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Overview of the current status of familial hypercholesterolaemia care in over 60 countries - The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)

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HIGHLIGHTS

- The EAS FHSC is an international initiative involving a network of investigators interested in FH from around 70 countries.
- Information on FH prevalence is lacking in most countries; where available, data tend to align with contemporary estimates.
- FH diagnosis and management varies widely across countries, with overall suboptimal identification and under-treatment.
- In most countries diagnosis primarily relies on DLCN criteria, and less frequently on Simon Broom or MEDPED.
- Therapy for FH is not universally reimbursed, and criteria vary across countries. Access to PCSK9i and apheresis is limited.

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ABSTRACT

Background and aims: Management of familial hypercholesterolaemia (FH) may vary across different settings due to factors related to population characteristics, practice, resources and/or policies. We conducted a survey among the worldwide network of EAS FHSC Lead Investigators to provide an overview of FH status in different countries.

Methods: Lead Investigators from countries formally involved in the EAS FHSC by mid-May 2018 were invited to provide a brief report on FH status in their countries, including available information, programmes, initiatives, and management.

Results: 63 countries provided reports. Data on FH prevalence are lacking in most countries. Where available, data tend to align with recent estimates, suggesting a higher frequency than that traditionally considered. Low rates of FH detection are reported across all regions. National registries and education programmes to improve FH awareness/knowledge are a recognised priority, but funding is often lacking. In most countries, diagnosis primarily relies on the Dutch Lipid Clinics Network criteria. Although available in many countries, genetic testing is not widely implemented (frequent cost issues). There are only a few national official government programmes for FH. Under-treatment is an issue. FH therapy is not universally reimbursed. PCSK9-inhibitors are available in ~2/3 countries. Lipoprotein-apheresis is offered in ~60% countries, although access is limited.

Conclusions: FH is a recognised public health concern. Management varies widely across countries, with overall suboptimal identification and under-treatment. Efforts and initiatives to improve FH knowledge and management are underway, including development of national registries, but support, particularly from health authorities, and better funding are greatly needed.

1. Introduction

Familial hypercholesterolaemia (FH) is a now major public health concern [1,2]. Untreated FH confers a significantly higher and earlier atherosclerotic cardiovascular disease (CVD) risk [1,3]. Furthermore, contemporary studies suggest FH to be more common than previously estimated [4]. Yet reports indicate it is still widely underdiagnosed and under-treated [1]. Population characteristics, together with differences in health systems and policies, clinical practice, resources, or available information, among other factors, contribute to variations in FH identification and management across different sites and settings, and countries.

The European Atherosclerosis Society FH Studies Collaboration (EAS FHSC) is an international initiative which aims to develop a worldwide, cross-regional registry of FH patients and promote a network of investigators interested in FH (www.eas-society.org/fhsc). The EAS FHSC protocol is described elsewhere [5]. Currently, investigators from ~70 countries are involved [6], with > 10,000 cases already included in the registry. Taking advantage of the wide network of FHSC Lead Investigators (FHSC-LI), we conducted a survey to provide an overview of FH status (prevalence/management/initiatives) in different countries involved in the EAS FHSC.

2. Materials and methods

All FHSC-LI from countries formally involved in the EAS FHSC by mid-May 2018 were invited by email to provide a brief report on FH status in their countries. Specifically, FHSC-LI were asked about (1) “Available information on FH in the country”; (2) “FH programmes and initiatives”; (3) “FH management in the country”. Where more than one FHSC-LI from the same country responded, a final joint report was agreed. Methods are described in detail in the Supplementary Material.

Table 1
FH diagnostic criteria and availability of therapies in the different countries involved in the EAS FHSC network and some reported data on prevalence of HeFH.

	FH diagnosis criteria commonly used in clinical practice	Availability of therapies for FH apart from statins (at the time of the present article submission) (statin therapy, including high-intensity statins, available in all countries listed)			Some reported specific data on prevalence of HeFH (see text for details and references)
		Ezetimibe	PCSK9 inhibitors	Lipoprotein apheresis	
AFRICA					
Nigeria	SB	No	No	No	
South Africa	Clinical diagnosis, supported by genetic diagnosis for founder mutations in certain ethnic groups	Yes	No	No	Afrikaner population: 1:83; South African Indian population: approx. 1:100
AMERICAS					
Argentina	DLCN	Yes	Yes	Limited (one private centre)	1:291 (FH Detection Program)
Brazil	DLCN	Yes	Yes	No	1:263 (ELSA Study)
Canada	Canadian FH definition; DLCN; SB	Yes	Yes	Yes	Up to 1:80 in some areas with founder effects
Chile	DLCN	Yes	No	No	1:243 (National Health Survey, LDL-C ≥230 mg/dL)
Mexico	DLCN; SB	Yes	Yes (only private healthcare)	No	
Uruguay	DLCN	Yes	Yes	No	1:360 (clinical setting)
Venezuela	Clinical diagnosis	Limited	No	No	1:314 (endocrinology unit)
EASTERN MEDITERRANEAN					
Egypt	DLCN	Yes	Yes	No	
Iran	DLCN	Yes	No	No	
Iraq	DLCN	Yes	No	No	
Kuwait	DLCN	Yes	Yes	No	
Lebanon	MEDPED	Yes	Yes	Yes	
Oman	DLCN	Yes	Yes	Yes	
Qatar	DLCN	Yes	Yes	Yes	
Saudi Arabia	SB	Yes	Yes	Yes	
EUROPE					
Austria	DLCN	Yes	Yes	Yes	
Belgium	DLCN	Yes	Yes	Yes	
Bosnia and Herzegovina	DLCN	No	No	No	
Bulgaria	DLCN	Yes	Yes	No	
Croatia	MEDPED	Yes	Yes	Yes	
Cyprus	Definitive diagnosis (TC > 260 mg/dl if < 16 years; TC > 290 mg/dl in adults; LDL-C > 190 mg/dl in adults and tendon xanthoma in patient or 1st/2nd degree relative)	Yes	Yes	Yes	
Czech Republic	Modified MEDPED	Yes	Yes	Yes	
Denmark	DLCN; SB	Yes	Yes	Yes	1:223 clinically, 1:217 genetically (Copenhagen General Population Study)
Estonia	DLCN	Yes	Yes	Yes	1:440 (North Estonia Medical Centre database)
Finland	DLCN	Yes	Yes	Yes	1:500 founder LDLR mutations carriers
France	DLCN	Yes	Yes	Yes	
Germany	DLCN; SB	Yes	Yes	Yes	1:278–295 (DETECT Study)
Greece	DLCN	Yes	Yes	Yes	
Hungary	DLCN	Yes	Yes	Yes	
Ireland	DLCN	Yes	Yes (early access programme only)	No	
Israel	MEDPED	Yes	Yes	Yes	1:355 (regional healthcare database)

(*continued on next page*)

Table 1 (*continued*)

	FH diagnosis criteria commonly used in clinical practice	Availability of therapies for FH apart from statins (at the time of the present article submission) (statin therapy, including high-intensity statins, available in all countries listed)			Some reported specific data on prevalence of HeFH (see text for details and references)
		Ezetimibe	PCSK9 inhibitors	Lipoprotein apheresis	
Italy	DLCN	Yes	Yes	Yes	1:526 (Health Search IMS Health Longitudinal Patient Database)
Kyrgyzstan	DLCN	No	No	No	
Latvia	DLCN; LDL-C 95th percentile in cascade screening for relatives	Yes	Yes	No	
Lithuania	DLCN	Yes	Yes	Yes	
Malta	DLCN	Yes	Only exceptionally	No	
Netherlands	DLCN	Yes	Yes	Yes	1:200–250 (based on studies on HoFH prevalence and primary care)
Norway	Genetic testing; if negative, clinical diagnosis DLCN	Yes	Yes	Yes	Estimated 1:300
Poland	Genetic testing; DLCN	Yes	Yes	Yes	1:250 (meta-analysis of observational studies in Poland)
Portugal	SB	Yes	No	Yes	
Russia	DLCN	Yes	Yes	Yes	1:147–417 in 2 Siberian regions (Epidemiology of Cardiovascular Risk Factors and Diseases Study)
Serbia	DLCN	Yes	Yes	Yes	
Slovakia	DLCN; SB; MEDPED	Yes	Yes	No	
Slovenia	Children: genetic testing; Adults: DLCN	Yes	Yes	Yes	Genetically confirmed FH in 1:500 children born in 2008
Spain	DLCN	Yes	Yes	Yes	Estimated 1:300
Switzerland	Genetic testing (SAPPHIRE-FH Program); DLCN	Yes	Yes (limited)	No	1:125–135 overall (*APOB* pathogenic variants: 1:209; *LDLR* variants: 1:317)
Turkey	DLCN	Yes	Yes	Yes	
Ukraine	MEDPED; DLCN	No	Only in trials on HoFH	No	
United Kingdom	SB; DLCN	Yes	Yes	Yes	
Uzbekistan	DLCN	Yes	No	Yes (private clinics)	
SOUTH EAST ASIA AND WESTERN PACIFIC					
Australia	DLCN	Yes	Yes	Yes	1:250–350
China	DLCN; Chinese FH criteria	Yes	No	Yes (limited)	1:357
Hong Kong	DLCN	Yes	Yes	Yes (plasmapheresis)	
India	DLCN; SB	Yes	No	No	
Japan	JAS criteria	Yes	Yes	Yes	
Malaysia	DLCN; SB	Yes	Yes	Yes	Estimated 1:100
Singapore	SB	Yes	Yes	No	
Taiwan	DLCN; Taiwan FH criteria	Yes	Yes	Yes	
Vietnam	DLCN	Yes	No	No	

DETECT: Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment of Treatment Study; DLCN: Dutch Lipid Clinics Network criteria; ELSA: Longitudinal Study of Adult Health; FH: familial hypercholesterolaemia; HeFH: heterozygous familial hypercholesterolaemia; HoFH: homozygous familial hypercholesterolaemia; JAS: Japanese Atherosclerosis Society; LDL-C: low-density lipoprotein-cholesterol; MEDPED: "Make Early Diagnosis to Prevent Early Deaths" criteria; PCSK9: proprotein convertase subtilisin/kexin type 9; SAPPHIRE-FH (Swiss Awareness Program for Primary Hypercholesterolemia: Identification of Risk Elevation in Families with High cholesterol); SB: Simon-Broome criteria.

3. Results

73 of the 81 FHSC-LI responded to the survey, corresponding to 63 countries (from the overall 68 countries in the FHSC network at the time of the study). Information is summarised by WHO region [7] below and in Table 1 and Figs. 1–4.

3.1. AFRICA

3.1.1. Nigeria

The EAS-FHSC collaborative study is the first FH initiative in Nigeria, established at University of Benin Teaching Hospital (UBTH). After implementation at UBTH, it will be extended to other centres. Dyslipidemias are managed by cardiology and endocrinology clinics. Genetic testing is unavailable. The Centre for Disease Control of UBTH operates a subsidised general population screening programme for a variety of conditions including lipid testing, which will be used for recruiting FH patients. Costs of care are mainly paid out-of-pocket, while a few, mostly government workers, have health insurance. To date, 7 patients have been diagnosed.

3.1.2. South Africa

The diverse ethnic profile and presence of founder effects among selected groups (Afrikaners, Jews) make it difficult to accurately determine the true FH prevalence. The estimated prevalence in the Afrikaner population is among the highest worldwide (1:83) due to a founder effect (3 founder mutations account for ~90% of cases) [8]. The estimated prevalence in the South African Indian population is ~1:100 but it is uncertain whether this is a true founder effect [9]. Information on prevalence in black South Africans remains limited [10]; interestingly, the *LDLR* mutation c.137_142del ("CapeTown-1" or "FH-Pedi-1") was identified in several black Africans with a clinical FH diagnosis and may be a common African mutation.

3.2. AMERICAS

3.2.1. Argentina

The FH Detection Program estimates a prevalence of 1:291 (Dutch Lipid Clinics Network criteria [DLCN]; > 100,000 cases expected). Genetic testing is performed for individuals with DLCN > 6; among patients studied so far, 33% have mutations in *LDLR* (95%) and *APOB*

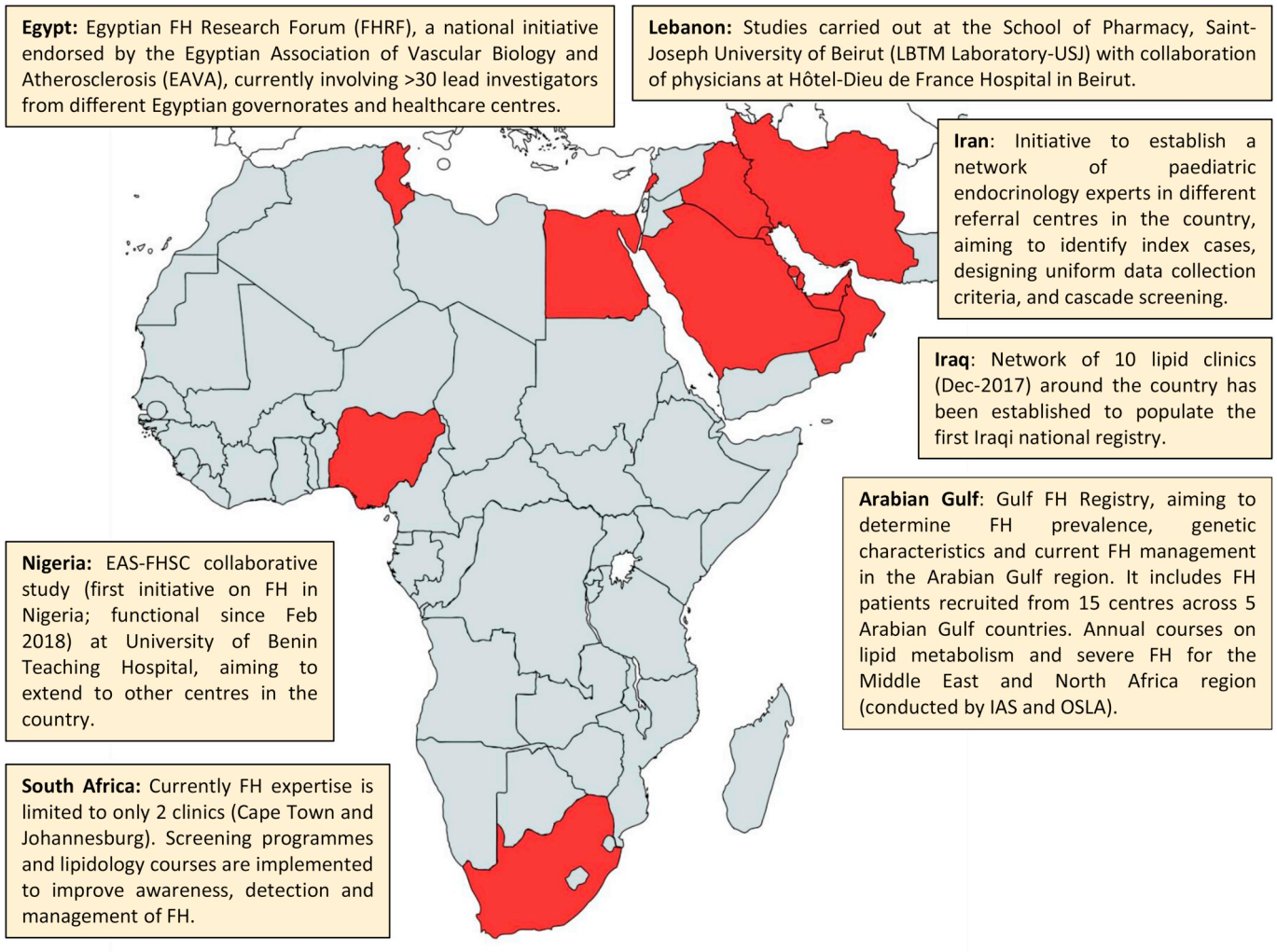
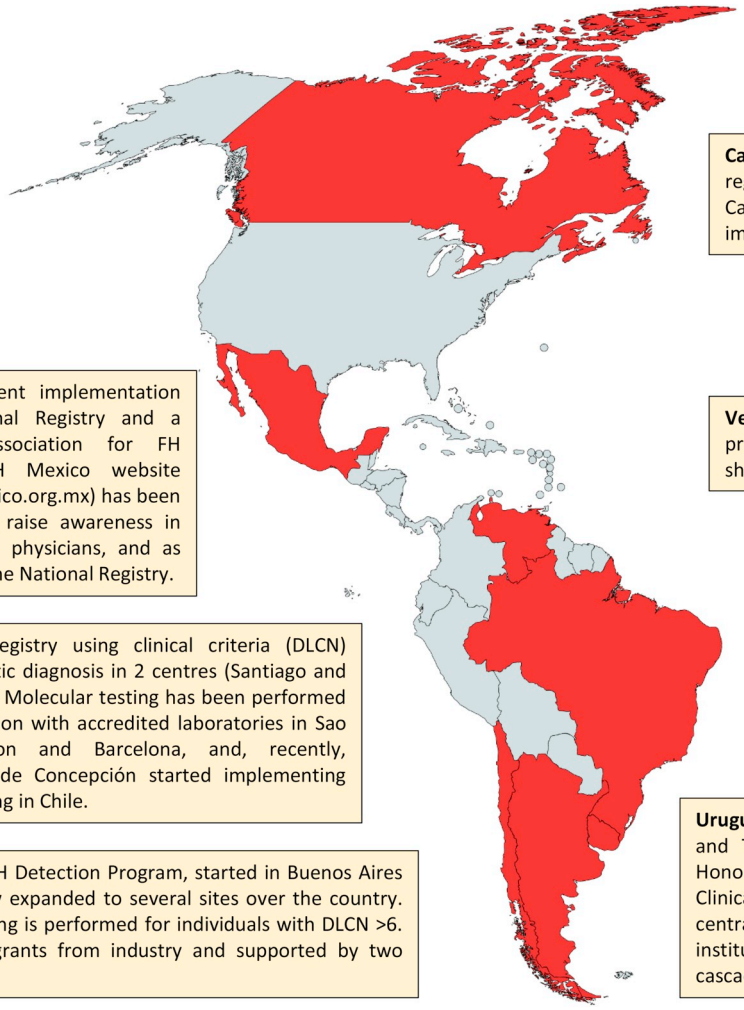


Fig. 1. FH-related initiatives in countries involved in the EAS FHSC network in the Africa and Eastern Mediterranean WHO regions.
In red, countries currently involved in the EAS FHSC network. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



Canada: FH Canada (www.fhcanada.net), national registry across 19 academic sites acting as "hubs" in Canada designed to identify subjects with FH to improve health and healthcare delivery.

Mexico: recent implementation of a National Registry and a National Association for FH patients. FH Mexico website (www.fhmexico.org.mx) has been launched to raise awareness in patients and physicians, and as the site for the National Registry.

Venezuela: Individual efforts of FH investigators to promote diagnosis, raise awareness and overcome shortage of medicines in the country.

Brazil: Hipercol Brasil (HB), genetic cascade screening programme in Sao Paulo, performing genetic testing for adults with LDL-C ≥230 mg/dL. HB also started an itinerant programme in some remote country areas, to identify possible founder effects. Brazilian FH association (AHF; www.ahfcolesterol.org), aims to increase awareness and interacts with organisations from other countries.

Chile: FH Registry using clinical criteria (DLCN) and/or genetic diagnosis in 2 centres (Santiago and Concepción). Molecular testing has been performed in collaboration with accredited laboratories in Sao Paulo, Lisbon and Barcelona, and, recently, Universidad de Concepción started implementing genetic testing in Chile.

Uruguay: GENYCO, a National Program for Early Detection and Treatment of FH, developed and funded by the Honorary Commission for Cardiovascular Health (GENYCO Clinical Coordination Unit) (www.cardiosalud.org). The centralised registry, being implemented in all health institutions, provides access to free genetic testing, cascade screening, follow-up and treatment for FH.

Argentina: FH Detection Program, started in Buenos Aires in 2015, now expanded to several sites over the country. Genetic testing is performed for individuals with DLCN >6. Funded by grants from industry and supported by two Universities.

Fig. 2. FH-related initiatives in countries involved in the EAS FHSC network in the Americas WHO region.
In red, countries currently involved in the EAS FHSC network. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(5%), 8 had homozygous FH (HoFH), and 4 mutations were novel [11,12]. Cascade screening was performed in 22 families, clinically and/or genetically. A polygenic risk score is used to assess polygenic causes. FH care is reliant on individual physicians.

3.2.2. Brazil

The ELSA Study suggests heterozygous FH (HeFH) may affect 1:263 Brazilians (~766,000 individuals). Currently, the only active genetic cascade screening program in Brazil is Hipercol Brasil in Sao Paulo (genetic testing for adults with low-density lipoprotein cholesterol (LDL-C) ≥230 mg/dL, to maximise cost-effectiveness), with 1719 heterozygotes, 25 homozygotes, 13 compound-heterozygotes and one double-heterozygote identified by March 2018. To date, 4340 individuals from 440 families were screened. Genetic testing is funded by a government tax reduction programme (PROADI-SUS), and cascade screening by partnering between Samaritano Hospital and Heart Institute (InCor) University of Sao Paulo. Most FH patients are under non-specialist care and currently under-treated.

3.2.3. Canada

Estimated prevalence is 1:250 overall [13] (up to 1:80 in some areas with founder effects [14]), with < 10% of estimated cases identified. FH Canada, a national registry, had included > 3100 FH patients by December 2017. Diagnosis is made using the newly developed, simplified Canadian FH definition, based on DLCN and Simon-Broome (SB) criteria. Efforts are underway to develop clinically-approved assays for genetic testing in several provinces. A free smartphone app is available to impute baseline LDL-C and FH diagnosis using the Canadian definition, DLCN and SB [15]. Healthcare delivery for FH follows the Canadian Clinical Practice Guidelines [16].

3.2.4. Chile

The 2010 National Health Survey detected 7 cases with LDL-C ≥230 mg/dL from 1700 subjects with lipid measurements. Although likely underestimating the true figure, available data suggest FH prevalence is 1:243 (> 69,000 cases [20–60 HoFH] in a 17,300,000 population). A registry using clinical criteria and/or genetic diagnosis has been developed in Santiago and Concepción (4 HoFH and 67 HeFH registered so far). Draft Ministry of Health guidelines consider FH care for the first time. Genetic testing and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) for severe FH have been proposed for incorporation into national law regulations funding the cost of rare and expensive diseases.

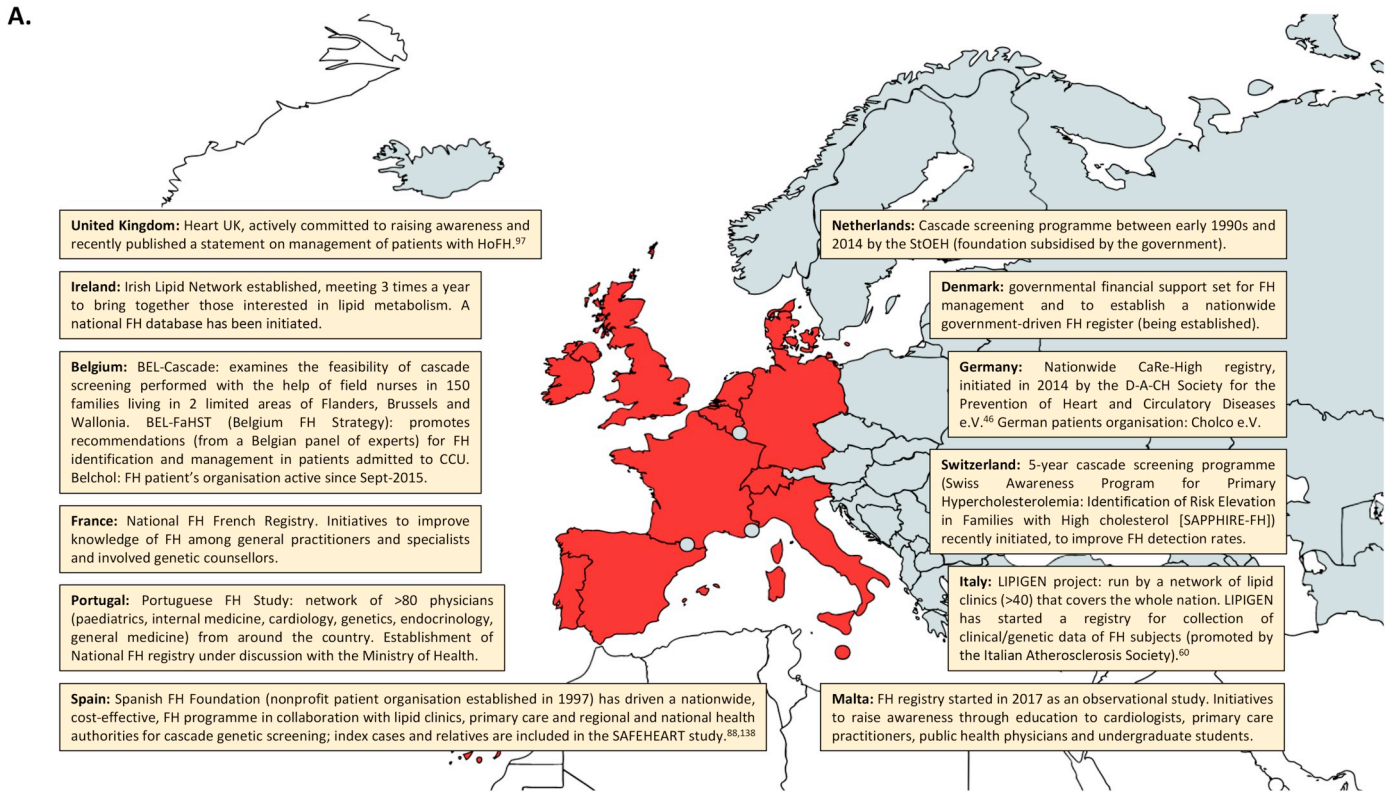


Fig. 3. FH-related initiatives in countries involved in the EAS FHSC network in the WHO region of Europe (A–C).
In red, countries currently involved in the EAS FHSC network [138]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.2.5. Mexico

A national registry and non-government patient organisation have been initiated to replace previous isolated initiatives. A large proportion of FH cases are undiagnosed. Cases are treated mainly in reference centres. Diagnosis is mostly clinical (genetic testing is only available in referral centres). Accumulated data show that *LDLR* mutations (including some novel) are the most frequent [12,17]. Currently each institution has its own FH model of care (no government-supported programmes or national guidelines). The healthcare system does not universally cover high-dose statins and ezetimibe and medications are generally out-of-pocket expenses.

3.2.6. Uruguay

Estimated prevalence is ~1:360 (~9100 patients; 2.47% cases identified to date) based on analysis of lipid profiles from a routine clinical setting. In 2014, a Ministry of Health National Law and Regulatory Decree established a National Program for Early Detection and Treatment of FH (GENYCO). Suspected FH cases are selected in reference clinics using software incorporating the DLCN criteria. The Clinical Coordination Unit selects the index cases for genetic testing. The registry currently includes 805 FH cases, 225 with positive molecular diagnosis (68 index cases/139 relatives with *LDLR* or *APOB* mutations and 18 index cases with positive polygenic FH score). FH treatment is covered by the Integrated National Health System.

3.2.7. Venezuela

A prevalence of ~1:300 was estimated from patients attending an endocrinology unit in Ciudad Bolívar [18]. FH is diagnosed clinically (previously, genetic diagnosis was also used in some patients) [19,20]. A major problem is the general shortage of medicines (including up to 85% of previously available drugs such as statins or ezetimibe) and lack of PCSK9i or apheresis. This situation compromises the efforts to tackle the FH burden and highlights the need for implementation of health policies.

3.3. EASTERN MEDITERRANEAN

3.3.1. Arabian Gulf (Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates)

High consanguinity rate in the region (up to 50%) [21] suggests that prevalence may be higher than that reported. Latest censuses suggest ~130,693 HeFH and 87 HoFH cases. Only 57 mutations have been reported in 17 Middle East and North Africa countries, attributed to the lack of national registries and screening programmes [22]. A cross-national Gulf FH-Registry initiated in February 2017. Although lipid clinics and lipoprotein apheresis centres are available in the region, FH remains under-treated. Only 13% of patients with acute coronary syndrome (ACS) achieve an LDL-C < 70 mg/dL (Gulf-COAST registry) [23].

3.3.2. Egypt

Preliminary data from the Egyptian Cardiorisk project showed premature atherosclerosis in 47% of men and 69% of women admitted with ACS, of whom ~50% may have HeFH [24,25]. A higher incidence may occur in areas where consanguinity is common. The Egyptian FH Research Forum is a national initiative aiming to empower the medical

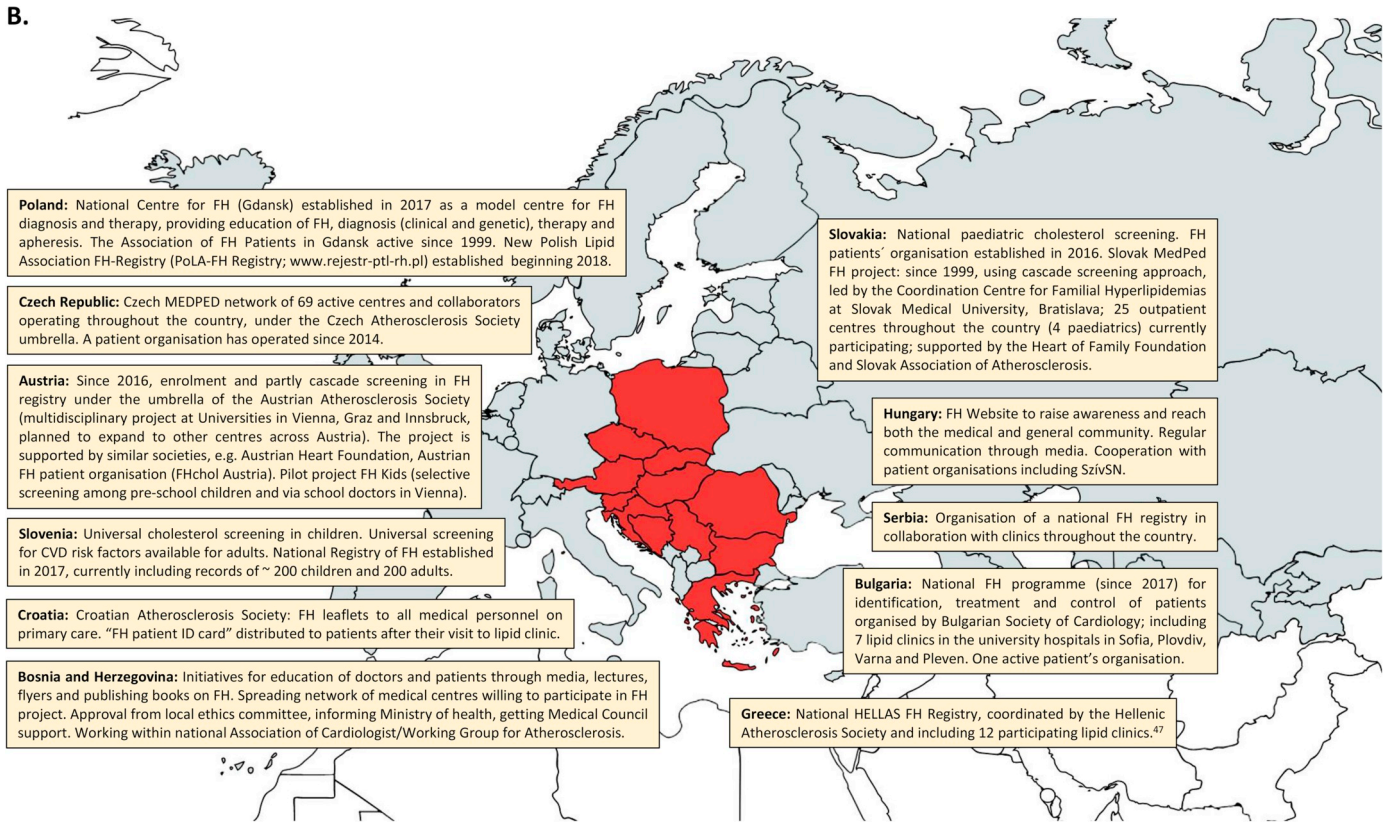


Fig. 3. (*continued*)

community and organisations to promote FH detection and management to reduce the burden of premature atherosclerosis in Egypt.

3.3.3. Iran

FH awareness/knowledge are limited. An initiative to establish a network of paediatric endocrinology experts in different referral centres in Iran is planned. Currently, genetic testing has been performed in 32 probands (definite clinical FH) and first-degree relatives in collaboration with MRL (Belgium) and UCL (UK), with diagnosis of 16 HoFH, 28 HeFH, and 1 compound HeFH. Most probands are children/adolescents with *LDLR* mutations. There has been a call for identified cases to undergo clinical, biochemical, echocardiographic and ophthalmological examinations. Funding and personnel for the future development of this project, cooperation with the global network, and access to novel treatments, are needed.

3.3.4. Iraq

The first lipid clinic was established in February 2017 in Diwaniyah, aiming to initiate the first lipid clinic network and FH Registry in Iraq. Subsequent efforts led to opening 9 more clinics; participating physicians attend specific training courses in Muscat, Oman. Genetic testing is offered in the Sultan Qaboos Bin Saeed University Hospital, Oman. Future plans involve improving quality of care and physician skills for FH.

3.3.5. Lebanon

FH is particularly common (e.g. HoFH is 10-fold higher than in other populations), attributable to founder effects and high consanguinity rates [26,27]. The p.Cys681X mutation ("Lebanese allele") is responsible for FH in 81.5% of Lebanese probands from different regions or religious communities [28]; We also showed that *PCSK9* was a modifier gene [28]. Other less frequent mutations in *LDLR* and *LDLRAP1* genes have also been reported [28,29]. The healthcare system partially reimburses conventional FH treatment. The Ministry of Public Health partially covers LDL-apheresis at the National LDL-Apheresis Centre at a governmental Hospital. Genetic testing is available mainly through research studies in universities.

3.4. EUROPE

3.4.1. Austria

HeFH/HoFH patients are thought to number ~40,000/100 (only 15 HoFH identified so far). Genetic testing is available, but not routinely reimbursed by the Austrian health system. There is no common rule as to how FH patients are managed – partly by internists, endocrinologists, cardiologists, paediatric lipid centres and general practitioners (GPs). PCSK9i are generally only reimbursed in secondary prevention or with proven statin intolerance.

3.4.2. Belgium

There are no quantitative estimates of HeFH prevalence; 9 HoFH cases are identified to date. Negotiations for establishing a centralised registry within the National Institute of Health (NIH) e-health platform are ongoing. The FH management setting varies, including the few lipid clinics. Genetic testing is covered by NIH and may be prescribed by any clinicians, ideally for those with DLCN > 5. Reimbursement for statin, ezetimibe and PCSK9i is based on DLCN score. Lipoprotein apheresis is only reimbursed through solidarity funding.

3.4.3. Bosnia and Herzegovina

Data are collected individually using DLCN and cascade screening (no official national registry). Overall, ~3%/11% of definite/probable

Fig. 3. (*continued*)

FH cases have been identified, suggesting an estimated prevalence of > 1:200. FH management is affected by lack of funding for laboratory and genetic testing, and under-treatment with the only available therapy (statins). Significant steps towards raising FH awareness are ongoing [30].

3.4.4. Bulgaria

EUROASPIRE-IV estimated a 9% age-standardised prevalence of potential FH [31]. A study in 12 cardiology hospitals identified 196 FH subjects (DLCN; 27 definite, 94 probable, 74 possible) from 24,000 subjects with ≥2 lipids measurements (2015–2016) [32]. Genetic testing is paid by patients. Patients requiring combination therapy are managed by lipid clinics, with 5% of very high- and 14.5% of high-risk FH patients achieving LDL-C goals [32]. The health system reimburses PCSK9i at 75% (if DLCN > 6, on high-intensity statin, and LDL-C > 3.6 mmol/L if very-high risk, > 2.6 mmol/L if multiple atherothrombotic events, > 5 mmol/L for primary prevention); statins for secondary prevention at 25%; and fixed atorvastatin-ezetimibe at 50%. Since the programme started, 120 more patients are on PCSK9i.

3.4.5. Croatia

About 200 FH cases (MEDPED; one HoFH) are identified from the estimated 15,000 (~1% detection rate) [33]. A pilot regional screening programme in ACS patients showed that 1:12 has possible FH. Genetic testing will soon be available in a pilot project at the University of Zagreb. Preliminary results suggest no FH patient achieved an LDL-C < 1.8 mmol/L despite statin or statin/ezetimibe. FH patients are managed in lipid clinics by lipid specialists, and also by cardiologists and endocrinologists. PCSK9i are prescribed only in hospitals, covered by the Croatian National Insurance (from hospitals own budgets).

3.4.6. Cyprus

There are no data on prevalence and no formal registry. Screening is opportunistic at the discretion of the treating physician, who can refer patients/relatives for genetic testing available centrally at a National Institute. Studies have revealed clustering for *LDLR* mutations, possibly due to low migration rates and high consanguinity [34]. Care is free for those entitled to National Health Care (NHC). Most FH patients are managed by cardiologists and internists, and treated with statins or plasmapheresis (available in public hospitals) [35]; PCSK9i are becoming available privately and in the NHC (selected patients).

3.4.7. Czech Republic

Since joining the worldwide MEDPED initiative in 1998, a nationwide network of 69 centres has been established [36]. Currently, the Czech National MEDPED Database includes 7784 FH patients (modified MEDPED criteria; 19 HoFH) in 5884 families (19.5% of expected FH patients in the Czech Republic, if prevalence is 1:250). Cascade screening is facilitated using genetic testing. DNA samples are available from 4963 unrelated patients (*LDLR, APOB, and PCSK9* mutations were

detected in 961, 488, and 1 patients, respectively). Statins/ezetimibe/PCSK9i are fully reimbursed (PCSK9i restricted to secondary prevention with LDL-C > 3 mmol/L, or HeFH with LDL-C > 4 mmol/L, on maximum tolerated lipid modifying treatment [LMT]); LDL-apheresis is fully reimbursed but restricted (few cases).

3.4.8. Denmark

HeFH prevalence is 1:223 clinically [37] or 1:217 genetically [38] (Copenhagen General Population Study). A 2017 government report concluded that, with a prevalence of 1:200–250, only 11–13% of HeFH patients are identified (particularly lacking identification of children). A 1:220 HeFH prevalence would translate to an allele frequency of 1:440 and 1:193,600 HoFH frequency (expected 28 HoFH individuals; very few already diagnosed). FH diagnosis/treatments are covered by the healthcare system, including genetic testing where needed.

3.4.9. Estonia

The North Estonia Medical Centre (NEMC) electronic database includes ~1800 possible/probable/definite FH patients, suggesting a prevalence of 1:440. An algorithm introduced to the NECM IT system mandates DLCN scoring if LDL-C ≥5 mmol/L (pure hypercholesterolaemia) and informs on treatments according to individual scores. Genetic testing is funded but used in limited cases. FH is mainly managed by cardiologists in lipid clinics. Statins and ezetimibe are reimbursed, unlike PCSK9i, used only in a few patients; use of lipoprotein apheresis is limited.

3.4.10. Finland

National guidelines for FH management are available, but there is no national screening programme or registry. The mutation spectrum in Finland is restricted and unique; 5 distinctive founder *LDLR* mutations are identified, with a combined estimated heterozygous carrier rate of 1:500 [39,40]. If FH prevalence is ~1:200, a substantial proportion of Finnish FH is still molecularly undefined [1]. Up to 27,500 may have FH, but, according to nationwide statistics, only ~5000 patients receive reimbursement for LMT for hereditary dyslipidemia.

3.4.11. France

About 8000 FH patients are followed in lipid clinics (~3.3% of the expected 240,000 if prevalence is 1:250). In 2015, a national network of physicians (mainly endocrinologists and cardiologists) and geneticists created the national French FH Registry, sponsored by the Nouvelle Société Francophone d'Athérosclérose (NSFA) [41]. Inclusion is based on DLCN (probable diagnosis) and/or genetic mutation. By March 2018, 4660 adults and children from 15 lipid clinics were included throughout France, almost two-thirds with a genetic diagnosis [42]. NSFA recommendations for FH management are guidelines for standard practice in France [43]. PCSK9i are reimbursed (alirocumab for HeFH with LDL-apheresis criteria; evolocumab for HoFH).

3.4.12. Germany

An estimated prevalence of 1:300 (HoFH: 1:860,000) [44,45] suggests ~275,000 individuals may have FH, but only a minority are diagnosed/treated. Genetic testing is available if indicated by the treating physician, covered by statutory health insurance. Private health insurance is, however, reluctant to cover costs. There are no national FH guidelines; patients are managed in primary care, internal medicine, cardiology, and lipid clinics. The only systematic approach to collect more information is the nationwide CaRe-High registry [46] (already > 500 individuals). CaRe-High also offers support for cascade screening and cooperates with Cholco (German patient organisation). PCSK9i and lipoprotein apheresis are available, covered by insurance.

3.4.13. Greece

The estimated prevalence is 1:250 (~40,000 cases; > 90% remain undiagnosed). Two university centres offer genetic testing, although costs are met by patients. The national HELLAS FH Registry was recently established [47]. Patients with LDL-C > 190 mg/dL (> 160 mg/dL in children) are evaluated for FH; if at least possible FH, they are registered and offered cascade screening (genetic testing is free to selected patients). FH is mainly managed in lipid clinics in large cities. PCSK9i and lomitapide are offered free-of-charge to selected patients. Three centres offer lipoprotein apheresis (reimbursed). Few patients achieve LDL-C goals [48].

3.4.14. Hungary

FH may affect ~20,000–40,000 individuals. The national network involves 2 national centres (Budapest and Debrecen), and 18 regional centres. The Hungarian FH-Registry includes 301 patients. The Registry uses an automated programme that calculates the DLCN score; patients with suspected FH are referred to regional centres. Genetic testing is performed if needed (limited/partial funding). There are 2 LDL apheresis centres (Budapest, Debrecen); PCSK9i are available but not subsidised.

3.4.15. Ireland

Studies suggest a decline in cholesterol levels in Ireland since the 1980s [49–51]. A recent study identified one possible FH case among 259 of the public screened [49]. A national FH database has been initiated, supported by industry, which also funds lipid nurses for FH screening. Cascade screening is offered [52]. Genetic testing became available recently at St James Hospital (referrals based on DLCN score). Patients receive treatment in different settings, particularly in cardiology, diabetes and a small number (n = 5) of lipid clinics. Reimbursement for management of lipid disorders is currently unavailable. PCSK9i have been utilised only as part of an early access programme which is now full.

3.4.16. Israel

FH research began > 20 years ago as part of the MEDPED initiative. The estimated HeFH prevalence is 1:355 [53]. Currently ~500 families are followed; among 455 FH patients, 176 are mutation-positive, representing < 5% of expected FH cases. The common mutations identified reflect the various ethnicities in the country (characteristic founder effects identified in each ethnicity) [54,55]. 25 HoFH patients were identified, reflecting a cultural tendency towards consanguinity. Most patients are treated in lipid clinics; most > 40-year-old hypercholesterolaemic patients are on statins; data in younger adults/children and on LDL-C goal attainments in all age groups are lacking.

3.4.17. Italy

Data from Health Search IMS Health Longitudinal Patient Database showed a prevalence (DLCN ≥6) of 1:526 [56]. Using only an LDL-C cut-off of ≥250 mg/dL identified 1:1038 and 1:369 among non-treated and statin-treated subjects, respectively [57]. Among patients admitted to rehabilitation and secondary prevention programmes, FH prevalence was 1:27 [58]. Data from Sardinia and Sicily, two insular regions, reported a 1:2500 rate of *ARH1* mutation carriers (1:140,000 homozygous) [59]. Patients are generally referred to lipid clinics [60]. Subjects with suspected clinical FH undergo genetic testing (reimbursed by the National Health Service [NHS]). Available treatments include lipoprotein apheresis and PCSK9i, reimbursed under NHS specific monitoring programme.

3.4.18. Kyrgyzstan

There is a high cardiovascular morbidity rate. Earlier studies showed that atherogenic lipid levels were lower in the Kyrgyz ethnic group than in individuals of Caucasian descent. Although prevalence is unknown, FH is thought to be more common than in other countries. Genetic testing is unavailable. FH is managed by cardiologists and internists and treated with statins (not reimbursed). There are no accurate data on LDL-C goal attainment.

3.4.19. Latvia

Prevalence is unknown but assumed at 1:250. There is no state programme and few patients were diagnosed before the Latvian FH Registry was established in 2015. To date, the Registry has identified 181 cases (2.3% of 7876 estimated HeFH cases; no HoFH). Cascade screening is performed in first-degree relatives of index cases with probable/definite FH. Genetic testing is not reimbursed but has been funded by research grants for a few patients/relatives. About 5% of patients had LDL-C at target before inclusion in the Registry [61]. Statins are reimbursed 50% in primary prevention; statins and ezetimibe, 75–100% in secondary prevention; PCSK9i are available, but not reimbursed.

3.4.20. Lithuania

Cardiovascular mortality rates are extremely high (56.1% in 2017). With a population of 2,847,904, it is estimated that there are 14,240 (1:200) HeFH cases and 18 (1:160,000) HoFH cases. ~15% of FH cases are diagnosed. The nationwide Lithuanian High Cardiovascular Risk primary prevention program [62,63], covered by the health system since 2006, screens > 200,000 individuals every year; in > 93,000 middle-aged adults included in the electronic database for detailed analysis, 3.2% had LDL-C ≥6 mmol/L. High-risk patients with dyslipidaemia are managed in preventive cardiology units by cardiologists, geneticists, apheresis specialists, and followed-up in primary care. Genetic testing is reimbursed. Statins are reimbursed for primary/secondary prevention; PCSK9i are not reimbursed yet.

3.4.21. Malta

Up to 10% of the estimated 1500 FH individuals are identified. An FH Registry started in 2017, run on a voluntary basis (no official funds); inclusion has changed from opportunistic to cascade screening, with relatives considered at lower cut-off LDL-C [64]. Genetic testing is unavailable. Patients are managed at the only national lipid clinic (or internal medicine clinics with the same physicians). FH patients are entitled to free treatment with statins, fibrates, and cholestyramine but other therapies are not funded; PCSK9i are made available exceptionally. 96% of patients identified are on statins (60% at LDL-C goal).

3.4.22. Netherlands

Cascade screening was practised routinely between the early 1990s and 2014 by StOEH, a government-subsidised foundation. Diagnosis was based on the presence of mutations in *LDLR/APOB/PCSK9*. Genetic analyses were performed by a core laboratory (Academic Medical Centre, Amsterdam), while patient care was mostly at local lipid clinics. Initially, only molecular diagnostics were performed in the screening programme, with lipid testing included after the early 2000s. Based on studies on HoFH prevalence and among primary care, a 1:200–250 HeFH prevalence is estimated (40% [~30,000] patients identified) [65–67].

3.4.23. Norway

Since 1991, the Unit for Cardiac and Cardiovascular Genetics (Oslo University Hospital) performs all genetic testing and cascade screening free-of-charge (government funded). Currently, > 8000 patients (~800 < 18 years; 13 HoFH) have been diagnosed. Estimated prevalence is 1:300, i.e. ~17,000 cases. The National Advisory Unit on FH was established in 2014. Diagnosis of index patients has increased from < 100 patients/year previously to > 350 patients/year in the last 2 years. There are 10 lipid clinics (largest in Oslo, with > 1300 FH patients seen every year). Few patients attain LDL-C goal with statins/ezetimibe [68]. PCSK9i are available if LDL-C > 5 mmol/L (> 4 mmol/L if CVD) on statin/ezetimibe, or if eligible for apheresis.

3.4.24. Poland

Estimated prevalence is 1:250 (based on a meta-analysis of 6 observational studies) or 136,300 adults (only 2% diagnosed) [69,70]. Based on LIPIDOGRAM studies (2004–2015, ~50,000 participants), prevalence might be < 1:200 [71,72]. Five HoFH cases are described [73,74]. Patients with DLCN ≥3 are referred for genetic testing, funded by the National Health Program. The National Centre for FH at University Clinical Hospital, Medical University of Gdansk, was established in 2017, financed by the Ministry of Health. From August 2017, 345 patients underwent genetic testing (153 positive, including 46 relatives; 1 HoFH). Since 1999, 1884 patients (562 families) have undergone genetic testing and cascade diagnosis (data from the National Polish FH Registry, Medical University of Gdansk, established in 2000). PCSK9i are not reimbursed (under discussion with the Ministry of Health).

3.4.25. Portugal

There is no government programme for FH identification. However, since 1999, the National Institute of Health "Dr Ricardo Jorge" promoted the Portuguese FH Study [75]; to December 2017, 801 index cases (clinical diagnosis) and > 1000 relatives (cascade screening) were referred, of whom 772 (319 index cases, 453 relatives, 11 HoFH) had a potential pathogenic mutation. Establishment of a National FH Registry is under discussion with the Ministry of Health. Statins and ezetimibe (partly) and LDL-apheresis (fully) are covered by the health system. Overall, < 10% of patients attain LDL-C goal.

3.4.26. Russia

The estimated number of HeFH patients is at least ~590,000 (if prevalence is 1:250 [13]). The Epidemiology of Cardiovascular Risk Factors and Diseases Study in 2 Siberian regions reported prevalence for definite/probable FH of 0.24%/0.68% [76]. Genetic testing is available commercially but is used only in studies or paid by patients. FH care is provided by cardiologists, and by lipid clinics in several large cities. Ezetimibe and PCSK9i are commercially available but not reimbursed by the health system. Apheresis is available in some large cities but is not reimbursed. Few patients meet LDL-C goal [77]; in a study in 4 lipid clinics (> 500 FH patients –DLCN ≥8 with coronary heart disease) only 6.6% achieved an LDL-C < 1.8 mmol/L [78].

3.4.27. Serbia

CVD is the leading cause of mortality (51.7%). 13.2% of the population have hypercholesterolaemia [79,80]. There are no data on FH prevalence and no national registry, but an active FH programme is in place. Estimated FH prevalence is 1:500 (14,400–15,000 in > 7 million population). The only lipid unit (Clinical Centre of Serbia, Belgrade) initiated a local registry based on opportunistic and cascade screening, identifying > 700 FH patients (7 suspected HoFH). Genetic testing is unavailable. Statins, ezetimibe and apheresis are reimbursed, but not PCSK9i. Preliminary data suggest LDL-C goal attainment is low (statins are frequently under-dosed).

3.4.28. Slovakia

Estimated FH cases range from 10,858–21,716 (1:250–500 prevalence). Prevalence of the FDB_R3500Q mutation is 0.09% in the general population [81]; 2 HoFH patients have been identified. The MEDPED-Slovakia Registry collects information on identified FH patients (DLCN, SB, MEDPED) and includes 1184 probands from 2246 registered patients. Genetic testing availability is limited to research grants and health insurance [82]. National paediatric cholesterol screening (at 11 and 17 years) was initiated in 2004. Statins, ezetimibe and PCSK9i are reimbursed by the health system.

3.4.29. Slovenia

One in 500 children born in 2008 have genetically confirmed HeFH (3 HoFH) [83]. As mandated by law, total cholesterol is universally screened at age 5 years [83]; those with elevated levels are referred to UMC Ljubljana (UMCL) for genetic testing (funded by hospital funds/research projects). Universal nationwide screening for CVD risk factors is available in adults aged 35–70-years, with referral to lipid clinics if FH is suspected (e.g. total cholesterol > 8.0 mmol/L). FH children are followed by paediatricians, adults at the UMCL lipid clinic. Statins/ezetimibe are introduced from 8 to 10 years. Statins are fully reimbursed; ezetimibe is co-paid for primary prevention in adults; PCSK9i are reimbursed for FH adults with LDL-C > 5.0 mmol/L, > 4.0 mmol/L or > 3.6 mmol/L in primary prevention, secondary prevention or progressive CVD, respectively, on maximal statin/ezetimibe (or with documented statin intolerance).

3.4.30. Spain

Although FH prevalence is estimated at 1:300 (> 150,000 subjects; HoFH: 1:450,000) only ~20% of cases have been detected (97 with HoFH), 65% with clinical criteria and 35% with genetic testing (funded by the NHS, indicated if the index case has DLCN ≥6) [84–86]. FH is managed in lipid clinics and primary care. Lipoprotein apheresis, PCSK9i and other LMT for FH are covered by the NHS. About 80% of FH patients are on treatment; LDL-C goals are attained by 11% of adults and 42% of children/adolescents [87,88]. A cardiovascular risk equation for FH developed from SAFEHEART might improve risk stratification and indication for emerging treatments [89].

3.4.31. Switzerland

The highest worldwide prevalence of *APOB* pathogenic variants (1:209) was discovered in Switzerland [90]. Along with *LDLR*-variants (1:317), FH prevalence is 1:125–135. From the estimated 65,000 patients, > 1500 are listed in the nationwide Swiss FH Center (diagene Research Institute). By 2018, available data suggest 0.8–3.3% of FH-patients are diagnosed, similar to 1998 (2.3%) [91], highlighting the need for the provision of additional resources to improve current detection. The detection rate is considerably lower than the estimated 13% detection rate published in 2013 by others [1]. The discordance between these estimates may have implications for resource allocation and highlights the importance of the present Swiss initiative and the FHSC to global health.

3.4.32. Turkey

A high prevalence (1:150–200; ~420,000 cases) is expected due to founder effects and high consanguinity (23%) [92,93]. EUROASPIRE-IV suggested 8.9% of coronary patients have potential FH [31]. FH is mainly diagnosed clinically due to the high cost of genetic testing. Several registries are ongoing; A-HIT1, a nationwide survey of 88 HoFH patients undergoing LDL-apheresis, showed that most experience ineffective apheresis [94,95], and A-HIT2 (1000 FH adults from 30 clinics) showed that FH is undertreated even in specialized centres (LDL-C goal attainment: 9.1%) [94]. A-HIT3 is in FH patients admitted to coronary care units with premature MI. Statins, ezetimibe and apheresis are reimbursed. PCSK9i are available (only evolocumab is reimbursed for HoFH).

3.4.33. Ukraine

The prevalence of total cholesterol > 5 mmol/L is 69.4% (LDL-C > 5 mmol/L, 8.1%) [96], partly influenced by high rates of secondary hypercholesterolaemia (13% hypothyroidism, 50% prediabetes/diabetes, 45.7% obesity). About 160,000 FH patients (~0.4% of the population) are expected (if prevalence is 1:250). There is no government funding/support. Cascade screening is conducted. Genetic testing is paid by patients (including 8 HoFH). Currently, the FHSC-related registry in Ukraine includes 165 patients (63% possible/20% probable/17% definite FH). There are no specialized lipid clinics. FH care is coordinated by the Dyslipidaemia Department, M.D. Strazhesko Institute of Cardiology NAMS of Ukraine. State reimbursement for statins began in 2018.

3.4.34. United Kingdom

Estimates suggest only 10–20% of HeFH cases are diagnosed (~60 HoFH) [97]. *LDLR/APOB/PCSK9* mutations are carried by ~93%/5%/2% of identified HeFH [98]. NICE 2017 updated guidelines recommend SB or DLCN for diagnosis [99]. In 2008, NICE recommended DNA testing to diagnose index cases, followed by family cascade testing. Access to genetic testing remains limited, however, and few regions have screening programmes supported by DNA testing. The imminent re-design of Genomic Laboratory Service in England will improve access to genetic testing. PCSK9i are commissioned by NHS (NICE technology appraisals 393/394). NHS England commissioned evolocumab and lomitapide for HoFH.

3.4.35. Uzbekistan

Estimated prevalence is ~160,000 HeFH/30 HoFH cases (based on prevalence 1:200; 32.653 million population). FH identification is based on target screening in outpatient departments and in the CAD and Atherosclerosis Laboratory of the Republican Specialized Centre of Cardiology (RSCC), Tashkent. Genetic testing is not routinely available (since 2018, available in the Scientific Laboratory of Molecular Genetic Studies). The RSCC database includes 105 HeFH (< 0,01% of estimated cases) and 3 HoFH (10%) patients. Patients are monitored by the RSCC CAD and Atherosclerosis Laboratory. LDL-apheresis is available in private clinics.

3.5. South-east Asia and western Pacific

3.5.1. Australia

HeFH prevalence is 1:250–350 [100,101]. A web-based registry across Australia has included > 1000 subjects [102]. Cascade screening from a local centrally coordinated clinical service has demonstrated cost-effectiveness but requires nationwide implementation [103–105]. Screening in coronary care units is useful for detecting FH and elevated lipoprotein(a) [106,107]. In primary care, electronic screening tools can identify FH patients. FH is managed in lipid clinics, by cardiologists/endocrinologists, and in primary care according to a model of care [108,109]. Lipoprotein apheresis for refractory FH with progressive CHD is available, funded by the health system [109]. PCSK9i are reimbursed according to FH severity.

3.5.2. China

The reported FH prevalence is 0.28% (7.1% in premature MI) [110,111]. On this basis, there could be 5.6 million HeFH and ~5000 HoFH cases. Recent research showed that mean untreated LDL-C was 15.1 ± 3.8 mmol/L in HoFH/compound HeFH, and 5.7 ± 1.3 in HeFH [112]. Previously, DLCN was used widely and genetic testing was self-funded. In 2018, an expert consensus group proposed diagnostic criteria for Chinese FH [113]. There are few lipid clinics in China, and widespread FH awareness is lacking, with many patients misdiagnosed/under-treated. Only 4.2% definite/probable FH patients are treated with high-intensity therapy [110] (statins/ezetimibe/probucol), covered by health insurance.

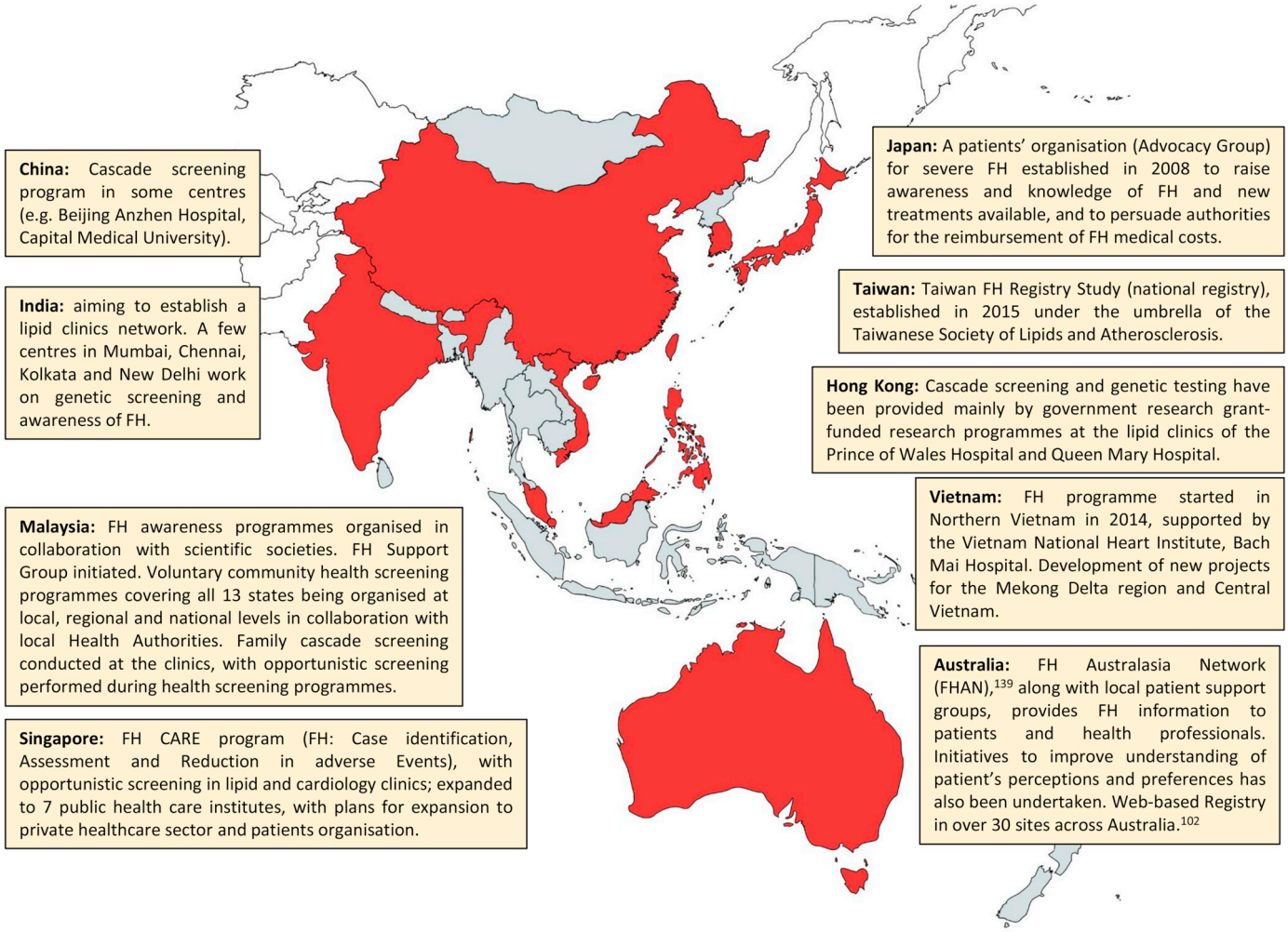


Fig. 4. FH-related initiatives in countries involved in the EAS FHSC network in South-East Asia and Western Pacific WHO regions.
In red, countries currently involved in the EAS FHSC network 139. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.5.3. Hong Kong

About 500 FH patients have been identified in 2 main centres (≤2% of cases according to global data) [1]. Originally, MEDPED was used to identify patients, with data presented at the second WHO Consultation in Geneva (1998) [114]. More recently, DLCN was adopted after recommendation in recently developed local consensus guidance. FH patients are usually managed in lipid/other specialist clinics in government hospitals. Statins/ezetimibe are generally provided at nominal charge [115]. Plasmapheresis is used at Queen Mary Hospital for severe cases.

3.5.4. India

There are no accurate data on FH prevalence [116]. A survey on FH awareness in 79 GPs showed that 67% were unaware of FH definition and 72% were unaware of FH prevalence [117]. An ongoing study in Mumbai has enrolled 10/13/87 definite/probable/possible cases (DLCN). Genetic screening for *PCSK9* will use RT-PCR and sequencing. Similar studies are being performed in South, North and East India [118,119]. FH is treated in routine consultations at hospitals or private clinics, but, due to the lack of lipid clinics, treatments rely on statins only.

3.5.5. Japan

The estimated prevalence is 1:200–500 (1:160,000–1,000,000 for HoFH). Clinical characteristics of HeFH/HoFH were reported by the Research Committee of the Ministry of Health [120]. The Japanese Atherosclerosis Society has published criteria for FH diagnosis in adults/children [121–123]. Genetic testing is recommended for diagnosis (required for HoFH), but it is not yet covered by health insurance and only available in several institutions. FH is managed by lipidologists/cardiologists/internists and primary care physicians. Health insurance covers 70% of medical costs for HeFH and 80% (up to a limit of 100$) for HoFH.

3.5.6. Malaysia

Estimated HeFH prevalence is ~1:100 (~0.4% identified) [124]. 29 HoFH cases with *LDLR* mutations have been identified in 14 families [124–127]. This research group has identified ~707 clinical FH patients (190 screened for genetic mutations). Overall, 1524 cases have been clinically diagnosed from various clinics and community; genetic testing was performed in 1007 (43.9% with *LDLR/APOB100/PCSK9* mutations) [124–130]. Genetic testing is not government-funded. FH is managed in specialist lipid, endocrine and metabolic medicine, cardiology, internal medicine and primary care clinics. Excluding PCSK9i and apheresis, treatment is covered by the health system. Only 12.1% of high-risk patients receive LMT (32.5% attain LDL-C goal) [131].

3.5.7. Singapore

There are an estimated 22,000 HeFH individuals among the ~5.5 million population. The 2016 Ministry of Health Clinical Practice

Guidelines recommended SB for clinical diagnosis [132]. Among 96 identified FH patients in one centre, 52% were heterozygous for *LDLR* mutations and 4.2% heterozygous for *APOB* mutations [133]. The FH programme in Singapore started in 2015, with proband identification via opportunistic screening [133]. Cascade screening is challenging as probands are reluctant to inform relatives. FH care is shared across primary and tertiary care, public and private institutions. One single centre study showed that only 57.7% of patients received LMT, and 56.3% attained goals (LDL-C < 1.8 mmol/L or ≥50% reduction) [133].

3.5.8. Taiwan

Prevalence is estimated at 1:200–300. A national registry (Taiwan FH Registry Study) was established in 2015 supported by the Taiwanese Society of Lipids and Atherosclerosis, which published the "Taiwan Lipid Guideline for High Risk Patients" in 2017 [134]. Four *LDLR* mutations and one *APOB* mutation (among 136 reported) account for 34% of FH cases in Han Chinese population [135]. Genetic testing for screening will be available from late 2018 at the National Taiwan University Hospital (available for genetic diagnosis for Taiwan/other countries). Recently, the Taiwan National Health Insurance approved reimbursement of PCSK9i for HoFH.

3.5.9. Vietnam

The FH programme started in North Vietnam in 2014 using opportunistic screening to identify index cases, followed by cascade screening. The social health insurance system partly covered the cost of treatment. Currently, the registry includes 70 FH patients (DLCN and age- and gender-specific LDL-C criteria) [64] (53 HeFH/8 HoFH genetically confirmed). After diagnosis, only 15.7% of patients (6 HeFH, 5 HoFH) were regularly followed by cardiologists. LMT included statins (100%), ezetimibe (36.4%), stanols (27.3%), and plasma exchange (9.1%). 83.3% of HeFH cases had LDL-C < 2.5 mmol/L. Mean LDL-C in HoFH before and after treatment was 17.5 ± 6.0 and 10.2 ± 4.1 mmol/L, respectively.

4. Discussion

This survey highlights the lack of information on FH prevalence in most countries. Where available, data tend to agree with contemporary estimates, higher than that traditionally considered [1]. In the absence of data, the general reported figure of 1:250–500 [1] are frequently assumed and extrapolated to local populations. There are, however, several factors that influence FH identification/diagnosis and, thus, estimation of the burden of disease. These include, among others: (i) population characteristics, e.g. presence of different ethnicities, migration patterns, mutation spectrum (which may differ widely across the world) [136], founder effects, consanguinity rate, and population cholesterol levels (and factors that may influence them, e.g. dietary patterns, lifestyle); (ii) general FH awareness among the community, healthcare professionals and policy-makers [137]; (iii) socio-cultural factors (e.g. disease visibility and social acceptance); (iv) lack of standardisation in diagnostic criteria and of adjustment to specific population characteristics (e.g. the most widely used DLCN criteria use absolute LDL-C levels as cut-offs, which may fit well with Western populations with similar LDL-C frequency distribution like the Netherlands; however in other regions or ethnicities or living standards (even within the same countries, e.g. urban vs. rural) the 90th-95th percentiles may vary considerably, and by using the Dutch cut-offs the estimated or recorded FH prevalences may be over- or under-estimated); (v) accessibility to genetic testing, or presence (and coverage) of screening programmes; (vi) variability in clinical practice [4]. Consideration of all these factors makes it difficult to accurately model FH prevalence in a particular setting/population, and extrapolations between regions are likely inappropriate. Nevertheless, low rates of FH identification are reported universally. To address this, national registries have been initiated in many countries, in some cases prompted by participation in the EAS FHSC. Education programmes to improve FH awareness and knowledge are a recognised priority. In most cases, initiatives are promoted in association with scientific societies, academic/research institutions, and patient groups. Support and funding for FH management and initiatives are often lacking.

In most countries, diagnosis primarily relies on DLCN, and less frequently on SB or MEDPED. Whether these traditional criteria are applicable to more contemporary populations and different regions is uncertain. There is a need for country/region-specific tools for FH diagnosis (for the reasons discussed above, it is unlikely that a one-fits-all standard, e.g. for LDL-C cut-off levels, be applicable to all populations, but adjustments are likely needed); however, only a minority have regionally-modified criteria. Though often available, genetic testing is not widely implemented, with cost being a frequent issue (in some cases self-funded or only available in the context of research). Where available, genetic testing is mainly used to confirm diagnosis where there is a strong likelihood of FH based on clinical criteria. About one-third of countries offer genetic cascade screening, albeit usually on a regional basis with few offering nationwide coverage. Only a minority of "national government programmes" are promoted by health authorities.

FH management varies across (and frequently within) countries (specialist lipid clinics, non-lipid specialists, and/or in primary care), and under-treatment is common. High-intensity statins, usually with add-on ezetimibe, are the standard of care. However, therapy for FH is not universally reimbursed, and criteria vary across countries. In 4 countries ezetimibe is not available. PCSK9i are available in ~two-thirds of countries, but with restricted use. Lipoprotein apheresis is offered in ~60% of countries, usually limited to one centralised or a few reference centres, sometimes in private healthcare.

In conclusion, this survey of > 60 countries participating in the EAS FHSC reinforces the need to improve FH awareness, identification and management worldwide. Registries (including data linkage studies), both national and international, are essential for driving improvement in FH care and policy. The EAS FHSC registry, which aims to generate large-scale, cross-regional data on FH, will play a major role in this respect.

Conflicts of interest

A full disclosure of authors' potential conflicts of interest is shown in the Supplemental Material.

Author contributions

This manuscript was conceived by AJVV, MDM and KKR. The lead investigators wrote a report for their corresponding country/region. AJVV and MDM collated all reports and edited and merged them for inclusion in the manuscript. AJVV and MDM drafted the manuscript. All authors critically reviewed the manuscript and approved its submission.

The funding organisations had no influence on the design and conduct of the study; collection, management, and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.08.051.

Appendix

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