American Journal of Epidemiology
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Vol. 160, No. 5
Printed in U.S.A.
DOI: 10.1093/aje/kwh238

Familial Hypercholesterolemia, Peripheral Arterial Disease, and Stroke: A HuGE Minireview

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Received for publication November 24, 2003; accepted for publication April 26, 2004.

Heterozygous familial hypercholesterolemia (FH) is an autosomal dominant disorder known to be associated with elevated cholesterol levels and increased risk of premature coronary heart disease. Since increased cholesterol levels lead to atherosclerosis, FH has also been proposed as a risk factor for peripheral vascular and ischemic cerebrovascular disease. Currently, the association between clinical FH and risk of stroke is unclear: Two studies conducted in the 1980s indicated an increased risk of stroke in FH subjects; however, two others found no higher risk, and all had methodological limitations. A recent prospective study of familial hypercholesterolemia by the United Kingdom-based Simon Broome Register Group did not find an excess risk of stroke mortality for subjects with clinical FH. By contrast, the prevalence of peripheral arterial disease is increased from five- to 10-fold in FH subjects compared with non-FH controls. In addition, the intima-media thickness of the carotid and/or femoral artery is increased in FH subjects. Better understanding of the association between FH and the incidence of ischemic stroke events could have a public health impact by improving the diagnosis, prognosis, and treatment of individuals with FH and their relatives and by elucidating the relation between cholesterol levels and ischemic cerebrovascular disease.

APOB; cerebrovascular accident; epidemiology; genetics; hypercholesterolemia, familial; *LDLR*; peripheral vascular diseases

Abbreviations: FH, familial hypercholesterolemia; SD, standard deviation.

Editor's note: *This article is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/reviews.htm).*

GENES AND GENE VARIANTS

Familial hypercholesterolemia (FH) is an autosomal dominant disorder affecting approximately one of 500 Caucasians (1). The clinical phenotype is marked by elevated cholesterol levels, tendinous xanthomata, and a family history of premature coronary disease, and the phenotype is considerably more severe for homozygotes than heterozygotes (2). The clinical FH phenotype was first shown to result from mutations in the low density lipoprotein receptor gene (*LDLR*) (3, 4) located on chromosome 19p13.1-p13.3 (5). The FH clinical phenotype can also result from the mutations in the apolipoprotein B-100 gene (*APOB*) (6, 7), located on chromosome 2p23-24 (8–10). Recent work has localized a third gene, proprotein convertase subtilisin/kexin type 9 (*PCSK9*), associated with the clinical FH phenotype (11). This gene is located on chromosome 1p34.1-p32 and encodes NARC-1, a novel proprotein convertase (11).

Two mutations in *APOB* (*R3500Q* and *R3500W*) (7, 12) and over 700 mutations in *LDLR* (13, 14) have been identified in studies of individuals with a clinical FH phenotype. The prevalence of these mutations in FH subjects from different populations and ethnic groups has been reviewed for the Human Genome Epidemiology Network (15), while the *PCSK9* gene has not yet been studied at the population

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level. The prevalence review showed that there are a few founder populations in which a small number of mutations predominate, but most populations have a large spectrum of distinct *LDLR* mutations among FH individuals, with each mutation found in only a small number of individuals (15). Furthermore, studies often fail to detect the underlying mutation in 15–40 percent, or more, of the subjects screened for *LDLR* and *APOB*, indicating additional genetic and/or environmental causes for the FH phenotype (15).

DISEASES

Cerebrovascular disease and peripheral vascular disease are both composite terms that encompass a number of phenotypes and etiologic pathways. These conditions fall under the broader category of cardiovascular disease, along with coronary heart disease. The relation between FH and coronary heart disease is reviewed separately (16).

Cerebrovascular disease and its clinical manifestation of stroke comprise ischemic stroke (cerebral thrombosis and cerebral embolisms) and hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage) (17), and these categories can be further divided into heterogeneous subtypes (18). Stroke is the third leading cause of death in the United States (17) and is a leading cause of death worldwide (19). Stroke is also a major cause of morbidity in Western countries (17), with over 1 million American adults reporting long-term disabilities due to stroke events (20).

Peripheral vascular disease is defined by the American Heart Association as "diseases of blood vessels outside of the heart and brain" (17, p. 26). This review follows that definition and includes the extracranial carotid vessels. Peripheral arterial disease, the most common form of peripheral vascular disease, results from atherosclerotic buildup in the peripheral arteries (17), with clinical manifestations ranging from intermittent claudication (leg pain during exercise) to critical limb ischemia, gangrene, and amputation (21). Peripheral arterial disease affects approximately 27 million people in Europe and North America (22), and it is a strong predictor of morbidity and mortality (22). Often asymptomatic and underdiagnosed, the public health significance of peripheral arterial disease should not be underestimated (21, 23). The risk of death within 10 years is sixfold higher for symptomatic and asymptomatic peripheral arterial disease patients compared with patients without peripheral arterial disease (21).

According to recent reviews (17, 23), the risk factors for both cerebrovascular disease and peripheral vascular disease include smoking, diabetes, advanced age, male gender, hypertension, hyperlipidemia, family history of cardiovascular disease, and prior heart or vascular disease. Therefore, as a predictor of elevated cholesterol levels, FH seems a logical risk factor for both peripheral vascular disease and cerebrovascular disease. The association between elevated cholesterol levels and disease risk is fairly well established for peripheral arterial disease as an atherosclerotic disease (21) and, while cholesterol is not thought to be associated with hemorrhagic stroke events, it is traditionally listed as a potential risk factor for ischemic stroke (17).

However, current literature does not fully support the paradigm of elevated cholesterol levels as a risk factor for stroke events. An investigation of 10-year trends in the incidence and mortality of coronary heart disease and stroke in 15 populations worldwide showed that trends in stroke and heart disease differ, implying differences in underlying risk factors (24), with one possibility being that cholesterol is a strong risk factor for coronary heart disease but not for stroke. In addition, the results of several recent large-scale cohort studies indicate that cholesterol levels are not associated with ischemic stroke events (25, 26). This is in contrast to the results of other observational studies that have found an association between cholesterol levels and stroke (27, 28) and to the results of clinical trials of statins that have demonstrated that the decrease in cholesterol levels is accompanied by a decrease in the risk of stroke events (29), although it had been suggested that this may be due to cholesterol-independent actions of statins (30). Since individuals with clinical FH have roughly twofold elevated cholesterol levels from birth until diagnosis and treatment and they often continue to have elevated cholesterol levels even when treated (31), studies of stroke risk in FH subjects will contribute to this debate.

ASSOCIATIONS

To identify epidemiologic studies of FH, stroke, and peripheral arterial disease, we searched MEDLINE and PubMed using combinations of the terms "familial hypercholesterolemia," "LDLR" [low density lipoprotein receptor], "apolipoprotein B" ("APOB"), "stroke," "cerebrovascular disease," "peripheral vascular disease," "peripheral arterial disease," and "intima-media thickness." Articles were identified through September 2003. We identified additional studies by reviewing the reference lists of all retrieved articles.

Stroke events

Epidemiologic studies of the association of the clinical FH phenotype with stroke events by geographic location are summarized in Web table 1. (This information is described in the first of three supplementary tables; each is referred to as "Web table" in the text and is posted on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/reviews.htm) as well as on the *Journal*'s website (http://aje.oupjournals.org/).) Three studies conducted in the 1980s had contrasting results. A Finnish study prospectively followed 54 subjects with clinical FH (34 men and 20 women aged 21–50 years) for an average of 10 years (32). The incidence of brain infarction was 7.4/1,000 years, a level 20 times that of the general population (32). Unfortunately, the study lacked a defined control group so there was potential for surveillance bias. Specifically, since physicians were closely following the FH subjects, the FH subjects may be more likely to be diagnosed with cerebrovascular disease. Furthermore, a large proportion (77 percent) of the patients had preexisting coronary heart disease or cerebrovascular disease at entry into the study (32). Such patients may represent individuals with

more severe forms of FH, and thus the results are likely to be biased.

A case-only study in India examined 25 young patients (15 males and 10 females aged 9–38 years) with cerebral infarction of unknown etiology (33). Examination of the patients found 15 to be hyperlipidemic, nine with familial forms of the disease. Further examination of family members showed that two of the 25 (8 percent) had pedigrees indicative of FH (33). Again, the study lacked a control group, but the prevalence of FH in stroke survivors was higher than that of the general population and was similar to early findings that 5 percent of myocardial infarction survivors have FH (34, 35).

A Japanese study prospectively followed 15 individuals with homozygous FH and 527 individuals with heterozygous FH (36). Forty-one heterozygous individuals died during the 10-year follow-up, including four from cerebrovascular events. The study calculated proportional mortality, using autopsy reports, hospital records, and physician interviews, to determine the proportion of deceased individuals who died from stroke. The observed proportional mortality for strokes of 9.8 percent was similar to the proportional mortality for stroke events based on census information in the general Japanese and British populations (36). These results complemented an earlier cross-sectional study in Norway, which also found mortality for cerebrovascular disease to be lower in xanthomata patients (likely FH heterozygotes) compared with that in the general population (37).

The contrasting results from these three studies from the 1980s may be due to spurious results due to small sample sizes, and they may also be due to differences in the endpoints measured. The first two studies (32, 33) examined young adults who survived incident cases of ischemic stroke, and they found an association between FH and stroke. In contrast, the third study (36) examined overall mortality from stroke and did not find an association. Given the large competing risk of death due to coronary disease, studies of cerebrovascular mortality are likely to underestimate the actual risk of disease in FH patients (38). Further, the inclusion of hemorrhagic strokes, which are not associated atherosclerosis, could attenuate the observed association toward the null.

A more recent Danish study examined 36 female and 44 male patients with ischemic stroke events before 50 years of age (39). Patients were screened for five *LDLR* mutations known to be common in the Danish population and for three mutations in *APOB*. None of the subjects was found to carry a mutation in either gene (39). However, since less than 50 percent of clinical FH patients in Denmark carry one of these eight mutations, this does not completely rule out the possibility of FH among the stroke patients studied (40). The authors noted a higher mean cholesterol level for the stroke cases compared with a control group of 3,366 individuals from the general Danish population, and they postulated that some patients might have rare *LDLR* mutations (39). Ideally, future studies of molecular causes of FH will comprehensively screen for mutations in *LDLR*, *APOB*, and *PCSK9*.

A recent well-designed study by the United Kingdom-based Simon Broome Familial Hypercholesterolemia Register Group followed 1,405 men and 1,466 women prospectively from 1980 to 1998 for 22,992 person-years (38). All participants were diagnosed with clinical FH, and the mean age at registration was 42.3 years. A total of nine deaths from stroke were observed. This number is similar to the 11.4 deaths expected based on 5-year age and 5-year calendar year mortality rates for stroke in the general population of England and Wales. The estimated relative risk, presented as a standardized mortality ratio, was 0.79 (95 percent confidence interval: 0.36, 1.50), indicating no excess risk of death from stroke for subjects with clinical FH (38). The proportional mortality for stroke was also similar to that of the general population. As noted in their paper, interpretation of these results is limited by low statistical power resulting from the small number of events observed, the use of stroke mortality rather than ischemic stroke incidence as the endpoint, and the widespread use of statins in the population. Further analysis did not note a difference in the standardized mortality ratio for the pre- and post-statin eras (38), whereas coronary heart disease deaths were approximately halved (41).

Peripheral arterial disease

Early studies of clinical manifestations of FH reported the prevalence of symptomatic peripheral arterial disease, as indicated by intermittent claudication, to be 8–16 percent in clinical FH heterozygotes (42–44). The use of echo-Doppler methods in the 1980s allowed for presymptomatic assessment of arterial lesions and measures of reduced blood flow. Using this method, two studies identified prevalent peripheral arterial disease in 30–45 percent of FH patients, with the severity increasing with age (45, 46).

Several other studies have also reported that the prevalence of peripheral arterial disease is greatly increased in FH subjects relative to non-FH controls (Web table 2). An Italian study of 62 FH patients (13 homozygous and 49 heterozygous) and 50 controls of similar age found a fivefold increase in arterial lesions in iliac arteries and an increase of from threefold to fourfold in the prevalence of reduced blood flow in the leg arteries (47). A small Finnish study of 20 FH patients and 20 age- and sex-matched controls found an abnormal ankle/arm blood pressure ratio in 65 percent of the cases compared with only 5 percent of the controls (48). Similar results were found in a 1995 study of 72 FH subjects in the Netherlands (49). This study noted a nearly 10-fold increase in the prevalence of peripheral arterial disease measured by ankle/arm blood pressure ratios and femoral artery blood flow in FH patients (31 percent) compared with age-, sex-, weight-, smoking-, and hypertension-matched controls (3.7 percent). Peripheral vascular disease was apparent in FH heterozygotes as young as 30 years, and, contrary to the pattern for coronary heart disease, the age of onset of peripheral arterial disease was similar for males and females (49).

Intima-media thickness

Since the 1990s, a frequent surrogate measure of peripheral arterial disease is the intima-media thickness of the carotid and/or femoral artery. This noninvasive measure-

ment can identify preclinical stages of atherosclerosis, and large-scale epidemiologic studies have shown an association between increased intima-media thickness and future coronary heart disease and stroke events (50, 51). As a result, intima-media thickness is often presented as an intermediate phenotype in studies of cardiovascular disease (50–54) in the general population.

Studies of 53 Swedish FH subjects and 53 age-, height-, and sex-matched controls showed that the intima-media thickness of both the femoral and carotid arteries is increased for FH subjects (55, 56). These results have been corroborated by additional studies that have shown an increase of from 1.17-fold to 1.52-fold in common carotid intima-media thickness for FH individuals versus both normolipidemic (57–61) and hyperlipidemic (62, 63) controls (Web table 3). Two studies did not find a significant increase in the common carotid intima-media thickness; however, both noted other signs of arterial disease in FH patients (60, 64). A French study of FH children (64) found increased stiffness in the common carotid artery, and a Norwegian study (60) found an increase in carotid bifurcation intima-media thickness (in millimeters) for both men (FH subjects: mean = 0.81, standard deviation (SD) = 0.15; controls: mean = 0.74, SD = 0.19) and women (FH subjects: mean = 0.74, SD = 0.17; controls: mean = 0.66, SD = 0.15).

Intima-media thickness can also serve as an intermediate phenotype for cardiovascular risk in FH subjects. For example, a study of 248 FH subjects in the Netherlands found that intima-media thickness levels were predictive of coronary heart disease severity (65), with the mean intima-media thickness higher in FH subjects with coronary heart disease than in subjects without coronary heart disease. As an intermediate phenotype, intima-media thickness has been used as a marker to study environmental and genetic risk factors within FH individuals. Family history (62), gender (60, 66), lipoprotein levels (62, 66, 67), underlying *LDLR* mutation (63), and the paraoxonase 1 (*PON1*) gene (68) have all been shown to be associated with increased intima-media thickness and, by extension, are postulated as risk factors for cardiovascular disease, including clinical manifestations of cerebrovascular disease and peripheral vascular disease, in FH subjects.

Intima-media thickness has also been used to evaluate treatment regimens for FH. For example, a clinical trial comparing two different statin regimens in 325 patients with FH found that the decreased low density lipoprotein cholesterol levels were accompanied by decreased intima-media thickness, particularly in the group randomized for the more aggressive treatment (69). Similar results have been found in observational studies, with a regression of carotid intima-media thickness being noted in patients undergoing treatment with statins (59, 70–72). However, as with any intermediate phenotype, caution should be used when extrapolating from measures of intima-media thickness to predictions of risk for future coronary heart disease or cerebrovascular events. Of concern is the fact that treatments might alter intima-media thickness levels without impacting cardiovascular disease risk.

CONCLUSIONS AND RECOMMENDATIONS

Although FH is known to be associated with coronary heart disease and peripheral arterial disease, the impact of this clinical phenotype on the risk of stroke is still equivocal. To date, epidemiologic studies of an association between FH and stroke events have been inconclusive and have had methodological limitations. Specifically, the studies that found evidence for an association did not use a well-defined control group, whereas the studies that did not find an association may have been underpowered. Further research should be conducted to assess the strength of the association between incident ischemic stroke events and FH. Such studies would have a public heath impact by improving the prognosis, diagnosis, and treatment of individuals with FH and their relatives, and they would have a basic science impact by helping to elucidate the relation among cholesterol levels, atherosclerotic processes, and cerebrovascular disease.

ACKNOWLEDGMENTS

This project was supported under a cooperative agreement from the Centers for Disease Control and Prevention through the Association of Schools of Public Health (grants U36/CCU300430-20 and U36/CCU300430-22). This research was also supported by National Institutes of Health grant HL-49513 from the National Heart, Lung, and Blood Institute. S. E. H. is supported by the British Heart Foundation and in part by a grant from the Department of Health and Departments of Trade and Industry to the London Genetics Knowledge Park.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Association of Schools of Public Health.

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WEB TABLE 1. Association studies of clinical familial hypercholesterolemia (FH) and stroke, by geographic location

Country/Ethnicity	Study Design and Study Sample	Definition of FH	Definition of Stroke	Risk Measure Assessed	Risk Measure Value	Reference
Asia						
India/Indian	Case-only study of 25 subjects (15 males, 10 females) who survived cerebral infarction at age 40 or less from Medical College and Hospital Rohtak, India.	Two or more first degree relatives with elevated low-density lipoprotein particle levels and normal triglyceride levels. Cut off established as mean + 2 standard deviations in control subjects.	Incident cases of nonembolic ischemic stroke of unknown etiology.	Prevalence of clinical FH	Prevalence for stroke subjects: 2/25=8% Prevalence for general population of India: Estimated prevalence for Caucasians is 1/500=0.2% (73)	Bansal et al. 1986 (33)
Japan/Japanese	Propotional mortality study of 41 deceased individuals (25 males mean age 54 years, 16 females mean age 68 years) from a cohort of 527 FH subjects from Konazawa Hospital in Japan.	(a) total cholesterol >270 mg/dl with tendon xanthomatas, or (b) total cholesterol >270 mg/dl and 1st degree relative fulfilling criteria (a).	Stroke mortality as indicated in autopsy study, hospital records or interview with attending doctor.	Proportional Mortality (proportion of deceased individuals who died from stroke)	Proportional Mortality for FH subjects: 4/41= 9.8% Proportional Mortality for general population of Japan: Exact value not given, but stated not to be different from that of FH subjects.	Mabuchi et al. 1986 (36)

WEB TABLE 1 continued

Country/Ethnicity	Study Design and Study Sample	Definition of FH	Definition of Stroke	Risk Measure Assessed	Risk Measure Value	Reference
Europe						
Denmark/Danish	Case-control study of 80 subjects (44 males, 36 females) with ischemic cerebrovascular disease before age 50 from Rigshospitalet in Copenhagen. Control population was derived from Copenhagen City Heart Study.	One of the following mutations: *LDLR* mutations *W23X*, *W66G*, *W556S*, *313+1G→A*, *1846-1G→A*. *APOB* mutations *R3500Q*, *R3500W*, *R3531C*	Incident cases of ischemic stroke or transient ischemic stroke	Prevalence of common FH mutations	Prevalence for stroke subjects: All 8 mutations: 0% Prevalence for general population of Denmark: *R3500Q* and *R3531C*: 0.08% (73), *R3500W*: 0.0% (73), *LDLR* mutations: unknown	Frikke-Schmidt et al. 1999 (39)
Finland/Finnish	Cohort study of 54 FH heterozygotes (34 male, 20 female) from lipid clinics in Helsinki, Finland. Subjects were followed prospectively for a total of 540 person years, mean age at enrollment was 37 (range 21-50 years)	Total serum cholesterol > 368 mg/dl, tendon xanthomas and positive family history.	Incident cases of transient ischemic attack or brain infarction.	Incidence of brain infarction	Incidence of brain infarction in FH subjects: 7.4/1000/yr Incidence of all cause stroke in general Helsinki population age 35-44 years: 0.38/1000/yr Standardized incidence Ratio: 20.0 (95% CI: 5.5-51.2)	Kaste and Koivisto 1988 (32)

WEB TABLE 1 continued

Country/Ethnicity	Study Design and Study Sample	Definition of FH	Definition of Stroke	Risk Measure Assessed	Risk Measure Value	Reference
United Kingdom/British	Cohort study of 2871 FH heterozytoes (1405 male, 1466 female) from lipid clinics in the United Kingdom. Subjects were followed prospectively for 22,992 person years (median age at enrollment 42.3 for males, 49.2 for females).	FH defined according to the Simon Broome Register criteria (74).	Stroke mortality as indicated on death certificate by ICD-9 codes 430-438.	Standardized mortality ratio.	Mortality rate from stroke in FH subjects: 0.39/1000 person years Standardized mortality ratio compared to the general population of England and Wales: 0.79 (95% CI: 0.36-1.50).	Huxley et al. 2003 (38)

WEB TABLE 2. Association studies of clinical familial hypercholesterolemia (FH) and peripheral arterial disease (PAD), by geographic location

Country/Ethnicity	Study Design and Study Sample[†]	Definition of FH	Definition of PAD	Risk Measure Assessed	Risk Measure Value	Reference
Europe						
Finland/Finnish	Cross sectional study of 20 FH heterozygotes (6 male, 14 female; mean age 54 (3.1) years) attending the University of Helsinki hospital and 20 age and sex matched controls admitted for elective non-vascular surgery.	Total cholesterol > 10 mmol/l. Tendon xantomas in patient or at least one family member.	Ankle-arm systolic blood pressure < 0.97 on either side	Prevalence of PAD	Prevalence for FH subjects: 13/20=65% Prevalence for controls: 1/20=5% Prevalence ratio: 13.0 (95% CI: 1.9, 90.2)	Perhoniemi et al. 1989 (48)
Italy, Italians	Cross sectional study of 42 FH patients (5 homozygous, 37 heterozygous; 24 male, 18 female; age 20-59 years) at the University of Naples. 50 controls (30 male, 20 female; age 20-59) randomly selected from administrative employees at the University of Naples.	Total serum cholesterol > 7.0 mmol/l, LDLC[*] > 5.2 mmol/l, xanthomas, and autosomal dominant pattern of inheritance in family.	Ankle-arm systolic blood pressure < 0.95, each side counted separately.	Prevalence of PAD	Prevalence for FH subjects (84 legs): 6/84 = 7.1% Prevalence for controls (100 legs): 2/100 = 2% Prevalence ratio: 3.57 (95% CI: 0.74-17.23)	Rubba et al. 1988 (47)

WEB TABLE 2 continued

Country/Ethnicity	Study Design and Study Sample[†]	Definition of FH	Definition of PAD	Risk Measure Assessed	Risk Measure Value	Reference
The Netherlands/ Dutch	Cross sectional study of 68 FH patients (29 males, 39 females; mean age 45.8 (11.6) years) attending University Hospital of Nijmegen. Control subjects (13 male, 14 female; mean age 44.0 (10.9) years) were hospital volunteers.	LDLC> 95% for sex and age, tendon xanthomata, CAD[*] < age 55 for males or < age 65 for females; and/or 1st degree family member with same criteria.	Ankle/arm systolic blood pressure < 0.90 and/or ≥ 0.20 decrease in ankle/arm pressure during reactive hyperaemia.	Prevalence of PAD	Prevalence for FH subjects: 21/68 = 30.9% Prevalence for controls: 1/27=3.7% Prevalence ratio: 8.34 (95% CI: 1.18-58.96)	Kroon et al. 1995 (49)

* LDLC, low-density lipoprotein cholesterol; CAD, coronary artery disease

† Mean age presented as mean (standard deviation).

WEB TABLE 3. Summary of studies comparing intima-media thickness (IMT) in familial hypercholesterolemia (FH) subjects vs. controls, by geographic location

Country/Ethnicity	Description of FH Subjects[†]	Description of Controls	Mean IMT of common carotid artery in FH subjects (SD) [‡]	Mean IMT of common carotid artery in controls (SD)	Relative increase for FH vs controls	Reference
Africa						
South Africa/Afrikaner	20 FH heterozygous subjects (9 male, 11 female; mean age 32 (12.4) years) from lipid clinic in Johannesburg. FH defined using Simon Broome criteria (74).	20 normocholesterolemic subjects (12 male, 8 female; mean age 31 (4.2) years) with no family history of hypecholestolemia or CAD[‡].	0.76 (0.1) mm	0.65 (0.7) mm	1.17 fold increase**	Raal et al. 1999 (57)
Asia						
Japan/Japanese	97 FH heterozygous subjects (32 male, mean age 50 (15.0) years; 63 female, mean age 56 (10.0) years) from Chiba University Hospital, Chiba, Japan. FH defined as TC[‡] >6.7 mmol/l and one of (a) TX[‡], (b) TX in 1st or 2nd degree relative, or (c) reduced LDL[‡]-receptor activity in fibroblasts.	132 non FH type IIa hyperlipidemic subjects (50 male, mean age 53 (15.0) years; 82 female, mean age 59 (8.0) years). Non FH hyperlipidemia defined as total cholesterol >6.7 mmol/l without other criteria for FH.	1.13 (0.3) for males 0.93 (0.3) for females	0.74 (0.19) for males 0.71 (0.16) for females	1.52 fold increase for males *** 1.30 fold increase for females **	Taira et al. 2002 (62)

WEB TABLE 3 continued

Country/Ethnicity	Description of FH Subjects	Description of Controls	Mean IMT of common carotid artery in FH subjects (SD)	Mean IMT of common carotid artery in controls (SD)	Relative increase for FH vs controls (p value from t-test)	Reference
Europe						
Belgium/Belgian	122 subjects (63 male, mean age 44.8 (11.0) years; 59 female, mean age 46.0 (12.0) years) with severe hypercholesterolaemia, defined as TC > 95% for age and sex and at least one 1st degree relative with CVD‡ before 55 years in men or 65 years in women and an identified mutation in either *LDLR* or *APOB*.	151 subjects (87 male, mean age 46.6 (9.0) years; 64 females mean age 51.5 (11.0) years) with severe hypercholesterolemia but no identified *LDLR* or *APOB* mutation.	1.16 (0.47)	0.97 (0.37)	1.20 fold increase**	Descamps et al. 2001 (63)
France/French	30 male children (mean age 11.1 (2.0) years). FH defined as with LDLC > 4.9mmol/l, xanthomas and family history of hyercholesterolemia.	27 male normocholesterolemic controls (mean age 11.1 (3.0) years).	0.52 (0.03)	0.50 (0.03)	1.04 fold increase	Aggoun et al (2000) (64)
The Netherlands/ Dutch	21 subjects (mean age 48 (11.0) years). FH defined as elevated plasma LDLC and TX	28 normocholesterolemic controls (mean age 39 (11.0) years)	0.98 (0.29)	0.70 (0.09)	1.4 fold increase**	Smilde et al. 1998 (58)
The Netherlands/ Dutch	153 subjects (84 male, 96 female; mean age 46.2 (13.0) years) FH defined using Dutch Lipid Clinic criteria (75).	normocholesterolemic controls (mean age 45.9 years)	1.07 (0.23)	0.73 (0.20)	1.46 fold increase**	de Sauvage Notling et al. (59)

WEB TABLE 3 continued

Country/Ethnicity	Description of FH Subjects	Description of Controls	Mean IMT of common carotid artery in FH subjects (SD)	Mean IMT of common carotid artery in controls (SD)	Relative increase for FH vs controls (p value from t-test)	Reference
Norway/Norwegian	79 subjects (41 male, 38 female; mean age 38.1 (5.3) years) attending lipid clinic. FH defined by identification of a mutation in *LDLR*.	79 normocholesterolemic controls (41 male, 38 female; mean age 38.0 (5.3) years).	0.61 (0.13) for males 0.52 (0.09) for females	0.55 (0.14) for males 0.53 (0.07) for females	1.10 fold increase for males* 0.98 fold increase for females	Tonstad et al. 1998 (60)
Slovenia/ Slavic	28 subjects (12 male, 16 female; mean age 20 years, range 11-27 years) selected from offspring at lipid clinic. FH defined using MED-PED criteria (76).	28 normocholesterolemic controls (12 male, 16 female; mean age 20 years, range 11-27 years).	0.71 (0.15)	0.49 (0.08)	1.45 fold increase**	Lavrencic et al. 1996 (61)
Sweden/Swedish	53 subjects (30 male, 23 female; mean age 52.8 (11.8) years) selected from lipid clinic. FH defined as either: 1) TC >90th percentile and one of (a) TX, (b) TX in 1st or 2nd degree relative, or (c) reduced LDL-receptor activity in fibroblasts; or 2) TC>90th percentile, triglycerides<3.0 mmol/l, HDLC < 2.0 mmol/l and one of (a) hyperlipoprotenia in 1st or 2nd degree relative, or (b) premature CHD in 1st or 2nd degree relative.	53 normocholesterolimic controls (30 male, 23 female; mean age 52.2 (12.1) years).	0.85 (0.22)	0.72 (0.13)	1.18 fold increase**	Wendelhag et al. 1992 (48)

* p< 0.05, ** p<0.001, *** p<0.0001, p-value from two sided t-test.

† Mean age presented as mean (SD).

‡ HDLC, high-density lipoprotein cholesterol; LDL, low-density lipoproteins; LDLC, low-density lipoprotein cholesterol; CAD, coronary artery disease; CVD, cardiovascular disease; SD, standard deviation; TX, tendon xanthomata.

APPENDIX

Web Table References for “Familial Hypercholesterolemia, Peripheral Arterial Disease, and Stroke: A HuGE Minireview”

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