia in a rural Afrikaner community by direct screening for three Afrikaner founder low density lipoprotein receptor gene mutations. *Hum Genet* 1996;**98**:479–84.

46 Vuorio AF, Turtola H, Piilahti KM, *et al.* Familial hypercholesterolemia in the Finnish north Karelia. A molecular, clinical, and genealogical study. *Arterioscler Thromb Vasc Biol* 1997;**17**:3127–38.

47 Perak AM, Ning H, de Ferranti SD, *et al.* Long-Term Risk of Atherosclerotic Cardiovascular Disease in US Adults With the Familial Hypercholesterolemia Phenotype. *Circulation* 2016;**134**:9–19. doi:10.1161/CIRCULATIONAHA.116.022335

48 Yang S, Hwang JS, Park HK, *et al.* Serum lipid concentrations, prevalence of dyslipidemia, and percentage eligible for pharmacological treatment of Korean children and adolescents; data from the Korea National Health and Nutrition Examination Survey IV (2007-2009). *PloS One* 2012;**7**:e49253. doi:10.1371/journal.pone.0049253

49 Pang J, Martin AC, Mori TA, *et al.* Prevalence of Familial Hypercholesterolemia in Adolescents: Potential Value of Universal Screening? *J Pediatr* 2016;**170**:315–6. doi:10.1016/j.jpeds.2015.11.019

50 Benn M, Watts GF, Tybjærg-Hansen A, *et al.* Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. *Eur Heart J* 2016;**37**:1384–94. doi:10.1093/eurheartj/ehw028

51 Shi Z, Yuan B, Zhao D, *et al.* Familial hypercholesterolemia in China: prevalence and evidence of underdetection and undertreatment in a community population. *Int J Cardiol* 2014;**174**:834–6. doi:10.1016/j.ijcard.2014.04.165

52 Abul-Husn NS, Manickam K, Jones LK, *et al.* Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science* 2016;**354**. doi:10.1126/science.aaf7000

53 Guglielmi V, Bellia A, Pecchioli S, *et al.* What is the actual epidemiology of familial hypercholesterolemia in Italy? Evidence from a National Primary Care Database. *Int J Cardiol* 2016;**223**:701–5. doi:10.1016/j.ijcard.2016.08.269

54 Safarova MS, Liu H, Kullo IJ. Rapid identification of familial hypercholesterolemia from electronic health records: The SEARCH study. *J Clin Lipidol* 2016;**10**:1230–9. doi:10.1016/j.jacl.2016.08.001

55 Vickery AW, Ryan J, Pang J, *et al.* Increasing the Detection of FH Using General Practice Electronic Databases. *Heart Lung Circ* Published Online First: 15 November 2016. doi:10.1016/j.hlc.2016.09.012

56 Sterne JA, Bradburn MJ, Egger M. Meta–Analysis in Stata™. *Syst Rev Health Care Meta-Anal Context Second Ed* 2008;:347–69.

57 Palmer TM, Peters JL, Sutton AJ, *et al.* Contour-enhanced funnel plots for meta-analysis. *Stata J* 2008;**8**:242.

58 Wald DS, Bestwick JP, Morris JK, *et al.* Child–Parent Familial Hypercholesterolemia Screening in Primary Care. *N Engl J Med* 2016;**375**:1628–37. doi:10.1056/NEJMoa1602777

59 DeSA UN. World population prospects: the 2015 revision. *Popul Div Dep Econ Soc Aff U N Secr N Y* 2015.

60 Nordestgaard BG, Chapman MJ, Humphries SE, *et al.* Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J* 2013;**34**:3478–90. doi:10.1093/eurheartj/eht273

61 Henneman L, McBride CM, Cornel MC, *et al.* Screening for Familial Hypercholesterolemia in Children: What Can We Learn From Adult Screening Programs? *Healthcare* 2015;**3**:1018–30. doi:10.3390/healthcare3041018

62 Hopcroft KA. Child-parent screening may have adverse psychological effects. *BMJ* 2007;**335**:683–683. doi:10.1136/bmj.39353.368553.BE

63 Calonge N, Guirguis-Blake J. Screening for familial hypercholesterolaemia. *BMJ* 2007;**335**:573–4. doi:10.1136/bmj.39335.668646.80

64 Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. *BMJ* 2007;**335**:599. doi:10.1136/bmj.39300.616076.55

65 Weng SF, Kai J, Neil HA, *et al.* Improving identification of familial hypercholesterolaemia in primary care: Derivation and validation of the familial hypercholesterolaemia case ascertainment tool (FAMCAT). *Atherosclerosis* 2015;**238**:336–43. doi:10.1016/j.atherosclerosis.2014.12.034

66 WHO | World Health Statistics 2016: Monitoring health for the SDGs. WHO. http://www.who.int/gho/publications/world_health_statistics/2016/en/ (accessed 9 Sep2016).

67 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 2011;**128 Suppl 5**:S213–56. doi:10.1542/peds.2009-2107C

68 Jacobson TA, Maki KC, Orringer CE, *et al.* National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. *J Clin Lipidol* 2015;**9**:S1–122.e1. doi:10.1016/j.jacl.2015.09.002

69 Gidding SS, Champagne MA, de Ferranti SD, *et al.* The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. *Circulation* 2015;**132**:2167–92. doi:10.1161/CIR.0000000000000297

70 US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, *et al.* Screening for Lipid Disorders in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016;**316**:625–33. doi:10.1001/jama.2016.9852

71 Urbina EM, de Ferranti SD. Lipid Screening in Children and Adolescents. *JAMA* 2016;**316**:589–91. doi:10.1001/jama.2016.9671

72 Cuchel M, Bruckert E, Ginsberg HN, *et al.* Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014;**35**:2146–57. doi:10.1093/eurheartj/ehu274

73 Cochrane Handbook for Systematic Reviews of Interventions. http://handbook.cochrane.org/ (accessed 15 Mar2016).

74 Armijo-Olivo S. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. ;**18**:12–8.

Figure 1 | Flow of studies included in systematic review of FH prevalence

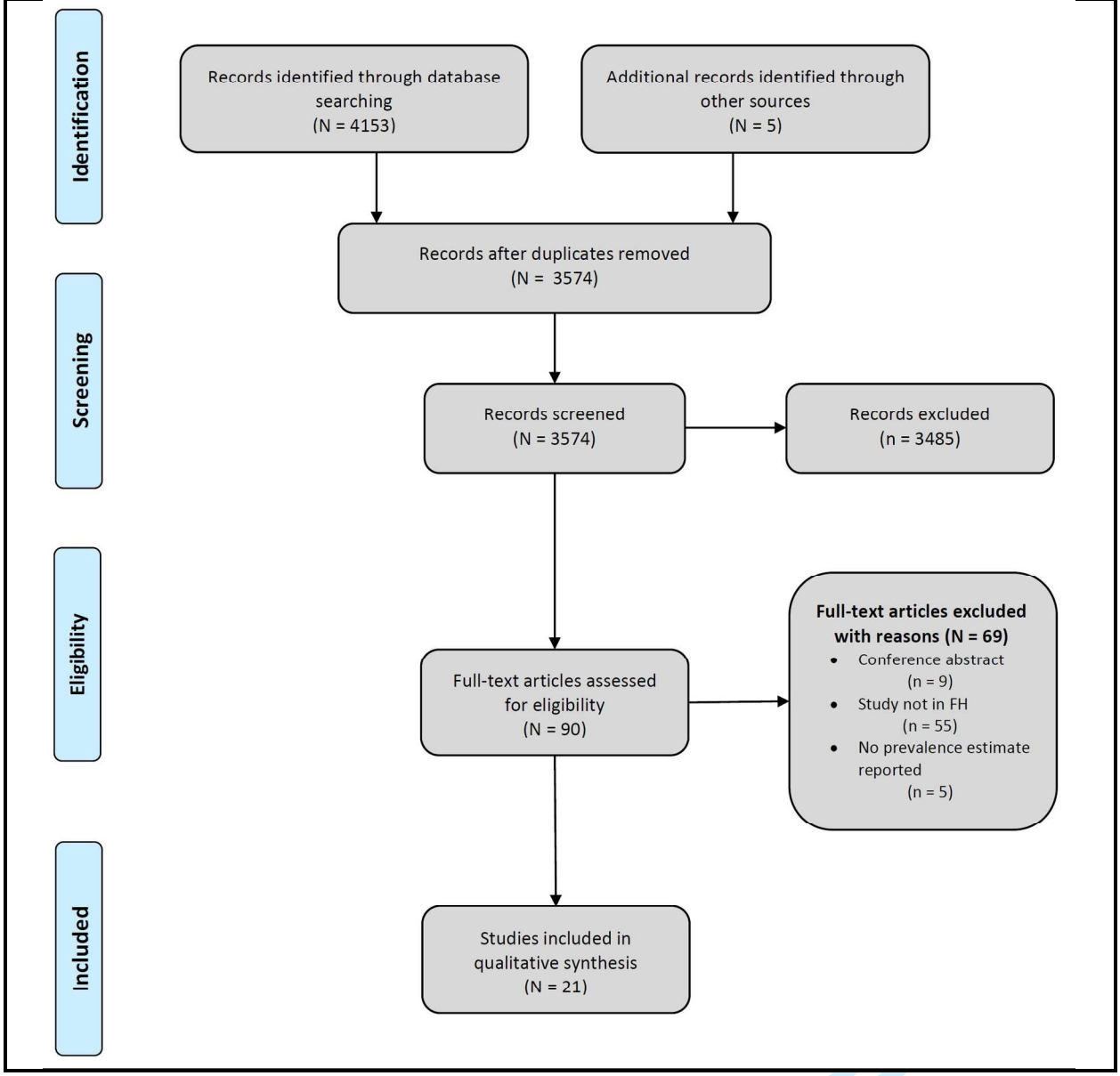


Figure 2 | Pooled prevalence of heterozygous familial hypercholesterolemia in adults

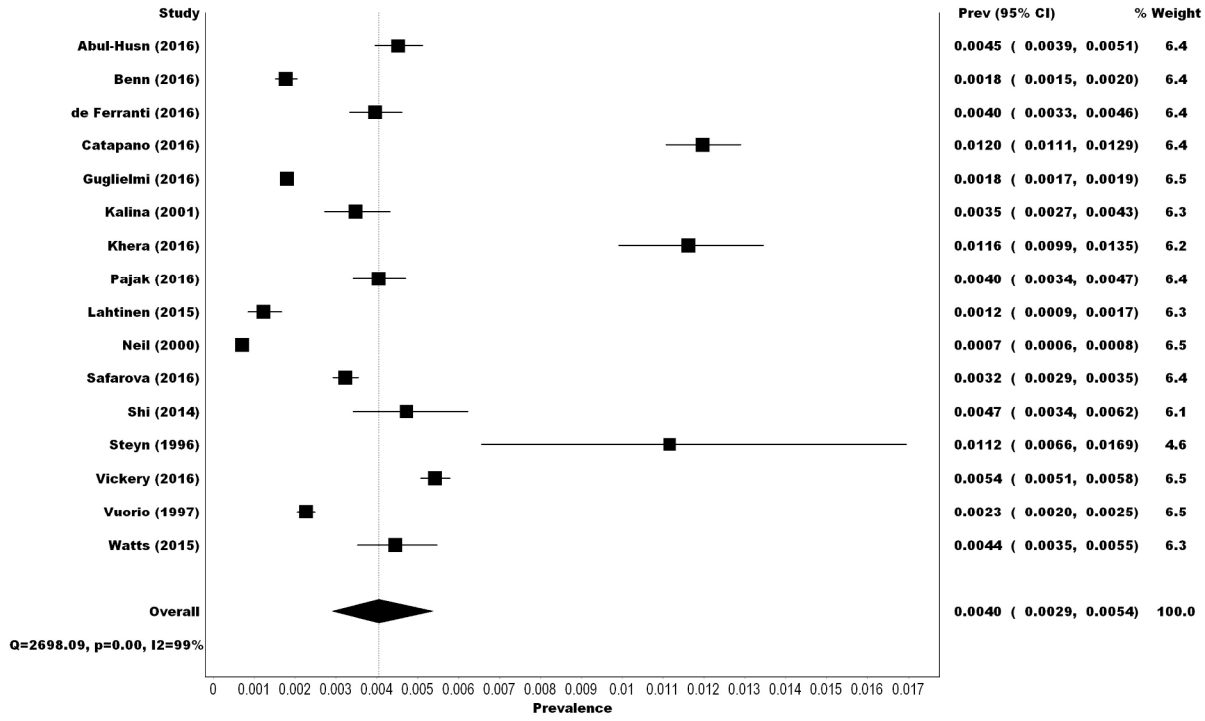


Figure 3 | Pooled FH prevalence estimates and 95% Confidence Intervals (CIs) from studies stratifying by age

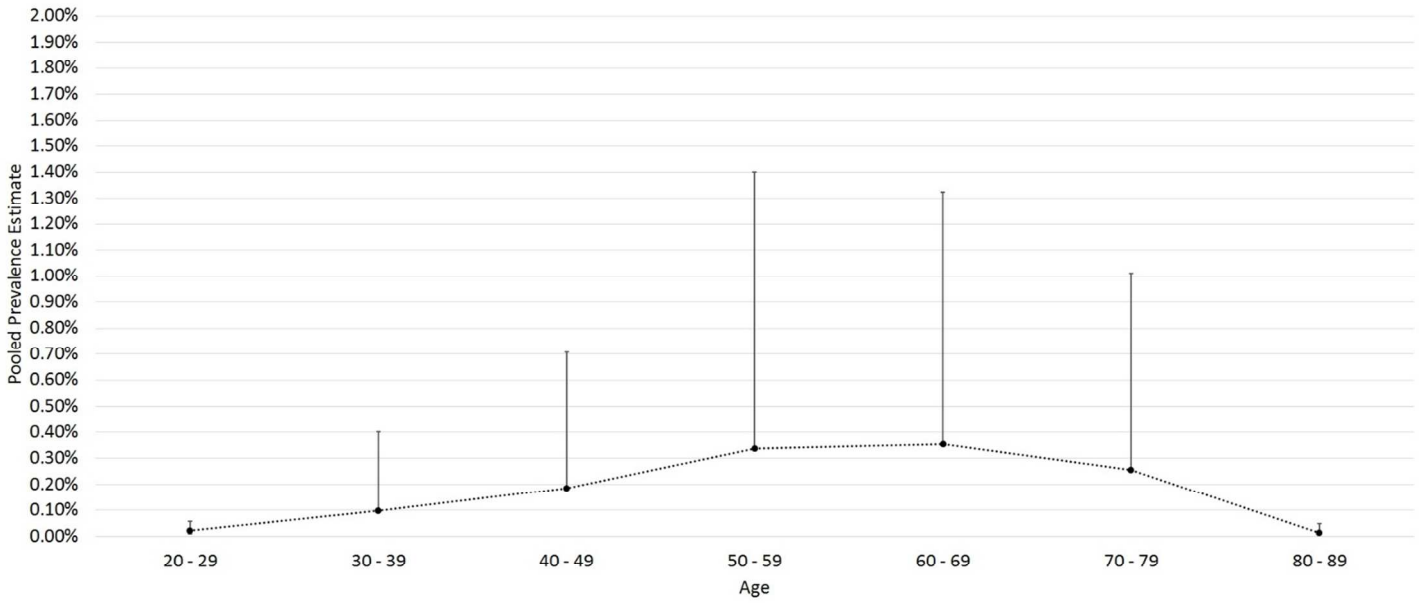
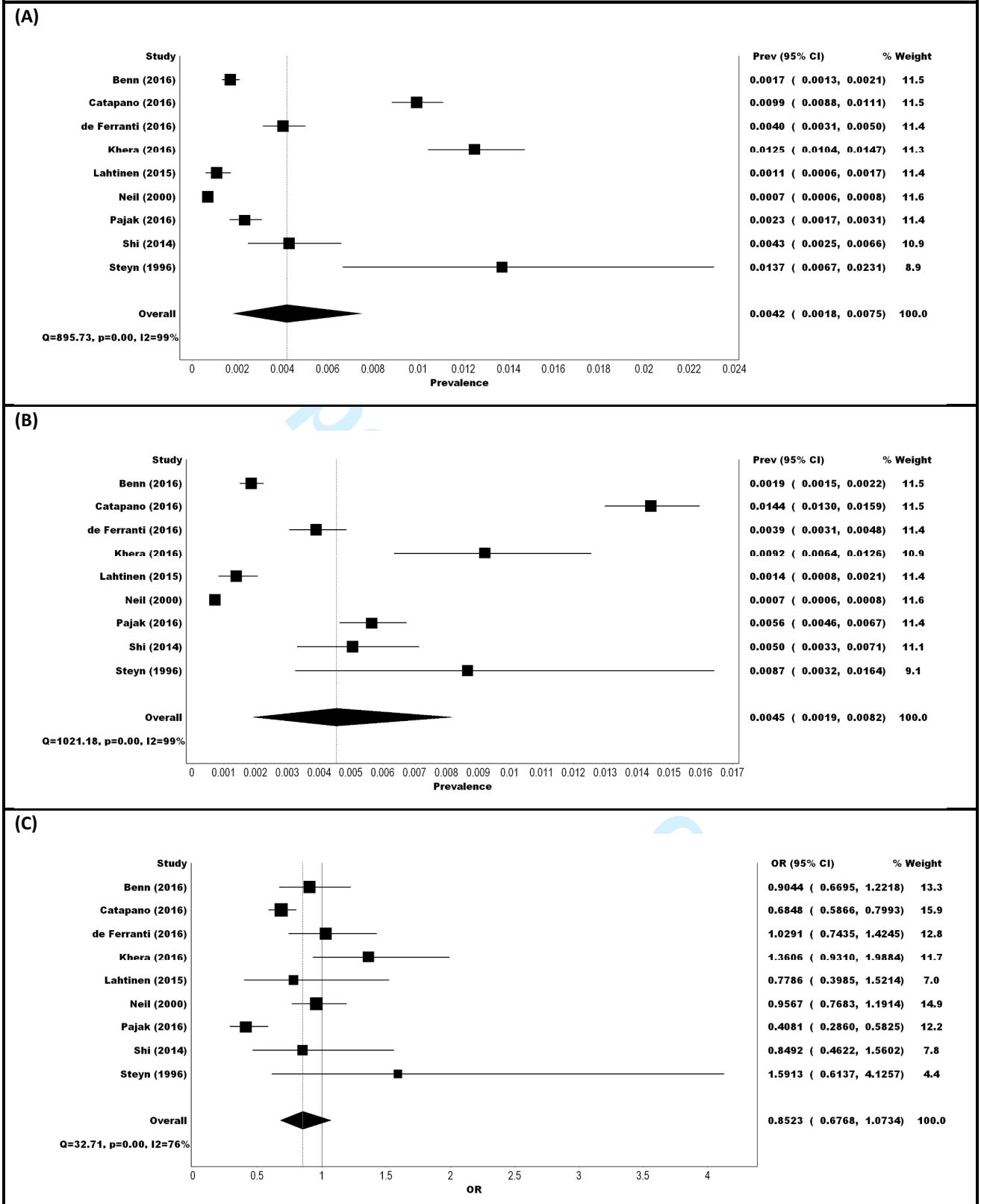


Figure 2 presents age-stratified pooled point estimates of FH prevalence. Error bars are representative of 95% Cis for each pooled estimate. Lower Cis are omitted; all cross 0%.

Figure 4 | Sex-stratified prevalence of FH in adults



(A) Pooled male prevalence of FH; (B) Pooled female prevalence of FH; (C) Pooled odds ratio for male:female FH prevalence.

Table 1 | Characteristics of studies included in systematic review of FH prevalence

Study author (publication year)	Country	Data source(s)	Enrollment period (years)	Diagnostic criteria	Sample size	Age (years)	Female, N (%)	FH cases, N	Prevalence estimate (95% CI)‡	Study quality
Studies reporting on FH prevalence in adults										
Abdul-Husn (2016) [52]	USA	Geisinger Health System EHR	NR	DNA	50726	18+	30334(59.8%)	229	0.45% (0.40%, 0.51%)	★★★
Benn (2012) [11]	Denmark	Copenhagen General Population Study	2003+	DLCN	69016	20-100	37959 (55.0%)	502	0.73% (0.67%, 0.79%)	★★★
				DNA	60710			20	0.03% (0.02%, 0.04%)	
				SB	69016			2830	4.10% (3.95%, 4.25%)	
				MEDPED	69016			552	0.80% (0.73%, 0.87%)	
Benn (2016) [50]	Denmark	Copenhagen General Population Study	2003+	DLCN	98098	20-100	53958 (55.0%)	341	0.35% (0.31%, 0.39%)	★★★
				DNA	98098			174	0.18% (0.15%, 0.20%)	
				SB	98000			3905	3.98% (3.86%, 4.11%)	
				MEDPED	93398			789	0.84% (0.79%, 0.90%)	
Catapano (2016) [40]	Multinational study†	DYSIS	2008-2013	DLCN	54811	45+	24884 (45.5%)	656	1.20% (1.11%, 1.29%)	★★
de Ferranti (2016) [41]	USA	NHANES	1999-2012	DLCN	36949	20+	18991 (51.4%)	146	0.40% (0.33%, 0.46%)	★★★
Guglielmi (2016) [53]	Italy	Health Longitudinal Patient Database	NR	DLCN	1135000	15+	NR	2043	0.18% (0.17%, 0.19%)	★★★
Kalina (2001) [6]	Hungary	Family doctors' registers	1996 – 1998	MEDPED	21000	NR	NR	39	0.19% (0.13%, 0.25%)	★★★
Khera (2016) [10]	Multinational study††	MiGen Consortium CHARGE Consortium	NR	DNA	20485	NR	3696 (26.2%)	24	0.12% (0.07%, 0.17%)	★★
				LDL-C				1386	6.77% (6.43%, 7.11%)	
Lahtinen (2015) [44]	Finland	FINRISK Cohort	1992, 1997, 2002	DNA	28465	25-74	14501 (50.9%)	35	0.12% (0.09%, 0.17%)	★★★
		Health 2000 Cohort	2000-2001			30+				
Neil (2000) [7]	United Kingdom	Simon Broome Register	1980-1999	SB	456550	20+	231796 (50.8%)	320	0.07% (0.06%, 0.08%)	★★
Pajak (2016) [42]	Poland	POL-MONICA Krakow	1983-1984 1987-1988 1992-1993	DLCN	37889	35-64	NR	153	0.40% (0.34%, 0.47%)	★★★
		POL-MONICA Warszawa	1984 1988 1993			35-64				
		WOBASZ	2003-2004			20-74				
		Pilot HAPIEE	2001-2002			45-64				
		HAPIEE	2003-2005			45-70				
		NATPOL 2011	2011			20-74				
Perak (2016) [47]	USA	FHS	1948	LDL-C	68565	30-62	19693 (41.0%)	3850	5.62% (5.44%, 5.79%)	★★
		FOS	1971			5-70				
		CARDIA	1985-1986			18-30				
		ARIC	1987-1989			45-64				
		NHANES III – Mortality	1988-1994			17-90				
		CHS	1989-1990			65+				

Safarova (2016) [54]	USA	Mayo ECH	1993 – 2014	DLCN	131000	18+	77290(59.0%)	423	0.32% (0.29%, 0.35%)	★★★
Shi (2014) [51]	China	Jiangsu Nutrition Study	2007	DLCN	9324	20+	5356 (57.4%)	26	0.28% (0.18%, 0.40%)	★★★
				LDL-C	9280			44	0.47% (0.34%, 0.62%)	
Steyn (1996) [45]	South Africa	Random sample from south-western Cape	NR	DNA	1612	15-64	809 (50.2%)	18	1.12% (0.66%, 1.69%)	★★
Vickery (2016) [55]	Australia	General practitioners' offices in Perth	NR	DLCN	157290	18-70	NR	782	0.050% (0.46%, 0.53%)	★★★
Vuorio (1997) [46]	Finland	Outpatient lipid clinic of North Karelia, Joensuu	1992-1996	DNA	180000	NR	NR	407	0.23% (0.20%, 0.25%)	★★★
Watts (2015) [43]	Australia	AusDiab	1999-2000	DLCN	18222	NR	NR	81	0.44% (0.35%, 0.55%)	★★
		Baker IDI	2005-2012							
Studies reporting on FH prevalence in children										
de Ferranti (2016) [41]	USA	NHANES	1999-2012	DLCN	13343	12-19	18991 (51.4%)	146	0.42% (0.32%, 0.54%)	★★★
Pang (2016) [49]	Australia	Western Australia Pregnancy Cohort Study	1989-1991	LDL-C	2868	14/17	770 (48.1%)	6	0.37% (0.12%, 0.74%)	★
Wald (2016) [58]	United Kingdom	General Medical Practices	2012-2015	DNA	10095	12.4-13.3 months	4882 (48.4%)	28	0.28% (0.18%, 0.39%)	★★★
Yang (2012) [48]	Korea	KNHANES IV	2007-2009	LDL-C	2363	10-18	1118 (47.3%)	9	0.38% (0.17%, 0.68%)	★★

Abbreviations

ARIC – Atherosclerotic Risk in Communities Study; ATVB – Atherosclerosis, Thrombosis, and Vascular Biology Italian Study; AusDiab – Australian Diabetes, Obesity and Lifestyle Study; Baker IDI - Baker IDI Heart and Diabetes Institute; CARDIA – Coronary Artery Risk Development in Young Adults Study; CHARGE – Cohorts for Heart and Aging Research in Genomic Epidemiology; CHS – Cardiovascular Health Study; DYSIS – Dyslipidemia International Study; ECH – Employee & Community Health System; EHR – Electronic Health Records; EOMI – Exome Sequencing Project (Early-Onset Myocardial Infarction); ERFS – Erasmus Rucphen Family Study; FHS – Framingham Heart Study; FOS – Framingham Offspring Study; JHS – Jackson Heart Study; KNHANES – Korean National Health and Nutrition Examination Survey; Munich-MI – Munich Myocardial Infarction Study; NHANES III – National Health and Nutrition Examination Survey III; OHS – Ottawa Heart Study; PROMIS – Pakistan Risk of Myocardial Infarction Study; RBS – Rotterdam Baseline Study

Legend

★ - weak, ★★ - moderate, ★★★ - strong

† - Austria, Belgium, Baltic states, Canada, China, Germany, Denmark, Egypt, France, Greece, United Arab Emirates, Israel, Ireland, Italy, Lebanon/Jordan, Netherlands, Norway, Portugal, Russia, Saudi, Slovakia, Slovenia, South Africa, Spain, Sweden, United Kingdom

†† - MiGen (ATVB, EOMI, JHS, Munich-MI, OHS, PROCARDIS, PROMIS): Canada, Germany, Italy, Pakistan, USA; CHARGE (ARIC, CHS, FHS, RBS, ERFS): Denmark, Netherlands, USA

‡ - 95% confidence interval (CI) not presented in articles but calculated from sample size and prevalence estimate

Table 2 | Meta-regression analyses for pooled estimate of adult FH prevalence

Covariate	Observations	Coefficient	95% CI	P	Adjusted R^2	I^2 Residual
Age	11	997.71	-773.52, 2768.942	0.23	5.87%	100.00%
Diagnostic Criteria**	15	NA	NA	0.00	100.00%	0.00%
Geographical Location**	15	NA	NA	0.00	100.00%	0.00%
Sex	11	37.75	-13.29, 88.79	0.13	15.22%	99.96%
Sample size	15	-2.55×10^7	-6.88×10^7, 1.79×10^7	0.23	4.20%	100.00%
Study quality*	15	-152.41	-287.16, -17.65	0.03	26.20%	100.00%

* - $P < 0.05$; ** - $P < 0.001$
NA – not applicable
Observations – number of studies with observations included in the meta-regression model
Adjusted R^2 – proportion of between-study variance explained with Knapp-Hartung modification
I^2 residual – percent residual variation due to heterogeneity

SUPPLEMENTARY APPENDIX

Estimating the prevalence of heterozygous familial hypercholesterolemia: a systematic review and meta-analysis

Leo E. Akioyamen[1,2], BScN; Jacques Genest[3,4], MD; Shubham D. Shan[1,2], HBSc; Rachel L. Reel[1], BSc; Jordan M. Albaum[1], MSc; Anna Chu[2] MHSc; Jack V. Tu[1,2,5] MD, PhD

1 – Faculty of Medicine, University of Toronto, Toronto ON, M5S 1A8, Canada
2 – Institute for Clinical Evaluative Sciences, Toronto ON, M4N 3M5, Canada
3 – Faculty of Medicine, McGill University, Montreal QC, H3G 2M1, Canada
4 – McGill University Health Centre, Royal Victoria Hospital, Montreal QC, H3A 1A1, Canada
5 – Schulich Heart Centre, Sunnybrook Health Sciences Centre, Toronto ON, M4N 3M5, Canada

eTable 1 | Search strategy for Medline

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1 exp Hyperlipoproteinemia Type II/ (5647)

2 ("familial hypercholesterolemia" or "familial hypercholesterolaemia").mp. (5157)

3 exp Coronary Disease/ or exp Atherosclerosis/ (224905)

4 exp Mortality/ or exp Mortality, Premature/ (314243)

5 exp Myocardial Infarction/ (156095)

6 exp Stroke/ (102093)

7 exp Heart Failure/ (98464)

8 exp Peripheral Vascular Diseases/ (48037)

9 exp Myocardial Ischemia/ (383424)

10 exp Cardiovascular Diseases/ (2068438)

11 exp Risk/ or exp Risk Factors/ or exp Prevalence/ or exp Incidence/ or exp Prognosis/ (2274061)

12 (prevalence or "risk factors" or incidence or prevalence or prognosis).mp. (2177998)

13 ('familial hypercholesterolemia'.mp. or exp Hyperlipoproteinemia Type II/) and ('systematic review' or 'meta-analysis').mp. (51)

14 1 or 2 (7403)

15 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (2314576)

16 11 or 12 (3062771)

17 14 and 15 and 16 (942)

18 13 or 17 (985)

19 limit 18 to (human and english language and yr="1990 -Current") (724)

****

eTable 2 | Detailed inclusion/exclusion criteria for systematic review of FH prevalence

1. **FULL-TEXT peer-reviewed publication?**
   - Yes (**include**)
   - No - e.g., conference abstract/proceeding (exclude)
   - Can't decide (**include**)

2. **Live HUMAN subjects or study participants?**
   - Yes (**include**)
   - No (exclude)
   - Can't decide (**include**)

3. **Is the study in HETEROZYGOUS familial hypercholesterolemia?**
   - Yes (**include**)
   - No (exclude)
   - Can't decide (**include**)

4. **AGEs of subjects or study participants:**
   - Adults 18 years and over (**include**)
   - Children / Adolescents (**include** – separate)
   - Can't decide (**include**)

5. **TYPE of study reported in this article:**
   - Report of a cohort/registry (**include**)
   - Other observational studies (e.g. Case Control, Cross-Sectional, Case Report/Series, Survey) (**include**)
   - Meta-analyses/systematic reviews/health technology assessments (exclude – separate)
   - Findings from a controlled clinical trial (exclude – separate)
   - Protocol of methods for a controlled clinical trial (exclude)
   - Practice/treatment guideline (exclude)
   - Academic/Narrative Review, Comment, Editorial, Letter, Note, Patient Handout, Study Design Description (exclude)
   - Can't decide (**include**)

6. **Is this study in ENGLISH?**
   - Yes (**include**)
   - No (exclude)
   - Can't decide (**include**)

7. **Does the study report disease PREVALENCE in the subjects or study participants?**
   - Yes (**include**)
   - No (exclude)
   - Can't decide (**include**)

If PREVALENCE is reported, how is it determined?

A) DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation
B) Dutch Lipid Clinic Network Criteria
C) Simon Broome Registry Criteria
D) Making Early Diagnosis to Prevent Early Death (MEDPED) Criteria
E) ADULT: Total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L)
F) CHILD: (< 16 years of age): Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)
G) Hardy-Weinberg equilibrium (exclude)

eTable 3 | The Dutch Lipid Clinic Network (DLCN) criteria	
Criteria	**Score**
Family History	
First-degree relative with premature coronary and/or vascular disease (men ≤ 55 years, women ≤ 60 years) **OR** First-degree relative with known LDL-cholesterol (LDL-C) ≥ 95th percentile for age and sex	**1**
First-degree relative with tendon xanthomata and/or arcus cornealis **OR** Children aged ≤ 18 years with known LDL-C ≥ 95th percentile for age and sex	**2**
Clinical History	
Patient with premature coronary artery disease (age as above)	**2**
Patient with premature cerebral or peripheral vascular disease (age as above)	**1**
Physical Examination	
Tendon xanthomas	**6**
Arcus cornealis at age ≤ 45 years	**4**
LDL-C mmol/L (mg/dL)	
LDL-C ≥ 8.5 (330)	**8**
LDL-C 6.5-8.4 (250-329)	**5**
LDL-C 5.0-6.4 (190-249)	**3**
LDL-C 4.0-4.9 (155-189)	**1**
DNA Analysis	
Functional mutation in LDLR, APOB or PCSK9	**8**
Stratification	**Total Score**
Definite FH	**8**
Probable FH	**6-8**
Possible FH	**3-5**
Unlikely FH	**<3**

eTable 4 | Simon Broome Register diagnostic criteria	
A diagnosis of DEFINITE FH requires either (1), (2) or (3)	
(1)	Total cholesterol > 290 mg/dL (7.5 mmol/L) or LDL-C > 189 mg/dL (4.9 mmol/L) in adults
	Tendon xanthomas in patient or a first- or second-degree relative
(2)	Total cholesterol > 259 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L) in a child under 16 years of age
	Tendon xanthomas in patient or a first- or second-degree relative
(3)	DNA-based evidence of a function LDLR, PCSK9 or ApoB mutation
A diagnosis of PROBABLE FH requires either (1), (2) or (3)	
(1)	Total cholesterol > 290 mg/dL (7.5 mmol/L) or LDL-C > 189 mg/dL (4.9 mmol/L)
	Family history of myocardial infarction
(2)	Total cholesterol > 259 mg/dL (6.7 mmol/L) or LDL-C > 4.0 mmol/L in a child under 16 years of age
	Family history of myocardial infarction before 50 years of age in a second-degree relative or below age 60 in a first-degree relative
(3)	Family history of elevated total cholesterol in a first or second-degree relative (> 7.5 mmol/L in an adult; > 6.7mmol/L in child or sibling aged under 16 years)

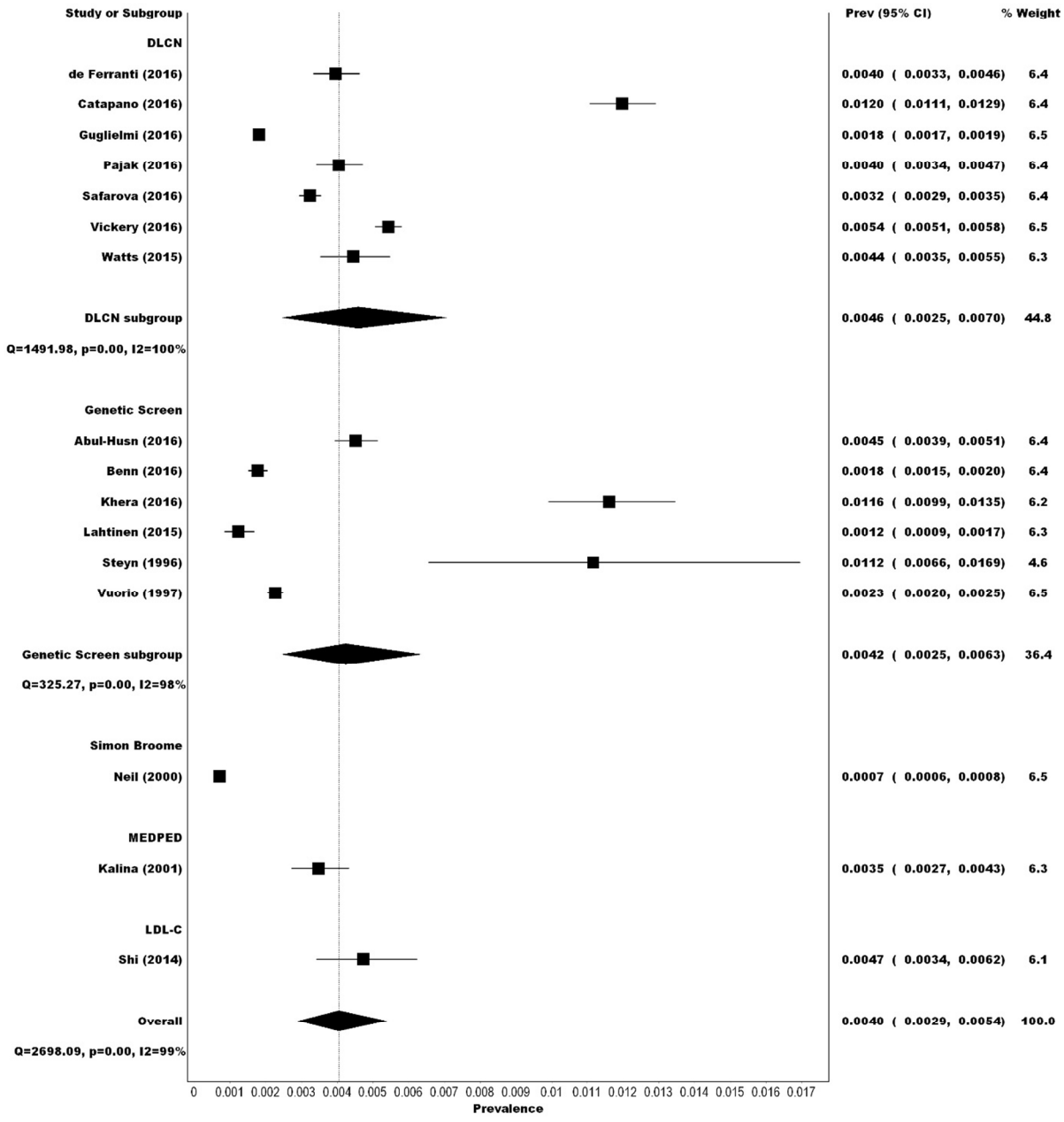
eTable 5 | MEDPED Program diagnostic criteria for FH				
	Total cholesterol threshold (mmol/L)			
	First-degree relative with FH	Second-degree relative with FH	Third-degree relative with FH	General population
Age (years)				
<20	5.7	5.9	6.2	7.0
20-29	6.2	6.5	6.7	7.5
30-39	7.0	7.2	7.5	8.8
≥ 40	7.5	7.8	8.0	9.3
FH is diagnosed if the total cholesterol levels exceed the specified threshold.				

eTable 6 | Considerations of the Effect Public Health Practice Project Quality Assessment Tool	
Component Ratings	**Domains Assessed**
A) Selection Bias	1. Are the individuals selected to participate in the study likely to be representative of the target population? 2. What percentage of selected individuals agreed to participate?
B) Study Design	1. Indicate the study design. 2. Was the study described as randomized? If NO, go to component C. 3. If YES, was the method of randomization described? 4. If YES, was the method of randomization appropriate?
C) Confounders	1. Were there important differences between groups prior to the intervention? 2. If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g., stratification, matching) or analysis)?
D) Blinding	1. Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants? 2. Were the study participants aware of the research question?
E) Data Collection Methods	1. Were data collection tools shown to be valid? 2. Were data collection tools shown to be reliable?
F) Withdrawals & Dropouts	1. Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group? 2. Indicate the percentage of participants completing the study.
G) Intervention Integrity	1. What percentage of participants received the allocated intervention or exposure of interest? 2. Was the consistency of the intervention measured? 3. Is it likely that the subjects received an unintended intervention (contamination or co-intervention) that may influence the results?
H) Analyses	1. Indicate the unit of allocation. 2. Indicate the unit of analysis. 3. Are the statistical methods appropriate for the study design? 4. Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?
Source: http://www.ephpp.ca/tools.html Note: Only sections A-F are used in generating the global assessment of study quality.	

eTable 7 | Quality assessment for studies included in systematic review of FH prevalence							
Study author	**Selection bias**	**Study design**	**Confounders**	**Blinding**	**Data collection methods**	**Withdrawal & dropouts**	**Globing rating**
Abul-Husn (2016)	★★★	★★	★★★	★★	★★★	★★★	★★★
Benn (2012)	★★★	★★	★★★	★★	★★★	★★★	★★★
Benn (2016)	★★★	★★	★★★	★★	★★★	★★★	★★★
Catapano (2016)	★	★★	★★	★★	★★★	★★★	★★
de Ferranti (2016)	★★★	★★	★★★	★★	★★★	★★★	★★★
Kalina (2001)	★★	★★	★★	★★	★★★	★★★	★★★
Guglielmi (2016)	★★★	★★	★★	★★	★★	★★★	★★★
Khera (2016)	★	★★	★★	★★	★★★	★★★	★★
Lahtinen (2015)	★★★	★★	★★★	★★	★★★	★★	★★★
Neil (2000)	★★★	★★	★	★★	★★★	★★★	★★
Pajak (2016)	★★★	★★	★★★	★★	★★	★★★	★★★
Pang (2016)	★★	★★	★	★★	★★	★	★
Perak (2016)	★	★★	★★★	★★	★★★	★★	★★
Safarova (2016)	★★★	★★	★★	★★	★★	★★★	★★★
Shi (2014)	★★★	★★	★★★	★★	★★★	★★★	★★★
Steyn (1996)	★	★★	★★★	★★	★★★	★★★	★★
Vickery (2016)	★★	★★	★★	★★	★★★	★★★	★★★
Vuorio (1997)	★★★	★★	★★★	★★	★★★	★★	★★★
Watts (2015)	★★	★★	★★	★★	★★★	★★★	★★
Wald (2016)	★★★	★★	★★★	★★	★★★	★★★	★★★
Yang (2012)	★★	★★	★★★	★★	★★★	★	★★
★ - weak; ★★ - moderate; ★★★ - strong							

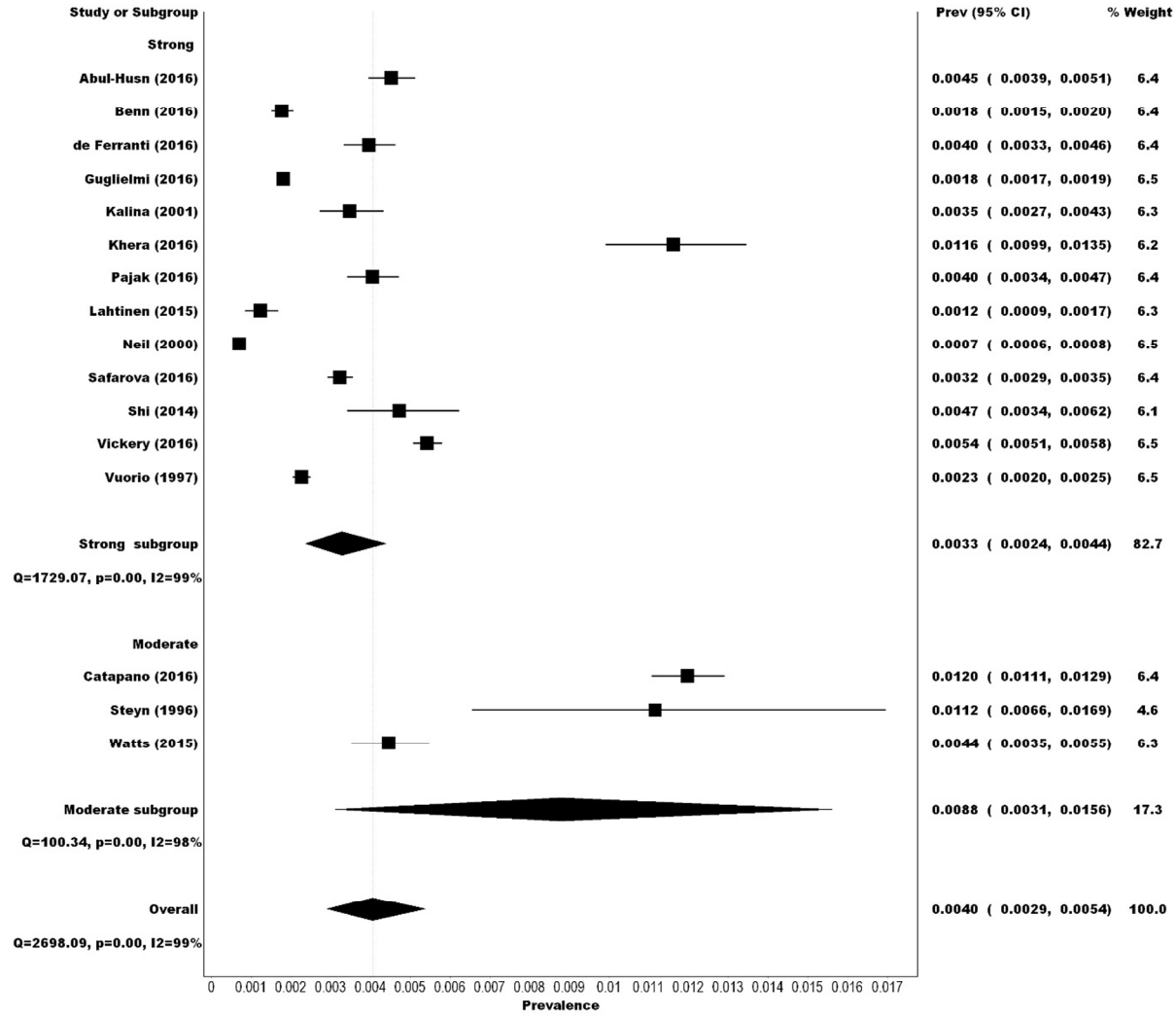
eTable 8 | Pooled prevalence of FH in children (ages 0 – 19)				
Study	**Prevalence**	**LCI 95%**	**HCI 95%**	**Weight (%)**
de Ferranti (2016)	0.42%	0.32%	0.54%	45.60
Pang (2016)	0.37%	0.12%	0.74%	7.16
Wald (2016)	0.28%	0.18%	0.39%	36.90
Yang (2012)	0.38%	0.17%	0.68%	10.35
Pooled	**0.36%**	**0.29%**	**0.45%**	**100**
Statistics				
I-squared	13.32%	0.00%	86.73%	
Cochran's Q	3.46			
Chi2, p	0.33			
tau2	0.00			

eFigure 1 | Pooled adult FH prevalence stratified by diagnostic criteria employed in included studies

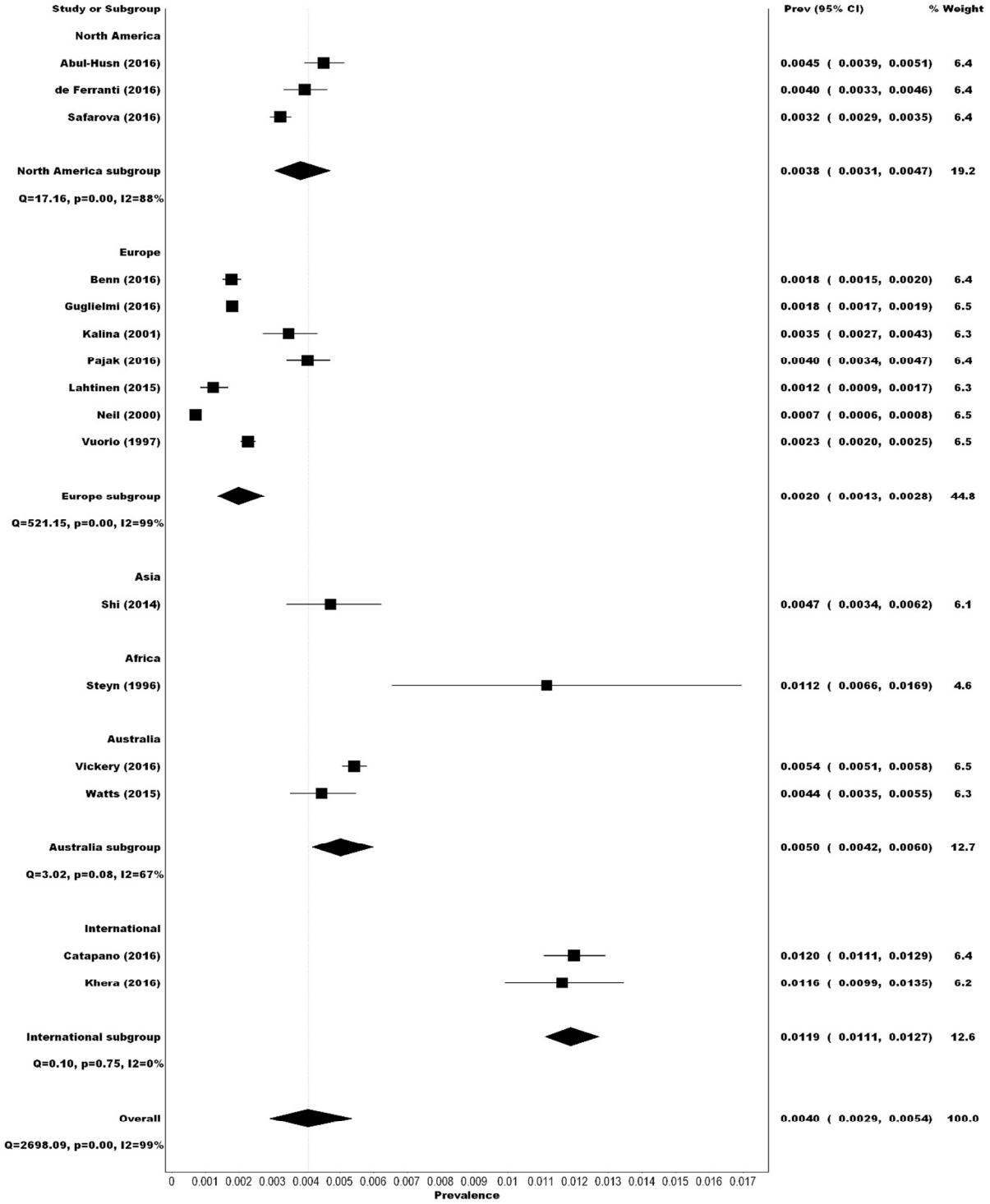


Abbreviations: DLCN – Dutch Lipid Clinic Network Criteria; Genetic Screen – DNA-based evidence of an LDLR, ApoB, or PCSK9 mutation; Simon Broome – Simon Broome Registry criteria; MEDPED - Making Early Diagnosis to Prevent Early Death

eFigure 2 | Pooled FH prevalence stratified by study quality

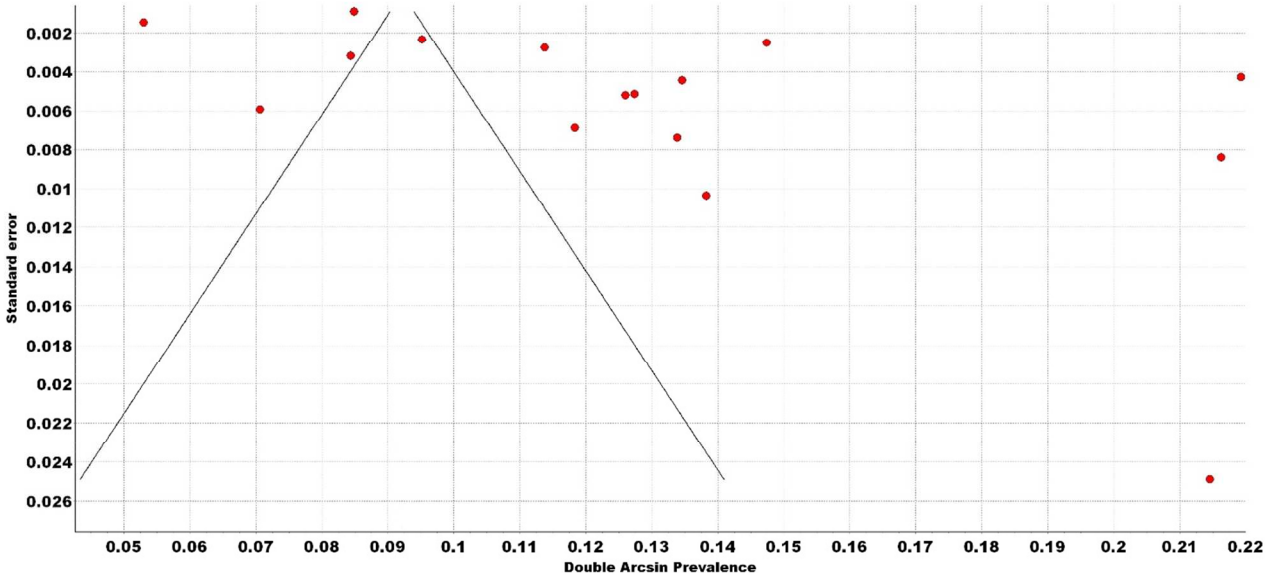


eFigure 3 | Pooled adult FH prevalence stratified by geographic location

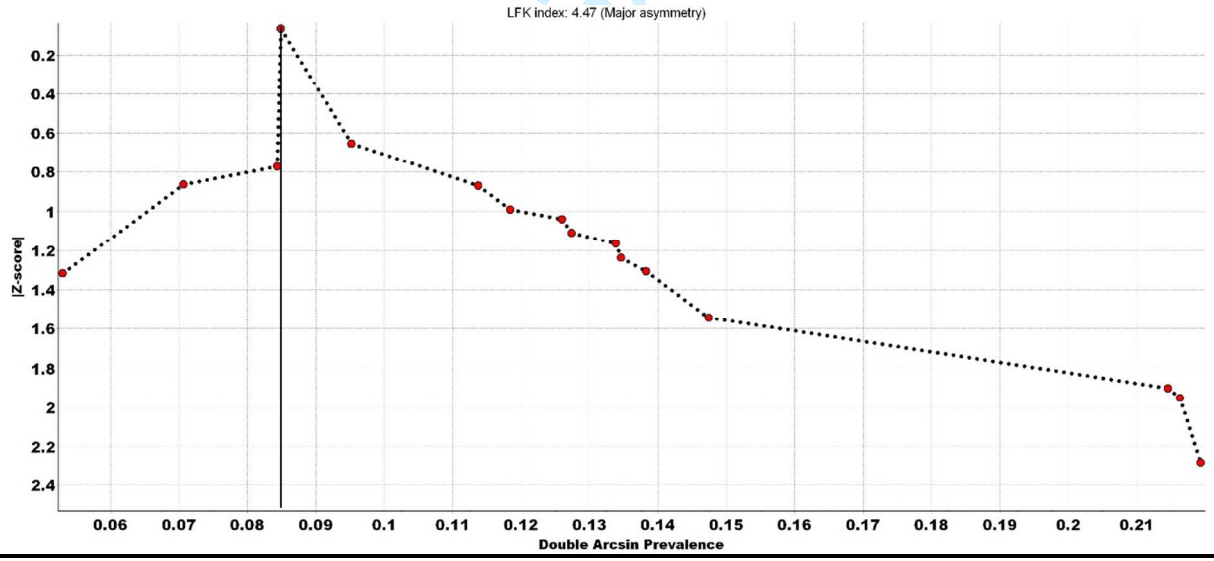


eFigure 4 | Publication bias in studies reporting on adult FH prevalence

(A)



(B)



Interpretation of eFigure 4

We present the Begg Funnel plot in (A). Here, the horizontal line indicates a fixed-effects summary estimate derived under inverse variance weighting. The sloping lines that straddle the horizontal demonstrate the expected 95% confidence intervals for the given standard error, assuming no heterogeneity between studies. We plot the standard error of individual study's effect sizes on the horizontal axis and the effect sizes (i.e., prevalence estimates) on the vertical axis.

The Doi plot for publication bias is presented in (B). Here, double arcsine transformed prevalence estimates derived under random effects meta-analysis are plotted against an absolute value of a z-score attained by assigning each study a rank based on the standard error of its effect size. When studies included in an analysis are symmetrical, the most precise studies will approach zero on the z-score axis and define a midpoint around which other studies will scatter. By contrast, smaller, less precise trials should scatter widely as their absolute z-score increases and studies become more likely to report findings on either side of the midpoint. The result, in the absence of asymmetry should resemble a symmetrical triangle, with a z-score approaching zero as its peak. A dissimilar number of studies on either side of the triangle or a lack of equal spread or both are indicative of the existence of asymmetry.

Summary

Visually assessed, both Begg's plot (A) and the Doi plot(B) suggest asymmetry among estimates derived from included studies. This asymmetry was confirmed by Egger's weighted regression ($p = 0.03$).

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	N/A
3	Description of study outcome(s)	4
4	Type of exposure or intervention used	N/A
5	Type of study designs used	4
6	Study population	4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	NR
8	Search strategy, including time period included in the synthesis and key words	4; Supplement
9	Effort to include all available studies, including contact with authors	4
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	4
12	Use of hand searching (eg, reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	eFigure 1 (Supplement)
14	Method of addressing articles published in languages other than English	4
15	Method of handling abstracts and unpublished studies	4
16	Description of any contact with authors	NR
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	NR
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	18-21; Supplement
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	20
26	Table giving descriptive information for each study included	18-19
27	Results of sensitivity testing (eg, subgroup analysis)	8.9
28	Indication of statistical uncertainty of findings	8,9

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Supplement
30	Justification for exclusion (eg, exclusion of non-English language citations)	Supplement
31	Assessment of quality of included studies	Supplement
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	9-11
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	9-11
34	Guidelines for future research	9-11
35	Disclosure of funding source	12

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

BMJ Open

Estimating the prevalence of heterozygous familial hypercholesterolemia: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016461.R1
Article Type:	Research
Date Submitted by the Author:	17-Jun-2017
Complete List of Authors:	Akioyamen, Leo ; University of Toronto Faculty of Medicine Genest, Jacques; McGill University Faculty of Medicine, Canada Shan, Shubham; University of Toronto Faculty of Medicine Reel, Rachel; University of Toronto Faculty of Medicine Albaum, Jordan; University of Toronto Faculty of Medicine Chu, Anna; Institute for Clinical Evaluative Sciences Tu, Jack; The Institute for Clinical,
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Coronary heart disease < CARDIOLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY

TITLE: Estimating the prevalence of heterozygous familial hypercholesterolemia: a systematic review and meta-analysis

SHORT TITLE: Prevalence of heterozygous FH

Leo E Akioyamen[a,b] BScN, MD(c) (sele.akioyamen@mail.utoronto.ca)

Jacques Genest MD[c,d] (jacques.genest@mcgill.ca)

Shubham D Shan HBSc, MD(c)[a.b] (shubham.shan@mail.utoronto.ca)

Rachel L Reel HBSc[a] (rachel.reel@gmail.com)

Jordan M Albaum MSc, MD(c)[a] (jordan.albaum@mail.utoronto.ca)

Anna Chu MHSc[a,b] (anna.chu@ices.on.ca)

Jack V Tu MD, PhD[a,b,e] (tu@ices.on.ca)

a – Faculty of Medicine, University of Toronto, Toronto ON, M5S 1A8, Canada
b – Institute for Clinical Evaluative Sciences, Toronto ON, M4N 3M5, Canada
c – Faculty of Medicine, McGill University, Montreal QC, H3G 2M1, Canada
d – McGill University Health Centre, Royal Victoria Hospital, Montreal QC, H3A 1A1, Canada
e – Schulich Heart Centre, Sunnybrook Health Sciences Centre, Toronto ON, M4N 3M5, Canada

CORRESPONDING AUTHOR
Jack V. Tu MD, PhD
Institute for Clinical Evaluative Sciences
G106-2075 Bayview Avenue
Toronto, ON
M4N 3M5
tu@ices.on.ca

TABLES: 2
FIGURES: 5
WORD COUNT: 3572

SOURCES OF FUNDING
LA was supported by the Comprehensive Research Education for Medical Students Scholar Program at the University of Toronto. JG holds the McGill/Novartis Chair at McGill University. JT is funded by a Canada Research Chair in Health Services Research from the Canadian Institutes of Health Research (CIHR) and an Eaton Scholar Award from the Department of Medicine at the University of Toronto. This research is also funded by an Institute for Circulatory Health-Canadian Institutes of Health Research Chronic Diseases Team grant (no. TCA 118349) to the Cardiovascular Health in Ambulatory Care Research Team (http://www.canheart.ca); and the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ABSTRACT

Objectives

Heterozygous familial hypercholesterolemia (FH) confers a significant risk for premature cardiovascular disease CVD). However, the estimated prevalence of FH varies substantially amongst studies. To provide a summary estimate of FH prevalence in the general population and assess variations in frequency across different sociodemographic characteristics.

Setting, participants and outcome measures

We searched MEDLINE, EMBASE, Global Health, the Cochrane Library, PsycINFO, and PubMed for peer-reviewed literature using validated strategies. Results were limited to studies published in English between January 1990 and January 2017. Studies were eligible if they determined FH prevalence using clinical criteria or DNA-based analyses. We determined a pooled point prevalence of FH in adults and children and assessed the variation of the pooled frequency by age, sex, geographical location, diagnostic method, study quality and year of publication. Estimates were pooled using random-effects meta-analysis. Differences by study-level characteristics were investigated through subgroups, meta-regression, and sensitivity analyses.

Results

The pooled prevalence of FH from nineteen studies including 2,458,456 unique individuals was 0.40% [95% CI: 0.29%, 0.52%] which corresponds to a frequency of 1 in 250 individuals. FH prevalence was found to vary by age and geographical location but not by any other covariates. Results were consistent in sensitivity analyses.

Conclusions

Our systematic review suggests that FH is a common disorder, affecting 1 in 250 individuals. These findings underscore the need for early detection and management to decrease CVD risk.

Keywords: familial hypercholesterolemia, prevalence, frequency, systematic review, meta-analysis

STRENGTHS & LIMITATIONS

- Use of an extensive search strategy and adherence to predetermined inclusion/exclusion criteria.
- Use of evidence-based inverse variance weighted random effects meta-analysis to quantify a robust estimate of the pooled frequency of heterozygous familial hypercholesterolemia in adults.
- Our study possesses a large sample-size (n = 2,458,456).
- We include only English-language peer-reviewed studies making it possible that some relevant articles were not included.
- Our analyses possessed considerable amount of quantifiable heterogeneity.

BACKGROUND

The frequency of heterozygous familial hypercholesterolemia (FH) was originally reported as 1 in 500 (0.2 percent) [1]. This estimate is based on work that determined the prevalence in homozygous individuals and used Hardy-Weinberg principles to calculate the frequency in heterozygotes [2]. Similar frequencies have been described in subsequent reports of population-based samples[3–7]. However, this estimate has recently been criticized for its imprecision[8]. Human behavior does not adhere to Hardy-Weinberg assumptions (e.g., random mating, no migration) and violations of these principles have been shown to significantly impact the results of gene-disease association studies[9]. Further, recent work indicates as many as 1 in 200 people may be affected by FH [10–12] and there is some data to suggest that regional variations in FH frequency exist [13–19].

The population prevalence of FH is difficult to determine for several reasons. Most countries lack national FH registers or large observational databases. Yet even when such databases exist, they often contain insufficient data on aspects of clinical histories essential for FH diagnosis. No uniform criteria for FH diagnosis exist and the three sets of criteria commonly used vary in the amount of emphasis placed on clinical characteristics in determining FH. Additionally, the ability to detect such findings may vary based on the clinical acumen and experiences of assessors[20]. Genetic diagnosis has the potential to mitigate confounding inherent in clinical diagnostic criteria. However, the feasibility and cost-effectiveness of genetic screening continues to be debated, [8,21–23] a high proportion of patients with clinical FH diagnoses may not be identified[24] and all of the genetic mutations that cause FH may not yet be known. Together, these factors suggest the potential for a different FH frequency than original estimates.

Ascertaining the prevalence of FH has important clinical and public health implications, especially in light of the availability of new but expensive treatments (e.g., proprotein convertase subtilisin/kexin type 9 [PCKS9] inhibitors) for this condition. FH is caused by defects in the low-density lipoprotein receptor (LDLR) pathway, resulting in elevated LDL-cholesterol (LDL-C) concentrations that are largely resistant to caloric restriction, weight loss, and physical exercise interventions in affected individuals[24]. FH also predicts a very high risk of cardiovascular disease even in the absence of other traditional risk factors as patients possess these LDL-C concentrations from

birth[25]. Early diagnosis and treatment of FH with lipid lowering therapy has proven to be both cost efficient and effective in mitigating cardiovascular morbidity and mortality risk[26,27]. Despite these benefits, numerous reports suggest that FH is currently underdiagnosed in the general population [27] and that in some jurisdictions, a large proportion of affected individuals have difficulty accessing effective lipid-lowering therapies [28]. Clinicians routinely consider estimates of disease prevalence, variations in different population groups (e.g., age, sex, ethnicity), and the presence of known risk factors in formulating differential diagnoses. These factors also form important considerations when evaluating national strategies for the optimal identification and treatment of individuals[29]. Thus, determining the prevalence of FH and its variation by sociodemographic factors provides an important first step in reducing disease burden.

While a number of narrative and systematic reviews have summarized studies of FH[8,13,30–34], there has been no attempt to consolidate these studies to derive a robust prevalence estimate or to assess variation according to sociodemographic factors. We therefore aimed to systematically review the existing literature presenting estimates of FH in the adult general population and explore variation in prevalence estimates by age, sex, geographical location and study quality.

METHODS

We carried out a systematic review and meta-analyses in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) consensus statement[35]. The protocol for this review was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42016042208).

Study Identification & Selection

This study was part of a series of systematic reviews with a standardized search strategy examining the disease burden posed by heterozygous familial hypercholesterolemia. We searched MEDLINE, EMBASE, PsycINFO, Global Health, the Cochrane Library, and Pubmed (for publications ahead of print) for published, peer-reviewed literature using controlled vocabulary and keywords related to familial hypercholesterolemia and relevant epidemiological terms. Results were limited to human studies published in English between January 1 1990 and January 31 2017.

We reviewed reference lists of all included articles and relevant literature reviews, systematic reviews and meta-analyses for additional eligible studies. A detailed search strategy is included in the supplement to this manuscript (eTable 1).

Titles and abstracts and full-texts were evaluated in duplicate by independent reviewers (LEA, SDS) using standardized forms (eTable 2). Disagreements were resolved through discussion to consensus. For inclusion in the systematic review of prevalence, studies were required to include live human participants and to report on the prevalence of FH. Studies were included if they ascertained FH frequency using one of the following methods (eTables 3-5): (1) DNA-based evidence of LDLR, Apolipoprotein-B (Apo B), or PCSK9 mutations; (2) Dutch Lipid Clinic Network (DLCN) Criteria; (3) Simon Broome Registry (SBR) Criteria; (4) Making Early Diagnosis to Prevent Early Death (MEDPED) Criteria; or (5) total cholesterol levels (> 290 mg/dL or 7.5 mmol/L) or LDL-C levels (> 189 mg/dL or 4.9 mmol/L)[34]. We did not include articles reporting on the prevalence of or regional variations in specific LDLR, Apo B or PCSK9 mutations in study populations given their potential to underestimate FH frequencies.

Data Extraction

One reviewer (LEA) independently extracted data regarding study characteristics (e.g., design, population characteristics, diagnostic measures, prevalence estimates) from the full-text of included articles. Another reviewer (RLR) checked the extracted data and any detected discrepancies were resolved. We did not attempt to contact authors of studies with missing or incomplete data nor did we exclude any such studies from our synthesis.

Study Quality Assessment

Two reviewers (LEA, RLR) independently assessed the quality of eligible studies using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (http://www.ephpp.ca/tools.html) and resolved discrepancies through consensus. It has been shown to be acceptable for use in evaluating a variety of study designs including randomized controlled trials, before-and-after studies and case control studies (eTable 6). The tool assesses study quality across six domains: [1] selection bias; [2] study design; [3] confounding variables;

[4] blinding protocols; [5] data collection methods; and [6] handling of withdrawals and dropouts. Each dimension is rated on a three-point scale - strong, moderate, and weak – and these ratings feed into a global rating of study quality. Global study quality is considered to be strong if none of the quality domains is rated as weak, moderate if one domain is rated as weak, and weak if two or more domains are rated as weak.

Data Synthesis

Our primary analysis consisted of a pooled estimate of prevalence across all studies using a random effects model[36,37]. We also pooled data from studies separately under the model in order to calculate the pooled prevalence of FH in children (ages 0 – 19) and adults (>20 years of age). Where studies presented multiple diagnostic criteria, estimates derived from genetic testing were used in the analysis as this was thought to provide a more conservative estimate. Where studies derived estimates using DLCN criteria, we pooled reported cases of "definite" or "probable" FH to determine individual study estimates. Similarly, "definite" or "possible" FH diagnoses using Simon Broome criteria were pooled in the meta-analyses. Where multiple studies reported prevalence estimates from a single cohort, estimates were taken from the paper reporting the largest sample and the other paper, excluded from the analysis. Potential influences on prevalence estimates were investigated using subgroup analyses and meta-regression. Where studies allowed, we descriptively compared prevalence estimates by age, sex, prevalence estimation method, study quality, and geographical location within studies. We then assessed the influence of these factors on variation in the estimated prevalence using meta-regression models.

Statistical analysis

We calculated a pooled prevalence figures with 95% confidence intervals (CIs) using the DerSimonian & Laird random effects model[37]. In meta-analyses of prevalence using inverse variance methods, when the frequency estimate of a single study approaches the limits of prevalence (i.e., 0% or 100% of the population), the variance for that study moves toward zero, leading to the resulting weight in the meta-analysis being overestimated [36]. To accommodate for this, we conducted the meta-analysis with prevalence estimates that had been transformed using the double arcsine method[36]. The final pooled result and 95% CIs were then back transformed and expressed as percentages for ease of interpretation. We assessed heterogeneity in our pooled analyses using the

I^2 statistic as it is not sensitive to the scale of effect size or the total number of studies included in the meta-analysis[38]. Finally, publication bias was examined formally using Egger's weighted regression, with significance set at P < 0.10 [39]. Publication bias was also assessed visually using Begg's funnel plot as well as a *Doi* plot [40,41]. If publication bias was present, we used the trim and fill method to adjust for publication bias [40]. Analyses were performed using the MetaXL add-in for Microsoft Excel (www.epigear.com). Forest plots were generated using DistillerSR Forest Plot Generator from Evidence Partners (https://www.evidencepartners.com/resources/forest-plot-generator/).

Meta-regression was used to discern the influence of age, sex, prevalence estimation method, study quality, geographical location, year of publication, and study setting (i.e., electronic health records versus general population registers) on our pooled prevalence estimate. We used Stata version 13.1 to perform the meta-regression analysis on the log scale of the back transformed effect size (i.e., prevalence), with each trial weighting equal to the that derived under the random effects model and between study variance estimated with the restricted maximum likelihood method. The log of the pooled prevalence estimate was used as the dependent variable whereas, sample size, study quality scores, mean sample age and study proportions of female participants used as continuous predictive variables. Categorical covariates such as prevalence estimation method and geographical location were dummy-coded and examined through a joint test for all dummy-coded covariates.

Sensitivity analyses

We conducted additional analyses to assess the robustness of our pooled prevalence estimate. We examined the impact of time on the diagnosis of FH by sequentially excluding studies published before the year 2000, and 2010. We also assessed the impact of study setting by comparing estimates derived from population-based databases with those in patient cohorts (i.e., community clinics, patient registries, electronic health records). Finally, we excluded studies using LDL-C to diagnose FH as well as those from countries with known founder populations as both were likely to result in a higher pooled frequency.

RESULTS

Study Selection

Our search identified 4153 citations, of which 3574 were unique. After applying our inclusion and exclusion criteria 90 articles progressed to screening at the full-text level, of which 21 articles were included in this review. The flow of included studies is presented in Figure 1.

Characteristics of included studies

Twenty one studies estimating point prevalence of FH were included in this review (Table 1). The majority of these studies were European (n = 9), while others were conducted in North America (n = 4), Asia (n = 2), Australia (n = 3), and Africa (n = 1). Two of the studies pooled data from international cohorts[10,42]. Combined, they represented data from 28 countries across four continents. Studies representing multiple countries included data from coronary artery disease[10] and dyslipidemia cohorts[42]. FH is overexpressed among those with coronary heart disease as well as statin-treated individuals[24]. For these reasons, we elected against pulling country-specific data from these papers. Among all included studies, females comprised between 26.4% and 55.0% of the total sample. Four studies diagnosed FH using DLCN criteria[42–45], three studies used genetic sequencing[46–48], three studies utilized LDL-C measurements[49–51], one study used SBR criteria[7] and one employed MEDPED criteria[6]. Another four included studies reported prevalence estimates using more than one method for comparison [10,11,52,53]. Prevalence estimates reported in individual studies ranged from 0.05% [95% CI: 0.05%, 0.06%] to 5.62% [95% CI: 5.44%, 5.79%]. When evaluated by the EPHPP tool, most studies were rated as being moderate (n = 7) or strong (n = 13) in quality. On EPHPP domains, studies were most likely to receive weak ratings due to a low likelihood of representing the general population, a failure to accounting for missing participant data or adjust for relevant confounders (eTable 7).

Meta-analysis

Overall pooled prevalence

Nineteen estimates were included in the meta-analysis of overall prevalence, representing 2,458,456 unique individuals [6,7,10,42–48,50,51,53–58]. A further two studies reported data from cohorts represented by other

studies within a shorter sampling frame, creating the potential for the overlap of cohorts [11,49]. These estimates were excluded to avoid overweighting a population. The overall random effects pooled prevalence of FH was 0.40% [95% CI: 0.29%, 0.52%] (Figure 2).

Prevalence of FH in adults

Sixteen prevalence estimates were included in the meta-analysis of adult prevalence, representing 2,431,053 unique individuals [6,7,10,42–48,53–57]. The overall random effects pooled prevalence of FH was 0.40% [95% CI: 0.29%, 0.54%](eTable 8).

Prevalence of FH in children

Combining four studies (n = 27,403) which reported FH prevalence estimates in individuals aged under 19 (eTable 9), we calculated a pooled prevalence of 0.36% [95%: 0.28%, 0.45%], with little heterogeneity [I^2 = 13.32%][43,50,51,58].

Variation in prevalence by age

Six studies[7,11,43,49,53,55] reported age-stratified data on the adult prevalence of FH, but only two of these presented data in forms amenable for pooled analysis (Figure 3) [7,53]. All studies showed variation in FH frequency with age, with an increase in prevalence that peaked between ages 60 and 69 and declined thereafter, a trend reflected in our pooled estimates.

Variation in prevalence by sex

Nine studies presented prevalence figures by sex, [7,10,42–44,46,47,52,53] most of which reported similar FH frequencies between men and women. Our pooled prevalence estimates (Figure 4) were comparable between males [0.42%; 95% CI: 0.18%, 0.75%; n = 364,130] and females [0.45%; 95% CI: 0.19%, 0.82%; n = 319,726] [OR: 0.85; 95% CI: 0.0.69, 1.07; n = 639,717].

Variation in prevalence by geographic location

When FH was analyzed by continent (Figure 5), European (7 studies; n = 1,957,002) and Asian studies (1 study; n = 9324) tended to report lower prevalence estimates than our overall pooled prevalence estimate, while North American (3 studies; n = 236,537) and Australasian (2 studies; n= 175,512) studies reported estimates comparable to it. The one study from South Africa (n = 1,612) reported a greater pooled FH prevalence than our pooled estimate; as did studies of international cohorts.

Variation in prevalence by diagnostic criteria

Frequencies from studies in DNA-based analysis subgroup were comparable to the pooled prevalence estimate [0.40%; 95% CI: 0.24%, 0.58%] while DLCN – [0.46%; 95% CI: 0.25%, 0.70%] and LDL-C – based estimates [0.45%; 95% CI: 0.34, 0.57%] tended to report slightly higher frequencies (eFigure 1). Of two studies exclusively using SBR[7] or MEDPED[6] criteria; both reported lower frequencies than our pooled prevalence estimate.

Variation in prevalence by study quality

When stratified by study quality ratings, studies rated strong had a lower estimate of FH prevalence with greater precision [0.33%; 95% CI: 0.24%, 0.43%] than studies rated moderate in quality [0.75%; 95% CI: 0.29%, 1.29%] or low quality [0.37%, 95%CI: 0.12%, 0.74%] (eFigure 2).

Meta-regression analyses

Considerable heterogeneity existed between studies [I^2: 99.34%; 95% CI: 99.24%, 99.44%]. The results of eight meta-regression analyses (Table 2) showed little evidence of an effect of age (p = 0.79), sex (p = 0.17), sample size (p = 0.06), diagnostic criteria (p = 0.23) study setting (p = 0.50), quality (p = 0.82) or year of publication (p = 0.52) on our pooled prevalence estimate. Joint meta-regression tests showed significant differences in prevalence estimates among categories of studies when stratified by geographical location (p = 0.04). Major asymmetry was present in both Begg's funnel plot and the Doi plot (eFigure 3) and the results of Egger's test suggested that publication bias may have been present (p < 0.001)[59]. When we used the trim and fill method to control for

publication bias, nine additional studies were generated with estimates comparable to or lower than our pooled prevalence estimate, bringing the pooled prevalence of FH to 0.20% [95% CI: 0.10%, 0.40%].

Sensitivity analyses

Pooled prevalence estimates were broadly consistent in seven sensitivity analyses (eTable 10). Studies estimating FH prevalence in patient cohorts [0.33%; 95% CI: 0.21%, 0.47%] tended to report lower frequencies than those in large population-based samples [0.45%; 95% CI: 0.26%, 0.68%]. Heterogeneity of these estimates was significant and comparable (>99%)

DISCUSSION

Our meta-analysis of 19 cohort studies including 2,458,456 unique individuals found an FH prevalence of 0.40% in the general population. This suggests that as many as 1 in 250 individuals may be affected by FH [95% CI: 1 in 345, 1 in 192], equating to nearly 30 million people worldwide[60]. This is a higher frequency than observed in prior reports and supports current thinking that FH is underdiagnosed, and thus likely undertreated in the general population [61]. This is further supported by sensitivity analyses in which patient cohort studies were found to report lower prevalence estimates than those using large population databases.

Interestingly, we detected a slightly lower prevalence of FH in those aged 0-19 [1 in 278; 95% CI: 1 in 345, 1 in 222]. Further, FH prevalence tended to increase with age. This trend runs counterintuitively to expectations given that FH is a genetic condition with a high risk of CVD-related mortality – frequency estimates should be comparable in adults and children save for age-related declines in prevalence associated with premature mortality. Our findings may be explained by insufficient dyslipidemia screening in children and adolescents[62–64]. Indeed, follow-up data from the Simon Broome FH registry, following more than 300,000 patients, found that only a quarter of affected patients received diagnoses by middle age, with the highest rates of under-diagnosis among children and adolescents[7]. However, LDL-C levels also rise with age, making it likely for older individuals to be diagnosed using established clinical criteria. It remains possible that the disparity in prevalence may be due to the

inability of population-based studies to account for age-related increases in LDL-C and the reduced sensitivity this confers in detecting FH [65].

Our finding that FH affects males and females equally has important implications. Many cases of FH are diagnosed following the first cardiac event, which has a later onset for women relative to men[27]. This makes it possible that women with FH may go unrecognized for longer. Yet, more women may be expected to qualify for diagnosis using clinical characteristics at later ages, primarily due to the delayed onset of coronary artery disease. Whether delayed FH detection in women relative to men confers poorer clinical outcomes has yet to be formally explored in the literature. However, one of our included studies observed that after age 60, higher proportions of women met criteria for an FH diagnosis, suggesting that many men with FH had died at an earlier age[11]. Identifying sex-related differences in FH presentation may allow for earlier FH diagnosis and represents an important clinical priority. New diagnostic criteria developed through improved use of routinely collected health data may make this possible[66].

We also found lower prevalence reports in Europe relative to regions elsewhere. Thus far, much of the regional variation in FH prevalence has been attributed to the presence of founder populations. Founder effects occur when subpopulations are formed by the immigration of "founder subjects", leading to a higher proportion of individuals who share a mutation in subsequent generations due to genetic drift[13]. Though influenced by a predominance of European studies, our review suggests the potential for variations in FH frequency between countries extending beyond founder effects. This is important given that for many of the world's countries, rates of FH still remain unknown. This includes North America, where studies from the USA comprise the evidence base for ascertaining study prevalence. Cardiovascular disease remains the leading cause of death worldwide [67] and, left untreated, nearly 85% of males and 50% of females with FH are expected to suffer coronary events prior to age 65[27]. Thus, greater efforts should be made to explore region-specific frequencies of FH prevalence and more accurately characterize disease burden. Accurate prevalence estimates, augmented by recent big data approaches

and the introduction of *International Classification of Diseases, 10th Revision* codes for FH should facilitate increased awareness and improved management.

How FH should be identified remains an area of continued debate. A number of organizations have recommended universal lipid screening in childhood as a strategy to identify FH [68–70]. However, a recent report by the US Preventive Services Task Force concluded that there was "inadequate direct evidence on the benefit of screening for familial hypercholesterolemia" [71]. In addition, these programs come with the added risks of potential over-diagnosis, fiscal and non-fiscal health system burden, and adverse psychosocial impacts for children and families[71]. As an alternative, some European countries have developed genetic FH screening strategies. However, such programs are not currently universally accessible nor deemed to be cost-effective [8,21–23]. Yet, DNA-based identification may fail to capture individuals with undiscovered mutations or those with polygenic forms of FH that still demonstrate the clinical phenotype[72]. Finally, the diagnostic accuracy of these programs has been challenged by findings that up to 30% of estimated cases may not be identified in countries with some of the most robust screening programs, due lack of index cases to inform cascade screening [73]. In light of these limitations, the high degree of concordance between our pooled prevalence estimates derived through DLCN and DNA-based analyses are clinically important. Due to a simplified approach – facilitated by the use of readily observable clinic characteristics and biochemical parameters – DLCN criteria may facilitate the more ready identification of patients affected by FH in primary care. Though other clinical criteria may have comparable clinical utility, our study currently provides insufficient evidence in strong support of them. Regardless, improving the identification of FH and mitigating cardiovascular disease and mortality requires a multi-faceted approach involving clinical, biochemical and genetic parameters.

These findings provide new insights into FH prevalence. Yet, they should be interpreted in light of some important limitations. First, despite an extensive search strategy, we included only peer-reviewed English language studies indexed in six online databases and it remains possible that other relevant studies went unpublished or were indexed in other languages, in print repositories or within the grey literature[74]. Second, we did not contact study

authors for additional data or clarifications of their published studies. While this was counterbalanced in part by the use of a tool with high inter-rater agreement for quality assessment[75], agreement levels between reviewers and authors have yet to be explored with the EPHPP tool. Third, while geographical location of our included studies was significantly associated with variance in FH prevalence, our analyses possessed a considerable amount of between-study heterogeneity, the majority of which remains unexplained. This may be attributed to limited power in our meta-regression analyses due to small numbers of observations[38]. In which case, our subgroup analyses provide more credible insight into the sociodemographic variation of FH prevalence though even these are limited by the lack of interaction tests in our subgroup analyses. It is important to note that the high degree of heterogeneity in our meta-analyses does not imply imprecision in our prevalence estimate [38]. Indeed, a key strength of our study is its sample size and the greater power and precision it conferred to our analyses. The heterogeneity between studies are thus more likely reflective of real differences in study populations, designs, and outcome measurements [36]. This heterogeneity was anticipated and accommodated for through random effects meta-analysis.

CONCLUSIONS

Our systematic review found that FH currently affects 1 in 250 people in the adult population. While FH affects males and females equally, regional and age specific variations exist in FH frequency. With the range of treatment options available for this condition increased, particularly with the recent advent of PCKS9 inhibitors, greater efforts should be made to identify individuals who could stand to benefit from therapy.

ACKNOWLEDGEMENTS

The authors would like to thank staff at the Institute for Clinical Evaluative Sciences for logistical support of this systematic review.

AUTHOR CONTRIBUTIONS

LA – conceived and designed the study; conducted the study; provided methodological support; conducted the analyses; interpreted the results; wrote, read and edited the manuscript.

JG – interpreted the results; read and edited the manuscript.

SS – conducted the study; read and edited the manuscript.

RR – conducted the study; read and edited the manuscript.

JA – conducted the study; read and edited the manuscript.

AC – conceived and designed the study; provided methodological support; and read and edited the manuscript.

JT – conceived and designed this study; provided methodological support; interpreted the results; guided the analysis; and read and edited the manuscript.

COMPETING INTERESTS

The authors have no competing interests to declare.

DATA SHARING AGREEMENT

Additional data is presented in supplemental files.

REFERENCES

1 Goldstein JL, Schrott HG, Hazzard WR, *et al.* Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest* 1973;**52**:1544–68. doi:10.1172/JCI107332

2 Slack J. Inheritance of familial hypercholesterolemia. *Atheroscler Rev* 1979;**5**:35–66.

3 Heiberg A, Berg K are. The inheritance of hyperipoproteinaemia with xanthomatosis: A study of 132 kindreds. *Clin Genet* 1976;**9**:203–233.

4 Andersen GE, Lous P, Friis-Hansen B. SCREENING FOR HYPERLIPOPROTEINEMIA IN 10 000 DANISH NEWBORNS Follow-up Studies in 522 Children with Elevated Cord Serum VLDL-LDL-Cholesterol. *Acta Paediatr* 1979;**68**:541–5. doi:10.1111/j.1651-2227.1979.tb05052.x

5 Mabuchi H, Haba T, Ueda K, *et al.* Serum lipids and coronary heart disease in heterozygous familial hypercholesterolemia in the Hokuriku district of Japan. *Atherosclerosis* 1977;**28**:417–23. doi:10.1016/0021-9150(77)90068-5

6 Kalina Á, Császár A, Czeizel AE, *et al.* Frequency of the R3500Q mutation of the apolipoprotein B-100 gene in a sample screened clinically for familial hypercholesterolemia in Hungary. *Atherosclerosis* 2001;**154**:247–51. doi:10.1016/S0021-9150(00)00648-1

7 Neil HA, Hammond T, Huxley R, *et al.* Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. *BMJ* 2000;**321**:148.

8 Marks D, Wonderling D, Thorogood M, *et al.* Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. *BMJ* 2002;**324**:1303. doi:10.1136/bmj.324.7349.1303

9 Trikalinos TA, Salanti G, Khoury MJ, *et al.* Impact of Violations and Deviations in Hardy-Weinberg Equilibrium on Postulated Gene-Disease Associations. *Am J Epidemiol* 2006;**163**:300–9. doi:10.1093/aje/kwj046

10 Khera AV, Won H-H, Peloso GM, *et al.* Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. *J Am Coll Cardiol* 2016;**67**:2578–89. doi:10.1016/j.jacc.2016.03.520

11 Benn M, Watts GF, Tybjaerg-Hansen A, *et al.* Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease, and Cholesterol-Lowering Medication. *J Clin Endocrinol Metab* 2012;**97**:3956–64. doi:10.1210/jc.2012-1563

12 Goldberg AC, Gidding SS. Knowing the Prevalence of Familial Hypercholesterolemia Matters. *Circulation* 2016;**133**:1054–1057.

13 Austin MA, Hutter CM, Zimmern RL, *et al.* Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am J Epidemiol* 2004;**160**:407–20. doi:10.1093/aje/kwh236

14 Patterson D, Slack J. Lipid abnormalities in male and female survivors of myocardial infarction and their first-degree relatives. *Lancet Lond Engl* 1972;**1**:393–9.

15 Moorjani S, Roy M, Gagne C, *et al.* Homozygous familial hypercholesterolemia among French Canadians in Québec province. *Arterioscler Thromb Vasc Biol* 1989;**9**:211–216.

16 Slimane MN, Pousse H, Maatoug F, *et al.* Phenotypic expression of familial hypercholesterolaemia in central and southern Tunisia. *Atherosclerosis* 1993;**104**:153–158.

17 Seftel HC, Baker SG, Sandler MP, *et al.* A host of hypercholesterolaemic homozygotes in South Africa. *Br Med J* 1980;**281**:633–636.

18 Seftel HC, Baker SG, Jenkins T, *et al.* Prevalence of familial hypercholesterolemia in Johannesburg Jews. *Am J Med Genet* 1989;**34**:545–547.

19 Rubinsztein DC, Van der Westhuyzen DR, Coetzee GA, *et al.* Monogenic primary hypercholesterolaemia in South Africa. *SOUTH Afr Med J-CAPE TOWN-Med Assoc SOUTH Afr* 1994;**84**:339–339.

20 Hegele RA. Improving the Monitoring and Care of Patients With Familial Hypercholesterolemia∗. *J Am Coll Cardiol* 2016;**67**:1286–8. doi:10.1016/j.jacc.2016.01.041

21 Oliva J, López-Bastida J, Moreno SG, *et al.* [Cost-effectiveness analysis of a genetic screening program in the close relatives of Spanish patients with familial hypercholesterolemia]. *Rev Esp Cardiol* 2009;**62**:57–65.

22 Wonderling D, Umans-Eckenhausen MAW, Marks D, *et al.* Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. *Semin Vasc Med* 2004;**4**:97–104. doi:10.1055/s-2004-822992

23 Chen CX, Hay JW. Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. *Int J Cardiol* 2015;**181**:417–24. doi:10.1016/j.ijcard.2014.12.070

24 Najam O, Ray KK. Familial Hypercholesterolemia: a Review of the Natural History, Diagnosis, and Management. *Cardiol Ther* 2015;**4**:25–38. doi:10.1007/s40119-015-0037-z

25 Sharifi M, Rakhit RD, Humphries SE, *et al.* Cardiovascular risk stratification in familial hypercholesterolaemia. *Heart* 2016;:heartjnl-2015-308845. doi:10.1136/heartjnl-2015-308845

26 Versmissen J, Oosterveer DM, Yazdanpanah M, *et al.* Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008;**337**:a2423.

27 Civeira F, International Panel on Management of Familial Hypercholesterolemia. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2004;**173**:55–68. doi:10.1016/j.atherosclerosis.2003.11.010

28 Knowles JW, Howard WB, Karayan L, *et al.* Access to Nonstatin Lipid-Lowering Therapies in Patients at High Risk of Atherosclerotic Cardiovascular Disease. *Circulation* 2017;**135**:2204–6. doi:10.1161/CIRCULATIONAHA.117.027705

29 Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. *Science* 1996;**274**:740–3.

30 Austin MA, Hutter CM, Zimmern RL, *et al.* Familial hypercholesterolemia and coronary heart disease: a HuGE association review. *Am J Epidemiol* 2004;**160**:421–9. doi:10.1093/aje/kwh237

31 Hutter CM, Austin MA, Humphries SE. Familial hypercholesterolemia, peripheral arterial disease, and stroke: a HuGE minireview. *Am J Epidemiol* 2004;**160**:430–5. doi:10.1093/aje/kwh238

32 Wong B, Kruse G, Kutikova L, *et al.* Cardiovascular Disease Risk Associated With Familial Hypercholesterolemia: A Systematic Review of the Literature. *Clin Ther* 2016;**38**:1696–709. doi:10.1016/j.clinthera.2016.05.006

33 Mundal L, Retterstl K. A systematic review of current studies in patients with familial hypercholesterolemia by use of national familial hypercholesterolemia registries: *Curr Opin Lipidol* 2016;**27**:388–97. doi:10.1097/MOL.0000000000000300

34 Henderson R, O'Kane M, McGilligan V, *et al.* The genetics and screening of familial hypercholesterolaemia. *J Biomed Sci* 2016;**23**. doi:10.1186/s12929-016-0256-1

35 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–12.

36 Barendregt JJ, Doi SA, Lee YY, *et al.* Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;**67**:974–978.

37 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88. doi:10.1016/0197-2456(86)90046-2

38 Borenstein M, Hedges LV, Higgins JPT, *et al.* Identifying and Quantifying Heterogeneity. In: *Introduction to Meta-Analysis*. John Wiley & Sons, Ltd 2009. 107–25.http://onlinelibrary.wiley.com/doi/10.1002/9780470743386.ch16/summary (accessed 7 Aug 2016).

39 Egger M, Smith GD, Schneider M, *et al.* Bias in Meta-Analysis Detected by a Simple, Graphical Test. *ResearchGate* 1997;**315**:629--634.

40 Doi SAR, Williams GM, editors. *Methods of Clinical Epidemiology*. Berlin, Heidelberg: : Springer Berlin Heidelberg 2013. http://link.springer.com/10.1007/978-3-642-37131-8 (accessed 7 Aug 2016).

41 Duval S, Tweedie R. Trim and Fill: A Simple Funnel-Plot–Based Method of Testing and Adjusting for Publication Bias in Meta-Analysis. *Biometrics* 2000;**56**:455–63. doi:10.1111/j.0006-341X.2000.00455.x

42 Catapano AL, Lautsch D, Tokgözoglu L, *et al.* Prevalence of potential familial hypercholesteremia (FH) in 54,811 statin-treated patients in clinical practice. *Atherosclerosis* 2016;**252**:1–8. doi:10.1016/j.atherosclerosis.2016.07.007

43 de Ferranti SD, Rodday AM, Mendelson MM, *et al.* Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation* 2016;**133**:1067–72. doi:10.1161/CIRCULATIONAHA.115.018791

44 Pajak A, Szafraniec K, Polak M, *et al.* Prevalence of familial hypercholesterolemia: a meta-analysis of six large, observational, population-based studies in Poland. *Arch Med Sci AMS* 2016;**12**:687–96. doi:10.5114/aoms.2016.59700

45 Watts GF, Shaw JE, Pang J, *et al.* Prevalence and treatment of familial hypercholesterolaemia in Australian communities. *Int J Cardiol* 2015;**185**:69–71. doi:10.1016/j.ijcard.2015.03.027

46 Lahtinen AM, Havulinna AS, Jula A, *et al.* Prevalence and clinical correlates of familial hypercholesterolemia founder mutations in the general population. *Atherosclerosis* 2015;**238**:64–9. doi:10.1016/j.atherosclerosis.2014.11.015

47 Steyn K, Goldberg YP, Kotze MJ, *et al.* Estimation of the prevalence of familial hypercholesterolaemia in a rural Afrikaner community by direct screening for three Afrikaner founder low density lipoprotein receptor gene mutations. *Hum Genet* 1996;**98**:479–84.

48 Vuorio AF, Turtola H, Piilahti KM, *et al.* Familial hypercholesterolemia in the Finnish north Karelia. A molecular, clinical, and genealogical study. *Arterioscler Thromb Vasc Biol* 1997;**17**:3127–38.

49 Perak AM, Ning H, de Ferranti SD, *et al.* Long-Term Risk of Atherosclerotic Cardiovascular Disease in US Adults With the Familial Hypercholesterolemia Phenotype. *Circulation* 2016;**134**:9–19. doi:10.1161/CIRCULATIONAHA.116.022335

50 Yang S, Hwang JS, Park HK, *et al.* Serum lipid concentrations, prevalence of dyslipidemia, and percentage eligible for pharmacological treatment of Korean children and adolescents; data from the Korea National Health and Nutrition Examination Survey IV (2007-2009). *PloS One* 2012;**7**:e49253. doi:10.1371/journal.pone.0049253

51 Pang J, Martin AC, Mori TA, *et al.* Prevalence of Familial Hypercholesterolemia in Adolescents: Potential Value of Universal Screening? *J Pediatr* 2016;**170**:315–6. doi:10.1016/j.jpeds.2015.11.019

52 Benn M, Watts GF, Tybjærg-Hansen A, *et al.* Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. *Eur Heart J* 2016;**37**:1384–94. doi:10.1093/eurheartj/ehw028

53 Shi Z, Yuan B, Zhao D, *et al.* Familial hypercholesterolemia in China: prevalence and evidence of underdetection and undertreatment in a community population. *Int J Cardiol* 2014;**174**:834–6. doi:10.1016/j.ijcard.2014.04.165

54 Abul-Husn NS, Manickam K, Jones LK, *et al.* Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science* 2016;**354**. doi:10.1126/science.aaf7000

55 Guglielmi V, Bellia A, Pecchioli S, *et al.* What is the actual epidemiology of familial hypercholesterolemia in Italy? Evidence from a National Primary Care Database. *Int J Cardiol* 2016;**223**:701–5. doi:10.1016/j.ijcard.2016.08.269

56 Safarova MS, Liu H, Kullo IJ. Rapid identification of familial hypercholesterolemia from electronic health records: The SEARCH study. *J Clin Lipidol* 2016;**10**:1230–9. doi:10.1016/j.jacl.2016.08.001

57 Vickery AW, Ryan J, Pang J, *et al.* Increasing the Detection of FH Using General Practice Electronic Databases. *Heart Lung Circ* Published Online First: 15 November 2016. doi:10.1016/j.hlc.2016.09.012

58 Wald DS, Bestwick JP, Morris JK, *et al.* Child–Parent Familial Hypercholesterolemia Screening in Primary Care. *N Engl J Med* 2016;**375**:1628–37. doi:10.1056/NEJMoa1602777

59 Sterne JA, Bradburn MJ, Egger M. Meta–Analysis in Stata™. *Syst Rev Health Care Meta-Anal Context Second Ed* 2008;:347–369.

60 DeSA UN. World population prospects: the 2015 revision. *Popul Div Dep Econ Soc Aff U N Secr N Y* 2015.

61 Nordestgaard BG, Chapman MJ, Humphries SE, *et al.* Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J* 2013;**34**:3478–90. doi:10.1093/eurheartj/eht273

62 Henneman L, McBride CM, Cornel MC, *et al.* Screening for Familial Hypercholesterolemia in Children: What Can We Learn From Adult Screening Programs? *Healthcare* 2015;**3**:1018–30. doi:10.3390/healthcare3041018

63 Hopcroft KA. Child-parent screening may have adverse psychological effects. *BMJ* 2007;**335**:683–683. doi:10.1136/bmj.39353.368553.BE

64 Calonge N, Guirguis-Blake J. Screening for familial hypercholesterolaemia. *BMJ* 2007;**335**:573–4. doi:10.1136/bmj.39335.668646.80

65 Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. *BMJ* 2007;**335**:599. doi:10.1136/bmj.39300.616076.55

66 Weng SF, Kai J, Neil HA, *et al.* Improving identification of familial hypercholesterolaemia in primary care: Derivation and validation of the familial hypercholesterolaemia case ascertainment tool (FAMCAT). *Atherosclerosis* 2015;**238**:336–43. doi:10.1016/j.atherosclerosis.2014.12.034

67 WHO | World Health Statistics 2016: Monitoring health for the SDGs. WHO. http://www.who.int/gho/publications/world_health_statistics/2016/en/ (accessed 9 Sep 2016).

68 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 2011;**128 Suppl 5**:S213-256. doi:10.1542/peds.2009-2107C

69 Jacobson TA, Maki KC, Orringer CE, *et al.* National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. *J Clin Lipidol* 2015;**9**:S1–122.e1. doi:10.1016/j.jacl.2015.09.002

70 Gidding SS, Champagne MA, de Ferranti SD, *et al.* The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. *Circulation* 2015;**132**:2167–92. doi:10.1161/CIR.0000000000000297

71 US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, *et al.* Screening for Lipid Disorders in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016;**316**:625–33. doi:10.1001/jama.2016.9852

72 Urbina EM, de Ferranti SD. Lipid Screening in Children and Adolescents. *JAMA* 2016;**316**:589–91. doi:10.1001/jama.2016.9671

73 Cuchel M, Bruckert E, Ginsberg HN, *et al.* Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014;**35**:2146–57. doi:10.1093/eurheartj/ehu274

74 Cochrane Handbook for Systematic Reviews of Interventions. http://handbook.cochrane.org/ (accessed 15 Mar 2016).

75 Armijo-Olivo S. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. ;**18**:12–8.

FIGURE LEGENDS

Figure 1 | Flow of studies included in systematic review of heterozygous familial hypercholesterolemia prevalence

Figure 2 | Forest plot of overall pooled prevalence (%) of heterozygous familial hypercholesterolemia. I^2 – between-study heterogeneity; LCL – lower confidence limit; POP – population; PREV – prevalence; UCL – upper confidence limit; WGHT – weight under the random-effects model. Note: prevalence estimates were derived using the double-arcsine method, back-transformed and expressed as percentages for ease of interpretation.

Figure 4 | (A) Forest plot of pooled prevalence (%) of heterozygous familial hypercholesterolemia (FH) in the male population. (B) Forest plot of pooled prevalence (%) of FH in the female adult population. (C) Forest plot of pooled odds ratio (OR) of male:female FH prevalence. I^2 – between-study heterogeneity; LCL – lower confidence limit; POP – population; PREV – prevalence; UCL – upper confidence limit; WGHT – weight under the random-effects model. Note: prevalence estimates were derived using the double-arcsine method, back-transformed and expressed as percentages for ease of interpretation.

Figure 5 | Forest plot of overall pooled prevalence (%) of heterozygous familial hypercholesterolemia stratified by population geography. I^2 – between-study heterogeneity; LCL – lower confidence limit; POP – population; PREV – prevalence; UCL – upper confidence limit; WGHT – weight under the random-effects model. Note: prevalence estimates were derived using the double-arcsine method, back-transformed and expressed as percentages for ease of interpretation.

Table 1 | Characteristics of studies included in systematic review of FH prevalence

Study author (publication year)	Country	Data source(s)	Enrollment period (years)	Diagnostic criteria	Sample size	Age (years)	Female, N (%)	FH cases, N	Prevalence estimate (95% CI)‡	Study quality
Studies reporting on FH prevalence in adults										
Abdul-Husn (2016) [54]	USA	Geisinger Health System EHR	NR	DNA	50726	18+	30334(59.8%)	229	0.45% (0.40%, 0.51%)	★★★
Benn (2012) [11]	Denmark	Copenhagen General Population Study	2003+	DLCN	69016	20-100	37959 (55.0%)	502	0.73% (0.67%, 0.79%)	★★★
				DNA	60710			20	0.03% (0.02%, 0.04%)	
				SB	69016			2830	4.10% (3.95%, 4.25%)	
				MEDPED	69016			552	0.80% (0.73%, 0.87%)	
Benn (2016) [52]	Denmark	Copenhagen General Population Study	2003+	DLCN	98098	20-100	53958 (55.0%)	341	0.35% (0.31%, 0.39%)	★★★
				DNA	98098			174	0.18% (0.15%, 0.20%)	
				SB	98000			3905	3.98% (3.86%, 4.11%)	
				MEDPED	93398			789	0.84% (0.79%, 0.90%)	
Catapano (2016) [42]	Multinational study†	DYSIS	2008-2013	DLCN	54811	45+	24884 (45.5%)	656	1.20% (1.11%, 1.29%)	★★
de Ferranti (2016) [43]	USA	NHANES	1999-2012	DLCN	36949	20+	18991 (51.4%)	146	0.40% (0.33%, 0.46%)	★★★
Guglielmi (2016) [55]	Italy	Health Longitudinal Patient Database	NR	DLCN	1135000	15+	NR	2043	0.18% (0.17%, 0.19%)	★★★
Kalina (2001) [6]	Hungary	Family doctors' registers	1996 – 1998	MEDPED	21000	NR	NR	39	0.19% (0.13%, 0.25%)	★★★
Khera (2016) [10]	Multinational study††	MiGen Consortium CHARGE Consortium	NR	DNA	20485	NR	3696 (26.2%)	24	0.12% (0.07%, 0.17%)	★★
				LDL-C				1386	6.77% (6.43%, 7.11%)	
Lahtinen (2015) [46]	Finland	FINRISK Cohort	1992, 1997, 2002	DNA	28465	25-74	14501 (50.9%)	35	0.12% (0.09%, 0.17%)	★★★
		Health 2000 Cohort	2000-2001			30+				
Neil (2000) [7]	United Kingdom	Simon Broome Register	1980-1999	SB	456550	20+	231796 (50.8%)	320	0.07% (0.06%, 0.08%)	★★
Pajak (2016) [44]	Poland	POL-MONICA Krakow	1983-1984 1987-1988 1992-1993	DLCN	37889	35-64	NR	153	0.40% (0.34%, 0.47%)	★★★
		POL-MONICA Warszawa	1984 1988 1993			35-64				
		WOBASZ	2003-2004			20-74				
		Pilot HAPIEE	2001-2002			45-64				
		HAPIEE	2003-2005			45-70				
		NATPOL 2011	2011			20-74				
Perak (2016) [49]	USA	FHS	1948	LDL-C	68565	30-62	19693 (41.0%)	3850	5.62% (5.44%, 5.79%)	★★
		FOS	1971			5-70				
		CARDIA	1985-1986			18-30				
		ARIC	1987-1989			45-64				
		NHANES III – Mortality	1988-1994			17-90				

		CHS	1989-1990			65+				
Safarova (2016) [56]	USA	Mayo ECH	1993 – 2014	DLCN	131000	18+	77290(59.0%)	423	0.32% (0.29%, 0.35%)	★★★
Shi (2014) [53]	China	Jiangsu Nutrition Study	2007	DLCN	9324	20+	5356 (57.4%)	26	0.28% (0.18%, 0.40%)	★★★
				LDL-C	9280			44	0.47% (0.34%, 0.62%)	
Steyn (1996) [47]	South Africa	Random sample from south-western Cape	NR	DNA	1612	15-64	809 (50.2%)	18	1.12% (0.66%, 1.69%)	★★
Vickery (2016) [57]	Australia	General practitioners' offices in Perth	NR	DLCN	157290	18-70	NR	782	0.050% (0.46%, 0.53%)	★★★
Vuorio (1997) [48]	Finland	Outpatient lipid clinic of North Karelia, Joensuu	1992-1996	DNA	180000	NR	NR	407	0.23% (0.20%, 0.25%)	★★★
Watts (2015) [45]	Australia	AusDiab	1999-2000	DLCN	18222	NR	NR	81	0.44% (0.35%, 0.55%)	★★
		Baker IDI	2005-2012							
Studies reporting on FH prevalence in children										
de Ferranti (2016) [43]	USA	NHANES	1999-2012	DLCN	13343	12-19	NR	146	0.42% (0.32%, 0.54%)	★★★
Pang (2016) [51]	Australia	Western Australia Pregnancy Cohort Study	1989-1991	LDL-C	2868	14/17	770 (48.1%)	6	0.37% (0.12%, 0.74%)	★
Wald (2016) [58]	United Kingdom	General Medical Practices	2012-2015	DNA	10095	12.4-13.3 months	4882 (48.4%)	28	0.28% (0.18%, 0.39%)	★★★
Yang (2012) [50]	Korea	KNHANES IV	2007-2009	LDL-C	2363	10-18	1118 (47.3%)	9	0.38% (0.17%, 0.68%)	★★

Abbreviations

ARIC – Atherosclerotic Risk in Communities Study; ATVB – Atherosclerosis, Thrombosis, and Vascular Biology Italian Study; AusDiab – Australian Diabetes, Obesity and Lifestyle Study; Baker IDI - Baker IDI Heart and Diabetes Institute; CARDIA – Coronary Artery Risk Development in Young Adults Study; CHARGE – Cohorts for Heart and Aging Research in Genomic Epidemiology; CHS – Cardiovascular Health Study; DYSIS – Dyslipidemia International Study; ECH – Employee & Community Health System; EHR – Electronic Health Records; EOMI – Exome Sequencing Project (Early-Onset Myocardial Infarction); ERFS – Erasmus Rucphen Family Study; FHS – Framingham Heart Study; FOS – Framingham Offspring Study; JHS – Jackson Heart Study; KNHANES – Korean National Health and Nutrition Examination Survey; Munich-MI – Munich Myocardial Infarction Study; NHANES III – National Health and Nutrition Examination Survey III; OHS – Ottawa Heart Study; PROMIS – Pakistan Risk of Myocardial Infarction Study; RBS – Rotterdam Baseline Study

Legend

★ - weak, ★★ - moderate, ★★★ - strong

† - Austria, Belgium, Baltic states, Canada, China, Germany, Denmark, Egypt, France, Greece, United Arab Emirates, Israel, Ireland, Italy, Lebanon/Jordan, Netherlands, Norway, Portugal, Russia, Saudi, Slovakia, Slovenia, South Africa, Spain, Sweden, United Kingdom

†† - MiGen (ATVB, EOMI, JHS, Munich-MI, OHS, PROCARDIS, PROMIS): Canada, Germany, Italy, Pakistan, USA; CHARGE (ARIC, CHS, FHS, RBS, ERFS): Denmark, Netherlands, USA

‡ - 95% confidence interval (CI) not presented in articles but calculated from sample size and prevalence estimate

Table 2 | Meta-regression analyses for pooled estimate of familial hypercholesterolemia prevalence

Covariate	Observations	Coefficient	95% CI	P	Adjusted R^2 (%)	I^2 Residual (%)
Age	11	8.26×10^{-3}	-0.06, 0.08	0.79	-10.29	99.65
Diagnostic Criteria	15	NA	NA	0.23	12.77	99.45
Geographical Location*	19	NA	NA	0.04	75.92	99.00
Sex	13	-4.07	-10.18, 2.00	0.17	8.99	99.67
Sample size	19	-1.21×10^{-6}	-2.47×10^{-6}, 3.66×10^{-8}	0.06	4.20	100.00
Study quality	19	0.02	-0.16, 0.20	0.82	-5.64	99.54
Study setting	19	0.24	-0.49, 0.96	0.50	-2.65	99.28
Year of Publication	19	0.16	-0.04, 0.07	0.52	-2.54	99.41

* - $P < 0.05$; ** - $P < 0.001$
NA – not applicable
Observations – number of studies with observations included in the meta-regression model
Adjusted R^2 – proportion of between-study variance explained with Knapp-Hartung modification
I^2 residual – percent residual variation due to heterogeneity

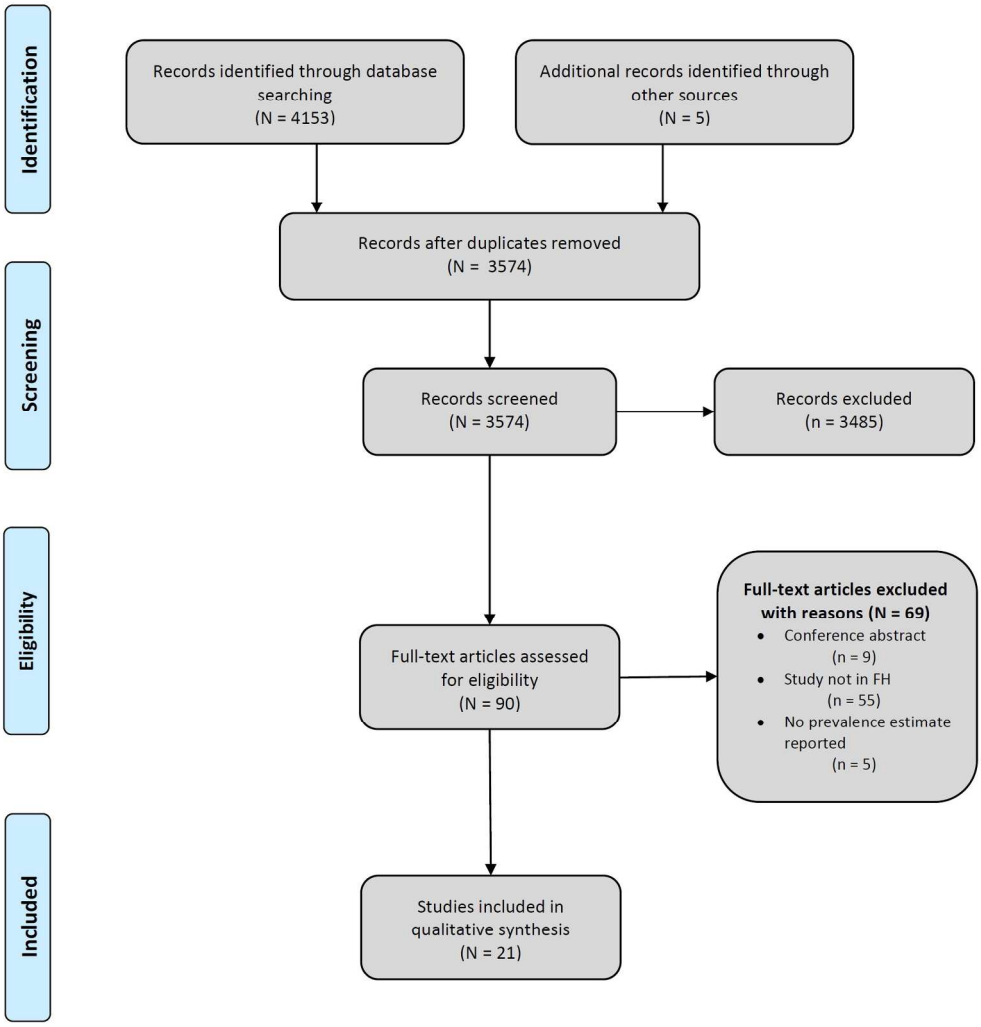


Figure 1 | Flow of studies included in systematic review of heterozygous familial hypercholesterolemia prevalence

222x230mm (240 x 240 DPI)

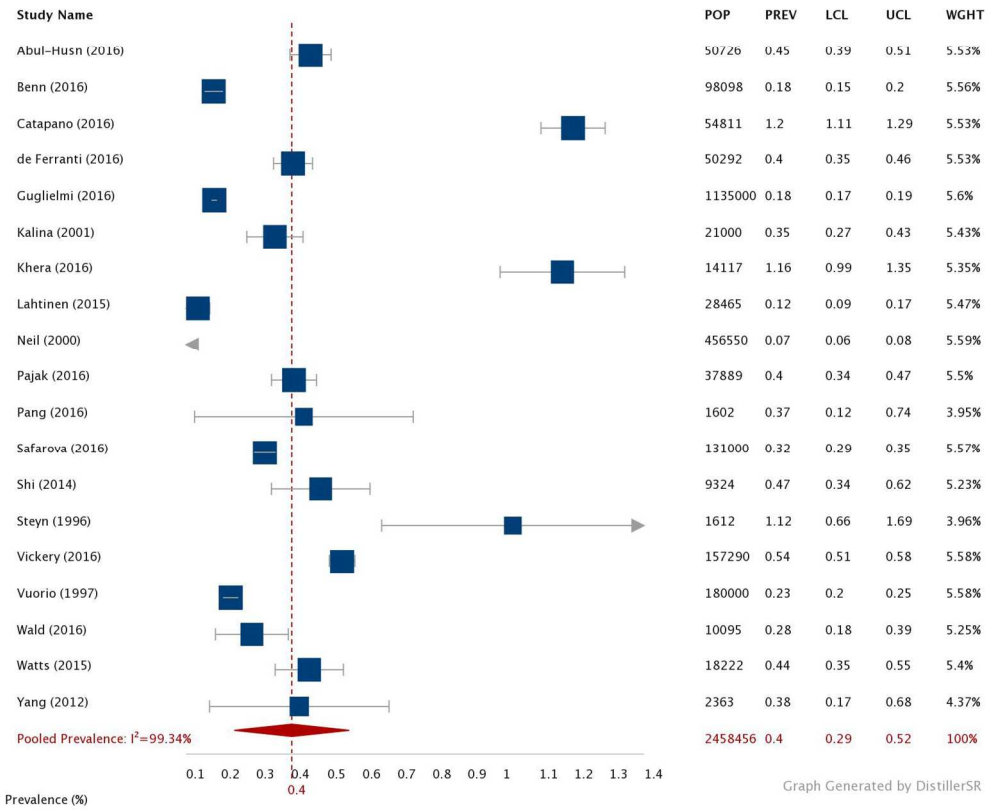
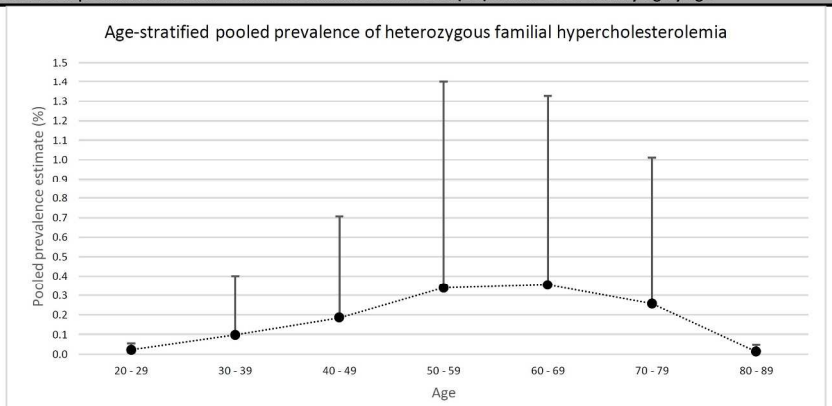


Figure 2 | Forest plot of overall pooled prevalence (%) of heterozygous familial hypercholesterolemia. I2 – between-study heterogeneity; LCL – lower confidence limit; POP – population; PREV – prevalence; UCL – upper confidence limit; WGHT – weight under the random-effects model. Note: prevalence estimates were derived using the double-arcsine method, back-transformed and expressed as percentages for ease of interpretation.

584x529mm (72 x 72 DPI)

Figure 3 | Pooled FH prevalence estimates and 95% Confidence Intervals (CIs) from studies stratifying by age



Ages	Number of studies	Population	Prevalence (%)	LCL (%)	UCL (%)	I^2 (%)
20-29	2	89,583	0.02	0.01	0.03	0.00
30-39	2	103,927	0.10	0.00	0.30	78.23
40-49	2	83,879	0.19	0.00	0.52	88.54
50-59	2	73,506	0.34	0.00	1.06	96.11
60-69	2	52,615	0.35	0.00	0.97	92.31
70-79	2	40,664	0.26	0.00	0.76	87.74
80-89	1	21,700	0.01	0.00	0.04	0.00

Figure 3 presents age-stratified pooled point estimates of FH prevalence. Error bars are representative of 95% CIs for each pooled estimate. Lower CIs are omitted; all cross 0%. I^2 – between-study heterogeneity; LCL – lower confidence limit; P – significance value for Cochran's Q statistic; UCL – upper confidence limit

301x185mm (240 x 240 DPI)

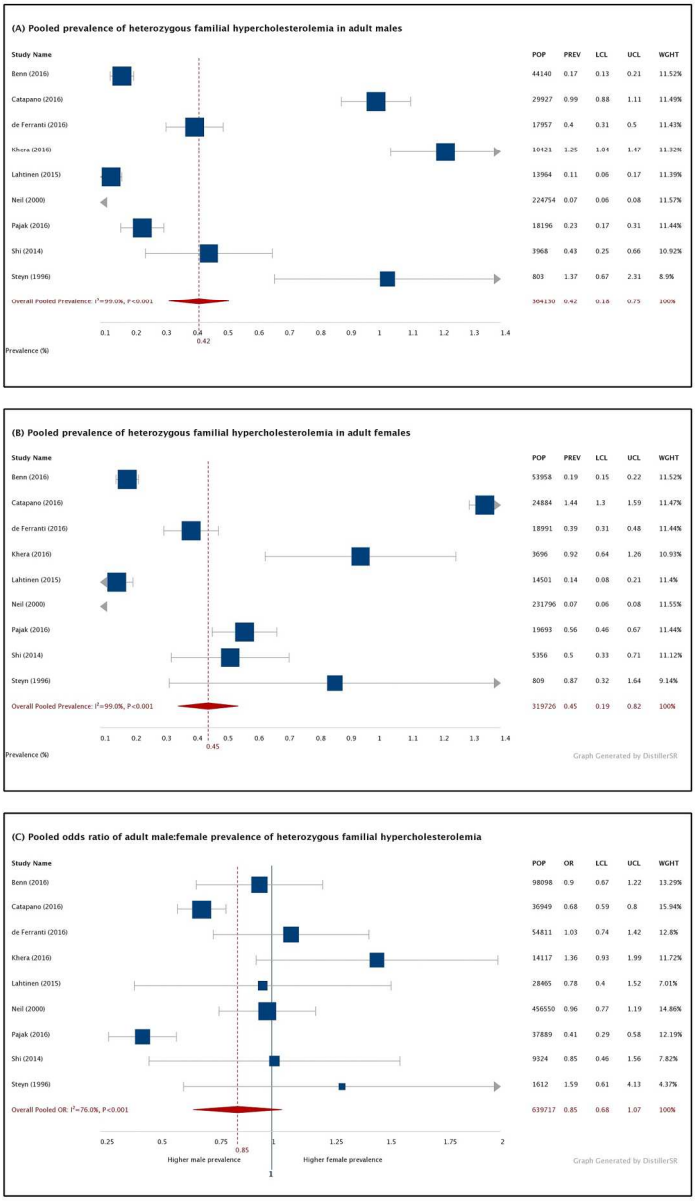


Figure 4 | (A) Forest plot of pooled prevalence (%) of heterozygous familial hypercholesterolemia (FH) in the male population. (B) Forest plot of pooled prevalence (%) of FH in the female adult population. (C) Forest plot of pooled odds ratio (OR) of male:female FH prevalence.I2 – between-study heterogeneity; LCL – lower confidence limit; POP – population; PREV – prevalence; UCL – upper confidence limit; WGHT – weight under the random-effects model. Note: prevalence estimates were derived using the double-arcsine method, back-transformed and expressed as percentages for ease of interpretation.

150x259mm (240 x 240 DPI)

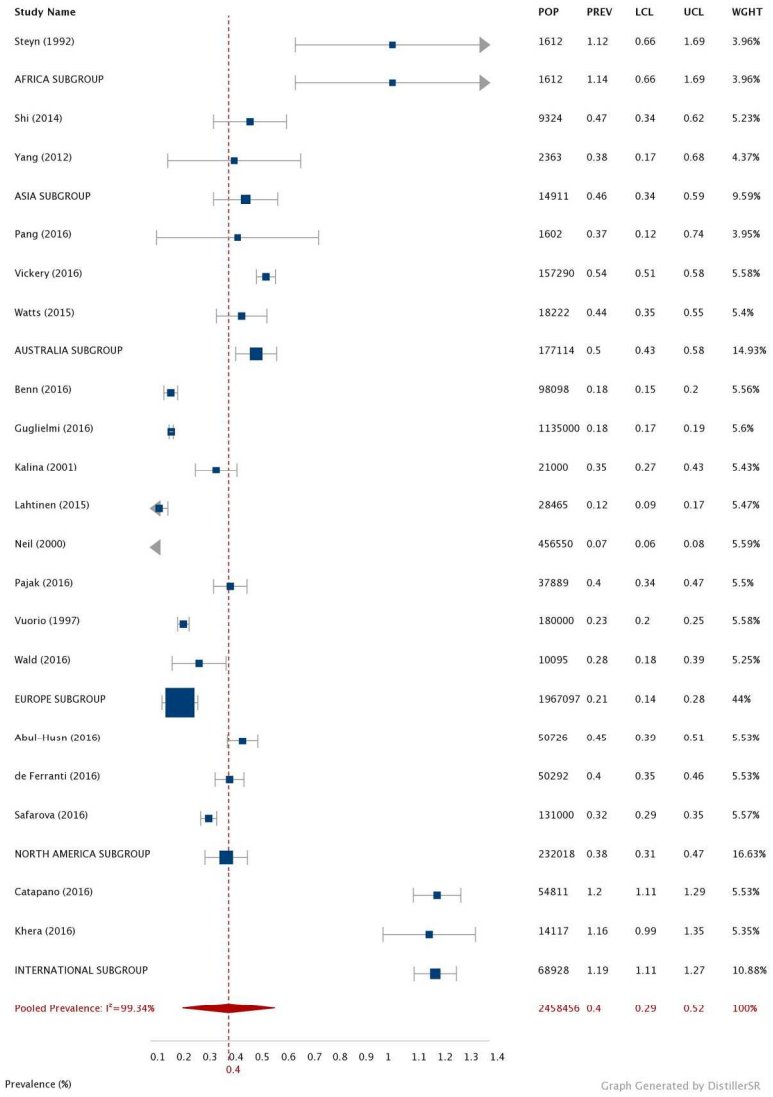


Figure 5 | Forest plot of overall pooled prevalence (%) of heterozygous familial hypercholesterolemia stratified by population geography. I2 – between-study heterogeneity; LCL – lower confidence limit; POP – population; PREV – prevalence; UCL – upper confidence limit; WGHT – weight under the random-effects model. Note: prevalence estimates were derived using the double-arcsine method, back-transformed and expressed as percentages for ease of interpretation.

564x874mm (72 x 72 DPI)

SUPPLEMENTARY APPENDIX

Estimating the prevalence of heterozygous familial hypercholesterolemia: a systematic review and meta-analysis

Leo E. Akioyamen[1,2], BScN MD(c); Jacques Genest[3,4], MD; Shubham D. Shan[1,2], HBSc MD(c); Rachel L. Reel[1], BSc; Jordan M. Albaum[1], MSc MD(c); Anna Chu[2] MHSc; Jack V. Tu[1,2,5] MD PhD

1 – Faculty of Medicine, University of Toronto, Toronto ON, M5S 1A8, Canada
2 – Institute for Clinical Evaluative Sciences, Toronto ON, M4N 3M5, Canada
3 – Faculty of Medicine, McGill University, Montreal QC, H3G 2M1, Canada
4 – McGill University Health Centre, Royal Victoria Hospital, Montreal QC, H3A 1A1, Canada
5 – Schulich Heart Centre, Sunnybrook Health Sciences Centre, Toronto ON, M4N 3M5, Canada

eTable 1 | Search strategy for Medline

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1 exp Hyperlipoproteinemia Type II/ (5647)

2 ("familial hypercholesterolemia" or "familial hypercholesterolaemia").mp. (5157)

3 exp Coronary Disease/ or exp Atherosclerosis/ (224905)

4 exp Mortality/ or exp Mortality, Premature/ (314243)

5 exp Myocardial Infarction/ (156095)

6 exp Stroke/ (102093)

7 exp Heart Failure/ (98464)

8 exp Peripheral Vascular Diseases/ (48037)

9 exp Myocardial Ischemia/ (383424)

10 exp Cardiovascular Diseases/ (2068438)

11 exp Risk/ or exp Risk Factors/ or exp Prevalence/ or exp Incidence/ or exp Prognosis/ (2274061)

12 (prevalence or "risk factors" or incidence or prevalence or prognosis).mp. (2177998)

13 ('familial hypercholesterolemia'.mp. or exp Hyperlipoproteinemia Type II/) and ('systematic review' or 'meta-analysis').mp. (51)

14 1 or 2 (7403)

15 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (2314576)

16 11 or 12 (3062771)

17 14 and 15 and 16 (942)

18 13 or 17 (985)

19 limit 18 to (human and english language and yr="1990 -Current") (724)

****

eTable 2 | Detailed inclusion/exclusion criteria for systematic review of FH prevalence

1. **FULL-TEXT peer-reviewed publication?**
   - Yes (**include**)
   - No - e.g., conference abstract/proceeding (exclude)
   - Can't decide (**include**)

2. **Live HUMAN subjects or study participants?**
   - Yes (**include**)
   - No (exclude)
   - Can't decide (**include**)

3. **Is the study in HETEROZYGOUS familial hypercholesterolemia?**
   - Yes (**include**)
   - No (exclude)
   - Can't decide (**include**)

4. **AGEs of subjects or study participants:**
   - Adults 18 years and over (**include**)
   - Children / Adolescents (**include** – separate)
   - Can't decide (**include**)

5. **TYPE of study reported in this article:**
   - Report of a cohort/registry (**include**)
   - Other observational studies (e.g. Case Control, Cross-Sectional, Case Report/Series, Survey) (**include**)
   - Meta-analyses/systematic reviews/health technology assessments (exclude – separate)
   - Findings from a controlled clinical trial (exclude – separate)
   - Protocol of methods for a controlled clinical trial (exclude)
   - Practice/treatment guideline (exclude)
   - Academic/Narrative Review, Comment, Editorial, Letter, Note, Patient Handout, Study Design Description (exclude)
   - Can't decide (**include**)

6. **Is this study in ENGLISH?**
   - Yes (**include**)
   - No (exclude)
   - Can't decide (**include**)

7. **Does the study report disease PREVALENCE in the subjects or study participants?**
   - Yes (**include**)
   - No (exclude)
   - Can't decide (**include**)

If PREVALENCE is reported, how is it determined?

A) DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation
B) Dutch Lipid Clinic Network Criteria
C) Simon Broome Registry Criteria
D) Making Early Diagnosis to Prevent Early Death (MEDPED) Criteria
E) ADULT: Total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L)
F) CHILD: (< 16 years of age): Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)
G) Hardy-Weinberg equilibrium (exclude)

eTable 3 | The Dutch Lipid Clinic Network (DLCN) criteria	
Criteria	**Score**
Family History	
First-degree relative with premature coronary and/or vascular disease (men ≤ 55 years, women ≤ 60 years) **OR** First-degree relative with known LDL-cholesterol (LDL-C) ≥ 95th percentile for age and sex	**1**
First-degree relative with tendon xanthomata and/or arcus cornealis **OR** Children aged ≤ 18 years with known LDL-C ≥ 95th percentile for age and sex	**2**
Clinical History	
Patient with premature coronary artery disease (age as above)	**2**
Patient with premature cerebral or peripheral vascular disease (age as above)	**1**
Physical Examination	
Tendon xanthomas	**6**
Arcus cornealis at age ≤ 45 years	**4**
LDL-C mmol/L (mg/dL)	
LDL-C ≥ 8.5 (330)	**8**
LDL-C 6.5-8.4 (250-329)	**5**
LDL-C 5.0-6.4 (190-249)	**3**
LDL-C 4.0-4.9 (155-189)	**1**
DNA Analysis	
Functional mutation in LDLR, APOB or PCSK9	**8**
Stratification	**Total Score**
Definite FH	**8**
Probable FH	**6-8**
Possible FH	**3-5**
Unlikely FH	**<3**

eTable 4 | Simon Broome Register diagnostic criteria	
A diagnosis of DEFINITE FH requires either (1), (2) or (3)	
(1)	Total cholesterol > 290 mg/dL (7.5 mmol/L) or LDL-C > 189 mg/dL (4.9 mmol/L) in adults
	Tendon xanthomas in patient or a first- or second-degree relative
(2)	Total cholesterol > 259 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L) in a child under 16 years of age
	Tendon xanthomas in patient or a first- or second-degree relative
(3)	DNA-based evidence of a function LDLR, PCSK9 or ApoB mutation
A diagnosis of PROBABLE FH requires either (1), (2) or (3)	
(1)	Total cholesterol > 290 mg/dL (7.5 mmol/L) or LDL-C > 189 mg/dL (4.9 mmol/L)
	Family history of myocardial infarction
(2)	Total cholesterol > 259 mg/dL (6.7 mmol/L) or LDL-C > 4.0 mmol/L in a child under 16 years of age
	Family history of myocardial infarction before 50 years of age in a second-degree relative or below age 60 in a first-degree relative
(3)	Family history of elevated total cholesterol in a first or second-degree relative (> 7.5 mmol/L in an adult; > 6.7mmol/L in child or sibling aged under 16 years)

eTable 5 | MEDPED Program diagnostic criteria for FH				
	Total cholesterol threshold (mmol/L)			
	First-degree relative with FH	Second-degree relative with FH	Third-degree relative with FH	General population
Age (years)				
<20	5.7	5.9	6.2	7.0
20-29	6.2	6.5	6.7	7.5
30-39	7.0	7.2	7.5	8.8
≥ 40	7.5	7.8	8.0	9.3
FH is diagnosed if the total cholesterol levels exceed the specified threshold.				

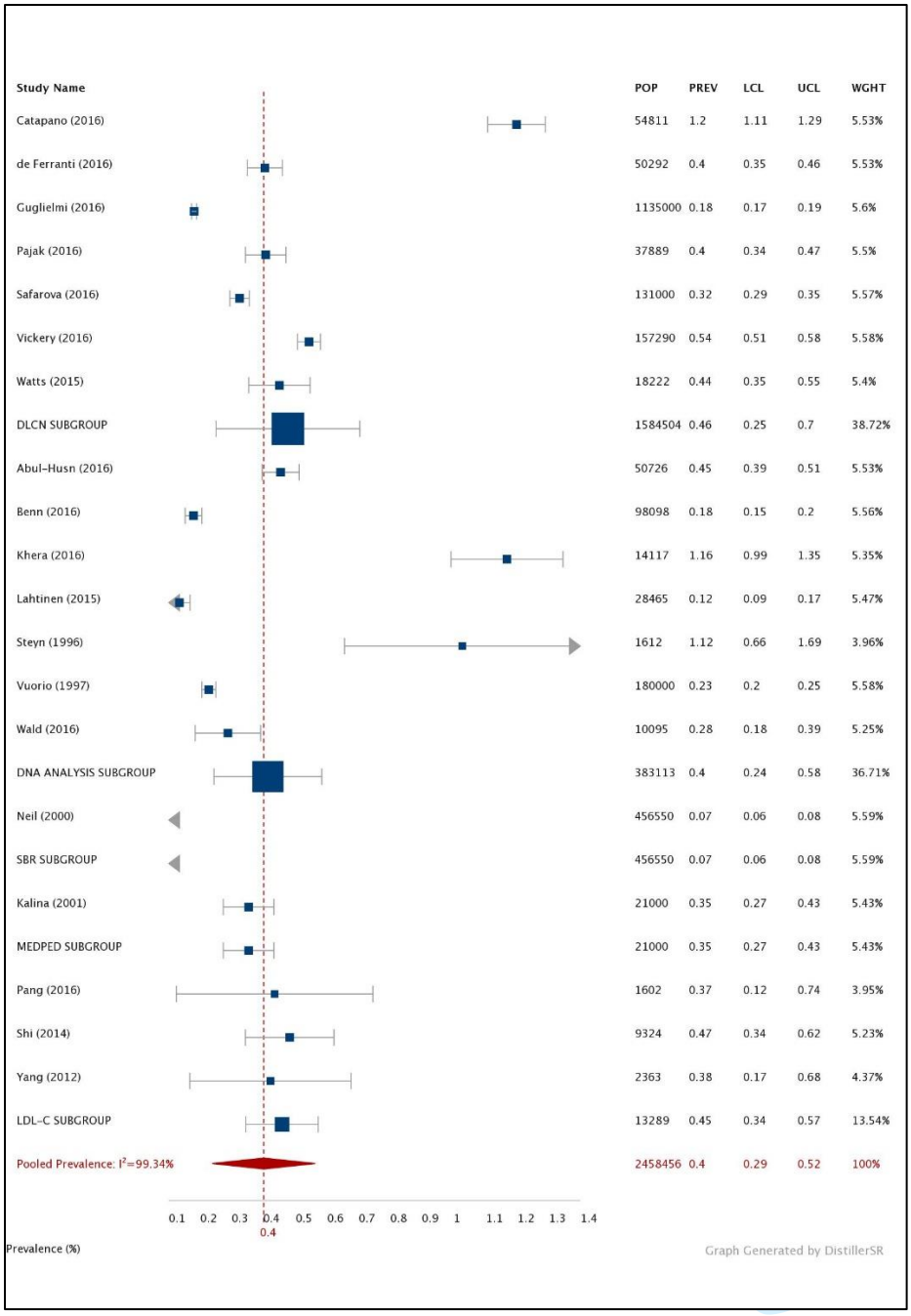
eTable 6 | Considerations of the Effect Public Health Practice Project Quality Assessment Tool	
Component Ratings	**Domains Assessed**
A) Selection Bias	1. Are the individuals selected to participate in the study likely to be representative of the target population? 2. What percentage of selected individuals agreed to participate?
B) Study Design	1. Indicate the study design. 2. Was the study described as randomized? If NO, go to component C. 3. If YES, was the method of randomization described? 4. If YES, was the method of randomization appropriate?
C) Confounders	1. Were there important differences between groups prior to the intervention? 2. If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g., stratification, matching) or analysis)?
D) Blinding	1. Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants? 2. Were the study participants aware of the research question?
E) Data Collection Methods	1. Were data collection tools shown to be valid? 2. Were data collection tools shown to be reliable?
F) Withdrawals & Dropouts	1. Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group? 2. Indicate the percentage of participants completing the study.
G) Intervention Integrity	1. What percentage of participants received the allocated intervention or exposure of interest? 2. Was the consistency of the intervention measured? 3. Is it likely that the subjects received an unintended intervention (contamination or co-intervention) that may influence the results?
H) Analyses	1. Indicate the unit of allocation. 2. Indicate the unit of analysis. 3. Are the statistical methods appropriate for the study design? 4. Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?
Source: http://www.ephpp.ca/tools.html Note: Only sections A-F are used in generating the global assessment of study quality.	

eTable 7 | Quality assessment for studies included in systematic review of FH prevalence							
Study author	**Selection bias**	**Study design**	**Confounders**	**Blinding**	**Data collection methods**	**Withdrawal & dropouts**	**Globing rating**
Abul-Husn (2016)	★★★	★★	★★★	★★	★★★	★★★	★★★
Benn (2012)	★★★	★★	★★★	★★	★★★	★★★	★★★
Benn (2016)	★★★	★★	★★★	★★	★★★	★★★	★★★
Catapano (2016)	★	★★	★★	★★	★★★	★★★	★★
de Ferranti (2016)	★★★	★★	★★★	★★	★★★	★★★	★★★
Kalina (2001)	★★	★★	★★	★★	★★★	★★★	★★★
Guglielmi (2016)	★★★	★★	★★	★★	★★	★★★	★★★
Khera (2016)	★	★★	★★	★★	★★★	★★★	★★
Lahtinen (2015)	★★★	★★	★★★	★★	★★★	★★	★★★
Neil (2000)	★★★	★★	★	★★	★★★	★★★	★★
Pajak (2016)	★★★	★★	★★★	★★	★★	★★★	★★★
Pang (2016)	★★	★★	★	★★	★★	★	★
Perak (2016)	★	★★	★★★	★★	★★★	★★	★★
Safarova (2016)	★★★	★★	★★	★★	★★	★★★	★★★
Shi (2014)	★★★	★★	★★★	★★	★★★	★★★	★★★
Steyn (1996)	★	★★	★★★	★★	★★★	★★★	★★
Vickery (2016)	★★	★★	★★	★★	★★★	★★★	★★★
Vuorio (1997)	★★★	★★	★★★	★★	★★★	★★	★★★
Watts (2015)	★★	★★	★★	★★	★★★	★★★	★★
Wald (2016)	★★★	★★	★★★	★★	★★★	★★★	★★★
Yang (2012)	★★	★★	★★★	★★	★★★	★	★★
★ - weak; ★★ - moderate; ★★★ - strong							

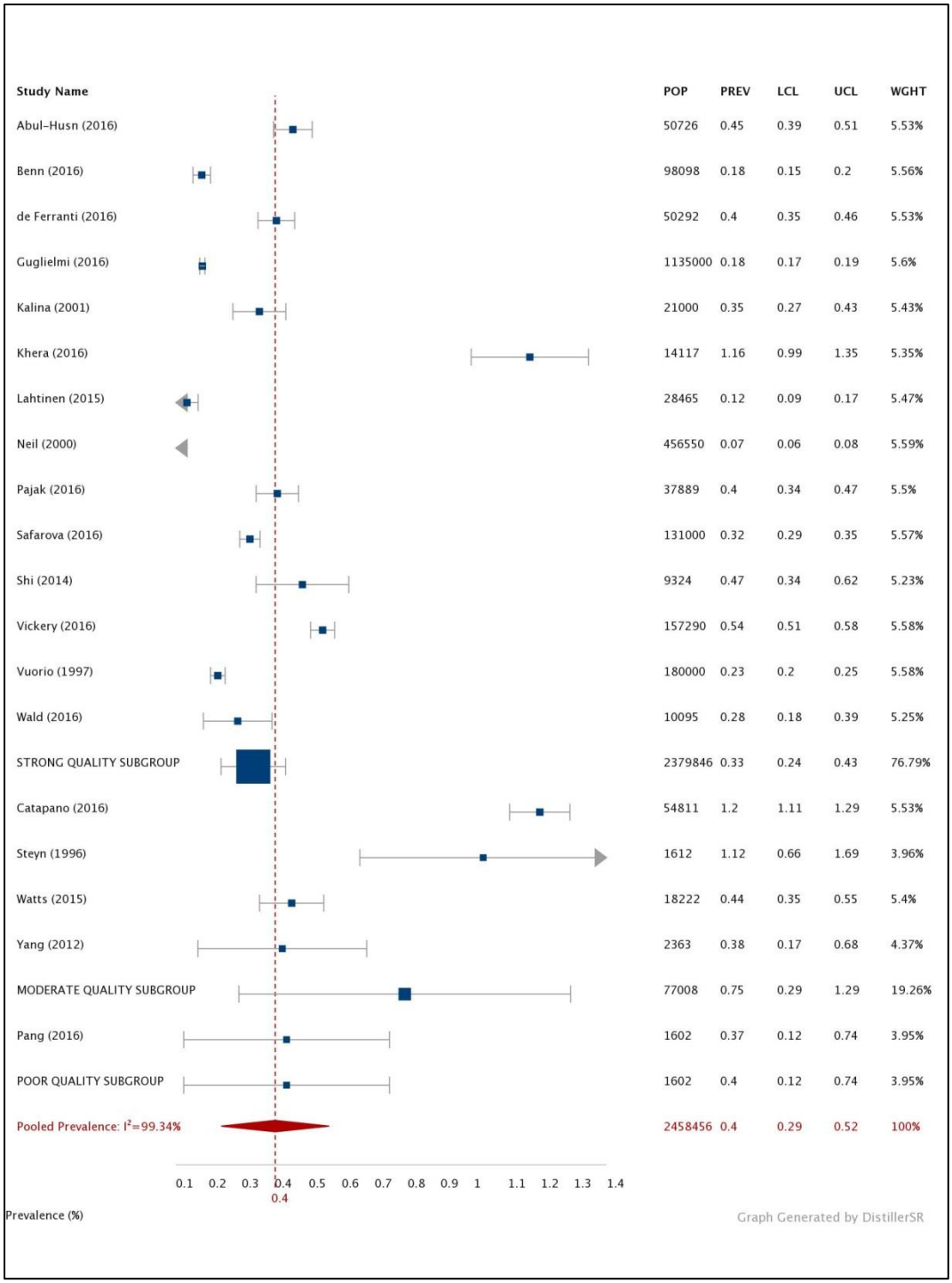
eTable 8 | Pooled prevalence of FH in children (ages 0 – 19)					
Study	**Prevalence (%)**	**LCL 95% (%)**	**UCL 95% (%)**	**Weight (%)**	**Population**
de Ferranti (2016)	0.42	0.32	0.50	45.60	13,343
Pang (2016)	0.37	0.12	0.74	7.16	1,602
Wald (2016)	0.28	0.18	0.39	36.90	10,095
Yang (2012)	0.38	0.17	0.68	10.35	2,363
Pooled	**0.36%**	**0.29**	**0.45**	**100**	**27,403**
Statistics					
I-squared	13.32%	0.00%	86.73%		
Cochran's Q	3.46				
Chi2, p	0.33				
tau2	0.00				

eTable 9 | Pooled prevalence of FH in adults (ages >20)					
Study	**Prevalence (%)**	**LCL 95% (%)**	**UCL 95% (%)**	**Weight (%)**	**Population**
Abul-Husn (2016)	0.45%	0.39%	0.51%	6.40	50,726
Benn (2016)	0.18%	0.15%	0.20%	6.44	98.098
Catapano (2016)	0.40%	0.33%	0.46%	6.37	54,811
de Ferranti (2016)	1.20%	1.11%	1.29%	6.41	50,292
Guglielmi (2016)	0.18%	0.17%	0.19%	6.48	1,135,000
Kalina (2001)	0.35%	0.27%	0.43%	6.28	21,000
Khera (2016)	1.16%	0.99%	1.35%	6.19	14,117
Lahtinen (2015)	0.40%	0.34%	0.47%	6.37	28,465
Neil (2000)	0.12%	0.09%	0.17%	6.33	456,550
Pajak (2016)	0.07%	0.06%	0.08%	6.47	37,889
Safarova (2016)	0.32%	0.29%	0.35%	6.45	131,000
Shi (2014)	0.28%	0.18%	0.40%	6.05	9,324
Steyn (1996)	1.12%	0.66%	1.69%	4.59	1,612
Vuorio (1997)	0.54%	0.51%	0.58%	6.46	157,290
Vickery (2016)	0.23%	0.20%	0.25%	6.46	180,000
Watts (2015)	0.44%	0.35%	0.55%	6.25	18,222
Pooled	**0.40%**	**0.29**	**0.54**	**100**	**2,431,053**
Statistics					
I-squared	99.44%	99.35%	99.52%		
Cochran's Q	2680.181				
Chi2, p	0.00				
tau2	0.00				

eTable 10 | Sensitivity analyses						
Analysis	**Number of studies**	**Population**	**Prevalence (%)**	**LCL 95% (%)**	**UCL 95% (%)**	**I^2(%)**
2000s and later studies only	17	2,276,844	0.39	0.27	0.52	99.41
2010s and later studies only	15	1,799,294	0.42	0.29	0.57	99.23
General population studies only	10	444,581	0.45	0.26	0.68	98.97
Patient cohort studies only	9	2,013,875	0.33	0.21	0.47	99.37
LDL-C based studies excluded	15	2,248,379	0.39	0.27	0.52	99.41
Founder effects studies excluded	16	2,445,167	0.39	0.28	0.52	99.44
LDL-C + Founder studies excluded	13	2,152,048	0.40	0.27	0.56	99.55



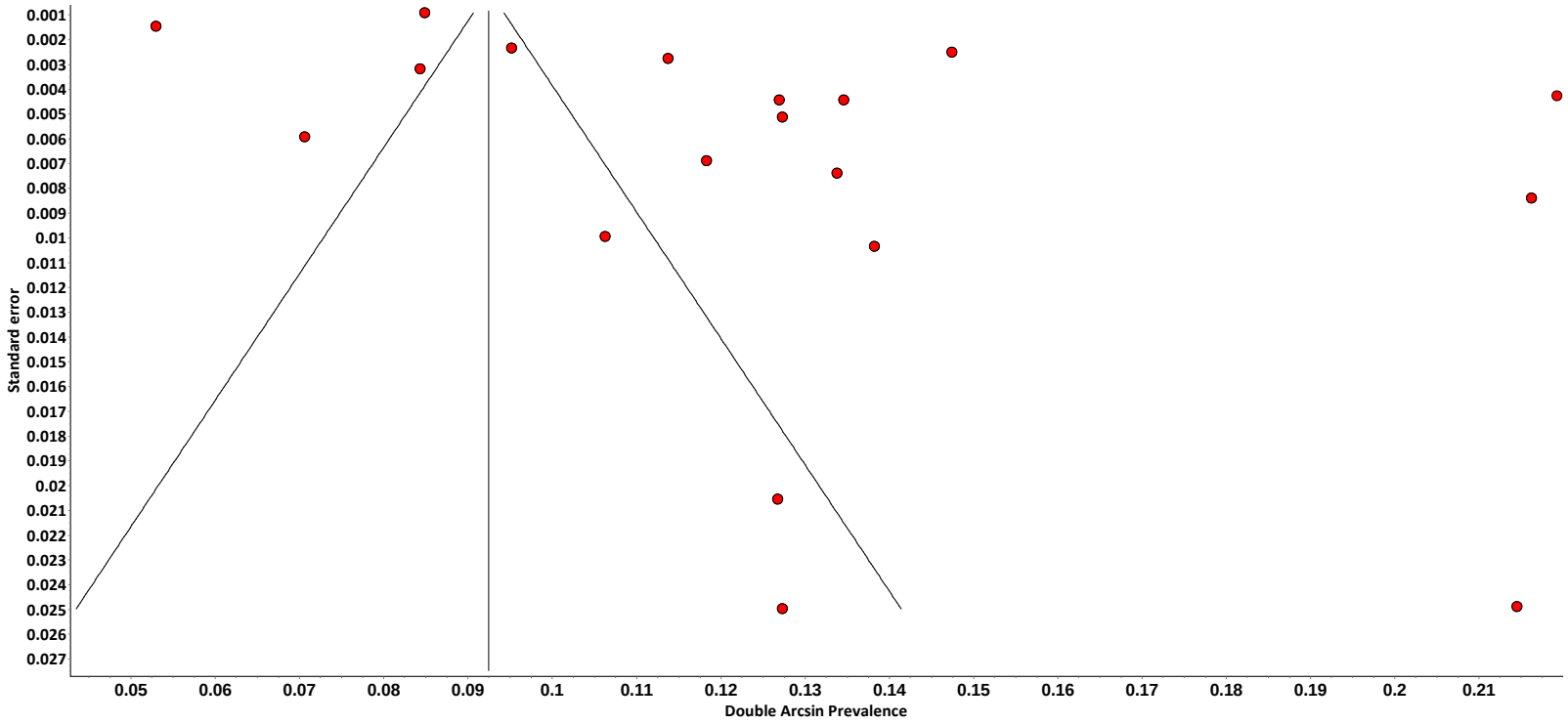
eFigure 1 | Forest plot of overall pooled prevalence (%) of heterozygous familial hypercholesterolemia stratified by diagnostic criteria employed. DLCN subgroup – Dutch Lipid Clinic Network Criteria; DNA subgroup – DNA-based evidence of an LDLR, ApoB, or PCSK9 mutation; LDL-C subgroup – low density lipoprotein-cholesterol > 189 mg/dL (4.9 mmol/L); MEDPED - Making Early Diagnosis to Prevent Early Death criteria; SBR –Simon Broome Registry criteria. I^2 – between-study heterogeneity; LCL – lower confidence limit; POP – population; PREV – prevalence; UCL – upper confidence limit; WGHT – weight under the random-effects model. Note: prevalence estimates were derived using the double-arcsine method, back-transformed and expressed as percentages for ease of interpretation.



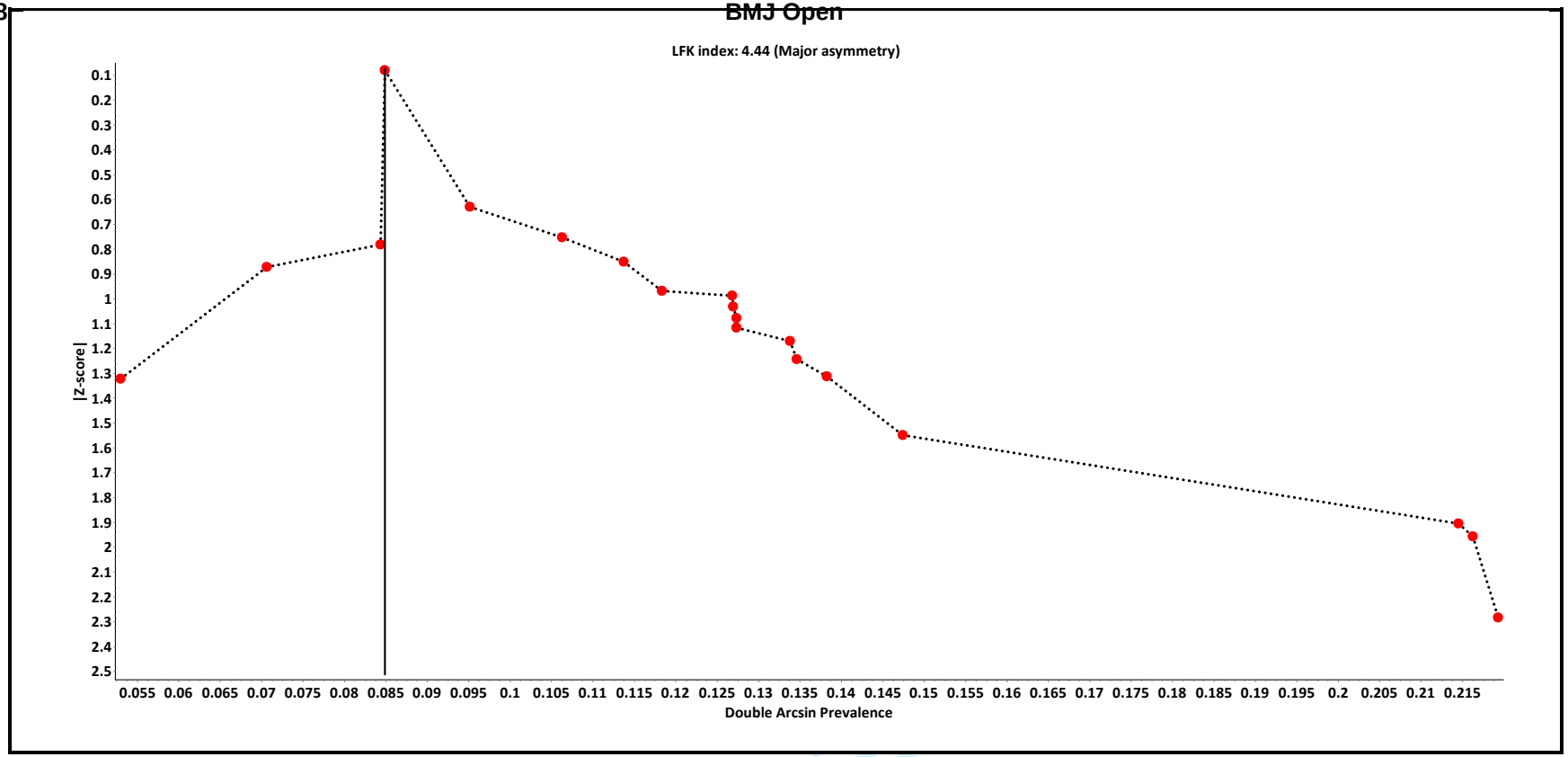
eFigure 2 | Forest plot of overall pooled prevalence (%) of heterozygous familial hypercholesterolemia stratified by study quality. I^2 – between-study heterogeneity; LCL – lower confidence limit; POP – population; PREV – prevalence; UCL – upper confidence limit; WGHT – weight under the random-effects model. Note: prevalence estimates were derived using the double-arcsine method, back-transformed and expressed as percentages for ease of interpretation.

eFigure 3 | Publication bias in studies reporting on adult FH prevalence

(A)



(B)



Interpretation of eFigure 3

We present the Funnel plot in (A). Here, the vertical line indicates a fixed-effects summary estimate derived under inverse variance weighting. The sloping lines that straddle the horizontal demonstrate the expected 95% confidence intervals for the given standard error, assuming no heterogeneity between studies. We plot the standard error of individual study's effect sizes on the vertical axis and the effect sizes (i.e., prevalence estimates) on the vertical axis.

The Doi plot for publication bias is presented in (B). Here, double arcsine transformed prevalence estimates derived under random effects meta-analysis are plotted against an absolute value of a z-score attained by assigning each study a rank based on the standard error of its effect size. When studies included in an analysis are symmetrical, the most precise studies will approach zero on the z-score axis and define a midpoint around which other studies will scatter. By contrast, smaller, less precise studies should scatter widely as their absolute z-score increases and studies become more likely to report findings on either side of the midpoint. The result, in the absence of asymmetry should resemble a symmetrical triangle, with a z-score approaching zero as its peak. A dissimilar number of studies on either side of the triangle or a lack of equal spread or both are indicative of the existence of asymmetry.

Summary

Visually assessed, both the Forest plot (A) and the Doi plot(B) suggest asymmetry among estimates derived from included studies. This asymmetry was confirmed by Egger's weighted regression (p = 0.03).

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	N/A
3	Description of study outcome(s)	4
4	Type of exposure or intervention used	N/A
5	Type of study designs used	4
6	Study population	4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	NR
8	Search strategy, including time period included in the synthesis and key words	4; Supplement
9	Effort to include all available studies, including contact with authors	4
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	4
12	Use of hand searching (eg, reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	eFigure 1 (Supplement)
14	Method of addressing articles published in languages other than English	4
15	Method of handling abstracts and unpublished studies	4
16	Description of any contact with authors	NR
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	NR
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	18-21; Supplement
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	20
26	Table giving descriptive information for each study included	18-19
27	Results of sensitivity testing (eg, subgroup analysis)	8.9
28	Indication of statistical uncertainty of findings	8,9

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Supplement
30	Justification for exclusion (eg, exclusion of non-English language citations)	Supplement
31	Assessment of quality of included studies	Supplement
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	9-11
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	9-11
34	Guidelines for future research	9-11
35	Disclosure of funding source	12

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.