Lack of Association Between Subclinical Hypothyroidism and Carotid–Femoral Pulse Wave Velocity in a Cross-Sectional Analysis of the ELSA–Brasil

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BACKGROUND
There is little available data on carotid–femoral pulse wave velocity (cf-PWV) in subjects with subclinical hypothyroidism (SCH). We aimed to analyze the association between SCH and cf-PWV using baseline data from the Brazilian Longitudinal Study of Adult Health (ELSA–Brasil).

METHODS
We included subjects with normal thyroid function (thyrotropin (TSH): 0.4–4.0 mIU/l, and normal free thyroxine (FT4: 0.8–1.9 ng/dl) and SCH (TSH > 4.0 mIU/l and normal FT4) evaluated for cf-PWV in a cross-sectional analysis. We excluded individuals using medications that interfere in thyroid function, antihypertensives, or diuretics, and subjects with chronic kidney disease or previous cardiovascular disease. Generalized linear and logistic regression models evaluated cf-PWV as a dependent variable and SCH as an independent variable, adjusted for cardiovascular risk factors.

RESULTS
Of 8,341 subjects (52.3% women), 7,878 (94.4%) were euthyroid and 463 (5.6%) showed SCH. The median age was 50 years (interquartile range: 44–56). The groups differed by age, sex, body mass index, glomerular filtration rate, and C-reactive protein. SCH was not associated with cf-PWV in the full-adjusted linear model ($\beta = -0.039$; $P = 0.562$) and with cf-PWV >75th percentile in the full-adjusted logistic model (odds ratio = 0.94; 95% confidence interval = 0.72–1.22).

CONCLUSION
In a large sample, SCH was not associated with increased cf-PWV.

Keywords: artery stiffness; blood pressure; cardiovascular risk factors; hypertension; pulse wave velocity; subclinical atherosclerosis; subclinical hypothyroidism; thyroid dysfunction.

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Subclinical hypothyroidism (SCH) has been associated with coronary heart disease risk and mortality,[1] as well as with surrogate markers of subclinical atherosclerosis, such as carotid intima-media thickness[2] and abdominal aortic calcification.[3,4] Increased levels of thyrotropin (TSH) even in range of SCH may be linked to hypertension,[5] dyslipidemia,[6] metabolic syndrome, and insulin resistance.[7]

In recent decades, the use of a new measurement of cardiovascular risk, the arterial stiffness assessed by pulse wave velocity (PWV) has been increasing.[8,9] A previous study has shown an association between raised PWV and an increasing risk of cardiovascular death, nonfatal myocardial infarction, and stroke.[10] A meta-analysis of 12 studies showed that an increase in aortic PWV of 1 m/s corresponded to an increase of 14% in total cardiovascular events, and 15% in cardiovascular and all-cause mortality even after multivariate adjustment for confounders.[11]

The possible influence of SCH on arterial stiffness may be explained by different pathways. Thyroid hormones have important effects on cardiac function. Therefore, in hypothyroidism, there is a decrease in cardiac contractility, cardiac output, heart rate, and left ventricular compliance as well as an increase in total peripheral vascular resistance that may be associated to an increase in arterial stiffness.[12,13] Although these effects on cardiac function are more clear in overt hypothyroidism,[14] some studies suggest they also occur in SCH.[5–7,15] SCH are also associated to other cardiovascular risk factors such as hypertension that is associated to increased arterial stiffness.[5–7,15] Thyroid hormones are also involved in vascular smooth cell relaxation as a direct effect as well as in the process of smooth cell calcification and both may be associated to an increase in arterial stiffness.[16,17]

There is little available data on the possible association between PWV and SCH.[18–22] Therefore, we conducted a

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cross-sectional evaluation of the association between SCH and carotid–femoral PWV (cf-PWV), using the baseline data of the Brazilian Longitudinal Study of Adult Health (ELSA–Brasil), a prospective cohort study in Brazil with both information on SCH and PWV.

METHODS

Study participants

This study is a cross-sectional analysis using baseline data of the ELSA–Brasil, collected from August 2008 to December 2010. We analyzed the association between SCH and subclinical atherosclerosis in subjects with SCH and individuals with normal thyroid function, using cf-PWV as a surrogate marker. Briefly, this study included 15,105 civil servants, aged 35–74 years, from 6 institutions in 6 different Brazilian cities, with the aim of determining the incidence of cardiovascular diseases and diabetes, and their associated risk factors.[23,24] The ELSA–Brasil protocol has been published elsewhere[23,24] and was approved at all 6 centers by the Institutional Review Boards for research on human participants, in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participants.

Definition of thyroid function

The TSH and free thyroxine (FT4) were dosed by a third generation immunoenzymatic assay (Siemens, Deerfield, IL) in serum obtained from venous blood samples after an overnight fast. FT4 levels were only evaluated in participants who presented altered TSH levels. In this study, the reference range levels were 0.4–4.0 mIU/l for TSH and 0.8–1.9 ng/dl for FT4, similar to those used in the National Health and Nutritional Examination Survey (NHANES III)[25] and recommended by Surks *et al.*[26]

Participants in ELSA–Brasil were classified in 5 categories of thyroid function, according to TSH and FT4 (if TSH was altered) levels and information on the use of medication to treat thyroid disorders: overt hyperthyroidism (low-serum TSH and high levels of FT4 or use of medication to treat hyperthyroidism), subclinical hyperthyroidism (low-serum TSH, normal levels of FT4, and no use of thyroid drugs), euthyroidism (normal TSH and no use of thyroid drugs), SCH (high TSH levels, normal levels of FT4, and no use of thyroid drugs), and overt hypothyroidism (high TSH and low FT4 levels or use of levothyroxine to treat hypothyroidism).

Exclusion of participants

Participants with overt thyroid disorders, those with subclinical hyperthyroidism, or those using any medication that could interfere with thyroid function, such as amiodarone, carbamazepine, carbidopa, phenytoin, furosemide, haloperidol, heparin, interferon, levodopa, lithium, metoclopramide, propranolol, primidone, rifampicin, or valproic acid, were excluded from the sample.[27] This analysis included only participants who were euthyroid or had SCH.

Similar to previous publications about PWV,[28,29] we excluded from the analysis participants who were under antihypertensive or diuretics use that can interfere with PWV.[30,31] We also excluded participants with chronic kidney disease (CKD), or with a previous history of angina, myocardial infarction, coronary heart disease myocardial revascularization, stroke, or heart failure.

Pulse wave velocity

Measurement of cf-PWV is described elsewhere.[30,31] We used an automatic and validated device (Complior, Artech Medicale, France), in a room with temperature between 20 °C and 24 °C. Before the cf-PWV measurement, blood pressure (BP) was measured in the supine position with an automatic device (Omron 705 CP, Japan) in the right arm. cf-PWV was calculated by dividing the distance from the suprasternal notch to the femoral pulse by the time lag between the carotid and femoral pulses. The value for each participant was the arithmetic average obtained in 10 consecutive cardiac cycles in regular heart rhythm. As the cf-PWV is influenced by the pressure inside the artery at the time of the test, cf-PWV was adjusted by the systolic BP measured immediately before the exam in the logistic and linear models.[30] A centralized Reading Center was responsible for validating the exams of all ELSA–Brasil participants.

Cardiovascular risk factors

Each participant was interviewed at the workplace, by trained personal and with strict quality control, and also visited the Research Center for clinical exams, conducted according to standard protocols.[31] The questionnaires addressed age, gender, self-reported race (White, Mixed, Black, Asian, Indigenous), smoking status (never, former, and current), and family history of cardiovascular and cerebrovascular disease. Physical activity was measured using the long form of the International Questionnaire for Physical Activity (IPAQ) and categorized as mild, moderate, and vigorous.[32] All prescription and medications taken for the prior 15-day period were reviewed.

Height and weight were measured using light clothes, and body mass index was calculated as weight divided by height in squared meters. Obesity was defined as body mass index ≥30 kg/m^2. We used sex-specific cutoffs for waist circumference (≥88 cm in women and ≥102 cm in men) to define abdominal obesity. BP measurements were taken using the validated Omron HEM 705CPINT oscillometric device. Three measurements were taken at 1-minute intervals, and the mean of the 2 latter measurements was considered as the participant's BP. We defined hypertension as use of antihypertensive medication, or systolic BP ≥140 mm Hg, or diastolic BP ≥90 mm Hg. Diabetes was defined as previous medical history of diabetes, use of medication to treat diabetes, fasting plasma glucose ≥126 mg/dl, 2-hour plasma glucose ≥200 mg/dl, or HbA_{1C} ≥6.5%. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥130 mg/dl or use of lowering cholesterol medications. Low high-density lipoprotein cholesterol was defined as high-density

lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women. Hypertriglyceridemia was defined as serum triglyceride levels ≥ 150 mg/dl. Urinary sodium was measured in a 12-hour urine sample.

CKD was defined as glomerular filtration rate <60 ml/min/1.73 m2 according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[33] as seen in previously published data about CKD in the ELSA–Brasil cohort.[34] Absolute 10-year cardiovascular risk was estimated using the Framingham Risk Score, according to criteria described elsewhere.[35]

Other laboratory tests

To measure fasting and postload glucose, we used the hexokinase method (ADVIA 1200, Siemens); for fasting and postload insulin, the immunoenzymatic assay; for glycated hemoglobin, high-performance liquid chromatography (HPLC) (Bio-Rad Laboratories, Hercules, CA); and for total and high-density lipoprotein cholesterol and triglycerides, the enzymatic colorimetric assay (ADVIA 1200, Siemens, Deerfield, IL). Low-density lipoprotein cholesterol was calculated using the Friedewald equation, except in participants with elevated triglyceride levels (>400 mg/dl), when the enzymatic colorimetric assay was used (ADVIA 1200, Siemens). High-sensitive C-reactive protein was measured by immunochemistry (nephelometry, Siemens). Creatinine, by the enzymatic colorimetric assay (Jaffé) (ADVIA 1200, Siemens). Overnight 12-hour urine collections was obtained and sodium was measured by potentiometry (ion-selective electrodes) (ADVIA Chemistry).

Statistical analysis

Continuous variables were expressed as mean and SD or median and interquartile range, and were compared using ANOVA or the Mann–Whitney *U* test, as deemed appropriate after assessing normality assumptions. Statistical normality was checked using the Kolmogorov–Smirnov test and Q–Q plots. Categorical variables were expressed as proportions and compared using the chi-square test.

Logistic regression models were built using cf-PWV as the dependent variable (categorized as ≤P 75th or > P 75th percentile) and SCH as the independent variable. Odds ratio and 95% confidence interval (95% CI) was presented as crude and adjusted. Model 1 was adjusted for age, sex, race, and systolic BP before cf-PWV. Model 2 was adjusted for variables in Model 1 plus smoking status, hypertension, diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides glomerular filtration rate by CKD-EPI, body mass index, and high-sensitive C-reactive protein. Further, we adjusted multivariate models for leisure time physical activity and sodium intake. Linear regression models were built using cf-PWV as a continuous variable in m/s. Data were presented as beta-coefficients and 95% CIs. Multiple linear models were adjusted by the same variables used in the logistic models. Further multivariate models adjusted for all variables in model 2 plus physical activity and urinary sodium were built. We further restricted the analysis to participants not using statins and aspirin.

Analyses were performed using SPSS 20.0 (IBM, Chicago, IL). P <0.05 was considered as significant, and all tests were 2-tailed.

RESULTS

Flow chart of study participants and exclusions are presented in Web Appendix (Supplementary Figure 1). Briefly, of all 15,105 participants, we excluded 212 participants that have no available PWV measurement at baseline, 1,442 with overt thyroid disorders or subclinical hyperthyroidism; 437 using medications that alters thyroid function; 3,696 using diuretics and antihypertensives; 527 with CKD and 450 with self-reported angina, myocardial infarction, cardiac revascularization, heart failure, or stroke; and 18 with missing data in the questionnaire.

After exclusions, we included 8,341 subjects, 7,878 (94.4%) euthyroid and 463 (5.6%) had SCH. The median age was 50 years (interquartile range: 44–56); 4,383 (52.5%) were women. Only 87 (1.0%) and 27 (0.35%) subjects presented TSH ≥7.0 mIU/l and >10 mIU/l, respectively, and only 471 (5.6%) presented cf-PWV above 12.0 m/s.

Table 1 shows differences between euthyroid and SCH groups. Differences were significant for age, frequency of females and White race, body mass index, glomerular filtration rate, and C-reactive protein, all of them higher in the SCH group, except for the glomerular filtration rate.

Table 2 shows linear regression models that included cf-PWV as a dependent variable. All adjusted models show a lack of association between cf-PWV and SCH in the full-adjusted model: β = −0.039 (95% CI = −0.170 to 0.092), P = 0.562. Table 3 shows the results using logistic regression models, with results consistent to those from linear models.

Tables 2 and 3 also show sensitivity analyses, with inclusion of subjects with and without CKD. Even considering participants with CKD in the analysis, the association between SCH and cf-PWV >75th percentile remained non-significant in linear (β = −0.003; 95% CI = −0.131 to 0.125) and logistic odds ratio = 1.00 (95% CI = 0.77–1.29) full models, respectively. Raising the cutoff for SCH diagnosis for a TSH ≥7.0 mIU/l (compared to 4.0 mIU/l used in the main analysis) and for cf-PWV to >12 m/s (rather than 75th percentile, as in the main analysis), the lack of association remained.

We also restricted analysis to participants using statins and/or acetylsalicylic acid in logistic and linear models, but the results did not materially change (Supplementary Tables 1 and 2). Further adjustment for physical activity and urinary sodium in multivariate models did not change the results (Supplementary Tables 3 and 4).

DISCUSSION

In this study, we found lack of association between SCH and high cf-PWV values after multivariate adjustment for other cardiovascular risk factors and exclusion of subjects with CKD. In spite of this negative result, to our knowledge, ELSA–Brasil is the largest study to date to evaluate the association between cf-PWV and SCH and thus had high power to detect an association if present.

Table 1. General characteristics of the sample according to the presence of subclinical hypothyroidism

	Euthyroidism	Subclinical hypothyroidism	Total	
	N = 7,878	*N* = 463	*N* = 8,341	*P*
Age (years)[a]	50 (44–56)	52 (45–58)	50 (44–56)	**<0.0001**
Women (%)	4,119 (52.3)	264 (57.0)	4,383 (52.5)	**0.047**
Race (%)				**<0.0001**
White	3,992 (51.2)	277 (60.3)	4,269 (51.7)	
Mixed	2,299 (29.5)	125 (27.2)	2,424 (29.4)	
Black	1,235 (15.8)	42 (9.2)	1,277 (15.5)	
Other[b]	266 (3.4)	15 (3.3)	281 (3.4)	
Body mass index[c] (kg/m^2)	26.6 (4.5)	27.0 (4.9)	26.6 (4.5)	**0.040**
Systolic blood pressure[c,d] (mm Hg)	125.2 (16.7)	125.3 (17.1)	125.2 (16.7)	0.872
Smoking (%)				0.051
Never	4,621 (58.7)	271 (58.5)	4,892 (58.7)	
Past	2,220 (28.2)	147 (31.7)	2,267 (28.4)	
Current	1,037 (13.2)	45 (9.7)	1,082 (13.0)	
Hypertension (%)	2,136 (27.1)	128 (27.6)	2,264 (27.1)	0.804
Diabetes mellitus (%)	1,262 (16.0)	63 (13.6)	1,325 (15.9)	0.167
Dyslipidemia (%)	4,281 (54.3)	244 (52.7)	4,525 (54.3)	0.491
Total cholesterol (mg/dl)[c]	214.8 (41.2)	217.6 (42.2)	215.0 (41.3)	0.161
HDL cholesterol (mg/dl)[c]	56.7 (14.5)	57.8 (14.3)	56.8 (14.5)	0.136
LDL cholesterol (mg/dl)[c]	131.7 (34.6)	132.6 (35.3)	131.8 (34.6)	0.620
Triglycerides (mg/dl)[a]	112 (80–163)	114 (81–174)	112 (80–163)	0.111
GFR (ml/min/1.73 m2)	85.8 (13.5)	83.0 (13.0)	85.7 (13.5)	**<0.0001**
TSH (mIU/l)[a]	1.48 (1.03–2.17)	5.00 (4.42–6.41)	1.55 (1.06–2.33)	**<0.0001**
Free thyroxine (ng/dl)[a]	1.10 (0.91–1.21)	1.10 (1.00–1.20)	1.10 (1.00–1.20)	0.951
C-reactive protein (mg/l)[a]	1.36 (0.67–3.08)	1.50 (0.84–3.46)	1.36 (0.68–3.10)	**0.009**
10-year CHD (%)[a]	5 (2–9)	5 (3–9)	5 (2–9)	0.581
cf-PWV >75th percentile (%)	1,957 (24.8)	123 (26.6)	2,080 (24.9)	0.405
cf-PWV (m/s)[c]	9.12 (1.74)	9.15 (1.73)	9.12 (1.74)	0.672

Bold values means statistically significant ones. Abbreviations: Cf-PWV, carotid–femoral pulse wave velocity; CHD, coronary heart disease risk (Framingham risk score); GFR, glomerular filtration rate.

[a]Median and interquartile range.

[b]Other refers to Asian and indigenous.

[c]Mean (SD).

[d]Measurements of blood pressure were performed before cf-PWV evaluation.

Previous studies have evaluated this relationship with conflicting results. One cross-sectional study showed that aortic or central PWV was associated with increased brachial–ankle PWV in 40 subjects with SCH, compared with 50 euthyroid matched controls.[18] In the same center, a cross-sectional study showed increased levels of PWV in 50 subjects with SCH, in a univariate comparison with 50 euthyroid matched subjects.[19]

By contrast, 1 small Polish study that included 15 subjects with SCH and 41 with overt hypothyroidism, 26 with severe thyroid insufficiency, defined as TSH >70 mIU/l, failed to show any association between SCH and ba-PWV. However, interestingly, they showed a strong association of overt hypothyroidism with artery stiffness.[36] Another small study, from the United Kingdom, which included a sample of 19 subjects with SCH, compared with 10 euthyroid control detected reduction in ba-PWV associated with TSH levels, but not with FT4, after up to 6 months of levothyroxine replacement.[20]

An open clinical trial with 42 subjects with SCH, 81% women, showed that values of ba-PWV decreased after 4 months of levothyroxine replacement only in a subgroup of females with SCH and high-baseline ba-PWV and pulse pressure, without multivariate adjustment.[21] Nevertheless, 1 randomized placebo-controlled study, which included 95 females with autoimmune SCH, 48 randomized to levothyroxine replacement therapy and 47 to placebo, and further 48 euthyroid matched subjects, failed to show a multivariate

Table 2. Beta-coefficients of generalized linear models that evaluated association between pulse wave velocity (**cf-PWV)** as continuous variable (in m/s) and subclinical hypothyroidism (SCH) vs. euthyroid subjects

	Crude	Model 1	Model 2
	cf-PWV (*N* = 8,341)		
Subclinical hypothyroidism	0.035 (−0.128 to 0.198)	−0.053 (−0.185 to 0.080)	−0.039 (−0.170 to 0.092)
P value	0.672	0.436	0.562
Sensitivity analysis including chronic kidney disease: cf-PWV (*N* = 8,810)			
Subclinical hypothyroidism	0.137 (−0.024 to 0.298)	−0.006 (−0.135 to 0.122)	−0.003 (−0.131 to 0.125)
P value	0.096	0.922	0.961
TSH ≥ 7.0 mIU/l	**0.453 (0.096 to 0.811)**	0.069 (−0.216 to 0.354)	0.097 (−0.184 to 0.378)
P value	**0.013**	0.636	0.500

Model 1—adjusted for age, sex and race/skin color, and systolic blood pressure before cf-PWV; Model 2—plus BMI, smoking; and diabetes mellitus, hypertension, HDL cholesterol, triglycerides, LDL cholesterol, glomerular filtration rate by CKD-EPI, and C-reactive protein. Bold values means statistically significant ones. Abbreviations: cf-PWV, carotid–femoral pulse wave velocity; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyrotropin.

Table 3. Odds ratio and 95% confidence interval of pulse wave velocity (**cf-PWV)** above 75th percentile with subclinical hypothyroidism using euthyroid subjects as the reference

	Crude	Model 1	Model 2
	All (*N* = 8,341)		
	cf-PWV >75th percentile (>9.9 m/s)		
Subclinical hypothyroidism	1.05 (0.84–1.31)	0.90 (0.70–1.17)	0.94 (0.72–1.22)
Euthyroidism	1.0 (reference)	1.0 (reference)	1.0 (reference)
Sensitivity analysis including those with chronic kidney disease (*N* = 8,810)			
cf-PWV >75th percentile (>9.9 m/s)			
Subclinical hypothyroidism	1.10 (0.89–1.35)	0.96 (0.75–1.23)	1.00 (0.77–1.29)
Euthyroidism	1.0 (reference)	1.0 (reference)	1.0 (reference)
cf-PWV > 12 m/s			
TSH ≥ 7.0 mIU/l	**2.20 (1.22–3.97)**	1.93 (0.96–3.90)	2.04 (0.99–4.18)
Euthyroidism	1.0 (reference)	1.0 (reference)	1.0 (reference)

Model 1—adjusted for age, sex, race/skin color and systolic blood pressure before cf-PWV; Model 2—plus BMI, smoking, diabetes mellitus, hypertension, HDL cholesterol, triglycerides, LDL cholesterol, glomerular filtration rate by CKD-EPI, and C-reactive protein. Bold values means statistically significant ones. Abbreviations: cf-PWV, carotid–femoral pulse wave velocity; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyrotropin.

association between normalization of thyroid function and normalization or decrease in ba-PWV, after adjustment for age and pulse pressure.[22]

It is important to highlight some points. As shown previously, all studies used brachial–ankle PWV to evaluate this association and included small samples.[18–22] There are differences between the brachial artery and the aorta in relation to the amount of elastic fibers and pathophysiology of atherosclerosis, which may result in differences between brachial–ankle and cf-PWV measurements.[36] Of these 5 studies with positive results, 4 did not perform multivariate adjustment for possible confounders.[18,19,21,22] To date, the majority of positive results for the relationship between SCH and PWV are restricted to 1 center in Japan.[18,19,21,22] Compared to these results, ELSA–Brasil included a larger sample with different population characteristics. The cutoff values of cf-PWV to consider an increase in PWV are somewhat controversial, with large differences across studies.[11] Although 1 consensus defined only 1 cutoff at 12 m/s and other study considered the cutoff at 95th percentile adjusted for age and sex,[37] the majority of studies considered the cutoff at the 75th percentile.[11]

Study limitations

These results must be considered within the context of its design. This is a cross-sectional analysis that can evaluate association, but not causality. We considered only 1 measurement of TSH for inclusion criteria, and we did measure either thyroid autoantibodies or FT4 for all samples and FT3, to evaluate the subgroup of autoimmune disease and additional associations with thyroid hormones.

Our study also had some strengths; it is the largest study to date to evaluate the association between cf-PWV and SCH in a healthy adult population, with the exclusion of prevalent cases of cardiovascular disease and CKD and multivariate adjustment for possible confounders. In the measurement of cf-PWV, in ELSA–Brasil, we followed a strict protocol.[30]

In conclusion, we did not find any association between cf-PWV and SCH, compared with euthyroid subjects, after adjustment for sociodemographic data and cardiovascular risk factors.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

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