PLOS ONE

RESEARCH ARTICLE

Regional and demographic variations of Carotid artery Intima and Media Thickness (CIMT): A Systematic review and meta-analysis

V. Abeysuriya[1,2]*, **B. P. R. Perera**[1], **A. R. Wickremasinghe**[1]

1 Department of Public Health, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka, **2** Nawaloka Hospital Research and Education Foundation, Nawaloka Hospitals PLC, Colombo, Sri Lanka

* visulasrilanka@hotmail.com

Check for updates

OPEN ACCESS

Citation: Abeysuriya V, Perera BPR, Wickremasinghe AR (2022) Regional and demographic variations of Carotid artery Intima and Media Thickness (CIMT): A Systematic review and meta-analysis. PLoS ONE 17(7): e0268716. https://doi.org/10.1371/journal.pone.0268716

Editor: Andreas Zirlik, Medizinische Universitat Graz, AUSTRIA

Received: July 19, 2021

Accepted: May 5, 2022

Published: July 12, 2022

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0268716

Copyright: © 2022 Abeysuriya et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All data files are available from the figshare database (Abeysuriya, Visula (2022): CIMT Dataset. figshare. Dataset. https://doi.org/10.6084/m9.figshare.19360925.v1).

Abstract

Background and objective

Carotid artery intima media thickness (CIMT) is a strong predictor of Coronary Heart Disease (CHD) and independent phenotype of early atherosclerosis. The global variation of CIMT and its demographic association is yet unclear. We evaluated regional variations of CIMT based on WHO regions and assessed the differences by age and sex.

Methods

A systematic search was conducted on studies published between 1980 January up to December 2020. PubMed, Oxford Medicine Online, EBSCO, Taylor & Francis, Oxford University Press and Embase data bases were used for searching. Supplementary searches were conducted on the Web of Science and Google Scholar. Grey literature was searched in "Open Grey" website. The two major criteria used were "adults" and "carotid intima media". The search strategy for PubMed was created first and then adapted for the Oxford Medicine Online, EBSCO, Taylor & Francis, Oxford University Press and Embase databases. Covidence software (Veritas Health Innovation, Melbourne, Australia; http://www.covidence.org) was used to manage the study selection process. Meta-analyses were done using the random-effects model. An $I^2 \geq 50\%$ or $p< 0{:}05$ were considered to indicate significant heterogeneity.

Results

Of 2847 potential articles, 46 eligible articles were included in the review contributing data for 49 381 individuals (mean age: 55.6 years, male: 55.8%). The pooled mean CIMT for the non-CHD group was 0.65mm (95%CI: 0.62–0.69). There was a significant difference in the mean CIMT between regions ($p = 0.04$). Countries in the African (0.72mm), American (0.71mm) and European (0.71mm) regions had a higher pooled mean CIMT compared to those in the South East Asian (0.62mm), West Pacific (0.60mm) and Eastern Mediterranean (0.60mm) regions. Males had a higher pooled mean CIMT of 0.06mm than females in the non CHD group (p = 0.001); there were also regional differences. The CHD group had a significantly higher mean CIMT than the non-CHD group (difference = 0.23mm, $p = 0.001$) with

Funding: VA received the funds from Nawaloka Hospital Research and Education Foundation, Nawaloka hospitals PLC, Colombo-02 Sri Lanka. Grant number is NHREF/01/2020. Funder web site: https://www.nawaloka.com. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. the funder provided support in the form of salaries for the author [VA] but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section.

Competing interests: The authors have declared that no competing interests exist.

regional variations. Carotid artery segment-specific-CIMT variations are present in this population. Older persons and those having CHD group had significantly thicker CIMTs.

Conclusions

CIMT varies according to region, age, sex and whether a person having CHD. There are significant regional differences of mean CIMT between CHD and non-CHD groups. Segment specific CIMT variations exist among regions. There is an association between CHD and CIMT values.

Introduction& rationale

The global burden of non-communicable diseases (NCD)varies between developed and developing countries showing regional differences [1–4]. NCDs are the leading cause of death and disability worldwide. In 2005, NCDs caused an estimated 35 million deaths comprising 60% of all deaths globally; 80% of these deaths were in low income and middle-income countries [5, 6]. NCDs are inextricably linked to many modifiable and non-modifiable risk factors [1, 7–9]. Coronary heart disease (CHD) is the leading cause of premature deaths [10–12].

An accurate, non-invasive, convenient and low-cost screening tool to detect CHD is needed for mass screening of at-risk population. The Carotid intima-media thickness (CIMT) is a reliable, non-invasive indicator which predicts the risk of coronary artery disease (CAD) and is widely used in practice as an inexpensive, reliable, non-radiation and reproducible method [13–19].

CIMT is mostly associated with traditional cardiovascular risk factors such as age, sex and race [20–22]. Smoking, alcohol consumption, lack of exercise, high blood pressure, dyslipidemia, poor dietary patterns, risk-lowering drug therapy, glycemia, hyperuricemia, obesity-related anthropometric parameters and obesity-related diseases increase CIMT [23–25]. Traditional risk factors do not explain all of the risk of CHD. It has been reported that more than 60% of CHD cases were not explained by demographic and traditional cardiovascular risk factors [26]. This may probably be due to the effects of novel risk factors such as heredity, presence of certain genotypes, immunological diseases, inflammatory cytokines and hematological parameters [27–30].

Majority of research on CIMT and its association with future risk of cardiovascular disease (CVD) independent of conventional risk factors has been done in Western populations. Only one study has been conducted in Asia in a Japanese population with a limited sample size [31]. Literature suggests that using CIMT cut-off values of western populations for risk prediction of Asians may not be appropriate [32]. CIMT values are strongly affected by age, sex and population [33]. Therefore, CIMT cut-offs are needed for its clinical use as a screening tool to predict future cardiovascular risk [33]. The manner in which CIMT is assessed and the definitions used are still not universally defined [16, 34, 35].

It is not possible to review CIMT values for each country as such values are not available for many countries. Therefore, we reviewed available literature by WHO region, assuming that populations within the region are more homogenous, to derive potential CIMT cut-off values by age and sex that may be used by different countries in the regions.

Method and analysis

We followed guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements, the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines, and methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions [36–38] to conduct this review and meta-analysis.

Eligibility criteria

Study designs. Studies of observational and interventional research were included. The following study designs having adults with a mean age of 40 years and above, with or without CHD were considered: longitudinal, case–control, nested case-control and cross-sectional studies. Case reports, case series, opinion papers, letters to the editor, comments, conference proceedings, review articles, policy papers and meta-analyses were excluded from the analysis. Animal studies, non-English manuscripts and study protocols without baseline data were excluded. The outcome measure was the intima-media thickness of the carotid artery measured by ultrasonography. There was no restriction by time duration of follow-up or observation.

Setting. Data from all countries were considered. There was no restriction by type of setting. The countries were later categorized into WHO regions.

The six WHO regions are 1) African Region (AFR); 2) Eastern Mediterranean Region (EMR); 3) European Region (EUR); 4) Region of the Americas (PAHO); 5) South-East Asia Region (SEAR); and 6) Western Pacific Region (WPR) (40).

Search strategy. Potential articles were systematically searched in the following electronic databases; PubMed, Oxford Medicine Online, EBSCO, Taylor & Francis, Oxford University Press and Embase for publications between January 1980 to December 2020. Supplementary searches were done on Web of Science and Google Scholar. Grey literature was searched in "OpenGrey" website using two criteria "adults" and "carotid intima media". The search strategy for PubMed was created first and then adapted for the Oxford Medicine Online, EBSCO, Taylor & Francis, Oxford University Press and Embase data bases (S1 File). The references of these selected articles were hand-searched for more relevant articles.

Study selection. After removing duplicates and obviously unrelated articles, the titles and abstracts were screened against pre-specified criteria by two independent reviewers. Pre-determined inclusion criteria were based on the following key words: "carotid intima media thickness", "coronary heart disease", "healthy adults", "adults with coronary heart disease", and "studies in English language". Exclusion criteria included "children", "paediatric", "any person with a history of stroke or TIA", "history of malignancy", "who has undergone carotid end arterectomy", "history of connective tissue disease", "history of an ongoing infection", "studies on cadaver or corpse", "studies on animals", "other languages", "meta–analysis", "reviews", and "letters to editor". Discrepancies were resolved through discussion. If consensus was not reached, arbitration was done with a third reviewer. Full text articles were assessed for eligibility. The systematic reviews software Covidence (Veritas Health Innovation, Melbourne, Australia; http://www.covidence.org) was used to manage the study selection process.

Data extraction. The following data were extracted: name of first author; year of publication; country (according to WHO regions), study design, number of patients, age, proportion of males and females, number of CHD and non-CHD persons, segment measured, measurement protocol, risk factors, mean and maximum values of CIMT. Two authors independent of each other extracted data. Disagreements were resolved by discussion or, if necessary, with the arbitration of a third reviewer. Calibration exercises were conducted before this review stage to enhance consistency between assessors. The study team collated information provided in

multiple reports of the same study. For articles on the same population, the more comprehensive one was selected. Apart from inclusion and exclusion criteria, authors selected studies with adjusted CIMT values and study quality assessment statements were considered. When CIMT measurements were available for several time points, the time point closest to the end of the intervention or the follow-up period was selected for data extraction. When essential information was missing from the published reports, the principal investigator contacted the authors of the original studies by email or through "Research gate" to request for missing data. A maximum of two email attempts per study was made.

Study quality. The quality of selected studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria [39], the "STROBE statement" quality assessment tool and "The Newcastle-Ottawa Scale" were used to assess quality and heterogeneity of case control, cross sectional and cohort studies, and risk of bias [40]. Quality appraisal was performed independently by two reviewers. The protocol of ultrasound measurement of CIMT and reliability was assessed based on "A Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force" [41].

Data analysis

Data analysis was carried out using STATA version 16 (Stata Corp. 2019. Stata Statistical Software: Release 16. College Station, TX: Stata Corp LLC).

Measures of association

Differences in CIMT by age, sex and selected risk factors in countries between WHO regions.

Descriptive analyses. The characteristics of the study population including details of publication, country, WHO region, age, gender, sample size, measurement site, CIMT assessment, ultrasound protocol and process, identified risk factors, factors adjusted for and adjusted predictors of CIMT in each study are presented in the text and as tables.

Steps of meta-analyses

The mean CIMT were pooled according to WHO regions. Based on the literature we expected to have heterogeneity between the pooled data [16, 41–44]. Therefore, meta-analyses were done using random-effects models with inverse variance-weighted average. Results are presented graphically as forest plots. Meta regression analysis of CIMT values was conducted with and without adjusting for coronary heart disease status, region, mean age and ultrasound technique used.

Assessment of heterogeneity of studies. Heterogeneity was tested using the Cochran's Q test and quantified using the I^2 [38]. An $I^2 \geq 50\%$ or $p < 0.05$ was considered as indicating significant heterogeneity [45]. Sensitivity analyses were carried out by excluding studies with relatively small sample sizes and low-quality studies based on the scores of QUADAS-2 criteria, "STROBE statement "and "The Newcastle-Ottawa Scale".

Assessment of strength of evidence. Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria, "STROBE statement"and "The Newcastle-Ottawa Scale" were applied to evaluate the quality of the included articles [39]. QUADAS-2 criteria assess the strength of evidence by categorizing studies into low risk, high risk and unclear based on patient selection, index test, and reference standard, flow and timing domains. The "STROBE statement" checklist consists of 22 items that relate to the title, abstract, introduction, methods, results, and discussion sections of articles. Eighteen items are common to all three study designs and four are specific for cohort, case-control, or cross-sectional studies. The primary outcome was the STROBE score, defined as the number of the 22 STROBE items adequately reported divided

by the number of applicable items, expressed as a percentage [46, 47]. Publication quality grades of STROBE score are as follows: excellent (more than 85%), good (85 to 70%), fair (70 to 50%) and poor (less than 50%). The Newcastle-Ottawa Scale considers study selection, comparability and outcome categories when assessing the quality of selected studies. The points are considered as follows: 4 points for selection, 2 points for comparability, and 3 points for outcomes. Study quality was categorized according to total points obtained by each study (very good [9], good [7–8], satisfactory [5–6] and unsatisfactory [0–4] [48, 49]).

Results

2847 [(records identified through data bases: n = 2647; published Literature (PL): 2502 (94.5%); grey literature (GL): 145(5.5%) and records identified through other sources (n = 200); PL: 192(96%); GL: 8(4%))] relevant articles were obtained; 93 records were duplicates and were removed (Fig 1). The abstract and titles were screened, and 2201 articles were removed due to different populations, disease outcomes and study designs, other methods of CIMT measurement, animal studies and non-English publications. Full texts of the remaining 553 publications were evaluated for eligibility (n = 553, published literature: 549(99.2%); grey literature: 4(0.8%)). From the review of the full texts, an additional 507 articles were removed due to different study designs, study populations, outcomes and settings, insufficient data and paediatric population. Finally, 46 eligible articles were reviewed [PubMed: 11(23.9%), EBSCO: 9(19.6%), Taylor & Francis 9(19.6%), Embase 7(15.2%), Oxford Medicine6 (13.0%), Oxford University Press 4(8.7%)] (Fig 1).

Two independent reviewers conducted the full text review. The agreement between the two reviewers was 90% with a Cohen's kappa of 0.733. All the studies were evaluated using QUADAS-2, "STROBE statement" and "The Newcastle-Ottawa Scale" for cross sectional, case control and cohort studies, respectively. QUADAS-2 risk of bias and applicability of the selected studies is shown in Fig 2. The percentages of low-risk studies based on patient selection, index test, reference standard and flow and timing domains were 93.5%, 84.7%, 65.2% and 65.2%, respectively. In the applicability category, it was 64.4% for patient selection, 82.7% for index test and 52.2% for reference standard.

91.3% (42/46) of the studies fulfilled the criteria of the STROBE statement (S1 Table). The Newcastle–Ottawa scale was used to assess the quality of selected studies. Average total quality score for Newcastle–Ottawa scale of cross sectional, case control and cohort studies were7, 7 and 8, respectively (S2–S4 Tables, respectively).

Table 1 provides an overview of the 46 studies included in the systematic review and meta-analyses. The studies were categorized based on the countries they were conducted in according to WHO regions: African Region (AFR) had6(13%) studies; Eastern Mediterranean Region (EMR) had 4(8%); European Region (EUR) had 12(26%); Region of the Americas (PAHO) had8(17%); South-East Asia Region (SEAR) had 7(15%); and the Western Pacific Region (WPR) had 9(20%) studies. There were 24(52%) cross sectional studies, 20(445%) case control studies, 01(2%) prospective study and 01(2%) retrospective cohort study included in the systematic review. There was heterogeneity when measuring the CIMT value among the studies. The commonest segment measured was the far wall of the common carotid artery (CCA) (both sides) (19/46 = 41%), followed by the far wall of CCA, carotid bulb (CB) and internal carotid artery (ICA) (both sides) (6/46 = 13%) and the far and near walls of CCA, CB and ICA (both sides) (4/46 = 9%). The most common IMT definition used was mean CIMT (30/46 = 65%). Definition of plaque was reported in 58% of studies (27/46). ECG gating at acquisition was reported in 28%(13/46) of studies. All studies had used a linear transducer with the frequency varying from 3MHz to 15MHz. Only five studies used Digital Imaging and

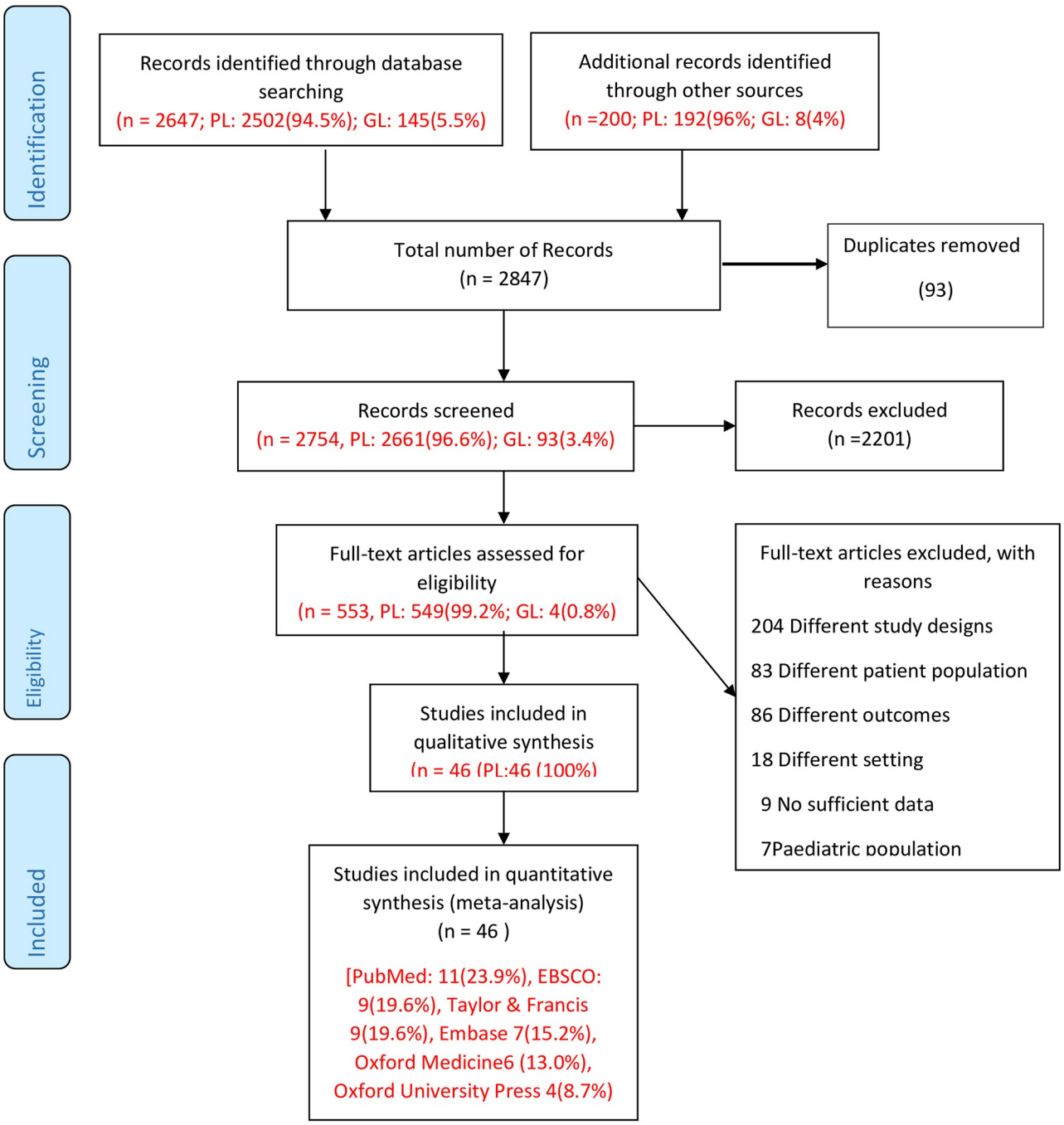

Fig 1. PRISMA flow diagram. Abbreviation: PL: publish literature, GL: Grey literature.

https://doi.org/10.1371/journal.pone.0268716.g001

Communications in Medicine (DICOM) software. Traditional modifiable risk factors were the commonest predictors of CIMT (21/46 = 45.6%) followed by non-modifiable risk factors of age and gender (13/46 = 28%). Three studies reported age as a single predictor of CIMT (3/46 = 7%). One study reported air pollution as a risk factor for CIMT. Three studies reported socio-economic status as a predictor of CIMT. HIV infection, CRP levels and metabolic

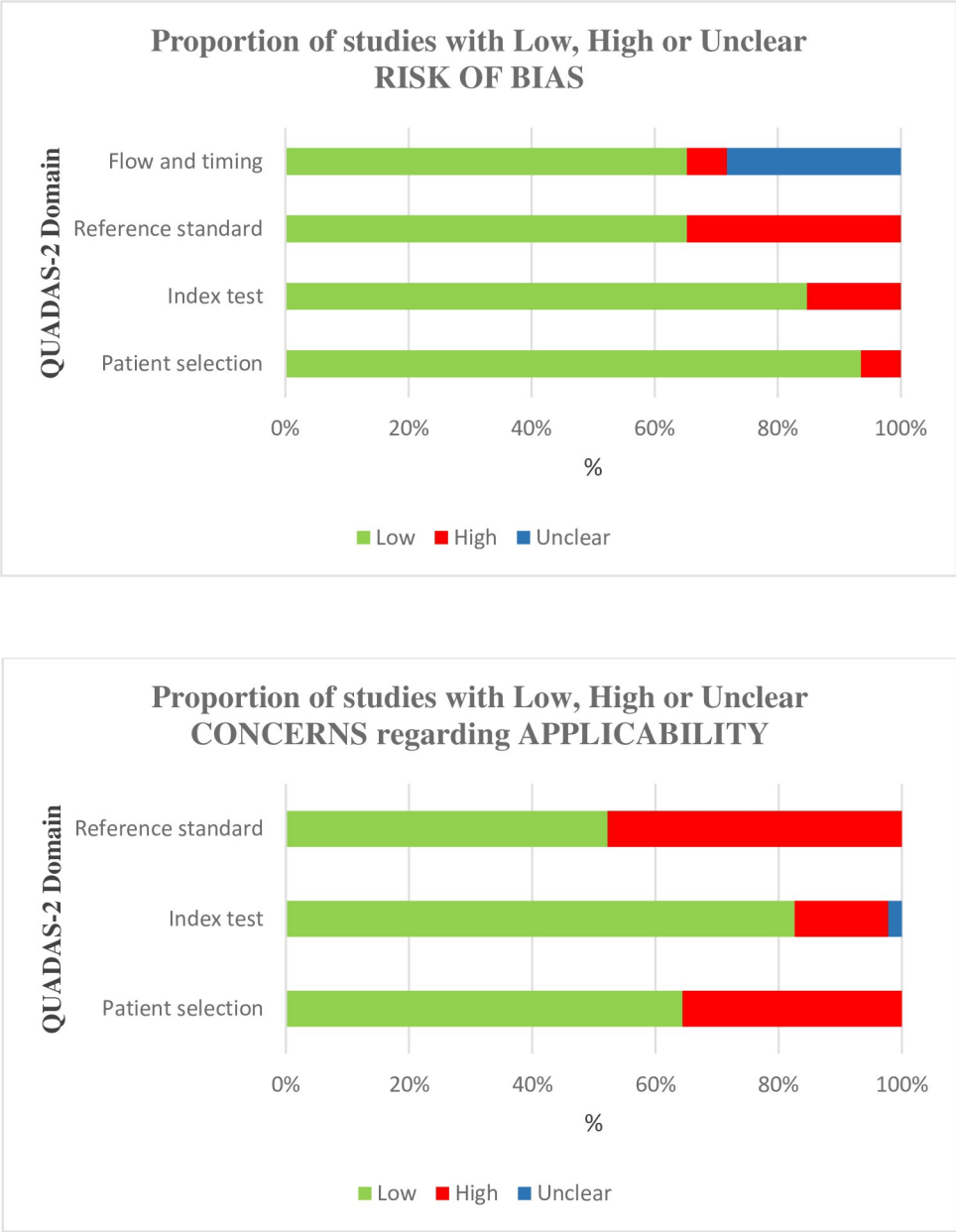

Fig 2. QUADAS-2 risk of bias and applicability of selected studies.

https://doi.org/10.1371/journal.pone.0268716.g002

syndrome were reported as predictors of CIMT in a few studies. Only one study reported that none of the traditional risk factors predicted CIMT.

Table 2 shows the mean CIMT values of different carotid segments by WHO region in the non-CHD and CHD groups. The mean CIMT values of CCA vary from 0.58±0.09mm to 0.74 ±0.11mm. The mean CIMT of CB ranges from 0.65±0.08mm to 0.81±0.09mm. The range for the mean CIMT of ICA was 0.65±0.10mm to 0.69±0.06. In each region, the highest mean CIMT value was in the CB followed by the CCA and the ICA. The highest mean CIMT value of CCA of 0.74±0.11mm was in EUR countries. The mean CIMT values of CCA in SEAR and

Table 1. Summary of studies used in systematic review and meta-analysis, reporting demography, IMT measurement protocols and predictors of CIMT.

Publication	Country	WHO regions	Design	Sample size	Mean age (years)	Male N, %	Carotid segments	IMT definition	Definition of plaque	Ultrasound scan specifications	ECG gating at acquisition	Factors adjusted for
Denise et al. 2018 [50]	Nigeria	AFRO	Cross-sectional study	100	58.3	N = 44, 44.0%	CCA, CB, ICA, both sides, far wall	Mean CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5 -10MHz, Edge detection: Not used	Not used	Age, gender, smoking, BMI and hypertension
Ayoola et al. 2015 [51]	Nigeria	AFRO	Case control study	100	54.9	N = 50, 50.0%	CCA, both sides, far wall	Mean CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5-10MHz, Edge detection: Not used	Not used	Hypertension, gender, FBS dyslipidemia
Ofonime et al. 2019 [52]	Nigeria	AFRO	Cross-sectional study	122	52.7	N = 36, 29.5%	CCA, CB, ICA, both sides, far wall	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear:7.5-10MHz, Edge detection: Not used	Not used	Age, DBP, gender, Family history of heart disease, BMI, Physical activity, Waist circumference and SBP
Okeahialam et al. 2011 [53]	Nigeria	AFRO	Cross-sectional study	71	50	N = 35, 49.3%	CCA, both sides, far wall	Mean CIMT	Not reported	DICOM- Not used, Transducer-Linear:7.5MHz, Edge detection: Not used	Not used	Gender, Diabetes and hypertension
Zaiboonnisa et al. 2009 [54]	South Africa	AFRO	Prospective study	53	47.1	N = 41, 77.3%	CCA, CB, ICA, both sides, far wall	Mean and maximum CIMT	Reported	DICOM- Not used, Transducer-Linear:11MHz, Edge detection: Not used	Not used	Age
Nonterah et al. 2018 [55]	Sub-Saharan Africa	AFRO	Cross-sectional study	8872	49.87	N = 4507, 50.8%	CCA, both sides, far wall	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear:7.5-10MHz, Edge detection: Not used	Not used	Gender, BMI, TRF, Socio-economic factors and HIV
Kamran et al. 2014 [56]	Iran	EMRO	Case control study	500	60	N = 287, 57.4%	CCA, both sides	Mean and maximum CIMT	Not reported	DICOM- Not used, Transducer- Linear:7.5-15MHz, Edge detection: Not used	Not used	Age, gender, Hypertension, smoking, and Hyperlipidemia
Pourafkari et al. 2006 [57]	Iran	EMRO	Cross-sectional study	113	44	NR	CCA and ICA, both sides	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear:7.5-15MHz, Edge detection: Not used	Not used	Age and gender
Mirza et al. 2017 [58]	Pakistan	EMRO	Cross-sectional study	257	45	N = 97,38%	CCA and ICA, both sides	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear: NR, Edge detection: Used	Not used	Age, diabetes, and gender
Mustafa et al. 2013 [59]	Sudan	EMRO	Cross-sectional study	11	41.6	N = 6,54.5%	CCA, both sides, far wall	Mean CIMT	Not reported	DICOM- Not used, Transducer-Linear:6MHz, Edge detection: Not used	Not used	Age, smoking, and gender
Haghi et al. 2005 [60]	Germany	EURO	Case control study	151	61.5	N = 120,79.5%	CCA, both sides, far wall.	Mean CIMT	Reported	DICOM- Not used, Transducer-Linear:7.5MHz, Edge detection: Not used	Not used	Age and gender
Kotsis et al. 2005 [61]	Greece	EURO	Cross-sectional study	390	61.2	N = 345,88.5%	CCA and ICA, both sides, far wall.	Mean CIMT	Not reported	DICOM- Not used, Transducer-Linear:7MHz, Edge detection: Used	Not used	Age, alcoholic, and gender
Mauro Amato et al. 2007 [62]	Italy	EURO	Cross-sectional study	48	61	N = 36,75%	CCA, CB and ICA, both sides, far and near wall.	Mean CIMT	Not reported	DICOM- Not used, Transducer-Linear:6.7MHz, Edge detection: Not used	Not used	NR

(*Continued*)

Table 1. (Continued)

Publication	Country	WHO regions	Design	Sample size	Mean age (years)	Male N, %	Carotid segments	IMT definition	Definition of plaque	Ultrasound scan specifications	ECG gating at acquisition	Factors adjusted for
Del Sol et al. 2001 [63]	Netherlands	EURO	Case control study	1690	71	N = 686,40.6%	CCA, CB and ICA, both sides, far and near wall.	Mean of Max. CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5MHz, Edge detection: Used	Used	NR
Ziembicka et al. 2005 [64]	Poland	EURO	Cross-sectional study	558	57.5	N = 438,78.5%	CCA, CB and ICA, both sides, far and near wall.	Mean of Max. CIMT	Not reported	DICOM- Not used, Transducer- Linear:5-10MHz, Edge detection: Used	Used	Age, gender, hypertension, smoking, alcoholic, FBS diabetes and Obesity
Lisowska et al. 2009 [65]	Poland	EURO	Case control study	231	49	NR	CCA and CB, both sides, far wall.	Mean CIMT	Reported	DICOM- Not used, Transducer- Linear:3-11MHz, Edge detection: Not used	Not used	Age, gender, diabetes, dyslipidemia, and GFR
Timo´ teo et al. 2013 [66]	Portugal	EURO	Case control study	300	64.5	N = 176, 58.7%	CCA, both sides, far wall.	Mean of Max. CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5MHz, Edge detection: Not used	Not used	Gender
Sait et al. 2003 [67]	Turkey	EURO	Case control study	233	59	N = 131,56.2%	CCA, both sides, far wall.	Mean CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5MHz, Edge detection: Not used	Not used	Age, SBP, smoking, alcoholic, diabetes mellitus and total cholesterol
SelcanKoc et al. 2019 [68]	Turkey	EURO	Retrospective study	644	54.6	N = 314,48.5%	CCA and ICA, both sides, far wall.	Mean of Max. CIMT	Reported	DICOM- Not used, Transducer- Linear:5-12MHz, Edge detection: Used	Not used	Age, gender and SBP, FBS
Mehmet et al. 2006 [69]	Turkey	EURO	Case control study	144	53.2	N = 87, 60.4%	CCA and CB, both sides, far wall.	Mean of Max. CIMT	Reported	DICOM- Not used, Transducer- Linear:NR, Edge detection: Not used	Not used	NR
Geroulakos et al. 1994 [70]	UK	EURO	Case control study	122	58	NR	CCA, both sides, far wall.	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear:7.5MHz, Edge detection: Not used	Not used	NR
Ebrahim et al. 1999 [71]	UK	EURO	Cross-sectional study	800	66	N = 425,53.1%	CCA and CB, both sides, far wall.	Mean of Max. CIMT	Reported	DICOM- Not used, Transducer- Linear:7MHz, Edge detection: Used	Used	Age, gender, Alcohol, smoking, BMI, hypertension, FBS and social class
Alejandro et al. 2018 [72]	Argentina	PAHO	Cross-sectional study	1012	42	N = 621, 61.36%	CCA, ICA and ECA, both sides, far wall	Mean CIMT	Reported	DICOM- Not used, Transducer- Linear:4-13MHz, Edge detection: Used	Used	Gender, FBS, SBP, MBP, DBP, and PP
Rosa et al. 2003 [73]	Brazil	PAHO	Case control study	58	50.1	N = 32,55.2%	CCA: both sides, far walls	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear:5MHz, Edge detection: Used	Not used	Alcoholic, Smoking, dyslipidemia
Amer et al. 2016 [74]	Canada	PAHO	Case control study	318	64	N = 128, 40.3%	CCA, CB, ICA, both sides, far and near wall	Mean CIMT	Reported	DICOM- Used, Transducer- Linear:7.5MHz, Edge detection: Used	Used	Age
Catherine et al. 2010 [75]	USA	PAHO	Cross-sectional study	472	52.4	N = 214,45.3%	CCA Both sides, Far wall	Mean CIMT	Reported	DICOM- Not used, Transducer- Linear:NR, Edge detection: Used	Used	Age, gender, FBS, diabetes mellitus, dyslipidemia, and smoking

(*Continued*)

Table 1. (Continued)

Publication	Country	WHO regions	Design	Sample size	Mean age (years)	Male N, %	Carotid segments	IMT definition	Definition of plaque	Ultrasound scan specifications	ECG gating at acquisition	Factors adjusted for
Polak et al. 2011 [76]	USA	PAHO	Case control study	2965	60.1	N = 1336, 45.1%	CCA, both sides, far wall	Mean CIMT	Reported	DICOM- Not used, Transducer- Linear:12MHz, Edge detection: Used	Used	NR
Cao et al. 2007 [77]	USA	PAHO	Cross-sectional study	5020	72.6	N = 2008,40%	CCA and ICA: near and far walls on both sides.	Mean and Maximum CIMT	Reported	DICOM- Not used, Transducer- Linear:7-10MHz, Edge detection: Not used	Not used	Age, gender, CRP levels
Chambless et al. 1997 [78]	USA	PAHO	Case control study	12841	55.3	N = 5552,43.2%	CCA, CB, ICA, both sides, far wall	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear:NR, Edge detection: Not used	Not used	Age, race, gender FBS, diabetes, LDL, HDL, hypertension, smoking status
Hensley et al. 2020 [79]	USA	PAHO	Case control study	58	60	N = 39,67.2%	CCA: both sides, far walls	Mean and Maximum CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5MHz, Edge detection: Used	Not used	NR
Gupta et al. 2003 [80]	India	SEAR	Case control study	241	47.2	N = 205, 85.1%	CCA, CB and ICA, both sides, far wall	Mean and Maximum CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5MHz, Edge detection: Not used	Used	Age and gender
Sudhir et al. 2018 [81]	India	SEAR	Case control study	200	43.1	NR	CCA and ICA, both sides	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear:5-12MHz, Edge detection: Not used	Not used	Age
Agarwal et al. 2008 [82]	India	SEAR	Case control study	111	59.2	N = 66, 59.4%	CCA, both sides, far wall	Mean CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5MHz, Edge detection: Not used	Not used	NR
Kasliwal et al. 2016 [83]	India	SEAR	Cross-sectional study	818	43	N = 438, 53.5%	CCA, both sides, far wall	Mean CIMT	Reported	DICOM- Used, Transducer- Linear:7.5MHz, Edge detection: Used	Used	Age, SBP, FBS, BMI, DBP and serum triglycerides
Paul et al. 2012 [15]	India and Bangladesh	SEAR	Cross-sectional study	96	44.34	N = 53,55.2%	CCA and ICA, both sides, far wall	Mean CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5MHz, Edge detection: Not used	Used	Age and gender
Rinambaan et al. 2016 [84]	Indonesia	SEAR	Cross-sectional study	356	56	N = 236, 66.3%	CCA, both sides, Near and far wall	Mean and Maximum CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5-10MHz, Edge detection: Not used	Not used	Age, triglyceride levels had association. But Weight, BMI, Waist circumference, Glucose, LDL-c, HDL-c.
Barakoti et al. 2016 [85]	Nepal	SEAR	Case control study	104	55.1	N = 59, 56.7%	CCA, both sides, far wall	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear:10MHz, Edge detection: Not used	Not used	NR
Adams et al. 1995 [86]	Australia	WPR	Cross-sectional study	350	60	N = 249,71%	CCA, both sides, far wall.	Mean and Maximum CIMT	Reported	DICOM- Not used, Transducer- Linear:7MHz, Edge detection: Not used	Used	NR
Bin Liu et al. 2017 [87]	China	WPRO	Cross-sectional study	3789	58.8	N = 1560,41.2%	CCA, Both sides, far and near wall.	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear:5-12MHz, Edge detection: Used	Not used	Age, gender, low education level, smoking, hypertension, SBP, FBS and LDL-c

(*Continued*)

Table 1. (Continued)

Publication	Country	WHO regions	Design	Sample size	Mean age (years)	Male N, %	Carotid segments	IMT definition	Definition of plaque	Ultrasound scan specifications	ECG gating at acquisition	Factors adjusted for
Xuefang et al. 2020 [88]	China	WPR	Cross-sectional study	1039	72.3	N = 498,47.9%	CCA, both sides, far and near wall.	Mean CIMT	Reported	DICOM-Used, Transducer- Linear:5-12MHz, Edge detection: Used	Not used	Age, gender and hypertension, FBS
Fujihara et al. 2014 [89]	Japan	WPR	Case control study	116	60.5	N = 78,67.2%	CCA, both sides, far wall.	Mean and Maximum CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5MHz, Edge detection: Used	Not used	NR
Matsushima et al. 2004 [90]	Japan	WPR	Case control study	103	62	N = 71, 68.9%	CCA not mentioned sides and wall	Mean CIMT	Not reported	DICOM- Used, Transducer- Linear:7.5MHz, Edge detection: Used	Not used	Age, BMI, SBP, DBP, HDL-c, LDL-c and HbA1C
Young-Hoon et al. 2014 [91]	Korea	WPR	Cross-sectional study	2595	58.7	N = 713,27.5%	CCA and CB, both sides far wall.	Mean CIMT	Reported	DICOM- Not used, Transducer- Linear:7.5 MHz, Edge detection: Used	Not used	Age, Metabolic syndrome
Young Jin et al. 2011 [92]	Korea	WPR	Cross-sectional study	433	55	N = 107,24.7%	CCA, both sides, far wall	Mean CIMT	Not reported	DICOM- Not used, Transducer- Linear:NR, Edge detection: Not used	Used	Age, gender, BMI, LDL-C level and history of diabetes mellitus.
Chua et al. 2014 [93]	Malaysia	WPR	Cross-sectional study	123	55	N = 74,60.2%	CCA, both sides, far and near wall.	Mean and Maximum CIMT	Not reported	DICOM- Not used, Transducer- Linear:13MHz, Edge detection: Used	Not used	Age, TC and LDL-c
Ta-Chen et al. 2015 [94]	Taiwan	WPR	Cross-sectional study	689	51	N = 497,72.1%	CCA, CB, ICA, both sides, far wall	Mean and Maximum CIMT	Reported	DICOM- Used, Transducer- Linear:3.5-10MHz, Edge detection: Used	Used	Age, gender, diabetes and air pollution

AFR: African Region, EMRO: Eastern Mediterranean Region, EUR: European Region, PAHO: Region of the Americas, SEAR: South-East Asia Region, WPR: Western Pacific Region, CCA: Common carotid artery, CB: Carotid bulb, ICA: internal carotid artery, ECA: External carotid artery, IMT: Intima-media thickness, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PP: Pulse pressure, FBS: Fasting blood sugar, TC: Total cholesterol, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, HbA1C:, CRP: C-reactive protein, GFR: Glomerular filtration rate, TRF: Traditional risk factors, BMI: Body mass index, HIV: human immunodeficiency virus, DICOM: Digital Imaging and Communications in Medicine, NR: Not reported.

https://doi.org/10.1371/journal.pone.0268716.t001

Table 2. The mean CIMT values of different carotid segments by WHO region and CHD group.

Segment	CCA				CB				ICA			
Group	Non-CHD		CHD		Non-CHD		CHD		Non-CHD		CHD	
WHO region	N	Mean±SD (mm)	N	Mean±SD (mm)	N	Mean±SD (mm)	N	Mean±SD (mm)	N	Mean±SD (mm)	N	Mean±SD (mm)
AFR	9244	0.70±0.08[a]	4380	0.92±0.13*	8994	0.75±0.06[a]		NR	8994	0.69±0.06[a]		NR
EMR	870	0.58±0.09[b]	261	0.86±0.26**	500	0.71±0.12[b]		NR		NR		NR
EUR	4668	0.74±0.11[c]	698	0.92±0.20*	877	0.77±0.11[c]	145	0.93±0.19*	464	0.66±0.11[b]	255	0.86±0.16
PAHO	22628	0.71±0.07[d]	839	0.89±0.15***	8457	0.81±0.09[d]	1798	0.93±0.16*	1802	0.65±0.10[b]	720	0.87±0.17
SEAR	1004	0.62±0.10[e]	251	0.87±0.21**		NR		NR		NR		NR
WPR	8215	0.61±0.06[e]	1391	0.87±0.16**	239	0.65±0.08[e]	239	0.89±0.19**		NR		NR

AFR: African Region, EMR: Eastern Mediterranean Region, EUR: European Region, PAHO: Region of the Americas, SEAR: South-East Asia Region, WPR: Western Pacific Region, CCA: Common carotid artery, CB: Carotid bulb, ICA: internal carotid artery, NR: Not reported. N: Number of participants.

Note: The pooled mean was calculated weighting the studies on sample size.

[a,b,c,d,e]Means having a superscript with the same letter are similar (Non-CHD group).

*, **, *** Means having a superscript with the same letter are similar (CHD group).

https://doi.org/10.1371/journal.pone.0268716.t002

WPR countries were significantly different from those of countries from AFR, EMR, EUR and PAHO regions (P<0.01). There were significant differences in the mean CIMT values of CB between the regions (P<0.01). The mean CIMT value of ICA was significantly higher in countries in AFR in comparison to countries EUR and PAHO (P<0.01).

The mean CIMT values of CCA vary from 0.86±0.26mm to 0.92±0.20mm. The mean CIMT of CB ranges from 0.89±0.19mm to 0.93±0.19mm. The range for the mean CIMT of ICA was 0.86±0.16mm to 0.87±0.17. In each region, the highest mean CIMT value was in the CB. The highest CIMT values of CCA were reported in AFR and EUR countries. The mean CIMT values of CCA in EMR, SEAR and WPR countries were significantly different from those of countries from AFR, EUR and PAHO regions (P<0.01). There were significant differences in the mean CIMT values of CB in WPR countries in comparison to EUR and PAHO countries (P<0.01). The mean CIMT value of ICA was not significantly different in EUR and PAHO (t-test: 0.819; df: 973; p = 0.793) (Table 2).

Meta-analysis

The pooled mean CIMT value for healthy persons in all regions was 0.65mm (95%CI–0.62–0.69; I^2 = 13.79%) (Fig 3). There was a significant difference in the mean CIMT values between the regions (Test of group difference, $Q_{(40)}$ = 11.51, P = 0.04). Subgroup analyses show no significant difference of mean CIMT values within the regions. Countries in AFR, (0.72mm), PAHO (0.71mm) and EUR (0.71mm) had a higher pooled mean CIMT compared to countries in SEAR (0.62mm), WPR (0.60mm) and EMR (0.60mm) (Fig 4). The pooled mean CIMT values were significantly different between different age groups ($Q_{(3)}$ = 19.32, P<0.001) (Fig 4).

The pooled mean CIMT difference between healthy males and females was 0.06mm (95% CI: 0.04–0.07). There were differences in the mean CIMT between males and females within regions (AFR: 0.04mm, p = 0.04; PAHO: 0.05mm, p<0.001: and WPR: 0.04mmp<0.001) (Fig 5).

There was a significant mean difference of the pooled CIMT values between CHD and non-CHD groups (0.23mm, p = 0.001) (Fig 6). PAHO (I^2 = 97.18%, $Q_{(3)}$ = 56.63, p<0.001), SEAR (I^2 = 99.22%, $Q_{(3)}$ = 376.54, p<0.001) and EUR (I^2 = 78.98%%, $Q_{(4)}$ = 18.13, p<0.001)

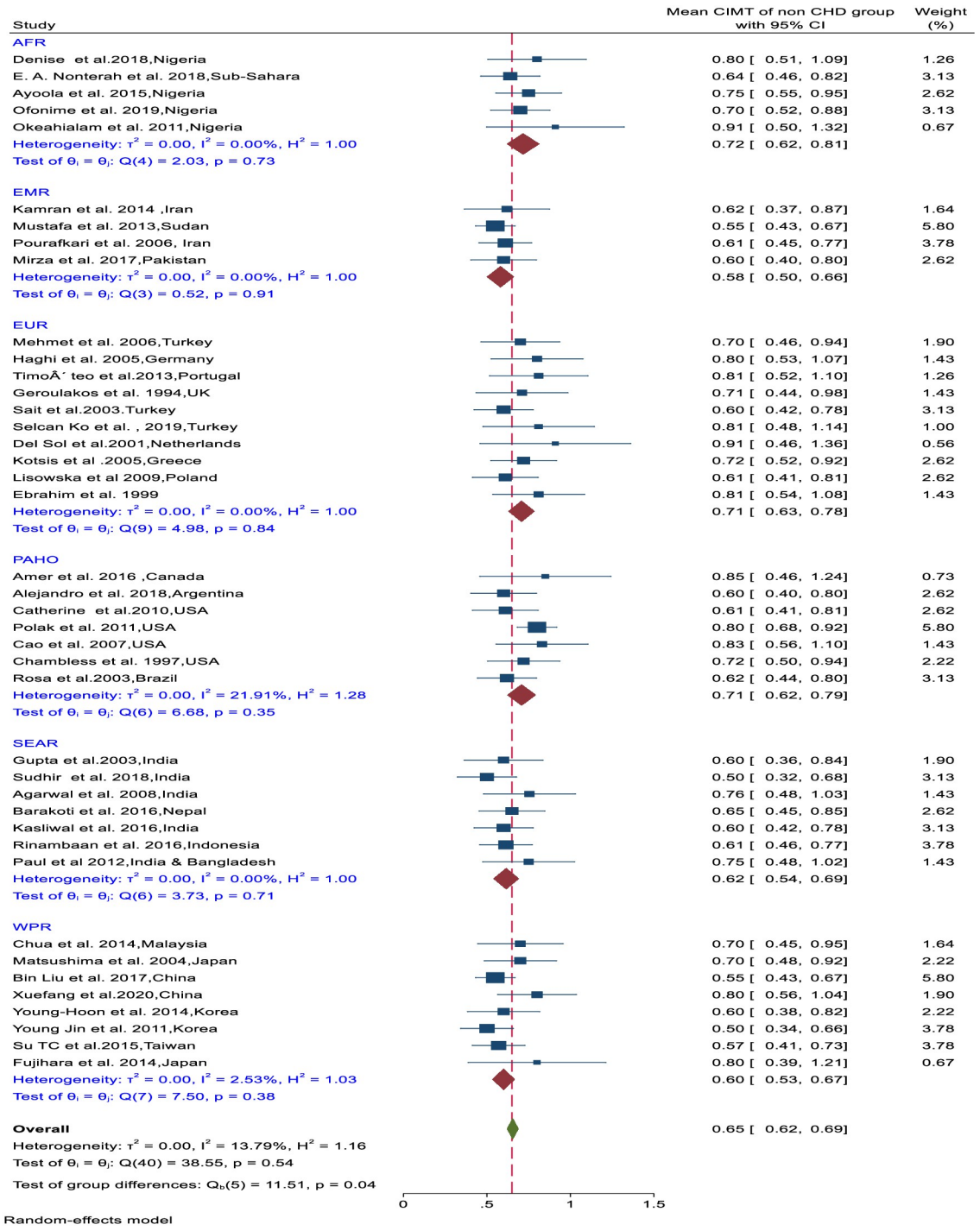

Fig 3. Forest plot of the mean CIMT for healthy persons by WHO regions.

https://doi.org/10.1371/journal.pone.0268716.g003

countries had significant differences in the mean CIMT difference between the CHD and non-CHD groups within the respective region (Fig 6).

Table 3 shows the summary of the Meta regression analysis of CIMT values. In the adjusted model, CHD group, WHO region and age were significantly associated with CIMT. The mean

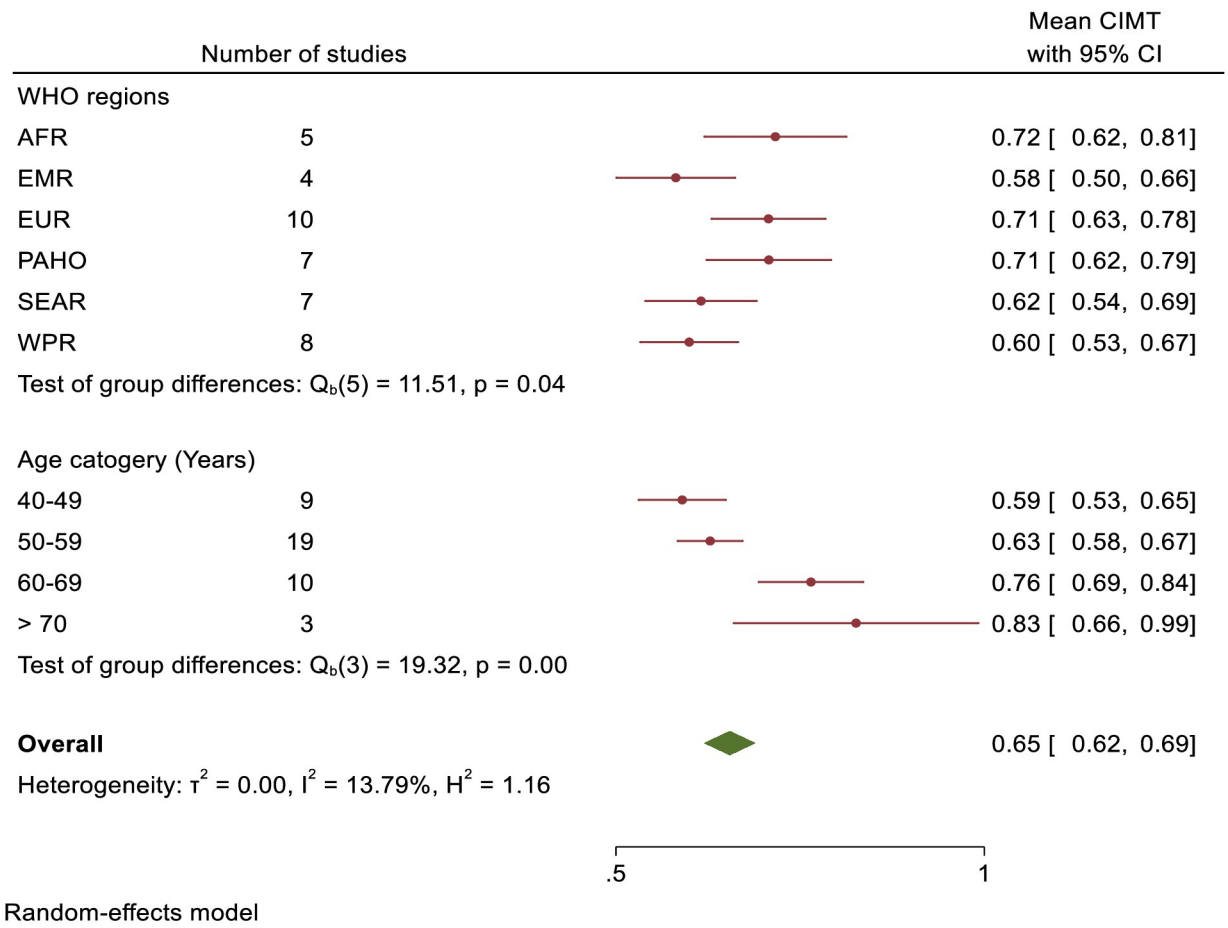

Fig 4. Summary of mean CIMT values by age and WHO region in healthy persons.

https://doi.org/10.1371/journal.pone.0268716.g004

CIMT value in the CHD group was 0.214 mm greater than that of the non-CHD group after adjusting for the other variables. The mean CIMT was significantly less among populations in SEAR and WPR as compared to populations from PAHO after adjustment. With age there was a significant increase in the mean CIMT values.

Discussion

Coronary heart disease (CHD) is the most important cause of morbidity, mortality and premature deaths of NCDs. We included 46 eligible articles comprising data of 49 381 individuals. The highest number of studies was from the European region while the lowest was from the Eastern Mediterranean region.

Modifiable risk factors

45.6% of the studies reviewed showed that modifiable risk factors were predictors of CIMT. There was a significant difference in CIMT values among the non-CHD group between regions. Higher CIMT values were observed in countries in the African, American and European regions. The mean difference in CIMT values between CHD and non-CHD groups were significantly different between and within regions. Differences in the CIMT values between regions may be due to socio-economic status [95, 96], environmental conditions, smoking

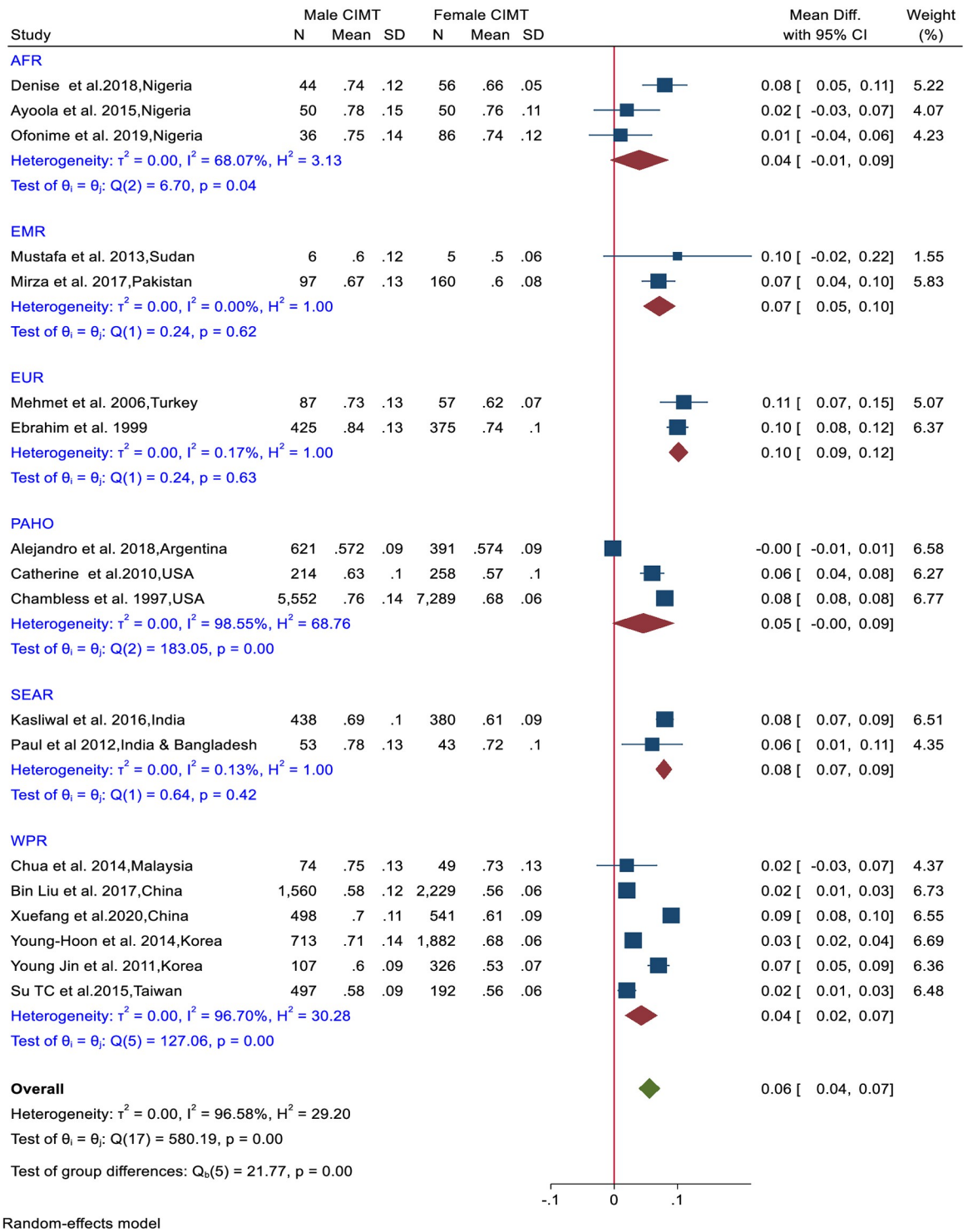

Fig 5. Forest plot of mean difference of CIMT between healthy males and females.

https://doi.org/10.1371/journal.pone.0268716.g005

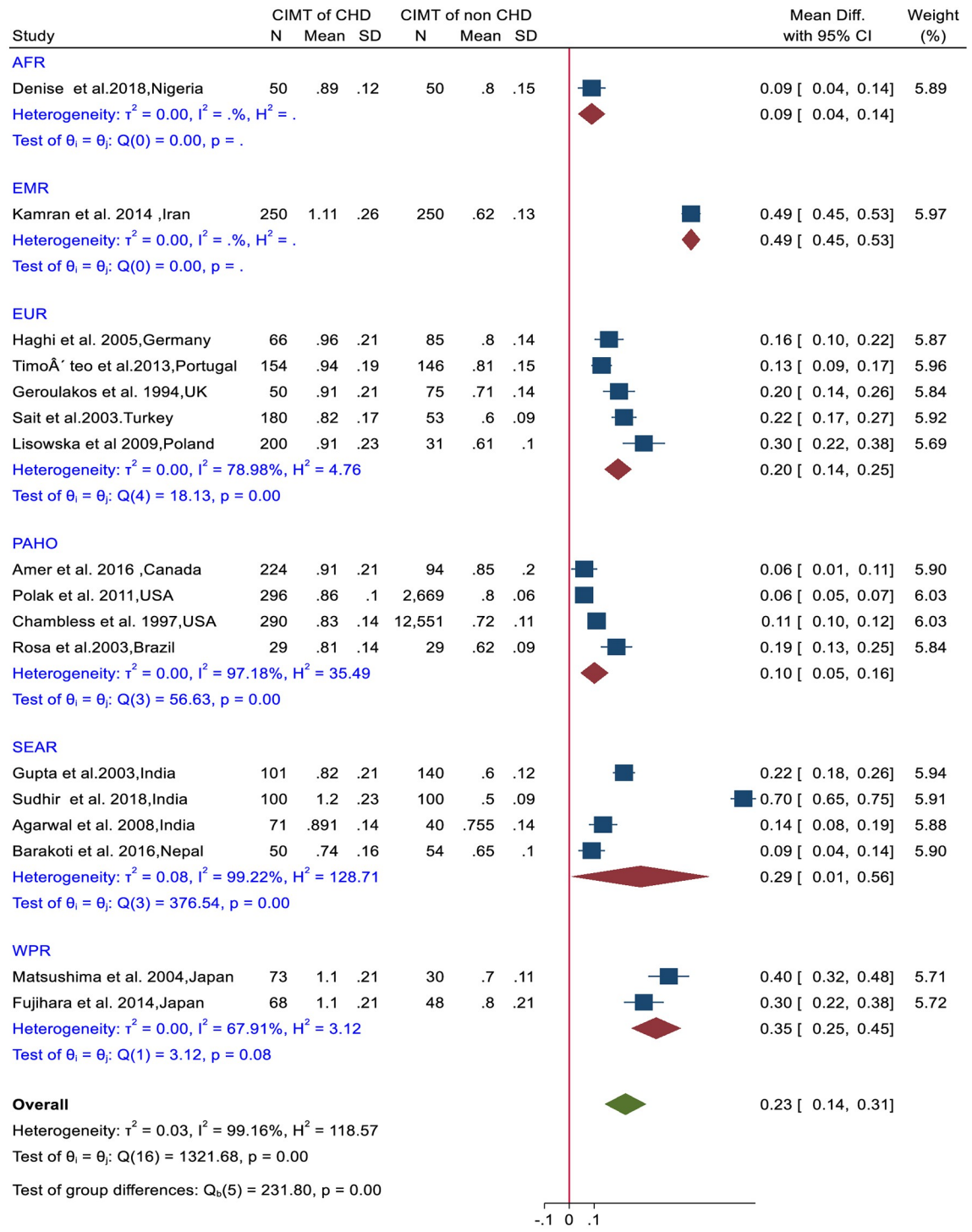

Fig 6. Forest plot of mean difference of CIMT between CHD and non-CHD groups.

https://doi.org/10.1371/journal.pone.0268716.g006

Table 3. Summary of meta regression analysis of CIMT values.

Variable	Unadjusted Regression coefficient	95%CI	Adjusted regression coefficient	95%CI
Age (years)	**0.008***	**0.004 to 0.013**	**0.006***	**0.001 to 0.011**
AFR	0.001	-0.121 to 0.122	0.026	-0.112 to 0.175
EMR	**-0.141***	**-0.256 to -0.027**	-0.064	-0.217 to 0.087
EUR	0.006	-0.096 to 0.109	-0.013	-0.141 to 0.112
SEAR	**-0.173***	**-0.279 to -0.067**	**-0.149***	**-0.287 to -0.012**
WPR	**-0.107***	**-0.207 to -0.006**	**-0.117***	**-0.217 to -0.165**
Region of the Americas	Reference category			
Automatically	-0.050	-0.144 to 0.044	0.016	-0.067 to 0.099
Automatically with ECG gating	-0.023	-0.142 to 0.094	0.018	-0.097 to 0.133
Manual ultrasound technique	Reference category			
CHD group	**0.228***	**0.153 to 0.304**	**0.214***	**0.139 to 0.289**
Non CHD group	Reference category			
Constant			**0.578**	

AFR: African Region, EMR: Eastern Mediterranean Region, EUR: European Region, PAHO: Region of the Americas, SEAR: South-East Asia Region, WPR: Western Pacific Region.

*significant variables.

https://doi.org/10.1371/journal.pone.0268716.t003

habits, harmful consumption of alcohol, physical activity, dietary patterns, sedentary behaviors and body mass indices [23, 24, 97–100], and prevalence of co-morbidities such as diabetes, hypertension, dyslipidemia, cancer and chronic kidney disease [101, 102].

Age-adjusted cardiovascular death rates have declined in several developed countries in the past decades. In contrast, the death rates of cardiovascular disease have risen greatly in lower middle income countries [103–105]. Several publications underscore the high burden of disease associated with non-communicable diseases and its economic impact on lower middle income countries [4, 104, 106]. Due to this reason, non-communicable diseases in lower middle income countries have received increasingly more global attention by scientists, public health advocates and policy makers. A recent study has identified that NCDs and CHD risk factors such as demographic transition, environmental pollution, metabolic risk factors, lack of education, unhealthy food habits and unhealthy lifestyles have similar effects in both developed and developing countries [109].

Some studies reported that non-traditional risk factors such as HIV infection, metabolic syndrome, infections and inflammation as predictors of CIMT. Some studies have highlighted that during chronic infections and inflammation, elevated levels of the pro-inflammatory cytokines interleukin (IL)-6 and C-reactive protein (CRP) are associated with subclinical atherosclerosis [107, 108]. Intima-medial thickening is a complex process. Modifiable risk factors contribute in different stages in different proportions. Factors that vary stress and blood pressure, which may cause a local delay in lumen transportation, may lead to the accumulation of potentially atherogenic particles in the arterial wall and stimulate CIM thickening and plaque formation [109]. Risk factors which cause endothelial destruction and functional abnormalities are associated with higher carotid IMT and were associated with a higher risk of atherosclerotic disease [110].

Non- modifiable risk factors

28.5% of the studies we reviewed reported that non-modifiable risk factors such as age and gender are associated with CIMT. The CIMT values of males are significantly higher than that

of females (pooled difference of 0.06 mm) across regions. In our meta-analysis there was a significant difference in the pooled mean CIMT values between the age groups with older age groups having higher CIMT values.

Heredity and certain genotypes [27, 28], immunological diseases [111, 112], inflammatory cytokines, hematological parameters [30,112–114] and vitamin D [115] have been reported to be potential risk factors for increased CIMTs. In our review, we did not find these to be risk factors probably due to the specific study designs, study populations and outcomes considered by us.

The Meta regression analysis demonstrated that CIMT values were influenced by WHO region, age and CHD group. Even though there is a clear association between CIMT and CHD its usability as a risk predictor for CHD needs to be further investigated. Approaches to prevention as well as screening of at-risk populations for CHD may need to consider regional variations of CIMT.

Most studies included in this review had not documented the ethnic composition of their samples. Therefore, we were unable to evaluate CIMT variations among different ethnicities. It is reported that healthy UK black African-Caribbean children have higher CIMT levels, not explained by conventional cardiovascular risk markers, as compared to other ethnicities [116]. Ethnicity significantly modifies the associations between risk factors, CIMT values and cardiovascular events [122]; the association between CIMT and age, HDL cholesterol, total cholesterol and smoking was weaker among Blacks and Hispanics [117]. Systolic blood pressure was associated more strongly with CIMT in Asians [117]. These differences could be due to varying interactions between different risk factors and ethnicities. These differences provide insight into the etiology of cardiovascular disease among ethnic groups and aid the ethnic-specific implementation of primary prevention.

Segmental variation of CIMT

We have summarized variations in the mean CIMT values of CCA, CB and ICA within and between regions. These differences may be due to different influences of risk factors on the different segments. A Korean study reported associations between cardiovascular risk factors and different segments of the carotid artery: in men, alcohol use (CIMT at the bifurcation); physical activity (CIMT at the common and internal carotid segments); BMI (CIMT of all segments); diabetes (CIMT at the bifurcation and internal carotid segment); hypertension (CIMT at the internal carotid segment); and HDL-cholesterol (CIMT at the bifurcation and the common carotid segment): in women, smoking (CIMT at the bifurcation), hypertension (CIMT at the common carotid segment), total and LDL cholesterol (CIMT at the bifurcation and internal carotid segment), and hs-CRP (CIMT at the common and internal carotid segments) [118]. Furthermore, the Malmö Diet and Cancer Study (MDCS) reported that HDL was associated with IMT progression in the CCA but not at the bifurcation. The same showed that diabetes was associated with IMT progression at the bifurcation, but not in the CCA [119, 120].

This study summarized that CIMT values of non-CHD population vary among regions. Age and gender have a significant effect on CIMT differences. Furthermore, there were marked differences of mean CIMT values between non-CHD and CHD groups. It was different from region to region as well as within regions.

Ultrasound protocol for CIMT measurement

There were variations in the ultrasound assessment of CIMT. The transducer frequency ranged from 3MHz to 15MHz; five studies used DICOM software. Variations in the ultrasonography protocol are likely to affect CIMT values. There are different arguments with regard to various ultrasound protocols during CIMT measurement [44]. Mannheim Carotid Intima-

Media Thickness consensus (2004–2006) is a useful guideline to achieve homogeneity of CIMT measurement among studies [121]. A common protocol will ensure reproducibility and comparison of findings of different studies.

There was no uniformity in the selection of the site for measurement or the reporting of the CIMT measurement. The far wall of CCA (both sides) was the commonest site (41%) selected. The mean CIMT value was reported in 65% of studies. Plaque formation was reported in 59% of studies. It has been reported that this is unlikely to alter the results by much in populations with a low prevalence of plaque [44]. Some studies imaged only one side of the neck, whereas others imaged both sides [122]. Some included imaging of a single segment while multiple segments were imaged in others [77, 123, 124]. Some studies imaged the far wall of multiple segments, whereas others imaged both the near and far walls [125, 126]. Studies also differed in the type of IMT measurements made and the use of different arbitrary cut-off points of CIMT to predict risk. Our review also shows that ECG gating at acquisition was reported only by 28% of studies. The phase of the cardiac cycle (end-systole vs. end-diastole) when CIMT is measured also differs among studies. Because of systolic lumen diameter expansion that leads to thinning of CIMT during systole, CIMT values obtained from end-systole are lower than those obtained in end-diastole [16]. In our meta-analysis we categorized ultrasound technique of measuring CIMT into three categories; manually, automatically and automatically with ECG gating. Literature shows that CIMT measured by General Electric (GE) semi-automated edge-detection software and Artery Measurement semi-automated software (AMS) have significant differences when measuring mean CIMT [127]. Hence, results obtained from different CIMT software systems should be compared with caution. CIMT variations using similar software may be explained by the position/angle of ultrasound transducer, and the specific combinations of segments and walls examined [128]. These factors are associated with differences in reproducibility, magnitude, and precision of progression of CIMT over time. To avoid these discrepancies, it is recommended to measure CIMT in multiple segments with different angles [128]. In our review, we found that most of the studies have obtained an average CIMT value by multiple measurements. This may be a reason that significant differences were not found when multiple segments were examined.

Conclusion

CIMT among the non-CHD group varies between and within regions, and by age and sex. The mean CIMT values between non-CHD and CHD groups were significantly different within and between WHO regions possibly due to varying influences of modifiable and non-modifiable risk factors. CHD group had a significantly thicker mean CIMT after adjusting for age, WHO region and ultrasound machine used. Segment specific CIMT variations exist among regions.

Limitation of study

Our review consisted of few studies with small sample sizes. But Egger's test showed no significant small study effect in our review. Some studies had large sample sizes which contributed most to our analyses. We were unable to capture some new risk factors such as genetic composition, immune disorders and cytokine's effect on CIMT due to the selection criteria we used. However, these studies had small sample sizes which may not have been generalizable. It is unlikely that exclusion of these risk factors would have influenced our findings.

The way we grouped countries by WHO regions may not be the most appropriate grouping to consider as WHO regions have been established taking into consideration political considerations as well. For example, the Republic of Korea (South Korea) is in the WPR whereas the Democratic People's Republic of Korea (North Korea) is in the SEAR. Similarly, Pakistan and

Afghanistan, both South Asian countries, are in the EMR, though all other South Asian countries (Bangladesh, Bhutan, India, Maldives, Nepal and Sri Lanka) are in the SEAR together with Myanmar, Thailand, Indonesia and Timor Leste. Therefore, there is a likelihood of ethnic and cultural diversity influencing CIMT values among countries within regions.

Studies included in our review had not specified the ethnic composition of the study samples. Consequently, we were unable to examine CIMT variations by ethnicity. Further studies to explore this variability in future are warranted.

Supporting information

S1 File. Search strategy for PubMed.
(DOCX)

S1 Table. Summary of STROBE statement.
(XLSX)

S2 Table. Newcastle–Ottawa Scale for cross sectional study.
(XLSX)

S3 Table. Newcastle–Ottawa Scale for case—Control study.
(XLSX)

S4 Table. Newcastle–Ottawa Scale for Cohort studies.
(XLSX)

S1 Checklist. PRISMA checklist.
(DOCX)

Acknowledgments

The authors thank Department of Public Health, Faculty of Medicine, University of Kelaniya for providing support and resources.

Author Contributions

Conceptualization: V. Abeysuriya, B. P. R. Perera, A. R. Wickremasinghe.

Data curation: V. Abeysuriya.

Formal analysis: V. Abeysuriya, B. P. R. Perera, A. R. Wickremasinghe.

Funding acquisition: V. Abeysuriya.

Investigation: V. Abeysuriya.

Methodology: V. Abeysuriya, B. P. R. Perera, A. R. Wickremasinghe.

Project administration: V. Abeysuriya, A. R. Wickremasinghe.

Resources: V. Abeysuriya, B. P. R. Perera.

Software: V. Abeysuriya.

Supervision: A. R. Wickremasinghe.

Validation: V. Abeysuriya, B. P. R. Perera.

Writing – original draft: V. Abeysuriya, A. R. Wickremasinghe.

Writing – review & editing: V. Abeysuriya, B. P. R. Perera, A. R. Wickremasinghe.

References

1. Wang Y, Wang J. Modelling and prediction of global non-communicable diseases. BMC Public Health. 2020; 20: 822. https://doi.org/10.1186/s12889-020-08890-4 PMID: 32487173
2. World Health Organization. Global status report on noncommunicable diseases—2014. Geneva: WHO; 2014. http://www.who.int/nmh/publications/ncd-status-report-2014/en/
3. World Health Organization. Global health observatory—2011. Geneva: WHO; 2012. https://www.who.int/gho/publications/world_health_statistics/2011/en/.
4. Abegunde DO, Mathers CD, Adam T, Ortegon M, Strong K. The burden and costs of chronic diseases in low-income and middle-income countries. Lancet. Elsevier; 2007. pp. 1929–1938. https://doi.org/10.1016/S0140-6736(07)61696-1 PMID: 18063029
5. Habib SH, Saha S. Burden of non-communicable disease: Global overview. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. Elsevier Ltd; 2010. pp. 41–47. https://doi.org/10.1016/j.dsx.2008.04.005
6. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases: 2013–2020. Geneva: WHO; 2013. https://www.who.int/nmh/events/ncd_action_plan/en/
7. Zeba AN, Delisle HF, Renier G. Dietary patterns and physical inactivity, two contributing factors to the double burden of malnutrition among adults in Burkina Faso, West Africa. Journal of Nutritional Science. 2014; 3: e50. https://doi.org/10.1017/jns.2014.11 PMID: 26101618
8. Al Ali R, Rastam S, Fouad FM, Mzayek F, Maziak W. Modifiable cardiovascular risk factors among adults in Aleppo, Syria. International Journal of Public Health. 2011; 56: 653–662. https://doi.org/10.1007/s00038-011-0278-0 PMID: 21814848
9. Menon J, Vijayakumar N, Joseph JK, David PC, Menon MN, Mukundan S, et al. Below the poverty line and non-communicable diseases in Kerala: The Epidemiology of Non-communicable Diseases in Rural Areas (ENDIRA) study. International Journal of Cardiology. 2015; 187: 519–524. https://doi.org/10.1016/j.ijcard.2015.04.009 PMID: 25846664
10. WHO. Noncommunicable diseases. 2018 [cited 17 Jan 2021]. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases
11. Frieden TR, Cobb LK, Leidig RC, Mehta S, Kass D. Reducing Premature Mortality from Cardiovascular and Other Non-Communicable Diseases by One Third: Achieving Sustainable Development Goal Indicator 3.4.1. Global Heart. Ubiquity Press; 2020. p. 50. https://doi.org/10.5334/gh.531 PMID: 32923344
12. The Lancet Global Health. Getting to the heart of non-communicable diseases. The Lancet Global Health. 2018; 6: e933. https://doi.org/10.1016/S2214-109X(18)30362-0 PMID: 30103982
13. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: Executive summary: A report of the American College of cardiology foundation/American Heart association task force on practice guidelines. Circulation. 2010; 122: 2748–2764. https://doi.org/10.1161/CIR.0b013e3182051bab PMID: 21098427
14. Darabian S, Hormuz M, Latif MA, Pahlevan S, Budoff MJ. The role of carotid intimal thickness testing and risk prediction in the development of coronary atherosclerosis. Current Atherosclerosis Reports. 2013; 15: 306. https://doi.org/10.1007/s11883-012-0306-4 PMID: 23328906
15. Paul J, Shaw K, Dasgupta S, Ghosh MK. Measurement of intima media thickness of carotid artery by B-mode ultrasound in healthy people of India and Bangladesh, and relation of age and sex with carotid artery intima media thickness: An observational study. Journal of Cardiovascular Disease Research. Medknow Publications; 2012. pp. 128–131. https://doi.org/10.4103/0975-3583.95367 PMID: 22629031
16. Den Ruijter HM, Peters SAE, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. Common carotid intima-media thickness measurements incardiovascular risk prediction: A meta-analysis. JAMA—Journal of the American Medical Association. 2012; 308: 796–803. https://doi.org/10.1001/jama.2012.9630 PMID: 22910757
17. de Groot E, van Leuven SI, Duivenvoorden R, Meuwese MC, Akdim F, Bots ML, et al. Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. Nature Clinical Practice Cardiovascular Medicine. Nature Publishing Group; 2008. pp. 280–288. https://doi.org/10.1038/ncpcardio1163 PMID: 18332891
18. Kume T, Akasaka T, Kawamoto T, Watanabe N, Toyota E, Neishi Y, et al. Assessment of Coronary Intima—Media Thickness by Optical Coherence Tomography. Circulation Journal. 2005; 69: 903–907. https://doi.org/10.1253/circj.69.903 PMID: 16041157
19. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease

incidence: The Multi-Ethnic Study of Atherosclerosis (MESA). Archives of Internal Medicine. 2008; 168: 1333–1339. https://doi.org/10.1001/archinte.168.12.1333 PMID: 18574091

20. van den Munckhof ICL, Jones H, Hopman MTE, de Graaf J, Nyakayiru J, van Dijk B, et al. Relation between age and carotid artery intima-medial thickness: a systematic review. Clinical Cardiology. John Wiley and Sons Inc.; 2018. pp. 698–704. https://doi.org/10.1002/clc.22934 PMID: 29752816

21. Juonala M, Kähönen M, Laitinen T, Hutri-Kähönen N, Jokinen E, Taittonen L, et al. Effect of age and sex on carotid intima-media thickness, elasticity and brachial endothelial function in healthy adults: The Cardiovascular Risk in Young Finns Study. European Heart Journal. 2008; 29: 1198–1206. https://doi.org/10.1093/eurheartj/ehm556 PMID: 18079136

22. Gooty VD, Sinaiko AR, Ryder JR, Dengel DR, Jacobs DR, Steinberger J. Association between Carotid Intima Media Thickness, Age, and Cardiovascular Risk Factors in Children and Adolescents. Metabolic Syndrome and Related Disorders. 2018; 16: 122–126. https://doi.org/10.1089/met.2017.0149 PMID: 29412763

23. Burns DM. Epidemiology of smoking-induced cardiovascular disease. Progress in Cardiovascular Diseases. 2003; 46: 11–29. https://doi.org/10.1016/s0033-0620(03)00079-3 PMID: 12920698

24. Kiriyama H, Kaneko H, Itoh H, Yoshida Y, Nakanishi K, Mizuno Y, et al. Effect of cigarette smoking on carotid artery atherosclerosis: a community-based cohort study. Heart and Vessels. 2020; 35: 22–29. https://doi.org/10.1007/s00380-019-01455-5 PMID: 31222551

25. Britton AR, Grobbee DE, den Ruijter HM, Anderson TJ, Desvarieux M, Engström G, et al. Alcohol consumption and common carotid intima-media thickness: The USE-IMT study. Alcohol and Alcoholism. 2017; 52: 483–486. https://doi.org/10.1093/alcalc/agx028 PMID: 28525540

26. Santos IS, Alencar AP, Rundek T, Goulart AC, Barreto SM, Pereira AC, et al. Low impact of traditional risk factors on carotid intima-media thickness: The ELSA-brasil cohort. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015; 35: 2054–2059. https://doi.org/10.1161/ATVBAHA.115.305765 PMID: 26183615

27. Strawbridge RJ, Ward J, Bailey MES, Cullen B, Ferguson A, Graham N, et al. Carotid Intima-Media Thickness. Arteriosclerosis, Thrombosis, and Vascular Biology. 2020; 40: 446–461. https://doi.org/10.1161/ATVBAHA.119.313226 PMID: 31801372

28. Arya R, Escalante A, Farook VS, Restrepo JF, Battafarano DF, Almeida M, et al. A genetic association study of carotid intima-media thickness (CIMT) and plaque in Mexican Americans and European Americans with rheumatoid arthritis. Atherosclerosis. 2018; 271: 92–101. https://doi.org/10.1016/j.atherosclerosis.2017.11.024 PMID: 29482039

29. Evelein AMV, Visseren FLJ, Van Der Ent CK, Grobbee DE, Uiterwaal CSPM. Allergies are associated with arterial changes in young children. European Journal of Preventive Cardiology. 2015; 22: 1480–1487. https://doi.org/10.1177/2047487314554863 PMID: 25301873

30. Klop B, van de Geijn G-JMJM, Bovenberg SA, van der Meulen N, Elte JWF, Birnie E, et al. Erythrocyte-Bound Apolipoprotein B in Relation to Atherosclerosis, Serum Lipids and ABO Blood Group. Eller P, editor. PLoS ONE. 2013; 8: e75573. https://doi.org/10.1371/journal.pone.0075573 PMID: 24069429

31. Zaid M, Fujiyoshi A, Kadota A, Abbott RD, Miura K. Coronary Artery Calcium and Carotid Artery Intima Media Thickness and Plaque: Clinical Use in Need of Clarification. Journal of Atherosclerosis and Thrombosis. 2017; 24: 227–239. https://doi.org/10.5551/jat.RV16005 PMID: 27904029

32. Liao X, Norata GD, Polak JF, Stehouwer CDA, Catapano A, Rundek T, et al. Normative values for carotid intima media thickness and its progression: Are they transferrable outside of their cohort of origin? European Journal of Preventive Cardiology. 2016; 23: 1165–1173. https://doi.org/10.1177/2047487315625543 PMID: 26746227

33. Ravani A, Werba J, Frigerio B, Sansaro D, Amato M, Tremoli E, et al. Assessment and Relevance of Carotid Intima-Media Thickness (C-IMT) in Primary and Secondary Cardiovascular Prevention. Current Pharmaceutical Design. 2015; 21: 1164–1171. https://doi.org/10.2174/1381612820666141013121545 PMID: 25312737

34. Akazawa S, Tojikubo M, Nakano Y, Nakamura S, Tamai H, Yonemoto K, et al. Usefulness of carotid plaque (sum and maximum of plaque thickness) in combination with intima-media thickness for the detection of coronary artery disease in asymptomatic patients with diabetes. Journal of Diabetes Investigation. 2016; 7: 396–403. https://doi.org/10.1111/jdi.12403 PMID: 27330727

35. Nambi V, Chambless L, He M, Folsom AR, Mosley T, Boerwinkle E, et al. Common carotid artery intimamedia thickness is as good as carotid intimamedia thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. European Heart Journal. 2012; 33: 183–190. https://doi.org/10.1093/eurheartj/ehr192 PMID: 21666250

36. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clinical research ed). 2009; 339. https://doi.org/10.1136/bmj.b2700 PMID: 19622552

37. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Journal of the American Medical Association. 2000; 283: 2008–2012. https://doi.org/10.1001/jama.283.15.2008 PMID: 10789670

38. Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. 2011. www.handbook-5-1.cochrane.org.

39. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. Quadas-2: A revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine. American College of Physicians; 2011. pp. 529–536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009 PMID: 22007046

40. Maier W, Philipp M, Buller R, Schiegel S. Reliability and validity of the Newcastle Scales in relation to ICD-9-classification. Acta Psychiatrica Scandinavica. 1987; 76: 619–627. https://doi.org/10.1111/j.1600-0447.1987.tb02932.x PMID: 3442254

41. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Disease Risk: A Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force Endorsed by the Society for Vascular. Journal of the American Society of Echocardiography. 2008; 21: 93–111. https://doi.org/10.1016/j.echo.2007.11.011 PMID: 18261694

42. van den Oord SCH, Sijbrands EJG, ten Kate GL, van Klaveren D, van Domburg RT, van der Steen AFW, et al. Carotid intima-media thickness for cardiovascular risk assessment: Systematic review and meta-analysis. Atherosclerosis. 2013; 228: 1–11. https://doi.org/10.1016/j.atherosclerosis.2013.01.025 PMID: 23395523

43. Bauer M, Caviezel S, Teynor A, Erbel R, Mahabadi A, Schmidt-Trucksäss A. Carotid intima-media thickness as a biomarker of subclinical atherosclerosis. Swiss Medical Weekly. 2012. https://doi.org/10.4414/smw.2012.13705 PMID: 23135891

44. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. Circulation. 2007; 115: 459–467. https://doi.org/10.1161/CIRCULATIONAHA.106.628875 PMID: 17242284

45. Liu D, Du C, Shao W, Ma G. Diagnostic role of carotid intima-media thickness for coronary artery disease: A meta-analysis. BioMed Research International. Hindawi Limited; 2020. https://doi.org/10.1155/2020/9879463 PMID: 32185231

46. Ramke J, Palagyi A, Jordan V, Petkovic J, Gilbert CE. Using the STROBE statement to assess reporting in blindness prevalence surveys in low and middle income countries. 2017. https://doi.org/10.1371/journal.pone.0176178 PMID: 28481888

47. Bastuji-Garin S, Sbidian E, Gaudy-Marqueste C, Ferrat E, Roujeau JC, Richard MA, et al. Impact of STROBE Statement Publication on Quality of Observational Study Reporting: Interrupted Time Series versus Before-After Analysis. PLoS ONE. 2013; 8. https://doi.org/10.1371/journal.pone.0064733 PMID: 23990867

48. Lo CKL, Mertz D, Loeb M. Newcastle-Ottawa Scale: Comparing reviewers' to authors' assessments. BMC Medical Research Methodology. 2014; 14: 45. https://doi.org/10.1186/1471-2288-14-45 PMID: 24690082

49. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality if Nonrandomized Studies in Meta-Analyses—ScienceOpen. [cited 24 Feb 2022]. https://www.scienceopen.com/document?vid=54b48470-4655-4081-b5d4-e8ebe8d1792e

50. Ogholoh Oghenetejiri Denise IBO-E and AA. Comparative Ultrasonographic Evaluation of the Carotid Intima-media Thickness in Hypertensives with Computed Tomographic Features of Stroke and Normotensives in Benin. Annals of Medical and Health Sciences Resear. 2018; 8: 24–28.

51. Ayoola O, Onuwaje M, Akintomide A. Sonographic assessment of the carotid intima-media thickness on B-mode ultrasonography in a Nigerian population. Nigerian Medical Journal. 2015; 56: 357. https://doi.org/10.4103/0300-1652.170384 PMID: 26778889

52. Ukweh ON, Ekpo EU. Carotid Intima-Media Thickness and Carotid Plaque: A Pilot Study of Risk Factors in an Indigenous Nigerian Population. Journal of Stroke and Cerebrovascular Diseases. 2019; 28: 1346–1352. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.01.035 PMID: 30777620

53. Okeahialam BN, Alonge BA, Pam SD, Puepet FH. Carotid intima media thickness as a measure of cardiovascular disease Burden in Nigerian Africans with hypertension and diabetes mellitus. International Journal of Vascular Medicine. 2011; 2011. https://doi.org/10.1155/2011/327171 PMID: 21748020

54. Holland Z, Ntyintyane LM, Gill G V, Raal FJ. Carotid intima-media thickness is a predictor of coronary artery disease in South African black patients. Cardiovascular Journal of Africa. 2009; 20: 237–239. PMID: 19701535

55. Nonterah EA, Klipstein-Grobusch K, Boua R, Oduro AR, Grobbee D, Ramsay M, et al. MS06.4 Subclinical Atherosclerosis In Sub-Saharan African Countries Is Driven By Prevailing Socio-Economic Conditions, HIV and Classical Cardiovascular Risk Factors: Findings From the Africa-Wits-INDEPTH Partnership For Genomic Studies. Global Heart. 2018; 13: 380. https://doi.org/10.1016/j.gheart.2018.09.024

56. Azarkhish Kamran, Mahmoudi Khalil M M, Ghajarzadeh M. Mean Right and Left Carotid Intima-Media Thickness Measures in Cases with/without Coronary Artery Disease. Acta Medica Iranica. 2014; 52: 884–888. PMID: 25530049

57. P M., TB E., J A.H., MAJID S. Ultrasonic Measurement of Carotid Intima-Media Thickness in a Group of Iranian with No Cardiovascular Risk Factors. IRANIAN JOURNAL OF RADIOLOGY; 2006 Jan.

58. Mirza W, Arain M, Ali A, Bari V, Ali M, Fatima K. Carotid Intima Media Thickness Percentiles for Pakistani Population. Journal of the College of Physicians and Surgeons Pakistan. 2017; 27. https://doi.org/2708 PMID: 29017680

59. Mahmoud MZ. Sonography of common carotid arteries' intima: Media thickness in the normal adult population in Sudan. North American Journal of Medical Sciences. 2013; 5: 88–94. https://doi.org/10.4103/1947-2714.107523 PMID: 23641368

60. Haghi D, Papavassiliu T, Hach C, Kaden JJ, Kalmar G, Borggrefe M, et al. Utility of combined parameters of common carotid intima-media thickness or albuminuria in diagnosis of coronary artery disease in women. International Journal of Cardiology. 2005; 105: 134–140. https://doi.org/10.1016/j.ijcard.2004.11.026 PMID: 16243103

61. Kotsis VT; Pitiriga VCh; Stabouli SV; Papamichael CM; Toumanidis ST; Rokas SG, et al. Carotid artery intima-media thickness could predict the presence of coronary artery lesions. Am J Hypertens. 2005; 18: 601–6. https://doi.org/10.1016/j.amjhyper.2004.11.019 PMID: 15882541

62. Amato M, Montorsi P, Ravani A, Oldani E, Galli S, Ravagnani PM, et al. Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: Correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. European Heart Journal. 2007; 28: 2094–2101. https://doi.org/10.1093/eurheartj/ehm244 PMID: 17597051

63. del Sol AI, Moons KGM, Hollander M, Hofman A, Koudstaal PJ, Grobbee DE, et al. Is Carotid Intima-Media Thickness Useful in Cardiovascular Disease Risk Assessment? Stroke. 2001; 32: 1532–1538. https://doi.org/10.1161/01.str.32.7.1532 PMID: 11441197

64. Kablak-Ziembicka A; Przewlocki T; Tracz W; Pieniazek P; Musialek P; Sokolowski A. Gender differences in carotid intima-media thickness in patients with suspected coronary artery disease. Am J Cardiol. 2005; 96: 1217–22. https://doi.org/10.1016/j.amjcard.2005.06.059 PMID: 16253585

65. Lisowska A, Musiał WJ, Lisowski P, Knapp M, Małyszko J, Dobrzycki S. Intima-media thickness is a useful marker of the extent of coronary artery disease in patients with impaired renal function. Atherosclerosis. 2009; 202: 470–475. https://doi.org/10.1016/j.atherosclerosis.2008.05.051 PMID: 18621374

66. Timóteo AT, Carmo MM, Ferreira RC. Carotid Intima–Media Thickness and Carotid Plaques Improves Prediction of Obstructive Angiographic Coronary Artery Disease in Women. Angiology. 2013; 64: 57–63. https://doi.org/10.1177/0003319711435935 PMID: 22323838

67. Alan S, Ulgen MS, Ozturk O, Alan B, Ozdemir L, Toprak N. Relation Between Coronary Artery Disease, Risk Factors and Intima-Media Thickness of Carotid Artery, Arterial Distensibility, and Stiffness Index. Angiology. 2003; 54: 261–267. https://doi.org/10.1177/000331970305400301 PMID: 12785018

68. Koç AS, Sümbül HE. Age should be considered in cut-off values for increased carotid intima-media thickness. Turk Kardiyoloji Dernegi Arsivi. 2019; 47: 301–311. https://doi.org/10.5543/tkda.2018.94770 PMID: 31219455

69. Kanadaşı M, Çaylı M, Şan M, Aikimbaev K, Alhan CC, Demir M, et al. The Presence of a Calcific Plaque in the Common Carotid Artery as a Predictor of Coronary Atherosclerosis. Angiology. 2006; 57: 585–592. https://doi.org/10.1177/0003319706293123 PMID: 17067981

70. GEROULAKOS G, O'GORMAN DJ, KALODIKI E, SHERIDAN DJ, NICOLAIDES AN. The carotid intima-media thickness as a marker of the presence of severe symptomatic coronary artery disease. European Heart Journal. 1994; 15: 781–785. https://doi.org/10.1093/oxfordjournals.eurheartj.a060585 PMID: 8088266

71. Ebrahim S; Papacosta O; Whincup P; Wannamethee G; Walker M; Nicolaides AN, et al. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. Stroke. 1999; 30: 841–50. https://doi.org/10.1161/01.str.30.4.841 PMID: 10187889

72. Diaz A, Bia D, Zócalo Y, Manterola H, Larrabide I, Lo Vercio L, et al. Carotid Intima Media Thickness Reference Intervals for a Healthy Argentinean Population Aged 11–81 Years. International Journal of Hypertension. 2018; 2018: 1–13. https://doi.org/10.1155/2018/8086714 PMID: 29992052

73. Rosa EM; Kramer C; Castro I. Association between coronary artery atherosclerosis and the intima-media thickness of the common carotid artery measured on ultrasonography. Arq Bras Cardiol. 2003; 80: 589–92. https://doi.org/10.1590/s0066-782x2003000600002 PMID: 12856069

74. Johri AM, Behl P, Hétu MF, Haqqi M, Ewart P, Day AG, et al. Carotid Ultrasound Maximum Plaque Height-A Sensitive Imaging Biomarker for the Assessment of Significant Coronary Artery Disease. Echocardiography. 2016; 33: 281–289. https://doi.org/10.1111/echo.13007 PMID: 26122814

75. Pastorius Catherine A., Medina-Lezama Josefina, Fernando Corrales-Medina, Bernabé-Ortiz A, Roberto Paz-Manrique, Salinas-Najarro Belissa, et al. Normative values and correlates of carotid artery intima-media thickness and carotid atherosclerosis in Andean-Hispanics: The PREVENCION Study. Atherosclerosis. 2010; 211: 499–505. https://doi.org/10.1016/j.atherosclerosis.2010.04.009 PMID: 20510418

76. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB. Carotid-Wall Intima–Media Thickness and Cardiovascular Events. New England Journal of Medicine. 2011; 365: 213–221. https://doi.org/10.1056/NEJMoa1012592 PMID: 21774709

77. Cao JJ, Arnold AM, Manolio TA, Polak JF, Psaty BM, Hirsch CH, et al. Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: The cardiovascular health study. Circulation. 2007; 116: 32–38. https://doi.org/10.1161/CIRCULATIONAHA.106.645606 PMID: 17576871

78. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: The Atherosclerosis Risk in Communities (ARIC) study, 1987–1993. American Journal of Epidemiology. 1997; 146: 483–494. https://doi.org/10.1093/oxfordjournals.aje.a009302 PMID: 9290509

79. Hensley B; Huang C; Cruz Martinez CV; Shokoohi H; Liteplo A. Ultrasound Measurement of Carotid Intima-Media Thickness and Plaques in Predicting Coronary Artery Disease. Ultrasound Med Biol. 2020; 46: 1608–1613. https://doi.org/10.1016/j.ultrasmedbio.2020.03.004 PMID: 32386846

80. Hansa G, Bhargava K, Bansal M, Tandon S, Kasliwal RR. Carotid intima-media thickness and coronary artery disease: An Indian perspective. Asian Cardiovascular and Thoracic Annals. 2003; 11: 217–221. https://doi.org/10.1177/021849230301100308 PMID: 14514551

81. Sachar Sudhir, Premi Vimugdha, Pahwa Ila, Sachar Saurabh, Sukriti Verma UUR. Role of Carotid Intima Media Thickness As A Surrogate Marker of Cardiovascular Events. International Journal of Contemporary Medical Research. 2018; 5.

82. Agarwal AK, Gupta PK, Singla S, Garg U, Prasad A Y R. Carotid Intimomedial Thickness in Type 2 Diabetic Patients and Its Correlation with Coronary Risk Factors. Journal of the Assiociation of Physicians of India. 2008; 56. PMID: 19051701

83. Kasliwal RR, Bansal M, Desai N, Kotak B, Raza A, Vasnawala H, et al. A Study to derive distribution of carotid intima media thickness and to determine its COrrelation with cardiovascular Risk factors in asymptomatic nationwidE Indian population (SCORE-India). Indian Heart Journal. 2016; 68: 821–827. https://doi.org/10.1016/j.ihj.2016.04.009 PMID: 27931554

84. Kaligis Rinambaan W. M., Suko Adiarto E, Nugroho Johanes, Pradnyana Bagus Ari, Lefi Achmad, Sodiqur Rifqi M. Carotid Intima-Media Thickness in Indonesian Subjects with Cardiovascular Disease Risk Factors Who Were Not Receiving Lipid-Lowering Agents. International Journal of Angiology. 2016; 25: 174–180.

85. Barakoti Murari Prasad, Poudyal Ratna Raj Ghimire Ram Kumar Panta S. CJ S. PRESENTING, CAROTID INTIMA-MEDIA THICKNESS IN PATIENTS INFARCTION, WITH ACUTE MYOCARDIAL. World Journal of Pharmaceutical Research. 2016; 6: 850–858.

86. Adams MR; Nakagomi A; Keech A; Robinson J; McCredie R; Bailey BP, et al. Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. Circulation. 1995; 92: 2127–34. https://doi.org/10.1161/01.cir.92.8.2127 PMID: 7554192

87. Liu B, Ni J, Shi M, Bai L, Zhan C, Lu H, et al. Carotid Intima-media Thickness and its Association with Conventional Risk Factors in Low-income Adults: A Population-based Cross-Sectional Study in China. Scientific Reports. 2017; 7: 1–7. https://doi.org/10.1038/srep41500 PMID: 28134279

88. Yu X, Bian B, Huang J, Yao W, Wu X, Huang J, et al. Determinants of carotid intima-media thickness in asymptomatic elders: a population-based cross-sectional study in rural China. Postgraduate Medicine. 2020; 132: 544–550. https://doi.org/10.1080/00325481.2020.1757266 PMID: 32297560

89. Fujihara K; Suzuki H; Sato A; Ishizu T; Kodama S; Heianza Y, et al. Comparison of the Framingham risk score, UK Prospective Diabetes Study (UKPDS) Risk Engine, Japanese Atherosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC) and maximum carotid intima-media thickness for

predicting coronary artery stenosis. J Atheroscler Thromb. 2014; 21: 799–815. https://doi.org/10.5551/jat.20487 PMID: 24717757

90. Matsushima Y, Kawano H, Koide Y, Baba T, Toda G, Seto S, et al. Relationship of carotid intima-media thickness, pulse wave velocity, and ankle brachial index to the severity of coronary artery atherosclerosis. Clinical Cardiology. 2004; 27: 629–634. https://doi.org/10.1002/clc.4960271110 PMID: 15562933

91. Lee YH, Shin MH, Kweon SS, Nam HS, Park KS, Choi JS, et al. Normative and mean carotid intima-media thickness values according to metabolic syndrome in Koreans: The Namwon Study. Atherosclerosis. 2014; 234: 230–236. https://doi.org/10.1016/j.atherosclerosis.2014.02.023 PMID: 24681913

92. Youn YJ, Lee NS, Kim JY, Lee JW, Sung JK, Ahn SG, et al. Normative values and correlates of mean common carotid intima-media thickness in the Korean rural middle-aged population: The atherosclerosis RIsk of rural areas iN Korea general population (ARIRANG) study. Journal of Korean Medical Science. 2011; 26: 365–371. https://doi.org/10.3346/jkms.2011.26.3.365 PMID: 21394304

93. CHUA Seng Keong, KILUNG Andrew; ONG Tiong Kiam, FONG Alan Y Y Y KL, KHIEW Ning Zan, HANIM M A NOR, et al. Carotid Intima Media Thickness and High Sensitivity CReactive Protein as Markers of Cardiovascular Risk in a Malaysian Population. Med J Malaysia. 2014; 69: 166–174. PMID: 25500844

94. Su TC; Hwang JJ; Shen YC; Chan CC. Carotid Intima-Media Thickness and Long-Term Exposure to Traffic-Related Air Pollution in Middle-Aged Residents of Taiwan: A Cross-Sectional Study. Environ Health Perspect. 2015; 123: 773–8. https://doi.org/10.1289/ehp.1408553 PMID: 25793433

95. Allen L, Williams J, Townsend N, Mikkelsen B, Roberts N, Foster C, et al. Socioeconomic status and non-communicable disease behavioural risk factors in low-income and lower-middle-income countries: a systematic review. The Lancet Global Health. 2017; 5: e277–e289. https://doi.org/10.1016/S2214-109X(17)30058-X PMID: 28193397

96. Yusuf PS, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet. 2004; 364: 937–952. https://doi.org/10.1016/S0140-6736(04)17018-9 PMID: 15364185

97. Johnson HM, Piper ME, Jorenby DE, Fiore MC, Baker TB, Stein JH. Risk Factors for Subclinical Carotid Atherosclerosis Among Current Smokers. Preventive Cardiology. 2010; 13: 166–171. https://doi.org/10.1111/j.1751-7141.2010.00068.x PMID: 20860639

98. Jin Y, Kim D, Cho J, Lee I, Choi K, Kang H. Association between Obesity and Carotid Intima-Media Thickness in Korean Office Workers: The Mediating Effect of Physical Activity. BioMed Research International. 2018; 2018. https://doi.org/10.1155/2018/4285038 PMID: 30155478

99. Walker TJ, Heredia NI, Lee MJ, Laing ST, Fisher-Hoch SP, McCormick JB, et al. The combined effect of physical activity and sedentary behavior on subclinical atherosclerosis: A cross-sectional study among Mexican Americans. BMC Public Health. 2019; 19: 161. https://doi.org/10.1186/s12889-019-6439-4 PMID: 30727990

100. Bennett PC, Gill PS, Silverman S, Blann AD, Lip GYH. Ethnic differences in common carotid intima-media thickness, and the relationship to cardiovascular risk factors and peripheral arterial disease: The Ethnic-Echocardiographic Heart of England Screening Study. QJM. 2011; 104: 245–254. https://doi.org/10.1093/qjmed/hcq187 PMID: 20956456

101. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: An analysis of burden of disease and life expectancy. The Lancet. 2012; 380: 219–229. https://doi.org/10.1016/S0140-6736(12)61031-9 PMID: 22818936

102. Ezzati M, Pearson-Stuttard J, Bennett JE, Mathers CD. Acting on non-communicable diseases in low- and middle-income tropical countries. Nature. Nature Publishing Group; 2018. pp. 507–516. https://doi.org/10.1038/s41586-018-0306-9 PMID: 30046068

103. Ebrahim S, Smeeth L. Non-communicable diseases in low and middle-income countries: A priority or a distraction? International Journal of Epidemiology. Int J Epidemiol; 2005. pp. 961–966. https://doi.org/10.1093/ije/dyi188 PMID: 16150869

104. Alwan A, MacLean DR, Riley LM, D'Espaignet ET, Mathers CD, Stevens GA, et al. Monitoring and surveillance of chronic non-communicable diseases: Progress and capacity in high-burden countries. The Lancet. Elsevier B.V.; 2010. pp. 1861–1868. https://doi.org/10.1016/S0140-6736(10)61853-3 PMID: 21074258

105. Samb B, Desai N, Nishtar S, Mendis S, Bekedam H, Wright A, et al. Prevention and management of chronic disease: A litmus test for health-systems strengthening in low-income and middle-income countries. The Lancet. Elsevier B.V.; 2010. pp. 1785–1797. https://doi.org/10.1016/S0140-6736(10)61353-0 PMID: 21074253

106. Lim SS, Gaziano TA, Gakidou E, Reddy KS, Farzadfar F, Lozano R, et al. Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs. Lancet. Elsevier B.V.; 2007. pp. 2054–2062. https://doi.org/10.1016/S0140-6736(07)61699-7 PMID: 18063025

107. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, et al. Inflammatory Markers and the Risk of Coronary Heart Disease in Men and Women. New England Journal of Medicine. 2004; 351: 2599–2610. https://doi.org/10.1056/NEJMoa040967 PMID: 15602020

108. Amar J, Fauvel J, Drouet L, Ruidavets JB, Perret B, Chamontin B, et al. Interleukin 6 is associated with subclinical atherosclerosis: A link with soluble intercellular adhesion molecule. Journal of Hypertension. 2006; 24: 1083–1088. https://doi.org/10.1097/01.hjh.0000226198.44181.0c PMID: 16685208

109. Bartels S, Franco AR, Rundek T. Carotid intima-media thickness (cIMT) and plaque from risk assessment and clinical use to genetic discoveries. Perspectives in Medicine. 2012; 1–12: 139–145. https://doi.org/10.1016/j.permed.2012.01.006

110. Campuzano R, Moya JL, García-Lledó A, Salido L, Guzmán G, Tomas JP, et al. Endothelial dysfunction and intima-media thickness in relation to cardiovascular risk factors in patients without clinical manifestations of atherosclerosis. Revista Española de Cardiología. 2003; 56: 546–554. https://doi.org/10.1016/s0300-8932(03)76915-2 PMID: 12783729

111. Amaya-Amaya J, Montoya-Sánchez L, Rojas-Villarraga A. Cardiovascular involvement in autoimmune diseases. BioMed Research International. Hindawi Publishing Corporation; 2014. https://doi.org/10.1155/2014/367359 PMID: 25177690

112. Qu B, Qu T. Causes of changes in carotid intima-media thickness: a literature review. Cardiovascular Ultrasound. 2015; 13: 1–10. https://doi.org/10.1186/1476-7120-13-1 PMID: 26666335

113. Balta S, Celik T, Mikhailidis DP, Ozturk C, Demirkol S, Aparci M, et al. The Relation between Atherosclerosis and the Neutrophil-Lymphocyte Ratio. Clinical and Applied Thrombosis/Hemostasis. 2014; 22: 405–411. https://doi.org/10.1177/1076029615569568 PMID: 25667237

114. Cingoz F, Iyisoy A, Demirkol S, Sahin MA, Balta S, Celik T, et al. Carotid Intima-Media Thickness in Patients With Slow Coronary Flow and Its Association With Neutrophil-to-Lymphocyte Ratio. Clinical and Applied Thrombosis/Hemostasis. 2014; 20: 393–399. https://doi.org/10.1177/1076029613485283 PMID: 23613039

115. Lu Y-W, Chou R-H, Liu L-K, Chen L-K, Huang P-H, Lin S-J. The relationship between circulating vitamin D3 and subclinical atherosclerosis in an elderly Asian population. Scientific Reports. 2020; 10: 18704. https://doi.org/10.1038/s41598-020-75391-0 PMID: 33127933

116. Whincup PH, Nightingale CM, Owen CG, Rapala A, Bhowruth DJ, Prescott MH, et al. Ethnic Differences in Carotid Intima-Media Thickness Between UK Children of Black African-Caribbean and White European Origin. Stroke. 2012; 43: 1747–1754. https://doi.org/10.1161/STROKEAHA.111.644955 PMID: 22569936

117. Gijsberts CM, Groenewegen KA, Hoefer IE, Eijkemans MJC, Asselbergs FW, Anderson TJ, et al. Race/Ethnic Differences in the Associations of the Framingham Risk Factors with Carotid IMT and Cardiovascular Events. Apetrei C, editor. PLOS ONE. 2015; 10: e0132321. https://doi.org/10.1371/journal.pone.0132321 PMID: 26134404

118. Lee K, Sung J, Lee SC, Park SW, Kim YS, Lee JY, et al. Segment-specific carotid intima-media thickness and cardiovascular risk factors in Koreans: The Healthy Twin Study. European Journal of Preventive Cardiology. 2012; 19: 1161–1172. https://doi.org/10.1177/1741826711422763 PMID: 21914685

119. Rosvall M, Persson M, Östling G, Nilsson PM, Melander O, Hedblad B, et al. Risk factors for the progression of carotid intima-media thickness over a 16-year follow-up period: The Malmö Diet and Cancer Study. Atherosclerosis. 2015; 239: 615–621. https://doi.org/10.1016/j.atherosclerosis.2015.01.030 PMID: 25746169

120. Müller-Scholden L, Kirchhof J, Morbach C, Breunig M, Meijer R, Rücker V, et al. Segment-specific association of carotid-intima-media thickness with cardiovascular risk factors—Findings from the STAAB cohort study. BMC Cardiovascular Disorders. 2019; 19: 84. https://doi.org/10.1186/s12872-019-1044-0 PMID: 30947692

121. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness consensus (2004–2006): An update on behalf of the advisory board of the 3rd and 4th Watching the Risk Symposium 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovascular Diseases. 2007; 23: 75–80. https://doi.org/10.1159/000097034 PMID: 17108679

122. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC: Cardiovascular Imaging. Elsevier Inc.; 2014. pp. 1025–1038. https://doi.org/10.1016/j.jcmg.2013.11.014 PMID: 25051948

123. Price J, Tzoulaki I, Lee A. 2007. Ankle brachial index and intima media thickness predict cardiovascular events similarly and increased prediction when combined. J of clinical epidemiology, Elsevier. [cited 25 Nov 2020]. https://www.sciencedirect.com/science/article/pii/S0895435607000832 PMID: 17884603

124. Van Der Meer IM, Bots ML, Hofman A, Del Sol AI, Van Der Kuip DAM, Witteman JCM. Predictive Value of Noninvasive Measures of Atherosclerosis for Incident Myocardial Infarction: The Rotterdam Study. Circulation. 2004; 109: 1089–1094. https://doi.org/10.1161/01.CIR.0000120708.59903.1B PMID: 14993130

125. Peters SAE, Lind L, Palmer MK, Grobbee DE, Crouse JR, O'Leary DH, et al. Increased age, high body mass index and low HDL-C levels are related to an echolucent carotid intima-media: The METEOR study. Journal of Internal Medicine. 2012; 272: 257–266. https://doi.org/10.1111/j.1365-2796.2011.02505.x PMID: 22172243

126. Naqvi TZ, Mendoza F, Rafii F, Gransar H, Guerra M, Lepor N, et al. High prevalence of ultrasound detected carotid atherosclerosis in subjects with low framingham risk score: Potential implications for screening for subclinical atherosclerosis. Journal of the American Society of Echocardiography. 2010; 23: 809–815. https://doi.org/10.1016/j.echo.2010.05.005 PMID: 20554155

127. Ring M, Eriksson MJ, Jogestrand T, Caidahl K. Ultrasound measurements of carotid intima–media thickness by two semi-automated analysis systems. Clinical Physiology and Functional Imaging. 2016; 36: 389–395. https://doi.org/10.1111/cpf.12241 PMID: 26046377

128. Dogan S, Duivenvoorden R, Grobbee DE, Kastelein JJP, Shear CL, Evans GW, et al. Ultrasound protocols to measure carotid intima-media thickness in trials; Comparison of reproducibility, rate of progression, and effect of intervention in subjects with familial hypercholesterolemia and subjects with mixed dyslipidemia. Annals of Medicine. 2010; 42: 447–464. https://doi.org/10.3109/07853890.2010.499132 PMID: 20645885