

# THE LANCET

## Supplementary appendix

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**GLOBAL PERSPECTIVE OF FAMILIAL HYPERCHOLESTEROLAEMIA: A CROSS-SECTIONAL STUDY FROM THE EAS FAMILIAL HYPERCHOLESTEROLAEMIA STUDIES COLLABORATION (FHSC)**

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**APPENDIX 1 – EAS FAMILIAL HYPERCHOLESTEROLAEMIA STUDIES COLLABORATION (FHSC) COMMITTEES AND INVESTIGATORS**

**APPENDIX 2 – SUPPLEMENTAL MATERIAL**

## APPENDIX 1

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## APPENDIX 2 – SUPPLEMENTAL MATERIAL

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## SUPPLEMENTAL METHODS

The methods of the FHSC are described in further detail within the FHSC protocol, which can be accessed (open access) at “*Atheroscler Suppl* 2016; 22: 1–32”, <https://doi.org/10.1016/j.atherosclerosissup.2016.10.001>.

### Data entry criteria

The FHSC Registry inclusion criteria comprise both adults and children, with a clinical and/or genetic diagnosis of heterozygous (HeFH) or homozygous (HoFH) FH. Where the diagnosis is clinical, this must conform with accepted clinical criteria (or modified criteria thereof) such as the Dutch Lipid Clinic Network (DLCN), Make Early Diagnosis to Prevent Early Deaths (MEDPED), Simon-Broome criteria, Canadian definition of FH, or Japanese Atherosclerosis Society FH criteria. Where data is available (through cascade screening or other), unaffected (non-FH) relatives of index cases are also included. Exclusion criteria includes cases relying only on a self-reported history of FH and those with secondary causes of hypercholesterolaemia. Additionally, quality and operational criteria are required: the data must be in electronic format and should add relevant information to the registry; participants included should be representative of the target population and the data must have been collected rigorously, with defined inclusion/exclusion criteria and standard definitions of variables; data sharing must be compliant with local ethical and security requirements, data must have been de-identified prior to transferring to the FHSC, and a data sharing agreement between the data supplier and the FHSC must be in place prior to any data sharing with the FHSC.

### Data management

The FHSC Global Registry draws upon data from an international consortium of investigators with access to patients managed in specialist clinics which serve as national, regional or local registries of FH. Individual data from these diverse data sources are then harmonised and merged into a single global FH Registry. Data is transferred by the appointed FHSC country lead (responsible for the coordination of regional or country-level data from individual sites within the specific country) to the FHSC Coordinating Centre (Imperial College London, United Kingdom) through the bespoke FHSC web-based platform (Supplemental Figure 1). The platform accepts the transfer of individual participant data as whole datasets or entered individually by the lead investigators or their affiliated centres via a bespoke individual data entry application in a pseudoanonymised fashion. The data shared by each provider are checked for quality, consistency, and accuracy at the Coordinating Centre first through automated data validation algorithms upon reception of the data and then manually at the analysis stage. Any discrepancies are resolved by raising queries with the respective individual investigators. The information is saved into a central Data Warehouse securely on a restricted server at the Coordinating Centre in strict adherence with data safety protocols and regulatory requirements. A comprehensive data dictionary has been produced for multiple variables which allow standardisation of information irrespective of its source. Within the FHSC data warehouse, country (provider)-specific bespoke electronic algorithms mapped to the data dictionary automatically transform incoming data into a standardised output, thus allowing seamless mapping of incoming data and merging into a single coherent FHSC global dataset.

### Present Study

In the present study we conducted a cross-sectional assessment of adult patients (age  $\geq 18$  years) with probable or definite HeFH (possible and definite using Simon-Broome criteria) at the time individuals were entered into the respective parent registries. Descriptive assessment of characteristics of the cohort included demographics,

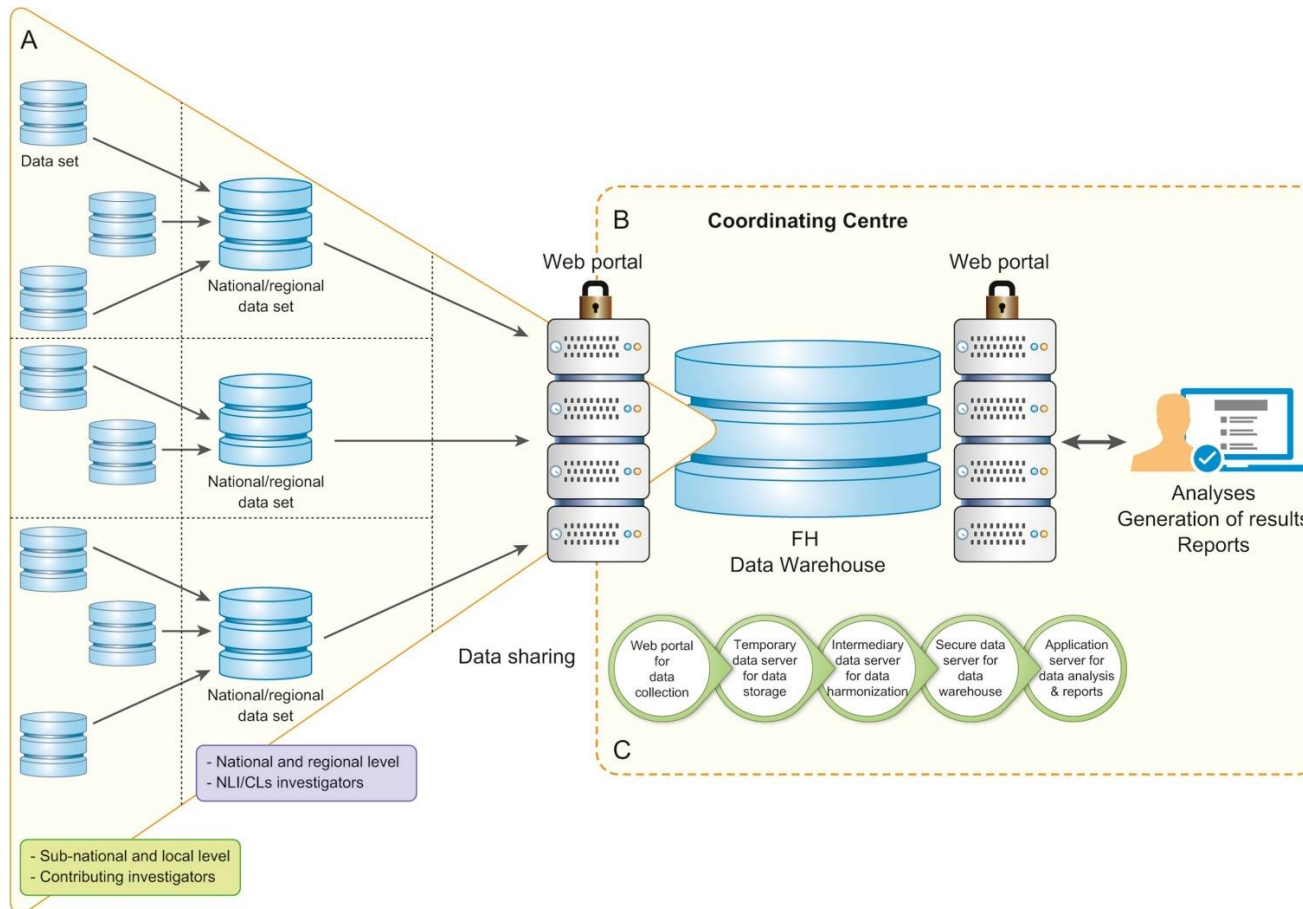


cardiovascular risk factors (CVRF) and co-morbidities, time of FH diagnosis, lipid levels, proportion of patients taking lipid-lowering medication (LLM) and type of medication, and among patients on LLM, the proportion of patients below recommended LDL-C goals.

Merged data were analysed at individual-level on the composite dataset. Where a data supplier/investigator of a specific country was not granted approval by their local ethical/research committee to provide individual-level data to the FHSC, similar analyses to those conducted on the merged dataset were conducted by the corresponding investigator on their respective individual-level dataset, and the aggregated results were shared with the FHSC. In this instance, summary data for each relevant output of interest were combined with the results from the merged dataset in case of categorical variables, whereas summary of results for quantitative variables are presented separately. In all cases except France (French Registry of Familial Hypercholesterolaemia) data were provided at an individual-level and were merged and analysed as one composite dataset. A total of 42,167 adults with HeFH from 56 countries were included in the present analysis, Supplemental Figure 2 (including 37,972 cases with individual-level data available and 4,195 cases with aggregated data [French registry]).

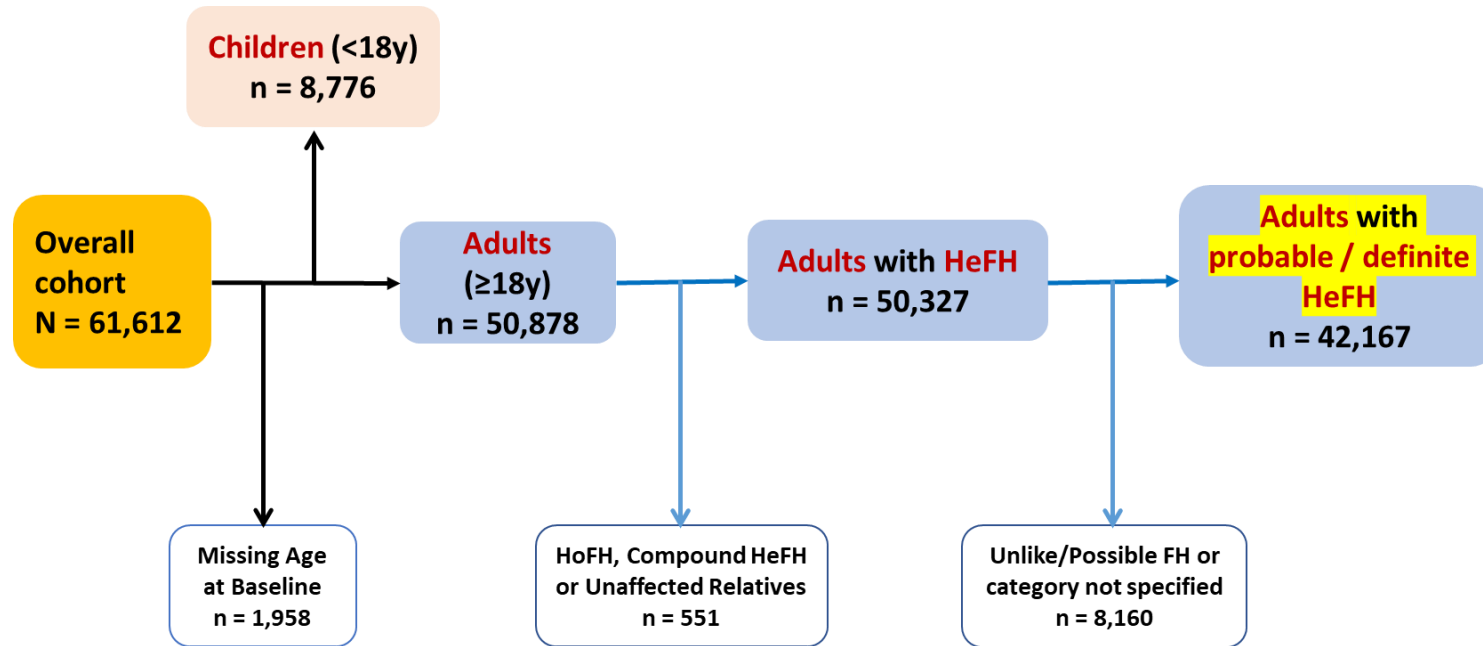
## SUPPLEMENTAL FIGURES

Supplemental Figure 1. Data flow and management in the Familial Hypercholesterolaemia Studies Collaboration (FHSC) Registry.



Reproduced with permission from "EAS Familial Hypercholesterolaemia Studies Collaboration. *Atheroscler Suppl* 2016; 22: 1–32. doi: 10.1016/j.atherosclerossup.2016.10.001". ©2016 Elsevier Ireland Ltd. FH, Familial Hypercholesterolaemia; NLI/CL, National Lead investigator/Country Lead.

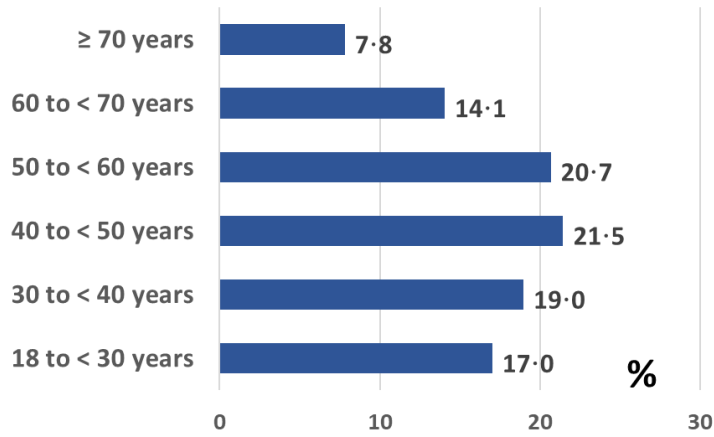
Supplemental Figure 2. Selection of adult participants with Heterozygous Familial Hypercholesterolaemia for inclusion in the present study from the overall FHSC Registry participants.



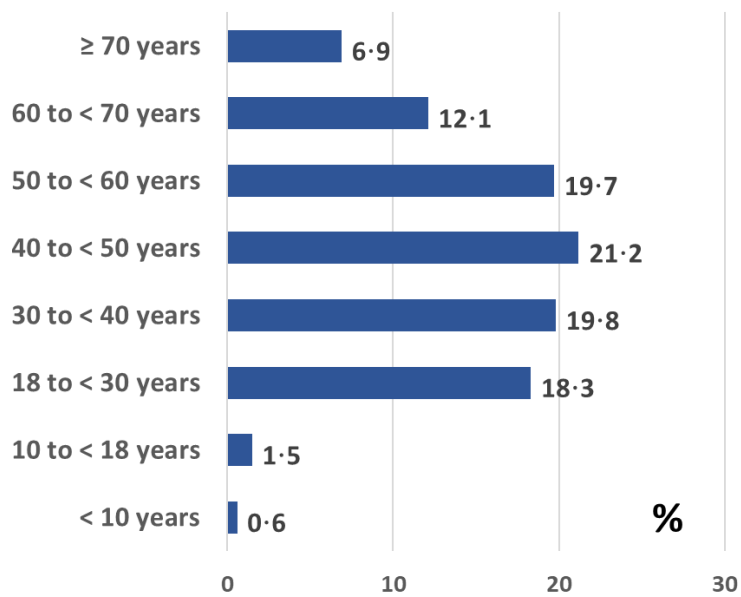
Further details are described in the Methods section of the Article. FH, Familial Hypercholesterolaemia; HeFH, Heterozygous Familial Hypercholesterolaemia; HoFH, Homozygous Familial Hypercholesterolaemia; y, years.

**Supplemental Figure 3. Distribution of participants by age at entry in the registry (A) and at FH diagnosis (B).**

**(A) By age at entry in the registry.**

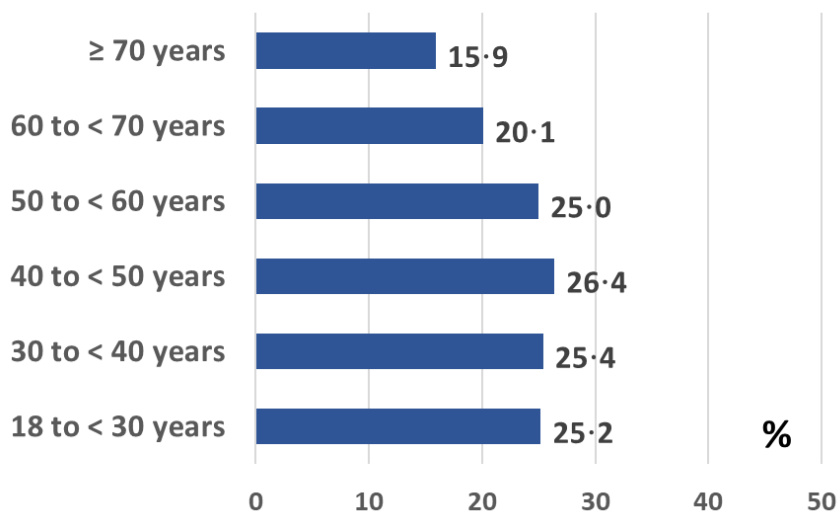


**(B) By age at FH diagnosis.**

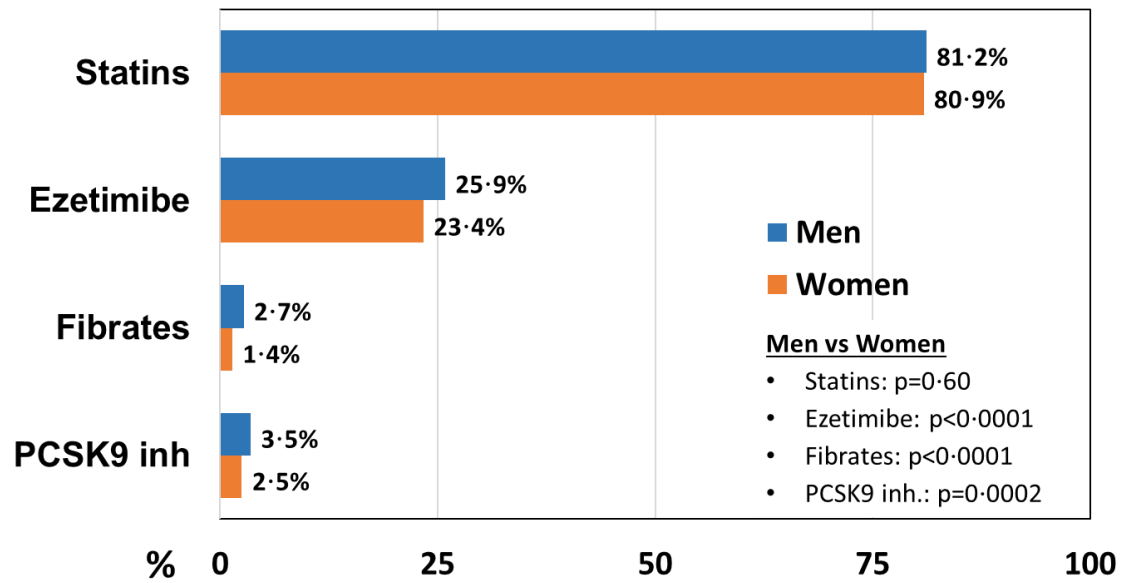


Inclusion criteria for the study was age at entry in the registry 18 years or older. FH, familial hypercholesterolaemia.

**Supplemental Figure 4. Prevalence of smoking (current smokers) by age.**



**Supplemental Figure 5. Type of lipid-lowering medication stratified by sex among participants taking lipid lowering medication at registry entry.**

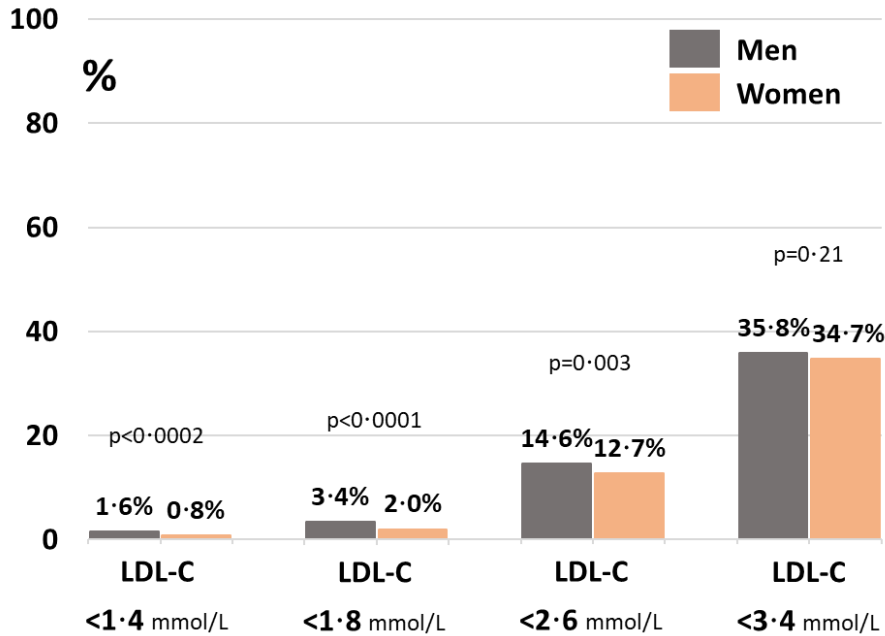


**Combination therapy**  
**(Statins +/- ezetimibe +/- PCSK9 inh)**  
 Men: 22.7%  
 Women: 19.9%  
 Men vs Women, p<0.0001

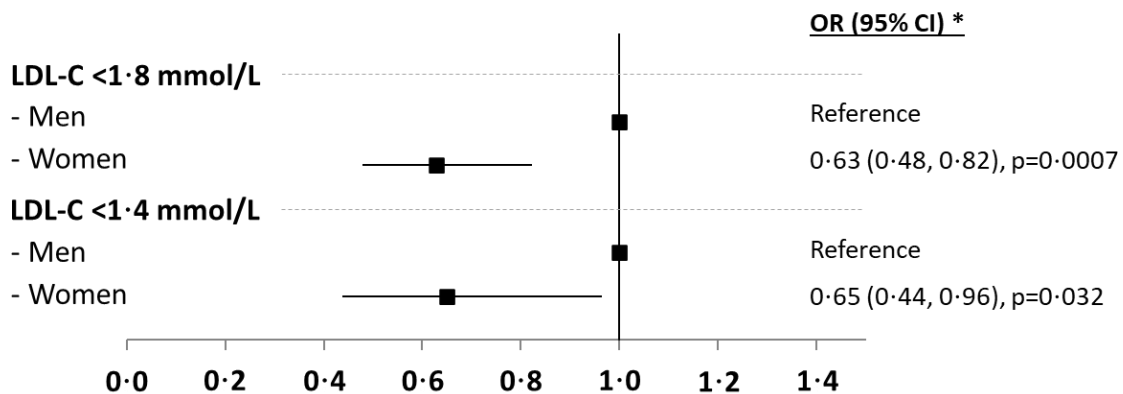
PCSK9 inh, proprotein convertase subtilisin/kexin type 9 inhibitors.

**Supplemental Figure 6. Attainment of LDL-C targets among patients on LLM (statins, ezetimibe and/or PCSK9 inhibitors) stratified by sex.**

**(A) Percentage of patients on lipid-lowering medication with an LDL-C below different thresholds stratified by sex.**



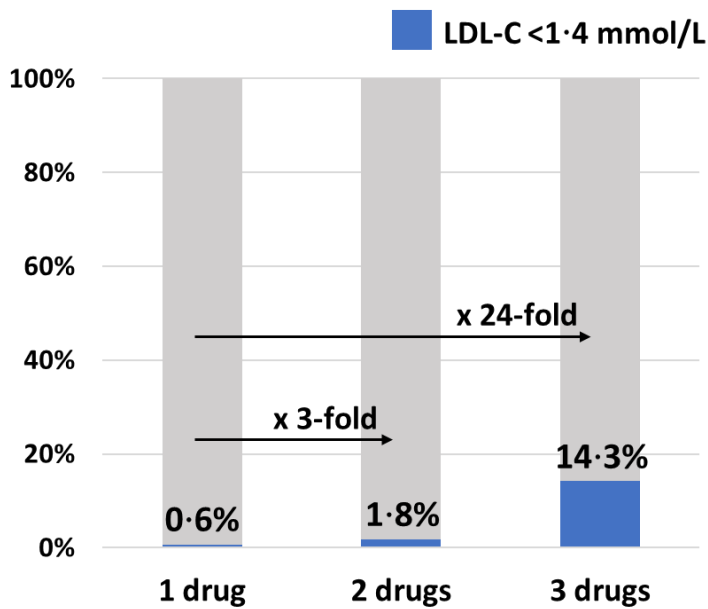
**(B) Association of sex with having an LDL-C below different thresholds.**



\* Adjusted by age, baseline comorbidities (hypertension, diabetes, smoking, body mass index), high-density lipoprotein cholesterol, log(triglycerides), lipid-lowering medication, and index case status. CI, confidence interval, LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

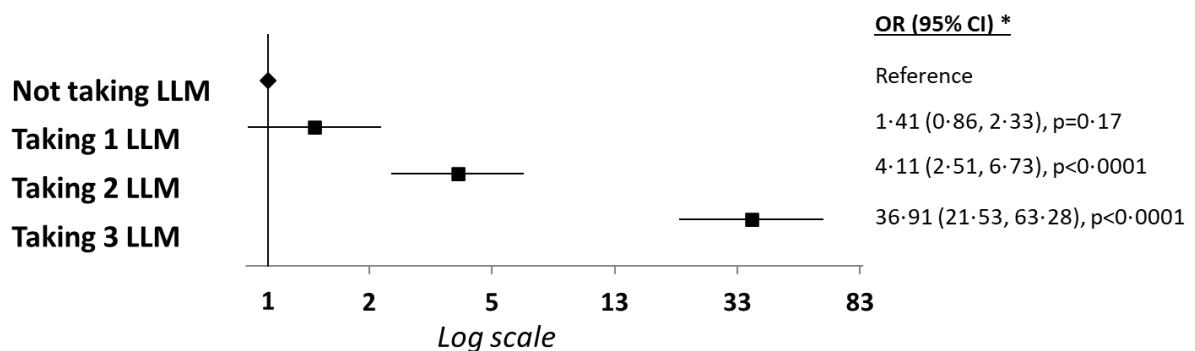
**Supplemental Figure 7. Attainment of LDL-C <1.4 mmol/L among patients on lipid-lowering medication (statins, ezetimibe and/or PCSK9 inhibitors)**

**(A) Percentage of patients with an LDL-C <1.4 mmol/L based on the number of lipid-lowering medication taken.**



LDL-C, low-density lipoprotein cholesterol.

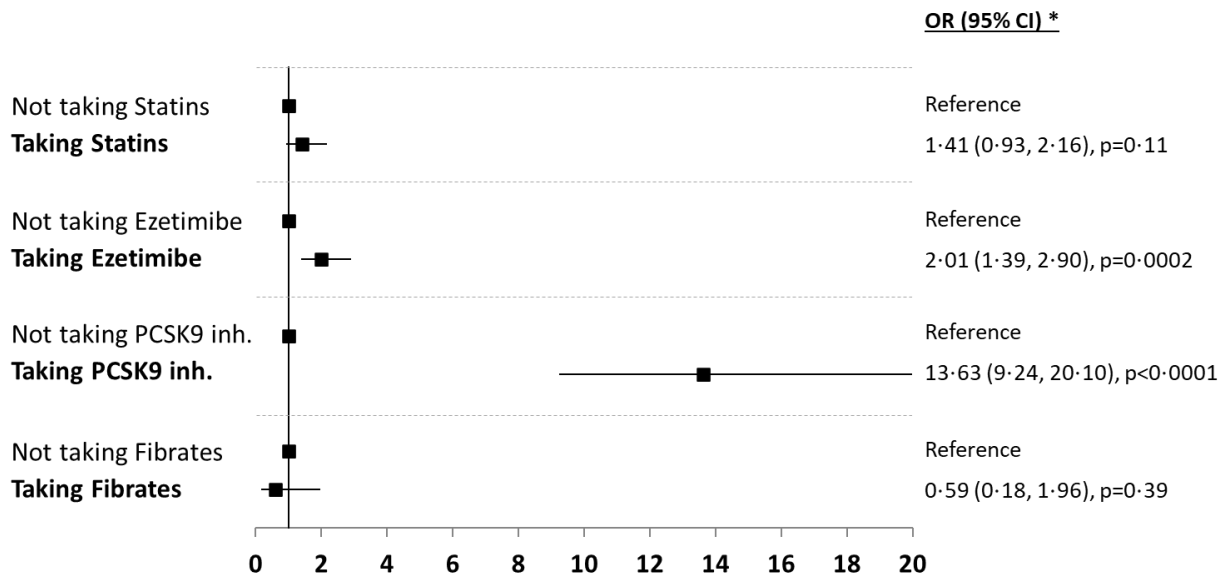
**(B) Association of number of lipid-lowering medications taking with having an LDL-C <1.4 mmol/L**



\* Adjusted by age and sex. CI, confidence interval, LDL-C, low-density lipoprotein cholesterol; LLM, lipid-lowering medication; OR, odds ratio.

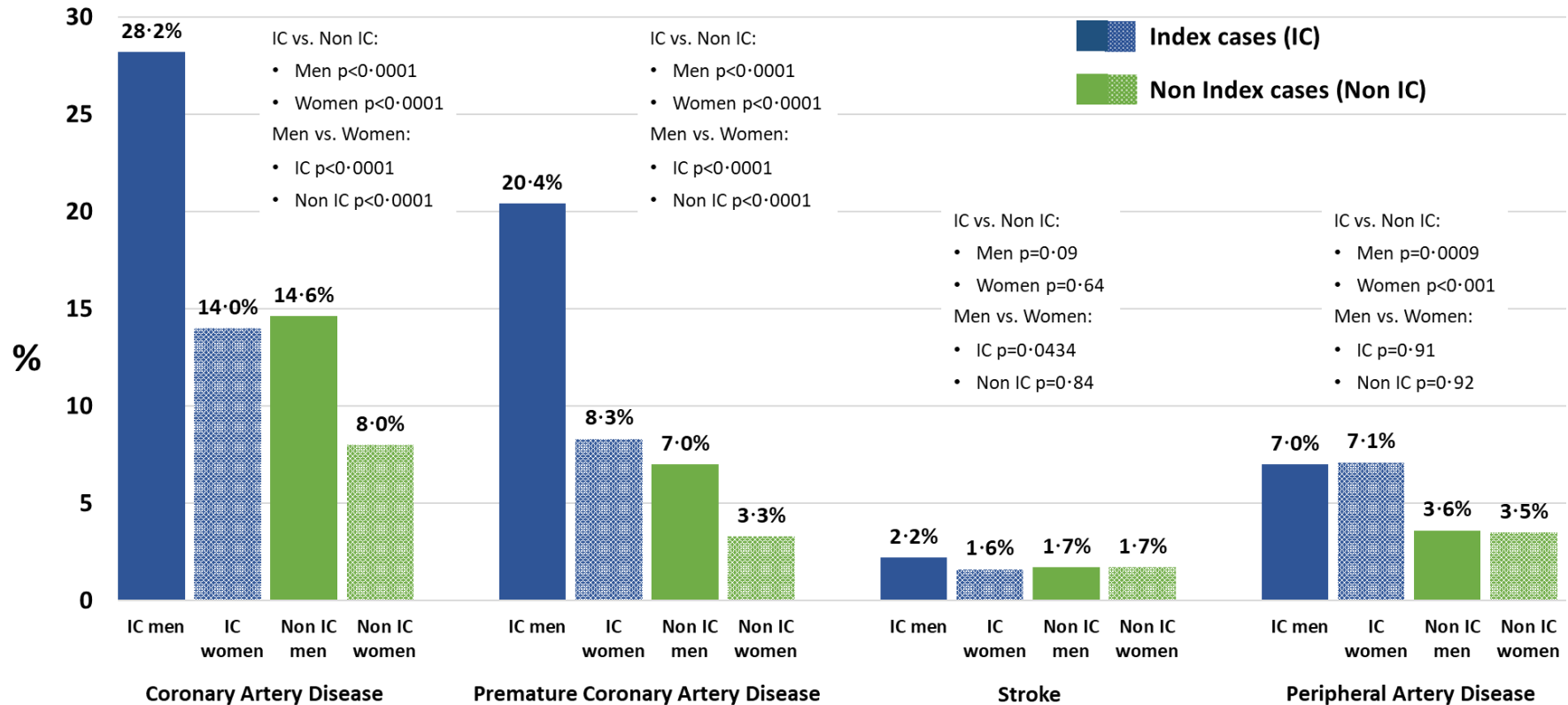


**(C) Association of type of lipid-lowering medication taking with having an LDL-C <1.4 mmol/L**



\* Each one adjusted by age, sex and the other types of lipid-lowering medications. CI, confidence interval, LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PCSK9 inh, proprotein convertase subtilisin/kexin type 9 inhibitors.

Supplemental Figure 8. Cardiovascular Disease by index case and sex.



## SUPPLEMENTAL TABLES

**Supplemental Table 1. Characteristics of the individual registries contributing with data to the FHSC Registry at the time of the present analysis.**

| Country                             | Registry Name           | Ref | Registry Inclusion Criteria   | Registry Exclusion Criteria   | FH Diagnosis Criteria for Inclusion  | Period Included in the FHSC Registry | Data Source   | Registry Geographical Coverage     | Number of participants included in the present Study |
|-------------------------------------|-------------------------|-----|---|---|--|--------------------------------------|---|------------------------------------|--|
| <b>AFRICA</b>                       |                         |     |   |   |  |                                      |   |                                    |  |
| <b>NIGERIA</b>                      | The Benin FH Registry   | -   | Adults with LDL-C $\geq$ 4 mmol/L with a diagnosis of probable or definite HeFH according to DLCN criteria  | Secondary dyslipidaemia   | DLCN   | 2016 – 2019                          | Health screening clinic                                   | Mid-Western Nigeria                | 5  |
| <b>SOUTH AFRICA</b>                 | -                       | -   | Genetically confirmed FH with Afrikaner founder mutations   | Clinical FH not confirmed on genetic testing or those with other FH mutations | Genetic test FH Afrikaner mutation   | Past 10–15 years                     | Lipid clinic  | Johannesburg and surrounding areas | 839  |
|                                     | -                       | -   | Adults and children with a diagnosis of probable (LDL-C $>$ 5 mmol/L and dominantly inherited in family with premature CAD) or definite (tendon xanthoma with LDL-C $>$ 5 mmol/L) HeFH among patients referred for assessment of severe dyslipidaemia | Secondary hypercholesterolaemia   | As defined in the registry inclusion criteria  | 1990 – 2014                          | Clinical notes and research lab records                   | Local (Cape Town)                  |  |
| <b>AMERICAS</b>                     |                         |     |   |   |  |                                      |   |                                    |  |
| <b>ARGENTINA</b>                    | DA VINCI                | -   | Adults and children; clinical diagnosis of HeFH (DLCN score $\geq$ 6)   | Secondary dyslipidaemia   | DLCN   | 2015 – 2019                          | Primary care and specialist care (cardiology, lipidology) | Province of Buenos Aires           | 78   |
| <b>BRAZIL</b>                       | Hipercol Brasil         | 1   | Genetic diagnosis of FH   | Secondary dyslipidaemia   | Genetic  | 2013 – 2017                          | Cascade screening at a tertiary Hospital                  | National                           | 905  |
| <b>CANADA</b>                       | FH Canada Registry      | 2   | Diagnosis of possible, probable or definite FH as per Simon Broome, DLCN or Canadian Definition for FH  | Secondary hypercholesterolaemia   | Simon-Broome, DLCN, or Canadian Definition of FH (Ref 3), depending on site and time of data acquisition | 2014 – 2017                          | Lipid clinics   | National                           | 1,505  |
| <b>CHILE</b>                        | -                       | -   | Adults and children with a clinical (DLCN score $\geq$ 6) or genetic diagnosis of FH  | -   | DLCN; Genetic  | 2005 – 2018                          | Lipid clinic  | Local (Santiago)                   | 50   |
| <b>MEXICO</b>                       | Registro Mexicano de HF | 4,5 | Adults and children with an LDL-C $>$ 4.9 mmol/L with a diagnosis of possible, probable or definite FH according to DLCN criteria.  | Other types of primary dyslipidaemia. Secondary hypercholesterolaemia         | DLCN   | 2017 – 2019                          | Lipid clinics   | National                           | 530  |
| <b>URUGUAY</b>                      | GENYCO                  | 6,7 | Positive genetic test for a causative mutation of FH, and unaffected (non-FH) relatives   | DLCN score $<$ 3. Secondary hypercholesterolaemia                             | DLCN   | 2004 – 2018                          | Primary care and specialist care                          | National                           | 194  |
| <b>EASTERN MEDITERRANEAN REGION</b> |                         |     |   |   |  |                                      |   |                                    |  |

| Country      | Registry Name                              | Ref   | Registry Inclusion Criteria   | Registry Exclusion Criteria  | FH Diagnosis Criteria for Inclusion | Period Included in the FHSC Registry | Data Source                       | Registry Geographical Coverage  | Number of participants included in the present Study |
|--------------|--|-------|---|--|-------------------------------------|--------------------------------------|-----------------------------------|---|--|
| EGYPT        | Egyptian FH Research Forum Registry        | 8     | Prior established diagnosis of FH. Premature atherosclerosis with possible, probable or definite FH diagnosis according to DLCN criteria            | Secondary dyslipidaemia. Drug or substance abuse "in case of premature CAD". Thyroid dysfunction   | DLCN                                | 2017 – 2019                          | Cardiology clinics                | National  | 36   |
| IRAQ         | Iraqi FH registry                          | -     | Adults and children with a diagnosis of possible, probable and definite FH according to DLCN criteria   | Secondary hypercholesterolaemia including DM and CKD   | DLCN                                | 2018 – 2019                          | Primary care, lipid clinics       | North (Erbil, Kirkuk) and Central (Baghdad, Balad, Diwaniyah) regions | 15   |
| KUWAIT       | KtFH                                       | 9,10  | Age 18-70 years old with an LDL-C $\geq$ 4.9 mmol/L and/or TC $\geq$ 7.5 mmol/L meeting the DLCN criteria for probable or definite HeFH             | TG >5 mmol/L. Untreated hypothyroidism. Proteinuria $\geq$ 1 g/L. Obstructive liver disease. CKD. HIV infection. Taking immunosuppressant, steroid or psychiatric drugs. LDL-C <4.9 mmol/L after applying correction factors to account for LLM in those on LLM                                      | DLCN                                | 2017 – 2018                          | Cardiology and lipid clinics      | National  | 27   |
| LEBANON      | -  | -     | Adults and children with a clinical diagnosis of FH according to MEDPED/WHO or DLCN criteria (probable and definite FH), or genetic diagnosis of FH | Secondary hypercholesterolaemia  | MEDPED/WHO criteria, DLCN, Genetic  | 2012 – 2019                          | Lipid clinic                      | Several regions   | 13   |
| OMAN         | Oman FH                                    | -     | Genetic diagnosis of FH   | TG >5 mmol/L. Untreated hypothyroidism. Proteinuria $\geq$ 1 g/L. Obstructive liver disease. CKD. HIV infection. Use of immunosuppressants, steroids or psychiatric medications  | DLCN                                | 2015 – 2019                          | Hospital records                  | National  | 39   |
| PAKISTAN     | Pakistan FH Registry                       | -     | Adults and children with a clinical diagnosis of FH according to modified DLCN criteria (score $\geq$ 5)  | Secondary dyslipidaemia  | DLCN                                | 2016 – 2019                          | Hospital records and primary care | Mainly Lahore and Islamabad   | 12   |
| SAUDI ARABIA | Partially included in the Gulf FH registry | 11,12 | Genetic diagnosis of FH   | Non-nationals. Obstructive liver disease. Hypothyroidism. CKD (>1.4 mg/dL or as defined by the investigator, or GFR <60 ml/min/1.73 m <sup>2</sup> , or >60 with other markers of kidney damage e.g.proteinuria. Proteinuria >1 g/L. Taking steroids, immunosuppressants, or HIV drugs. TG >5 mmol/L | Simon-Broome                        | 2015 – 2018                          | Cardiovascular Prevention Unit    | National  | 238  |

| Country                       | Registry Name   | Ref   | Registry Inclusion Criteria   | Registry Exclusion Criteria   | FH Diagnosis Criteria for Inclusion    | Period Included in the FHSC Registry | Data Source   | Registry Geographical Coverage | Number of participants included in the present Study |
|-------------------------------|---|-------|---|---|--|--------------------------------------|---|--------------------------------|--|
|                               | Part of the Gulf FH registry  | 10    | LDL-C $\geq$ 4.9 mmol/L and/or TC $\geq$ 7.5 mmol/L and meeting the DLCN criteria for possible, probable and definite FH                                      | TG >5 mmol/L. Untreated hypothyroidism, proteinuria $\geq$ 1 g/L, obstructive liver disease, CKD, HIV infection. Taking steroid or immunosuppressant or psychiatric medications. LDL-C <4.9 mmol/L after applying correction factors to treated LDL-C for patients on LLM | DLCN                                   | 2016 – 2019                          | Lipid clinic, hospital cardiology departments, tertiary hospitals               | National                       |  |
| <b>UNITED ARAB EMIRATES</b>   | Part of the Gulf FH registry  | 10    | Age 18-70 years old) with an LDL-C $\geq$ 4.9 mmol/L or TC $\geq$ 7.5 mmol/L, on or off LLM, and meeting the DLCN criteria for FH                             | TG >5 mmol/L. Untreated hypothyroidism. Proteinuria $\geq$ 1 g/L. Obstructive liver disease. CKD. HIV infection. Taking steroid or immunosuppressant or psychiatric medications. LDL-C <4.9 mmol/L after applying correction factor for patient on LLM                    | DLCN                                   | 2016 – 2018                          | Laboratory Information System of Hospital and Primary Care Clinics              | National                       | 12   |
| <b>EUROPE</b>                 |   |       |   |   |  |                                      |   |                                |  |
| <b>AUSTRIA</b>                | “Fass dir ein Herz” FH Registry of the Austrian Atherosclerosis Society | -     | Diagnosis of FH according to clinical criteria (possible, probable and definite FH by DLCN for adults; possible and definite FH by Simon-Broome for children) | Secondary hypercholesterolaemia   | DLCN (adults); Simon-Broome (children) | 2016 – 2018                          | Primary care and specialist care (e.g. lipid clinics, cardiology, etc.)         | National                       | 248  |
| <b>BELGIUM</b>                | -   | -     | Age $\geq$ 18 years with a diagnosis of FH according to DLCN score $\geq$ 5, positive MEDPED or positive genetic testing                                      | Combined genetic hyperlipemia. Mixed dyslipidaemia. Secondary hypercholesterolaemia   | DLCN; MEDPED; Genetic                  | 2000 – 2019                          | Lipid clinics   | Wallonia and Brussel regions   | 667  |
| <b>BOSNIA AND HERZEGOVINA</b> | -   | 13-16 | LDL >5 mmol/l with diagnosis of FH by DLCN criteria   | Members FH family with cardiovascular events independently of LDL values  | DLCN                                   | May-2015 to Jan-2019                 | Hospital records mainly, out hospital examinations, cardiology, primary care    | Hospital one site              | 28   |
| <b>BULGARIA</b>               | FH Registry of the Bulgarian Society of Cardiology                      | 17    | Adults and children with a diagnosis of FH according to DLCN score >3   | -   | DLCN                                   | 2018                                 | Lipid clinics   | National                       | 121  |
| <b>CROATIA</b>                | -   | -     | Adults with a clinical (probable or definite by DLCN criteria) and/or genetic diagnosis of FH   | Mixed dyslipidaemia, secondary hypercholesterolaemia  | DLCN                                   | 2016 – 2019                          | Lipid clinics, cardiology   | North and west regions         | 72   |
| <b>CZECHIA</b>                | The Czech MEDPED database   | 18-20 | Age >18 years with a genetic diagnosis (confirmed mutation causative) of HeFH   | Secondary hypercholesterolaemia   | Genetic                                | 1998 – 2018                          | Czech MedPed centres (mainly lipid, internal medicine and cardiologist clinics) | National                       | 1,991  |

| Country    | Registry Name | Ref   | Registry Inclusion Criteria  | Registry Exclusion Criteria   | FH Diagnosis Criteria for Inclusion      | Period Included in the FHSC Registry          | Data Source   | Registry Geographical Coverage               | Number of participants included in the present Study |
|------------|---------------|-------|--|---|--|---|---|--|--|
| ESTONIA    | -             | -     | Diagnosis of HeFH by DLCN criteria   | Non-FH dyslipidemias  | DLCN                                     | 2018  | Hospital records  | Local (Tallinn)                              | 1  |
| FRANCE     | REFERCHOL     | 21-25 | Adults and children with a clinical (DLNC $\geq 6$ for adults) or genetic diagnosis of HeFH  | DLCN $< 6$ , refusal to participate, secondary hypercholesterolaemia  | DLCN, genetic (mainly genetic diagnosis) | Retrospective data without time limit to 2019 | Specialist care (e.g. endocrinology, cardiology, internal medicine)                                 | National registry, including overseas France | 4,195  |
| GERMANY    | CaRe High     | 26,27 | Adults and children with at least two of the following criteria: (i) LDL-C $> 4.9$ mmol/L without LLM (LDL-C values on LLM are corrected for drug and dose) or TC $> 7.50$ mmol/L; (ii) Tendon xanthomas; (iii) Family history of hypercholesterolaemia; (iv) Family history of MI before the age of 50 in grandparents, uncles or aunts, or before the age of 60 in parents, siblings or children; (v) First and second-degree relatives of FH patients | Apparent impairment of cognitive function; decompensated, acute psychiatric disease; acute, non-CVD; surgery within the last 3 months (not caused by CVD); chronic, non-cardiac diseases (e.g. severe CKD, dialysis, severe rheumatic arthritis, malignant disease within the last 5 years) | DLCN                                     | 2015 – 2018                                   | Most data from lipid clinics; also, primary care and other specialist care (cardiology, nephrology) | National                                     | 457  |
| GREECE     | HELLAS-FH     | 28,29 | Adults with a diagnosis of at least possible FH according to DLCN criteria, and children with a diagnosis based on the current EAS consensus statement on FH in children (Ref 30)  | DLCN score $< 3$ . Any clinically significant disorder which, at the discretion of the investigator, would exclude the safe completion of the study or limit the assessment of endpoints (e.g. major systemic diseases, patients with short life expectancy)                                | DLCN                                     | 2016 – 2019                                   | Lipid clinics   | National                                     | 756  |
| HUNGARY    | fhreg-hu      | 31    | Adults and children with a diagnosis of possible, probable and definite FH according to DLCN criteria  | Secondary hypercholesterolaemias  | DLCN                                     | 2016 – 2017                                   | Population-based, primary care and specialist care (lipid clinics, cardiology)                      | National                                     | 86   |
| IRELAND    | -             | -     | Adults and children with a diagnosis of possible, probable and definite FH according to DLCN criteria  | -   | DLCN                                     | 2019  | Lipid clinics   | Local (Dublin)                               | 7  |
| ISRAEL     | MEDPED Israel | 32,33 | Adults and children with a diagnosis of FH according to MEDPED criteria, including LDL-C $> 4.9$ mmol/L, stigmata of FH, family history.   | According to MEDPED   | MEDPED, Simon-Broome, Genetic            | 1989-2018                                     | Lipid clinic  | Local  | 755  |
| ITALY      | LIPIGEN       | 34-36 | Adults and children with a clinical (DLCN criteria) or genetic diagnosis of FH   | Secondary hypercholesterolaemia   | DLCN                                     | 2011 – 2018                                   | Lipid Clinics   | National                                     | 1,783  |
| KYRGYZSTAN | -             | -     | Adults and children with a clinical diagnosis of probable or definite FH according to DLCN criteria  | Secondary dyslipidaemia   | DLCN                                     | 2017 – 2019                                   | Primary care and hospital records   | National                                     | 98   |

| Country     | Registry Name  | Ref   | Registry Inclusion Criteria  | Registry Exclusion Criteria  | FH Diagnosis Criteria for Inclusion  | Period Included in the FHSC Registry | Data Source   | Registry Geographical Coverage | Number of participants included in the present Study |
|-------------|--|-------|--|--|--|--------------------------------------|---|--------------------------------|--|
| LATVIA      | Latvian Registry of FH   | 37    | Adults with (i) definite or probable FH according to DLCN criteria, and (ii) first degree relatives of index cases with LDL-C >95th percentile | First degree relatives of index cases with LDL-C <95th percentile. Suspected or confirmed secondary hypercholesterolaemia. Suspected or confirmed primary hypertriglyceridemia or primary mixed hyperlipidemia | Index cases: DLCN. First degree relatives: LDL-C >95th percentile                | 2015 – 2019                          | Hospital Cardiology outpatient department   | National                       | 65   |
| LITHUANIA   | National Screening Programme for FH and Nationwide Primary Prevention Programme in Lithuania | 38,39 | Adults and children with a clinical or genetic diagnosis of FH according to DLCN criteria  | Secondary dyslipidaemia  | DLCN   | 2018 – 2019                          | Mostly cardiology prevention unit   | National                       | 39   |
| MALTA       | FH Malta   | 40    | Adults with a diagnosis of possible, probable or definite HeFH according to DLCN criteria  | Secondary dyslipidaemia  | DLCN   | 2016 – 2018                          | Primary care and specialist care (lipid clinics, cardiology, diabetes clinic)                   | National                       | 24   |
| NETHERLANDS | StOEH  | 41,42 | Adults and children in the cascade screening project in the Netherlands, with a positive genetic testing for HeFH                              | -  | Genetics   | 1994 – 2014                          | Population based  | National                       | 19,529   |
| NORWAY      | FHNO-alfa  | 43,44 | Adults and children with a clinical or genetic diagnosis of HeFH and at least two visits to the Lipid Clinic                                   | Available data from only one visit. HoFH. Secondary hypercholesterolaemia  | Mainly genetic diagnosis. A few with clinical FH based on physicians' discretion | 2014 – 2015                          | Lipid Clinic  | Local (Oslo)                   | 356  |
| POLAND      | PoLA-FH-Registry   | -     | Adults and children with a diagnosis of definite and probable FH according to DLCN criteria  | DCLN score <6. Secondary hypercholesterolaemia   | DLCN   | 2018 – 2019                          | Primary care and ambulatory clinics; population-based; hospitalization at different departments | National                       | 1,433  |
|             | Polish FH Registry at Medical University of Gdansk   | 45-47 | Adults and children with a clinical (definite by DLCN score >8) or genetic diagnosis of FH   | Secondary hypercholesterolaemia  | DLCN   | 2006 – 2014<br>2017 – 2019           | Primary care and specialist care (lipid clinics, cardiology)                                    | National                       |  |
| PORTUGAL    | Portuguese FH Study  | 48    | Adults and children with a diagnosis of possible or definite FH according to Simon-Broome criteria   | -  | Simon-Broome   | 2015 – 2018                          | Primary care and specialist care (cardiology, internal medicine, endocrinology, paediatrics)    | National                       | 92   |

| Country     | Registry Name   | Ref   | Registry Inclusion Criteria   | Registry Exclusion Criteria   | FH Diagnosis Criteria for Inclusion                               | Period Included in the FHSC Registry | Data Source   | Registry Geographical Coverage       | Number of participants included in the present Study |
|-------------|---|-------|---|---|---|--------------------------------------|---|--------------------------------------|--|
| RUSSIA      | -   | 49,50 | Before year 2015: Family history of FH and/or CVD in first-degree relatives aged <50 years men and <60 years in women. From 2015 onward: Age ≥18 years old with a clinical diagnosis (DLCN score ≥6) of FH and at least 2 visits to lipid clinics | HoFH. Age <18 years. Secondary dyslipidaemias, including severe obesity and DM  | DLCN; Genetics  | 1984 – 2018                          | Population-based, lipid clinics, hospital records                   | Local (Moscow) and national registry | 1,186  |
|             | RuFH  | 51    | Age ≥18 years old with TC ≥7.5 mmol/L or LDL-C ≥4.9 mmol/L with a FH diagnosis according to DLCN or Simon-Broome criteria   | Secondary hypercholesterolaemia, including untreated DM (HbA1c >8%) or hypothyroidism (TSH >1.5 U/LN), renal failure (creatinine clearance <30 ml/min). Tumours within last 5 years                               | DLCN, Simon-Broome  | 2014 – 2017                          | Laboratory data set, primary care, lipid clinics                    | National                             |  |
| SERBIA      | -   | 52    | Adults and children with a clinical diagnosis of possible, probable and definite HeFH according to DLCN criteria  | Secondary dyslipidaemia   | DLCN  | 2012 – 2017                          | Lipid clinics and hospital records                                  | Central Serbia                       | -  |
| SLOVAKIA    | MEDPED FH Slovakia  | 53-57 | Adults and children with a diagnosis of probable or definite HeFH according to any of DLCN, Simon-Broome or MEDPED criteria, with at least 3 clinical visits at a centre  | Secondary hyperlipidaemias  | DLCN; Simon-Broome; MEDPED  | 1998 – 2019                          | Lipid, Cardiology and Internal Medicine clinics                     | National                             | 182  |
| SLOVENIA    | National Registry of FH and Rare Dyslipidemias                    | 58,59 | Young adults, adolescents, children and their parents (if diagnosed through child-parent screening); Genetically or clinically (Simon-Broome criteria) confirmed/very likely FH   | Secondary hypercholesterolaemia   | Genetic; if mutation negative: Simon-Broome                       | 2017 – 2019                          | Hospital records (clinical, genetic) and primary care reports       | National                             | 66   |
| SPAIN       | SAFEHEART Registry  | 60-66 | Age ≥18 years with a genetic diagnosis of FH  | Unaffected (non-FH) relatives   | Genetic   | 2013 - 2017                          | Lipid clinics (index cases, relatives) and primary care (relatives) | National                             | 508  |
| SWITZERLAND | MEDPED; DIAMOND; SAPPHIRE; at diagene Research Institute, Reinach | 67    | Adults and children with a clinically (Swiss Clinical Criteria for FH [modified DLCN criteria]) or genetically confirmed HeFH (OMIM #143890, #144010, #603776, #603813) and their relatives.  | Molecularly confirmed pathogenic genetic variants other than those in the <i>LDLR</i> (*606945), <i>APOB</i> (*107730), <i>PCSK9</i> (*607786) or <i>LDLRAP1</i> (*605747) genes. Secondary hypercholesterolaemia | Swiss Clinical Criteria for FH (modified DLCN criteria); Genetics | 1987 – 2019                          | Population-based, lipid clinics-based                               | National                             | 9  |
| TURKEY      | A-HIT2  | 68,69 | Age ≥18 years with a clinical diagnosis of at least possible FH according to DLCN criteria (DLCN ≥3)  | TG ≥4.5 mmol/L or secondary hyperlipidemia  | DLCN  | 2017 – 2018                          | Cardiology, Internal Medicine and Endocrinology outpatient clinics  | National                             | 489  |
| UKRAINE     | -   | -     | Adults and children with a diagnosis of FH according to either DLCN (score ≥3), Simon-Broome (possible, definite) or MEDPED criteria  | Secondary hypercholesterolaemia   | DLCN; Simon-Broome; MEDPED  | 2018 –2019                           | Primary care, Cardiology, hospital records                          | National                             | 58   |



| Country                | Registry Name       | Ref   | Registry Inclusion Criteria  | Registry Exclusion Criteria   | FH Diagnosis Criteria for Inclusion       | Period Included in the FHSC Registry | Data Source  | Registry Geographical Coverage  | Number of participants included in the present Study |
|------------------------|---------------------|-------|--|---|---|--------------------------------------|--|---|--|
| <b>UNITED KINGDOM</b>  | -                   | -     | Clinical diagnosis of possible and definite FH according to Simon-Broome criteria.   | Secondary dyslipidaemia   | Simon-Broome                              | 2018 – 2019                          | Lipid Clinics  | Local (Manchester)  | 67   |
| <b>UZBEKISTAN</b>      | RUzFH               | 70    | Adults and children with a diagnosis of FH according to a DLCN criteria score $\geq 5$ . Premature CAD, coronary revascularization, cerebral vascular disease or PAD were inclusion criteria | Age >75 years old. Statin intolerance. Chronic heart failure NYHA III-IV. CKD stage 4-5/5. Pregnant women | DLCN                                      | 2016 – 2019                          | Outpatient and inpatient departments of Cardiology                                   | National (Tashkent and regional registries at Andijan, Khorezm, Kashkadarya)          | 122  |
| <b>SOUTH-EAST ASIA</b> |                     |       |  |   |   |                                      |  |   |  |
| <b>INDIA</b>           | -                   | 71,72 | Adults and children with a clinical (possible, probable or definite by DLCN criteria) and/or genetic diagnosis of FH   | Secondary causes of dyslipidaemia   | DLNC                                      | 2015 – 2019                          | Health Check Clinics in hospitals  | Mumbai and New Delhi  | 68   |
| <b>THAILAND</b>        | Thai FH Registry    | -     | Adults with an LDL-C $\geq 4.9$ mmol/L during workplace health check-up, having a DLCN score $\geq 3$ . Known FH adult cases as shown in hospital records                                    | Secondary cause of hypercholesterolaemia  | DLCN                                      | 2018                                 | Workplace screening and hospital records   | Local (Bangkok)   | 95   |
| <b>WESTERN PACIFIC</b> |                     |       |  |   |   |                                      |  |   |  |
| <b>AUSTRALIA</b>       | -                   | 73    | Adult index cases with a genetic diagnosis of HeFH   | -   | Genetic                                   | 2004 – 2017                          | Lipid Clinic   | Western Australia   | 265  |
| <b>CHINA</b>           | Chinese FH Registry | 74-76 | Adults and children with a diagnosis of definite FH according to DLCN criteria   | Secondary hypercholesterolaemia   | DLCN                                      | 2015 – 2018                          | Primary care and specialist care (lipid clinics, cardiology)                         | National  | 202  |
|                        | -                   | -     | Adults and children with a diagnosis of FH according to the DLCN criteria.   | Secondary hypercholesterolaemia. Abnormal liver or kidney function  | DLCN                                      | 2005 – 2018                          | Atherosclerosis outpatient clinic  | Local (Beijing)   |  |
| <b>HONG KONG SAR</b>   | -                   | -     | Adults with a genetic diagnosis of FH  | Secondary hypercholesterolaemia   | DLCN; Genetic                             | 2011 – 2018                          | Lipid clinic   | Local (Shatin)  | -  |
| <b>JAPAN</b>           | -                   | -     | Adults and children with a diagnosis of HeFH according to the JAS guidelines criteria  | Secondary hypercholesterolaemia   | JAS guidelines criteria (Ref 77)          | 2018 – 2019                          | Lipid clinics  | National  | 253  |
|                        | PROLIPID            | -     | Adults and children with established diagnosis of HoFH, or clinical (JAS guidelines criteria) or genetic (LDLR, APOB or PCSK9 mutations) diagnosis of FH                                     | -   | Genetic; JAS guidelines criteria (Ref 77) | 2015 – 2018                          | Primary care and specialist care (lipid clinics, cardiology, metabolic clinic, etc.) | National  |  |
| <b>MALAYSIA</b>        | MyHEBAT-FH          | 78-86 | Adults and children; clinical (possible, probable and definite by DLCN or Simon-Broome) or genetic diagnosis of FH. Relatives of index cases without FH diagnosis                            | Secondary dyslipidaemia   | DLCN; Simon-Broome                        | 2006-2019                            | Primary care and specialist care   | West Malaysia (North, South, East & West Coast and Central regions) and East Malaysia | 742  |

| Country              | Registry Name   | Ref   | Registry Inclusion Criteria  | Registry Exclusion Criteria   | FH Diagnosis Criteria for Inclusion                  | Period Included in the FHSC Registry | Data Source   | Registry Geographical Coverage | Number of participants included in the present Study |
|----------------------|-----------------|-------|--|---|--|--------------------------------------|---|--------------------------------|--|
| SINGAPORE            | FHCARE          | 87    | Diagnosis of possible and definite FH according to Simon-Broome criteria; family members who were genetically diagnosed with FH  | Secondary hypercholesterolaemia   | Simon Broome Criteria                                | 2015 – 2019                          | Mainly lipid and cardiology clinics. Some from health screening | National                       | 265  |
| TAIWAN (Province of) | TAITAFH         | 88,89 | Adults and children with a diagnosis of probable or definite FH according to DLCN criteria   | Secondary causes of hyperlipidaemia   | DLCN   | 2002 – 2018                          | Primary care and specialist care (lipid clinics, cardiology)    | North regions                  | 240  |
| VIETNAM              | VINAFH Registry | 90,91 | Adults and children with a clinical diagnosis of probable or definite FH (DLCN or Starr <i>et al</i> criteria [ref 84]) or a genetic diagnosis of FH (LDLR, APOB or PCSK9 mutations) | Secondary dyslipidaemia. Among those without genetic testing: possible or unlikely FH. With genetic testing: no mutation in <i>LDLR</i> , <i>APOB</i> or <i>PCSK9</i> genes | DLCN; Genetic; Starr <i>et al.</i> criteria (Ref 92) | 2014 – 2018                          | Primary care, Cardiology and Hospital records                   | Northern regions               | 49   |

APOB: apolipoprotein B. CAD: coronary artery disease. CKD: chronic kidney disease. CVD: cardiovascular disease. DLCN: Dutch Lipid Clinics Network criteria. DM: diabetes mellitus. EAS: European Atherosclerosis Society. FH: familial hypercholesterolaemia. GFR: glomerular filtration rate. HeFH: heterozygous familial hypercholesterolaemia. HF: “hipercolesterolemia familiar” (familial hypercholesterolaemia). HIV: human immunodeficiency virus. HoFH: homozygous familial hypercholesterolaemia. JAS: Japanese Atherosclerosis Society. LDL-C: low-density lipoprotein cholesterol. LDLR: low-density lipoprotein receptor. LDLRAP1: Low Density Lipoprotein Receptor Adaptor Protein 1. LLM: lipid-lowering medication. MEDPED: Make Early Diagnosis to Prevent Early Deaths. MI: myocardial infarction. NYHA: New York Heart Association. OMIM: Online Mendelian Inheritance in Man. PAD: peripheral artery disease. PCSK9: Proprotein convertase subtilisin/kexin type 9. Ref: reference. TC: total cholesterol. TG: triglycerides. TSH: thyroid-stimulating hormone. ULN: upper limit of normal. WHO: World Health Organization.

**A-HIT:** A registry of familial hypercholesterolaemia in Turkey. **CaRe High:** Cascade Screening and Registry for High Cholesterol. **DA VINCI:** EstuDio Argentino PreValencia eN HiperColesterolemia Familiar. **DIAMOND:** DIAGnosis and Management Of familial hypercholesterolaemia in a Nationwide Design. **FHCARE:** Familial Hypercholesterolaemia – Case identification, Assessment and Reduction in adverse Events. **FHNO-alfa:** Quality of treatment project for FH, Oslo University Hospital. **fhreg.hu:** FH regiszter Hungary. **FHSC:** Familial Hypercholesterolaemia Studies Collaboration. **GENYCO:** Programa Nacional de Detección Temprana y Atención de Hipercolesterolemia Familiar (GENYCO – Genes y Colesterol). **HELLAS-FH:** Hellenic Familial Hypercholesterolaemia Registry. **LIPIGEN:** Lipid TransPort Disorders Italian GENetic Network Study. **MEDPED:** Make Early Diagnosis to Prevent Early Deaths. **MyHEBAT-FH:** MalaYsian HEalth & WellBeing AssesmentT – Familial Hypercholesterolaemia. **PoLA-FH-Registry:** Polish Lipid Association – Familial Hypercholesterolaemia registry. **PROLIPID:** PROspective registry study of primary hyperLIPIDemia. **REFERCHOL:** French REGistry of Familial HyperCHOLEsterolaemia. **RuFH:** Russian FH Registry. **RUzFH:** FH in the Uzbek population. **SAFEHEART Registry:** Spanish Familial Hypercholesterolaemia Cohort Study. **SAPPHIRE:** Swiss Awareness Program for Primary Hypercholesterolemia: Identification of Risk Elevation in Families with High cholesterol. **StOEH:** Stichting Opsporing Erfelijke Hypercholesterolemie. **VINAFH Registry:** Vietnam Familial Hypercholesterolaemia Registry.

**Supplemental Table 2. Data available for variables included in the present study.**

|  | Data available: absolute number and % respect to overall cohort |                                      |   | Comments  |
|--|---|--------------------------------------|---|---|
|  | Individual-level data merged into one FHSC dataset              | Aggregated data from France registry | Both, individual-level data and aggregated data, together |   |
|  | Overall, n=37,972   | Overall, n=4,195                     | Overall, n=42,167   |   |
| <b>Sex</b>                               | 36,835 (97.0%)  | 4,195 (100%)                         | 41,030 (97.3%)  |   |
| <b>Age at registry entry</b>             | 37,845 (99.7%)  | 4,194 (99.97%)                       | Presented separately                                      |   |
| <b>Age at FH diagnosis</b>               | 30,560 (80.5%)  | 2,241 (53.4%)                        | Presented separately                                      |   |
| <b>Hypertension</b>                      | 32,779 (86.3%)  | 3,809 (90.8%)                        | 36,588 (86.8%)  |   |
| <b>Diabetes mellitus</b>                 | 32,813 (86.4%)  | 3,866 (92.2%)                        | 36,679 (87.0%)  |   |
| <b>Body Mass Index</b>                   | 27,274 (71.8%)  | 3,361 (80.1%)                        | 30,635 (72.7%)  |   |
| <b>Smoking, current</b>                  | 33,869 (89.2%)  | 3,742 (89.2%)                        | 37,611 (89.2%)  |   |
| <b>Coronary Artery Disease</b>           | 30,701 (94.5%) *  | 4,195 (100%)                         | 34,896 (95.1%)  | (* Information on Coronary Artery Disease at baseline provided in datasets from countries = ARG, AUS, AUT, BEL, BIH, BRA, CAN, CHL, DEU, ESP, GBR, GRC, HUN, IND, IRL, JPN, KWT, LBN, LTU, LVA, MEX, MLT, MYS, NGA, NLD, NOR, OMN, POL, PRT, RUS, SGP, SVK, SVN, THA, TUR, TWN, UKR, URY, VNM and ZAF, n=32,505.                |
| <b>Premature Coronary Artery Disease</b> | 31,341 (95.7%) *  | 4,195 (100%)                         | 35,536 (96.2%)  | (* Information on Premature Coronary Artery Disease at baseline provided in datasets from countries = ARE, ARG, AUS, AUT, BEL, BIH, BGR, CHE, CHN, CHL, CZE, DEU, ESP, GBR, GRC, IND, IRL, ITA, JPN, KWT, LBN, LTU, LVA, MEX, MLT, MYS, NLD, NOR, OMN, PRT, RUS, SAU, SGP, SVN, THA, TUR, TWN, UKR, URY, VNM and ZAF, n=32,745. |
| <b>Stroke</b>                            | 28,853 (94.2%) *  | 4,195 (100%)                         | 33,048 (94.9%)  | (* Information on Stroke at baseline provided in datasets from countries = ARG, AUS, AUT, BEL, BIH, BRA, CHL, DEU, ESP, GBR, GRC, HUN, IND, IRL, JPN, LBN, LTU, LVA, MEX, MLT, MYS, NGA, NLD, OMN, POL, PRT, RUS, SGP, SVK, SVN, THA, TUR, TWN, UKR, URY, VNM and ZAF, n=30,617.  |
| <b>Peripheral Artery Disease</b>         | 8,024 (76.7%) *   | 4,195 (100%)                         | 12,219 (83.4%)  | (* Information on Peripheral Artery Disease at baseline provided in datasets from countries = ARG, AUS, AUT, BEL, BIH, BRA, DEU, ESP, GRC, IND, IRL, JPN, LBN, LTU, LVA, MEX, MLT, MYS, OMN, POL, RUS, SVK, THA, TUR, TWN, UKR, URY, VNM and ZAF, n=10,457.   |
| <b>Lipid-lowering medication</b>         | 34,779 (91.6%)  | 4,195 (100%)                         | 38,974 (92.4%)  |   |
| <b>Total cholesterol</b>                 | 26,532 (69.9%; excluding NLD: 88.4%) *                          | 3,790 (90.3%)                        | Presented separately                                      | (* NLD: available data 10,226 (52.4%). In NLD all cases are genetically confirmed FH  |
| <b>LDL-cholesterol</b>                   | 25,814 (68.0%; excluding NLD: 85.8%) *                          | 3,907 (93.1%)                        | Presented separately                                      | (* NLD: available data 9,982 (51.1%). In NLD all cases are genetically confirmed FH   |
| <b>HDL-cholesterol</b>                   | 25,605 (67.4%; excluding NLD: 84.6%) *                          | 3,737 (89.1%)                        | Presented separately                                      | (* NLD: available data 10,007 (51.2%). In NLD all cases are genetically confirmed FH  |
| <b>Triglycerides</b>                     | 25,597 (67.4%; excluding NLD: 84.6%) *                          | 3,775 (90.0%)                        | Presented separately                                      | (* NLD: available data 9,999 (51.2%). In NLD all cases are genetically confirmed FH   |

Data shown as absolute and relative frequencies [n (%)]. France registry (French Registry of Familial Hypercholesterolaemia, REFERCHOL): unable to share individual-level data due to regulatory restrictions. Results for coronary artery disease, premature coronary artery disease, stroke and peripheral artery disease are excluding data from Egypt and Uzbekistan, since both datasets have “having premature cardiovascular disease” (any) as inclusion criteria. FH, familial hypercholesterolaemia; FHSC, Familial Hypercholesterolaemia Studies Collaboration; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Country codes: ARE, United Arab Emirates; ARG, Argentina; AUS, Australia; AUT, Austria; BEL, Belgium; BGR, Bulgaria; BIH, Bosnia and Herzegovina; BRA, Brazil; CAN, Canada; CHE, Switzerland; CHL, Chile; CHN, China; CZE, Czech Republic; DEU, Germany; ESP, Spain; GBR, United Kingdom; GRC, Greece; HUN, Hungary; IND, India; IRL, Ireland; ITA, Italy; JPN, Japan; KWT, Kuwait; LBN, Lebanon; LTU, Lithuania; LVA, Latvia; MEX, Mexico; MLT, Malta; MYS, Malaysia; NGA, Nigeria; NLD, The Netherlands; NOR, Norway; OMN, Oman; POL, Poland; PRT, Portugal; RUS, Russia; SAU, Saudi Arabia; SGP, Singapore; SVK, Slovakia; SVN, Slovenia; THA, Thailand; TUR, Turkey; TWN, Taiwan; UKR, Ukraine; URY, Uruguay; VNM, Vietnam; ZAF, South Africa.

**Supplemental Table 3. Aggregated results for quantitative variables at entry in the registry in the France registry.**

| <b>French Registry of Familial Hypercholesterolaemia<br/>(REFERCHOL)</b> |   |
|--|---|
| n = 4,195  |   |
| <b>Type of diagnosis</b>   | Clinical: 1,637 (39.02%), Genetic: 2,558 (60.98%) |
| <b>Age at registry entry</b> (years)                                     | 53.8 (39.7 – 65.1)                                |
| <b>Age at FH diagnosis</b> (years)                                       | 23.5 (15.2 – 37.2)                                |
| <b>Body Mass Index</b> (kg/m <sup>2</sup> )                              | 24.0 (21.3 – 27.1)                                |
| <b>Total cholesterol</b> (mmol/L)  | 7.16 (5.77 – 8.66)                                |
| <b>LDL-cholesterol</b> (mmol/L)  | 5.17 (3.85 – 6.62)                                |
| <b>HDL-cholesterol</b> (mmol/L)  | 1.32 (1.11 – 1.60)                                |
| <b>Triglycerides</b> (mmol/L)  | 1.06 (0.77 – 1.52)                                |

France registry (French Registry of Familial Hypercholesterolaemia, REFERCHOL): unable to share individual-level data due to regulatory restrictions. Data shown as absolute and relative frequencies [n (%)] or median and interquartile range, as appropriate. Clinical diagnosis is made using DLCN clinical criteria. Lipid levels are presented overall, not stratified by patient taking and patients not taking lipid-lowering medication. FH, familial hypercholesterolaemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

**Supplemental Table 4. Cardiovascular Disease stratified by sex.**

|  | <b>Men</b>    | <b>Women</b>  | <b>p-value comparison<br/>men vs. women</b> |
|--|---------------|---------------|---|
| <b>Coronary Artery Disease</b>           | 3,009 (21.5%) | 2,060 (12.4%) | <0.00001                                    |
| <b>Premature Coronary Artery Disease</b> | 2,102 (14.6%) | 1,186 (7.0%)  | <0.0001                                     |
| <b>Stroke</b>                            | 269 (2.0%)    | 296 (1.9%)    | 0.41  |
| <b>Peripheral Artery Disease</b>         | 234 (6.5%)    | 251 (5.7%)    | 0.17  |

**Supplemental Table 5. Lipid lowering medication at the time of registry entry among patients in primary and secondary prevention of cardiovascular disease.**

|                   | <b>Primary prevention</b> | <b>Coronary Artery Disease</b> | <b>Premature Coronary Artery Disease</b> | <b>Stroke</b> | <b>Peripheral Artery Disease</b> |
|-------------------|---------------------------|--------------------------------|--|---------------|----------------------------------|
| <b>Taking LLM</b> | 15,561 (54.8%)            | 4,043 (82.7%)                  | 2,632 (83.3%)                            | 465 (86.4%)   | 393 (83.4%)                      |

**Supplemental Table 6. Type and dose of different classes of lipid lowering medication at the time of registry entry.**

**(A) Statins**

| Among those taking Statins (n=16,803) |               |                                   |                               |
|---------------------------------------|---------------|-----------------------------------|-------------------------------|
|                                       | n (%)         | Dose (mg/day) *                   | Information available on dose |
| Simvastatin                           | 4,390 (26.1%) | 31.2 ± 15.0<br>40.0 (20.0 – 40.0) | n=2996                        |
| Pravastatin                           | 628 (3.7%)    | 30.1 ± 15.7<br>30.0 (20.0 – 40.0) | n=437                         |
| Lovastatin                            | 259 (1.5%)    | 38.3 ± 20.7<br>40.0 (20.0 – 40.0) | n=211                         |
| Fluvastatin                           | 191 (1.1%)    | 45.1 ± 27.0<br>40.0 (20.0 – 80.0) | n=150                         |
| Atorvastatin                          | 6,413 (38.2%) | 39.3 ± 23.1<br>40.0 (20.0 – 40.0) | n=5356                        |
| Rosuvastatin                          | 4,173 (24.8%) | 24.2 ± 12.5<br>20.0 (10.0 – 40.0) | n=3726                        |
| Pitavastatin                          | 126 (0.7%)    | 3.0 ± 2.9<br>2.0 (2.0 – 4.0)      | n=123                         |
| Type of statin not specified          | 623 (3.7%)    | -                                 | -                             |

**(B) PCSK 9 inhibitors**

| Among those taking PCSK9 inh (n=527)  |             |                                   |                               |
|---------------------------------------|-------------|-----------------------------------|-------------------------------|
|                                       | n (%)       | Dose (mg/week) *                  | Information available on dose |
| Evolocumab                            | 175 (33.2%) | 73.4 ± 17.1<br>70.0 (70.0 – 70.0) | n=103                         |
| Alirocumab                            | 108 (20.5%) | 51.6 ± 18.3<br>37.5 (37.5 – 75.0) | n=85                          |
| Type of PCSK9 inhibitor not specified | 244 (46.3%) | -                                 | -                             |

**(C) Fibrates**

| Among those taking Fibrates (n=388), n (%) |             |
|--|-------------|
| Clofibrate                                 | 3 (0.8%)    |
| Bezafibrate                                | 56 (14.4%)  |
| Fenofibrate                                | 89 (22.9%)  |
| Gemfibrozil                                | 79 (20.4%)  |
| Type of fibrate not specified              | 161 (41.5%) |

\* Mean ± SD, median (IQR)



**Supplemental Table 7. Type of statins by sex among participants taking statins.**

|  | Men           | Women         | Mean difference (95% CI)<br>Men vs Women | p-value |
|--|---------------|---------------|--|---------|
|  | n=7,791       | n=8,780       | -  | -       |
| <b>Type unknown</b>                                      | 276 (3.5%)    | 342 (3.9%)    | -  | -       |
| <b>Simvastatin</b>                                       | 1,992 (25.6%) | 2,320 (26.4%) | -  | -       |
| > Dose   | 31.4 ± 14.9   | 31.1 ± 15.1   | 0.37 (-0.71, 1.45)                       | 0.51    |
| <b>Pravastatin</b>                                       | 270 (3.5%)    | 300 (3.4%)    | -  | -       |
| > Dose   | 33.1 ± 15.7   | 29.9 ± 15.6   | 3.16 (0.06, 6.25)                        | 0.046   |
| <b>Lovastatin</b>  | 113 (1.4%)    | 113 (1.3%)    | -  | -       |
| > Dose   | 39.4 ± 19.8   | 37.2 ± 21.6   | 2.28 (-3.35, 7.90)                       | 0.43    |
| <b>Fluvastatin</b>                                       | 83 (1.1%)     | 99 (1.1%)     | -  | -       |
| > Dose   | 47.0 ± 27.7   | 43.2 ± 26.4   | 3.85 (-4.96, 12.67)                      | 0.39    |
| <b>Atorvastatin</b>                                      | 3,022 (38.8%) | 3,359 (38.3%) | -  | -       |
| > Dose   | 40.7 ± 23.1   | 38.1 ± 23.1   | 2.68 (1.44, 3.92)                        | <0.001  |
| > Dose 80 mg/day   | 546 (21.5%)   | 525 (18.7%)   | -  | p=0.009 |
| <b>Rosuvastatin</b>                                      | 1,991 (25.6%) | 2,166 (24.7%) | -  | -       |
| > Dose   | 25.6 ± 12.5   | 22.9 ± 12.3   | 2.69 (1.89, 3.49)                        | <0.001  |
| > Dose ≥40 mg/day  | 699 (38.8%)   | 578 (30.2%)   | -  | <0.001  |
| <b>Pitavastatin</b>                                      | 44 (0.6%)     | 81 (0.9%)     | -  | -       |
| > Dose   | 3.1 ± 2.8     | 3.0 ± 3.0     | 0.09 (-1.02, 1.20)                       | 0.87    |
|  | <b>Men</b>    | <b>Women</b>  |  |         |
| <b>Atorvastatin 80 mg/day or Rosuvastatin ≥40 mg/day</b> | 1,245 (16.6%) | 1,103 (13.1%) | -  | <0.001  |

Data on dose are mean ± SD.

**Supplemental Table 8. Combination therapy among participants taking lipid-lowering medication at the time of registry entry.**

**(A) Combination therapy including Statins, ezetimibe and/or PCSK9 inhibitors**

| Combination therapy including Statins, Ezetimibe and PCSK9 inhibitors | n (%) among those on Lipid Lowering Medication |
|---|--|
| Any (2 or 3 drugs)  | 3,691 (21.2%)                                  |
| ▪ 2 drugs (any two)   | ▪ 3,409 (19.6%)                                |
| ○ Statin + Ezetimibe  | ○ 3281 (18.9%)                                 |
| ○ Statin + PCSK9 inhibitor  | ○ 98 (0.6%)                                    |
| ○ Ezetimibe + PCSK9 inhibitor   | ○ 29 (0.2%)                                    |
| ▪ 3 drugs   | ▪ 282 (1.6%)                                   |

Participants with information available on whether taking or not taking all the three drugs (statins, ezetimibe, PCSK9 inhibitors): n=17,368 (out of 20,829 on lipid-lowering medication).

**(B) Combination therapy with fibrates**

| Combination therapy with Fibrates                             | n (%) among those on Lipid Lowering Medication |
|---|--|
| Fibrate + any 1, 2 or 3 of statins/ezetimibe/PCSK9 inhibitors | 295 (1.6%)                                     |
| ▪ Fibrates + Statin   | ▪ 286 (1.5%)                                   |
| ▪ Fibrates + Ezetimibe  | ▪ 86 (0.5%)                                    |
| ▪ Fibrates + PCSK9 inhibitor                                  | ▪ 24 (0.1%)                                    |

Participants with information available on whether taking or not taking both statins and fibrates n=18,503 (out of 20,829 on lipid-lowering medication). Participants with information available on whether taking or not taking both ezetimibe and fibrates n=18,012 (out of 20,829 on lipid-lowering medication). Participants with information available on whether taking or not taking both PCSK9 inhibitors and fibrates n=17,256 (out of 20,829 on lipid-lowering medication).

**Supplemental Table 9. Comparison of lipid levels between FH patients not on lipid-lowering medication and FH patients taking lipid-lowering medication, overall and stratified by geographical region.**

|   | Overall cohort                | Overall cohort excluding The Netherlands | By World Health Organization (WHO) region |                                |                                 |                                  |                               |                                   |
|---|-------------------------------|--|---|--------------------------------|---------------------------------|----------------------------------|-------------------------------|-----------------------------------|
|   |                               |  | Africa                                    | Americas                       | Eastern Mediterranean           | Europe excluding The Netherlands | The Netherlands               | South-East Asia & Western Pacific |
| <b>Total cholesterol (mmol/L)</b>   | -                             | -  | -   | -                              | -                               | -                                | -                             | -                                 |
| Mean (95% CI) difference between patients not on LLM and patients taking LLM, p-value | 1.03 (0.97, 1.09)<br>p<0.0001 | 1.40 (1.32, 1.48)<br>p<0.0001            | 2.44 (2.20, 2.70)<br>p<0.0001             | -0.15 (-0.35, 0.05)<br>p=0.14  | 1.58 (0.99, 2.16)<br>p<0.0001   | 1.59 (1.49, 1.68)<br>p<0.0001    | 0.53 (0.47, 0.59)<br>p<0.0001 | 1.13 (0.87, 1.39)<br>p<0.0001     |
| <b>LDL-cholesterol (mmol/L)</b>   | -                             | -  | -   | -                              | -                               | -                                | -                             | -                                 |
| Mean (95% CI) difference between patients not on LLM and patients taking LLM, p-value | 1.06 (1.00, 1.11)<br>p<0.0001 | 1.45 (1.38, 1.53)<br>p<0.0001            | 2.50 (2.27, 2.74)<br>p<0.0001             | 0.33 (0.14, 0.51)<br>p=0.0007  | 1.11 (0.57, 1.65)<br>p<0.0001   | 1.59 (1.50, 1.68)<br>p<0.0001    | 0.51 (0.45, 0.57)<br>p<0.0001 | 1.03 (0.77, 1.29)<br>p<0.0001     |
| <b>HDL-cholesterol (mmol/L)</b>   | -                             | -  | -   | -                              | -                               | -                                | -                             | -                                 |
| Mean (95% CI) difference between patients not on LLM and patients taking LLM, p-value | 0.01 (-0.01, 0.02)<br>p=0.38  | 0.01 (-0.01, 0.03)<br>p=0.21             | -0.05 (-0.10, 0.01)<br>p=0.11             | 0.06 (0.02, 0.10)<br>p=0.004   | 0.03 (-0.15, 0.21)<br>p=0.76    | 0.00 (-0.02, 0.02)<br>p=0.99     | 0.00 (-0.02, 0.02)<br>p=0.98  | 0.01 (-0.05, 0.08)<br>p=0.72      |
| <b>Triglycerides (mmol/L)</b>   | -                             | -  | -   | -                              | -                               | -                                | -                             | -                                 |
| Mean (95% CI) difference between patients not on LLM and patients taking LLM, p-value | -0.03 (-0.04, 0.04)<br>p=0.88 | -0.06 (-0.11, -0.05)<br>p=0.031          | 0.04 (-0.09, 0.17)<br>p=0.53              | -0.23 (-0.46, 0.01)<br>p=0.057 | -0.40 (-0.64, -0.16)<br>p=0.001 | 0.00 (-0.06, 0.05)<br>p=0.91     | 0.07 (0.02, 0.11)<br>p=0.003  | -0.05 (-0.38, 0.29)<br>p=0.79     |

FH: familial hypercholesterolaemia; LLM: lipid-lowering medication.

**Supplemental Table 10. LDL-C levels stratified by age among participants not on lipid-lowering medication, overall and by sex.**

| Participants not on LLM                | Overall cohort     | Cohort stratified by sex |                    |                                       |                      |
|--|--------------------|--------------------------|--------------------|---------------------------------------|----------------------|
|  |                    | Men                      | Women              | Mean difference (95% CI) men vs women | p-value men vs women |
| <b>By age above and below 50 years</b> |                    |                          |                    |                                       |                      |
| 18 to <50 years                        | 5.34 (4.23 – 6.65) | 5.39 (4.22 – 6.70)       | 5.30 (4.23 – 6.61) | 0.04 (-0.07, 0.16)                    | 0.31                 |
| ≥50 years                              | 5.64 (4.57 – 6.93) | 5.20 (4.19 – 6.40)       | 5.93 (4.86 – 7.17) | -0.64 (-0.82, -0.47)                  | <0.0001              |
| <b>By age above and below 55 years</b> |                    |                          |                    |                                       |                      |
| 18 to <55 years                        | 5.39 (4.28 – 6.70) | 5.38 (4.24 – 6.65)       | 5.40 (4.31 – 6.70) | -0.06 (-0.16, 0.05)                   | 0.52                 |
| ≥55 years                              | 5.61 (4.50 – 6.93) | 5.12 (4.07 – 6.36)       | 5.86 (4.77 – 7.12) | -0.61 (-0.83, -0.40)                  | <0.0001              |

LDL-C levels are shown as median (IQR) unless otherwise specified. CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LLM, lipid-lowering medication.

**Supplemental Table 11. Lipid-lowering medications and prevalence of cardiovascular disease in women stratified by age of 50 years.**

|                                       | <b>Lipid-Lowering Medication</b> | <b>Coronary Artery Disease</b> | <b>Stroke</b> | <b>Peripheral Artery Disease</b> |
|---------------------------------------|----------------------------------|--------------------------------|---------------|----------------------------------|
| <b>Women</b>                          |                                  |                                |               |                                  |
| - <b>Age &lt;50 years</b>             | 5,029 (50.0%)                    | 396 (4.4%)                     | 38 (0.5%)     | 37 (2.0%)                        |
| - <b>Age ≥50 years</b>                | 5,888 (68.1%)                    | 1,663 (21.7%)                  | 258 (3.6%)    | 212 (8.5%)                       |
| <i>p-value between both subgroups</i> | <0.0001                          | <0.0001                        | <0.0001       | <0.0001                          |

**Supplemental Table 12. Cardiovascular Disease stratified by Index Case status.**

|  | <b>Index Cases</b> | <b>Non-Index Cases</b> | <b>p-value for comparison Index Cases vs. Non-Index Cases</b> |
|--|--------------------|------------------------|---|
| <b>Coronary Artery Disease</b>           | 1,721 (20.6%)      | 1,982 (11.2%)          | <0.0001   |
| <b>Premature Coronary Artery Disease</b> | 1,035 (13.8%)      | 839 (5.0%)             | <0.0001   |
| <b>Stroke</b>                            | 155 (1.9%)         | 304 (1.7%)             | 0.42  |
| <b>Peripheral Artery Disease</b>         | 270 (7.1%)         | 62 (3.5%)              | <0.0001   |

**Supplemental Table 13. Cohort of non-index cases stratified by “the Netherlands” and the “Overall cohort excluding the Netherlands”**

|   | NON-INDEX CASES<br>(n=18,017)       |                    |         |
|---|-------------------------------------|--------------------|---------|
|   | COHORT EXCLUDING<br>THE NETHERLANDS | THE NETHERLANDS    | p-value |
|   | n=2,448                             | n=15,569           | -       |
| <b>Women</b>                              | 1,257 (56.4%)                       | 8,241 (52.9%)      | 0.0022  |
| <b>Age at registry entry (years)</b>      | 45.0 (33.0 – 58.1)                  | 43.9 (32.0 – 57.5) | 0.0194  |
| <b>Age at FH diagnosis (years)</b>        | 41.1 (29.0 – 54.5)                  | 43.9 (32.0 – 57.5) | <0.0001 |
| <b>Hypertension</b>                       | 497 (22.3%)                         | 1,787 (11.5%)      | <0.0001 |
| <b>Diabetes mellitus</b>                  | 156 (6.9%)                          | 453 (2.9%)         | <0.0001 |
| <b>Body Mass Index (kg/m<sup>2</sup>)</b> | 25.4 (22.7 – 29.0)                  | 24.5 (22.1 – 27.2) | <0.0001 |
| <b>Smoking</b>                            | 326 (14.8%)                         | 4,873 (31.5%)      | <0.0001 |
| <b>Coronary Artery Disease</b>            | 391 (18.5%)                         | 1,591 (10.2%)      | <0.0001 |
| <b>Premature Coronary Artery Disease</b>  | 157 (14.3%)                         | 682 (4.4%)         | <0.0001 |
| <b>Stroke</b>                             | 46 (2.2%)                           | 258 (1.7%)         | 0.0772  |
| <b>Peripheral Artery Disease</b>          | 62 (3.5%)                           | -                  | -       |
| <b>Lipid-lowering medication</b>          | 1,256 (61.1%)                       | 9,483 (60.9%)      | 0.8344  |
| <b>Total cholesterol (mmol/L)</b>         |                                     |                    |         |
| - <b>Participants not on LLM</b>          | 7.63 (6.61 – 8.90)                  | 6.23 (5.35 – 7.19) | <0.0001 |
| - <b>Participants taking LLM</b>          | 7.01 (5.53 – 8.59)                  | 5.61 (4.87 – 6.60) | <0.0001 |
| <b>LDL-cholesterol (mmol/L)</b>           |                                     |                    |         |
| - <b>Participants not on LLM</b>          | 5.60 (4.68 – 6.90)                  | 4.42 (3.61 – 5.31) | <0.0001 |
| - <b>Participants taking LLM</b>          | 4.97 (3.49 – 6.34)                  | 3.81 (3.09 – 4.74) | <0.0001 |
| <b>HDL-cholesterol (mmol/L)</b>           |                                     |                    |         |
| - <b>Participants not on LLM</b>          | 1.29 (1.10 – 1.60)                  | 1.15 (0.92 – 1.42) | <0.0001 |
| - <b>Participants taking LLM</b>          | 1.27 (1.06 – 1.53)                  | 1.16 (0.93 – 1.42) | <0.0001 |
| <b>Triglycerides (mmol/L)</b>             |                                     |                    |         |
| - <b>Participants not on LLM</b>          | 1.22 (0.88 – 1.72)                  | 1.17 (0.78 – 1.76) | 0.0622  |
| - <b>Participants taking LLM</b>          | 1.28 (0.88 – 1.81)                  | 1.14 (0.78 – 1.70) | <0.0001 |

Data are shown as n (%) or median (IQR). FH, familial hypercholesterolaemia; HDL, high/density lipoprotein; LDL, low-density lipoprotein.

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