Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease

Consensus Statement of the European Atherosclerosis Society

Heterozygous familial hypercholesterolaemia (FH)
Pathophysiology & genetics
Pathophysiology of heterozygous familial hypercholesterolaemia.

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490
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LDL cholesterol burden in individuals with or without familial hypercholesterolaemia as a function of the age of initiation of statin therapy.

Adapted from Steve Humphries 2013
Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490
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Underdiagnosis & undertreatment
Estimated per cent of individuals diagnosed with familial hypercholesterolaemia in different countries/territories, as a fraction of those theoretically predicted based on a frequency of 1/500 in the general population.

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

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Prevalence of definite or probable familial hypercholesterolaemia according to Dutch Lipid Clinic Network Criteria in the Copenhagen General Population Study by 20-year age groups and by gender.

Adapted from Benn et al J Clin Endocrin Metab 2012; 97: 3956-3964
Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

Screening 69,000 persons from the Copenhagen General Population Study
Estimated millions of individuals worldwide with familial hypercholesterolaemia by WHO regions and by income groups.

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Risk of coronary heart disease as a function of the Dutch Lipid Clinic Network Criteria for a diagnosis of familial hypercholesterolaemia in individuals on or off statin from the general population.

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Whom to screen: how to find index cases?
We recommend:

children, adults, and families should be screened for FH if

- Family member presents with FH
- P-cholesterol in adult $\geq 8$mmol/L ($\geq 310$mg/dL)
- P-cholesterol in child $\geq 6$mmol/L ($\geq 230$mg/dL)
- Premature CHD
- Tendon xanthomas
- Sudden premature cardiac death

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Pedigree of a family with familial hypercholesterolaemia

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<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
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<tr>
<td><strong>Family history</strong></td>
<td></td>
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| First-degree relative with known premature coronary and/or vascular disease  
  (men <55 years, females <60 years)  
  OR First-degree relative with known LDL-C above the 95th percentile for age and sex | 1     |
| First-degree relative with tendinous xanthomata and/or arcus cornealis  
  OR Children aged less than 18 years with LDL-C above the 95th percentile  
  for age and sex | 2     |
| **Clinical history**                           |       |
| Premature coronary artery disease (men <55 years, females < 60 years) | 2     |
| Premature cerebral or peripheral vascular disease (men <55 years, females <60 years) | 1     |
| **Physical examination**                       |       |
| Tendinous xanthomata | 6      |
| Arcus cornealis prior to age 45 years | 4      |
| LDL-C (mmol/L)                                 |       |
| - 6.5 or higher | 8      |
| - 6.5 to 8.4 | 5      |
| - 5.0 to 6.4 | 3      |
| - 4.0 to 4.9 | 1      |
| DNA analysis: functional mutation in the LDLR, APOB or PCSK9 gene | 8      |

Stratification of familial hypercholesterolaemia (FH), as determined by total score using the Dutch Lipid Clinic Network Criteria:
- **Definite FH** = total score greater than 8
- **Probable FH** = total score between 6 and 8
- **Possible FH** = total score between 3 and 5
- **Unlikely FH** = total score of less than 3
Clinical diagnosis versus mutation diagnosis
Overlap of clinical and mutation diagnosis of heterozygous familial hypercholesterolaemia.

Adapted from Luis Masana
Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490
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Cascade screening preferred method
Pedigree of a family with Familial Hypercholesterolaemia

Index case: start of cascade screening

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LDL cholesterol targets: (heterozygous & homozygous FH)

- <3.5mmol/L(<135mg/dL) for children
- <2.5mmol/L(<100mg/dL) for adults
- <1.8mmol/L(<70mg/dL) for adults with known CHD or diabetes

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LDL lowering treatment

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Based on a consensus of
• opinions of experts
• small studies, retrospective studies, and registries

However
• effect of LDL cholesterol lowering in individuals without FH based on: randomised trials and meta-analyses

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490
Kaplan-Meier curve estimates of cumulative CHD-free survival among individuals with familial hypercholesterolaemia according to statin treatment (P < 0.001 for difference).

Adapted from Vermissen et al. BMJ 2008; 337: a2423
Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490
In addition to lifestyle and dietary counselling, treatment priorities are

**Children (from age 8-10):**
1. Statin
2. Ezetimibe
3. Bile acid binding resin
4. Lipoprotein apheresis in homozygotes

**Adults:**
1. Maximal potent statin dose
2. Ezetimibe
3. Bile acid binding resins
4. Lipoprotein apheresis in homozygotes & treatment-resistant heterozygotes with CHD

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490
Summary of diagnostic and treatment strategies.

**When to screen:** Index person or family member with
- Familial hypercholesterolaemia (FH)
- Cholesterol ≥8mmol/L (≥310mg/dL) for an adult (or)
- ≥95th percentile by age and gender for country
- Cholesterol ≥6mmol/L (≥230mg/dL) for a child
- ≥95th percentile by age and gender for country
- Premature coronary heart disease
- Tendon xanthomas
- Sudden premature cardiac death in a family member

**Diagnosis:** Use the Dutch Lipid Clinic Network criteria (Table 1). This cannot be used in children.

**Risk assessment:** Evaluate other cardiovascular risk factors, including elevated Lp(a)

**Cascade screen family using LDL cholesterol levels** (draw pedigree as in Figure 7)

**If Dutch Lipid Clinic Network criteria (Table 1) score > 5**
- Score for causative mutation in index case (if DNA test is available in country)
- Followed by genetic testing of family if causative mutation is found (genetic cascade screening)

**Lifestyle modifications, including smoking cessation and dietary advice—if needed from a certified dietician**

**Treatment priority:**
- Children: statin, ezetimibe, and bile acid-binding resin
- Adults: maximal potent statin dose, ezetimibe, bile acid-binding resin, fibrate, (niacin, novel therapies)
- Lipoprotein apheresis in homozygotes with coronary heart disease

**Diagnostic and treatment summary:** Familial hypercholesterolaemia

**Optional:**
Screen for asymptomatic atherosclerosis

**LDL cholesterol targets**
- <3.5mmol/L (<135mg/dL) for children
- <2.5mmol/L (<100mg/dL) for adults
- <1.8mmol/L (<70mg/dL) for adults with known coronary heart disease or diabetes

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These companies were not present at the Consensus Panel meetings, had no role in the design or content of the Consensus Statement, and had no right to approve or disapprove the final document.

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490