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Common Carotid Artery Intima-Media Thickness: The Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) Study Results

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Key Words

Atherosclerosis · Cardiovascular risk factors · Common carotid intima-media thickness · Carotid plaque · Intima-media thickness reference values

Abstract

Background: Measurement of far wall common carotid artery intima-media thickness (CCAIMT) has emerged as a predictor of incident cardiovascular events. The Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) study was the first large-scale population-based assessment of both CCAIMT and cardiovascular risk factor prevalence in 7 Latin American cities; the relationship between CCAIMT and cardiovascular risk markers was assessed in these urban Latin American centers. ***Methods:*** CARMELA was a cross-sectional, population-based, observational study using stratified, multistage sampling. The participants completed a questionnaire, were evaluated in a clinical visit and underwent carotid ultrasonography. Clinical measurements were obtained by health personnel trained, certified and supervised by CARMELA investigators. Mannheim intima-media thickness consensus guidelines were followed for measurement of CCAIMT. ***Results:*** In all cities and for both sexes, CCAIMT increased with higher age. CCAIMT was greater in the presence of cardiovascular risk factors than in their absence. In all cities, there was a statistically significant linear trend between increasing CCAIMT and a growing number of cardiovascular risk factors ($p < 0.001$). After adjustment for age and sex, metabolic syndrome was strongly associated with increased CCAIMT ($p < 0.001$ in all cities), as were hypercholesterolemia, obesity and diabetes ($p < 0.001$ in most cit-

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ies). By multivariate analysis, hypertension was independently associated with an increase in CCAIMT in all cities ($p < 0.01$). ***Conclusions:*** CARMELA was the first large-scale population study to provide normal CCAIMT values according to age and sex in urban Latin American populations and to show CCAIMT increases in the presence of cardiovascular risk factors and metabolic syndrome.

Introduction

Atherosclerosis, a progressive disease with an insidious onset, is the leading cause of cardiovascular morbidity and mortality worldwide. In more than half of the individuals with significant cardiovascular disease, the initial presentation is an acute event, such as a myocardial infarction or acute coronary syndrome [1]. Unfortunately, by that point in the disease process, substantial morbidity is present and patients are at high risk of poor outcomes and increased mortality.

Thickening of the intima-media of the peripheral blood vessels, including the carotid arteries, occurs even in the early stages of atherosclerosis when most patients do not experience overt symptoms of cardiovascular disease. Intima-media thickening and plaque formation precede the first clinical event by as much as a decade or more. As studies have correlated histological and angiographic measurements of change in vascular structure with the extent of coronary artery disease [1, 2], noninvasive measures of atherosclerotic changes, such as ultrasonography, hold promise as screening tools for the detection of early atherosclerosis [3].

The associations of increased common carotid artery intima-media thickness (CCAIMT) with the presence of cardiovascular risk factors such as hypertension, obesity, diabetes, smoking and dyslipidemia, have been well established [4–8]. Greater mean CCAIMT is predictive of an increased relative risk of coronary heart disease and stroke [9–13]. A recent meta-analysis found that the relative risks of myocardial infarction and stroke were 1.15 [95% confidence interval (CI) = 1.12–1.17) and 1.18 (95% CI = 1.16–1.21) per 0.10-mm CCAIMT increase, respectively [9]. CCAIMT has been shown to be a predictor of cardiovascular morbidity and mortality in secondary prevention patients; in a long-term study of men who had previously had coronary artery bypass graft surgery, the relative risk of nonfatal myocardial infarction or coronary death was 2.2 (95% CI = 1.4–3.6) and the relative risk of any coronary event was 3.1 (95% CI = 2.1–4.5) during the average of 8 years of follow-up for each 0.03-mm increase in CCAIMT per year [11]. Because of the strong predictive value of CCAIMT, it is now used as a surrogate endpoint in cardiovascular studies measuring the effectiveness of statins and blood pressure drugs [14–17].

Despite the correlation of CCAIMT with cardiovascular risk, epidemiologic studies report different normal CCAIMT values depending on the population and region studied [18]. Ethnic differences in CCAIMT values require that CCAIMT normal distribution within each population be defined in order for CCAIMT to be used as a cardiovascular risk assessment tool.

The objective of the Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) study was to evaluate and compare cardiovascular risk factor prevalence in 7 major Latin American cities: Barquisimeto, Bogotá, Buenos Aires, Lima, Mexico City, Quito and Santiago. CCAIMT data were collected to establish normal distributions and to evaluate associations between CCAIMT and the risk factors studied.

Methods

Study Design

CARMELA was a cross-sectional, population-based, observational study using stratified, multistage sampling, designed to enroll approximately 200 participants aged 25–64 years in 10-year age-sex groups in each of the 7 Latin American cities (about 1,600 participants per city). Between September 2003 and August 2005, the participants completed a questionnaire detailing demographic and cardiovascular risk factors. Designated health care institutions conducted clinical and anthropometric assessments. Clinical measurements were obtained by health personnel trained, certified and supervised by CARMELA investigators. The detailed study design and methodology have been published elsewhere [19].

Definitions

Modifiable risk factors were defined as: hypertension, blood pressure ≥140/90 mm Hg or current pharmacologic blood-pressure-lowering treatment; hypercholesterolemia, total cholesterol ≥240 mg/dl or current pharmacologic lipid-lowering treatment; diabetes, fasting blood glucose >126 mg/dl or self-reported diabetes; smoking, current daily or occasional consumption of cigarettes, cigars or pipe tobacco; obesity, body mass index ≥30. Nonmodifiable risk factors were defined as: personal cardiovascular disease history, prior stroke or myocardial infarction, self-reported; family cardiovascular disease history, father or brother had fatal or nonfatal myocardial infarction before the age of 55 years, or mother or sister had fatal or nonfatal myocardial infarction before the age of 65; early menopause, menopause before the age of 40. Herein, conventional cardiovascular risk factors include modifiable and nonmodifiable risk factors unless otherwise stated. Metabolic syndrome (using National Cholesterol Education

Program Adult Treatment Panel III criteria [20]) was defined as the presence of ≥3 of the following: waist circumference >102 cm in men, >88 cm in women; triglycerides ≥150 mg/dl; high-density lipoprotein cholesterol <40 mg/dl in men, <50 mg/dl in women; blood pressure ≥130/85 mm Hg, and fasting plasma glucose ≥110 mg/dl or self-reported diabetes.

Ultrasonography

All centers used linear-array 7.5-MHz transducers and ultrasound apparatuses that were no older than 7 years and M'AthStd® software (Intelligence in Medical Technologies, Paris, France) to automatically measure CCAIMT. The ultrasound methodology of the study was the same as that used in the Paroi Artérielle et Risque Cardiovasculaire (PARC) study, published previously [21]. Measurement of far wall CCAIMT followed the conventions established by the Mannheim intima-media thickness consensus [22, 23]. Briefly each sonographer had to send 3 test patients to be certified before starting inclusion of the first patient in the study. The measurements of CCAIMT were checked by the sonographers, who were required to measure CCAIMT in order to get a quality index >0.5 on a 10-mm length of the far wall of the CCA to improve the quality of data acquisition.

A central laboratory performed all data analyses (Intelligence in Medical Technologies). The readers who performed CCAIMT measurements were blinded to the identity, age and sex of the participants. They had no information on the site or sonographer who had performed the examination. Reproducibility of the method, published previously, showed an intraclass correlation coefficient of 0.97 [21].

Statistical Analysis

The first part of analysis was restricted to participants free of cardiovascular risk factors in order to determine normal CCAIMT values [mean of right and left common carotid arteries (CCA)] with 95% CI. The CCAIMT means (95% CI) were calculated according to age and sex strata, by city and in the overall population. Linear regression analysis was used to measure the impact of age on CCAIMT, taking into account the CARMELA sampling design. The change in mean CCAIMT between successive age groups (after adjustment for sex) was estimated, and the heterogeneity across cities was tested by introducing an interaction term into the model.

The second part of analysis included all CARMELA participants; the impact of the presence of the metabolic syndrome, and the presence, number and type of cardiovascular risk factors on mean CCAIMT was evaluated using multiple linear regression analyses for sample survey data. All analyses were adjusted for age and sex.

Statistical testing was done with a 2-tailed S level of 0.05. The data were analyzed using SAS software, release 9.1 (SAS Institute, Cary, N.C., USA).

Results

A total of 11,550 participants enrolled in CARMELA were evaluated. The basic demographics and cardiovascular risk factor prevalences for each city have been presented elsewhere [19]. Ultrasonography was performed on 10,826 of 11,550 participants (93.7%) – 5,021 men and 5,805 women. After the exclusion of 410 participants with poor sonogram quality index due to obesity, large neck and deep situation or tortuosities of the CCA (205 for right CCA, 168 for left CCA and 37 for both CCA), the mean of right and left CCAIMT measurements was available for 10,416 participants. Of these, overall 29% (n = 3,071) had no cardiovascular risk factors, ranging from 19% in Santiago (n = 311) to 39% in Lima (n = 585).

Plaque Prevalence

The plaque prevalence ranged from 4.5% (95% CI = 3.3–5.7) in Mexico City to 14% (95% CI = 11.8–16.2) in Barquisimeto [19].

Normal CCAIMT Values

The mean CCAIMT for the overall study population was 0.648 mm (95% CI = 0.643–0.653) and ranged between 0.597 mm (95% CI = 0.592–0.601) in Barquisimeto to 0.742 mm (95% CI = 0.737–0.748) in Buenos Aires. Table 1 shows the normal values for CCAIMT [mean ± standard error of the mean (SEM)] derived from participants without risk factors across sex and age groups, overall and by cities; percentile distributions are available in the supplementary material (online suppl. tables, www. karger.com/doi/10.1159/000320264). CCAIMT increased with age in linear fashion in both men and women; CCAIMT was higher in men than in women in all age groups except in Barquisimeto, Buenos Aires and Lima, where the reverse was true for participants 55–64 years of age. After adjustment for the effect of sex on CCAIMT, it was estimated that the mean CCAIMT increased in successive age groups by 0.031 mm (95% CI = 0.026–0.036) in Barquisimeto, 0.045 mm (95% CI = 0.034–0.051) in Bogotá, 0.037 mm (95% CI = 0.029–0.045) in Buenos Aires, 0.038 mm (95 % CI = 0.034–0.043) in Lima, 0.014 mm (95% CI = 0.010–0.018) in Mexico City, 0.050 mm (95% CI = 0.043–0.056) in Quito and 0.051 mm (95% CI = 0.044–0.058) in Santiago. The age-dependent increment in CCAIMT was smallest in Mexico City; this resulted in a significant difference in age effect across all cities.

Impact of Cardiovascular Risk Factors on CCAIMT

Significantly larger mean values for CCAIMT were found in the group with conventional cardiovascular risk factors in each of the cities than in the group without (data not shown). In addition, CCAIMT increased gradually with the number of cardiovascular risk factors (p for

Table 1. Mean CCAIMT values (millimeters) in men and women without risk factors by age group (years)

	Overall (n = 3,071)	Barquisimeto (n = 565)	Bogotá (n = 414)	Buenos Aires (n = 287)	Lima (n = 585)	Mexico City (n = 498)	Quito (n = 411)	Santiago (n = 311)
Men								
25–34	0.601 (0.594–0.608)	0.550 (0.537–0.563)	0.564 (0.552–0.576)	0.691 (0.674–0.709)	0.571 (0.560–0.582)	0.671 (0.661–0.681)	0.648 (0.631–0.665)	0.522 (0.507–0.538)
35–44	0.631 (0.623–0.640)	0.576 (0.558–0.594)	0.585 (0.570–0.600)	0.703 (0.678–0.727)	0.614 (0.598–0.629)	0.680 (0.669–0.690)	0.693 (0.671–0.714)	0.592 (0.567–0.616)
45–54	0.671 (0.661–0.680)	0.613 (0.593–0.633)	0.653 (0.630–0.677)	0.760 (0.725–0.795)	0.647 (0.630–0.663)	0.711 (0.693–0.729)	0.711 (0.686–0.736)	0.631 (0.597–0.665)
55–64	0.719 (0.705–0.732)	0.649 (0.620–0.677)	0.717 (0.679–0.756)	0.780 (0.738–0.823)	0.685 (0.659–0.710)	0.728 (0.700–0.752)	0.824 (0.789–0.858)	0.672 (0.642–0.701)
Women								
25–34	0.591 (0.586–0.596)	0.549 (0.539–0.558)	0.547 (0.538–0.557)	0.668 (0.657–0.680)	0.571 (0.564–0.578)	0.671 (0.665–0.678)	0.617 (0.606–0.629)	0.515 (0.506–0.523)
35–44	0.612 (0.606–0.618)	0.567 (0.556–0.578)	0.573 (0.560–0.585)	0.701 (0.686–0.716)	0.601 (0.589–0.613)	0.678 (0.669–0.687)	0.654 (0.636–0.672)	0.567 (0.555–0.579)
45–54	0.665 (0.656–0.674)	0.603 (0.589–0.616)	0.651 (0.629–0.674)	0.739 (0.716–0.762)	0.651 (0.635–0.667)	0.689 (0.677–0.702)	0.731 (0.712–0.750)	0.593 (0.567–0.620)
55–64	0.706 (0.694–0.717)	0.667 (0.644–0.690)	0.666 (0.641–0.692)	0.786 (0.744–0.827)	0.685 (0.659–0.712)	0.714 (0.692–0.736)	0.774 (0.745–0.802)	0.661 (0.630–0.692)

Figures in parentheses are 95% CI.

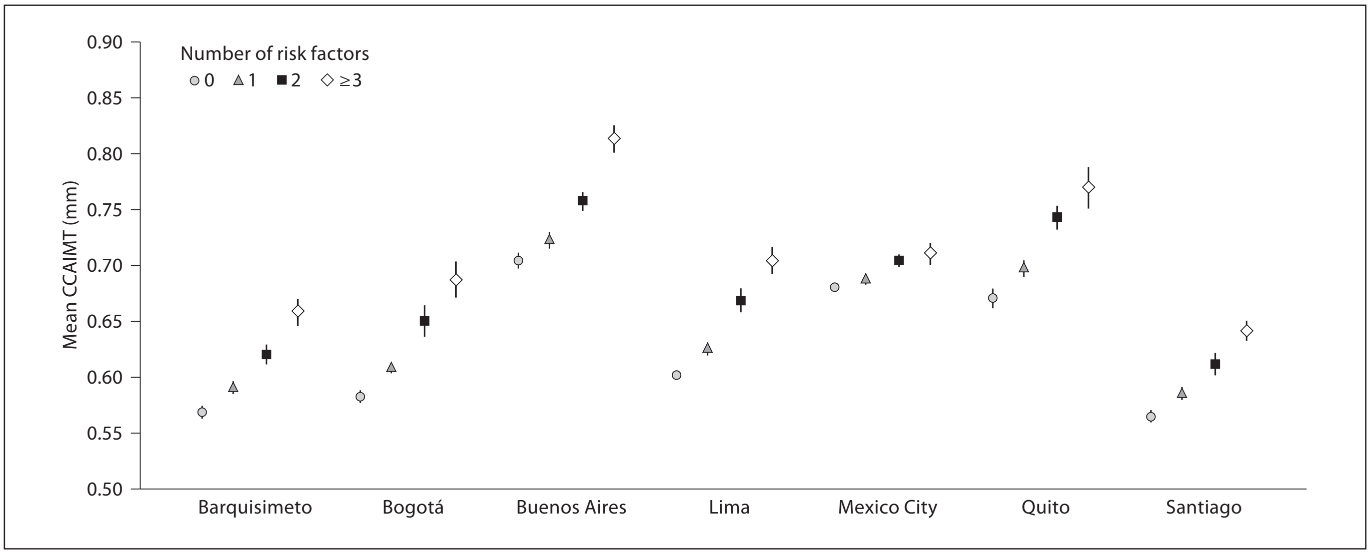

Fig. 1. Age- and sex-adjusted mean CCAIMT (95% CI) by number of conventional cardiovascular risk factors and city. Risk factors include hypercholesterolemia, hypertension, diabetes, obesity, current smoking, personal cardiovascular disease history, family cardiovascular disease history and early menopause.

trend <0.001, fig. 1). We found a significant heterogeneity in the relationship between the number of cardiovascular risk factors and CCAIMT across cities (p for interaction <0.001), again related to smaller increments with increasing number of risk factors in Mexico City than in the other cities (fig. 1). The age- and sex-adjusted change in CCAIMT per increase in number of risk factors was 0.003 mm (95% CI = 0.001–0.006) in Mexico City compared with 0.015 mm (95% CI = 0.011–0.019) in Barquisimeto, 0.013 mm (95% CI = 0.008–0.017) in Bogotá,

Table 2. Age- and sex-adjusted mean CCAIMT (millimeters) ± SEM by risk factor in each city

	Barquisimeto	Bogotá	Buenos Aires	Lima	Mexico City	Quito	Santiago
Hypercholesterolemia							
Absent	0.617 ± 0.002	0.635 ± 0.002	0.747 ± 0.002**	0.644 ± 0.002	0.703 ± 0.002	0.726 ± 0.003**	0.614 ± 0.002
Present	0.631 ± 0.006	0.651 ± 0.005	0.765 ± 0.005	0.660 ± 0.005	0.697 ± 0.003	0.743 ± 0.005	0.619 ± 0.004
Hypertension							
Absent	0.607 ± 0.002***	0.630 ± 0.002***	0.743 ± 0.003**	0.640 ± 0.002***	0.697 ± 0.002***	0.723 ± 0.002***	0.607 ± 0.002***
Present	0.640 ± 0.003	0.668 ± 0.005	0.768 ± 0.004	0.682 ± 0.005	0.724 ± 0.004	0.775 ± 0.007	0.635 ± 0.004
Obesity							
Absent	0.610 ± 0.002***	0.633 ± 0.002***	0.745 ± 0.002***	0.636 ± 0.002***	0.700 ± 0.002	0.726 ± 0.003*	0.609 ± 0.002***
Present	0.640 ± 0.003	0.655 ± 0.004	0.776 ± 0.005	0.680 ± 0.003	0.705 ± 0.003	0.748 ± 0.005	0.631 ± 0.003
Diabetes							
Absent	0.616 ± 0.002	0.635 ± 0.002	0.749 ± 0.002	0.645 ± 0.002	0.700 ± 0.002	0.729 ± 0.002	0.613 ± 0.002
Present	0.636 ± 0.007	0.656 ± 0.006	0.777 ± 0.009	0.672 ± 0.008	0.713 ± 0.005	0.743 ± 0.008	0.631 ± 0.007
Current smoking							
Absent	0.618 ± 0.003	0.638 ± 0.002	0.748 ± 0.003**	0.644 ± 0.002	0.701 ± 0.002	0.729 ± 0.003	0.614 ± 0.003
Present	0.616 ± 0.004	0.636 ± 0.004	0.756 ± 0.003	0.652 ± 0.003	0.702 ± 0.003	0.731 ± 0.004	0.616 ± 0.003
Personal CVD history							
Absent	0.616 ± 0.002**	0.637 ± 0.002	0.749 ± 0.002**	0.645 ± 0.002	0.701 ± 0.002	0.729 ± 0.002	0.614 ± 0.002
Present	0.652 ± 0.009	0.640 ± 0.010	0.781 ± 0.010	0.671 ± 0.008	0.714 ± 0.012	0.739 ± 0.009	0.627 ± 0.008
Family CVD history							
Absent	0.617 ± 0.002	0.637 ± 0.002	0.747 ± 0.002**	0.645 ± 0.002	0.702 ± 0.002	0.728 ± 0.002**	0.615 ± 0.002
Present	0.623 ± 0.004	0.641 ± 0.006	0.765 ± 0.005	0.654 ± 0.006	0.695 ± 0.005	0.745 ± 0.007	0.616 ± 0.004
Early menopause							
Absent	0.611 ± 0.002	0.635 ± 0.003	0.737 ± 0.003	0.642 ± 0.002	0.693 ± 0.002	0.730 ± 0.003***	0.605 ± 0.002
Present	0.621 ± 0.009	0.620 ± 0.014	0.730 ± 0.015	0.649 ± 0.011	0.690 ± 0.008	0.766 ± 0.014	0.594 ± 0.011

CVD = Cardiovascular disease; hypertension = blood pressure ≥140/90 mm Hg or current blood pressure-lowering treatment; hypercholesterolemia = total cholesterol ≥240 mg/dl or current lipid-lowering treatment; diabetes = fasting blood glucose >126 mg/dl or self-reported diabetes; smoking = current daily or occasional consumption of cigarettes, cigars or pipe tobacco, or cessation within the previous 12 months; obesity = body mass index ≥30; personal CVD history = prior stroke or myocardial infarction, self-reported; family CVD history = father or brother had fatal or nonfatal myocardial infarction before age 55 years, or mother or sister had fatal or nonfatal myocardial infarction before age 65 years; early menopause = menopause before age 40 years.

Early menopause: data for women. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ for absent versus present risk factors in multivariate analysis including age, sex and all risk factors described in the table.

0.016 mm (95% CI = 0.012–0.021) in Buenos Aires, 0.018 mm (95% CI = 0.015–0.022) in Lima, 0.015 mm (95% CI = 0.010–0.020) in Quito and 0.009 mm (95% CI = 0.006–0.013) in Santiago.

The CCAIMT values in the presence and absence of cardiovascular risk factors are displayed in table 2. The age- and sex-adjusted mean CCAIMT was greater in the presence of risk factors, particularly hypertension, obesity and diabetes. In multivariate analysis, hypertension was the only modifiable risk factor independently associated with an increase in CCAIMT in all cities. Obesity was also a consistent predictor of CCAIMT. The CCAIMT variance was explained by the fully adjusted model and ranged from 16.8% (Mexico City) to 46.8% (Lima). When data from all cities were combined (and after adjustment for city CCAIMT differences), age, sex, hypertension, obesity, dyslipidemia and diabetes were independent predictors of CCAIMT (all p values <0.01).

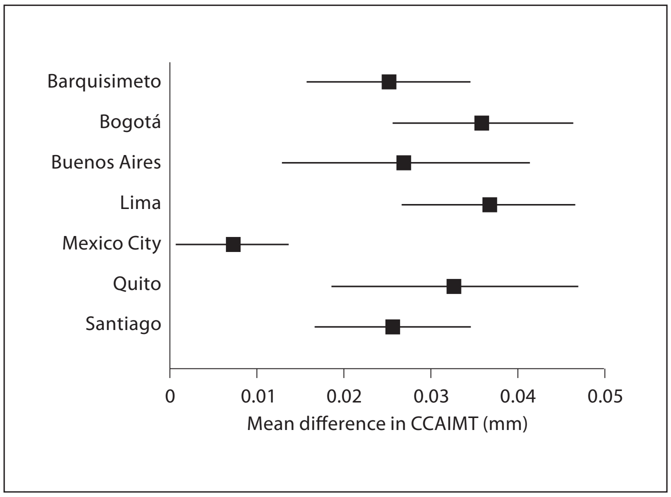

Fig. 2. Age- and sex-adjusted difference in mean CCAIMT (95% CI) between participants with and without metabolic syndrome by city.

CCAIMT and Metabolic Syndrome

In each city, CCAIMT was strongly associated with metabolic syndrome ($p < 0.001$). The age- and sex-adjusted mean difference between the presence and absence of metabolic syndrome ranged from 0.0073 to 0.0366 mm across cities, with a significant heterogeneity attributed to Mexico City (fig. 2).

Discussion

Differences in intima-media thicknesses correlate with cardiovascular disease morbidity and mortality. Because normal CCAIMT values differ among world regions, countries and ethnic groups, it is important to establish the distribution in a particular population when using CCAIMT values as a marker of atherosclerosis [24, 25]. For instance, in the USA, blacks were found to have significantly greater CCAIMT than non-Hispanic whites, and non-Hispanic whites had significantly greater CCAIMT than Hispanics [26]. These differences remained significant after adjustment for traditional cardiovascular risk factors and insulin resistance, and may explain variation in cardiovascular risk in these populations. CARMELA was the first large-scale study of CCAIMT values and their association with cardiovascular risk in Latin American populations; CARMELA provides normal CCAIMT values for male and female adult age groups in each city against which individuals can be compared.

The comparability of intima-media measurements depends on the standardization of methods and measurements used. The CARMELA study used procedures recommended by the Mannheim Intima-Media Thickness Consensus [23], as did the PARC study in France [21, 27] and the PARC study in Asia, Africa/Middle East and Latin America (PARC-AALA) [18]. The PARC and PARC-AALA studies together included >7,000 participants, reported normal values for their populations, and confirmed the correlation between CCAIMT and the Framingham cardiovascular score. The age-, sex- and BMI-adjusted population mean CCAIMT (±SEM) for all participants in the Africa/Middle East/Latin American regions was 0.699 ± 0.004 mm [18], which is similar to that reported in the CARMELA population. All the mean values drawn from CARMELA are in the CI of the corresponding PARC study values.

Higher age and male sex were strongly associated with increased CCAIMT; the addition of other conventional cardiovascular risk factors resulted in further CCAIMT increases. The highest CCAIMT values occurred in Buenos Aires, which may be explained by that city's relatively high prevalence of hypertension, hypercholesterolemia and smoking relative to other cities [19, 28, 29]. The CARMELA study results confirm the relationship between intima-media thickness – in this case, CCAIMT – and conventional cardiovascular risk factors that has been observed in other populations. Also, as noted in other studies [4, 30, 31], the metabolic syndrome and individual modifiable risk factors, such as diabetes, hypertension and hypercholesterolemia, predicted an increase in CCAIMT almost uniformly across cities. Details concerning the association of increased CCAIMT and plaque in CARMELA participants with increasing numbers of components of the metabolic syndrome are reported elsewhere.

The age-dependent increment in IMT in Mexico City was only half of the increment of most other cities, and the influence of risk factors on IMT and the proportion of variance in IMT explained by vascular risk factors were smaller in Mexico City compared to all other cities. It is unlikely that genetics could explain the variations observed between the different samples. Hence, an unexplained bias cannot be excluded in the Mexican population.

Although smoking, a preventable risk factor, has been shown to produce increased intima-media thickness in other populations, this association was not evident in these Latin American populations, except in Buenos Aires and Lima.

In the 2 cities with the highest prevalence of cardiovascular risk factors, Buenos Aires and Santiago [19], the mean CCAIMT measurements were the highest and lowest, respectively, regardless of age and sex. These differences may be partly related to differing genetic factors or to unaccounted for survival bias. The consistency of the difference observed in CCAIMT between Buenos Aires and Santiago in all the age groups for men and women free of cardiovascular disease indicates that these and other possible factors need to be investigated further.

CARMELA provides normal values so that increased CCAIMT might be used to screen populations at risk of cardiovascular events. Further prospective studies evaluating CCAIMT as a marker for conglomerate cardiovascular risk (like the Framingham risk score) are needed in Latin America and in populations worldwide that differ by geography, ethnicity, lifestyle and socioeconomic status. Risk/benefit analyses are necessary to determine the value of CCAIMT as an effective screening and assessment tool, which, if confirmed, should help local public health and improve clinical efforts to reduce cardiovascular risk in Latin American populations.

Conclusion

Noninvasive measures such as carotid ultrasound may identify individuals at risk of cardiovascular disease and consequent morbidity and mortality. CARMELA is the first large-scale population study characterizing the distribution of CCAIMT in Latin American populations. Further analyses will help delineate the causes of the intergeographic variations observed in the 7 CARMELA cities, and long-term observational studies should assess the predictive value of CCAIMT for cardiovascular events in Latin American populations. With early identification of individuals at cardiovascular risk, public health, education and clinical strategies can promote appropriate treatment, thereby preventing long-term medical and socioeconomic consequences of that risk.

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Disclosure Statement

The authors have no conflict of interest.

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