Københavns Universitet & Herlev og Gentofte Hospital

Betydning og behandling af familiær hyperkolesterolæmi

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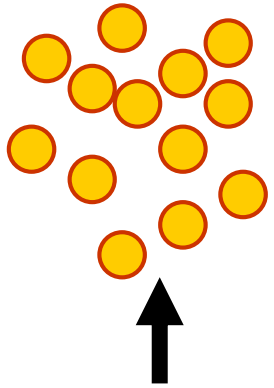
Arveligt højt kolesterol: Familiær hyperkolesterolæmi

- Arven med flest dødsfald
- Årsagen er velkendt
- Nem at diagnosticere, opspore og behandle

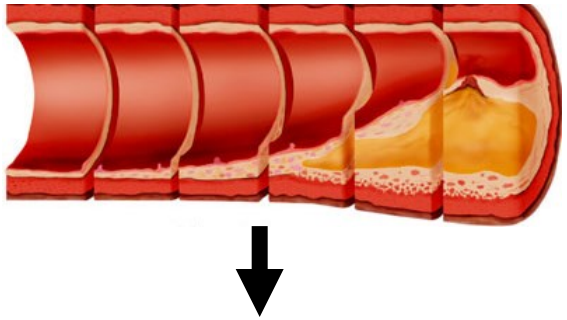
MEN

- Sygdommen er underdiagnosticeret og underbehandlet

Elevated LDL cholesterol

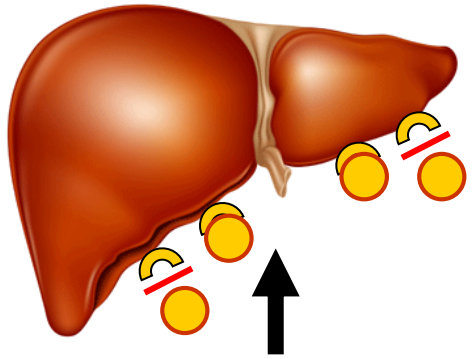


Atherosclerosis

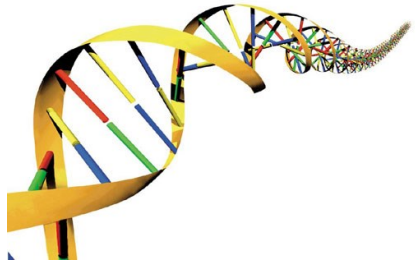


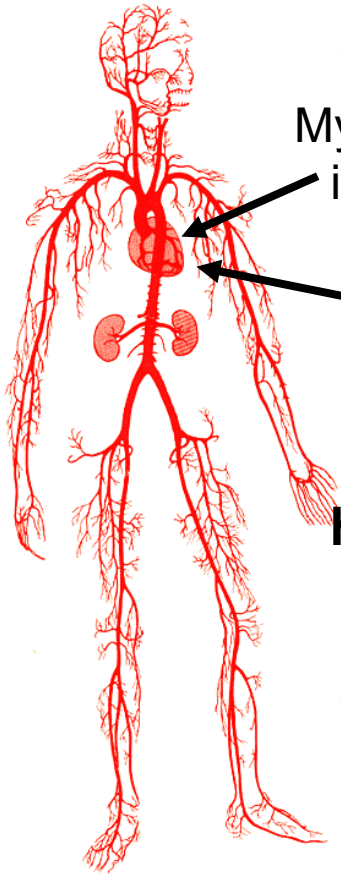
Coronary heart disease

Liver with only 50%
functional LDL receptors



Mutations in LDL receptor,
apolipoproteinB or PCSK9



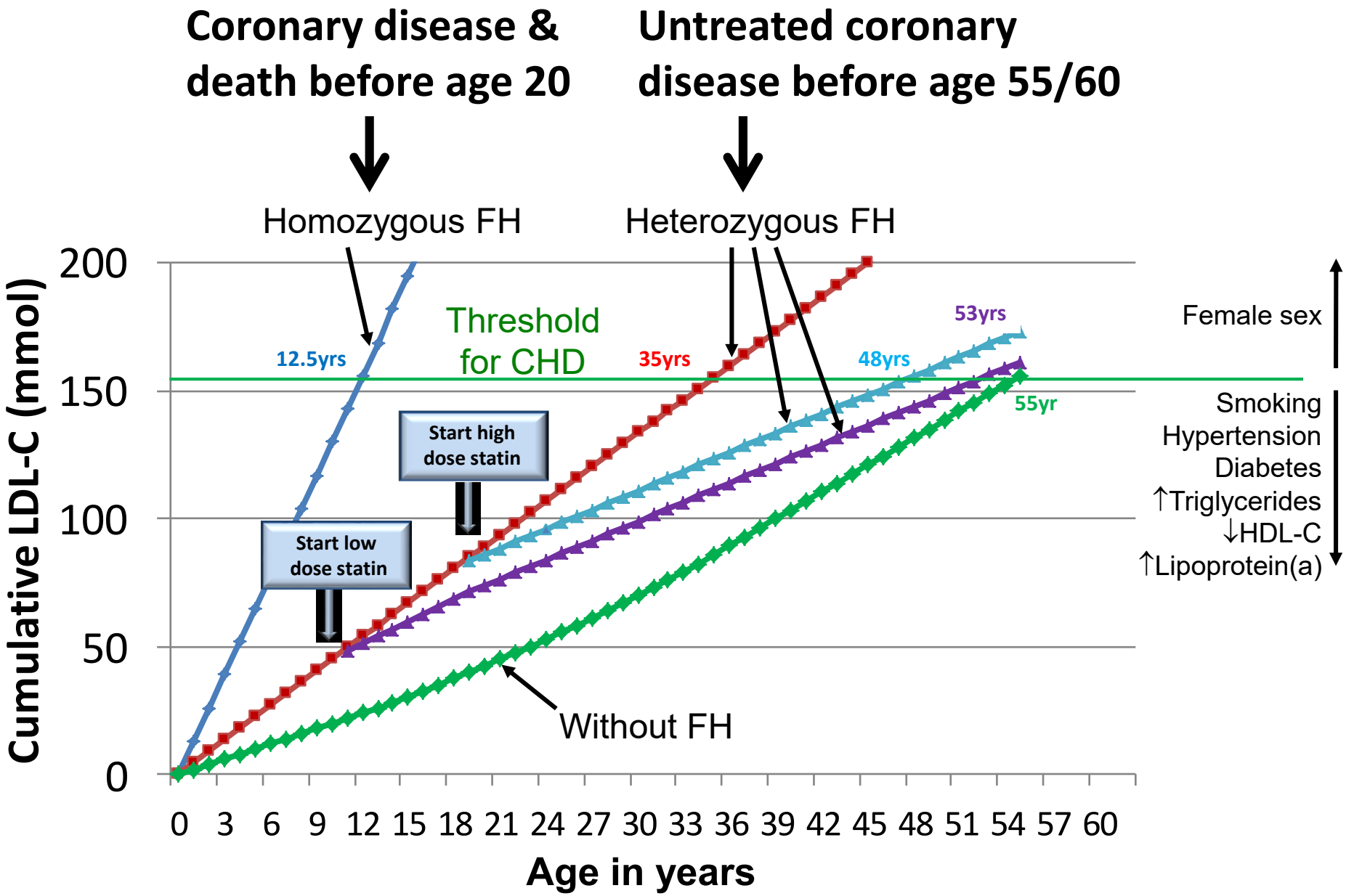


Myocardial
infarction

Angina
pectoris

Heterozygous familial hypercholesterolaemia

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



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

Fremtiden for 3 danske børn?

Rask hele livet Hjertesygdom 60-80 år Hjertesygdom før 60 år

Gennemsnitlig
5 millioner
Sund livsstil

Højrisiko
½ million
Sund livsstil
Medicin

Familiær hypercholesterolæmi
26.000
Familie opsporing
Medicin tidligt

FH prævalens

European Heart Journal (2016) **37**, 1384–1394
doi:10.1093/eurheartj/ehw028

CLINICAL RESEARCH
Prevention and epidemiology

Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217

Marianne Benn[1,2,3]*, Gerald F. Watts[4], Anne Tybjærg-Hansen[2,3,5], and Børge G. Nordestgaard[2,3,6]

Frequency of FH in general population

Study	Definition	Country	HeFH	HoFH
Benn JCEM 2012	Clinical	Denmark	1:223	1:200,000
Sjouke EHJ 2015	Genetic	Netherlands	1:244	1:300,000
Pajak AMC 2016	Clinical	Poland	1:250	1:250,000
Benn EHJ 2016	Genetic	Denmark	1:217	1:190,000
deFerranti Circ 2016	Clinical	USA	1:250	1:250,000
Safarova JCL 2016	Clinical	USA	1:310	1:385,000
Wald NEJM 2016	Gen+Clin	UK	1:250	1:250,000
Abul-Husn Science 2016	Genetic	USA	1:256	1:262,000

Nordestgaard 2017

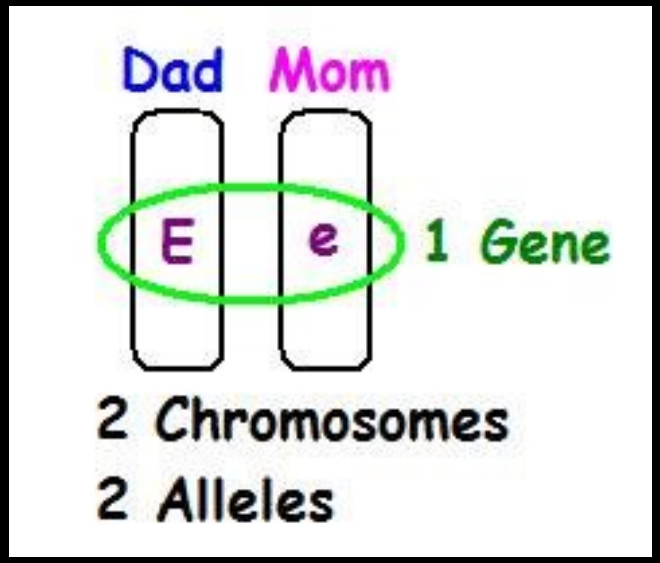
Heterozygot FH

Alleler

Homozygot FH

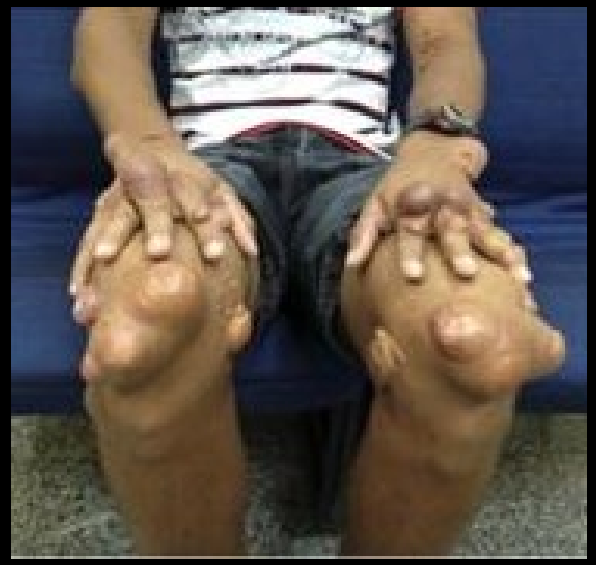
26.000 af 5,7 millioner

1/220



1/440

30 personer

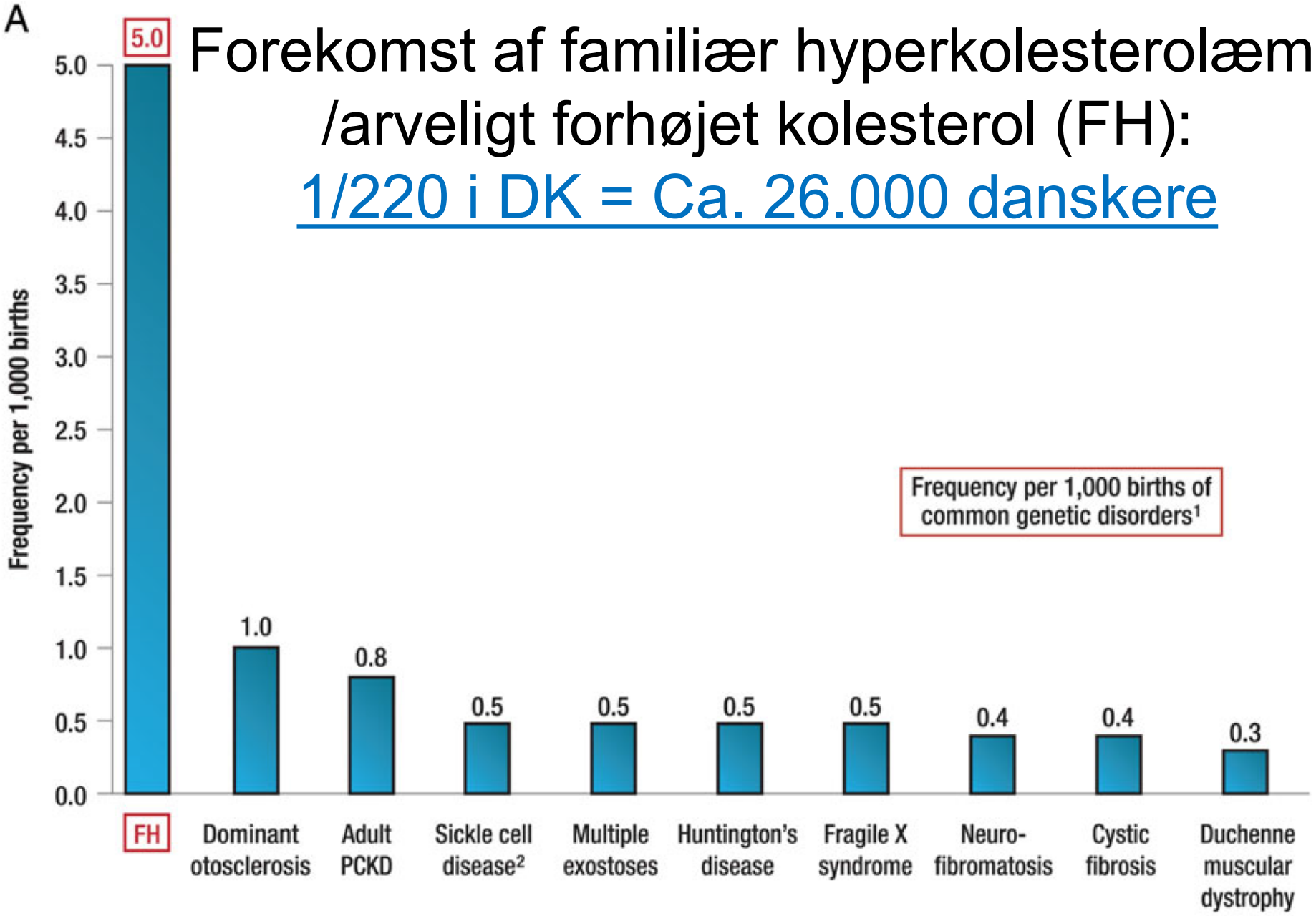


1/190,000
(1/440 x 1/440)

Tybjærg-Hansen & Nordestgaard 2020

Forekomst af familiær hyperkolesterolæmi /arveligt forhøjet kolesterol (FH):

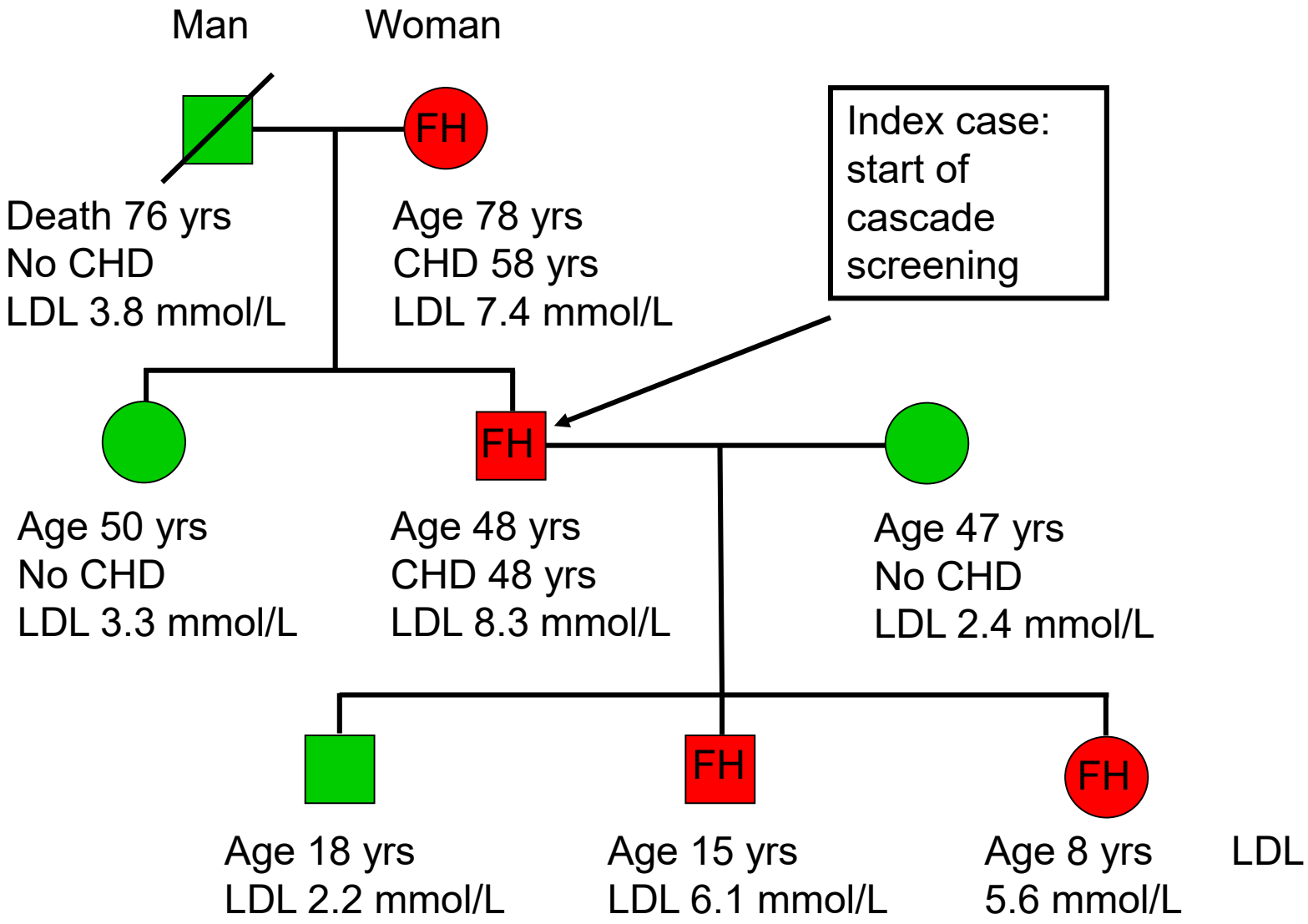
1/220 i DK = Ca. 26.000 danskere



Wiegman et al. EAS consensus. Eur Heart J 2016; 36: 2425-2437 (open access)

FH diagnostik

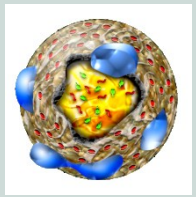
Family pedigree



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

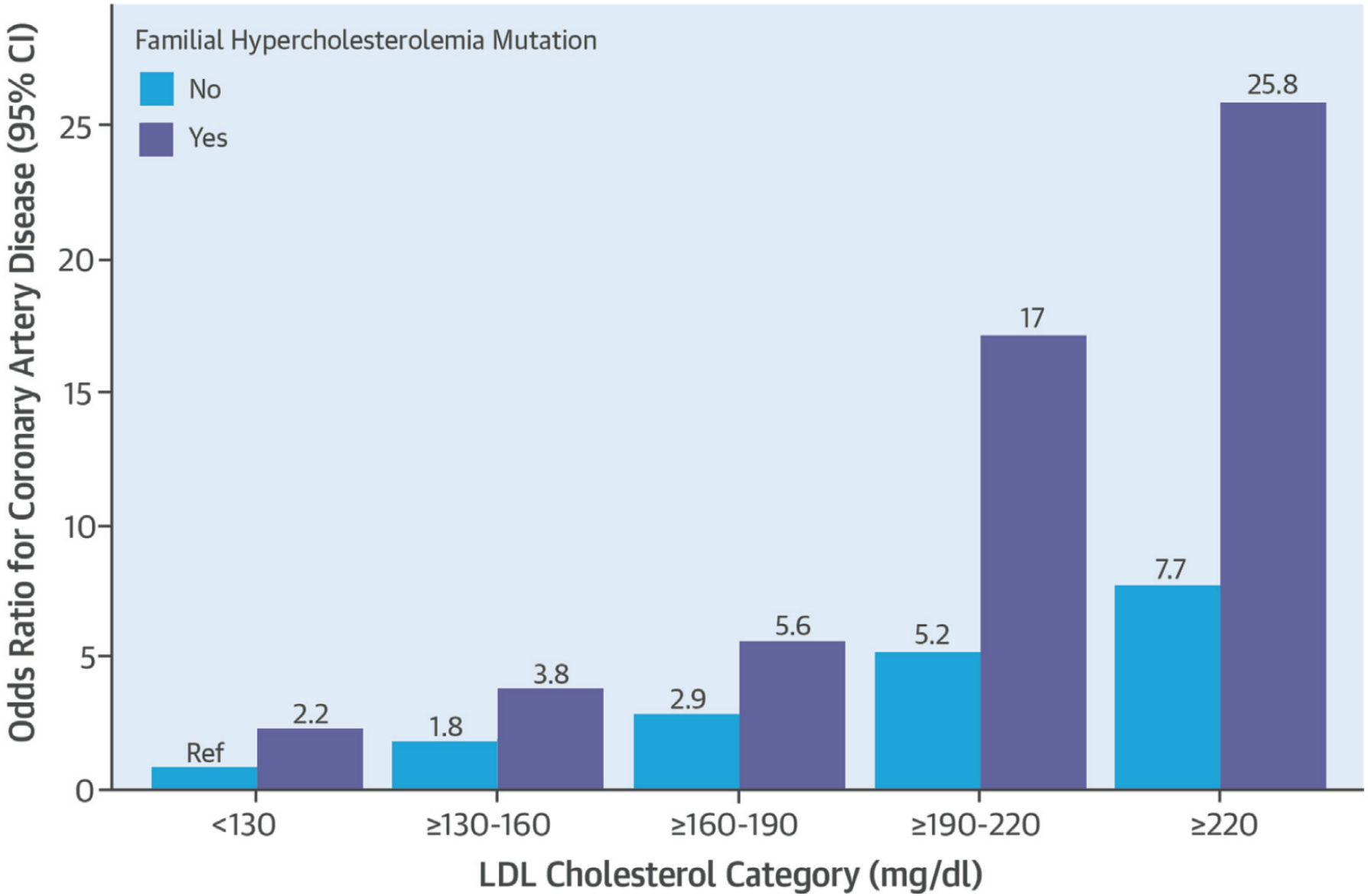
DUTCH FH CRITERIA

Feature	Score
Family history	
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) – 8.5 or higher – 6.5 to 8.4 – 5.0 to 6.4 – 4.0 to 4.9	 8 5 3 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

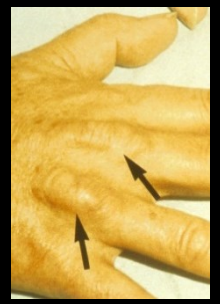


Khera, A.V. et al. J Am Coll Cardiol. 2016;67(22):2578-89.

High lipoprotein(a) as a cause of clinical familial hypercholesterolemia (FH)

Copenhagen General Population Study N=46,200

FH 1:220

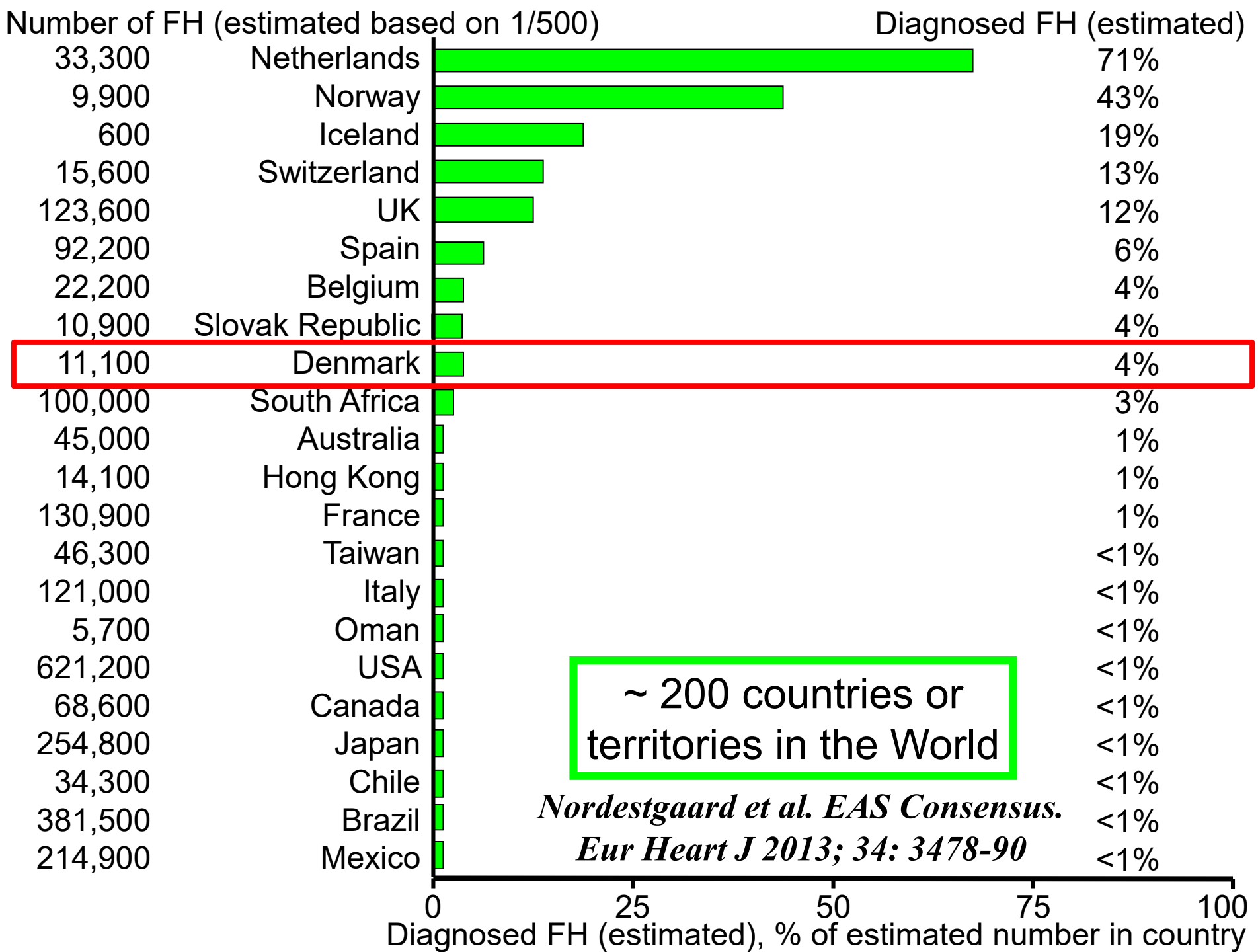


Ranked causes of clinical FH

1. *LDLR*
2. Lp(a) (25%)
3. *APOB*
4. *PCSK9*

Langsted et al. Lancet Diabetes Endocrinol 2016; 4 :577-87

FH opsporing


Number of FH (estimated based on 1/500)
Diagnosed FH (estimated)
33,300 Netherlands 71%
9,900 Norway 43%
600 Iceland 19%
15,600 Switzerland 13%
123,600 UK 12%
92,200 Spain 6%
22,200 Belgium 4%
10,900 Slovak Republic 4%
11,100 Denmark 4%
100,000 South Africa 3%
45,000 Australia 1%
14,100 Hong Kong 1%
130,900 France 1%
46,300 Taiwan <1%
121,000 Italy <1%
5,700 Oman <1%
621,200 USA <1%
68,600 Canada <1%
254,800 Japan <1%
34,300 Chile <1%
381,500 Brazil <1%
214,900 Mexico <1%
~ 200 countries or territories in the World
Nordestgaard et al. EAS Consensus. Eur Heart J 2013; 34: 3478-90
0
25
50
75
100
Diagnosed FH (estimated), % of estimated number in country

FH-indsats sammenlignet med lande, vi normalt sammenligner os med

Holland
71% FH fundet

Organiseret

Norge
43% FH fundet

Organiseret

Danmark
15% FH fundet

Uorganiseret

Ville en opsporingsgrad for kræft eller diabetes på 15% være OK?

We recommend:

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

- Family member presents with FH
- P-cholesterol in adult ≥8mmol/L (≥310mg/dL)
- P-cholesterol in child ≥6mmol/L (≥230mg/dL)
- Premature coronary heart disease
- Tendon xanthomas
- Sudden premature cardiac death

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

Plasma eller serum værdi for	ekstremt abnorme og potentielt livstruende værdier	Fodnoter i Labka eller tilsvarende laboratorie IT system
Triglycerider	>10mmol/L	Risiko for akut pancreatitis; udeluk sekundær årsag og overvej henvisning til lipidklinik
LDL kolesterol	>13 mmol/L	Henvis til lipid klinik p.g.a. sandsynlig homozygote familiær hyperkolesterolæmi
LDL kolesterol	>5 mmol/L	Muligvis familiær hyperkolesterolæmi; udeluk sekundær årsag og overvej henvisning til lipidklinik m.h.t. familieudredning
LDL kolesterol hos børn	>4 mmol/L	Muligvis familiær hyperkolesterolæmi; udeluk sekundær årsag og overvej henvisning til lipidklinik m.h.t. familieudredning

Lipid clinics in Denmark

The region of northern Jutland	Aalborg

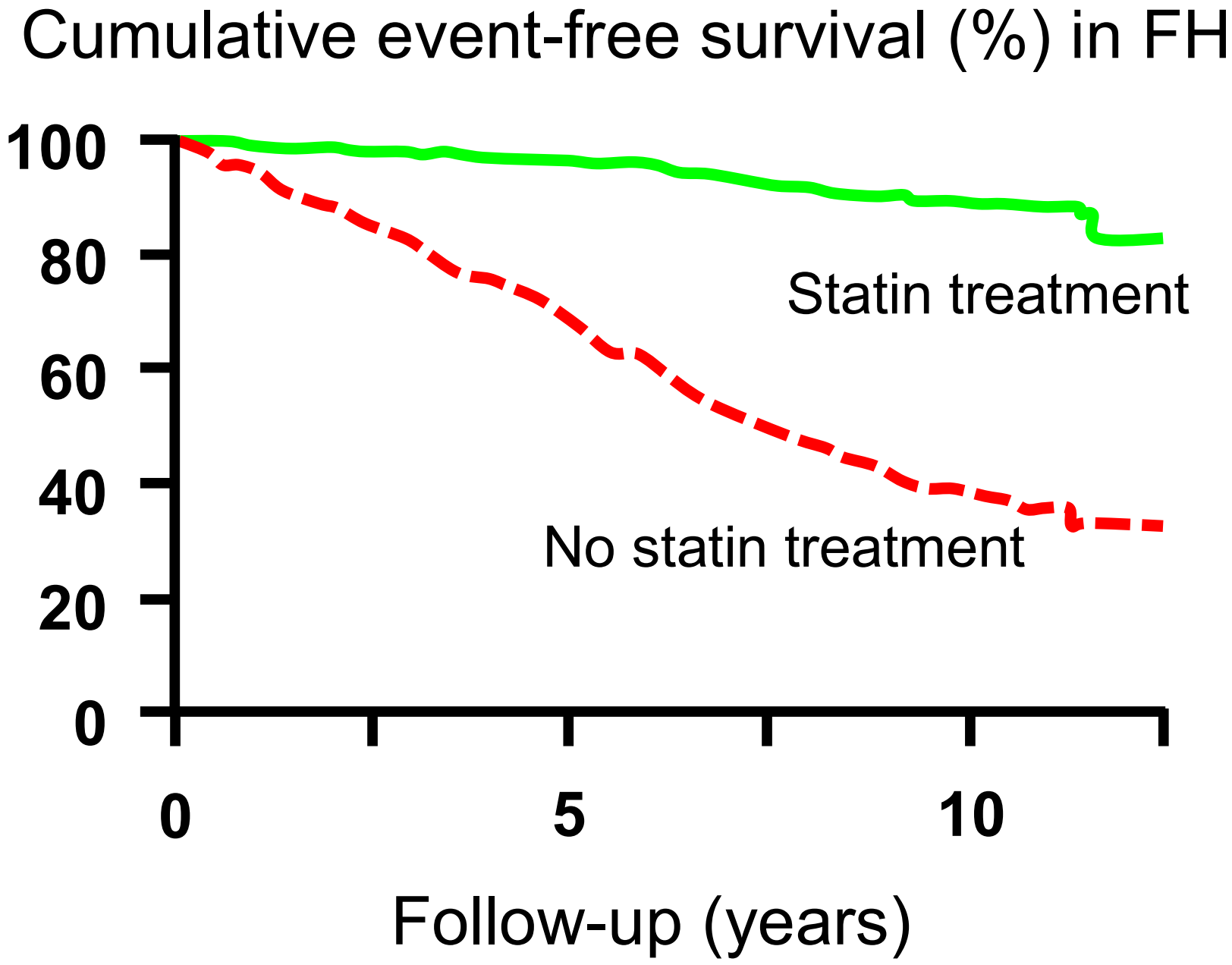
Central Jutland Region	Viborg
	Herning
	Aarhus

Region of southern Jutland	Vejle
	Kolding
	Aabenraa
	Esbjerg
	Odense

The capital region	Rigshospitalet/Glostrup
	Bispebjerg/Frederiksberg
	Herlev/Gentofte
	Amager/Hvidovre
	Hillerød/Frederikssund

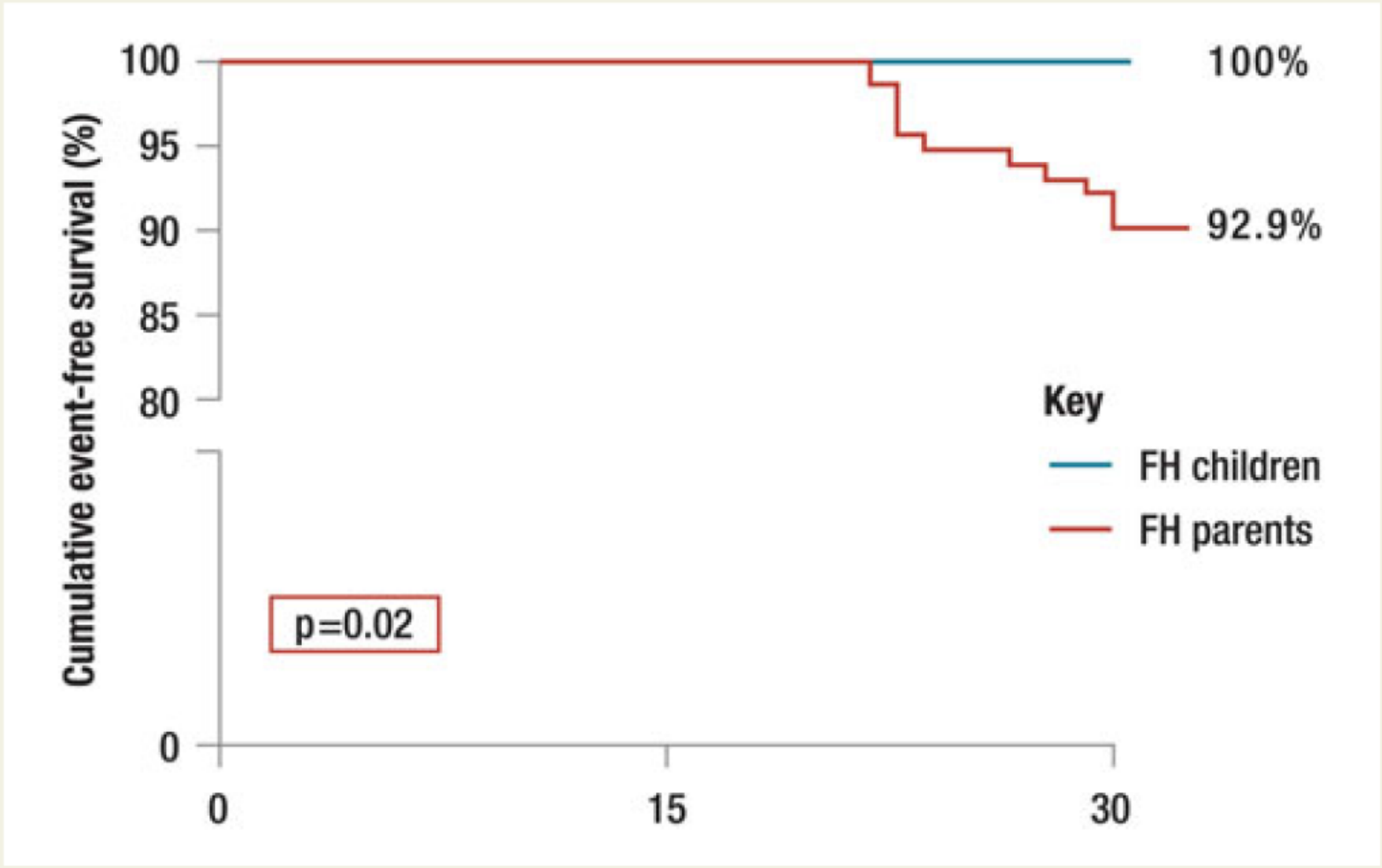
Region Zealand	Holbæk
	Roskilde

FH behandling



Adapted from Vermissen et al. BMJ 2008; 337: a2423

214 Dutch FH treated children compared with their FH parents (n=156) treated from adulthood



Wiegman et al. EAS consensus. Eur Heart J 2016; 36: 2425-2437 (open access)

Figur 3: Behandlingsmål for patienter med familiær hyperkolesterolæmi.

Voksne

- LDL-kolesterol <2,6 mmol/L.
    - Hos personer med særlig høj risiko herunder personer med hjertekarsygdom bør LDL-kolesterol være <1,8 mmol/L

Børn >10 år

- LDL-kolesterol <3,5 mmol/L

FH behandling

1. Kostvejledning og høj-intensitet statin (billigt)
2. + ezetimibe (billigt)
3. + PCSK9 hæmmer (dyrt)

Arveligt højt kolesterol: Familiær hyperkolesterolæmi

- Arven med flest dødsfald
- Årsagen er velkendt
- Nem at diagnosticere, opspore og behandle

MEN

- Sygdommen er underdiagnosticeret og underbehandlet