Intima-media thickness in treated and untreated patients with and without familial hypercholesterolemia: A systematic review and meta-analysis

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Abstract: Familial hypercholesterolemia (FH) is a common genetic disorder of lipoprotein metabolism leading to premature atherosclerosis. From early onset, status and progression of atherosclerosis of the large peripheral arterial walls can be quantified by ultrasound intima-media thickness (IMT) measurements. Here we describe differences in IMT in treated and untreated FH patients versus unaffected controls over a broad age range. We conducted a systematic literature search using MEDLINE, EMBASE and Trials.gov up to April 2020 for studies addressing IMT in FH patients and controls. Our search yielded 558 articles of which 42 (6,143 participants) were included. Meta-analysis showed a mean (95%CI) difference between FH patients vs controls of 0.11 (95%CI 0.06-0.15) mm in carotid IMT (p<0.001), and 0.47 (0.19-0.74) mm in femoral IMT (p<0.001). We found a smaller mean (95%CI) difference in carotid IMT in treated FH patients vs controls: 0.05 (0.03-0.08) mm (p<0.001), than in untreated FH patients vs controls 0.12 (0.03-0.21) mm (p=0.009). When plotted against age, the mean (95%CI) difference in carotid IMT between FH patients vs controls increases with 0.0018 (-0.0007-0.0042) mm/year. This increase was smaller in treated vs untreated FH patients, when compared to controls (0.0023 (0.0021 to 0.0025) mm/year vs 0.0104 (0.0100-0.0108) mm/year, respectively). Our findings suggest that more robust earlier treatment initiation and achieving treatment targets could be beneficial to reduce cardiovascular risk in patients with FH.

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Introduction

Familial hypercholesterolemia (FH) is an autosomal dominantly inherited disorder of lipoprotein metabolism. The heterozygous form of the disease affects an estimated one in 250 people worldwide. Patients with FH are characterized by elevated serum low-density lipoprotein cholesterol (LDL-C) from birth onwards, and are at increased risk for premature atherosclerosis and early cardiovascular events. Statins are the preferred pharmacological therapy in patients...
with FH, and data have shown that this treatment results in reduced serum LDL-C and a clinically relevant reduction of cardiovascular disease (CVD) morbidity and mortality in a wide range of patients.5,6

Subclinical atherosclerosis can be quantified non-invasively from early life into old age, by means of ultrasound imaging of the large peripheral arterial walls. The distance between the lumen-intima and media-adventitia ultrasound interfaces represents the thickness of the two innermost wall layers (tunica intima and tunica media) and is hence called intima-media thickness (IMT).7 IMT is usually measured in the carotid and/or femoral artery.8

In cross-sectional and follow-up epidemiological studies and clinical intervention trials, IMT has been proven to be a validated surrogate marker of the status and progression of atherosclerosis, and present and future cardiovascular disease risk.9

Several studies have shown an increased carotid IMT in untreated FH patients as compared to unaffected controls, even at a very young age.10,11 However, other studies, in both untreated children12 and untreated adult FH patients,13 reported no statistically significant differences in IMT as compared to unaffected controls. Over the last decades, FH patients have been treated with lipid-lowering agents to meet stringent LDL-C targets, preferably already from the age of 8 years, in order to reduce their future CVD risk. Indeed, several studies, showed a similar carotid IMT in treated FH patients and unaffected controls upon treatment.14-16

Atherosclerosis progresses more rapidly with age in FH patients than in unaffected controls.17 Efficacious and safe lipid-lowering treatment is known to decrease atherosclerosis progression, decrease CVD risk, and thus decrease IMT change. If compared to the reference of IMT of unaffected controls, it is therefore expected IMT in absolute sense is increased in FH. Also, IMT increase with age in treated FH patients is expected to become less apparent than in untreated FH patients.18 Therefore, in this systematic review, we compared IMT between FH-patients (treated or non-treated) with unaffected controls across a broad age range.

Searches were supplemented by checking reference lists of relevant publications, recent reviews and editorials; and by consulting experts in the field.

Study selection

We determined the eligibility of retrieved studies according to predetermined criteria. If it was unclear whether the criteria were fulfilled, we decided by consensus to include a study or not.

We selected studies with an experimental or observational study design (cross sectional, case-control or cohort) that evaluated the carotid and/or femoral IMT in patients with FH and unaffected controls and were written in English. FH was defined as a genetic diagnosis or a clinical diagnosis using internationally approved criteria.19

Studies were excluded if they were duplicate reports or preliminary reports of data later presented in full; if they did not report the same protocol for IMT-measurements within one study; if homozygous FH patients were included or if the unaffected controls had relevant comorbidity which could potentially affect IMT (for example; if this cohort consisted of patients with diabetes or patients who already experienced CVD).

Data extraction

Data of selected articles were extracted by two authors independently, using a predetermined form. The following information was retrieved from the included studies: first author, year of publication and study design. In addition, for the groups with and without FH separately, we extracted information on the number of participants, age, sex, body mass index (BMI), smoker behavior (current, former), comorbidity (hypertension, diabetes), and carotid and/or femoral IMT. In the FH group we also noted whether the patients were treated or not. FH patients were considered (partly) treated if ≥50% of the patients received treatment. FH patients were considered untreated if ≤10% of the patients received treatment. Disagreements were resolved by consensus and if necessary, by the opinion of a third reviewer.

Methods

Search strategy

We conducted a systematic literature search of MEDLINE (1992 – April 2020), EMBASE (1980 – December 2018) and ClinicalTrials.gov for studies addressing the carotid and/or femoral IMT of patients with FH and unaffected controls. We used two different domains of Mesh-terms and free text words combined with ‘AND’, and in each domain the terms were combined with ‘OR’. The first domain contained terms on IMT (including all different synonyms) and the second on FH (including all different synonyms and abbreviations). The complete search strategy is given in the supplemental data (Table S1).

Critical appraisal

Two reviewers assessed the methodological quality of the included studies by using the Newcastle Ottawa Scale (NOS).20 This scale consists of three domains: selection, comparability and outcome. Each domain has its own criteria. For the domain selection three of the four criteria are: the representativeness of the exposed cohort, the selection of the controls and the ascertainment of exposure (in this case: the definition of FH). The last criterion for this domain is the demonstration that outcome of interest was not present at start study, which is not relevant for our study and we therefore decided not to assess this criterion. The criteria for the domain comparability of FH patients and unaffected controls were assessed by looking at differences regarding age, etc.
sex and other risk factors for increased IMT (hypertension, smoking, BMI and diabetes). For the domain outcome the assessed criterion was: assessment of outcome (in this case: the method of the IMT-measurement). We decided not to assess the criteria about duration and adequacy of follow-up as we are studying the effect of a genetic disease, which means that ‘the exposure to FH’ is from birth onwards. Difference in judgement by the reviewers was solved by discussion and consensus.

With a maximum score of six stars and a minimum score of zero stars, we split up the assessed studies by degree of quality: studies allocated three stars or less were considered poor quality (high risk of bias), studies allocated four stars were considered medium quality (medium risk of bias), studies allocated five stars or more were considered high quality (low risk of bias).

**Statistical analysis**

We performed a meta-analysis for all included studies, as well as for the studies with treated and untreated FH patients separately. For the studies that reported both baseline data and follow-up data, we only included baseline data for the overall analysis; and for the analysis for treated and untreated FH patients separately, we used baseline data for the analysis of untreated FH patients and follow-up data for treated FH patients.

We calculated for each study the mean difference in carotid IMT and 95% confidence interval (CI) between patients with FH and unaffected subjects. Because the study populations were heterogeneous regarding age, comorbidities and medication use, we decided to combine study data using a random effects model according to the method of DerSimonian and Laird. By using the method of DerSimonian and Laird, the weights of the different studies are adjusted according to the heterogeneity or the extent of variation, among the observed intervention effects. For more details on this method, we refer to DerSimonian and Laird. A Z-test was performed to test the overall effect. All tests were performed using Review Manager 5.3 (Cochrane Collaboration).

We explored the difference in annual increase in IMT between FH patients and unaffected control subjects using linear regression analysis. For this analysis, we weighted the studies based on the sample size and standard error of the mean difference in IMT between FH patients and subjects without FH. GraphPad Prism 5 was used for this analysis. P-values <0.05 were considered statistically significant.

**Results**

**Description of the studies**

Our search yielded 558 publications, of which 305 full-text articles were assessed for eligibility. Of these, 263 full-text articles had to be excluded (Figure 1). Hence, 42 studies with 6,159 participants (ranging from 29 to 772 participants per study) remained for qualitative synthesis in this review: 38 cross-sectional studies (including 4 conference abstracts) and 4 prospective cohort studies were included.

Of the 42 included studies, 39 examined the carotid IMT, one study evaluated the femoral IMT, and two studies examined both. The characteristics of the studies examining the carotid artery, are given in Table 1a. In total, 3,796 (range: 16 to 572 per study) patients with FH and 2,363 (range: 15 to 268 per study) unaffected controls were studied. The 25 studies that were published after a previous systematic review are marked with a red dot. Mean age of FH patients ranged between 8.8 to 56.9 years, and unaffected controls between 8 to 61.2 years. Of all FH patients, 49% (range: 33% to 68%) was male, and this was 47% (range: 32% to 67%) for the unaffected controls. All femoral IMT measurements were performed in the common femoral artery (CFA) and the characteristics of these studies are summarized in Table 1b. In total, 196 (range: 21 to 146 per study) patients with FH and 254 (range: 28 to 193 per study) unaffected controls were studied. Mean age of FH patients was 44.9 years (range: 42.3 to 56.9 years) and mean age of unaffected controls was 49.4 (range: 39 to 57.8 years). Of all FH patients, 52.2% (range: 51% to 58%) was male, and this was 44.9% (range: 44% to 57%) for all unaffected controls.

Mean age and/or gender was not reported in 6 studies. 2 studies did not report the mean age and gender of the control cohort. Number of males in follow-up data of cohort studies were excluded. 1 cohort study did not report the baseline data of the femoral IMT measurements, therefore we included the follow-up data. Of the FH patients that were treated with cholesterol-lowering medication, in the studies that reported on type of treatment, all were receiving statins, often in combination with other drugs. Details on type of treatment can be found in Table 1.

**Methodological quality of included studies**

The assessment of the methodological quality of the included studies can be found in the supplemental data (Table S2). In general, the included studies were considered of high quality: 26 studies were identified as having a low risk of bias, nine studies were identified as medium risk of bias and seven studies were identified as having a high risk of bias. The most common reason for excluding studies because of a high risk of bias was when it was unclear whether the control cohort was drawn from the same population as the FH cohort. Another common reason was that the control cohort were not comparable with the FH cohort with respect to age, gender, and comorbidity.

**Difference in mean carotid IMT between subjects with and without FH**

Of the 41 studies that reported on the carotid IMT in patients with FH and unaffected controls, seven studies were not included in the meta-analysis because they did not re-
### Table 1  Clinical and demographic characteristics of the FH patients and subjects without FH of studies examining the IMT (ordered by publication year). Red dots represent the systematic article publications as:  

| First author, year (ref) | Study design | FH N | Mean age (yrs) | Male (%) | Comorbidity (%) | Smoker (%) | Treatment | IMT (mm) | Non-FH N | Mean age (yrs) | Male (%) | Comorbidity (%) | Smoker (%) | IMT (mm) |
|--------------------------|--------------|------|----------------|----------|-----------------|------------|-----------|----------|----------|----------------|----------|----------------|------------|---------|
| Mean carotid IMT         |              |      |                |          |                 |            |           |          |          |                |          |                 |            |         |
| Lurink (16)              | Cohort       | 184  | 31.7 ± 3.2     | 88 (48)  |                 | Current 41 | 0.555 ± 0.542 – 0.567 | 77       | 31.6 ± 3.0 | 43 (56)        |          |                 |            | 0.551 ± 0.531 – 0.570 |
| Rodríguez-Borjabad 2018 (35) | Cross-sectional | 82   | 9.28 ± 3.69    | 44 (53.8)| DM excluded     | Current 19 (15) | 0.42497 ± 0.07 | 101      | 10.80 ± 3.42 | 53 (52.6)       |          | DM excluded     | Current 55 (35) | 0.42097 ± 0.06 |
| Michikura 2017 (48)      | Cross-sectional | 130  | 53.2 ± 18.6    | 53 (41)  | Current 28 (22) | Former 45 | 0.9 ± 0.5 | 155      | 61.2 ± 13.4 | 71 (46)         |          | DM excluded     | Current 41 | 0.8 ± 0.2 |
| Braamskamp 2017 (14)     | Cohort       | 197  | 12.1 ± 3.3     | 87 (44)  | Excluded        | Baseline  | 0.397 ± 0.049 | 65       | 12.0 ± 3.5 | 33 (51)         |          | Excluded        | Baseline  | 0.377 ± 0.045 |
| Bos 2017 (49)            | Cross-sectional | 221  | 46 ± 15        | 107 (48) | Current 46 (21) | Current 72 (33) | 0.58 ± 0.13 | 103      | 47 ± 16 | 33 (32)         |          |                |            | 0.58 ± 0.12 |
| Hjuler Nielsen 2015 (50) | Cross-sectional | 30   | 45.5 ± 9.1     | 12 (40)  | Excluded        | No treatment | 0.64 ± 0.12 | 23       | 47 ± 10.1 | 8 (35)          |          | Excluded        | No treatment | 0.58 ± 0.07 |
| Kologlu 2014 (37)        | Cross-sectional | 38   | 8.8 ± 4.0      | 17 (45)  | DM excluded     | No treatment | 0.49 ± 0.12 | 24       | 8.0 ± 3.6 | 12 (50)         |          | DM excluded     | No treatment | 0.32 ± 0.07 |
| Vlahos 2014 (36)         | Cross-sectional | 30   | 12 ± 2         | 17 (55)  | Excluded        | Excluded    | 0.46 ± 0.05 | 30       | 12 ± 2  | 17 (55)         |          | Excluded        | Excluded    | 0.45 ± 0.03 |
| Walus-Miarka 2013 (43)   | Cross-sectional | 36   | 27.3 ± 6.6     | 36 (range)| Current 10 (27.8) | Current 2 | 0.60 ± 0.19 | 49       | 25.2 ± 6.7 | 18 (36.3)       |          | HT 8 (16.3) | Current 15 | 0.53 ± 0.07 |
| Bravo 2012 (23)          | Cohort       | 20   | 41.4 ± 3.0     | 6 – 18 (range) | No treatment | 0.7 ± 0.04 | 20       | 42.4 ± 2.3 | 7 (35)         |          | Excluded        | No treatment | 0.5 ± 0.02 |

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Table 1 (continued)

| First author, year | Study design | FH | Mean age (yrs) | Male (%) | Comorbidity (%) | Smoker (%) | Treatment | IMT (mm) | Non-FH | Mean age (yrs) | Male (%) | Comorbidity (%) | Smoker (%) |
|--------------------|--------------|----|----------------|----------|-----------------|------------|------------|----------|--------|----------------|----------|----------------|------------|
| Caballero 2012 (53) |
| Cross-sectional | 36 | 45.7 ± 10.9 | 18 (50.0) | HT 3 (8.3) | Current 17 (47.2) | Statins (combined with ezetimibe) | 0.94 ± 0.34 | 19 | 47.8 ± 11.3 | 10 (52.6) | HT 0 (0) | DM excluded | 0.61 ± 0.10 |
| Noto 2012 (30) | Cross-sectional | 17 | 16.9 ± 5.5 | 12 (71) | No treatment | 0.60 ± 0.02 | 15 | 0.42 ± 0.04 |
| Ershova 2012 (13) | Cross-sectional | 32 | 35 ± 10 | 12 (37.5) | HT 7 (21.9) | Current 16 (50) | No treatment | 0.64 ± 0.18 | 21 | 32 ± 11 | 8 (38.0) | HT 5 (23.8) | Current 8 (38) | 0.58 ± 0.13 |
| Alipour 2012 (54) | Cross-sectional | 20 | 55.1 ± 1.4 | 7 (35.0) | Current 2 (10.0) | Statins (combined with ezetimibe) | 0.66 ± 0.03 (SEM) | 33 | 55.1 ± 1.7 | 12 (36.4) | Current 3 (9.1) | 0.56 ± 0.02 (SEM) |
| Jarauta 2012 (52) | Cross-sectional | 572 | 45.0 ± 13.6 | 280 (49.0) | HT 106 (18.6) | CVD 49 (8.5) | Never 313 (54.8) | Former 123 (21.5) | Statins | 0.747 (0.734 – 0.759)* | 200 | 45.5 ± 16.4 | 82 (40.9) | HT 4 (2.1) | CVD (0) | DM (0) | Current 27 (13.5) | Never 139 (69.5) | Former 34.6 (17.3) | Mean 0.673 (0.652 – 0.695)* |
| Di Salvo 2011 (29) | Cross-sectional | 43 | 11 ± 3 | 27 (62.8) | HT 15 (12) | DM 2 (1.6) | Current 40 (32) | Stains (combined with ezetimibe) | 0.758 ± 0.280 (median + IR) | 59 | 47 ± 10 | 25 (42.4) | HT excluded | DM excluded | Current excluded | 0.635 ± 0.16 (median ± IR) | 0.628 (0.613 – 0.642)* |
| Khan 2011 (24) | Cross-sectional | 40 | 45 ± 13 | 61 (48.8) | HT 15 (12) | DM 2 (1.6) | Ever 66 (41) | Ever 66 (41) | Statins | 0.664 (0.648 – 0.679) | 145 | 42.3 ± 8.7 | 69 (48) | HT excluded | DM excluded | Current excluded | 0.635 ± 0.16 (median ± IR) | 0.628 (0.613 – 0.642)* |
| Plana 2011 (31) | Cross-sectional | 125 | 45 ± 13 | 61 (48.8) | HT 15 (12) | DM 2 (1.6) | Current 40 (32) | Stains (combined with ezetimibe) | 0.758 ± 0.280 (median + IR) | 59 | 47 ± 10 | 25 (42.4) | HT excluded | DM excluded | Current excluded | 0.635 ± 0.16 (median ± IR) | 0.628 (0.613 – 0.642)* |
| Huigen 2011 (47) | Cross-sectional | 162 | 35.2 ± 8.7 | 68 (42) | HT 10 (6) | DM 1 (1) | Ever 66 (41) | Ever 66 (41) | Statins | 0.664 (0.648 – 0.679) | 145 | 42.3 ± 8.7 | 69 (48) | HT excluded | DM excluded | Current excluded | 0.635 ± 0.16 (median ± IR) | 0.628 (0.613 – 0.642)* |
| Noto 2011 (38) | Cross-sectional | 55 | 13.7 ± 3.2 | 20 (36) | Excluded | Ever 66 (41) | Ever 66 (41) | Statins | 0.664 (0.648 – 0.679) | 145 | 42.3 ± 8.7 | 69 (48) | HT excluded | DM excluded | Current excluded | 0.635 ± 0.16 (median ± IR) | 0.628 (0.613 – 0.642)* |
| Group I | Cross-sectional | 20 | 11.9 ± 3.9 | 8 (53.3) | Excluded | Excluded | No treatment | No treatment | 0.57 ± 0.03 | 15 | 13.0 ± 1.4 | 7 (46.7) | Excluded | Excluded | 0.43 ± 0.02 |
| Group II | Cross-sectional | 17 | 15.3 ± 2.0 | 5 (25) | Excluded | Excluded | No treatment | Statins | 0.57 ± 0.03 | 15 | 13.0 ± 1.4 | 7 (46.7) | Excluded | Excluded | 0.43 ± 0.02 |
| Group III | Cross-sectional | 18 | 14.3 ± 3.2 | 7 (41.2) | Excluded | Excluded | No treatment | No treatment | 0.57 ± 0.03 | 15 | 13.0 ± 1.4 | 7 (46.7) | Excluded | Excluded | 0.43 ± 0.02 |
| Vladimirava-Kitova 2010 (57) | Cross-sectional | 250 | 41.3 ± 0.23 | 59 (48.3) | HT 14 (34) | DM 1 (2.5) | Excluded | Excluded | Statins | 0.77 ± 0.15 | 40 | 47.4 ± 3.9 | 13 (33) | HT 4 (10) | CVD (0) | DM (0) | Current 12 (29) | 0.71 ± 0.11 |
| Sivapalaratnam 2010 (55) | Cross-sectional | 40 | 48.4 ± 4.2 | 27 (68) | HT 6 (15) | CVD 14 (35) | DM 1 (2.5) | Excluded | Excluded | Statins (combined with ezetimibe or lopid) | 0.77 ± 0.15 | 40 | 47.4 ± 3.9 | 13 (33) | HT 4 (10) | CVD (0) | DM (0) | Current 12 (29) | 0.71 ± 0.11 |
| Riggio 2010 (12) | Cross-sectional | 18 | 11.8 ± 2.8 | 6 (33) | Current 14 (34) | DM 1 (2.5) | Excluded | Excluded | Statins (combined with ezetimibe or lopid) | 0.77 ± 0.15 | 40 | 47.4 ± 3.9 | 13 (33) | HT 4 (10) | CVD (0) | DM (0) | Current 12 (29) | 0.71 ± 0.11 |

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**Table 1 (continued)**

| First author, year (ref) | Study design | FH | Non-FH |
|--------------------------|--------------|----|--------|
|                           |              | N  | Mean age (yrs) | Male (%) | Comorbidity (%) | Smoker (%) | Treatment | IMT (mm) | N  | Mean age (yrs) | Male (%) | Comorbidity (%) | Smoker (%) | Treatment | IMT (mm) |
|                           |              |    | (range)        |          |                |            |           |          |    | (range)        |          |                |            |           |          |
| Junyent 2010 (34)         | Cross-sectional | 431 | 44 (18-82) (range) | 223 (51) | HT 68 (16) CVD 60 (14) DM 8 (2) | Ever 193 (44) | Statins, ezetimibe, resins or lipraites | 0.70 (0.68 – 0.71)* (medians and CI) | 268 | 49 (20-81) (range) | 140 (52) | HT 24 (9) CVD 0 DM 0 | Ever 81 (30) | 0.61 (0.59 – 0.62)* (medians and CI) |
|                           |              |    |                |          | HT 42 (16) CVD 42 (16) DM 5 (2) | Ever 116 (43) | | | | | | | | |
|                           |              |    |                |          | HT 24 (15) CVD 17 (11) DM 3 (2) | Ever 76 (47) | | | | | | | | |
|                          |               | 269 | 43 (18-82) (range) | 134 (50) | Never 66 (38.1) Current 45 (26.3) Former 62 (35.6) | No treatment | 0.742 (0.651 – 0.898) (median and IR)* | 64 | 42.4 ± 15.2 | 64 (100) | HT: 1 (1.6) CVD: 0 | Never 37 (57.1) Current 10 (15.9) Former 42 (27) | 0.656 (0.577 – 0.758) (median and IR)* |
| Guardamagna 2009 (39)    | Cross-sectional | 84  | 10.5 ± 3.3 | 47 (56) | HT: 39 (23.6) CVD: 25 (14.5) | Never 85 (58.1) Current 22 (14.8) Former 20 (13.6) | No treatment | 0.717 (0.628 – 0.828) (median and IR)* | 81 | 46.0 ± 17.6 | 0 | HT 1 (1.3) CVD 0 | Never 58 (71.6) Current 12 (14.8) Former 11 (13.6) | 0.590 (0.513 – 0.716) (median and IR)* |
|                           | Cross-sectional | 173 | 44.7 ± 11.7 | 173 (100) | Never 85 (38.1) Current 45 (26.3) Former 62 (35.6) | No treatment | 0.742 (0.651 – 0.898) (median and IR)* | 64 | | | | | | |
| Yeo 2008 (42)            | Cross-sectional | 32  | 36.0 ± 17.8 | 18 (56) | Excluded | Current 3 (9.4) | 1.1 ± 0.9 | 34 | 42.1 ± 17.0 | 17 (50) | Excluded | Current 1 (2.9) | 0.7 ± 0.1 |
| Martinez 2008 (46)       | Cross-sectional | 89  | 39 ± 14 (14 – 69) | 34 (38.2) | HT 12 (13.5) | Current 13 (14.6) | Statins | 0.653 ± 0.16 | 31 | 40 ± 12 (19-69) | 16 (51.6) | HT 1 (3.2) | Current 3 (9.6) | 0.593 ± 0.11 |
| Ellis 2007 (33)          | Cross-sectional | 30  | 52 (35 – 77) (median and range) | 18 (60) | Excluded | Current 7 (17.9) | 0.57 ± 0.13 | 25 | 30.6 ± 11.3 | 18 (60) | Excluded | | 0.48 ± 0.13 |
|                           |               |    |                |          | | | | | | | | | | |
| Soljanlahti 2005 (26)    | Cross-sectional | 39  | 30.0 ± 13.6 | | Current 7 (17.9) | Statins | 0.57 ± 0.13 | 25 | 30.6 ± 11.3 | 18 (60) | Excluded | | 0.48 ± 0.13 |
|                           |               |    |                |          | Current 7 (17.9) | Statins | 0.57 ± 0.13 | 25 | 30.6 ± 11.3 | 18 (60) | Excluded | | 0.48 ± 0.13 |
| Wiegman 2004 (11)        | Cross-sectional | 201 | 12.9 (12.5-13.4) | 90 (46.4) | HT 0 (11) | Current 22 | No treatment | 0.494 ± 0.051 | 80 | 13.0 (12.3-13.6) | 46 (55.4) | HT 0 (11) | Current 6 (7) | 0.472 ± 0.049 |

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| First author, year (ref) | Study design | FH N | Mean age (yrs) | Male (%) | Comorbidity (%) | Smoker (%) | Treatment | IMT (mm) | Non-FH N | Mean age (yrs) | Male (%) | Comorbidity (%) | Smoker (%) | IMT (mm) |
|-------------------------|-------------|-----|----------------|---------|-----------------|------------|------------|----------|-----------|----------------|---------|-----------------|------------|----------|
| Aggoun 2000 (27)        | Cross-sectional | 30  | 11.1 ± 2.0     | Excluded| Excluded        | Cholesterol-lowering drugs (cholestyramine, fenofibrate) | 0.52 ± 0.03 | 27       | 11.1 ± 3.0 | Excluded | 0.50 ± 0.03 |
| Treated cohort          |             |     |                |         |                 |            |            |          |           |                |         |                 |            |          |
| Un-treated cohort       |             |     |                |         |                 |            |            |          |           |                |         |                 |            |          |
| Raal 1999 (45)          | Cross-sectional | 20  | 11 ± 2         | Excluded| Excluded        | 0.51 ± 0.03 | 0.52 ± 0.03 |          | 20       | 11 ± 3         | Excluded | 0.65 ± 0.7 |
| Tonstad 1998 (44)       | Cross-sectional | 79  | 38.1 ± 5.3     | Excluded| Excluded        | Statins (combined with resins or acipimox) | 0.52 ± 0.03 | 79       | 38.0 ± 5.3    | Excluded | 0.50 ± 0.03 |
| Males                   |             |     |                |         |                 | CCA 0.61 ± 0.13 |            |          | 41       | 41 (100)       | Excluded | 0.55 ± 0.14 |
| Females                 |             |     |                |         |                 | Bif 0.81 ± 0.15 |            |          | 38       | 38 (100)       | Excluded | 0.53 ± 0.07 |
| Smilde 1998 (28)        | Cross-sectional | 21  | 46 ± 11        | CVD 14 (66.7) | Current 12 (57.1) | CCA post 0.98 ± 0.29 | CCA ant 0.99 ± 0.21 | Bulbus post 1.25 ± 0.35 | Bulbus ant 1.25 ± 0.22 | ICA post 1.08 ± 0.53 | 28 | 39 ± 11 | CVD 0 DM excluded | Current 0 0.70 ± 0.09 |
| Virkola 1997 (25)       | Cross-sectional | 23  | 2.8 – 19 (range) | 15 (65) | Excluded        | CCA 0.48 ± 0.70 | Bulbus 0.54 ± 0.10 | Bulbus 0.55 ± 0.10 | Bulbus 0.55 ± 0.09 | 23 | 2.8 - 19 (range) | 15 (65) | Excluded | CCA 0.46 ± 0.06 |
| Tonstad 1996 (40)       | Cross-sectional | 90  | 14.0 ± 2.3     | 61 (67.8) | 0 | No treatment | CCA 0.48 ± 0.07 | Bulbus 0.54 ± 0.10 | Bulbus 0.55 ± 0.10 | Bulbus 0.55 ± 0.09 | 30 | 14.1 ± 2.3 | 20 (66.7) | 0 | CCA 0.48 ± 0.06 |
| Males                   |             |     |                |         |                 | CCA 0.49 ± 0.07 | Bulbus 0.54 ± 0.10 | Bulbus 0.55 ± 0.10 | Bulbus 0.55 ± 0.09 | 20 | 14.2 ± 2.3 | 20 (100) | 0 | CCA 0.48 ± 0.06 |
| Females                 |             |     |                |         |                 | CCA 0.47 ± 0.07 | Bulbus 0.51 ± 0.09 | 10 | 13.9 ± 2.4 | 0 | 0 | CCA 0.42 ± 0.08 |

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Table 1 (continued)

| Study design | FH | Non-FH |
|--------------|----|--------|
| **First author, year (ref)** | **FH** | **Mean age (yrs) Male (%)** | **Comorbidty (%) Smoker (%)** | **Treatment** | **IMT (mm)** | **Non-FH** | **Mean age (yrs) Male (%)** | **Comorbidty (%) Smoker (%)** | **IMT (mm)** |
| **Wendelhag 1996 Cohort (15)** | 50 (49 IMT) | 56.9 ± 12.0 29 (58) | No treatment | Lipid-lowering | CCA 0.85 ± 0.22 | 47 (46 IMT) 57.8 ± 11.7 27 (57) | Current 9 (19) | CCA 0.78 ± 0.18 | Bulbus 0.88 ± 0.26 |
| **Wendelhag 1992 Cross-sectional (56)** | 51 | 52.2 ± 21.1 | Current (24) No treatment | Lipid-lowering | 0.85 ± 0.22 | 51 | 52.8 ± 11.8 | Current (22) | HT 5 (9.8) | Ever: 54 (28) 0.71 ± 0.53 |
| **Junyent 2008 (59)** | 123 | 40.7 (20-76) (range) 56 (46) | Ever 38 (31) | Statins (combined with fibrates, resins) | 193 | 49.5 (25-80) (range) 85 (44) | HT: 9 (5) DM: 0 | Ever: 54 (28) 0.71 ± 0.53 |
| **Asymptomatic FH** | 23 | 50.7 (28-70) (range) 18 (78) | Ever 12 (52) | Statins (combined with fibrates, resins) | 1.39 ± 0.91 |
| **FH with CHD** | 21 | 46 ± 11 | Current 12 (57) | Statins (combined with fibrates, resins) | 1.60 ± 0.72 | 28 | 39 ± 11 | CVD 0 DM excluded | Current 0 0.74 ± 0.23 |
| **Wendelhag 1996 Cohort (15)** | 50 (29 IMT) 56.9 ± 12.0 29 (58) | Current 10 (20) | Lipid-lowering | CCA 0.85 ± 0.22 | 47 (33 IMT) 57.8 ± 11.7 27 (57) | Current 9 (19) | CCA 0.78 ± 0.18 | Bulbus 0.88 ± 0.26 |
| **Baseline 5-year follow-up** | N=7 | 1.12 ± 0.48 | Ever 38 (31) | Statins (combined with fibrates, resins) | 1.38 ± 0.66 | 47 (33 IMT) 57.8 ± 11.7 27 (57) | Current 9 (19) | CCA 0.78 ± 0.18 | Bulbus 0.88 ± 0.26 |

Data extracted from: 16. Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, et al. 20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia. The New England journal of medicine. 2019;381(16):1547-56. Epub 2019/10/17.

Mean carotid IMT measured at one location (CCA).

Data are ± SDs or (95% CI) if not otherwise stated.

Only raw data is reported in Table 1. The mean carotid IMT is defined as the mean of carotid IMT measurements on multiple sections of the carotid artery right and left, if not otherwise stated.

HT: hypertension

DM: diabetes mellitus

CVD: cardiovascular disease

MI: myocardial infarct

CCA: common carotid artery

ICA: internal carotid artery

Bulbus: carotid sinus

Bif: aortic bifurcation

Post: posterior

Ant: anterior

SD: standard deviation

CI: confidence interval

SEM: standard error of the mean

**Note:** If there are any specific questions or need further clarification, feel free to ask!
port the participants’ age, reported only medians and interquartile ranges for IMT, baseline data of the cohorts were previously reported and therefore already included. Analyses of the pooled data of the remaining 34 studies showed a mean difference in carotid IMT between FH patients (n=2,850) and unaffected controls (n=1,851) of 0.11 mm (95% CI 0.06 to 0.15; P<0.001) (Figure 2A).

For the age category 1 to 20 years, data of 15 studies was available with a total of 974 FH patients and 579 unaffected controls. Analysis of the pooled data showed a significant difference in mean carotid IMT between FH patients and controls of 0.07 mm (95% CI 0.05 to 0.10; P<0.001).

Data of 8 studies was available for the age category 21 to 40 years with a total of 489 FH patients and 414 unaffected controls. Analysis of the pooled data showed a significant difference in mean carotid IMT between FH patients and controls of 0.06 mm (95% CI 0.03 to 0.08; P<0.001).

For the age category 41 to 60 years, data of 11 studies was available with a total of 1,387 FH patients and 858 unaffected controls. Analysis of the pooled data showed a significant difference in mean carotid IMT between FH patients and controls of 0.16 mm (95% CI 0.03 to 0.30; P=0.02).

Six studies also assessed carotid plaques, and of these showed a significantly more often occurrence of plaques in patients with FH as compared to unaffected controls. One study showed more often plaques in FH patient, but this was not significant.

**Difference in mean carotid IMT between untreated or treated FH patients and unaffected subjects**

Thirteen studies provided data on the mean carotid IMT in untreated FH patients (n=1,018) and unaffected controls (n=670). The vast majority of the studies showed a thicker carotid IMT in the FH patients (Figure 3A); the analysis of the pooled data resulted in a difference of 0.12 mm (95% CI 0.03 to 0.21; P=0.009).

We could use data of 13 studies to analyze the carotid IMT difference in (partly) treated FH patients (n=1,735) versus unaffected controls (n=1,010) (Figure 3B). One study split up the FH cohort in a treated and an untreated cohort, we used both data for Figure 3Ab and 3B. See Table S3 in the supplemental data for the number of treated patients per study. Analysis of the pooled data showed a significant difference in mean carotid IMT between (partly) treated FH patients and controls of 0.05 mm (95% CI 0.03 to 0.08; P<0.001), although less pronounced than in untreated FH patients versus controls.

We explored the association between age and the difference in mean carotid IMT (FH patients versus controls). Figure 4a shows the overall difference expressed against age, using data of 34 studies. Difference in IMT tends to be more distinct with increasing mean age (0.0018 mm/year; 95% CI -0.0007 to 0.0042). Figure 4b shows different regression lines for the difference in carotid IMT between controls versus untreated and untreated subjects.
A: Carotid IMT

B: Femoral IMT

Fig. 2 Forest plot of mean carotid IMT (A) and mean femoral IMT (B) in patients with FH and unaffected subjects (ordered by age). Red dots represent the newest publications (from 2010).

Discussion

In this systematic review and meta-analysis, we showed that the mean carotid IMT in (treated and untreated) FH patients is thicker in comparison with unaffected controls. In addition, we found that the mean carotid IMT in FH patients (partly) treated FH patients, respectively, using data of 24 studies. The difference in mean carotid IMT between untreated FH patients and unaffected controls shows a greater increase than the difference in mean carotid IMT between treated FH patients and unaffected controls (0.0104 mm/year, 95% CI 0.0100 to 0.0108 vs 0.0023 mm/year, 95% CI 0.0021 to 0.0025; P<0.001).

Difference in mean femoral IMT between subjects with and without FH

Three studies reported on the femoral IMT in FH patients (n=196) and unaffected controls (n=254) (Figure 2B). Pooled analysis showed a significant thicker mean femoral IMT in patients with FH patients compared to unaffected controls (mean difference: 0.47 mm 95% CI 0.19 to 0.74; P<0.001). One study also reported on femoral plaque assessment and showed significantly more often plaque occurrence in FH patients compared to unaffected controls.59

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increases with age to a greater extent than in unaffected controls. The difference in carotid IMT between FH patients and unaffected controls, as well as the increasing difference in carotid IMT with increasing age, is more pronounced in studies with untreated FH patients than in studies with treated patients. These results suggest that more robust or earlier treatment initiation might be beneficial to reduce cardiovascular risk in patients with FH. Lastly, we found the mean femoral IMT in FH patients is increased as compared to unaffected controls.

Our findings are in line with an earlier systematic review on this topic, in which studies from up to 2010 were included. Now a decade later, we were able to include more than 20 additional studies published after 2010, of which several studies in the pediatric age range. As it has been recommended since 2008 to start statin treatment in children from the age of 8 years, we were able to also study the effect of statin treatment on IMT after early treatment initiation.

Carotid IMT has been considered as a validated, well-established surrogate marker for cardiovascular disease and the ultrasound scan procedure is not time consuming, comfortable for participants, completely safe and can be performed at high reproducibility in a standardized fashion. In a recent large meta-analysis it was shown that although in follow-up intervention trials no associations with carotid IMT change and cardiovascular disease risk were detected, absolute mean carotid IMT was positively and robustly associated with cardiovascular disease risk.

We reported in this review on both the carotid IMT and the femoral IMT. While the carotid IMT is considered as a valid marker of cardiovascular disease risk, femoral IMT is not commonly performed. Because of the very limited number of 3 available studies that included femoral IMT data (n=3) and the lack of information on the occurrence of clinical cardiovascular disease in these studies, we can neither draw robust conclusions on the predictive value of femoral IMT data nor the relationships of femoral with carotid IMT data.

Several aspects of this review merit discussion. First of all, heterogeneity was high in several of our meta-analyses. In our study we deemed that heterogeneity was mostly due to the different ages of the study populations and the fact that both treated and untreated study cohorts were included. By dividing the population in different age groups, and by separating treated and untreated study cohorts, we tried to reduce heterogeneity. Heterogeneity may also be due to the presence of some outlying studies with results that conflict with the rest of the studies. Indeed, three of the included studies reported an extreme difference (≥0.3 mm) in carotid IMT between FH patients and unaffected controls. Although there was no obvious reason to exclude these studies, we also performed the analysis without these studies. Excluding these studies reduced heterogeneity in the analyses, and the overall mean difference in carotid IMT between FH patients and unaffected controls decreased slightly (0.08 mm [0.06 - 0.10] p<0.001). Besides that, we used a random-effects model according to the method of DerSimonian and Laird.

Fig. 3 Forest plot of mean carotid IMT in untreated FH patients versus non-FH subjects (A), and in (partly) treated FH patients versus non-FH subjects (B), (ordered by age). Red dots represent the newest publications (from 2010).
The limitation of this method is that, by estimating the degree of heterogeneity, confidence intervals are smaller than they should be to encompass full uncertainty. However, the difference in results is expected to be small when using a high number of studies for the meta-analysis.62

Secondly, the included studies all have a (slightly) different IMT-measurement protocol. Moreover, one of the included studies performed the IMT-measurements at one location of the carotid artery,15 while other studies calculated a mean carotid IMT out of multiple measurements on different sections of the carotid artery. However, the IMT of FH patients and unaffected controls within a study were performed in the same way. Additionally, two studies that were included in the meta-analyses reported IMT-measurements that were adjusted for sex, age, smoking behavior, body mass index, and/or systolic blood pressure.32,34 However, by taking the difference in carotid IMT between FH patients and unaffected controls and pooling these differences of the included studies, we deem that the different methods of measurement and adjustment for confounders have not significantly influenced our results.

Thirdly, almost all studies regarding treatment are open label studies. Randomized controlled studies would have been optimal to assess the treatment effect. However, since statin therapy is indicated in FH patients to reduce CVD, it would be unethical to have a placebo group. Because our main outcome is the difference in IMT between FH patients and unaffected controls, instead of the treatment effect in FH patients, we don’t think that this affected our results. Next to this, we considered FH patients (partly) treated if ≥50% of the patients received treatment. Ideally, 100% of the patients should be treated to draw conclusions about treatment effects, and this might have caused an underestimation of the difference in carotid IMT between ‘treated’ and ‘untreated’ FH patients. Furthermore, only one study reported information about adherence to medication.16 Assuming that not every FH patient is completely adherent, the difference in carotid IMT between treated FH patients and unaffected controls might be overestimated, and the difference between untreated and (partly adherent) treated FH patients might be underestimated. For most of the studies it is also unknown for how long FH patients had been treated. Moreover, in most cohorts of the studies, not all the FH patients were receiving treatment. This is not unique; Pijlman et al.63 and Béhiard et al.64 show that only a small part of FH patients achieves their treatment target. It is a paradox that FH patients are often undertreated while the importance of early disease management is well established, and treatment options are safe and very efficacious. The earlier treatment is initiated, and the higher the compliance, the lower is the “lifetime cholesterol exposure” and probably, the lower the cardiovascular risk. Indeed, in a recent 20-years follow-up study of early initiated statin use in FH patients in which an excellent compliance was reported, there was no statistically significant difference in carotid IMT between treated FH patients and their unaffected siblings.16 The results of our study again emphasize the need of treatment of FH patients.

Overall, we conclude that FH patients have a higher mean carotid and femoral IMT compared to unaffected controls. The fact that the difference in IMT increases with age between FH patients and unaffected controls, and is more pronounced in studies with untreated FH patients than in studies with treated patients, suggests that starting treatment already at a young age in patients with FH is preferred. However, despite treatment, IMT in treated FH patients is still thicker in comparison to subjects without FH. This sign of residual risk might suggest that more robust cholesterol lowering treatment and achieving treatment targets, or earlier treatment initiation, is needed to reduce IMT progression to non-FH conditions. Therefore, we must find and diagnose these patients, and treat them according to current guidelines.

Author declaration

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript. KBH, BH and DK conceived and designed the study. KBH, BH and DK collected the data. KBH, DK, BH and EG analyzed the data. KBH, BH and DK wrote the first draft of the manuscript. EG, IL and AW contributed to writing and finalizing the manuscript. All authors read and approved the final manuscript.
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Supplementary materials

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