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CLINICAL RESEARCH
Imaging

Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors

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Aims Common carotid artery intima-media thickness (CCIMT) is widely used as a surrogate marker of atherosclerosis, given its predictive association with cardiovascular disease (CVD). The interpretation of CCIMT values has been hampered by the absence of reference values, however. We therefore aimed to establish reference intervals of CCIMT, obtained using the probably most accurate method at present (i.e. echotracking), to help interpretation of these measures.

Methods and results We combined CCIMT data obtained by echotracking on 24 871 individuals (53% men; age range 15–101 years) from 24 research centres worldwide. Individuals without CVD, cardiovascular risk factors (CV-RFs), and BP-, lipid-, and/or glucose-lowering medication constituted a healthy sub-population ($n = 4234$) used to establish sex-specific equations for percentiles of CCIMT across age. With these equations, we generated CCIMT *Z*-scores in different reference sub-populations, thereby allowing for a standardized comparison between observed and predicted ('normal') values from individuals of the same age and sex. In the sub-population without CVD and treatment ($n = 14\,609$), and in men and women, respectively, CCIMT *Z*-scores were independently associated with systolic blood pressure [standardized βs 0.19 (95% CI: 0.16–0.22) and 0.18 (0.15–0.21)], smoking [0.25 (0.19–0.31) and 0.11 (0.04–0.18)], diabetes [0.19 (0.05–0.33) and 0.19 (0.02–0.36)], total-to-HDL cholesterol ratio [0.07 (0.04–0.10) and 0.05 (0.02–0.09)], and body mass index [0.14 (0.12–0.17) and 0.07 (0.04–0.10)].

Conclusion We estimated age- and sex-specific percentiles of CCIMT in a healthy population and assessed the association of CV-RFs with CCIMT *Z*-scores, which enables comparison of IMT values for (patient) groups with different cardiovascular risk profiles, helping interpretation of such measures obtained both in research and clinical settings.

Keywords Ageing • Atherosclerois • Carotid intima-media thickness • Echotracking • Reference intervals • Risk factors

Introduction

Measurement by ultrasonography of the common carotid artery intima-media thickness (CCIMT) was first described by Pignoli *et al.* in 1986.[1] Since then, the technique has been widely used for the assessment of arterial wall thickness *in vivo*. Numerous studies have shown that non-invasive measures of CCIMT can be measured with high reproducibility; correlate well with major cardiovascular risk factors (CV-RFs), prevalent disease, and severity of atherosclerosis in other vascular beds; and predict incident cardiovascular events; and that its progression over time may be deterred by targeted interventions (reviewed in 2–4). As such, CCIMT is a

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suitable surrogate marker for cardiovascular disease (CVD)[3] and is currently widely used for the pre-symptomatic detection of disease and its progression, in clinical and epidemiological studies, improving efficiency and aiming at decreasing follow-up time usually needed in studies with 'hard' cardiovascular endpoints.[3–6]

Despite attempts at normalization, the method for measuring CCIMT is highly variable, either in terms of signal processing [B-mode, M-mode, radiofrequency (RF) signal analysis] or anatomical location. The methodological heterogeneity accounts for individual variability in the value of CCIMT across studies. As such, values obtained in either research or clinical practice settings, obtained with different methodologies, are difficult to analyse in the absence of standardized reference values. Indeed, although age-dependent nomograms for CCIMT have been reported before,[7–11] their general use is limited. First, they refer to mere distributions of mean or median values in general populations without distinguishing between subjects with or without established CV-RFs and/or disease[8,10] and can thus not be used as reference for a 'normal' (i.e. healthy) population. Second, they refer to values of CCIMT as obtained by manual or automated analyses techniques of B-mode ultrasound (US) imaging,[7–11] whereas, at present, automated edge-detection on the basis of RF signal processing (hereafter 'echotracking') of B + M mode US imaging is probably the most accurate method.[12–15] Third, they are confined to a single-centre and/or country[7,9,11] and thus have limited sample sizes to properly cover the whole (adult) age range.

In view of these considerations, we combined subject-level data on established CV-RFs and CCIMT as obtained by echotracking systems from different study centres worldwide into one large data set—The Reference Values for Arterial Measurements Collaboration's CCIMT database. This was used to, first, establish age- and sex-specific percentiles (reference intervals—RIs) for CCIMT in individuals without CV-RFs (as conventionally defined), prior CVD and BP-, lipid-, and/or glucose-lowering medication, i.e. a healthy population; and second, to investigate the relation of CV-RFs and the use of BP-, lipid-, and/or glucose-lowering medication with CCIMT percentiles in individuals with or without prior CVD.

Methods

Study population

With a systematic literature review, we identified all cohort studies using echotracking for CCIMT measurement. Next, we personally contacted the principal investigators of the cohorts ($n = 55$) to inform them about the project and invite them to participate. We finally compiled subject-level data from 24 research centres/research groups—corresponding to 30 distinct cohorts—distributed across 14 countries worldwide (see the list in Supplementary material online, *Table S1*). A total of 25 166 individuals with data on CCIMT obtained using echotracking systems, age (range 5–101 years), sex (13 430 men/11 736 women), CVD status, and important CV-RFs were available for analysis. For the present study, we excluded 295 (53% girls) individuals who were aged <15 years because their data lacked sufficient variability with age (primarily concentrated at the age of five[16]), leaving 24 871 (47% women) individuals for analyses.

To generate age- and sex-specific normative tables for CCIMT, we selected a healthy sub-population composed of individuals who did not meet any of the following criteria: (i) history of CVD; (ii) use of BP-, lipid-, and/or glucose-lowering medication; (iii) hypertension [i.e. systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg][17]; (iv) current smoking; (v) diabetes [defined as self-reported diabetes and/or fasting plasma glucose ≥7.0 mmol/L (if available) and/or post-load plasma glucose ≥11.0 mmol/L (if available)][18]; (vi) total cholesterol >6.2 mmol/L[19]; (vii) HDL cholesterol <1.17 mmol/L (for men) and <1.30 (for women)[19]; and (viii) body mass index (BMI) ≥30 kg/m^2.[20] This healthy sub-population consisted of 4234 (53% women) individuals, which originated from 21 out of the 24 research centres (details in *Table A1*). The cut-off values used to define the healthy sub-population were chosen, whenever possible, to be similar to those used to indicate increased risk in current guidelines[17,18,20] (or risk algorithms[19]) to enable optimal comparison with other studies.

To investigate the relation of CV-RFs with individuals' levels of CCIMT percentiles, we stratified the total population according to a history of CVD and, in individuals without prior CVD only, by the use of BP-, lipid-, and/or glucose-lowering medication. This resulted in three reference sub-populations consisting of: (i) 14 609 (48% women) individuals without prior CVD and without the use of BP-, lipid-, and/or glucose-lowering medication; (ii) 5761 (52% women) individuals without prior CVD and who used BP-, lipid-, and/or glucose-lowering medication; and (iii) 4501 individuals (37% women) with prior CVD irrespective of medication use.

A flowchart describing the selection of the healthy and reference sub-populations and exact numbers per sex is presented in *Figure 1*.

Common carotid artery intima-media thickness measurements: methodological considerations

We included only CCIMT data obtained by means of echotracking (either pure echotracking or related techniques). These were measured at the far wall of the right and/or left common carotid artery only, because near-wall readings from echotracking devices may not reflect true thickness and are thus seldom obtained. Mean values of right and left CCIMT readings (if both sides were assessed) were used in the analyses, as previous studies have reported no differences between sides.[8,21]

Different types of US systems were used across centres; specifically, pure echotracking systems: the Wall Track System ($n = 13\,116$; WTS, ESAOTE, Maastricht, The Netherlands[22]) and the ART.LAB system ($n = 8519$; advanced version of WTS; ESAOTE, Maastricht, The Netherlands) or related techniques, which were validated against echotracking: the Vivid-7 US system ($n = 2524$; GE Vingmed Ultrasound, Horten, Norway) with Echopac post-processing; the Aloka SSD-650 US system ($n = 606$; Aloka, Tokyo, Japan) with dedicated post-processing software (M'ATHS, Metris, France)[23]; and the Carotid Studio ($n = 401$; Institute of Clinical Physiology, National Research Council, Pisa, Italy).[24] The exact anatomical location of the measurement of the CCIMT differed across centres: i.e. at 0–1 cm, centred at 1 cm, at 1–2 cm or centred at 2 cm proximal to the carotid bifurcation. Therefore, prior to further analyses, we standardized all CCIMT values obtained with different echotracking systems and anatomical locations (for details, please see *Table S1*). To this aim, original CCIMT values were rescaled to the same metric of the mostly used system and location, i.e. measurements with the ART.LAB system and centred at 1 cm proximal to the carotid bifurcation (see the Statistical analyses section).

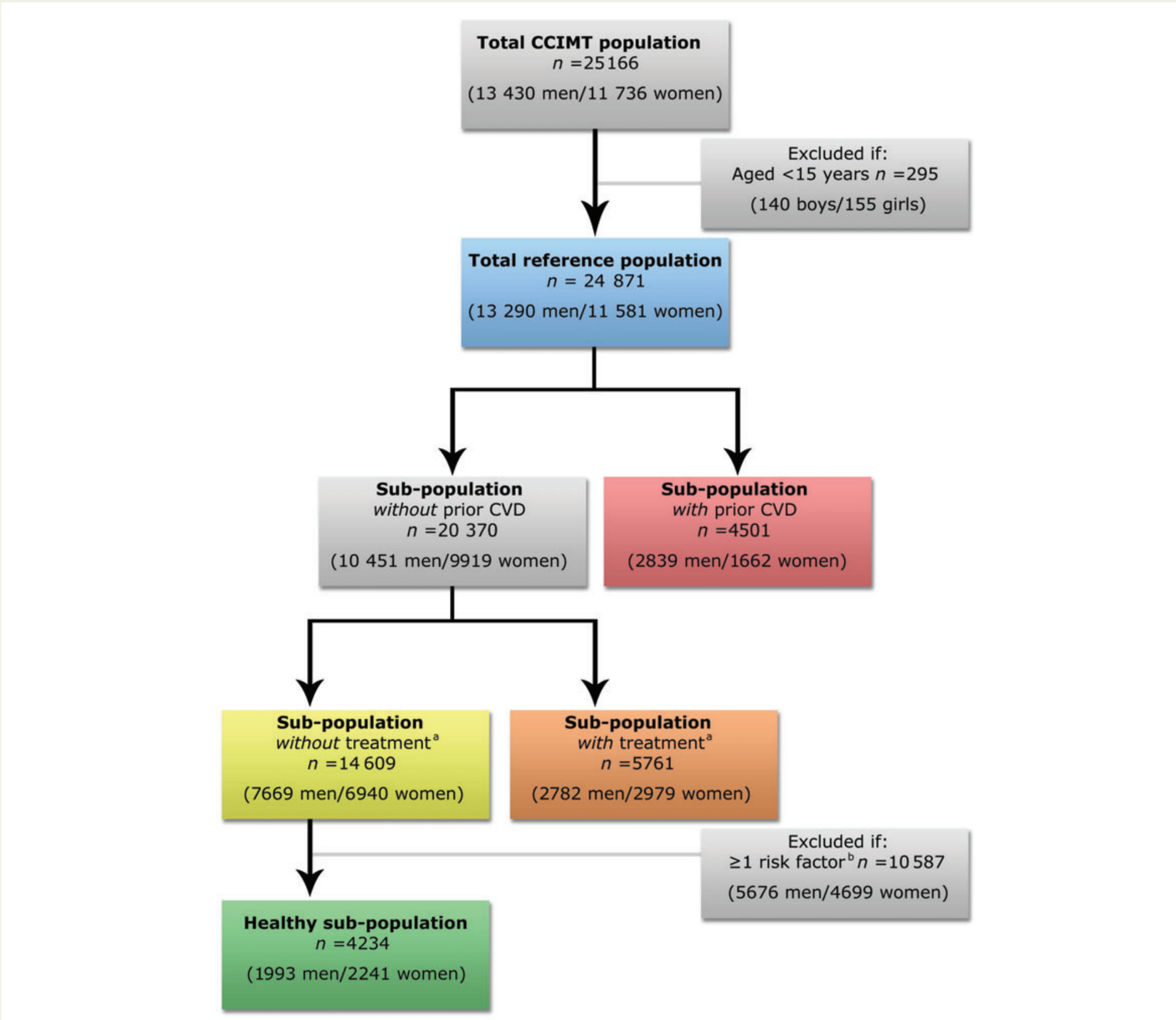

Figure 1 Study flowchart describing the selection and categorization of individuals from the total common carotid artery intima-media thickness (CCIMT) population to the reference and healthy sub-populations. [a]BP-, lipid-, and/or glucose-lowering medication. [b]Risk factors considered were hypertension (systolic blood pressure/diastolic blood pressure ≥140/90 mmHg), current smoking, diabetes [self-reported diabetes and/or fasting plasma glucose ≥7.0 and/or post-load plasma glucose ≥11.0 mmol/L (if available)], total cholesterol >6.2 mmol/L, HDL cholesterol <1.17 mmol/L (for men) and <1.30 mmol/L (for women), and body mass index ≥30 kg/m^2.

Statistical analyses

Multiple imputation of missing values in variables

A total of 4673 individuals (19% of the total reference population) had missing values for one ($n = 4391$) or more ($n = 282$) of the variables of interest. The percentage of missing values per variable varied from 0.4% (current smoking) to 11% (HDL cholesterol). We used multiple imputation chained equations to impute those values rather than perform complete case analyses in order to decrease bias and increase the power of the analyses[25,26] (for details, please see Supplementary material online).

Standardization of common carotid artery intima-media thickness measurements

We performed multiple linear regression analyses that included dummy variables for each echotracking system (with ART.LAB as reference) and anatomical location (with measurements centred at 1 cm proximal to the carotid bifurcation as reference) as independent determinants of CCIMT. These analyses were conducted in the total population ($n = 24\,871$) and included adjustments for all CV-RFs, history of CVD, and the use of BP- and/or lipid-lowering medication. The regression coefficients (β) for the dummy variables hereby obtained were used as 'calibration factors' to rescale individual CCIMT values to the reference technique (details in Supplementary material online, *Table S2*). We used these rescaled CCIMT values in all further analyses.

Definition of age- and sex-specific reference intervals

An extensive description of the methods used to define RIs for CCIMT is provided in Supplementary material online. In brief, calculation of age-specific RIs for CCIMT was performed in the healthy sub-population ($n = 4234$), and in men and women separately. To this aim, we used a parametric regression method based on fractional polynomials (FPs) as described by Royston and Wright[27] and implemented in the STATA software (version 11.0 Stata Corp., College Station, TX, USA).[28] Age-specific 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentile curves were calculated as $\text{mean}_{\text{CCIMT}} + Z_p \times \text{SD}$, where Z_p assumed the values of −1.96, −1.28, −0.67, 0, 0.67, 1.28, and 1.96, respectively.

Relation with risk factors

Based on the equations estimated as described above, we computed expected 'normal' mean CCIMT values for each individual in the reference sub-populations (i.e. those with and without CVD and/or medication) and calculated age- and sex-specific CCIMT *Z*-scores as $(\text{observed}_{\text{CCIMT}} - \text{expected}_{\text{CCIMT}})/\text{SDexpected}_{\text{CCIMT}}$; this allows for a standardized comparison between observed CCIMT values vs. those from healthy individuals of the same age and sex, expressed by the number of SDs an individual measurement lies above or below the healthy population mean (or 50th percentile).

The relation of known CV-RFs with the CCIMT *Z*-scores was then investigated in the different reference sub-populations, using multiple linear regression analyses to enable interpretation of CCIMT values across different risk groups. We also included age in these analyses to account for any potential residual influence of age in these sub-populations. In addition, we added interaction terms between sex and each of the CV-RFs to the models to assess potential effect modification.

Statistical analyses were performed using the Statistical Package for Social Sciences, version 18.0 (SPSS, Inc., Chicago, IL, USA) unless specified otherwise.

Results

Tables 1 and 2 show the participants' characteristics of the total, healthy, and reference sub-populations, in men and women, respectively. In the total reference population, women were slightly older and had, on average, lower values of CV-RFs compared with men.

Age- and sex-specific reference intervals for common carotid artery intima-media thickness in the healthy sub-population

The best fitting FPs' powers (p) for the $\text{mean}_{\text{CCIMT}}$ and SD_{CCIMT} curves were $p = 1$ for both men and women, indicating that linear regression lines described the age–CCIMT relationships well. Accordingly, the equations derived on the basis of the estimated coefficients were, for men:

$$\text{mean}_{\text{CCIMT}}(\text{in } \mu\text{m}) = 323.5 + 5.201 \times \text{age}, \quad (1)$$

$$\text{SD}_{\text{CCIMT}}(\text{in } \mu\text{m}) = 57.24 + 0.9027 \times \text{age}, \quad (2)$$

Table 1 Risk factors and clinical characteristics of the total, healthy, and reference sub-populations in men

	Total reference population	Healthy sub-population	Sub-population without CVD		Sub-population with CVD
			Without treatment[a]	With treatment[a]	
n	13 290	1993	7669	2782	2839
Age [years (range)]	56 (15–99)	50 (15–90)	53 (15–99)	59 (16–98)	63 (23–97)
Body mass index (kg/m^2)	26.3 ± 3.7	24.2 ± 2.6	25.8 ± 3.5	27.6 ± 3.9	26.6 ± 3.5
Systolic blood pressure (mmHg)	136 ± 19	123 ± 10	132 ± 17	142 ± 19	139 ± 20
Diastolic blood pressure (mmHg)	79 ± 11	74 ± 8	79 ± 11	82 ± 12	79 ± 11
Mean arterial pressure (mmHg)	98 ± 12	90 ± 8	96 ± 12	102 ± 13	99 ± 12
Hypertension [*n* (%)]	6951 (52)	–	2453 (32)	2324 (84)	2173 (77)
Total cholesterol (mmol/L)	5.5 ± 1.0	5.1 ± 0.7	5.5 ± 1.0	5.4 ± 1.1	5.3 ± 1.0
LDL cholesterol (mmol/L)	3.5 ± 0.9	3.1 ± 0.7	3.6 ± 0.9	3.4 ± 1.0	3.3 ± 0.9
HDL cholesterol (mmol/L)	1.3 ± 0.3	1.5 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.2 ± 0.3
Total-to-HDL cholesterol ratio	4.5 ± 1.5	3.4 ± 0.7	4.4 ± 1.4	4.6 ± 1.7	4.6 ± 1.6
Triglycerides (mmol/L)	1.3 (0.9–1.9)	0.9 (0.7–1.2)	1.2 (0.9–1.8)	1.4 (1.0–2.0)	1.4 (1.0–2.0)
Fasting glucose (mmol/L)	5.8 ± 1.5	5.2 ± 0.7	5.4 ± 1.0	6.2 ± 2.0	6.2 ± 1.8
Diabetes [*n* (%)]	1408 (11)	–	304 (4)	590 (21)	514 (18)
Current smoking [*n* (%)]	3126 (24)	–	1825 (24)	559 (20)	741 (26)
BP-lowering medication [*n* (%)]	2335 (18)	–	–	2073 (74)	1648 (58)
Lipid-lowering medication [*n* (%)]	877 (7)	–	–	1134 (41)	1129 (40)
Glucose-lowering medication [*n* (%)]	595 (5)	–	–	379 (14)	216 (8)
History of CVD [*n* (%)]	2839 (21)	–	–	–	*2839* (100)
CCIMT (μm)	653 ± 159	583 ± 131	631 ± 155	682 ± 151	685 ± 169

Data are presented as means ± SD, medians (inter-quartile ranges), or numbers (percentages), as appropriate.
[a]BP-, lipid-, and glucose-lowering treatment.

Table 2 Risk factors and clinical characteristics of the total, healthy, and reference sub-populations in women

	Total reference population	Healthy sub-population	Sub-population without CVD		Sub-population with CVD
			Without treatment[a]	With treatment[a]	
n	11 581	2241	6940	2979	1662
Age [years (range)]	58 (15–101)	48 (15–89)	54 (15–95)	63 (17–101)	64 (20–95)
Body mass index (kg/m^2)	25.8 ± 4.7	22.9 ± 2.8	24.9 ± 4.3	27.8 ± 5.0	26.4 ± 4.5
Systolic blood pressure (mmHg)	133 ± 21	118 ± 11	128 ± 19	142 ± 21	139 ± 21
Diastolic blood pressure (mmHg)	76 ± 11	72 ± 8	75 ± 10	79 ± 12	77 ± 11
Mean arterial pressure (mmHg)	95 ± 13	87 ± 8	93 ± 12	100 ± 13	98 ± 12
Hypertension [*n* (%)]	5519 (48)	–	1804 (26)	2608 (88)	1106 (66)
Total cholesterol (mmol/L)	5.8 ± 1.1	5.2 ± 0.7	5.8 ± 1.1	5.9 ± 1.1	5.9 ± 1.1
LDL cholesterol (mmol/L)	3.6 ± 1.0	3.0 ± 0.7	3.6 ± 1.0	3.6 ± 1.0	3.7 ± 1.0
HDL cholesterol (mmol/L)	1.6 ± 0.4	1.8 ± 0.3	1.7 ± 0.4	1.5 ± 0.4	1.6 ± 0.4
Total-to-HDL cholesterol ratio	3.8 ± 1.3	2.9 ± 0.6	3.7 ± 1.2	4.1 ± 1.4	4.1 ± 1.4
Triglycerides (mmol/L)	1.2 (0.8–1.6)	0.9 (0.7–1.1)	1.1 (0.8–1.5)	1.4 (1.0–1.9)	1.3 (0.9–1.8)
Fasting glucose (mmol/L)	5.6 ± 1.4	4.9 ± 0.6	5.2 ± 0.9	6.0 ± 1.8	5.9 ± 1.7
Diabetes [*n* (%)]	981 (9)	–	210 (3)	505 (17)	266 (16)
Current smoking [*n* (%)]	1983 (17)	–	1237 (18)	433 (15)	313 (19)
BP-lowering medication [*n* (%)]	2378 (21)	–	–	2405 (81)	767 (46)
Lipid-lowering medication [*n* (%)]	618 (5)	–	–	991 (33)	421 (25)
Glucose-lowering medication [*n* (%)]	356 (3)	–	–	260 (9)	96 (6)
History of CVD [*n* (%)]	1662 (14)	–	–	–	1662 (100)
CCIMT (μm)	639 ± 148	561 ± 123	610 ± 140	682 ± 150	677 ± 153

Data are presented as means ± SD, medians (inter-quartile ranges), or numbers (percentages), as appropriate.
[a]BP-, lipid-, and glucose-lowering treatment.

and, for women:

$$\text{mean}_{\text{CCIMT}}(\text{in } \mu\text{m}) = 321.7 + 4.971 \times \text{age}, \quad (3)$$

$$\text{SD}_{\text{CCIMT}}(\text{in } \mu\text{m}) = 54.50 + 0.8256 \times \text{age}. \quad (4)$$

The estimated *Z*-scores had a mean value of 0 and an SD of 1 and, when plotted against age, were randomly distributed above and below 0 (see Supplementary material online, *Figure S1*), indicating good model fit and no residual dependency on age.

Sex-specific percentile lines superimposed on the raw data are shown in *Figure 2*, and the respective levels of CCIMT by age category are presented in *Table 3*. Mean values of CCIMT were slightly higher in men than in women at any age ($P < 0.001$), but increases in CCIMT with ageing were similar in men (5.2 μm/year) and women (5.0 μm/year) (*P*-value for age by sex interaction = 0.144).

Relation of cardiovascular risk factors with common carotid artery intima-media thickness percentiles as defined in the healthy sub-population

In the sub-population without prior CVD and treatment, and both in men and women, higher CCIMT *Z*-scores (i.e. positive deviation from the healthy population mean) were significantly associated with SBP, smoking, diabetes, total-to-HDL cholesterol ratio, and BMI, whereas in the treated sub-population without prior CVD, diabetes and total-to-HDL cholesterol ratio were no longer independent determinants of the CCIMT *Z*-scores (*Table 4*). In the sub-population with prior CVD, SBP was the main determinant of CCIMT *Z*-scores in both men and women; BMI (adversely) and the use of lipid-lowering medication (protectively) were also determinants but in men only.

To enable comparison of the strength of the associations between the individual CV-RFs and CCIMT *Z*-scores within each sub-population, these associations are also shown as standardized regression coefficients (i.e. per-SD increase in CV-RF) (*Figure 3*). These analyses showed that, in the sub-population without CVD or treatment, smoking, diabetes, and SBP were the strongest determinants of the CCIMT *Z*-scores in men, whereas in women these were diabetes and SBP. Comparisons by sex showed that smoking and BMI were stronger determinants in men than in women (*P*-value for sex interactions were 0.005 and <0.001, respectively).

The regression coefficients shown in *Table 4*, reflecting the associations of CV-RFs with CCIMT *Z*-scores (i.e. the increase in SD from the mean CCIMT of healthy individuals of the same age and sex), can be converted into percentiles for a more meaningful interpretation of these analyses in the light of the RIs provided (*Figure 1* and *Table 3*). This is illustrated with two hypothetical

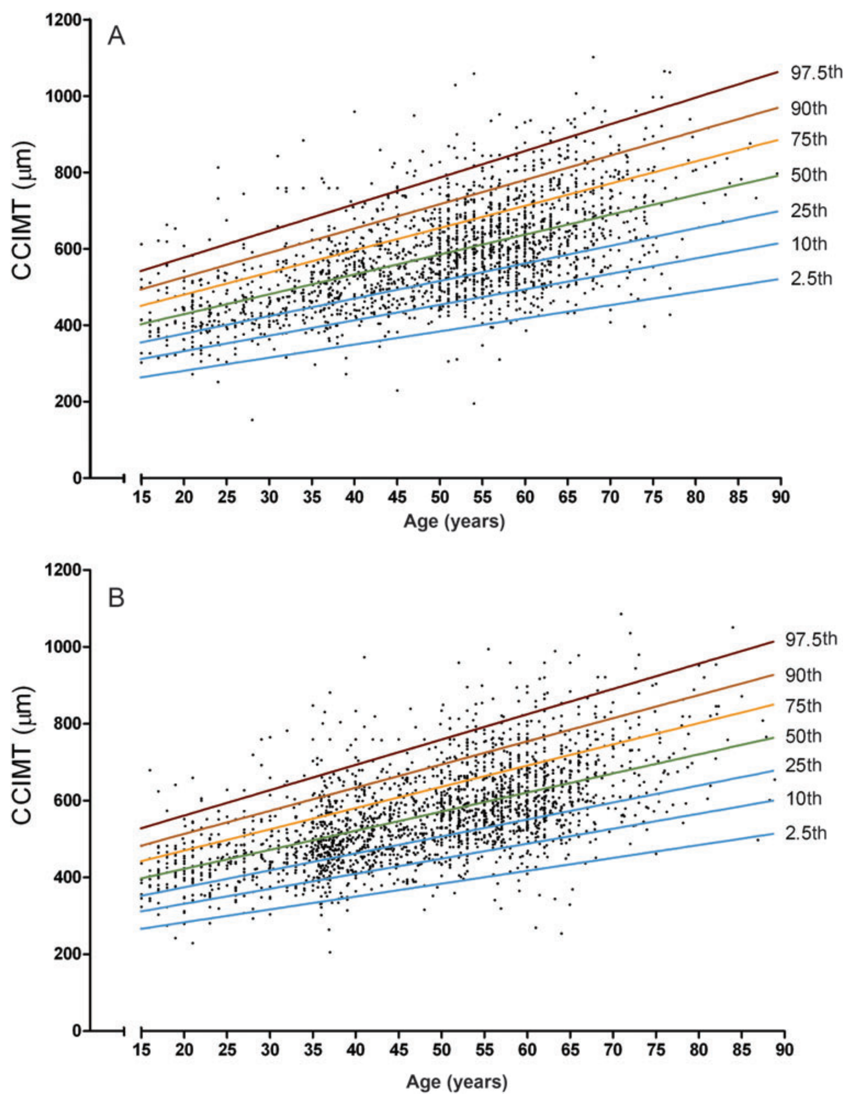

Figure 2 Age-specific percentiles of common carotid artery intima-media thickness (CCIMT) in the healthy sub-population: (*A*) men; (*B*) women.

subjects in *Table 5*: (i) a 50-year old man with SBP 160 mmHg, total-to-HDL cholesterol ratio 7.2, BMI 35 kg/m^2, who smokes and has no diabetes and (ii) a 50-year-old woman with SBP 130 mmHg, total-to-HDL cholesterol ratio 3.9, BMI 24 kg/m^2, who does not smoke and has no diabetes. Based on these risk profiles and the regression coefficients provided, the estimated CCIMT *Z*-scores for these individuals were 1.32 (man) and 0.19 (woman); these correspond, respectively, to the 91st and 58th percentiles of the CCIMT distribution in individuals of the same age and sex from the healthy sub-population. Similarly, CCIMT *Z*-scores can be estimated for any other combination of individuals' age and CV-RFs (i.e. risk profile) and conversion into percentiles can easily be retrieved using any standard normal distribution (*Z*) table, in which *Z*-scores of 0, 0.68, 1.28, and 1.65 correspond with the 50th, 75th, 90th, and 95th percentiles.

Additional analyses

We have also investigated whether the associations between CV-RFs and CCIMT *Z*-scores were modified by age, by adding interaction terms between the CV-RFs and age to our models. We found only significant interaction between age and SBP in the sub-population without prior CVD and treatment only, both in men ($P_{interaction} < 0.001$) and women ($P_{interaction} = 0.033$). This suggests that the association of SBP with CCIMT percentiles may be stronger among older than younger untreated individuals (see Supplementary material online, *Figure S2* and *Table S3*).

Discussion

In the present study, we estimated age- and sex-specific percentiles (RIs) of CCIMT obtained with echotracking in healthy individuals

Table 3 Age- and sex-specific percentiles of common carotid artery intima-media thickness (in μm) in the healthy sub-population

	Age (years)	Percentiles						
		2.5th	10th	25th	50th	75th	90th	97.5th
Men ($n = 1993$)	15	263	311	354	401	449	492	540
	20	280	331	377	427	478	524	575
	25	297	351	400	453	507	556	610
	30	314	372	423	479	536	587	645
	35	331	392	446	505	565	619	680
	40	349	412	468	531	594	651	714
	45	366	432	491	557	624	683	749
	50	383	452	514	583	653	715	784
	55	400	473	537	609	682	746	819
	60	417	493	560	635	711	778	854
	65	434	513	583	662	740	810	889
	70	451	533	606	688	769	842	924
	75	469	554	629	714	798	873	958
	80	486	574	652	740	827	905	993
	85	503	594	675	766	856	937	1028
Women ($n = 2241$)	15	265	311	351	396	441	482	527
	20	282	330	373	421	469	512	560
	25	299	350	395	446	497	542	593
	30	315	369	417	471	524	572	626
	35	332	389	439	496	552	602	659
	40	349	408	461	521	580	633	692
	45	366	428	483	545	607	663	725
	50	382	448	506	570	635	693	758
	55	399	467	528	595	663	723	791
	60	416	487	550	620	690	753	824
	65	433	506	572	645	718	783	857
	70	450	526	594	670	745	813	890
	75	466	545	616	694	773	843	923
	80	483	565	638	719	801	874	956
	85	500	585	660	744	828	904	989

aged 15–85 years, based on a large population obtained by combining data at the individual level from 24 research centres worldwide. We additionally assessed the association of CV-RFs with these CCIMT percentiles to enable comparison of CCIMT values across (patient) groups with different cardiovascular risk profiles with those from a healthy population.

CCIMT has been widely used as a surrogate marker for CVD risk in clinical and epidemiological studies. CCIMT measurements have also been proposed for screening and fine-tuning of individuals' risk prediction, as ascertained by current risk algorithms such as Framingham[19] and SCORE.[29] A recent meta-analysis of prospective studies showed that addition of CCIMT (measured by different methods) to the Framingham Risk Score led only to a small improvement in the 10-year risk prediction of first-time myocardial infarction or stroke, an improvement that is unlikely to be of clinical importance.[30] Further studies, also in populations with different risk profiles (e.g. with vs. without previous CVD, on vs. off treatment), may be needed to ascertain the added value, if any, of echotracking measurements of CCIMT measurements in individuals' risk stratification. For that purpose, RIs as presented herein may be helpful. In the present study, we chose to include echotracking data only to enable optimal comparison across current and future studies, since, at present, echotracking is probably the most accurate method to assess carotid properties.[12–15]

Current guidelines state that a CCIMT >900 μm can be regarded as a conservative estimate of existing abnormalities.[17] Only 52 individuals (1.2%) in the currently studied healthy sub-population showed CCIMT values >900 μm, which all corresponded to values above the age-specific 90th percentiles (*Figure 2*) and may thus indeed indicate increased risk. It should be emphasized, however, that the RIs provided do not necessarily translate to increased CVD risk, as we did not link these to hard cardiovascular outcome. However, the cut-off values for increasing percentiles indicate deviation from the healthy population means, which was amplified in the presence of CV-RFs, and thus most likely do indicate increased risk. Still, the extent to which these cut-offs should guide initiation of therapy needs to be further tested.

We found that, in the healthy sub-population, CCIMT was higher in men than in women but increased with ageing to a similar extent in men (5.2 μm/year) and women (5.0 μm/year). These rates are comparable with those previously reported in healthy individuals.[9] Given the cross-sectional design of these

Table 4 Relation of known cardiovascular risk factors with common carotid artery intima-media thickness *Z*-scores in the reference sub-populations

Sex	Risk factor	Sub-population without CVD						Sub-population with CVD (n = 4501)		
		Without treatment[a] (n = 14 609)			With treatment[a] (n = 5761)					
		β	95% CI	*P*-value	β	95% CI	*P*-value	β	95% CI	*P*-value
Men	Systolic pressure (10 mmHg)	0.111	0.093; 0.128	<0.001	0.070	0.045; 0.094	<0.001	0.080	0.055; 0.106	<0.001
	Current smoking (yes)	0.248	0.185; 0.312	<0.001	0.143	0.026; 0.259	0.016	0.100	−0.013; 0.213	0.082
	Diabetes (yes)	0.189	0.046; 0.332	0.010	0.056	−0.053; 0.166	0.315	0.108	−0.055; 0.271	0.192
	Total-to-HDL cholesterol ratio (unit)	0.051	0.029; 0.073	<0.001	0.022	−0.006; 0.049	0.118	0.008	−0.028; 0.044	0.660
	Body mass index (kg/m^2)	0.041	0.033; 0.049	<0.001	0.036	0.024; 0.048	<0.001	0.028	0.013; 0.042	<0.001
	Use of BP-lowering medication (yes)	–	–	–	–	–	–	−0.059	−0.161; 0.044	0.264
	Use of lipid-lowering medication (yes)	–	–	–	–	–	–	−0.182	−0.287; −0.077	0.001
	Use of glucose-lowering medication (yes)	–	–	–	–	–	–	−0.137	−0.370; 0.096	0.248
Women	Systolic pressure (10 mmHg)	0.097	0.080; 0.113	<0.001	0.100	0.078; 0.123	<0.001	0.101	0.068; 0.134	<0.001
	Current smoking (yes)	0.111	0.040; 0.181	0.002	0.204	0.078; 0.331	0.002	−0.107	−0.269; 0.054	0.192
	Diabetes (yes)	0.189	0.020; 0.359	0.029	0.010	−0.109; 0.128	0.872	0.052	−0.161; 0.265	0.633
	Total-to-HDL cholesterol ratio (unit)	0.043	0.016; 0.069	0.002	0.021	−0.016; 0.059	0.260	0.016	−0.034; 0.065	0.534
	Body mass index (kg/m^2)	0.017	0.010; 0.024	<0.001	0.010	0.000; 0.020	0.040	0.007	−0.008; 0.022	0.387
	Use of BP-lowering medication (yes)	–	–	–	–	–	–	0.072	−0.062; 0.205	0.292
	Use of lipid-lowering medication (yes)	–	–	–	–	–	–	−0.102	−0.250; 0.046	0.178
	Use of glucose-lowering medication (yes)	–	–	–	–	–	–	0.109	−0.209; 0.427	0.501

The regression coefficient β represents the increase in CCIMT (in SD from the healthy population mean among individuals of the same age and sex) per unit increase in each risk factor. βs were obtained from multivariable regression models including all risk factors and age.

[a]BP-, lipid-, and glucose-lowering treatment. Risk factor data available for the sub-populations without CVD and without treatment, without CVD with treatment, and with CVD, respectively, were n = 13 585, 5501, and 4196 for systolic pressure, n = 14 561, 5730, and 4474 for current smoking, n = 14 482, 5734, and 4425 for diabetes, n = 12 871, 5482, and 4078 for total-to-HDL cholesterol ratio, and n = 14 556, 5717, and 4458 for body mass index. Missing values were imputed before analyses (for details, please see Statistical analyses in the Methods section).

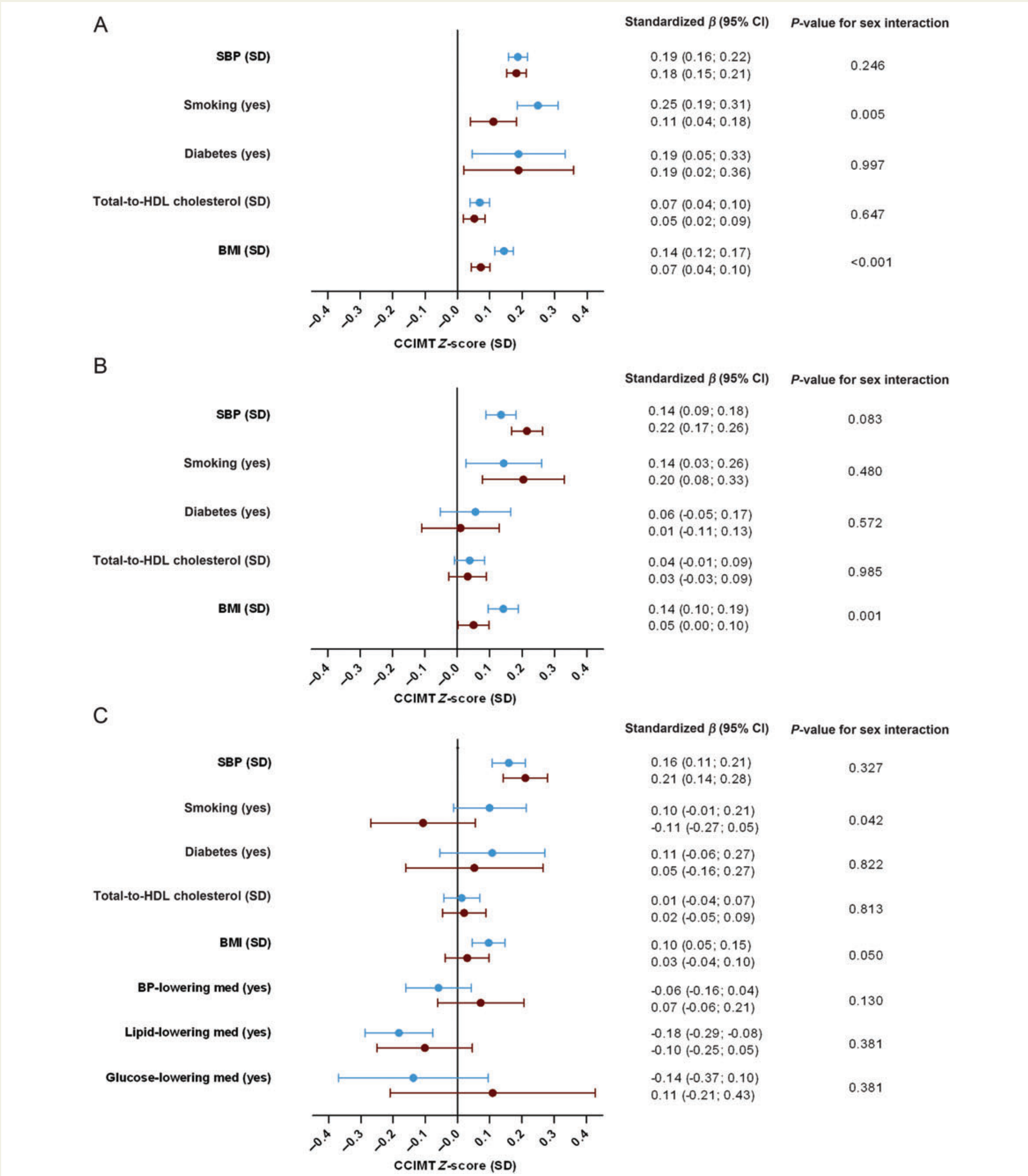

Figure 3 Point estimates and 95% confidence intervals represent the increase in common carotid artery intima-media thickness (CCIMT) *Z*-score (in SD from the healthy population mean) per SD increase (or for presence vs. absence) in risk factor resulting from a multivariable regression model including all risk factors and age. Data in blue and red concern men and women, respectively. BMI, body mass index; BP, blood pressure; med, medication; SBP, systolic blood pressure. (*A*) Reference sub-population without cardiovascular disease (CVD) or treatment. (*B*) Reference sub-population without cardiovascular disease with BP-, lipid-, and/or glucose-lowering treatment. (*C*) Reference sub-population with cardiovascular disease. Risk factor data available for the sub-population without cardiovascular disease and without treatment, without cardiovascular disease with treatment and with cardiovascular disease, respectively, were $n = 13\,585$, 5501, and 4196 for SBP, $n = 14\,561$, 5730, and 4474 for smoking, $n = 14\,482$, 5734, and 4425 for diabetes, $n = 12\,871$, 5482, and 4078 for total-to-HDL cholesterol, and $n = 14\,556$, 5717, and 4458 for BMI. Missing values were imputed before analyses (for details, please see Statistical analyses in the Methods section).

Table 5 Two examples of hypothetical subjects and their estimated common carotid artery intima-media thickness percentile

	Cardiovascular risk factors	Coefficient[a]	Observed[b]	Coefficient × observed
Men	Intercept = −2.604[c]			
	Age (10 years)[d]	0.020	50	0.100
	SBP (10 mmHg)	0.111	160	1.776
	Smoking (yes)	0.248	Yes (1)	0.248
	Diabetes (yes)	0.189	No (0)	0
	Total-to-HDL cholesterol ratio (unit)	0.051	7.2	0.367
	BMI (kg/m^2)	0.041	35	1.435
	Estimated CCIMT *Z*-score[f]			1.322
	Percentile[e]			91st
Women	Intercept = −1.507[c]			
	Age (years)[d]	−0.027	50	−0.135
	SBP (10 mmHg)	0.097	130	1.261
	Smoking (yes)	0.111	No (0)	0
	Diabetes (yes)	0.189	No (0)	0
	Total-to-HDL cholesterol ratio (unit)	0.043	3.9	0.168
	BMI (kg/m^2)	0.017	24	0.408
	Estimated CCIMT *Z*-score[f]			0.195
	Percentile[e]			58th

Note that these coefficients are expressed per 10 years and 10 mmHg, respectively, and therefore the products were computed as 50/10 × 0.020 (man) or 50/10 × −0.027 (woman) and 160/10 × 0.111 (man) or 130/10 × 0.097 (woman).
[a]Multiple linear regression coefficients for each risk factor (retrieved from *Table 4*).
[b]Hypothetical risk factor values for a male and female subject.
[c]The intercepts provided here are those associated with the regression model in *Table 4*.
[d]The coefficient for age reflects the residual influence of age on the CCIMT *Z*-score that was not already accounted for by equations (1) to (4) in this sub-population.
[e]Percentiles for each calculated *Z*-score can be retrieved by any standard normal distribution (*Z*) table.
[f]Estimated CCIMT *Z*-score was calculated as the sum of the intercept and the individual coefficient by risk factor products and compares individual's value to mean values among healthy subjects from the same age and sex.

studies, these data need to be interpreted with caution, because these may misestimate the longitudinal rates of change in CCIMT within individuals. Indeed, considerably higher rates of change in CCIMT have been reported in individuals from the longitudinal ARIC study (8.6 and 9.1 μm/year in men and women, respectively, age 45–64 years at baseline)[31] and in patients from control groups enrolled in lipid-lowering trials (14.7 μm/year, age ≥45 years),[4] but these CCIMT data were not obtained with echotracking techniques as included in the present study. Although large-scale data on CCIMT progression rates among individuals who are and remain healthy (i.e. free of CV-RFs and CVD) are currently lacking, the rates we reported for the healthy sub-population were quite similar to those described in two well-characterized longitudinal cohorts of young and healthy adults, despite the different methods of CCIMT assessment used in these studies.[32,33]

In the sub-population without prior CVD and treatment, we found that SBP, smoking, diabetes, total-to-HDL cholesterol ratio, and BMI were significant determinants of higher CCIMT both in men and women, an observation that is largely in line with previous studies.[9,31,34,35] Systolic blood pressure, smoking, and diabetes were more strongly associated with CCIMT than total-to-HDL cholesterol and BMI, suggesting that therapy targeting the former CV-RFs may be more effective in reducing CCIMT than targeting the latter. However, whether (treatment- and/or lifestyle-induced) changes in SBP, smoking, and glycaemia are also more strongly associated with CCIMT (and/or changes in CCIMT) than changes in cholesterol and BMI remains unclear and needs to be further investigated. The confidence intervals around the association estimates for diabetes and smoking were wider than those for the other CV-RFs considered. Factors such as the dichotomous scale (vs. continuous in other CV-RFs), but also the low prevalence of (untreated) diabetes in this study population (4 and 3% in men and women, respectively), differences in the definition of diabetes across centres (e.g. based on self-reports vs. OGTT tests), and self-reported data on smoking may have influenced the precision of these estimates.

The fact that the interaction between age and SBP was observed only in the absence of treatment and/or prior CVD suggests that age represents partly the time of exposition to CV-RFs and thereby truly represents the natural history of CV-RFs, explaining the lack of such interaction in the presence of treatment or prior CVD. Given the large number of interactions tested (36 in total), however, we cannot discard the possibility that the interactions between age and SBP may be spurious.

CV-RFs such as diabetes and total-to-HDL cholesterol ratio (in the sub-population with prior CVD and/or treatment) and also smoking (in the sub-population with CVD) were not associated with CCIMT *Z*-scores. These results may illustrate the phenomenon of index event bias,[36] resulting in differential risk factors for disease after an event (the index event) has occurred, and possible post-event lifestyle and/or treatment changes that may mask the 'effects' of the traditional CV-RFs. Further prospective (intervention) studies are required to fully address the question of how and why treatment may change the associations between CV-RFs and CCIMT.

The strength of the associations of some CV-RFs with CCIMT *Z*-scores differed between sexes such that BMI (in all subpopulations) and smoking (except in the sub-population without prior CVD but on treatment) were more strongly associated with increases in CCIMT percentiles (in the healthy population) in men than in women. Previous studies have also reported stronger associations of smoking[9,31] with CCIMT in men than in women. However, our findings seem not to link directly to the sex-specific associations between CV-RFs and incident CVD as reported in (recent meta-analyses of) prospective cohort studies.[37–42] For instance, smoking and diabetes were stronger RFs for incident coronary heart disease in women than in men,[37–39] whereas no such significant sex interactions have been reported in the associations of BMI and SBP with incident myocardial infarction and stroke.[40–42] The underlying pathophysiological mechanisms explaining sex differences in the impact of CV-RFs on CCIMT and/or CVD remain largely unknown and the current results may therefore only be used for hypothesis-generating purposes.

The influence of carotid diameter, an important arterial property in the context of arterial remodelling,[43] was not taken into account in the current study. Studies investigating the influence of carotid diameter on the associations between CCIMT and incident CVD have shown that either adjustment for diameter or calculation of a wall cross-sectional area ('arterial mass') yielded associations with myocardial infarction[43,44] and stroke[43] similar to those obtained using CCIMT values alone. Including diameter may thus be necessary in aetiological studies investigating carotid artery remodelling (possibly maladaptive) processes, which are also associated with poorer cardiovascular outcome, rather than in those investigating atherosclerosis in general.

This study has some limitations. First, we standardized differences in techniques between studies/centres by first adjusting CCIMT for all potential physiological/pathological factors supposed to influence CCIMT, surmising that the residual differences were of methodological origin. However, this calibration may still have been sub-optimal because of non-standardization of measurement in those factors that might transmit into calibration or because hidden confounders might have been missed. Nevertheless, these limitations also exist in real life and thus improve the external validity of our results. Second, several studies have suggested that ethnicity[8,10,45] and latitude[34] may influence CCIMT values. We did not examine the influence of these factors in the present study because we lacked sufficient variability to do so. Specifically, the bulk of the data in the current study originated from a 'Caucasian' (northern) European population. The potential influence of ethnicity and/or latitude on CCIMT values, however, may, to a great extent, have been captured by differences in CV-RFs between individuals, which we did examine. Last, in the present study we chose to include CCIMT data obtained using pure echotracking (88% of the data) or related techniques (12%) only, thus the present results might not fully apply to CCIMT data obtained by manual or other automated (imaging) edge-detection systems if not scaled against echotracking techniques. However, age- and sex-specific percentiles for CCIMT presented herein are comparable with those from smaller studies reported previously with CCIMT data obtained using other automated edge-detection systems.[9]

In conclusion, we estimated age- and sex-specific percentiles of CCIMT in a healthy population and assessed the influence of CV-RFs on CCIMT *Z*-scores, which enables comparison of CCIMT values for (patient) groups with different cardiovascular risk profiles, helping interpretation of such measures obtained both in research and clinical settings.

Contribution of the participating centres

Most of data management and statistical analysis have been performed by L.E., during her PhD project, under the supervision of I.F., C.G.S., C.D.S., P.B., and S.L. The contribution of the various centres participating in the 'Reference Values for Arterial Measurements Collaboration' was the following: conception and design of the research: L.E., I.F., C.D.S., P.B., and S.L.; acquisition of the data: all; analysis and interpretation of the data: all; statistical analysis: L.E., I.F., and P.B.; funding: S.L.; supervision: I.F., C.D.S., P.B., and S.L.; draft of the manuscript: L.E., I.F., C.D.S., P.B., and S.L.; important critical revision of the manuscript for important intellectual content: J.-P.E., L.v.B., P.S., M.B., J.F., C.G., and R.J.; other: most authors participated in an interim meeting during which the methods and strategies for managing and conducting the project were agreed upon.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

Appendix

Table A1 Author list and participating centres

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Continued

Table A1 (Continued)

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BE, Belgium; BR, Brazil; CDN, Canada; CH, Switzerland; CN, China; CZ, Czech Republic; D, Germany; F, France; H, Hungary; I, Italy; LT, Lithuania; N, Norway; NL, The Netherlands; PL, Poland.

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