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Review Article

Overview of a collaborative global effort to address the burden of familial hypercholesterolaemia

Alexander R.M. Lyons [a,*], Christophe A.T. Stevens [a], Kanika I. Dharmayat [a], Dr Antonio J. Vallejo-Vaz [a,b,c], Kausik K. Ray [a]

[a] Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, School of Public Health, Imperial College London, London, United Kingdom
[b] Department of Medicine, Faculty of Medicine, University of Seville, Seville, Spain
[c] Clinical Epidemiology and Vascular Risk, Instituto de Biomedicina de Sevilla, IBiS, Hospital Universitario Virgen Del Rocío, Universidad de Sevilla, CSIC, Seville, Spain

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ABSTRACT

This is an overview of the EAS Familial Hypercholesterolaemia (FH) Studies Collaboration (FHSC) global consortium and registry (established 2015), which broadly addresses the global burden of FH. Eighty-seven National Lead Investigators from 74 countries form this expanding global consortium, and this global registry currently includes pooled data on 70,000 participants from participating countries to facilitate FH surveillance. Published first results from this global registry concluded that FH is diagnosed late, and management of LDL-cholesterol falls below guideline recommendations, and therefore earlier detection of FH and wider use of combination therapy is required. Further FHSC studies will follow on updated data including new countries, participants and variables, and non-DNA genetic information, and on the remaining cohorts in the registry. FHSC cross-sectional collaborative global studies are expected to promote FH detection earlier in life to subsequently initiate early lipid lowering therapy to reduce lifelong exposure to cumulative LDL-cholesterol thus reducing cardiovascular disease risk.

1. Introduction

Familial hypercholesterolaemia (FH), characterised by defects in cholesterol related genes (*Low-density lipoprotein (LDL) receptor, apolipoprotein B (APOB), and proprotein convertase subtilisin/kexin type 9 (PCSK9)*),[1,2] is underdiagnosed and undertreated which increases risk of cardiovascular disease owing to lifelong exposure to clinically high LDL-cholesterol.[3,4] Recent meta-analyses estimates that overall prevalence of FH could affect ~1:311 individuals worldwide.[5,6] The 1998 World Health Organisation (WHO) Report on FH[7] recognised FH as a public health issue and advocated the need to address this globally, yet progress has been limited despite the fact that it is some 20 years since that report.[8]

This article provides an overview of the European Atherosclerosis Society (EAS) FH Studies Collaboration (FHSC) global consortium and registry, an observational study registered on clinicaltrials.gov (ID: NCT04272697), which is broadly addressing the global burden of FH. The mission of the EAS FHSC is to inform and encourage change in policy to address FH care worldwide, partly by promoting FH detection earlier in life to subsequently initiate early lipid lowering therapy to reduce lifelong exposure to cumulative LDL-cholesterol burden (cholesterol years) thus reducing cardiovascular disease risk.[9]

2. Familial hypercholesterolaemia global consortium

The EAS FHSC established in 2015[9] is led by the Coordinating Centre (based in UK),[10] and an international Executive Committee comprising an academic panel of experts in FH.[11] A Steering Committee comprising 87 National Lead Investigators (as of October 2021),[12] appointed by the Coordinating Centre, are responsible for leading FH activities within their respective countries or regions and supporting the EAS FHSC to achieve its aforementioned mission.[11] This global consortium currently includes investigators from 74 countries including India (Fig. 1)[12] which correspond to all WHO regions[13] thus a respectable global representation of participating countries. The EAS FHSC is expanding its global reach and the Coordinating Centre[10] welcomes interest from potential

* Corresponding author. Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, School of Public Health, Imperial College London, United Kingdom.
E-mail address: a.lyons@imperial.ac.uk (A.R.M. Lyons).

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new investigators.

The benefit of this global consortium was further demonstrated in 2018 when the EAS FHSC published a survey completed by participating National Lead Investigators from 63 countries on the status of FH care in each of these countries, including available information on prevalence, programmes, initiatives and management of FH at the time of study.[14] This global survey reported that although FH prevalence data are limited in most of these countries, available data tend to align with more contemporary estimates (~1 in 250–300), thus exceeding that of historical estimates (~1 in 500), and low rates of FH detection were also reported across all regions. This study also reported an overall lack of funding for national (local) registries and programmes to improve FH awareness despite these being recognised priorities by the authors. This survey showed the Dutch Lipid Clinics Network criteria was the most commonly used to diagnose FH, however, the gold-standard genetic (molecular) diagnosis was not widely implemented, which was often attributed to accessibility and cost restrictions in most of these countries, with only one-third offering molecular cascade testing. Given that the clinical diagnostic criteria are largely derived from Western Caucasian populations, the suggested LDL-cholesterol cut-offs in these criteria may need to be adjusted to non-western populations given the demographic and cultural differences to avoid misclassification. Lastly, this study suggests that FH is widely undertreated, and that treatment is not universally reimbursed, and lipoprotein-apheresis for those with the most severe form (homozygous FH) is only offered in approximately 60 % of these countries but this was mostly limited to a few centres of reference per country. The authors of this study concluded that FH is a public health concern, but management varies widely across these countries, generally with underdiagnosis and undertreatment, and efforts and initiatives such as development of local FH registries and education programmes are in progress but lack adequate support from health authorities and funding.

Overall, the findings of this global survey reinforce the unmet need for change in international policy of FH to encourage early diagnosis and subsequent early treatment to reduce cumulative risk of premature cardiovascular disease, as per the aforementioned mission of the EAS FHSC.

3. Familial hypercholesterolaemia global registry

The EAS FHSC has compiled a comprehensive FH global registry of both adults (≥18 years old) and children with a clinical and/or molecular diagnosis of either heterozygous or homozygous FH, and their unaffected relatives as controls where data available.[11] National Lead Investigators[12] compile their local FH datasets either from single or multiple sites and then share these, in an electronic format that meet the minimal standards outlined in the EAS FHSC protocol,[11] to a data warehouse via a bespoke, secure online data sharing platform developed and managed by the Coordinating Centre.[10] This EAS FHSC exclusive platform is a one-way channel to receive both full local datasets and individual level participant data entries on demographics, clinical variables and where available, non-DNA genetic variants, with participant identifiers removed prior to submission for anonymity.[11] The Coordinating Centre[10] then standardises all retrospective and prospective datasets received from the participating countries to a common data dictionary, inspects for accuracy and completeness, and pools and harmonises into the FH global registry.[11]

The FH global registry currently includes over 70,000 participants cumulatively from 66 of the 74 participating countries thus far. As the EAS FHSC continues to further expand its global consortium by recruiting new National Lead Investigators from countries yet to join, the FH global registry will accept new data from these countries which will further improve its global representation of FH. Additionally, as new cases are registered in active local registries, databases and cohorts which are already part of the EAS FHSC, these data will also be shared with the FH global registry.

The registry therefore serves as a comprehensive global database of both heterozygous and homozygous FH adults and children for the Coordinating Centre[10] on behalf of the EAS FHSC global consortium[12] to facilitate multiple studies on the surveillance of this condition across the 74 participating countries (Fig. 1) covering all WHO regions.[13]

4. Published findings on the familial hypercholesterolaemia global registry

The EAS FHSC has recently conducted an observational cross-

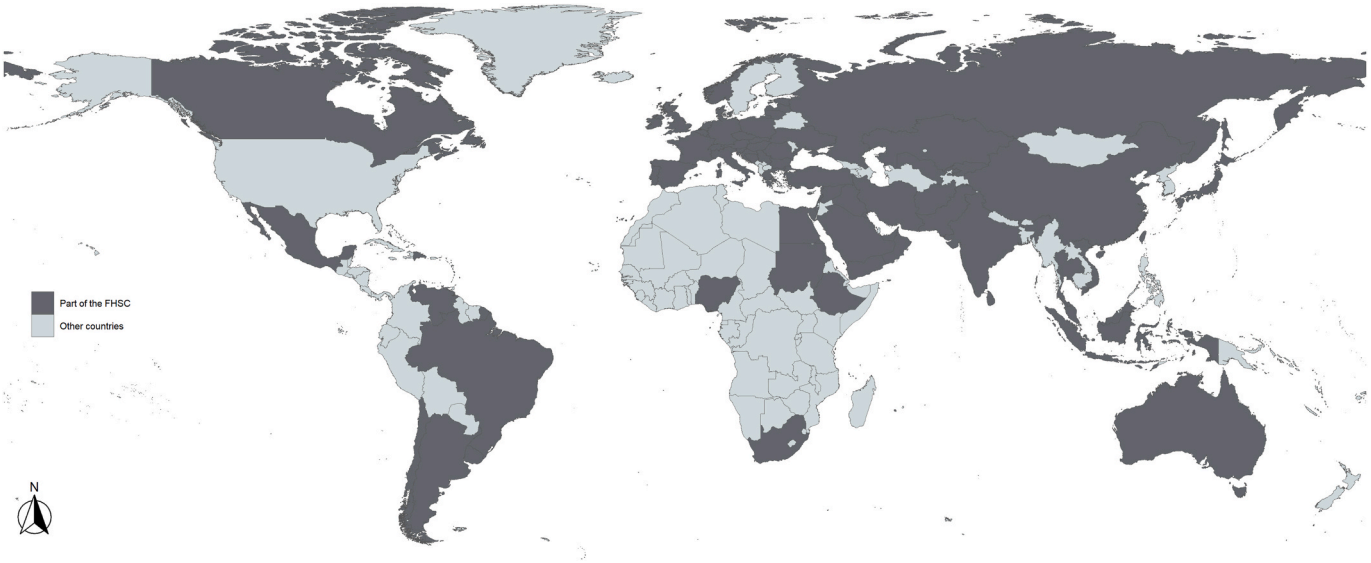

Fig. 1. Global representation of countries with investigators participating in the EAS FHSC: Afghanistan; Argentina; Australia; Austria; Bahrain; Belgium; Bosnia & Herzegovina; Brazil; Bulgaria; Canada; Chile; China; Hong Kong; Croatia; Cyprus; Czech Republic; Denmark; Dominican Republic; Egypt; Estonia; France; Germany; Greece; Hungary; India; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Japan; Jordon; Kazakhstan; Kuwait; Kyrgyzstan; Latvia; Lebanon; Lithuania; Luxembourg; Malaysia; Malta; Mexico; Netherlands; Nigeria; Norway; Oman; Pakistan; Poland; Portugal; Romania; Russia; Saudi Arabia; Serbia; Sri Lanka; Sudan; Singapore; Slovakia; Slovenia; South Africa; Spain; Switzerland; Syria; Taiwan; Thailand; Turkey; Ukraine; United Arab Emirates; United Kingdom; Uruguay; Uzbekistan; Venezuela; Vietnam; Yemen.

sectional study on the FH global registry focusing on the characteristics of 42,167 adults (≥18 years old) with a clinical and/or molecular diagnosis of definite or probable heterozygous FH at registry entry, whose data was available at the time of study, across 56 countries covering all WHO regions, which was published in September 2021 in *The Lancet*.[15]

This study demonstrated that although FH occurs in all WHO regions, some regional differences were observed. This study reported that FH is on average diagnosed in mid-40s in age indicating late detection resulting in many years of exposure to untreated cumulative high LDL-cholesterol levels, and also cardiovascular disease and cardiovascular disease risk factors were reported to increase with age of diagnosis which further emphasises need for early detection to address other determinants of long-term health together with LDL-cholesterol. This study also reported infrequent attainment of LDL-cholesterol levels in accordance with guideline recommendations, particularly when treated with a single drug, suggesting that FH management may benefit from combination therapy thus aligning clinical practice with guideline recommendations, however, accessibility and costs may be limited in low- and middle-income countries in particular. This study also reported a later diagnosis with higher LDL-cholesterol levels and higher prevalence of cardiovascular disease and cardiovascular disease risk factors in index cases compared with non-index cases (affected relatives identified via family screening following index case detection), which demonstrates the value of family screening following identification of an index case. This study lastly reported some differences between men and women in FH diagnosis and management whereby women were diagnosed slightly older, presented with lower prevalence of coronary heart disease, and less women were receiving high-potency statin doses and combination therapy compared to men, which may have consequences in care and outcomes.

This study therefore reinforces the value of wide screening programmes and the need for early detection and management of FH with appropriate use of lipid-lowering and combination therapies to attain LDL-cholesterol target levels aligned with clinical guidelines to reduce cardiovascular disease risk. All of these key findings may need to be addressed in policy.

The limitations of this observational project are that data in the FH global registry are received from different sources with certain variables not captured in some local datasets and therefore diverse in its original pre-processed format. However, inclusion/exclusion criteria are similar across all participating EAS FHSC counterparts. Additionally, this is mitigated through data quality checks and standardisation of the received data to a common data dictionary. Although the EAS FHSC has a global spread covering all WHO regions, representation is greater in regions of Europe over others at present. The EAS FHSC anticipates expanding to other countries yet to join the FH global consortium which will eventually help improve the representation from other regions.

5. Value to the medical community

Clinical registries support auditing of current practices, monitoring patients, recognising gaps in care, and informing guidelines and policy.[8] EAS FHSC combine efforts to provide a global perspective on FH, including countries previously underrepresented in the literature, attempting to surpass the variability of segregated local registries/cohorts via pooling and harmonising these diverse data into a single global registry through standardisation of nomenclature according to a data dictionary and the aforementioned bespoke data entry platform.[11] This approach may support more reliable comparisons of standardised robust data between and within different WHO regions and countries regarding how FH is diagnosed and managed, and geographical trends and differences in care and policy. The work of the EAS FHSC[15] provides additional novel findings on a worldwide scale and therefore represent the largest global initiative to address the burden of FH since the 1998 WHO report on FH[7] advocated such need.

The published findings of this work will also be translated into lay material in the form of text and webinars aimed at FH education for patients with this lifelong condition, and disseminated to the patient community by patient networks and organisations. FH educational programmes are typically supported by scientific societies, academic/research institutions, and patient advocacy groups.[14]

Among multiple factors that may lead to patients with FH or other dyslipidaemias not receiving the full care required to manage their condition may arguably be a lack of access to specialised lipid clinics. The patient and medical communities would therefore benefit from a worldwide directory of lipid clinics with an embedded search by location function to connect patients and non-lipid specialist healthcare professionals with lipid specialists and advocacy groups to get the specialist care and support required. The EAS FHSC Coordinating Centre[10] developed and recently launched an online worldwide directory of lipid clinics and dyslipidaemia patient advocacy groups via a patient-focused, user-friendly website called 'FindMyLipidClinic.com',[16] available in 29 languages, to address this unmet need. FindMyLipidClinic.com took advantage of the EAS FHSC global consortium by inviting all National Lead Investigators and their associates to contribute by providing details of their lipid clinics to be listed on this worldwide directory, and based on responses thus far (as of October 2021), 124 clinics in 39 countries across Europe, North and South America, Asia, Australia, and Africa (mainly in the MENA region and South Africa) have been listed. Also, 29 patient advocacy groups located in 27 countries mostly in Europe and one in Iraq have been listed. The Coordinating Centre[10] continues to openly invite specialist clinicians to list their lipid clinics, and patient advocacy groups to list their organisations on FindMyLipidClinic.com.[16]

6. Conclusion

This article provides an overview of the EAS FHSC global consortium and active registry that is broadly addressing the burden of FH. As the EAS FHSC continues to expand its global consortium by recruiting new National Lead Investigators from countries yet to join, the FH global registry will accept new data from these countries which will further improve its global representation of FH. The first results of a comprehensive analysis of the heterozygous FH adult cohort in the FH global registry has recently been published in *The Lancet*,[15] which concluded that FH is diagnosed late, and management of LDL-cholesterol falls below guideline recommendations, and therefore earlier detection of FH and wider use of combination therapy is required. Further studies will follow on updated data including new countries, participants and variables, and non-DNA genetic information, and on the remaining cohorts in the registry including homozygous FH, FH children and adolescents. The impact of these cross-sectional collaborative global studies is expected to inform and encourage change in policy to address the burden of FH, partly by promoting FH detection earlier in life to subsequently initiate early lipid lowering therapy to reduce lifelong exposure to cumulative LDL-cholesterol thus reducing cardiovascular disease risk.

Declaration of interests

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